THE
2024-25

Medical-Dental-Legal UPDATE

Medical Malpractice • Risk Management • Practice Management
Healthcare Law • Selected Clinical Topics

American Educational Institute, Inc.

111 E. Merrill Street • Suite 300
Birmingham, MI 48009

1 800 354-3507
AEIseminars.com

American Educational Institute, Inc.
Leading Edge Instruction Since 1982
111 E. Merrill Street • Suite 300 • Birmingham, Michigan 48009
Seminar Information (800) 354-3507 or (248) 433-0606
Fax (248) 433-0911
www.AEIseminars.com E-Mail: DVictor@ AEIseminars.com

David R. Victor, JD
CEO

Dear Registrant:

You practice in a dynamic and challenging environment. While keeping clinically current is imperative, it isn't enough. You must also acquire the skills necessary to navigate a professional liability minefield, manage a more effective and efficient practice, and master a maze of healthcare laws and regulations. ***The 2024-25 Medical-Dental-Legal Update*** is designed to assist you in that endeavor.

In one course you will receive 20 hours of vital instruction from national experts in the fields of law, medicine, public health, accounting, insurance, asset protection, pharmacology, and practice management. And their presentations include topics ranging from pain management, heart disease prevention, colorectal cancer screening, sleep medicine, and chest X-ray interpretation, to asset protection, fraud prevention, malpractice pitfalls, & financial intelligence.

To help you assess your level of comprehension we offer brief self-evaluations that may be taken either before or after the presentations concerned. These tests are included in this syllabus and are identified by the black edges of the pages on which they are featured.

As always, I am very interested in your reaction to this year's lecture series. Please do me the favor of taking the time to complete the evaluation questions presented on screen for each presentation. In addition, I encourage you to contact any of our faculty members directly with questions or comments.

Finally, I urge you to take advantage of the diversity of professionals enrolled this week. Chances are your classmates include physicians, dentists, and attorneys. What better way to gain another perspective on these multi-faceted issues than to discuss them via our real time chat room with a colleague from a different discipline.

Thank you for your participation and please accept my best wishes for a safe, enjoyable and enlightening visit.

Cordially,
American Educational Institute, Inc

David R. Victor, Esq
Chief Executive Officer

TABLE OF CONTENTS

TABLE OF CONTENTS

THE 2024-25

Medical-Dental-Legal UPDATE

COURSE OBJECTIVES

After completing ***The 2024-25 Medical-Dental-Legal Update*** you should have acquired the knowledge that will better enable you to better:

- Understand the evolution of and current state of **hypertension management**
- Identify **financial controls** to prevent fraud and increase revenue
- Appreciate the correlation between **brain health and sleep quality**
- Discuss the **impact of communication on practice risk**
- Identify and manage patients with **GERD**
- Appreciate the role of **the physician witness** and how it is best executed
- Identify medical findings revealed by **chest X-ray imaging**
- Understand the planning, negotiating, and implementing a **practice merger or acquisition**
- Offer informed **cardiovascular disease** diagnostic, prevention and treatment advice
- Understand methods to optimize **retirement planning and practice value**
- Identify current clinical practice guidelines and medications for the treatment of **heart failure**
- Identify screening, treatment and surveillance options for **colorectal cancer**
- Identify management approaches for **adult and adolescent acne**
- Identify and avoid **medical malpractice pitfalls**
- Understand new **cholesterol treatment** guidelines and medications
- Identify and manage **patients at risk for addiction**
- Appreciate the nature and benefits of **the Mediterranean Diet**
- Understand how the **Consolidated Appropriations Act of 2023** impacts effective retirement planning
- Consider new treatment options for **insomnia and obstructive sleep apnea**
- Identify ways to optimally **position a practice for sale or merger**

All learning objectives above address IOM/ACGME core competencies.

THE 2024-25

Medical-Dental-Legal UPDATE

FACULTY DISCLOSURES

The individuals listed below have control over the content of ***The 2024-25 Medical-Dental-Legal Update***. None of them have a financial relationship with an ineligible company.

David R. Victor, Esq., CEO, Course Director, *The 2024-25 Medical-Dental-Legal Update*
Thomas P. Cox, ARM, faculty member
David M. Ottenwess, Esq., faculty member
Louis Kuritzky, MD, faculty member
David B. Mandell, JD, MBA, faculty member
Stephanie P. Ottenwess, Esq., faculty member
Carole C. Foos, CPA, faculty member
John F. Dombrowski, MD, FASA, faculty member
C. Wayne Weart, PharmD, faculty member
Michael J. Howell, MD, FAAN, FAASM, faculty member
Joel K. Kahn, MD, FACC, faculty member
Erin King-Mullins, MD, faculty member
Bert Orlov, MBA, faculty member
Cullen Ruff, MD, FACR, faculty member

Louis Kuritzky, MD

Louis Kuritzky, MD, of Gainesville, Florida, is a board-certified, family practitioner and a certified Specialist in Hypertension with the American Society of Hypertension. He is clinical faculty at the UCF/HCA Family Medicine Residency Program in Gainesville and a clinical assistant professor emeritus at the University of Florida.

Dr. Kuritzky has given over 1,000 presentations to national and international medical audiences on dozens of clinical topics and has authored over 150 articles in journals including *New England Journal of Medicine, JAMA, Comprehensive Therapy, Hospital Practice, Consultant, Postgraduate Medicine, Journal of Pain and Palliative Care,* and *Patient Care*.

You may contact Dr. Kuritzky with any questions or comments at (352) 377–3193 or by email at lkuritzky@aol.com.

LOUIS KURITZKY, MD
4510 NW 17th Place
GAINESVILLE, FL 32605
(352) 377-3193 LKuritzky@aol.com

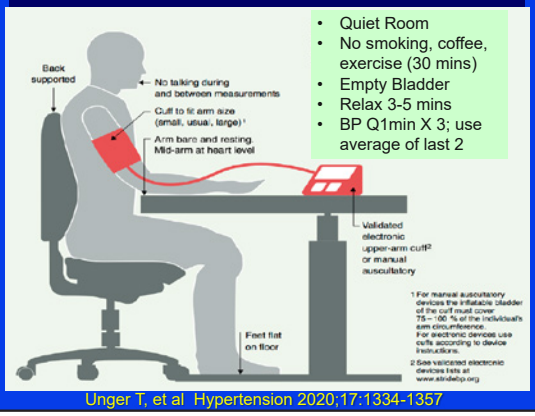
Hypertension Management: Where We are and How We Got Here

The Payoffs of Treating HTN

- MI: reduced ±25%
- Stroke: reduced ±40%
- CHF: reduced ±50%

Chobanian AV, et al. *Hypertension*. 2003;42(6):1206-1252.

2020 ISH Global HTN Guidelines



- Quiet Room
- No smoking, coffee, exercise (30 mins)
- Empty Bladder
- Relax 3-5 mins
- BP Q1min X 3; use average of last 2

Unger T, et al Hypertension 2020;17:1334-1357

HTN Where We Are TODAY

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

BP Patterns Office and Out-of-Office Measurements

	Healthcare Setting	Home/ABPM Setting
Normotensive	No HTN	No HTN
Sustained hypertension	HTN	HTN
Masked hypertension	No HTN	HTN
White coat hypertension	HTN	No HTN

ADAPTED

Out-of-Office and Self-Monitoring of BP

COR	LOE	Recommendation for Out-of-Office and Self-Monitoring of BP
I	A^{SR}	Use out-of-office BP both to confirm Dx of HTN and for titration of Meds

ADAPTED

Categories of BP in Adults*
≥2 readings on ≥ 2 occasions

Category	SBP		DBP
Normal	<120 mm Hg	**and**	<80 mm Hg
Elevated	120–129 mm Hg	**and**	<80 mm Hg
HTN			
Stage 1	130–139 mm Hg	**or**	80–89 mm Hg
Stage 2	≥140 mm Hg	**or**	≥90 mm Hg

*If 2 categories differ: designate higher BP category

ADAPTED

2020 Int Society HTN Guideline "Optimal" BP Rx Regimen

Step 1
Dual low dose* combo A + C

Step 2
Dual full dose combo A + C

Step 3
Triple combo A + C + D

Step 4
Triple Combo + S or O

A = ACE, ARB
C = CCB (DhP)
D = Diuretic
S = Spironolactone
O = Other (amiloride, doxazosin, eplerenone, clonidine, BB)

Unger T et al *Hypertension* 2020;75:1334-1357

2020 Int Society HTN Guideline BP Categorization: *Office*

Category	SBP mm Hg		DBP mm Hg
Normal	<130		<85
High Normal	130-139	&/or	85-89
Stage 1	140-159	&/or	90-99
Stage 2	≥160	&/or	≥100

Unger T et al *Hypertension* 2020;75:1334-1357

2020 Int Society HTN Guideline HTN Categorization: *Out of Office*

Category	SBP &/or DBP mm Hg
ABPM	
24 hr avg	≥130/80
Daytime avg	≥135/85
Overnite avg	≥120/70
Home BP	≥135/85

Unger T et al *Hypertension* 2020;75:1334-1357

2020 Int Society HTN Guideline BP Targets

Group	SBP/DBP mm Hg
<65 years	<130/80 (but >120/70)
+CAD,CVA,CKD	<130/80
≥65 years	<140/90
+CAD, CVA, CKD	<140/80
CHF (all ages)	<130/80 (but >120/70)

Unger T et al *Hypertension* 2020;75:1334-1357

Essential HTN Questions

- Does Lowering BP in REALLY BAD HTN Improve Outcomes? (1967 VA Cooperative Study I)
- Does Lowering BP in LESS BAD HTN Improve Outcomes? (1967 VA Cooperative Study II)
- Which is More Important: SBP or DBP? (MRFIT 1992)
- Why Do Older Folks Get ISH?
- How About Isolated Systolic HTN? (SHEP 1993)

Essential HTN Questions

- What Agent Should We Start With? (ALLHAT 2002)
- Can Tx of Pre-HTN Prevent HTN (TROPHY 2006)
- How About Really Old Folks? (HYVET)
- Since ALLHAT Proved That Most Patients Need at Least 2 Meds, Which TWO? (ACCOMPLISH 2008)

Essential HTN Questions

- Is Lower Better for HTN in T2DM (ACCORD)
- For High Risk non-DM patients is <120 mm Hg better than <140 mm Hg (SPRINT)
- Same question, for OLD FOLKS
- Goal BP (JNC 8 vs ACC AHA 2017)

Is There a Benefit from Treating Really BAD HTN?

VA Cooperative Study (I)

- Study: RDBPCT in Stage 3-4 HTN (n=143)
- Inclusion: DBP 115-129 mm Hg
- Demographics
  - 66 white, 77 AA men
  - Mean: age 51 yrs
- Rx (18 months) vs placebo :
  - Hydralazine 25-50 mg tid
  - Reserpine 0.1 mg bid
  - HCTZ 50 mg qd

VA Cooperative Study Group. *JAMA*. 1967;202:1028-1034.

The VA Cooperative Study (1967): Outcomes at 18 Months

*all p < 0.001	Placebo N=70	Active Drug* N = 73
Accelerated HTN	12	0
Stroke	4	1
Coronary event	2	0
CHF	2	0
Renal Damage	2	0
Death	4	0

VA Cooperative Study Group. *JAMA*. 1967;202:1028-1034.

What About BP That's Not QUITE So Bad?

VA Cooperative Study (II)

- Study: RDBPCT in Stage 2-3 HTN (n=380)
- Inclusion: DBP 90-114 mm Hg
- Demographics
  - 42% AA, 58% 'other'
  - Mean: age 50 yrs
- Rx (±39 months) vs placebo :
  - Hydralazine 25-50 mg tid
  - Reserpine 0.1 mg bid
  - HCTZ 50 mg qd

VA Cooperative Study Group. *JAMA*. 1970;213:11143-1152.

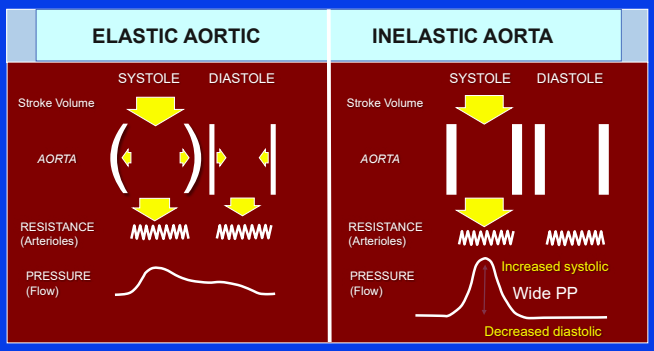
The VA Cooperative Study II (1970): Outcomes at 39 months

*all p < 0.001	Placebo N=194	Active Drug* N = 186
Accelerated HTN	4	0
Stroke	20	6
Coronary event	13	11
CHF	11	0
Renal Damage	3	0
Death	19	8

VA Cooperative Study Group. *JAMA*. 1970;213:1143-1152.

Why Do Older Folks Get Systolic HTN?

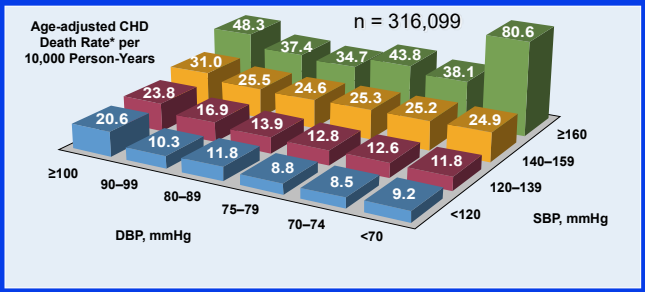
SBP/DBP Discrepancy with Aging



Victor RG, Kaplan NM. Systemic HTN: Mechanisms and Dx. *Braunwald's Heart Disease*. 8th ed. Philadelphia, PA: Saunders Elsevier; 2008:1027–1048.

Is SBP or DBP More Important?

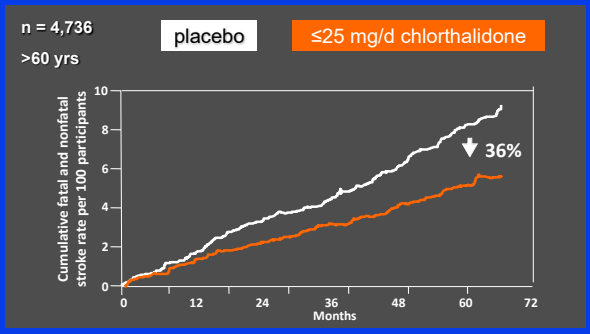
MRFIT: Effect of BP on CHD Mortality



Neaton JD et al. *Arch Intern Med*. 1992;152:56–64.

Does Rx of Isolated SBP Improve Outcomes?

Systolic Hypertension in the Elderly Program (SHEP)



SHEP Cooperative Research Group *JAMA* 1991;265:3255-3264

NEXT

A Bazillion CV Trials on Individual HTN Agents, ALL of Which Work to Some Degree

….fast forward 35 years, 1967-2002

Well EVERYTHING Seems to Work, so What is the BEST INITIAL HTN Rx?

U.S. Department of Health and Human Services

National Institutes of Health

National Heart, Lung, and Blood Institute

"Major Outcomes in High Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic"

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

The ALLHAT Collaborative Research Group

Sponsored by the National Heart, Lung, and Blood Institute (NHLBI)

JAMA. 2002;288:2891-2997 (Dec 18)

ALLHAT: Abstract

Context

"Antihypertensive Rx is well established to ↓ hypertension-related morbidity and mortality, but the optimal first-step Rx is unknown"

ALLHAT Collaborative Research Group "Major Outcomes in High-Risk Hypertensive Patients Randomized to ACEI or CCB vs Diuretic" JAMA 2002;288:2981-2997

ALLHAT: Abstract

Objective

"To determine whether Rx with a CCB or an ACEI lowers the incidence of CHD or other CVD vs Rx with a diuretic"

ALLHAT "Major Outcomes in High-Risk HTN Patients Randomized to ACEI or CCB vs Diuretic" JAMA 2002;288:2981-2997

ALLHAT: Abstract

Design & Setting

- RDB Active-Controlled Trial 1994-2002
- Age ≥ 55 (n=33,357) + ≥ 1 other CHD risk factor

ALLHAT "Major Outcomes in High-Risk HTN Patients Randomized to ACEI or CCB vs Diuretic" JAMA 2002;288:2981-2997

ALLHAT: Abstract

Interventions

- Chlorthalidone 12.5-25 mg/d (n=15,255)
- Amlodipine 2.5-10mg/d (n=9,048)
- Lisinopril 10-40 mg/d (n=9,054)
- Planned follow up 4-8 years

ALLHAT "Major Outcomes in High-Risk HTN Patients Randomized to ACEI or CCB vs Diuretic" JAMA 2002;288:2981-2997

ALLHAT: Abstract

Main Outcome Measures

- PRIMARY: Fatal CHD + nonfatal MI
- SECONDARY:
  - All Cause Mortality
  - Stroke (fatal + nonfatal)
  - Combined CHD (1^0 + PCTA + angina admit)
  - Combined CVD (CHD, stroke, angina, CHF, PAD)

ALLHAT "Major Outcomes in High-Risk HTN Patients Randomized to ACEI or CCB vs Diuretic" JAMA 2002;288:2981-2997

ALLHAT: Abstract

Results (at mean followup = 4.9 years)

- PRIMARY: CLTD = CCB =ACEI
- SECONDARY (RR= compared to CLTD):
  - All Cause Mortality: All groups =
  - CHF: CCB RR = 1.38 ACEI RR = 1.19
  - Combined CVD: ACEI RR = 1.10
  - Stroke: ACEI RR = 1.15

ALLHAT "Major Outcomes in High-Risk HTN Patients Randomized to ACEI or CCB vs Diuretic" JAMA 2002;288:2981-2997

ALLHAT: Abstract

Results (at mean followup = 4.9 years)

- SBP (mmHg Δ vs CLTD):
  - CCB = +0.8
  - ACEI = +2

ALLHAT "Major Outcomes in High-Risk HTN Patients Randomized to ACEI or CCB vs Diuretic" JAMA 2002;288:2981-2997

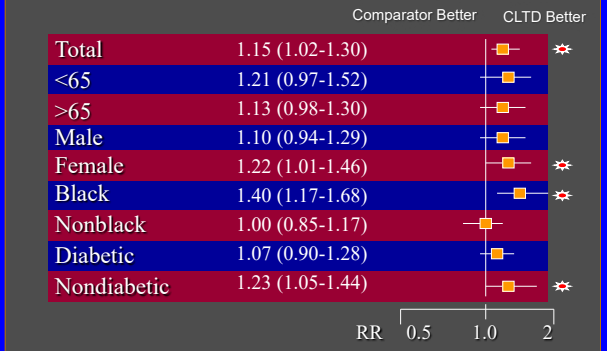
ALLHAT: Abstract

Conclusions

"Thiazide-type diuretics are superior in preventing 1 or more major forms of CVD and are less expensive. They should be preferred for first-step antiHTN therapy."

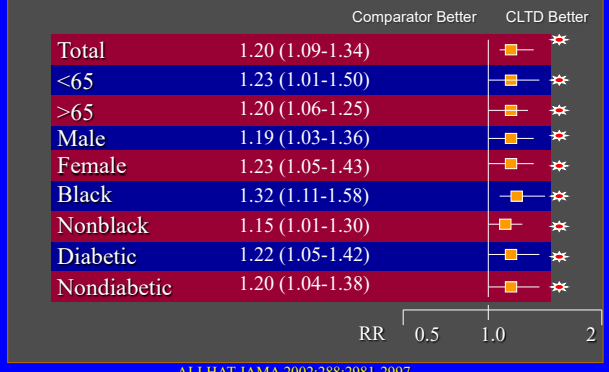
ALLHAT "Major Outcomes in High-Risk HTN Patients Randomized to ACEI or CCB vs Diuretic" JAMA 2002;288:2981-2997

Lisinopril vs Chlorthalidone: Stroke



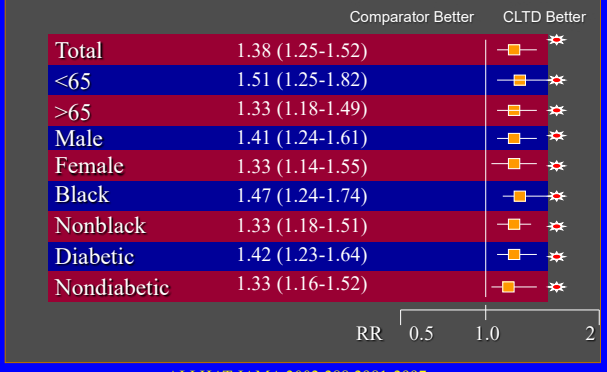
ALLHAT JAMA 2002;288:2981-2997

Lisinopril vs Chlorthalidone: Heart Failure



ALLHAT JAMA 2002;288:2981-2997

Amlodipine vs Chlorthalidone: Heart Failure



ALLHAT JAMA 2002;288:2981-2997

ALLHAT JAMA Editorial response: HCTZ vs Chlorthalidone

"Although thiazide-type diuretics are reasonably similar and ALLHAT results might be extrapolated to HCTZ, purists might argue that chlorthalidone should be used in view of its well-documented efficacy in trials."

Appel L J "The Verdict From ALLHAT—Thiazide Diuretics are the Preferred Initial Therapy for HTN" JAMA 2002;288(23)3039-3042

Rx of HTN is A Good Thing. What About Pre-HTN?

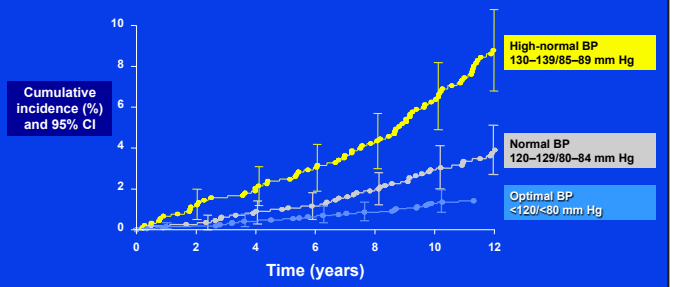
A Great Answer to the Question I DIDN'T Ask

Feasibility of Treating Prehypertension with an Angiotensin-Receptor Blocker

Julius S, Nesbitt SD, Egan BM, Weber MA, Michelson EL, Kaciroti N et al for the Trial of Preventing Hypertension (TROPHY) Study Investigators
NEJM 2006;354:1685-97

High-normal BP increases CV risk

Incidence of CV events in women: Framingham



Vasan RS et al. *N Engl J Med.* 2001;345:1291-7.

TROPHY: Study design

Patients with untreated prehypertension (n=772)
Ages 30–65 years

LIFESTYLE COUNSELING

Candesartan 16 mg qd n = 391

Randomized Double-blind Years 1 & 2

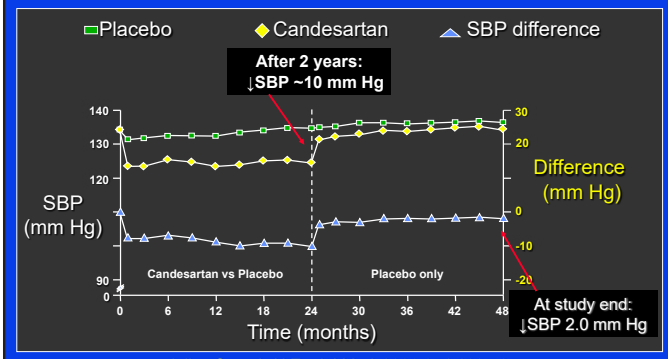
Placebo n = 381

Placebo
Years 3 & 4

Study end points:
Development of HTN at years 2 and 4

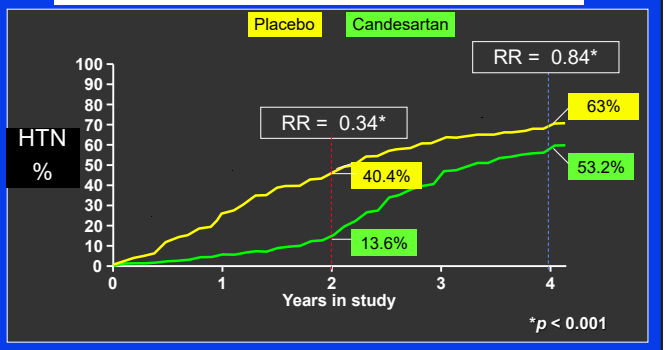
Julius S et al. *N Engl J Med.* 2006;354:1685-97.

TROPHY: BP by treatment group



Julius S et al. *N Engl J Med.* 2006;354:1685-97.

Development of Clinical HTN (SBP >140 mmHg OR DBP >90 mmHg)



Julius S et al. *N Engl J Med.* 2006;354:1685-97.

HTN Rx Works in Mid-Life. What About Super-Seniors (≥80 yrs)?

HTN in the Very Elderly Trial HYVET

- STUDY: PRDBPCT 2-year HTN trial in super-seniors (age ≥80 yrs)
- Inclusion: ≥ SBP 160 mm Hg
- Rx: SR-indapamide 1.5 mg/d
- Primary outcome: fatal/nonfatal stroke

Beckett NS et al N Engl J Med 2008;358(18):1887-1898

HYVET: Results

	Indap #(%)	PBO # (%)	HR	p
Stroke (all)	12.4 (51)	17.7 (69)	0.70	0.06
Stroke Death	6.5 (27)	10.7 (42)	0.61	0.046
All-Cause Mortality	196 (47.2)	235 (59.6)	0.79	0.02

Beckett NS et al N Engl J Med 2008;358(18):1887-1898

Since MOST Folks Require >1 HTN Med, Which is the Best COMBO to Start With?

ACCOMPLISH

Avoiding CV Events through Combination therapy in Patients Living with Systolic Hypertension

ACCOMPLISH

Abstract: BACKGROUND

"The optimal combination drug Rx for HTN is not established, although current US guidelines recommend inclusion of a diuretic. We hypothesized that ACE + dihydropyridine CCB would be more effective in reducing CV events….than …ACE + thiazide…."

The ACCOMPLISH Trial Investigators N Engl J Med 2008;359:2417-2428

ACCOMPLISH

Abstract: Methods

- HTN participants (n=11,506) assigned to:
  - Benazepril/amlodipine
  - Benazepril/HCTZ
- Primary outcome (MACE composite):
  - Nonfatal MI, nonfatal stroke, CV death, angina hospitalization, resuscitation after sudden cardiac arrest, coronary revascularization
- Mean f/u: 36 months

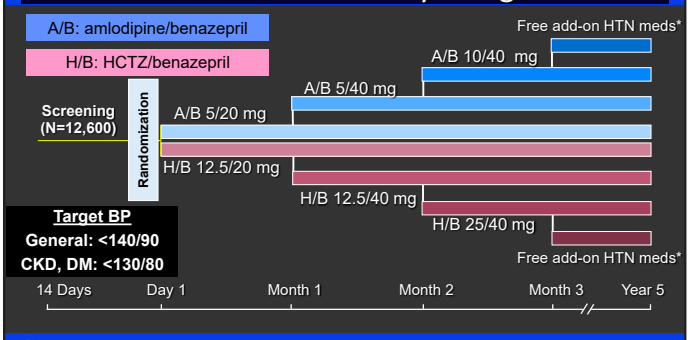
The ACCOMPLISH Trial Investigators N Engl J Med 2008;359:2417-2428

ACCOMPLISH
Eligibility: Inclusions

- HTN
- High risk for CV events:
  - Coronary events
  - MI
  - Stroke
  - Revascularization
  - CKD
  - LVH
  - DM
  - PAD

The ACCOMPLISH Trial Investigators N Engl J Med 2008;359:2417-2428

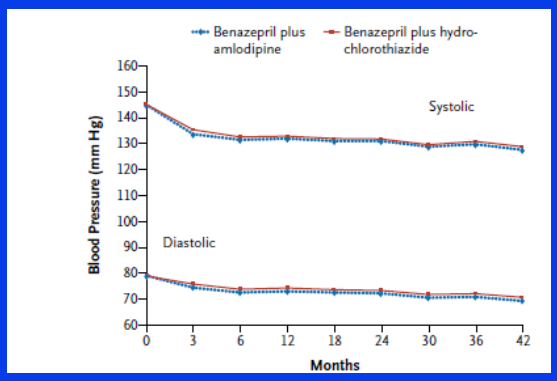
ACCOMPLISH: Study Design



*β-blockers; α-blockers; clonidine; loop diuretics.

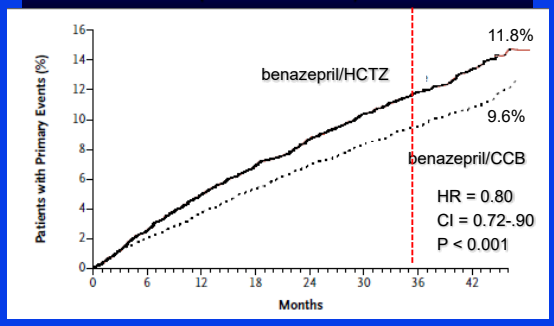
The ACCOMPLISH Trial Investigators N Engl J Med 2008;359:2417-2428

BP at Each Study Visit



The ACCOMPLISH Trial Investigators N Engl J Med 2008;359:2417-2428

ACCOMPLISH: Primary Outcome (at 36 Months)



The ACCOMPLISH Trial Investigators N Engl J Med 2008;359:2417-2428

ACCOMPLISH

Abstract: Conclusions

"The ACE+CCB combination was superior to the ACE+HCTZ combination in reducing CV events in patients with HTN who were at high risk for such events."

The ACCOMPLISH Trial Investigators N Engl J Med 2008;359:2417-2428

ACCORD
Action to Control CV Risk in Diabetes

ACCORD

Abstract: BACKGROUND

"There is NO EVIDENCE from randomized trials to support a strategy of lowering SBP below 135-140 mm Hg in persons with T2DM. We investigated whether therapy…to normal SBP (i.e., <120 mm Hg) reduces MACE in participants with T2DM at high risk for CV events."

*emphasis added

The ACCORD Study Group N Engl J Med 2010;March 14:10.1056/NEJMoa1001286

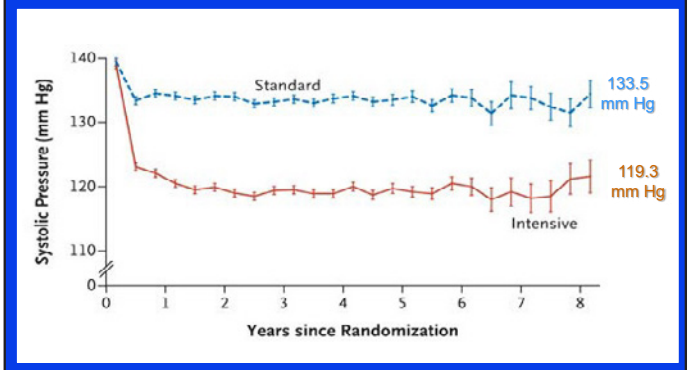
ACCORD

Abstract: Methods

- T2DM participants (n=4,733) assigned to:
  - Intensive Rx (target SBP < 120 mm Hg)
  - Standard Rx (target SBP < 140 mm Hg)
- Primary outcome (composite):
  - nonfatal MI, nonfatal stroke, and CV death
- Mean f/u: 4.7 yrs

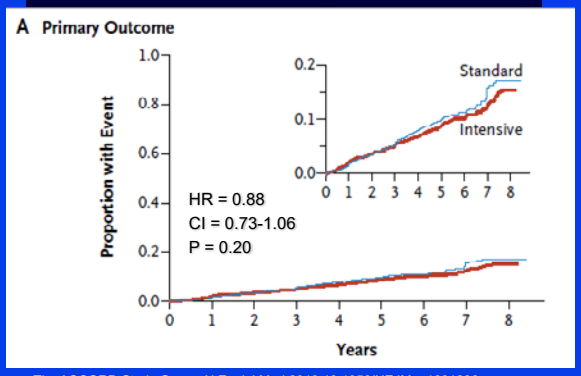
The ACCORD Study Group N Engl J Med 2010;March 14:10.1056/NEJMoa1001286

SBP (Mean) at Each Study Visit



The ACCORD Study Group. N Engl J Med 2010;10.1056/NEJMoa1001286

ACCORD: Primary Outcome

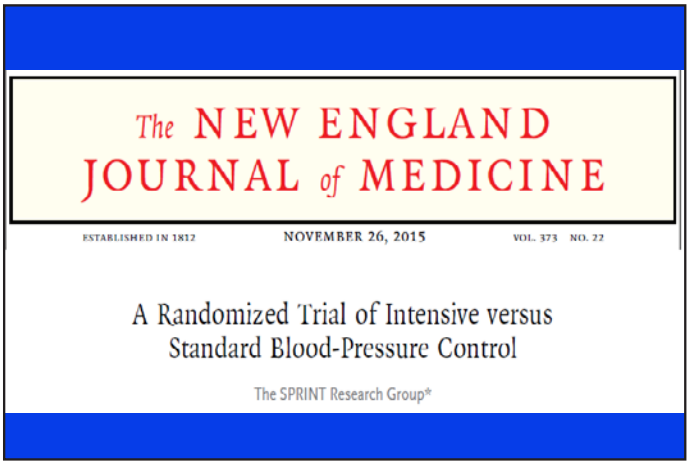


The ACCORD Study Group. N Engl J Med 2010;10.1056/NEJMoa1001286

ACCORD: Discussion

"Intensive antihypertensive therapy…did not significantly reduce the primary CV outcome or the rate of death from any cause, despite…a significant and sustained difference…in mean SBP."

The ACCORD Study Group. N Engl J Med 2010;10.1056/NEJMoa1001286



SPRINT Abstract

BACKGROUND

"The most appropriate targets for SBP to reduce CV morbidity and mortality among persons without diabetes remain uncertain."*

*emphasis added

Wright JT et al The SPRINT Research Group NEJM 2015;373(22):2103-2116

SPRINT Abstract

METHODS

- Non-diabetic adults (n = 9,361)
- SBP >130 mmHg + 'high CV Risk'
  - Previous stroke: excluded
- Randomized to SBP <140 mm Hg ('standard' Rx) vs <120 mm Hg ('intensive' Rx)
- 1^0 Outcome (composite): MACE
  - MACE = MI, ACS, CVA, HF, CV death

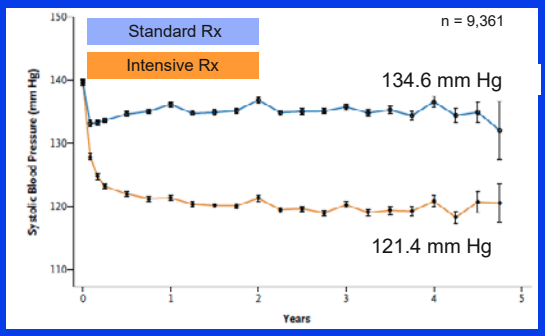
Wright JT et al The SPRINT Research Group NEJM 2015;373(22):2103-2116

SPRINT Inclusion as 'High Risk' Most Common Criteria

- Age ≥ 50 yrs (mean = 67.9 yrs; 28% > 75 yrs)
- CKD
- CVD
  - Hx of confirmed CVD (not stroke)
  - Framingham 10-yr CV risk ≥ 15%
  - Coronary Calcium Score >400
  - ABI < 0.9
  - LVH

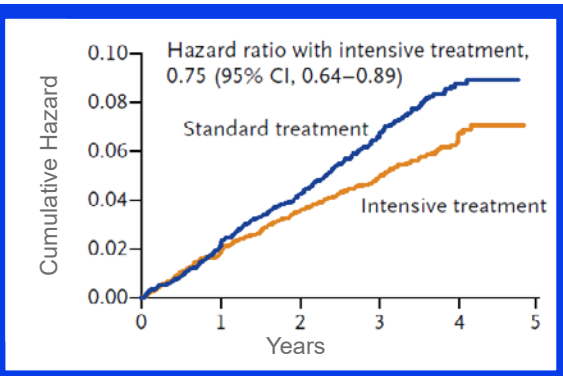
Wright JT et al The SPRINT Research Group NEJM 2015;373(22):2103-2116

SPRINT: SBP X 5 years



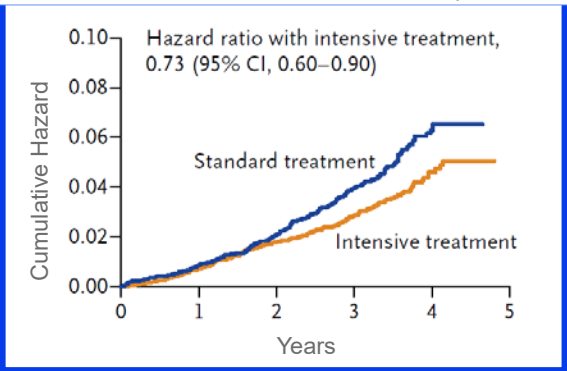
Wright JT et al The SPRINT Research Group NEJM 2015;373(22):2103-2116

SPRINT: Primary Outcome: MACE



Wright JT et al The SPRINT Research Group NEJM 2015;373(22):2103-2116

SPRINT: All-cause Mortality



Wright JT et al The SPRINT Research Group NEJM 2015;373(22):2103-2116

SPRINT Abstract

CONCLUSIONS

"Among patients at high risk for CV events but without DM, targeting a SBP of <120 mm Hg, as compared with <140 mm Hg, resulted in lower rates of fatal and nonfatal major CV events and death from any cause…."

Wright JT et al The SPRINT Research Group NEJM 2015;373(22):2103-2116

..and then there was SPRINT-SENIOR

Original Investigation

Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged ≥75 Years
A Randomized Clinical Trial

Jeff D. Williamson, MD, MHS; Mark A. Supiano, MD; William B. Applegate, MD, MPH; Dan R. Berlowitz, MD; Ruth C. Campbell, MD, MSPH; Glenn M. Chertow, MD; Larry J. Fine, MD; William E. Haley, MD; Amret T. Hawfield, MD; Joachim H. Ix, MD, MAS; Dalane W. Kitzman, MD; John B. Kostis, MD; Marie A. Krousel-Wood, MD; Lenore J. Launer, PhD; Suzanne Oparil, MD; Carlos J. Rodriguez, MD, MPH; Christianne L. Roumie, MD, MPH; Ronald I. Shorr, MD, MS; Kaycee M. Sink, MD, MAS; Virginia G. Wadley, PhD; Paul K. Whelton, MD; Jeffrey Whittle, MD; Nancy F. Woolard, Jackson T. Wright Jr, MD, PhD; Nicholas M. Pajewski, PhD; for the SPRINT Research Group

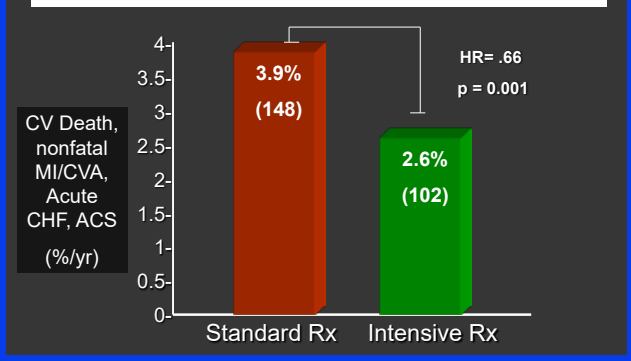
JAMA 2016;315(24):2673-2682

SPRINT-Seniors

- Study: RCT SPRINT subgroup (n = 2,636)
- Inclusion: > 75 yrs (mean age = 79.9)
- Followup: 3.14 yrs (mean)
- 1^0 Outcome: CV death + nonfatal MI/CVA + ACS
- 2^0 Outcome: All cause mortality

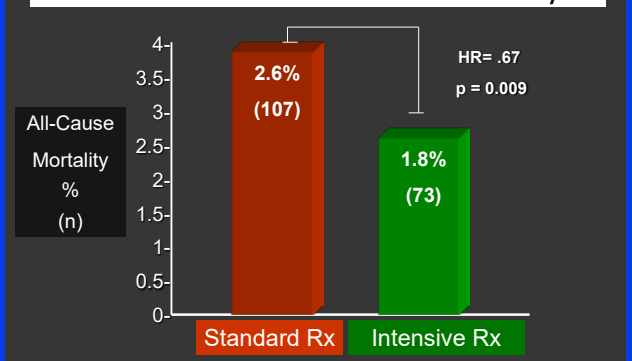
Williamson JD et al JAMA 2016;315(24):2673-2682

SPRINT-Seniors: 1^0 Outcome



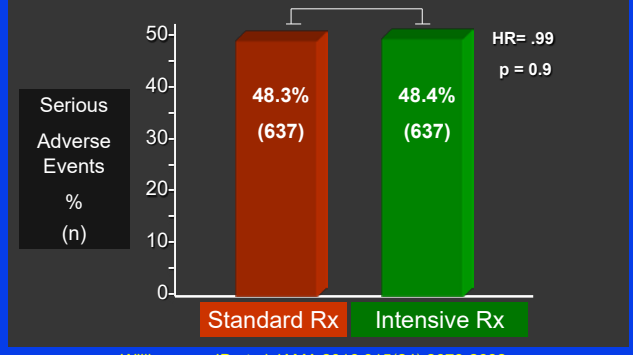
Williamson JD et al JAMA 2016;315(24):2673-2682

SPRINT-Seniors: All-Cause Mortality

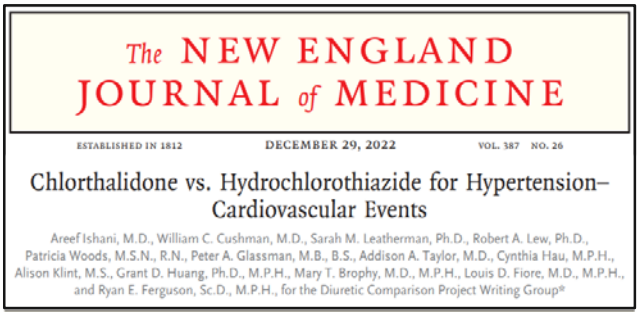


Williamson JD et al JAMA 2016;315(24):2673-2682

SPRINT-Seniors: Serious AEs



Williamson JD et al JAMA 2016;315(24):2673-2682



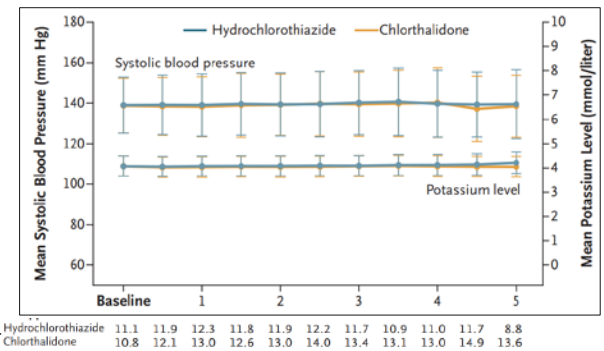
Ishani A et al *NEJM* 2022;387(26):2401-2410

Chlorthalidone vs HCTZ: CVD

- Study: PR Pragmatic Trial HTN pts on HCTZ
- Inclusion (n=13,523)
  - Willing to be randomized to chlorthalidone
  - Age ≥65
- Rx (x 2.4 yrs): HCTZ 25mg/d or 50 mg/d vs Chlorthalidone 12.5 mg/d or 25 mg/d
- 1^0 Endpoint (composite): nonfatal stroke, nonfatal MI, HF hospitalization, coronary revascularization, non-cancer mortality

Ishani A et al *NEJM* 2022;387(26):2401-2410

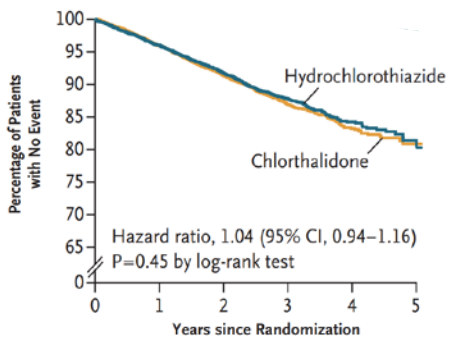
Chlorthalidone vs HCTZ: CVD



K+												
Hydrochlorothiazide	11.1	11.9	12.3	11.8	11.9	12.2	11.7	10.9	11.0	11.7	8.8
Chlorthalidone	10.8	12.1	13.0	12.6	13.0	14.0	13.4	13.1	13.0	14.9	13.6

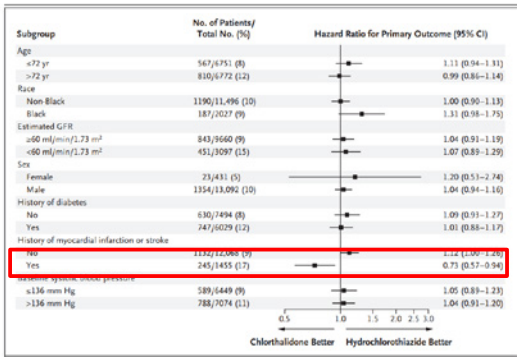
Ishani A et al *NEJM* 2022;387(26):2401-2410

Chlorthalidone vs HCTZ: CVD



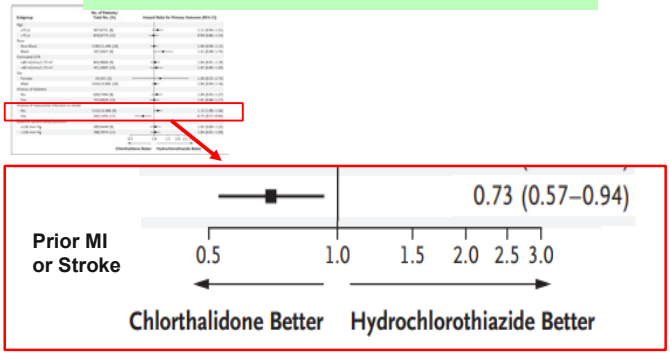
Ishani A et al *NEJM* 2022;387(26):2401-2410

Chlorthalidone vs HCTZ: CVD



Ishani A et al *NEJM* 2022;387(26):2401-2410

Chlorthalidone vs HCTZ: CVD



Ishani A et al *NEJM* 2022;387(26):2401-2410

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

AMERICAN COLLEGE of CARDIOLOGY

American Heart Association. life is why

Lab Tests for Primary HTN

Basic testing	Fasting blood glucose
	Complete blood count
	Lipid profile
	Serum creatinine with eGFR
	Serum sodium, potassium, calcium
	Thyroid-stimulating hormone
	Urinalysis
	Electrocardiogram
Optional testing	Echocardiogram
	Uric acid
	Urinary albumin to creatinine ratio

AMERICAN COLLEGE of CARDIOLOGY ADAPTED American Heart Association. life is why

BP Thresholds for and Goals of Pharmacological Therapy in Patients With Hypertension According to Clinical Conditions

Clinical Condition(s)	BP Threshold, mm Hg	BP Goal, mm Hg
General		
Clinical CVD or 10-year ASCVD risk ≥10%	≥130/80	<130/80
No clinical CVD and 10-year ASCVD risk <10%	≥140/90	<130/80
Older persons (≥65 years of age; noninstitutionalized, ambulatory, community-living adults)	≥130 (SBP)	<130 (SBP)
Specific comorbidities		
Diabetes mellitus	≥130/80	<130/80
Chronic kidney disease	≥130/80	<130/80
Chronic kidney disease after renal transplantation	≥130/80	<130/80
Heart failure	≥130/80	<130/80
Stable ischemic heart disease	≥130/80	<130/80
Secondary stroke prevention	≥140/90	<130/80
Secondary stroke prevention (lacunar)	≥130/80	<130/80
Peripheral arterial disease	≥130/80	<130/80

AMERICAN COLLEGE of CARDIOLOGY ADAPTED American Heart Association. life is why

SELF EVALUATION

Hypertension Management: Where We are and How We Got Here

1. Long-term treatment of hypertension requires motivation on the part of patients. What benefits can a hypertensive patient anticipate from pharmacologic treatment?
    a. ±25% reduction in MI
    b. ±40% reduction in stroke
    c. ±50% reduction in heart failure
    d. All of the above

2. The first randomized placebo-controlled trial of hypertension treatment was the VA Cooperative Trial in 1967. Inclusion in the trial required which of the following?
    a. DBP > 115 mm Hg
    b. History of MI
    c. History of stroke
    d. History of CKD

3. Which component of BP is associated with the greatest CVD adverse outcomes?
    a. SBP
    b. DBP

4. The preponderance of data from HTN clinical treatment trials involves persons aged 50-70 years. Is HTN treatment beneficial in 'super seniors' (age >80)?
    a. No trials in person >80 years have been performed
    b. The SPRINT Trial subgroup analysis in persons > 75 years showed that adverse effects of lowering BP (falls, dizziness) are too great of a risk to justify treatment
    c. The HYVET clinical trial (mean age 83) showed important CV benefits of HTN treatment

5. Based upon clinical trial outcomes data, what 2-drug combination should be preferred for the treatment of Stage 2 HTN (SBP >20 mm Hg above goal)?
    a. HCTZ + CCB (calcium channel blocker)
    b. Chlorthalidone + ARB (angiotensin receptor blocker)
    c. BB (beta blocker) + ACE inhibitor
    d. CCB + ACE inhibitor

Answer Key: 1. D, 2. A, 3. A, 4. C, 5. D

Carole C. Foos, CPA

Carole C. Foos, CPA, of Cincinnati, Ohio, is a partner in OJM Group, a physician focused financial planning and asset management firm and a Certified Public Accountant offering tax analysis and tax planning services to the firm's clients. Ms. Foos has over 25 years experience in accounting, tax planning and financial consulting and is a co-author of numerous books for physicians, including *Wealth Management Made Simple* and *Wealth Planning for the Modern Physician: Residency to Retirement*. Ms. Foos has authored numerous articles and presented many lectures, webcasts, and podcasts on tax planning and wealth management.

You may contact Ms. Foos with any questions or comments at (513) 309–3946 or by email at carole@ojmgroup.com.

OJMGROUP
Integrity. Collaboration. Expertise.

CORPORATE HEADQUARTERS
8044 MONTGOMERY ROAD, SUITE 440
CINCINNATI, OH 45236
877.656.4362 866.913.4911 WWW.OJMGROUP.COM
Other offices in Arizona and Florida

Preventing Fraud and Increasing Revenue through Effective Financial Controls

Carole C. Foos, CPA

DISCLAIMER

OJM Group, LLC ("OJM") is an SEC registered investment adviser with its principal place of business in the State of Ohio. SEC registration does not constitute an endorsement of OJM by the SEC nor does it indicate that OJM has attained a particular level or skill or ability. OJM and its representatives are in compliance with the current notice filing and registration requirements imposed upon registered investment advisers by those states in which such notice filing, and registration is required. OJM may only transact business in those states in which it is notice filed or qualifies for an exemption or exclusion from notice filing requirements. For additional information about OJM, including fees and services, send for our disclosure brochure using the contact information provided in this presentation or refer to the Investment Adviser Public Disclosure web site (www.adviserinfo.sec.gov).

Information contained in this presentation has been obtained from sources we consider reliable, but its accuracy is not guaranteed. Any opinions expressed are based on the interpretation of data available to OJM and are subject to change at any time without notice. This presentation is for informational purposes only and is not intended as an offer or solicitation for the purchase or sale of a security or the rendering of investment advice.

No client or prospective client should assume that any information presented or made available on or through this presentation, is a receipt of, or a substitute for personalized investment advice. Such advice may only be rendered after the following conditions are met: 1. delivery of our disclosure brochure to you, and 2. execution of an Investment Advisory and/or Financial Planning Agreement between us.

This presentation contains general information that is not suitable for everyone. The information contained herein should not be construed as personalized investment advice. Past performance is no guarantee of future results. There is no guarantee that the views and opinions expressed in this presentation will come to pass or that any particular investment strategy or asset class will be profitable.

OJMGROUP

DISCLAIMER

OJM is not engaged in the practice of law and does not provide legal advice. Always consult with an attorney regarding your specific legal situation.

The information contained in this presentation is general in nature and should not be acted upon in your specific circumstances without further details and/or professional advice. OJM Does not provide tax advice. Contact your personal tax advisor for specific advice related to your tax situation. These recommendations are not intended as a thorough, in-depth analysis of specific issues nor are they sufficient to avoid tax-related penalties.

OJM Group, LLC does not make any representations or warranties as to the accuracy, timeliness, suitability, completeness, or relevance of this information. All such information is provided solely for convenience purposes only and all users thereof should be guided accordingly. Past performance may not be indicative of future results. Therefore, no current or prospective client should assume that future performance of any specific investment, investment strategy or product made reference to directly or indirectly by OJM Group, LLC will be profitable or equal the corresponding indicated performance level(s).

Please refer to the insurance company's statement for specific details and current values. Please refer to the insurance company's full illustration which is not a guarantee and makes multiple assumptions that are not guaranteed. This statement is meant to be an approximation based on information provided by the insurance company. OJM Group is not affiliated with any insurance company.

OJMGROUP

FREE RESOURCES FOR AEI ATTENDEES

- Text **AEIOJM** to 844-418-1212
  - Click the link in the reply text
- Visit ojmbookstore.com and enter **AEIOJM** at checkout
- Scan the QR Code

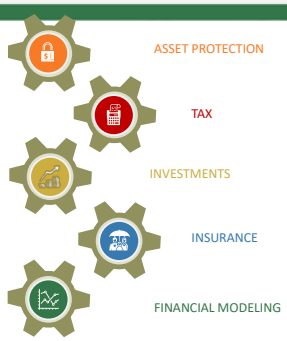
OJMGROUP

PERSONAL WEALTH PLANNING

DIAGNOSTIC vs. TREATMENT

ADVICE & EXPERTISE FOR A FLAT FEE

BUILDING A RELATIONSHIP



OJMGROUP

SPECIAL OFFER: FREE BOOKS FOR WEBINAR ATTENDEES

- **Text AEIOJM to 555-888.**
- Click the link in the reply text.
- Choose your title and book format (hard copy or eBook for Kindle or iPad).
- Enter your name and contact information.
- Click SUBMIT.
- OR **Visit ojmbookstore.com and enter promo code AEIOJM at checkout**

OJMGROUP

FINANCIAL ACTIVITIES MOST PRONE TO FRAUD

- Collection of payments
- Accounts Receivable
- Vendor overpayments
- Payroll

OJMGROUP

COMMON CONTROL ISSUES

- Payment to a fake vendor
- Improper patient refund
- Cash payment from patient not deposited
- Payments not posted to patient accounts
- Personal use of company credit card
- $$ out of petty cash for personal expense
- Payroll to fictitious employee
- Overpayment to employee

OJMGROUP

THE FRAUD TRIANGLE

OJMGROUP

WHAT ARE INTERNAL CONTROLS?

Internal controls are policies, procedures, and mechanisms that a medical practice can put in place to ensure the integrity of its financial and operational processes.

Within the practice these should include

- Separation of duties
- Access controls
- Documentation
- Regular reconciliations
- Audit trails
- Oversight and monitoring
- IT controls

OJMGROUP

WHY INTERNAL CONTROLS?

Fraud requires **Opportunity, Incentive, Rationalization**

- Difficult for you as owner to control motivation and rationalization
- Therefore, you must control opportunity
  - Opportunity exists where there is a breakdown in internal control or where no internal controls exist
- Every practice, large or small must have a set of internal controls
- Requires proper training of those who will be executing the controls
- No plan or training will be effective without oversight by owner or an outside party

OJMGROUP

HIRE THE RIGHT PEOPLE

For all employees utilize:

- Background checks
  - Can retroactively check current employees
- Verify past employment, education, licensing
- Written employee manual with zero tolerance policy
- Cross training of employees
- Required one-week continuous vacation for employees

Be wary of employees who:

- Oppose cross training / refuse help
- Are defensive / resistant to change
- Are overly friendly with vendors
- Refuse a promotion or transfer
- Manage patient refunds

OJMGROUP

SEPARATION OF DUTIES

- Person who bills should not handle cash receipts
- Same person cannot order, write, sign and mail checks
- Person accepting payments does not prepare or make deposits
  - Take patient payment, put into practice mgmt. system, someone else applies payment
  - Require that the cash drawer be counted and secured by one employee at close of business and that its total be verified and deposited the next day by a different employee.
- Separate the accounting function from the financial management function
- Person ordering medical supplies does not manage inventory
- Person opening mail does not pay bills
- Person coding does not also do billing
- More than one employee involved in accounting function

OJMGROUP

ACCESS CONTROLS

Limiting access to sensitive information and systems to authorized personnel only

- Use passwords or biometric authentication
  - Require strong passwords / dual authentication
  - Require that passwords be changed regularly
  - No sharing of passwords

- Role based access – staff members only access info needed for job
  - Front desk staff only successes scheduling and check in
  - Medical providers access EMR
  - Medical staff responsible for patient care different than staff maintaining medical records
- Secure physical access
  - Limit physical access to supply room, records storage, financial data with key cards, etc.
- Implement audit trail to track transactions and changes made to financial and operational records

OJMGROUP

REGULAR RECONCILIATIONS

- Reconcile receivables and charges daily
- Reconcile bank deposit to practice management system daily
- Reconcile your bank account each month without fail
- Close out credit card system daily with manager approval
- Review payroll records to ensure employee hours, wages and benefits are appropriate
- Issue a receipt for every transaction and have 2nd person verify daily receipt balances
- Routinely verify petty cash balances
- Routinely verify inventory records of medical supplies and equipment
- Reconcile accounts receivable ledger to endure accuracy and that payment plans are properly recorded

OJMGROUP

OVERSIGHT AND MONITORING

Oversight and monitoring promote transparency and accountability

- Hire an independent auditor to review financial records and internal control systems
- Review your financial statements and your bank and credit card statements
- Review A/R write-offs
- ASK QUESTIONS!!!!!
- Conduct periodic management reviews of internal control systems

- Implement fraud detection software to monitor transactions
- Establish a system for employees to report concerns / issues
- Provide compliance training to employees on internal controls and regulatory requirements
- Occasionally have employees review each other's work
- Open the mail yourself on occasion

OJMGROUP

DOCUMENTATION

- Document the policies and procedures related to internal control
- Create authorization forms for sensitive transactions such as payroll changes and requests for patient information, refunds, etc.
- Maintain transaction logs for key financial and operational transactions such as billings, collections, supply purchases, patient visits
- Require physician or appropriate management signature on checks
- Maintain an up-to-date employee manual which includes policies and procedures

OJMGROUP

AUDIT TRAIL

Have procedures in place to allow for tracking of all transactions and changes made to financial and operational records

- Electronic record that tracks access to patient information
- Patient visit log
- Cash and credit card receipt log
- Bank deposit log
- Bank reconciliations
- Approved vendor list
- Log of patient refunds / AR write-offs
- Petty cash register and receipts

OJMGROUP

IT CONTROLS

Ensure confidentiality, integrity and availability of sensitive information

- Restrict access
  - Passwords
  - 2 factor authentication
  - Restricted to essential personnel
- Encrypt data on servers, laptops, mobile devices
- Data backup and recovery
  - Backup stored in secure location
  - Develop disaster recovery plan
- Security monitoring of IT systems for suspicious activities and regular review of access logs
- Regular and timely updates and patches
- Ensure vendors and third-party providers have appropriate security measures in place
- Educate and train staff on IT security best practices

OJMGROUP

INTERNAL CONTROLS

ABC's of Internal Control:

Always Be Curious

OJMGROUP

CONTACT ME

- Schedule a free no-obligation consultation
- Contact the presenter:
  - Carole C. Foos, CPA
  - 877.656.4362
  - carole@ojmgroup.com

OJMGROUP

DISCLOSURE

The information, analysis, and opinions expressed herein are for general and educational purposes only. Nothing contained in this commentary is intended to constitute personalized legal, tax, accounting, securities, or investment advice, nor an opinion regarding the appropriateness of any investment, nor a solicitation of any type. All investments carry a certain risk, and there is no assurance that an investment will provide positive performance over any period of time. An investor may experience loss of principal. Investment decisions should always be made based on the investor's specific financial needs and objectives, goals, time horizon, and risk tolerance. The asset classes and/or investment strategies described may not be suitable for all investors and investors should consult with an investment advisor to determine the appropriate investment strategy. Past performance is not indicative of future results. Indices are unmanaged and their returns assume reinvestment of dividends and do not reflect any fees or expenses. It is not possible to invest directly in an index. Information obtained from third party sources are believed to be reliable but not guaranteed. All opinions and views constitute our judgments as of the date of writing and are subject to change at any time without notice.

OJMGROUP

SELF EVALUATION

Preventing Fraud and Increasing Revenue through Effective Financial Controls

1. T/F - The 3 elements of the fraud triangle are Opportunity, Incentive and Rationalization.

2. An example of separation of duties is

a. Having the front desk person open mail and make deposits.
b. Having the accounts payable clerk sign checks.
c. Having a medical assistant manage supplies inventory and the front desk person order supplies.
d. Having the billing clerk inputting medical coding.

3. One way to limit access is to

a. Require dual authentication
b. Require key card entry to the records storage room
c. Require that passwords be changed regularly
d. All of the above

4. T/F - A background check can be run on a current employee with the employee's permission.

5. T/F - The practice bank account should be reconciled daily.

6. T/F - Fraud opportunity exists where there is a breakdown of internal control.

7. T/F - Requiring each employee to take an annual one week continuous vacation is a good internal control policy.

Answer Key: 1. T, 2. C, 3. D, 4. T, 5. F, 6. T, 7. T

Michael J. Howell, MD, FAAN, FAASM

Michael J. Howell, MD, FAAN, FAASM, of Minneapolis, Minnesota, is an associate professor of Neurology at University of Minnesota where he is the Vice-Chair for Education. He is board certified in both neurology and sleep medicine and is a fellow of the American Academies of both specialties. Dr. Howell is a frequent international speaker, a co-investigator of numerous research projects, widely published and co-founder and president of Sleep Performance Institute.

You may contact Dr. Howell with your questions and comments at remwalkers@gmail.com.

Sleep: The 13th Reversible Brain Health Risk Factor

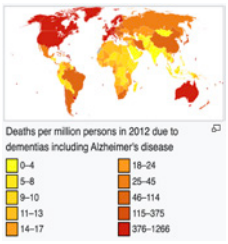
Contents

- The 21st century pandemic of dementing diseases.
  - Evidence based review of reversible risk factors.
- How poor sleep may lead to neurodegeneration.
  - Glymphatic Function
  - Orexin activity
- Strategies to improve sleep and promote brain health.

The 21st Century Pandemic: Neurodegenerative Disease

- Alzheimer's Dementia
  - Age related disease
    - 60-74 years: 5%
    - 74-84 years: 14%
    - > 85 years: 35%
  - Prevalence Increasing
    - 50 million worldwide in 2020
    - 150+ million worldwide in 2050

(Rajan et al 2021; Li et al 2021)



Wikimedia Commons

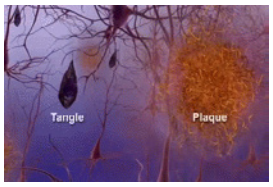
Defining and consolidating Neurodegenerative Diseases

- The big three: Alzheimer's, Parkinson's disease, Dementia with Lewy Bodies.
- Characterized by deposition of altered proteins in the brain followed by local inflammatory response, neuronal dysfunction, and ultimately neuronal loss.
  - Insoluble beta-amyloid and tau: Alzheimer's disease
  - Phosphorylated alpha-synuclein: Parkinson's disease and Dementia with Lewy Bodies.
  - Often overlap between the pathologies

(Lamptey et al 2022)

Wikimedia Commons

Alzheimer's disease

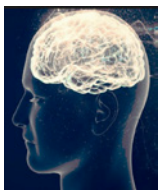


(Wikimedia Commons)

Reasons to be optimistic

- Medical Education on dementia should be significantly less fatalistic
- Reasons for optimism
  - 12 modifiable risk factors account for 40% of all worldwide dementia.
    - Improved sleep would be #13
  - Age-Specific incidence of dementia has fallen.
    - Related in large part to improvement of the 12 (13?) modifiable risk factors.

(Rajan et al 2021; Li et al 2021)

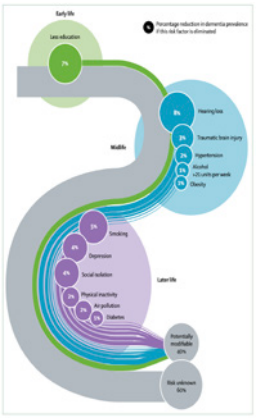


Wikimedia Commons

The Lancet Commissions

Dementia prevention, intervention, and care: 2020 report of the *Lancet* Commission

Gill Livingston, Jonathan Huntley, Andrew Sommerlad, David Ames, Clive Ballard, Sube Banerjee, Carol Brayne, Alistair Burns, Jiska Cohen-Mansfield, Claudia Cooper, Sergi G Costafreda, Amit Dias, Nick Fox, Laura N Gitlin, Robert Howard, Helen C Kales, Mika Kivimäki, Eric B Larson, Adesola Ogunniyi, Vasiliki Orgeta, Karen Ritchie, Kenneth Rockwood, Elizabeth L Sampson, Quincy Samus, Lon S Schneider, Geir Selbæk, Linda Teri, Naaheed Mukadam



The Lancet Commissions

Dementia prevention, intervention, and care: 2020 report of the Lancet Commission

(Livingston et al 2020)

Reversible Dementia Risk: Early Life

- Less Education
  - Accounts for 7% of all Dementia risk.

(Livingston et al 2020)

Wikimedia Commons

Reversible Dementia Risk: Mid-Life

- Hearting loss (8%)
  - Addressing is the strongest intervention
- Traumatic Brain Injury (3%)
- Hypertension (2%)
- Alcohol (1%)
  - > 21 drink units/week
- Obesity (1%)

(Livingston et al 2020)

Wikimedia Commons

Reversible Dementia Risk: Later-Life

- Tobacco Smoking (5%)
- Depression (4%)
- Social Isolation (4%)
  - Growing evidence that early retirement increases risk of Dementia
- Physical Inactivity (2%)
- Air pollution (2%)
- Diabetes (1%)

(Livingston et al 2020)

Wikimedia Commons

Sleep: The 13th Reversible Risk factor?

- The 2020 Lancet Commission carefully consider sleep as a potential reversible risk factor.
- Plausible mechanisms by which poor sleep may increase dementia:
  - Linked to Beta-Amyloid and Tau deposition
  - Promote low grade inflammation and hypoxemia
  - Cardiovascular disease in particular hypertension

(Livingston et al 2020)

Shepherdesses sleeping
Siberechts
Wikimedia Commons

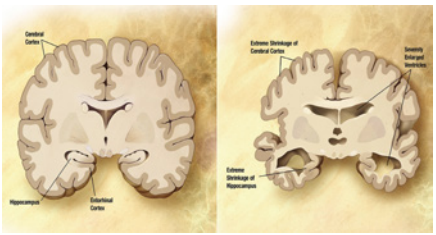
Sleep: The 13th Reversible Risk factor?

- Clinical trial data
  - Cross sectional as well as longitudinal studies (average of 10 year follow up) showed that sleep disturbances associated with dementia in general and Alzheimer's disease in particular.
  - Ultimately poor sleep was not included as a reversible risk factor due to the limited number of studies and some did not exclude cognitive impairment at baseline and concern that poor sleep could be a marker of other risk factors (depression, CV disease)
- Uncertainty regarding interventions:
  - Example: older sedatives (benzo's) are also associated with increased dementia risk.

(Bubu et al 2017, Shi et al 2018, Livingston et al 2020)

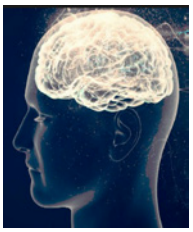
Sleep and Dementia

Wikimedia Commons



Some Functions of Sleep

Memory Consolidation
Synaptic Homeostasis
Replenish ATP
Toxin Clearance

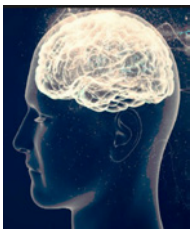


(Nedergaard et al 2020)

Wikimedia Commons

Some Functions of Sleep

Memory Consolidation
Synaptic Homeostasis
Replenish ATP
Toxin Clearance

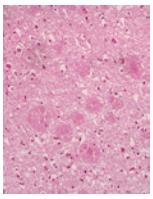


(Nedergaard et al 2020)

Wikimedia Commons

Clearance of CNS Toxins

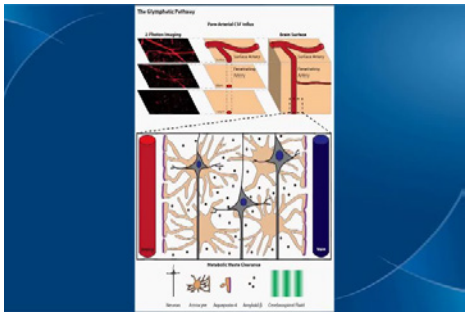
- Increased CSF flow through the brain parenchyma and into the glymphatic system while sleeping
- Greater clearance of insoluble beta-amyloid, tau, and phosphorylated alpha-synuclein



Amyloid Plaques

Wikimedia Commons

Sleep and Toxin Clearance



Used with Permission Jeffrey Iliff, Oregon Health Sciences University

Age and Dementia

- Age: Strongest risk factor for dementia is age.
  - 60-74 years: 5%
  - 74-84 years: 14%
  - > 85 years: 35%

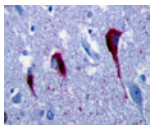
Auguste Deter

Wikimedia Commons

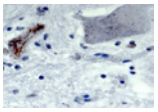
(Rajan et al 2021; Li et al 2021)

Protein aggregation

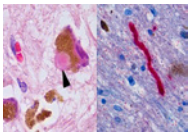
- Aggregates of misfolded and hyperphosphorylated proteins
  - Lack of CSF fluid flow promotes nucleation, aggregation
  - Accumulated protein clusters then lead to subsequent seeding and pathological spread.
    - AD-Amyloid-beta and Tau
    - FTD, CTE-phosphorylated tau
    - PD, DLB-alpha synuclein
    - ALS, FTD-TAR DNA binding protein (TDP-43)



Alzheimer's



ALS



Parkinson's

(Wikimedia Commons)

(Nedergaard et al 2020)

Position Paper

A biological definition of neuronal α-synuclein disease: towards an integrated staging system for research

Tanya Simuni*, Lana M Chahine*, Kathleen Poston, Michael Brumm, Teresa Buracchio, Michelle Campbell, Sohini Chowdhury, Christopher Coffey, Luis Concha-Marambio, Tien Dam, Peter DiBiaso, Tatiana Foroud, Mark Frasier, Caroline Gochanour, Danna Jennings, Karl Kieburtz, Catherine M Kopil, Kalpana Merchant, Brit Mollenhauer, Thomas Montine, Kelly Nudelman, Gennaro Pagano, John Seibyl, Todd Sherer, Andrew Singleton, Diane Stephenson, Matthew Stern, Claudio Soto, Caroline M Tanner, Eduardo Tolosa, Daniel Weintraub, Yuge Xiao, Andrew Siderowf, Billy Dunn, Kenneth Marek

Protein aggregation across the sleep wake cycle

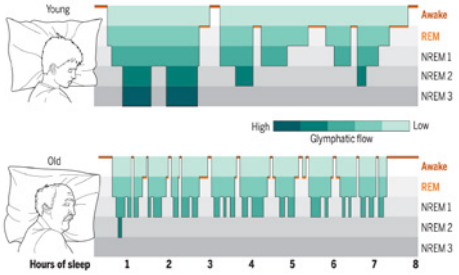
- Extracellular amyloid-beta, tau are higher at the end of wakefulness and decrease after a night of sleep.
  - One night of sleep deprivation results in increased amyloid-beta in hippocampus
  - Importantly promoting sleep through an orexin class of sleeping medications can clear amyloid-beta and tau .

Wikimedia Commons

(Kang et al 2009, Shokri-Kojori et al 2018, Holth et al 2019, Lucey et al 2023)

Sleep and Age

- 10 minutes less sleep per decade of life (in adulthood)
  - More sleep fragmentation, Less slow wave activity (Less N3 sleep)



(Nedergaard et al 2020)

Poor sleep as prodromal syndrome

- Increased sleep fragmentation precedes the development of Dementia, Alzheimer's, Parkinson's.
- Individuals with insomnia, Sleep apnea and shift work are at higher risk of neurodegenerative diseases.

Wikimedia Commons

(Malhotra 2018)

Poor sleep as prodromal syndrome

- Difficult to overstate how common sleep disruption is in AD and PD and typically precedes cognitive and motor symptoms.

Wikimedia Commons

(Nedergaard et al 2020)

Poor sleep as prodromal syndrome

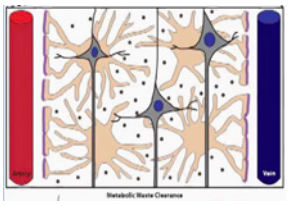
- Difficult to overstate how common sleep disruption is in AD and PD and typically precedes cognitive and motor symptoms.
- Conversely, good sleepers have brain that function better and last longer.

Wikimedia Commons

(Nedergaard et al 2020)

The Glymphatic System

- Glymphatic dysfunction helps tie aging, neurodegeneration, sleep, aging, and protein accumulation, and how dementia pathology spreads through the brain.
- Glymphatic function can be targeted (it can be enhanced)



Used with Permission Jeffrey Iliff, OHSU

(Nedergaard et al 2020)

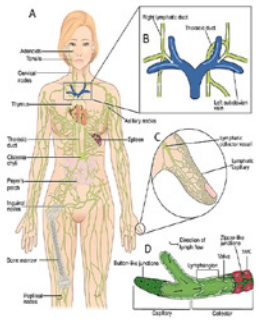
How does the brain clear waste proteins?

- The CNS does not transport proteins across blood brain barrier and there is no lymphatic extension to the CNS so how does it clear metabolic waste proteins?

(Nedergaard et al 2020)

The Lymphatic System

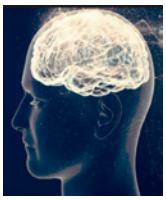
- Clearance of metabolic waste
- Described in the 5th century BCE

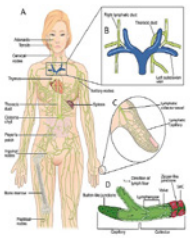


(Wikimedia Commons)

The Lymphatic System

- Clearance of metabolic waste
- Described in the 5th century BCE
- What about the brain?

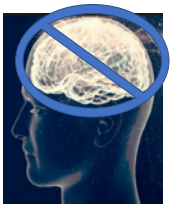


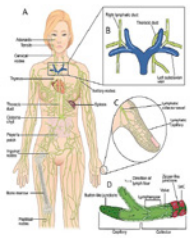


(Wikimedia Commons)

The Lymphatic System

- Clearance of metabolic waste
- Described in the 5th century BCE
- Lymphatics do not extend to the Central Nervous System.

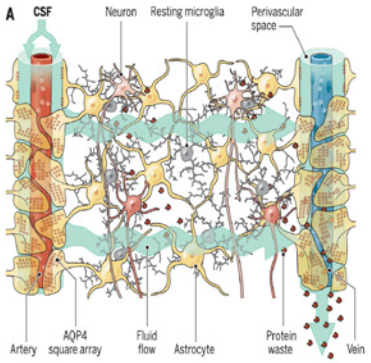




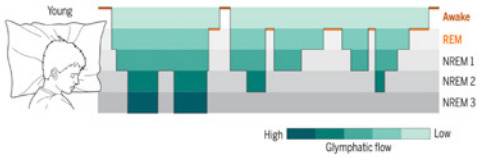
(Nedergaard et al 2020) (Wikimedia Commons)

The Healthy Glymphatic Pathway

(Nedergaard et al 2020)

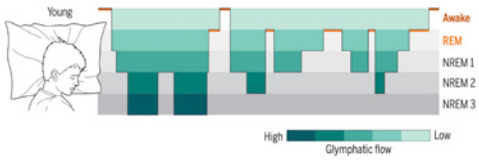


Why during sleep? Why NREM Sleep?



(Tononi et al 2020, Nedergaard et al 2020)

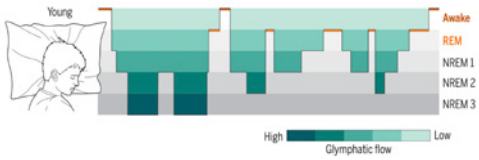
Why during sleep? Why NREM Sleep?



- CSF flow disrupts synaptic function with glutamate activating random synapses
- REM sleep is similar to wakefulness with purposeful circuit activation and potentiation (growth of synapses).

(Tononi et al 2020, Nedergaard et al 2020)

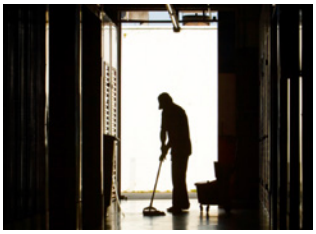
Why during sleep? Why NREM Sleep?



- CSF flow disrupts synaptic function with glutamate activating random synapses
- REM sleep is similar to wakefulness with purposeful circuit activation and potentiation (growth of synapses).
- N3 conversely is a decorticated state of depotentiation

(Tononi et al 2020, Nedergaard et al 2020)

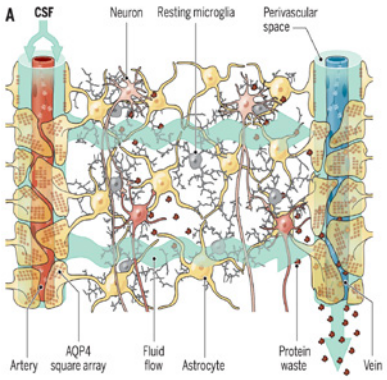
The Nighttime Custodian



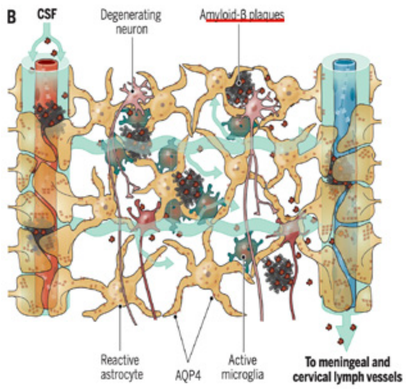
Wikimedia Commons

The Healthy Glymphatic Pathway

(Nedergaard et al 2020)

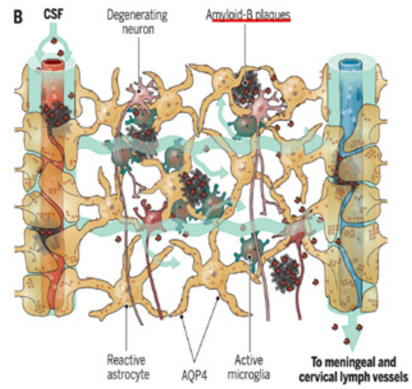


AN Unhealthy Glymphatic Pathway



(Nedergaard et al 2020)

An Unhealthy Glymphatic Pathway



Protein accumulation then leads to further blockage in CSF flow

(Nedergaard et al 2020)

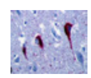
Decrease in Glymphatic Flow →

Aging
Sleep Disorders
Sleep Deprivation
TBI
AQP 4 Mislocation
CV disease

(Nedergaard et al 2020)

(Wikimedia Commons)

Decrease in Glymphatic Flow →



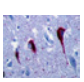
Protein Aggregation

Aging
Sleep Disorders
Sleep Deprivation
TBI
AQP 4 Mislocation
CV disease

(Nedergaard et al 2020)

(Wikimedia Commons)

Decrease in Glymphatic Flow ⇄



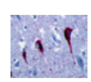
Protein Aggregation

Aging
Sleep Disorders
Sleep Deprivation
TBI
AQP 4 Mislocation
CV disease

(Nedergaard et al 2020)

(Wikimedia Commons)

Decrease in Glymphatic Flow ⇄

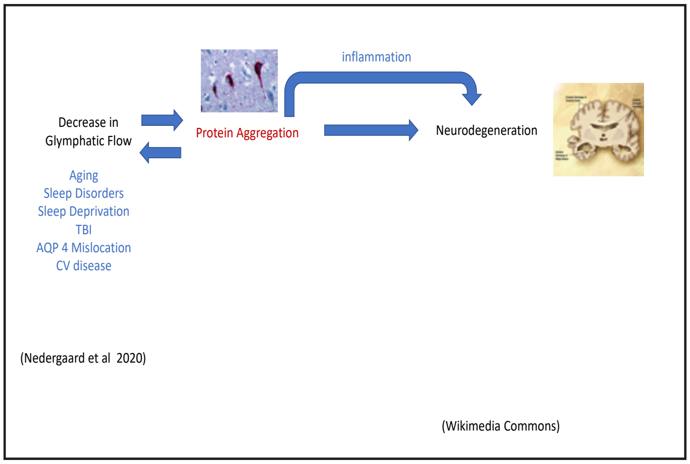


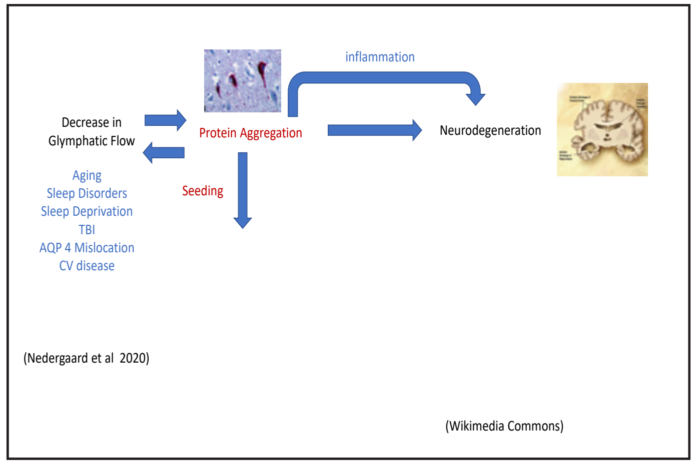
Protein Aggregation → Neurodegeneration

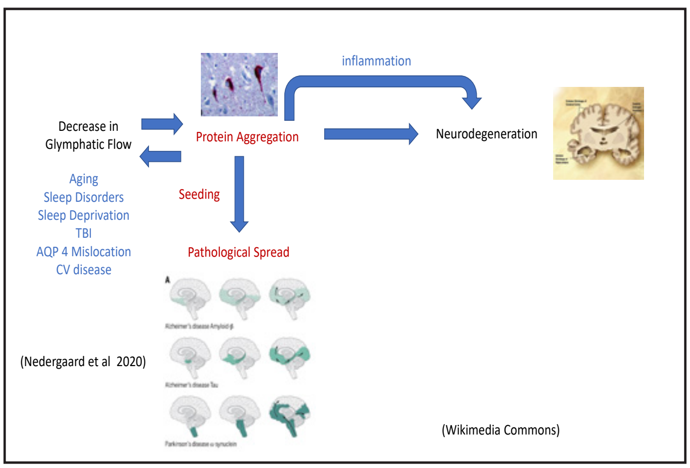
Aging
Sleep Disorders
Sleep Deprivation
TBI
AQP 4 Mislocation
CV disease

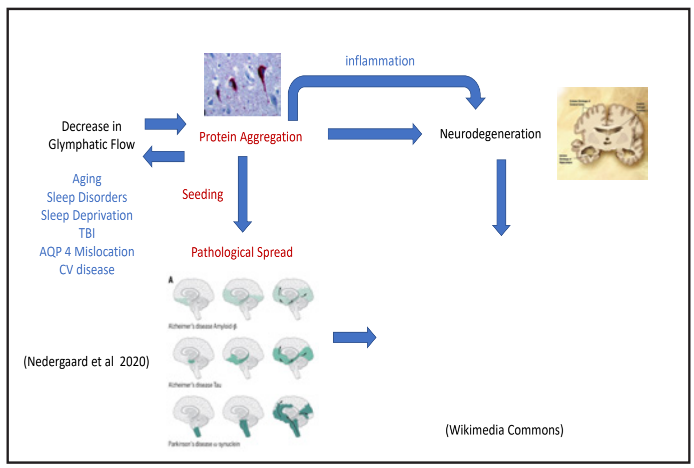
(Nedergaard et al 2020)

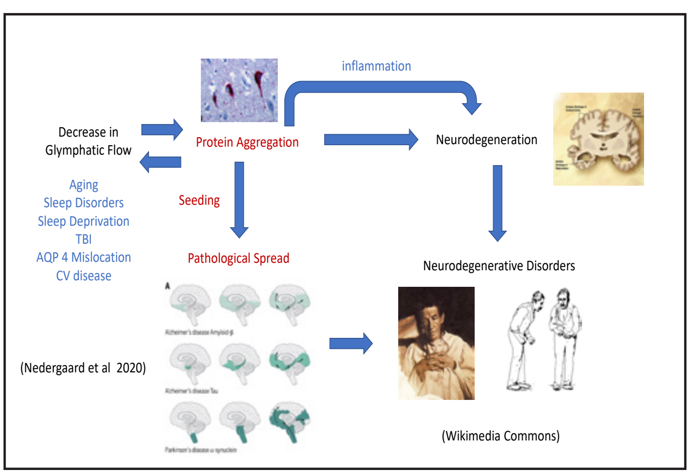
(Wikimedia Commons)





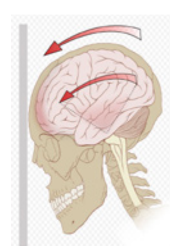






Glymphatic dysfunction as a explanation for CTE in TBI

- Acute (or multiple) Traumatic injury alone does not explain chronic accumulation of amyloid/tau pathology in CTE nor alpha-synuclein in pugilistic parkinsonism.

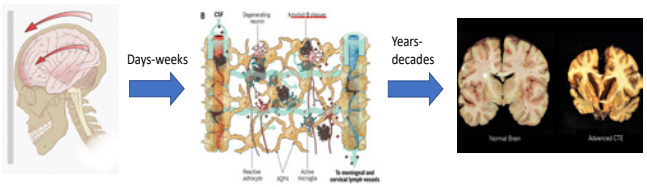


(Wikimedia Commons)

(Nedergaard et al 2020)

Glymphatic dysfunction as a explanation for CTE in TBI

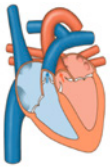
- However, amyloid and tau pathology are expected if traumatic disruption occurred to glymphatic channels.



(Nedergaard et al 2020)

(Wikimedia Commons)

Vascular health predicts long term cognitive health



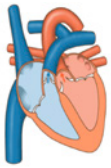
(Wikimedia Commons)

- Cognitive function, in particular memory, is predicted by cardiovascular health.
  - Typically assumed to be secondary to effective delivery of nutrients to brain cells.

(Wendell et al 2014)

(National Institutes of Health)

Vascular health predicts long term cognitive health



(Wikimedia Commons)

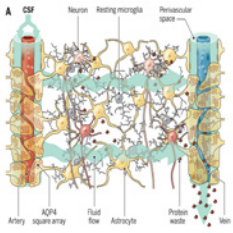
- Cognitive function, in particular memory, is predicted by cardiovascular health.
  - Typically assumed to be secondary to effective delivery of nutrients to brain cells.
    - Not the entire story.

(Wendell et al 2014)

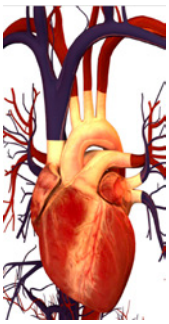
(National Institutes of Health)

Cardio-cerebro-vascular function

- 25% of cardiac output not only serves brains metabolic demand but also mechanical flow.



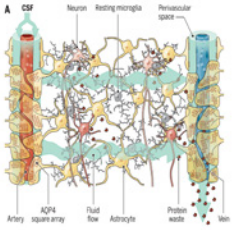
(Nedergaard et al 2020)



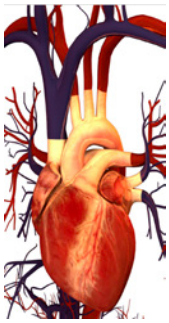
(Wikimedia Commons)

Cardio-cerebro-vascular function

- Strong pulse pressures (difference between systolic and diastolic) in healthy elastic vessels are needed to drive CSF glymphatic flow.



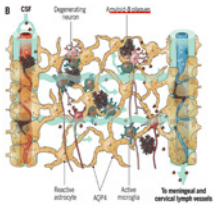
(Nedergaard et al 2020)



(Wikimedia Commons)

Glymphatic function and link to vascular disease

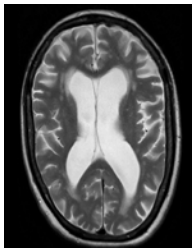
- Variety of pathologies that results in cognitive decline all result in decreased pressure waves.
  - Heart failure (preserved and non-preserved EF)
  - Atrial arrhythmia's
  - HTN
  - Thickened inelastic vessels, calcified with cholesterol depositions.



(Mestre et al 2017, Mestre et al 2018, Nedergaard et al 2020)

Historical Definition of Vascular Dementia

- Vascular dementia is commonly defined as dementia caused by a series of strokes.
  - This is very likely wrong
- Multiple small stroke lesions do not explain diffuse progressive cognitive impairment in setting of vascular disease, nor does it explain build up of amyloid and tau pathology.

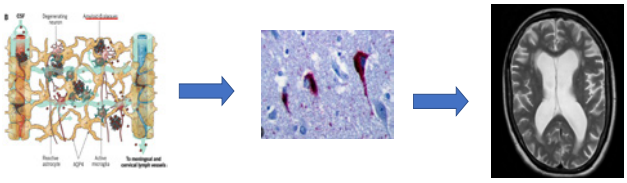


(Wikimedia Commons)

(Sweeney et al 2019, Nedergaard et al 2020)

Glymphatic dysfunction as an explanation for vascular dementia.

- However, amyloid and tau pathology are expected if there is a failure of arterial pulses from hypertensive, hypertrophic, stiff, calcified vessels with cholesterol depositions.



(Sweeney et al 2019, Nedergaard et al 2020)

So what can be done to improve sleep?

Promoting better sleep

- Addressing three common sleep conditions
  - Sleep deprivation
  - Obstructive Sleep Apnea
  - Insomnia

Promoting better sleep

- Sleep deprivation
  - Most common cause of excessive daytime sleepiness
  - Try to optimize not only the volume but the timing of your sleep as well.

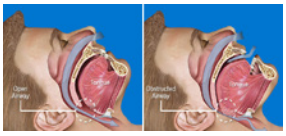
Snoring and obstructive sleep apnea (OSA)

- Collapse of the upper airway
  - Snoring-vibration of tissue
  - Hypopneas-partial restriction of airflow
  - Apneas-complete restriction of airflow
- OSA is a common condition
  - Relatively to pliable upper airway evolved for vocalization
  - Higher risk: men, weight gain, family history, increased neck circumference.

(Gottlieb et al 2020)

OSA-spectrum of disease

- Apnea-Hypopnea Index (AHI): number of times an individual stops breathing or nearly stops breathing per hour.
- Polysomnogram (sleep study) thresholds for diagnosis and severity (consensus based)
  - Ideal for adults: AHI < 5/hr
  - Mild: AHI 5-15/hr
  - Moderate: AHI 15-30/hr
  - Severe: AHI > 30/hr



(Gottlieb et al 2020)

(Wikimedia Commons)

OSA-mechanical problem in need of a mechanical solution

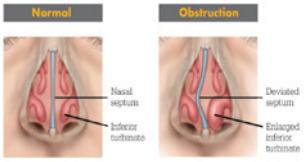
- Positive Airway Pressure (PAP) Therapy
  - Seals over the nose or mouth/nose.
  - Acts as a pneumatic splint to the upper airway.
- Adherence challenges
  - Works very well about 50% of the time it is tried.

(Wikimedia Commons)

(Gottlieb et al 2020)

OSA-what to do when PAP is not working

- Evaluate for possible nasal obstruction
  - Nasal endoscopy
- Relieve nasal obstruction-three benefits
  - Directly decreases AHI
  - Improve PAP and other OSA treatment adherence
  - Improved nasal breathing during the day



(Wikimedia Commons)

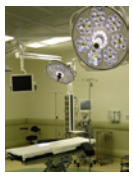
(Gottlieb et al 2020)

OSA-what to do when PAP is not working

- Consider oral appliance
  - Stabilize the mandible and prevent collapse
  - Similar to athletic mouthguards
  - See a AADSM Mastery Certified Dentist
- Consider upper airway stimulation
  - Stimulation of the hypoglossal nerve (CN XII).
  - Pacemaker for the tongue
- Weight loss strategies
  - GLP-1 agonist's
  - Bariatric procedures

(Gottlieb et al 2020)

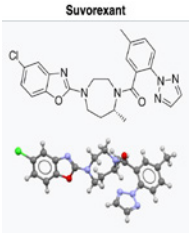
(Wikimedia Commons)



Insomnia

CNS hypervigilant Insomnia Treatment-Pharmacotherapies

- Gold Standard Therapy
  - Cognitive Behavioral Therapy for Insomnia (CBT-I)
    - Best chance of curing insomnia
    - Administered by a licensed psychologist or online program
- Orexin antagonists
  - suvorexant, lemborexant, daridorexant
  - Morning sedation, imbalance
  - Does not suppress respiration
  - May help prevent neurodegenerative pathology



(Wikimedia Commons)

(Mitchel et al 2019)

RESEARCH ARTICLE

Suvorexant Acutely Decreases Tau Phosphorylation and Aβ in the Human CNS

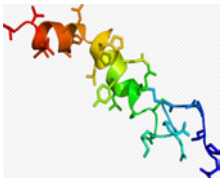
Brendan P. Lucey, MD, MSCI,[1,2,3] Haiyan Liu, MD,[1] Cristina D. Toedebusch, BS,[1] David Freund,[1] Tiara Redrick, MS,[1] Samir L. Chahin, MS,[1,2] Kwasi G. Mawuenyega, PhD,[4] James G. Bollinger, PhD,[1,2] Vitaliy Ovod, MS,[1,2] Nicolas R. Barthélemy, PhD,[1,2] and Randall J. Bateman, MD[1,2]

Objective: In Alzheimer's disease, hyperphosphorylated tau is associated with formation of insoluble paired helical filaments that aggregate as neurofibrillary tau tangles and are associated with neuronal loss and cognitive symptoms. Dual orexin receptor antagonists decrease soluble amyloid-β levels and amyloid plaques in mouse models overexpressing amyloid-β, but have not been reported to affect tau phosphorylation. In this randomized controlled trial, we tested the acute effect of suvorexant, a dual orexin receptor antagonist, on amyloid-β, tau, and phospho-tau.
Methods: Thirty-eight cognitively unimpaired participants aged 45 to 65 years were randomized to placebo (N = 13), suvorexant 10 mg (N = 13), and suvorexant 20 mg (N = 12). Six milliliters of cerebrospinal fluid were collected via an indwelling lumbar catheter every 2 hours for 36 hours starting at 20:00. Participants received placebo or suvorexant at 21:00. All samples were processed and measured for multiple forms of amyloid-β, tau, and phospho-tau via immunoprecipitation and liquid chromatography-mass spectrometry.
Results: The ratio of phosphorylated-tau-threonine-181 to unphosphorylated-tau-threonine-181, a measure of phosphorylation at this tau phosphosite, decreased ~10% to 15% in participants treated with suvorexant 20 mg compared to placebo. However, phosphorylation at tau-serine-202 and tau-threonine-217 were not decreased by suvorexant. Suvorexant decreased amyloid-β ~10% to 20% compared to placebo starting 5 hours after drug administration.
Interpretation: In this study, suvorexant acutely decreased tau phosphorylation and amyloid-β concentrations in the central nervous system. Suvorexant is approved by the US Food and Drug Administration to treatment insomnia and may have potential as a repurposed drug for the prevention of Alzheimer's disease, however, future studies with chronic treatment are needed.

ANN NEUROL 2023;94:27–40

Orexin as a possible driver of degeneration

- Orexin: wake promoting neuropeptide
  - Increased Orexin levels are associated with decreased sleep and propagates the AD pathological cascade of both tau based neurofibrillary tangles and insoluble beta amyloid-beta (Aβ) plaques.
  - Among patients with AD, CSF orexin levels increase in tandem with both sleep disruption and the clinical progression of dementia.



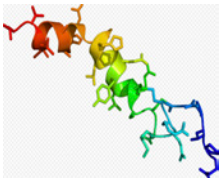
Orexin A

(Wikimedia Commons)

(Kang et al 2009, Liguori et al 2014, Deuschle et al 2014, Osorio et al 2016, Gao et al 2021)

Orexin as a possible driver of degeneration

- Elderly patients with Narcolepsy Type 1, who are orexin deficient, have a lower amyloid burden as measured by 1PET and a delayed appearance of amyloid plaques.
- Orexin signaling regulates the circadian oscillation of APOE genes expression.



Orexin A

(Wikimedia Commons)

(Ma et al 2016, Gabelle et al 2018)

Can orexin blockers prevent dementia

- These findings suggest that the treatment of insomnia, in particular with orexin blocking agents, might be a unique opportunity to delay, halt or potentially reverse AD pathology.
- FDA approved agents
  - Suvorexant
  - Lemborexant
  - Daridorexant

(Gao et al 2021)

RESEARCH ARTICLE

Suvorexant Acutely Decreases Tau Phosphorylation and Aβ in the Human CNS

Brendan P. Lucey, MD, MSCI,[1,2,3] Haiyan Liu, MD,[1] Cristina D. Toedebusch, BS,[1] David Freund,[1] Tiara Redrick, MS,[1] Samir L. Chahin, MS,[1,2] Kwasi G. Mawuenyega, PhD,[4] James G. Bollinger, PhD,[1,2] Vitaliy Ovod, MS,[1,2] Nicolas R. Barthélemy, PhD,[1,2] and Randall J. Bateman, MD[1,2]

Objective: In Alzheimer's disease, hyperphosphorylated tau is associated with formation of insoluble paired helical filaments that aggregate as neurofibrillary tau tangles and are associated with neuronal loss and cognitive symptoms. Dual orexin receptor antagonists decrease soluble amyloid-β levels and amyloid plaques in mouse models overexpressing amyloid-β, but have not been reported to affect tau phosphorylation. In this randomized controlled trial, we tested the acute effect of suvorexant, a dual orexin receptor antagonist, on amyloid-β, tau, and phospho-tau.
Methods: Thirty-eight cognitively unimpaired participants aged 45 to 65 years were randomized to placebo (N = 13), suvorexant 10 mg (N = 13), and suvorexant 20 mg (N = 12). Six milliliters of cerebrospinal fluid were collected via an indwelling lumbar catheter every 2 hours for 36 hours starting at 20:00. Participants received placebo or suvorexant at 21:00. All samples were processed and measured for multiple forms of amyloid-β, tau, and phospho-tau via immunoprecipitation and liquid chromatography-mass spectrometry.
Results: The ratio of phosphorylated-tau-threonine-181 to unphosphorylated-tau-threonine-181, a measure of phosphorylation at this tau phosphosite, decreased ~10% to 15% in participants treated with suvorexant 20 mg compared to placebo. However, phosphorylation at tau-serine-202 and tau-threonine-217 were not decreased by suvorexant. Suvorexant decreased amyloid-β ~10% to 20% compared to placebo starting 5 hours after drug administration.
Interpretation: In this study, suvorexant acutely decreased tau phosphorylation and amyloid-β concentrations in the central nervous system. Suvorexant is approved by the US Food and Drug Administration to treatment insomnia and may have potential as a repurposed drug for the prevention of Alzheimer's disease, however, future studies with chronic treatment are needed.

ANN NEUROL 2023;94:27–40

Orexin antagonism as possible neuroprotection

- Suvorexant: Acutely decreases tau phosphorylation and Ab in the CSF of healthy middle aged human adults.
- Clinical trials are currently ongoing with several orexin blocking medications.

(Lucey et al 2023)

SELF EVALUATION

Sleep: The 13th Reversible Brain Health Risk Factor

True/False

1. Both Alzheimer's and Parkinson's disease are characterized by deposition of altered proteins in the brain followed by local inflammatory response, neuronal dysfunction and later neuronal loss.

2. Hearing loss is a modifiable risk factor for dementia

3. Age-Specific Incidence of dementia has fallen

4. Toxins and metabolic wastes are removed from the brain through the lymphatic system

5. Glymphatic flow peaks during REM sleep

6. Impaired glymphatic function potentially explains the neurodegeneration associated with chronic traumatic encephalopathy

7. Once an OSA patient fails CPAP there are no other treatment options

8. Orexin antagonists represent a new approach for treating insomnia

Answer Key: 1. T, 2. T, 3. F, 4. F, 5. F, 6. T, 7. F, 8. T

Thomas P. Cox, ARM

Thomas P. Cox, ARM, of Richmond, Virginia, is president of Bluewater Solutions, LLC, a boutique risk and insurance management company focusing primarily on healthcare and related risks. He has over 30 years experience working almost exclusively with healthcare professionals. Mr. Cox has held executive positions with a large medical center, a major medical malpractice insurance company, and multiple insurance agencies before starting Bluewater Solutions in 2009. Bluewater Solutions offers all manner of risk and insurance management, consulting, and litigation stress coaching. Mr. Cox has a B.S. in Health Education, has done graduate work in Public Health, and earned his Associate in Risk Management designation from the Insurance Institute of America.

You may contact Mr. Cox at 804-221-4369 or by email at tpcox@bluewatersolutions.net.

WINNING FOCUS, INC.
Successful Litigation Stress Coaching

Thomas Cox, COO, Litigation Stress Coach
2312 Summerwood Drive, Henrico, VA 23233
804-221-4369
tpcox@bluewatersolutions.net
www.winfordoc.com

Reducing Practice Risk through Effective Communication

Objectives 3

At the end of this presentation the attendee will be able to:

1. List three or more forces affecting healthcare delivery today.
2. List three or more challenges to effective patient communication.
3. List three positive steps that can reduce the impact of litigation stress.

Objectives

Integrated issues:

- Who you are is what you do
  - Personally and professionally
- Information Technology
- Wall Street
- How can you lose what you have earned?

Wall Street and Health Care

- **Wall Street's Buying Up U.S. Health Care — Including In North Carolina** *Charlotte Observer*
- **Physicians, Hospitals Meet Their New Competitor: Insurer-Owned Clinics**
- **Consolidation of Health Care Driving Up Prices in Work Comp**

Wall Street and Health Care

BusinessweekFeature

- **How Private Equity Is Ruining American Health Care**

What happens when Wall Street takes over health care?

Private equity firms —which invest money for wealthy people, pension funds and endowments —are buying up medical practices and hospitals all over the U.S., expecting a big return on their money.

Technology

- Social media
  - Twitter, Mastodon, Facebook, WebMD, Sharecare, Trackyourdoctor, Beenverified, HealthGrades, etc.
- Electronic Records
  - Reimbursement tool, tracks what is done and not done, malpractice tool?
- Artificial Intelligence
  - ChatGP, BioGPT

Artificial Intelligence: ChatGPT

- ChatGPT is a large language model chatbot developed by OpenAI based on GPT-3.5
- Large language models perform the task of predicting the next word in a series of words. Large Language Models (LLMs) are trained with massive amounts of data to accurately predict what word comes next in a sentence.
- It was discovered that increasing the amount of data increased the ability of the language models to do more.
- Newest iterations can generate paragraphs from single sentence.
- ChatGPT passed a Medical School exam, but…
- GPT-4

How does ChatGPT work?

- **Step 1: Set a goal**

Determine an "objective function" or what it is you want the program to do, i.e., win chess games or predict the three-dimensional shapes of proteins using only amino acid sequences. Most LLM have one goal: given a line of text, predict what comes next.

- **Step 2: Collect lots of data**

This usually means scraping billions of pages from the internet, such as blog posts, tweets, Wikipedia articles and news stories, or medical and dental journals. In general, the more data we have, and the more diverse the sources, the better our model will be.

- **Question: at what point does this become copyright infringement?**

How does ChatGPT work?

- **Step 2 (continued)**
- Before we can feed the data into our model, we need to break it down into units called **tokens**, which can be words, phrases or even individual characters. Transforming text into bite-size chunks helps a model analyze it more easily.

- **Question: at what point does this become copyright infringement?**

How does ChatGPT work?

Step 3: Build a neural network

Once our data is tokenized, we need to assemble the A.I.'s "brain" — a type of system known as a **neural network**. This is a complex web of interconnected nodes (or "neurons") that process and store information. A relatively new type of neural network is the **transformer model**. This can analyze multiple pieces of text at the same time, making it faster and more efficient. (Transformer models are the key to systems like ChatGPT — whose full acronym stands for "Generative Pretrained Transformer").

Step 4: Train your neural network

Next, the model will analyze the data, token by token, identifying patterns and relationships. It might notice "Dear" is often followed by a name. By identifying these patterns, the A.I. learns how to construct messages that make sense. The system also develops a sense of context.

How does ChatGPT work?

Step 5: Fine-tune your model

Once our large language model is trained, it needs to be calibrated for a specific job. A chatbot used by a hospital might need to understand medical terms, for example. To fine-tune our Chatbot, we could ask it to generate a bunch of emails and articles, hire people to rate them on accuracy and then feed the ratings back into the model until it improves. This is a rough approximation of the approach that was used with ChatGPT, which is known as **reinforcement learning with human feedback**.

Step 6: Launch, carefully

Once our LLM has been trained and fine-tuned, it's ready to use. But no matter how good it seems, you're still going to want to keep tabs on your new assistant. As companies like Microsoft and Meta have learned the hard way, A.I. systems can be erratic and unpredictable, or even turn creepy and dangerous.

GPT-4

- March 16, 2023
- OpenAI announced the next-generation version of the artificial intelligence technology that underpins its viral chatbot tool, ChatGPT. The more powerful GPT-4 promises to blow previous iterations out of the water, potentially changing the way we use the internet to work, play and create. But it could also add to challenging questions around how AI tools can upend professions, enable students to cheat, and shift our relationship with technology.

BioGPT

- Source: *Futurism*
- Populated same as ChatGPT
- Microsoft's medicine/biology version of ChatGPT
- The answer you get depends on how you ask the question

BioGPT

- Microsoft's artificial intelligence system BioGPT, designed to answer questions about medicine and biology, produced inaccurate and possibly dangerous answers, including mystifying answers about **ghosts in hospitals** as well as **false information about vaccines**. BioGPT also **invented citations and fabricated studies to support its claims**, and Roxana Daneshjou, a clinical scholar at the Stanford University School of Medicine, says not only do people in medicine want to start using AI without fully understanding all the limitations, but the tools could also be used maliciously to "generate research papers that perpetuate misinformation and actually get published."

So….

To conclude the introduction:

- Integrated issues
- Increasing loss of control (*but more to come*)
- Wall Street
- Artificial Intelligence

Office Practice Risk Management

Premise

- Office practice policies and procedures for dentists and physicians have changed over the last 20 years, and the rate of change has accelerated due to automation and consolidation.
- **Patients** have changed over the last 20 years due to easy access to internet information.

Risk Management

- Risk Reduction
- Risk Control
- Risk Financing
- Enterprise Risk Management

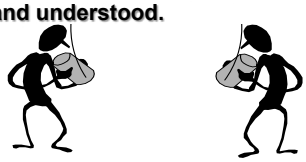
Physicians spending more time with computers than patients

STEVEN REZNICK, MD ; *PHYSICIAN*
MARCH 6, 2023

- My local community hospital has recently signed on to be a member of a **large regional not-for-profit hospital system**. In the past, I would access the hospital website and enter my user ID and password to log in. Now I must first enter the health system database using several levels of authentication, which proves it is me and not some mercenary trying to introduce a virus or kidnap the system. If I enter my information correctly, a prompt is sent to an app on my mobile phone. I must access that app, and then, if I enter everything correctly, a new sign-in window appears from my local hospital.

Communication in the Health Care Setting

- Communication:
  A process by which information is exchanged between individuals through a common system of symbols, signs, or behavior.
- To communicate means to share.
- **Good communication means what has been said is what has been heard and understood.**



Communication in the Health Care Setting

Some challenges:

- 90% of communication is nonverbal
- 47% of the adult elderly are either functionally illiterate or minimally literate
- Less than 10% of medical treatment decisions involve a fully informed patient
- Providers believe that 89% of patients understand the side effects of medication they are taking, while only 57% of patients claim to understand

Communication in the Health Care Setting

- **Impediments to successful communication in the healthcare setting:**

1. Literacy of patients
2. Health literacy of patients
3. Complexity of the health care delivery system.
4. Fragmentation of health care delivery system.
5. Business aspects of health care delivery system.
6. Keeping up with science and ignoring the human dynamic.

Communication in the Health Care Setting

- Impediments to successful communication in the medical office:

7. To which we have added:

Communication in the Health Care Setting

Traditional thought:

- Malpractice experience is determined by factors associated with the provider, case-load, and unpredictable circumstances, in addition to a litigious population and bad luck.
- "*There are three kinds of lies: lies, damn lies, and statistics*." -Benjamin Disraeli

Communication in the Health Care Setting

"*Patient Complaints and the Malpractice Risk*"
(The Journal of the American Medical Association, June 12, 2002)

"*Research has forced reconsideration of these traditional explanations of claims experience. Risk seems **not** to be predicted by patient characteristics, illness complexity, or even physicians' technical skills.*

Communication in the Health Care Setting

"*Patient Complaints and the Malpractice Risk*"
(The Journal of the American Medical Association, June 12, 2002)

"*Instead, risk appears related to patients' dissatisfaction with their physician's ability to establish rapport, provide access, administer care and treatment consistent with expectations, and communicate effectively*."

Communication in the Health Care Setting

Multiple studies were cited by the author of the article. This research studied the communication behaviors of physicians with multiple medical claims against them, as opposed to those of physicians with **no claims** against them. Audio tapes of 10 routine visits were examined for each group of physicians.

Communication in the Health Care Setting

Physicians with **no** claims against them:

- Used more statements of orientation (*educating patients about what to expect)*
- Laughed more, used more humor
- Tended to use more facilitation (*soliciting opinions, encouraging patients to talk, checking for understanding*).
- Validated patient's emotions

Communication in the Health Care Setting

Physicians with no claims against them:

- Those physicians without claims also, on average, spent an additional 3.3 minutes longer with each patient than those physicians with claims.

Communication in the Health Care Setting

Conclusion:

- *Patient dissatisfaction is critical.*
- *The combination of a bad outcome and patient dissatisfaction is a recipe for litigation.*
- *When faced with a bad outcome, patients and families are more likely to sue a health care provider if they feel they were not caring and compassionate.*
- *Highest claim frequency remains failure to diagnose or late diagnosis.*

Communication in the Health Care Setting

Literacy and Health Care

In 1992 The U.S Department of Education conducted a National Adult Literacy Survey (NALS) to measure the general literacy skills of 26,000 randomly selected adults

1. Functionally illiterate 20%
2. Marginally illiterate 27%
3. Marginally literate
4. Functionally literate
5. High level literacy <5%

Communication in the Health Care Setting

Literacy and Health Care

The NASL study also showed an *increase* in literacy problems with **aging**, due to:

- Declines in reading skills
- Vision
- Health
- Other communication skills

Communication in the Health Care Setting

Literacy and Health Care

The low literacy level in the elderly is only **one** contributing factor to their low ***health literacy***, however.

- 80% of adults over 65 have at least one chronic health condition.
- 50% of those have at least two chronic conditions.
- Elderly with chronic conditions see, on average, eight (8) different physicians annually.

Communication in the Health Care Setting

Literacy and Health Care

Low health literacy, however, is not limited to the elderly, nor is it limited to those with low literacy. According to an Institute of Medicine (IOM) report *Health Literacy: A Prescription to End Confusion:* "*Health literacy …includes a variety of components beyond reading and writing, including numeracy, listening, speaking, and cultural and conceptual knowledge*."

Communication in the Health Care Setting

Literacy and Health Care

The IOM report identified distinct causes of low health literacy, some or all or which may be present in any given patient:

1. Limited reading ability
2. Lack of background knowledge in health sciences or biology
3. Lack of familiarity with medical language or medical materials or documents
4. Cultural differences in approaches to health and health care.

Communication in the Health Care Setting

Reducing all of this to one basic concept:

Good communication means what has been said is what has been heard and understood.

The more you can do to ensure that what you say is what the patient hears and understands, the better off everybody will be.

So, what has changed?

Communication in the Health Care Setting

Literacy and Health Care

1. Electronic health records
2. Fewer "normal" patients

Communication in the Medical Office

Literacy and Health Care

Electronic Health Records

- Here to stay
- Reimbursement tool
- More time on computer, less time with, and attention paid to, patient
- Be aware of this (less laying on of hands)

Communication in the Medical Office

Literacy and Health Care

Fewer Normal Patients

The human body contains 206 bones, 32 teeth (more or less) 600 muscles, 39 trillion microbes, and dozens, maybe over 100, **man-made chemicals.**

Fewer "normal" patients

- *Center for Genomics and Personalized Medicine*, Stanford University
- Michael Snyder, Ph.D., Geneticist
- Over nine years of data
- Six different trials
- Two million gigabytes of his own health data stored

Fewer "normal" patients

- Why are our genes not sequenced at our annual wellness checkup?
- Estimated: 10% of cardiovascular disease, cancer, diabetes, neurodegenerative disease progression and development is driven by genes.
- Most of our maladies appear to be brought on by things we inflict on ourselves, such as lifestyle and environmental factors (exposure to air and water pollution, toxic waste, and chemicals) that turn on the gene.

Fewer "normal" patients

- 2021 study from University of California-San Francisco: 109 different industrial and consumer chemicals in study subject's blood.
- More than 50 never found in studies before.
- 42 were mystery chemicals of unknown origin.
- Over one generation or two, human beings have become petri dishes, part of an unplanned experiment in which chemicals and substances that have never existed in nature are interacting in ways science is just beginning to understand.

Fewer "normal" patients

"I had a doctor tell me, '*When I started my practice, all my patients were normal, but it has slowly shifted to all abnormal cases. Now it is weird to have a normal case.*'" Tracy Woodruff, Ph.D., UCSF

- Increasing cancer rates in people under 50 years of age
- Decreased quality of sperm
- Increased fertility problems
- Estimated more than 12 millions deaths each year due to toxic exposures

Fewer "normal" patients

Exposome

("Exposomics")

The concept that nearly all exposures, *starting in utero*, will have an impact on us.

- Forever chemicals
- Refineries
- Synthetic flavors
- Synthetic smells

Fewer "normal" patients

- Over 80,000 potentially toxic chemicals currently in use in the U.S.
- Dr. Snyder's "exposometer" captures everything he is exposed to in a day.
- To date, it has measured over 3,000 chemicals that he has been exposed to
- 158 identified
- 67 most likely dangerous

Fewer "normal" patients

Exposometer

- Approximately 33% are pesticides
- 21% from pharmaceuticals and personal care products
- 11% from plastic
- 10% known carcinogens

Fewer "normal" patients

Cause and Effect?

- Certain chemicals from plastics were associated with inflammatory markers and changes in the population of his gut biome.
- Some pesticides correlated with inflammatory effects involving his kidney and liver functions.

Fewer "normal" patients

Your exposome time capsule?

Baby teeth

Fewer "normal" patients

Manish Arora, Ph.D., Icahn School of Medicine at Mount Sinai

- Trained dentist
- Whatever is in your blood stream gets deposited in your teeth
- Baby teeth from Flint, MI, showed when the exposure to lead-contaminated water occurred…
- …**but** only about 50% were reported to be unwell.
- "Genetics loads the gun, and your environment pulls the trigger." Francis Collins, M.D., Ph.D., former NIH Director

How is this all connected?

"*The Body Keeps the Score*"

Bessel van der Kolk, M.D.

Professor of Psychiatry, Boston University School of Medicine

Published 2014

229 Weeks on New York Times Best-Seller List (Non-Fiction)

27 Weeks at #1

464 pages

The book explains what ***traumatic stress*** is, how it affects our minds and bodies, how it can change our lives for the worse, and the wide-ranging effects experienced not only by traumatized people, but also those around them.

The Body Keeps the Score

Trauma is incredibly common in our society today.

Traumas result from experiences of extreme stress or pain that leave an individual feeling helpless, or too overwhelmed, to cope with adversity.

Lack of control or a belief in lack of control.

The Body Keeps the Score

Flashbacks cause people to relive the mental and physical experience of trauma when they're reminded of it. Your mind might be aware that a traumatic event is over, but established science has shown that the processes your body uses to defend itself can result in patterns being formed. This prevents you from completely moving on.

Never "present"

The Body Keeps the Score

Childhood trauma has negative impacts, not just in a person's youth but well into adulthood, too. While normal memories fade and change, traumatic memories are vivid, unchanging and easily triggered. When they are re-lived, the body responds to what the mind is experiencing.

The Body Keeps the Score

Treat the symptoms, first.

The goal is not to work to stop keeping score, but to become aware that the body is keeping score and how it is doing so.

Treat the symptoms

The Body Keeps the Score

Treat the Physical Symptoms

Talk therapy: top down
- Talk it out to understand it

Somatic therapy: bottom up
- Recognize, understand, release

Mind-Body Balance
- Learn to "feel your body"

The Body Keeps the Score

What is your body trying to tell you?

Neuromuscular Relaxation

Communication in the Medical Office

Literacy and Health Care

Examples of challenges:

- 85% did not understand the direction “Take with food.”
- 61% did not understand the direction “Take with plenty of water.”
- 81% did not understand the direction “Do not take with dairy products.”

Communication in the Medical Office

Dealing with low health literacy patients

Cultural Considerations

Consider the Hispanic patient with hypertension who presented to the ER complaining of dizziness and low blood pressure, even though he was taking the two medications his doctor had given him two days ago. The directions were “Take once daily.”

Communication in the Medical Office

Literacy and Health Care

Examples of challenges:

- 80% of what doctors tell patients is forgotten as soon as they leave the office
- 50% of what is recalled by patients is incorrect
- 44% cannot accurately describe the nature of an upcoming surgical procedure
- 18% to 45% of patients are unable to recall the major risks of a treatment

Communication in the Medical Office

Clues to identifying low health-literacy patients

- Incomplete or inaccurate patient registration forms.
- Frequently missed appointments.
- Noncompliance with treatment regimens.
- Lack of follow through with lab tests, radiological tests, or referrals to specialists.
- Saying things such as “I forgot my glasses” when asked to read or write something.

Communication in the Medical Office

Clues to identifying low health literacy patients

- Saying things such as “I will take this home to discuss with my children/spouse.”
- Inability to name medication he/she is taking.
- Inability to explain what a medication is for.
- Inability to explain the dosage or how to take a medication.
- Identification of medications by looking at or describing the size, shape and color, rather than the names.

Communication in the Medical Office

Dealing with low health literacy patients

- Introduce yourself
- Slow down
- Use simple language
- Show or draw pictures or diagrams
- Give information in bite-sized pieces

Communication in the Medical Office

Dealing with low health literacy patients

- Use the "teach-back" technique to check comprehension
- Help patients avoid feeling ashamed
- Suggest bringing a friend or relative to office visits
- Enlist staff assistance

Communication in the Medical Office

Dealing with low health literacy patients:
Enlist staff assistance

Office staff can assist with filling out forms or reading information in a polite, discreet, cheerful and confidential manner. Staff also need to be aware of the shame and embarrassment many patients feel and should be sensitized to avoid embarrassing anyone.

Communication in the Medical Office

Dealing with low health literacy patients
Printed Materials

- Typeface: bland, not *quirky* (Garamond)
- Type Size: 12 point is recommended minimum
- Type weight and contrast: medium or semi-bold letters on a light background, not bold on white
- Capital letters: use both cases
- Design and layout: simple, clear, consistent, wide margins, not too much clutter, use pictures to illuminate the text, not muddy the water

Communication in the Medical Office

Dealing with "Problem" Patients:
Listening pitfalls

1. Assuming you know how the speaker feels.
2. Anticipating what the speaker is going to say.
3. Thinking about what you are going to say while the speaker is still talking.
4. Wishing the speaker would just get to the point.

Communication in the Medical Office

Dealing with "Problem" Patients:
Listening pitfalls

5. Getting defensive over criticism.
6. Determining to follow your own agenda.
7. Getting over-emotional.
8. Allowing your mind to wander.

Communication in the Medical Office

Dealing with "Problem" Patients:
Developing better listening skills

1. Control distractions
2. Concentrate on what the speaker is saying mentally and physically (make eye contact, lean forward, relax).
3. Be patient, don't interrupt.
4. Don't daydream.

Communication in the Medical Office

Dealing with "Problem" Patients:

Developing better listening skills

5. Avoid finishing sentences for the speaker unless the speaker is struggling, in which case it is best to suggest a word to help.
6. Agree when you can.
7. Paraphrase to check accuracy.

Communication in the Medical Office

Dealing with "Problem" Patients:

Key technique to master

1. Let the patient talk and listen to what is said.
2. When the patient is done, wait five seconds before saying anything. If the patient starts talking again, listen.
3. When the patient is done, re-state what you think the patient's primary concern is in your own words.
4. Once you and the patient agree on the main problem, determine a course of action. Solve problem, don't "win."

Communication in the Medical Office

Dealing with "Problem" Patients:

The long wait

- Studies have shown that patient satisfaction is tied to wait time.
- Apologize and explain, don't ignore.
- Give a realistic time, not a vague promise such as "*The doctor will see you soon.*" Instead state, "*I am sorry you have had to wait. You are the next patient and I expect Dr. Iamalwayslate to be with you in about 10 minutes. If it will be longer, I will let you know."*

Communication in the Medical Office

Dealing with "Problem" Patients:

Short-circuit the long wait

- Place a sign on the reception desk that lets patients know the office policy on waiting, such as:

  "*We know your time is valuable and we do our best to not keep you waiting. We will let you know if your doctor will not be able to see you within 15 minutes of you signing in. If you cannot wait, please talk with the receptionist to re-schedule your appointment. We are sorry if we inconvenienced you.*"

Communication in the Medical Office

Dealing with "Problem" Patients:

The long wait

- Don't show patients to an exam room until shortly before they will be seen, unless you have a very comfortable exam room.
- Explain why the doctor is running late, if possible.
- Thank patients who wait.
- Keep the waiting area a nice place to be (current magazines, clean, attractive, TV)

Communication in the Medical Office

Apologies

1. *Tactical* (Trying to soften someone up)
2. *Explanation* ("I am sorry, but…")
3. *Formalistic* (Socially expected)
4. *Authentic* (Feel and express genuine sympathy and regret, and take responsibility for actions, frequently leading to a change in feelings and restoration of trust)

Communication in the Medical Office

What are some things doctors can do to enhance communication?

- Ask permission before entering the exam or treatment room
- Introduce yourself (even if it is a returning patient)
- BEFORE inducing conscious sedation or anesthesia explain the procedure and how long it should take (document)
- If diagnostic tests are indicated, explain why, what will be done, and estimate how long until results are available (document)

Communication in the Medical Office

What are some things doctors can do to enhance communication?

- Before finishing the encounter, ask if the patient or family has any questions that have not been answered (document)
- If follow up will be required, explain an approximate time frame and what the expectation are for that session (document)
- Thank the patient and family for allowing you to be a part of the health care team

Communication in the Medical Office

What are some things doctors can do to enhance communication?

Delivering bad news

- Consider the emotional state of the patient and family
- Patient tends to not want to hear what is being said, while the doctor prefers to not want to say anything direct.
- In one Yale study, 100% of physicians stated they had given a prognosis, while 69% of patients stated they had received a prognosis.

Communication in the Medical Office

What are some things doctors can do to enhance communication?

Delivering bad news?

"SPIKES"

- SET UP the interview
- Assess the PATIENT'S perception
- Obtain an INVITATION to proceed
- Give the patient KNOWLEDGE and diagnostic information (the bad news)
- Respond with EMPATHY to the patient's EMOTIONS
- SUMMARIZE and STRATEGIZE

Communication in the Medical Office

Conclusion

- Most communication training is received very early on in residency, long before it is needed
- To effectively communicate means to be human
- To effectively communicate means that the message being delivered is the message being sent
- Communication skills CAN be improved, CAN be practiced and, as with any risk management activity, must be REPEATED to remain effective
- The key to more successful communication for many physicians resides in developing better listening skills.

Communication in the Medical Office

Conclusion

The computerization of offices continues and there are fewer "normal" patients, work to not let the computer become one more distraction between you and the patient and, maybe, start considering Zebras more often.

SELF EVALUATION

Reducing Practice Risk through Effective Communication

1. A challenge with the use of BioGPT Artificial Intelligence is:

a. It invents citations.
b. It references non-existent studies.
c. It can provide false information on vaccines.
d. All of the above.

2. Communication with patients can be impeded by:

a. The literacy of the patient.
b. The health literacy of the patient.
c. Provider focus on the Electronic Health Record.
d. All of the above.

3. T/F - In a 1992 study of 26,000 randomly selected Americans, the U.S. Department of Education determined that 47% of the participants were either functionally or marginally illiterate.

4. The perception of healthcare professionals that they are seeing fewer “normal” patients is likely related to:

a. Patients being unfamiliar with medical terminology.
b. Patients lacking background knowledge in health sciences or biology.
c. Patients having, on average, over 100 toxic, man-made chemicals in their bodies.
d. Providers missing non-verbal communication from patients.

5. Communication between healthcare professionals and patients:

a. Can be improved with practice.
b. Can be improved with better listening skills on the part of healthcare professionals.
c. Is better when providers re-state in their own words what the patient said.
d. All of the above.

Answer Key: 1. D, 2. D, 3. T, 4. C, 5. D

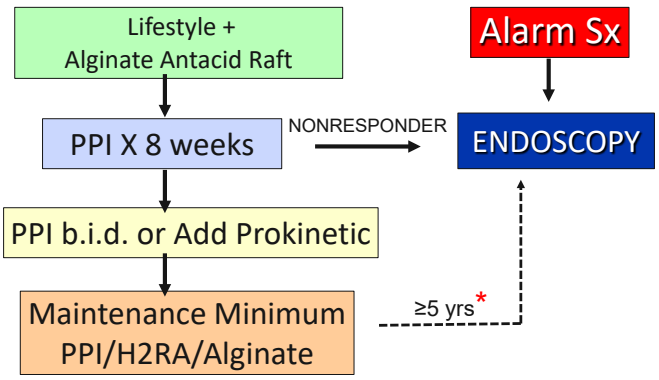
LOUIS KURITZKY, MD
4510 NW 17th Place
GAINESVILLE, FL 32605
(352) 377-3193 LKuritzky@aol.com

Managing Gastroesophageal Reflux Disease

GERD Category

The Things You Need to Know
A Lot About

Typical GERD Sx



*Reported to be cost effective in white males > age 50 yrs
Anderson WD et al Am Fam Phys 2015;91(10):692-697

Why Bother?
GERD Epidemiology

"In Western countries, 20% to 40% of adults suffer from episodes of heartburn due to GERD. In France, a questionnaire study of 8,000 adults representative of the general population found a 31.3% prevalence…."

Pouchain D et al *BMC Gastroenterology* 2012;12(18):1-8

GERD: Why Bother?
Adult Data (USA)

- Most common GI Dx in outpt clinics
- Dx = 2 episodes/week
- Adult Prevalence = 18 - 28%
- Heartburn frequency: Daily: ~7%
- OTC H2RA or antacid ≥1x/wk = ~20%

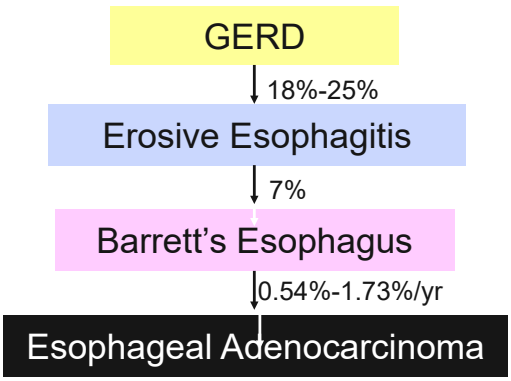
Ferri F *Ferri's Clinical Advisor* Elsevier (Philadelphia) 2022;662-663

GERD: Why Bother

- 1/3 treated patients disatisfied[1]
- Multiple Fixes
  - Easy
  - Safe
  - Well Tolerated
  - Inexpensive

[1]Pouchain D et al *BMC Gastroenterology* 2012;12(18):1-8

GERD: Why Bother?



Maret-Ouda J, et al *JAMA* 2020;324(24):2536-2547

Why Bother? Barrett's Esophagus

- 1950 Norman Barrett (British Surgeon): notes esophageal ulcerations, lined with "gastric" epithelium
- Opinion: segment of stomach must be tethered in chest due to congenitally short squamous-lined esophagus

Stollman N. *Postgrad Med* 2000;107(7):59-66

Barrett's Esophagus

1953 (Allison and Johnstone):

- columnar-lined structure lacks peritoneal covering (which stomach has)
- Esophageal-typical submucosal glands & muscularis propria present
- → Barrett capitulates, his name remains

Stollman N. *Postgrad Med* 2000;107(7):59-66

What Is Barrett's Esophagus?

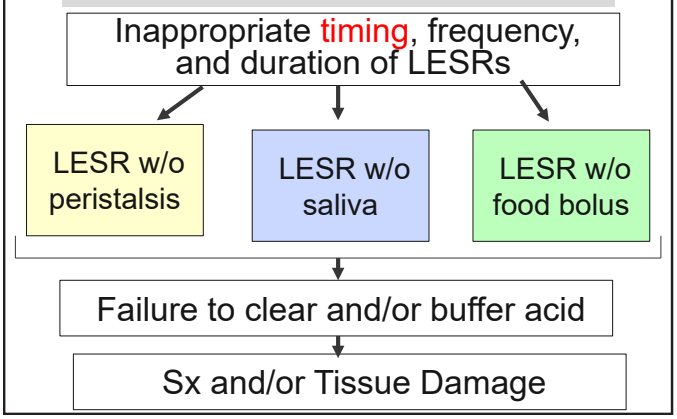
- Metaplastic change in the esophageal epithelium
- Normal squamous mucosa replaced by columnar intestinal-type mucosa

GERD Pathophysiology in a Nutshell

~~Acid Overproduction~~

GERD is the result of inappropriate timing, frequency, and duration of LESRs

GERD Pathophysiology in a Nutshell



GERD: Who DOES Need Endoscopy?

- Alarm Sx
  - Dysphagia/Odynophagia
  - Bleeding/Anemia
  - Weight Loss
  - Recurrent vomiting
- Persistent Sx ≥8 weeks post PPI

Adapted from
Ferri F *Ferri's Clinical Advisor* Elsevier (Philadelphia) 2021;593-594

GERD: The Bottom Line

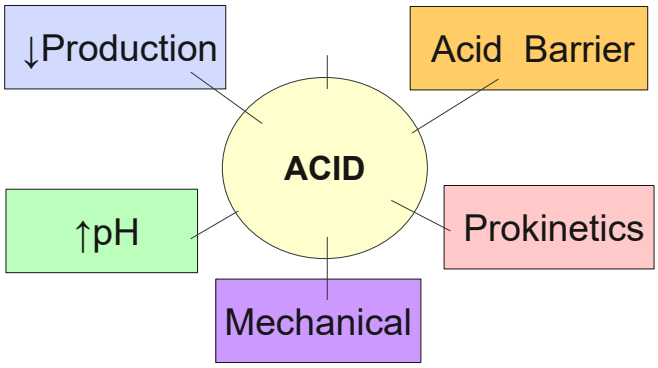
GERD is the result of inappropriate timing, frequency, and duration of LESRs

- Why?
- How to Fix?

Since We Can't Fix LESR Inappropriate T/F/D

- Acid
- Mechanical Interventions
- Diet

Since We Can't Fix LESR Inappropriate TFD



GERD: Lavish Evaluation? NOT

"Generally, when Sx of GERD are typical and the patient responds to Tx, there is no need for further diagnostic tests to verify the Dx."

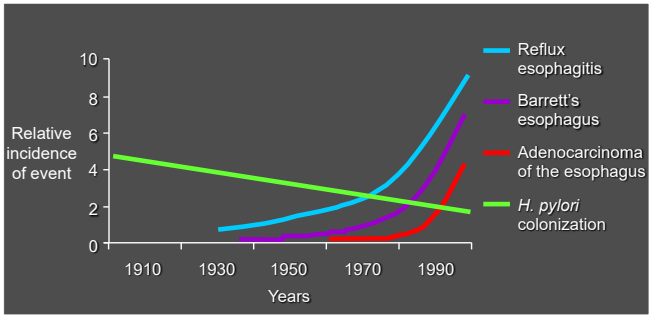
Ferri F *Ferri's Clinical Advisor* Elsevier (Philadelphia) 2022;662-663

GERD: Evaluate for Helicobacter?
What Part of NOT Did You Not Understand?

"*Helicobacter pylori* testing is not indicated in GERD."

Ferri F *Ferri's Clinical Advisor* Elsevier (Philadelphia) 2021;593-594

GERD and the ↓Incidence of *H. pylori*



Blaser MJ. *J Infect Dis*. 1999;179:1523-1530

GERD: *Helicobacter* NOT

Cite this article as: BMJ, doi:10.1136/bmj.38082.626725.EE (published 4 May 2004)

Primary care

Randomised controlled trial of effects of *Helicobacter pylori* infection and its eradication on heartburn and gastro-oesophageal reflux: Bristol helicobacter project

Richard F Harvey, J Athene Lane, Liam J Murray, Ian M Harvey, Jenny L Donovan, Prakash Nair

Harvey Rf et al *BMJ USA* 2004(4):395-397

GERD: *Helicobacter* NOT

- Study: RPCT Helicobacter impact upon GERD/heartburn (n=1,558)
- Rx: clarithromycin/ranitidine/bismuth vs placebo x 2 weeks
- Outcome (at 2 years): "…active Rx had no effect on the overall prevalence of heartburn or reflux and did not improve pre-existing Sx of heartburn or reflux."

Harvey Rf et al *BMJ USA* 2004(4):395-397

GERD: Helicobacter

"Established risk factors for developing GERD include ↑ BMI, tobacco smoking, and genetic predisposition, whereas infection with the gastric bacterium Helicobacter pylori can ↓ this risk."

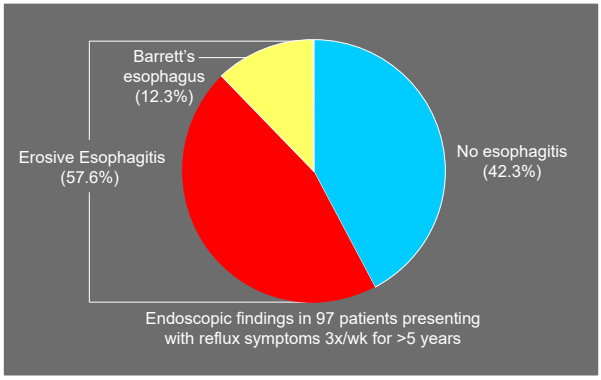
Maret-Ouda J, et al *JAMA* 2020;324(24):2536-2547

GERD: Who DOES Need Endoscopy?

- Alarm Sx
  - Dysphagia/Odynophagia
  - Bleeding/Anemia
  - Weight Loss
  - Recurrent vomiting
- Persistent Sx ≥8 weeks post PPI

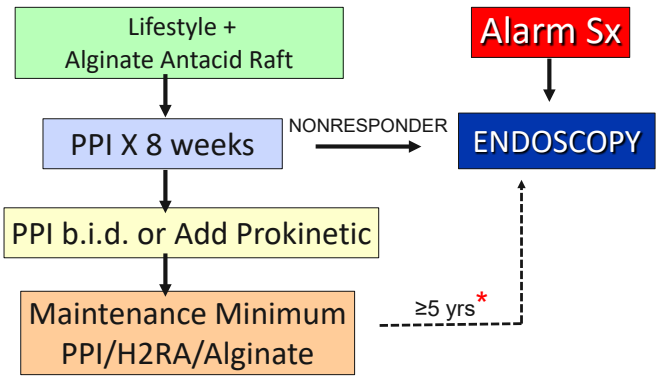
Adapted from
Ferri F *Ferri's Clinical Advisor* Elsevier (Philadelphia) 2021;593-594

GERD: Prevalence of Erosive Esophagitis



Winters C et al *Gastroenterology* 1987;92:118-124.

Typical GERD Sx



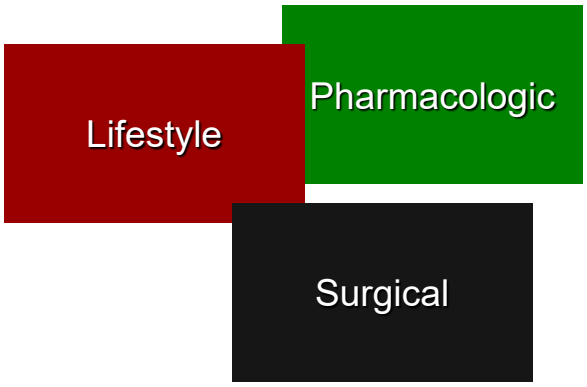
*Reported to be cost effective in white males > age 50 yrs
Anderson WD et al Am Fam Phys 2015;91(10):692-697

LESR Dysfunction:
Meds That ↓ LES Tone

- CCBs
- α-Blockers
- Nitrates
- Theophylline
- Anticholinergics
- β-Agonists
- PDE5i

Rx

GERD Rx



GERD Rx: Which is BEST?

It Depends
On Which Endpoint You Are Assessing

Sx

pH

Erosive Esophagitis Healing

GERD Rx

Lifestyle

Lifestyle Intervention:
Does it Work?

Absence of Evidence is Not Evidence of Inefficacy

GERD Rx: Lifestyle*

- Reduce meal Fat content
- PM meal ≥3 hrs. before bedtime
- Elevate head of bed
- Smoking Cessation

*Expert opinion, absent large RCTs

DeVault KR *Gastroenterol Clin North Am* 1999;28:831-845


REVIEW ARTICLE

Are Lifestyle Measures Effective in Patients With Gastroesophageal Reflux Disease?

An Evidence-Based Approach

Tonya Kaltenbach, MD; Seth Crockett, MD; Lauren B. Gerson, MD, MSc

Kaltenbach T et al *Arch Intern Med* 2006;166:965-971

Lifestyle Rx for GERD: Basis

"Recommendations…are based on the presumption that certain foods, body position, tobacco, alcohol, and obesity contribute to a dysfunction in the body's antireflux defense system."

Kaltenbach T et al *Arch Intern Med* 2006;166:965-971

Lifestyle Rx for GERD: Basis

"Although there was physiologic evidence that exposure to tobacco, alcohol, chocolate, and high-fat meals decreases LES pressure, there was no published evidence of the efficacy of dietary measures."

Kaltenbach T et al *Arch Intern Med* 2006;166:965-971

Lifestyle Rx for GERD: Results
Evidence Level B

- Alcohol cessation: no Δ pH, Sx
- Tobacco cessation: no Δ pH, Sx
- ↑Head of bed: improved time of pH >4
- Sleep L lateral decubitus: ↑ time of pH >4
- Weight loss: improved Sx & ↑ time of pH >4

Kaltenbach T et al *Arch Intern Med* 2006;166:965-971

LESR Dysfunction: Foods

- Chocolate
- Onions
- Peppermint
- Caffeine
- Coffee
- Alcohol[1]
- Citrus
- Tomatoes
- Carbonation
- Fried Food
- Experiential
- Garlic[1]

Adapted from
Ferri F *Ferri's Clinical Advisor* Elsevier (Philadelphia) 2021;593-594
[1]DeVault KR *Gastroenterol Clin North Am* 1999;28:831-845

The NEW ENGLAND JOURNAL of MEDICINE

OCCASIONAL NOTES

Chocolate Consumption, Cognitive Function, and Nobel Laureates

Franz H. Messerli, M.D.
2012;367(16):1562-1564

Dietary flavonoids, abundant in plant-based foods, have been shown to improve cognitive function. Specifically, a reduction in the risk of dementia, enhanced performance on some cognitive tests, cause the population of a country is substantially higher than its number of Nobel laureates, the numbers had to be multiplied by 10 million. Thus, the numbers must be read as the number

Chocolate & Cognitive Function

"A subclass of flavonoids called flavanols… widely present in cocoa, green tea, red wine, and some fruits, seems to be effective in slowing down or even reversing the reductions in cognitive performance that occur with aging."

Messerli FH *NEJM* 2012;367(16):1562-1564

Chocolate & Cognitive Function

"Dietary flavanols have also been shown to improve endothelial function and to lower BP by causing vasodilation in the peripheral vasculature and in the brain."

Messerli FH *NEJM* 2012;367(16):1562-1564

Chocolate and Nobel Laureates

Messerli FH NEJM 2012;367:16:11562-1564

HOW MUCH Chocolate, Then?

"The minimally effective chocolate dose seems to hover around 2 kg/year, and the dose-response curve reveals no apparent ceiling…"

Messerli FH *NEJM* 2012;367(16):1562-1564

Food for the Brain

Minimal effective Dose: 4.4 lb/yr (= 50 Chunky Bars/yr)

Vol. 293 No. 18 COFFEE, ACID SECRETION AND LES PRESSURE — COHEN AND BOOTH 897

GASTRIC ACID SECRETION AND LOWER-ESOPHAGEAL-SPHINCTER PRESSURE IN RESPONSE TO COFFEE AND CAFFEINE

SIDNEY COHEN, M.D., AND GLENN H. BOOTH, JR., M.D., PH.D.

Cohen S, Booth GH *NEJM* 1975;293;18:897-899

Gastric Acid and Gastrin Response to Decaffeinated Coffee and a Peptone Meal

Feldman EJ, Isenberg JI, Grossman MI
JAMA 1981;246(3):248-250

Decaffeinated Coffee & Gastric Acid: Introduction

- Known acid stimulants: protein, Ca^{++}, caffeine
- Prior acid comparison: coffee ≈ decaf
- Subjects: 8 healthy men
- Method: 500 ml (per NG tube) q 30 mins of
  - H_20
  - Decaf (= 0.5 cups coffee)
  - Peptone broth
- Active agent concentration ↑2x each 30 mins

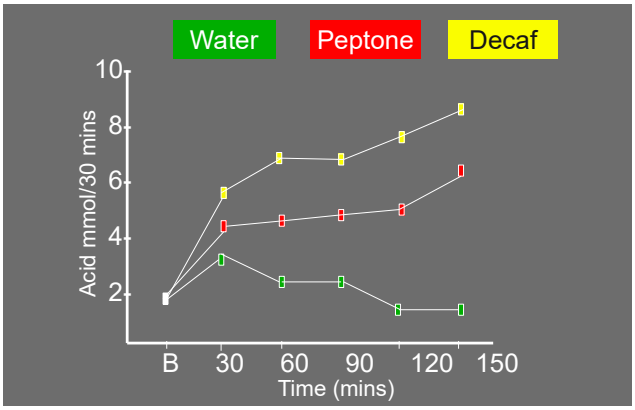
Feldman EJ et al *JAMA* 1981;246(3):248-250

Decaffeinated Coffee & Gastric Acid: Comments

"On a weight-for-weight basis, no stronger intragastric stimulant of gastric secretion and gastrin release than peptone had hitherto been identified."

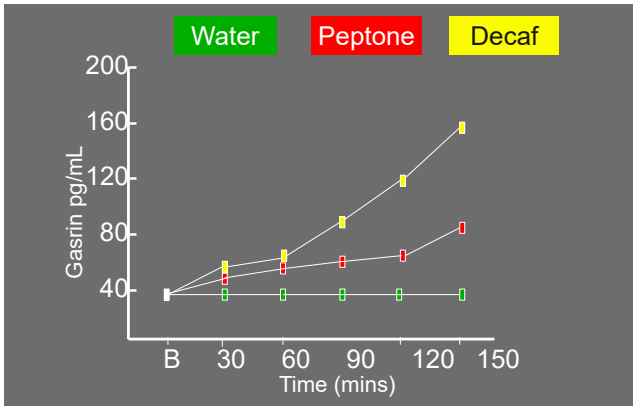
Feldman EJ et al *JAMA* 1981;246(3):248-250

Decaf Coffee: Acid Stimulation



Feldman EJ et al *JAMA* 1981;246(3):248-250

Decaf Coffee: Gastrin Stimulation



Feldman EJ et al *JAMA* 1981;246(3):248-250

Decaffeinated Coffee & Gastric Acid: Comments

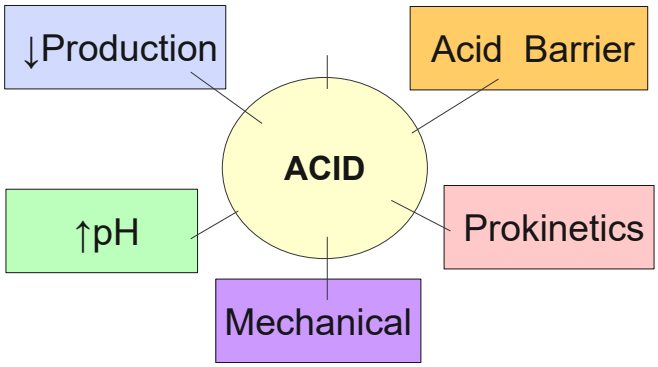
"On the basis of the present study, decaffeinated coffee appears to be the most potent intragastric stimulant of acid secretion and gastrin release identified to date."

Feldman EJ et al *JAMA* 1981;246(3):248-250

GERD Rx

PHARMACOLOGIC

Since We Can't Fix LESR Inappropriate TFD



GERD Sx: pH Control

"Rxs which maintain….pH >4…are associated with the highest healing rates. Peptic activity is minimized at or above ph 4…. [which] is significantly longer with the PPIs than the H2RAs or sucralfate."

Hunt RH *Aliment Pharmacol Ther* 1995;9(Suppl 1):3-7

GERD Erosive Esophagitis: pH Control

"The healing rate of erosive esophagitis by antisecretory drugs at weeks correlated directly with the duration of acid suppression achieved over the 24 hr period."

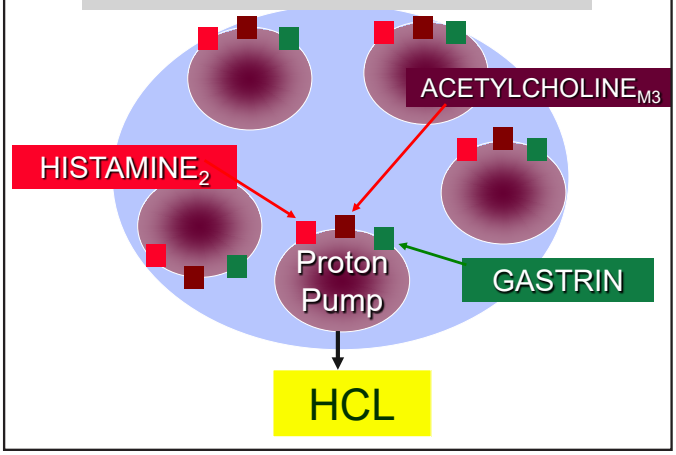
Hunt RH *Aliment Pharmacol Ther* 1995;9(Suppl 1):3-7

GERD: Pharmacologic Rx

- Efficacy (↓order)
  - PPI
  - Prokinetic (metoclopramide, nizatidine)
  - H2RA
  - Antacids
- Last pharmacological resort:
  - PPI + LESR antagonist (baclofen) + neuromodulator (desipramine)

Adapted from Ferri F *Ferri's Clinical Advisor* Elsevier (Philadelphia) 2021;593-594

PARIETAL CELL FUNCTION



GERD: Pharmacologic Rx

- Antacids
  - Neutralizers (Maalox, Mylanta)
  - Raft method (Gaviscon)
  - Sucralfate
- H2RA
- PPI
- Prokinetic

GERD Rx

PHARMACOLOGIC: ANTACIDS

OTC Antacids

	$AlOH_3$	$MgCO_3$	$CaCO_3$	Other
Maalox	+			
Mylanta	+	+		
Tums			+	
Amphogel	+			
Gaviscon	+	+		Alginic Acid

DeVault KR *Gastroenterol Clin North Am* 1999;28:831-845

OTC Antacids: How LONG Do They Work?

"A study found that antacids may prevent esophageal acidification for 90 minutes after a standard dose."

DeVault KR *Gastroenterol Clin North Am* 1999;28:831-845

OTC Antacids: How WELL Do They Work?

"Two long term trials suggest effective Sx relief in approximately 20% of patients with antacids."*

*Severe GERD

DeVault KR *Gastroenterol Clin North Am* 1999;28:831-845

Gaviscon® : What's The Deal?

Pouchain *et al. BMC Gastroenterology* 2012, **12**:18
http://www.biomedcentral.com/1471-230X/12/18

BMC Gastroenterology

RESEARCH ARTICLE Open Access

Gaviscon® vs. omeprazole in symptomatic treatment of moderate gastroesophageal reflux. a direct comparative randomised trial

Denis Pouchain[1*†], Marc-André Bigard[2†], François Liard[3†], Marc Childs[4†], Annick Decaudin[5] and Donna McVey[6]

Pouchain D, et al *BMC Gastroenterol* 2012;12(18):1-8

Alginic Acid MOA

"Alginic acid derivatives, or alginates, treat GERD via a unique mechanism by creating a mechanical barrier that displaces the postprandial acid pocket. In the presence of gastric acid, they precipitate into a gel and form a raft that localizes to the acid pocket in the proximal stomach"

Leiman DA et al *Dis Esoph* 2017;30:1-9

Alginic Acid: 1st Line Rx?

"Our study suggests that alginates alone provide superior benefit over antacids and therefore they could be considered as an initial Rx for patients with mild GERD Sx for whom chronic acid suppression was either undesirable or deemed unnecessary."

Leiman DA et al *Dis Esoph* 2017;30:1-9

CONTENTS (per tab)

- AlOH3 160 mg
- MgCO3 105mg
- Alginic Acid
- Dose: 2-4 tabs qid

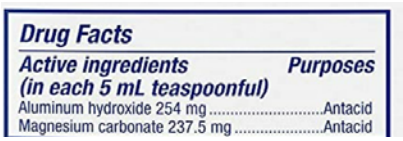
$14.49
100 tabs

Contents/tab

- $AlOH_3$ 160 mg
- $MgCO_3$ 105mg
- Alginic Acid
- Dose: 2-4 tabs qid

$9.99
100 tabs

Gaviscon Liquid



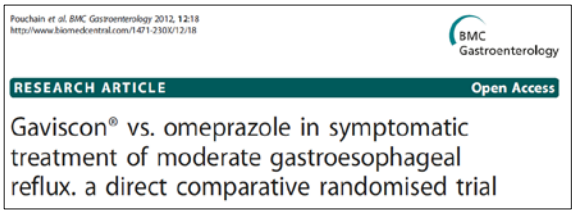
Drug Facts

Active ingredients (in each 5 mL teaspoonful)	Purposes
Aluminum hydroxide 254 mg	Antacid
Magnesium carbonate 237.5 mg	Antacid

- 4 tsp (20 ml) dose
  - Na alginate 1000 mg
  - NaHCO3 426 mg
  - CaCO3 650 mg

How Good is Antacid/Alginic Acid? GOOD Trial

Gaviscon vs Omeprazole in SymptOmatic Rx of MoDerate GERD


Pouchain et al. BMC Gastroenterology 2012, 12:18
http://www.biomedcentral.com/1471-230X/12/18

BMC Gastroenterology

RESEARCH ARTICLE Open Access

Gaviscon® vs. omeprazole in symptomatic treatment of moderate gastroesophageal reflux. a direct comparative randomised trial

How Good is Antacid/Alginic Acid? Gaviscon® vs omeprazole

- Study: RDBDD non-inferiority trial (n=278)
- Inclusion: GERD 2-6 episodes/wk
- Rx (X14 days):
  - Gaviscon® 10 ml t.i.d. ac & HS
  - omeprazole 20 mg qam
  - dummy Gaviscon or omeprazole
- 1^0 Outcome: time to 1^{st} 24hr Sx-free period

Pouchain D et al *BMC Gastroenterology* 2012;12(18):1-8

Gaviscon® vs omeprazole Conclusions

"Gaviscon… proved non-inferior to omeprazole 20 mg/day, and is thus a relevant and effective alternative treatment in case of moderate and episodic symptoms of GERD as managed in general practice."

Pouchain D et al *BMC Gastroenterology* 2012;12(18):1-8

Alginic Acid Bottom Line

A meta-analysis of 14 studies (2095 patients) found that alginate relieves GERD Sx better than antacids or placebo…and has approximately the same effect as PPIs or H2RAs…."

Maret-Ouda J, et al *JAMA* 2020;324(24):2536-2547

GERD Rx

PHARMACOLOGIC: H2RAs

H2RA2: United States

- Cimetidine (Tagamet®)
- Famotidine (Pepcid®)
- Nizatidine (Axid®)
- Ranitidine (Zantac®)

H2RAs in GERD: Any Differences?

"Although there are some differences in potency, duration, and rapidity of action, they may be generally used interchangeably."

DeVault KR *Gastroenterol Clin North Am* 1999;28:831-845

H2RA Pharmacokinetics/dynamics

- Onset of pH = 30 mins
- Duration of activity = 10 hrs
- Cimetidine: significant P450 interactions

DeVault KR *Gastroenterol Clin North Am* 1999;28:831-845

GERD Rx

PHARMACOLOGIC: PPIs

GERD Sx Lansoprazole vs Esomeprazole

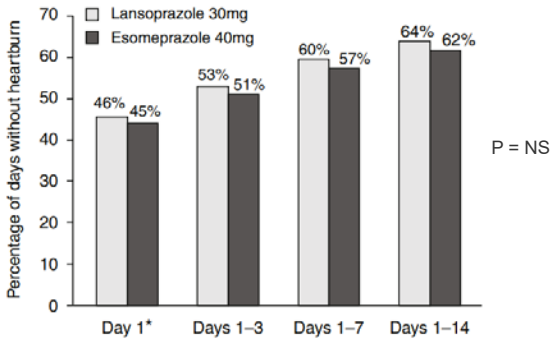
ORIGINAL RESEARCH ARTICLE

Lansoprazole and Esomeprazole in Symptomatic GERD
A Double-Blind, Randomised, Multicentre Trial in 3000 Patients Confirms Comparable Symptom Relief

William Chey,[1] Bidan Huang[2] and Robert L. Jackson[3]

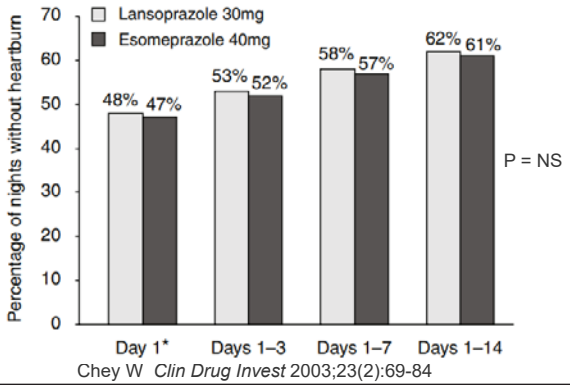
Chey W *Clin Drug Invest* 2003;23(2):69-84

GERD Sx: Lanso vs Eso X 2 weeks % DAYS Without Heartburn



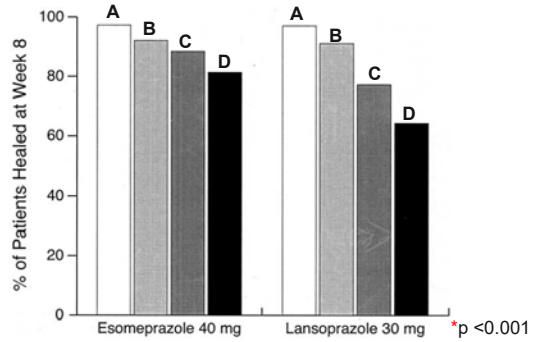
Chey W *Clin Drug Invest* 2003;23(2):69-84

GERD Sx: Lanso vs Eso X 2 weeks
% NIGHTS Without Heartburn



Chey W *Clin Drug Invest* 2003;23(2):69-84

Erosive Esophagitis
Esomeprazole vs Lansoprazole*



Castell DO et al *Am J Gastroenterol* 2002;97(3):575-583

Erosive Esophagitis
Esomeprazole vs Lansoprazole at 4 weeks

	Eso	Lanso	p
Heartburn Complete Resolution	62%	60.2%	<0.05
Heartburn free nights	87.1%	85.8%	<0.05
Time to sustained heartburn free (7d)	7	8	<0.01

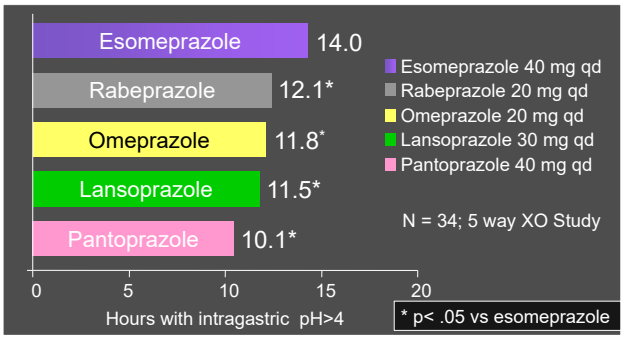
Castell DO et al *Am J Gastroenterol* 2002;97(3):575-583

Gastric Acid Control With Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, and Rabeprazole: A Five-Way Crossover Study

Philip Miner, Jr., M.D., Philip O. Katz, M.D., Yusong Chen, Ph.D., and Mark Sostek, M.D.

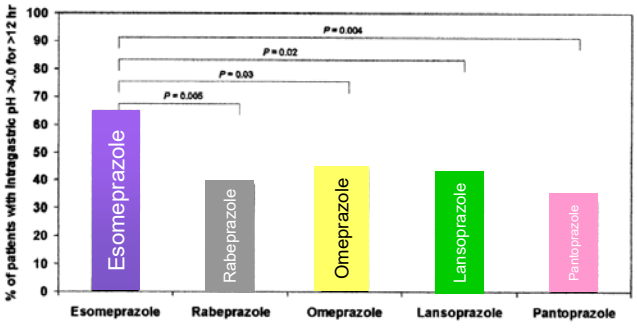
Am J Gastroenterol. 2003;98(12):2616-2620

PPI pH Durability



Miner P Jr, et al. *Am J Gastroenterol*. 2003;98(12):2616-2620.

PPI pH Durability
% with pH >4 for >12 hrs



Miner P Jr, et al. *Am J Gastroenterol*. 2003;98(12):2616-2620.

PPI's : Is There a Difference? A 'Real World' Study

Assessment of Patient Satisfaction with a Formulary Switch from Omeprazole to Lansoprazole in Gastroesophageal Reflux Disease Maintenance Therapy

Laura J. Condra, PharmD; Anthony P. Morreale, PharmD, BCPS, MBA; Stephen N. Stolley, PharmD, BCPS; and David Marcus, RPh

Condra LJ, et al *Am J Manag Care* 1999;5:631-638

PPI's : Is There a Difference? A 'Real World' Study

- BACKGROUND: VA Affairs Healthcare System signs omeprazole → lansoprazole switch contract
- STUDY: GERD pts (n=300) Rx > 4months on omeprazole, now switched to lansoprazole
- MEASURED: Sx Scores, AEs, preference

Condra LJ, Morreale AP et al *Am J Manag Care* 1999;5(5):631-638

PPI's : Is There a Difference? RESULTS

- Overall Sx scores: =
- 19% pts required additional clinic visit
- Side effects ↑ with lansoprazole
- Preference:
  - 64% Omeprazole
  - 36% Lansoprazole
- 69% willing to **PAY** additional fee for preferred agent

Condra LJ, et al *Am J Manag Care* 1999;5(5):631-638

PPI's: Is There a Difference? Conclusions

"Omeprazole was the medication preferred…. Patients were willing to pay an additional fee for their preferred agent. Fewer adverse events were reported with omeprazole. The potential cost savings of the formulary conversion may have been at the expense of patient satisfaction."

Condra LJ, et al *Am J Manag Care* 1999;5(5):631-638

PPIs: Is ther ANY Difference?

Journal of Gastroenterology and Hepatology (2003) 18, 1392–1398

TREATING REFLUX ESOPHAGITIS

Symptom relief in patients with reflux esophagitis: Comparative study of omeprazole, lansoprazole, and rabeprazole

KYOICHI ADACHI,* TOMOYUKI HASHIMOTO,† NAOHARU HAMAMOTO,† KAZUYA HIRAKAWA,† MASATOSHI NIIGAKI,† TATSUYA MIYAKE,† HIROYUKI TANIURA,** MASAHIRO ONO,† TAKEKAZU KAJI,† HIROSHI SUETSUGU,* JUNKO YAGI,* YOSHINORI KOMAZAWA,* TAKAFUMI MIHARA,* TOMOKO KATSUBE,* HIROFUMI FUJISHIRO,* TOSHIHIRO SHIZUKU,‡ SHUZO HATTORI,† SHUN YAMAMOTO‡ AND YOSHIKAZU KINOSHITA*

NO COI Disclosures
1st author: Med School Faculty

PPIs: Is there ANY Difference?

"Rabeprazole has a faster onset of antisecretory activity than omeprazole and lansoprazole. The aim of the present study was to clarify whether there is any difference in the speed of Sx relief…."

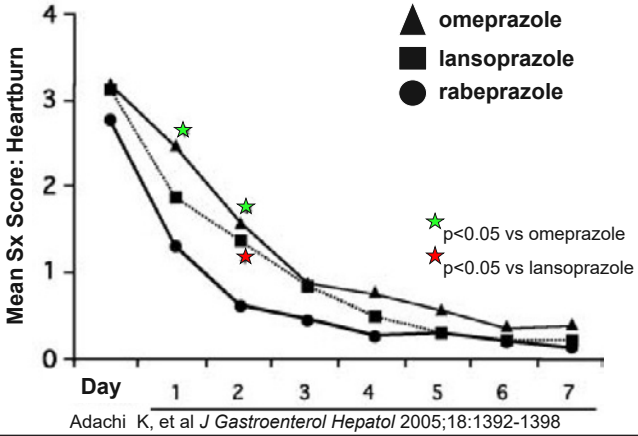
Adachi K, et al *J Gastroenterol Hepatol* 2005;18:1392-1398

PPIs: Is there ANY Difference?

- Study: RCT GERD (n=85)
- Rx: omeprazole 20 mg/d vs lansoprazole 30 mg/d vs rabeprazole 20 mg/d X 8 weeks
- Metrics:
  - 0-6 heartburn scale (6 = severe)
  - Healing of esophagitis

Adachi K, et al *J Gastroenterol Hepatol* 2005;18:1392-1398

PPIs: Is ther ANY Difference?



Adachi K, et al *J Gastroenterol Hepatol* 2005;18:1392-1398

Omeprazole IR/Sodium Bicarbonate
Zegerid® OTC

Sig: 1 capsule daily X 14 days

IR 20 mg Omeprazole + 1100 mg $NaHCO_3$

Omeprazole IR/Sodium Bicarbonate
Zegerid® Rx

- IR Omeprazole 20 mg + 1,680 mg $NaHCO_3$
- IR Omeprazole 40 mg + 1,680 mg $NAHCO_3$

$\therefore$

IR Omeprazole 20 mg/$NaHCO_3$ X 2
$\neq$
IR Omeprazole 40 mg /$NaHCO_3$

PPIs: PRN vs BTB

Aliment Pharmacol Ther 2005; 21: 805–812. doi: 10.1111/j.1365-2036.2005.02413.x

Long-term treatment of gastro-oesophageal reflux disease patients with frequent symptomatic relapses using rabeprazole: on-demand treatment compared with continuous treatment

B. BOUR*, J.-L. STAUB†, M. CHOUSTERMAN‡, D. LABAYLE§, B. NALET¶, O. NOUEL**, A. PARIENTE††, E. TOCQUE‡‡ & S. BONNOT-MARLIER‡‡

Bour B, et al *Aliment Pharmacol Ther* 2005;21:805-812

GERD: Rabeprazole QD vs PRN

- Study: RCT (open label) endoscopy-proven GERD mod-severe Sx (n= 152)
- Rx:
  - 4-week run-in rabeprazole qd to confirm responder status (Sx Score ≤2)
  - rabeprazole qd vs prn x 6 months
- Endpoint: Sx Score ≤2 (5-point scale)

Bour B, et al *Aliment Pharmacol Ther* 2005;21:805-812

Rabeprazole QD vs PRN
What Does 'PRN' Mean?

"The recurrence of your determining Sx at a level which you judge as incompatible with your well-being should lead to the start of the Rx. The disappearance of this Sx for 48 hr should lead to the discontinuation of the Rx"

Bour B, et al *Aliment Pharmacol Ther* 2005;21:805-812

Rabeprazole QD vs PRN
Outcome (6 months)

- Sx score ≤2: 84.6% vs 74.6% (p=NS)
- QOL score (0-100): 86.25 vs 84.95 (p = NS)
- # pills/month: 28.8 vs 9.3

Bour B, et al *Aliment Pharmacol Ther* 2005;21:805-812

GERD: PPI Risks

- Osteoporotic Fx
- Pneumonia
- Hypomagnesemia
- QT Prolongation
- SBP (in cirrhosis)
- Hepatic encephalopathy (in cirrhosis)
- P450 Drug interactions

Ferri F *Ferri's Clinical Advisor* Elsevier (Philadelphia) 2021;593-594

GERD Rx: The Fine Print
P450 Interactions

- Omeprazole & Esomeprazole inhibit 2C19
  - →↑ phenytoin levels
  - →↑ diazepam
  - Prevents activation of clopidogrel

Ferri F *Ferri's Clinical Advisor* Elsevier (Philadelphia) 2022;662-663

NaHCO3

Max Dose:
≤60 yrs: 24 tabs/d (240 gr/d or 15.6g/d)
>60 yrs: 12 tabs/d (120 gr/d or 7.8 g/d)

GERD Rx

PHARMACOLOGIC: Prokinetic

CLINICAL THERAPEUTICS®/VOL. 21, NO. 12, 1999

Prokinetic Activity of Nizatidine: Implications for the Management of Patients with Gastroesophageal Reflux Disease

Edwin J. Zarling, MD
Department of Medicine, Loyola University Medical Center, Maywood, Illinois

Zarling EJ *Clin Therapeutics* 1999;21(12):2038-2045

H2RAs : Just Acid Suppression?

- Nizatidine (Axid):
  - H2RA
  - ACHesterase-I activity →↑ cholinergic tone
- Prokinetic trial: nizatidine = cisapride
  - PPIs: no confirmed prokinetic effects
  - Other H2RAs: no confirmed prokinetic effects

Zarling EJ. "Prokinetic Activity of Nizatidine: Implications for the Management of Pts with GERD" *Clin Therap* 1999;21(12):2038-2046

H2RAs : Is There a Difference?

"…nizatidine has prokinetic activity comparable to that of cisapride, and its effect is evident <1 hour after administration…"

Zarling EJ. "Prokinetic Activity of Nizatidine: Implications for the Management of Pts with GERD" *Clin Therap* 1999;21(12):2038-2046

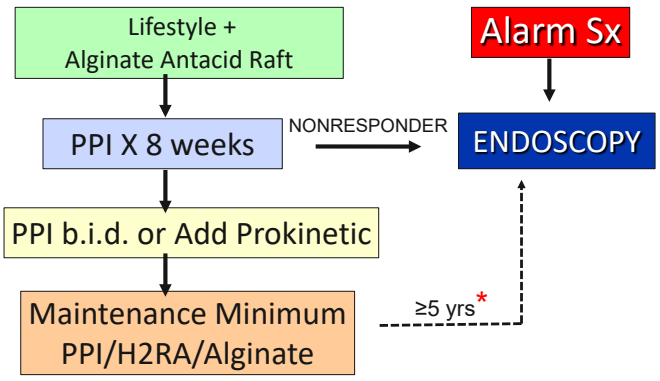
GERD Management: Common Errors

- PPI Misuse
  - PRN
  - Retroactive
  - With meals
  - Failure to advance from QD
  - No Rotation
  - Failure to add H2RA

GERD Rx

PHARMACOLOGIC:
Mucin Barrier Restoration

Typical GERD Sx



*Reported to be cost effective in white males > age 50 yrs
Anderson WD et al Am Fam Phys 2015;91(10):692-697

Rx Failure: Why? A Prevarication Misdemeanor

Rx Failure: Why?

"Clearly, the physiologic cause of the Sx and signs of GERD, whether erosive or non-erosive, is caused recurrent exposure to gastric refluxate that contains protonic acid, dissolved bile acids and serine proteases."

McCullough. *J Clin Gastroenterol Treat* 2020;6(1):1-19

What is Sucralfate?

"Sucralfate is a synthetic analog of a unit of gastric mucin….the aluminum hydroxide salt of octanesulfonated sucrose"

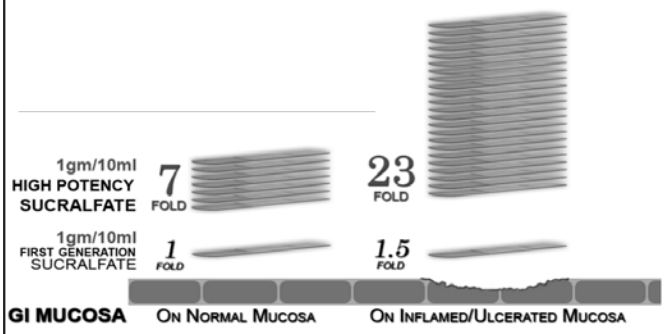
McCullough. *J Clin Gastroenterol Treat* 2020;6(1):1-19

Pre-polymerized Sucralfate
FDA 2005 Request for Designation (RFD)

"…if sucralfate is polymerized before ingestion, or pre-polymerized, then it is being used as a medical barrier device, having a physical mode of action and requiring no further chemical action to be clinically active."

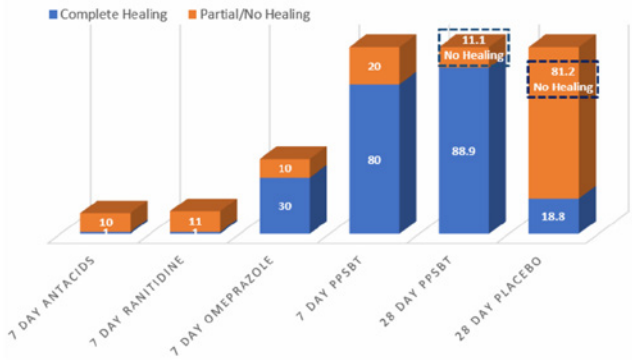
McCullough. *J Clin Gastroenterol Treat* 2020;6(1):1-19

Sucralfate: Pre-polymerized vs 1st Generation



McCullough. *J Clin Gastroenterol Treat* 2020;6(1):1-19

GERD: Erosive



McCullough. *J Clin Gastroenterol Treat* 2020;6(1):1-19

Pre-polymerized Sucralfate
A MEDICAL DEVICE?!

- Pre-polymerized Sucralfate (Device)
  - Biologically inert
  - Requires gastric acid activation to polymerize → definition as 'drug'
  - Class: non-systemic site protective agent

McCullough. *J Clin Gastroenterol Treat* 2020;6(1):1-19

GERD Rx

SPECIAL CIRCUMSTANCES

GERD: Pregnancy

Ranitidine is the best-studied agent effective for Rx…in pregnancy. Some antacids are effective, but it may be prudent to avoid them in the 1st trimester until better safety studies are published. Although sucralfate, metoclopramide, and the PPIs are probably safe in pregnancy, there are no data about their efficacy."

Koenig CJ *J Fam Pract* 2001;50(4):304-305

Double-Blind, Placebo-Controlled Study of Ranitidine for Gastroesophageal Reflux Symptoms During Pregnancy

JANET D. LARSON, MD, EDNA PATATANIAN, RPh, PHILIP B. MINER, Jr, MD, WILLIAM F. RAYBURN, MD, AND MALCOLM G. ROBINSON, MD

Larson JD, et al *Obstet Gynecol* 1997;90:83-87

GERD in Pregnancy: Ranitidine

- Study: DBRPCT GERD (n=20)
- Inclusion:
  - ≥20 weeks gestation
  - Heartburn >50% of days
  - Failed antacids, ↑ HOB, diet Δ, ETOH & smoking elimination
- Rx (30-60 mins ac x 4 weeks):
  - Ranitidine 150 mg ac (PM)
  - Ranitidine 150 mg ac (AM & PM)
  - PBO

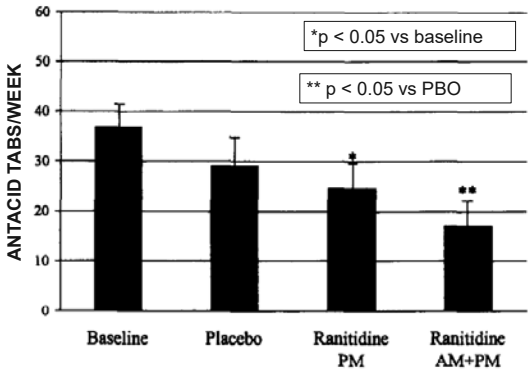
Larson JD, et al *Obstet Gynecol* 1997;90:83-87

GERD in Pregnancy: Ranitidine

- Endpoints:
  - Sx scores
  - # Antacid Rescue Doses (per week)
  - Global Assessment

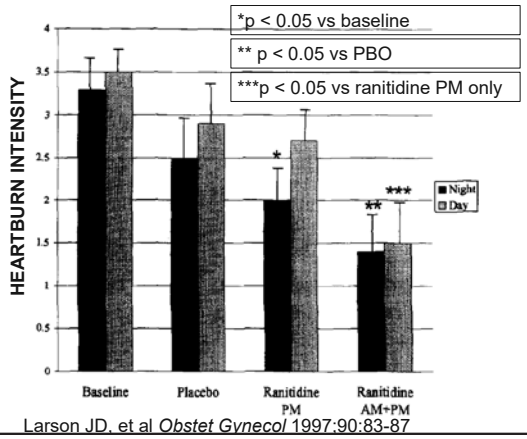
Larson JD, et al *Obstet Gynecol* 1997;90:83-87

GERD in Pregnancy: Ranitidine



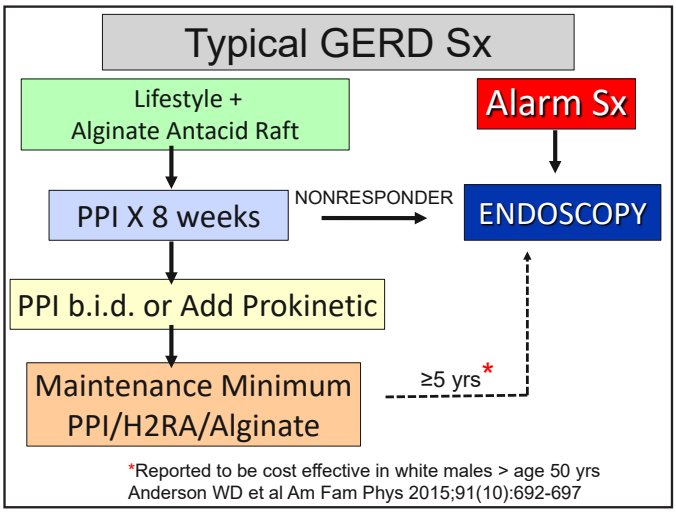
Larson JD, et al *Obstet Gynecol* 1997;90:83-87

GERD in Pregnancy: Ranitidine



Larson JD, et al *Obstet Gynecol* 1997;90:83-87

Typical GERD Sx



*Reported to be cost effective in white males > age 50 yrs
Anderson WD et al Am Fam Phys 2015;91(10):692-697

SELF EVALUATION

Managing Gastroesophageal Reflux Disease

1. Maintenance treatment of GERD may be done with

a. H2RA
b. PPI
c. Antacid Alginate Treatment
d. Any of the Above

2. In 1950 the British surgeon Norman Barret asserted that the esophageal columnar epithelium subsequently named for him was actually a foreshortened esophagus with a lower esophageal segment that was simply a proximal extension of the stomach. Was he correct?

a. Yes
b. No

3. Pathophysiologically, GERD is caused by

a. A defect in the esophageal mucosal barrier
b. Excessive production of stomach acid
c. Inappropriate timing, frequency, and duration of lower esophageal sphincter relaxations
d. Reduced gastric size resulting in overflow

4. The pH goal when treating GERD with a PPI or H2RA is

a. pH >1
b. pH >2
c. pH >3
d. pH >4

5. Only one H2RA has been noted to have prokinetic activity. Which one is it?

a. Omeprazole
b. Bismuth
c. Cimetidine
d. Nizatidine

Answer Key: 1. D, 2. B, 3. C, 4. D, 5. D

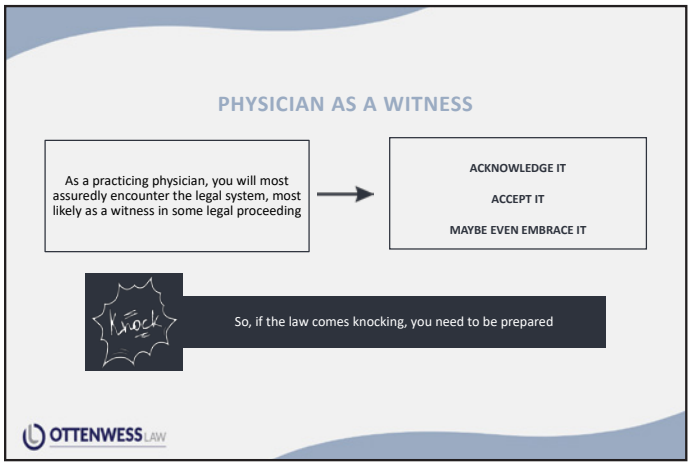
David M. Ottenwess, Esq.

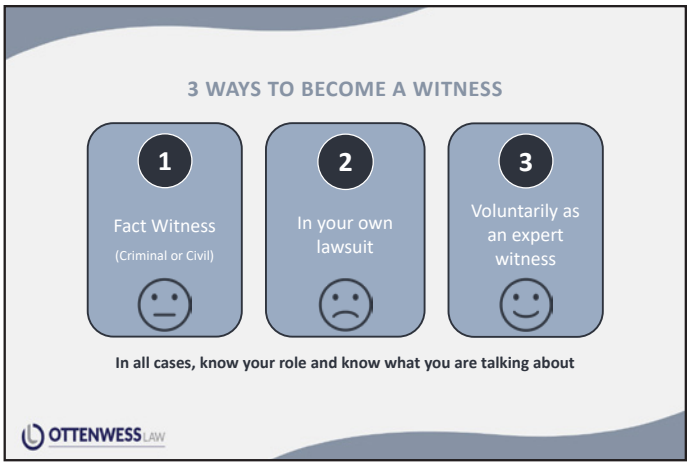
David M. Ottenwess, Esq., of Southfield, Michigan, is the founding partner of Ottenwess Law, a boutique firm serving a diverse clientele in litigation and transactional matters with particular focus on medical malpractice and professional liability defense. His practice focuses on civil litigation matters for which he has appeared before state and federal courts including the United States Supreme Court. Mr. Ottenwess has handled over 600 litigation matters including defending hospitals and physicians in medical malpractice and licensing matters. He is an advisor to hospitals and risk managers, has been featured in numerous top lawyer listings, was inducted into the American Board of Trial Advocates, and is a frequent speaker to legal and medical audiences.

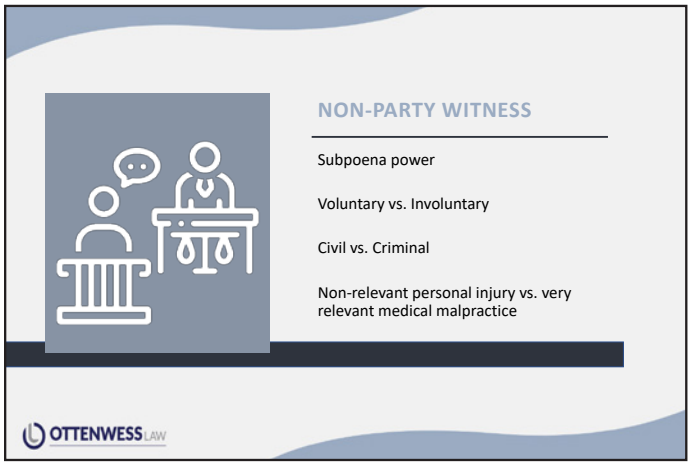
You may contact Mr. Ottenwess with your questions or comments at 313-965-2121, or by email at DOttenwess@OttenwessLaw.com.

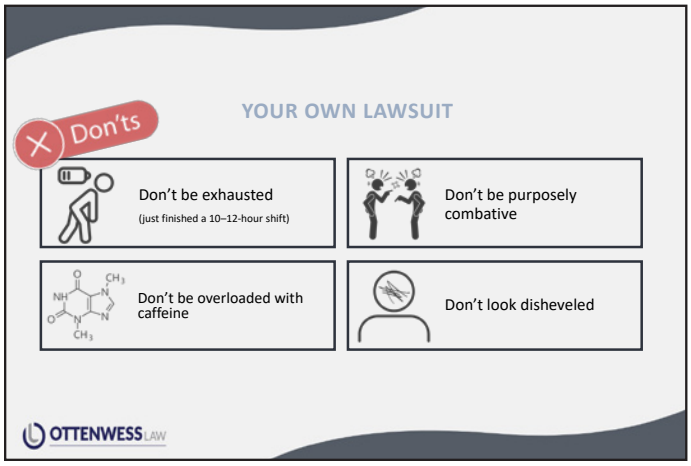
David M. Ottenwess | Ottenwess Law, PLC
3000 Town Center, Suite 2500 | Southfield, MI 48075 |P 313.965.2121 | F 313.965.7680 | D 313.788.7030
dottenwess@ottenwesslaw.com | www.ottenwesslaw.com

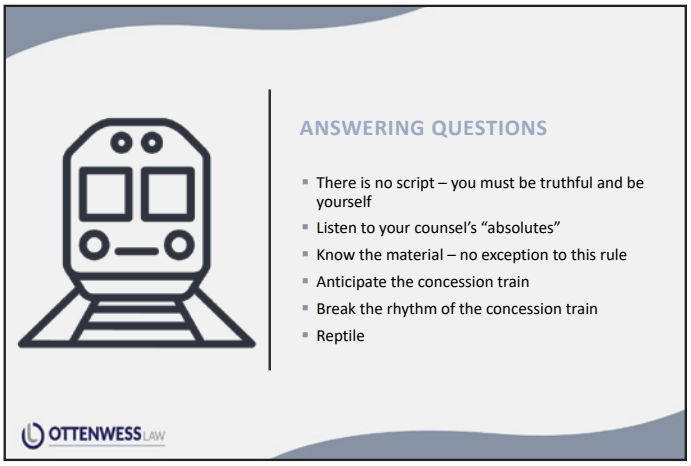
The Physician as a Witness











SELF EVALUATION

The Physician as a Witness

True/False

1. You can be forced to testify in a court proceeding only if you are named as a Defendant in a lawsuit.

2. You may ignore a subpoena served on you to testify in a court proceeding that is not your own case if your requested attendance is inconvenient for you or if you have a conflict.

3. You should always schedule your deposition testimony after a full day at work so you do not lose any income.

4. If you feel unprepared to testify in any proceeding, you should inform your counsel even if he/she tells you “don’t worry about it – you will be fine.”

5. Through your superior medical knowledge, you should make every effort to out-maneuver opposing counsel at deposition so you may achieve a quick and early dismissal.

Answer Key: 1. F, 2. F, 3. F, 4. T, 5. F

Cullen Ruff, MD, FACR

Cullen Ruff, MD, FACR, of Fairfax, VA is a board-certified radiologist and published author of the Amazon best-selling book *Looking Within: Understanding Ourselves Through Human Imaging*. He is in private practice with Fairfax Radiology Centers and is an associate professor of medical education at the University of Virginia. Dr. Ruff has authored numerous publications and articles in his field, and is the recipient of several teaching awards.

You may contact Dr. Ruff with your questions or comments by email at cullen.ruff@frcpc.org.

Cullen Ruff, MD
Associate Professor of Radiology
Virginia Commonwealth University School of Medicine
Fairfax, VA

Chest X-ray Case Review

Question

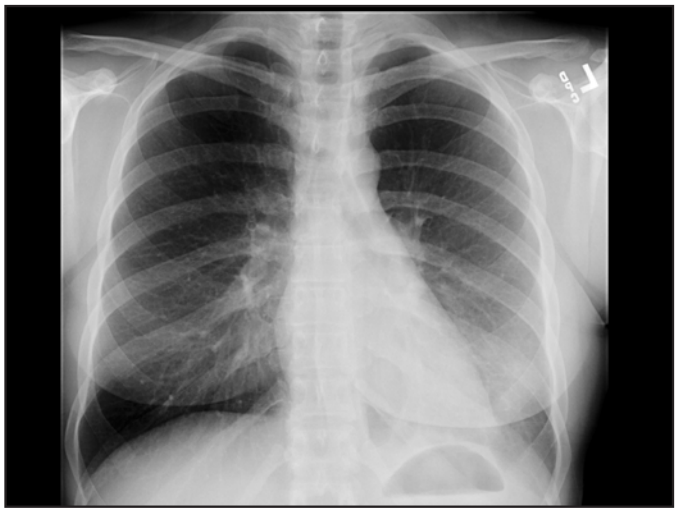
The average chest CT uses the radiation of how many CXR?

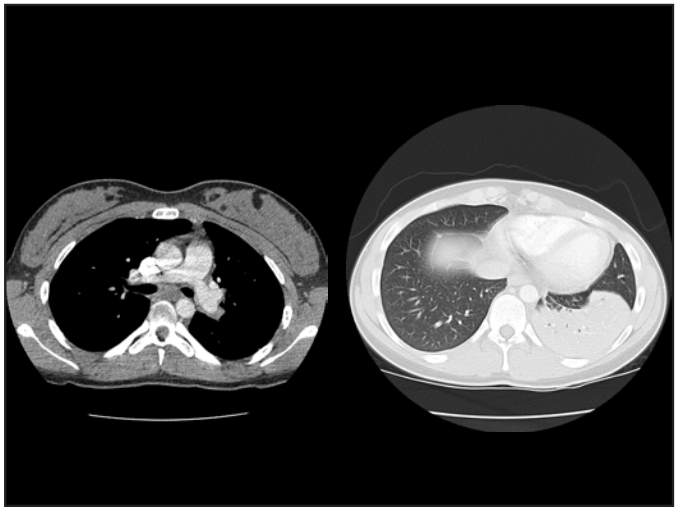
A. 5-20
B. 20-50
C. 50-150
D. 150-400

Question

The average chest CT uses the radiation of how many CXR?

A. 5-20
B. 20-50
C. 50-150
D. 150-400



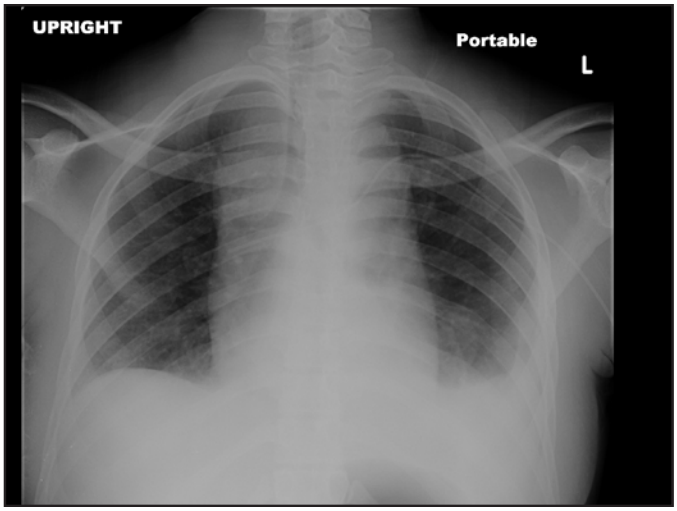


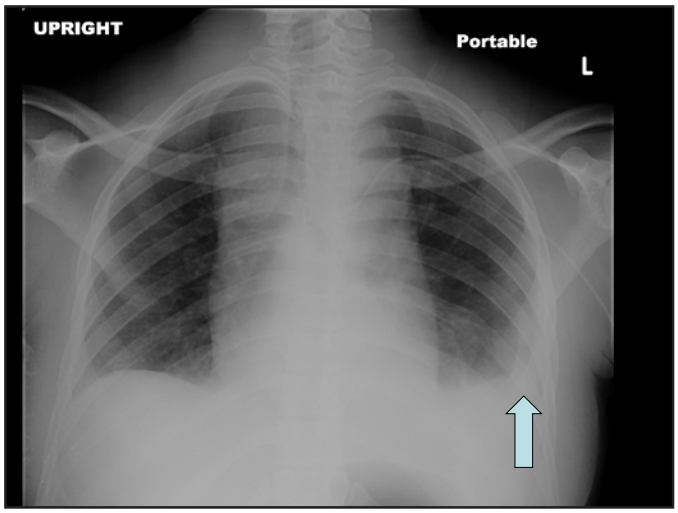
"Hidden" areas on CXR

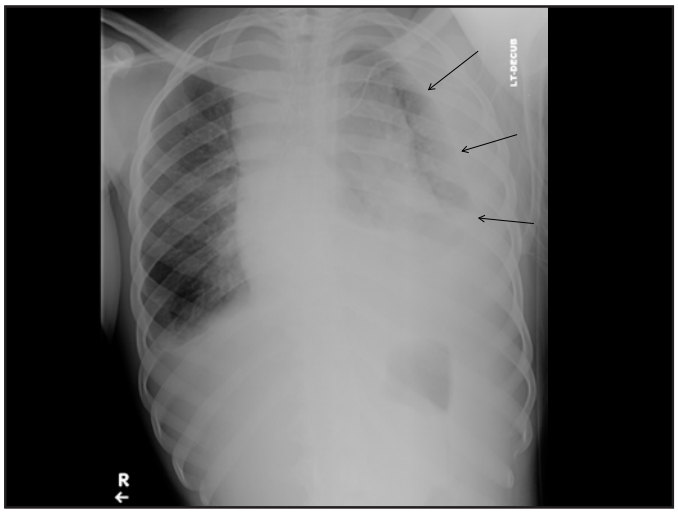
- Retrocardiac
- Apices
- Costophrenic sulci (lat. and post.)
- Hila, mediastinum

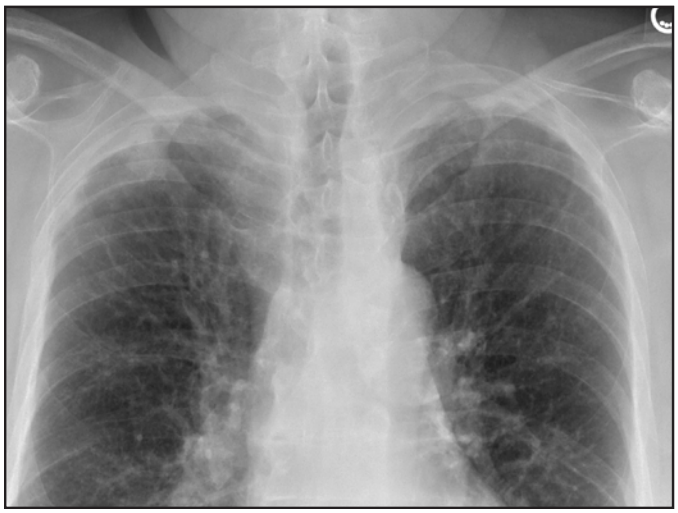
CXR Views

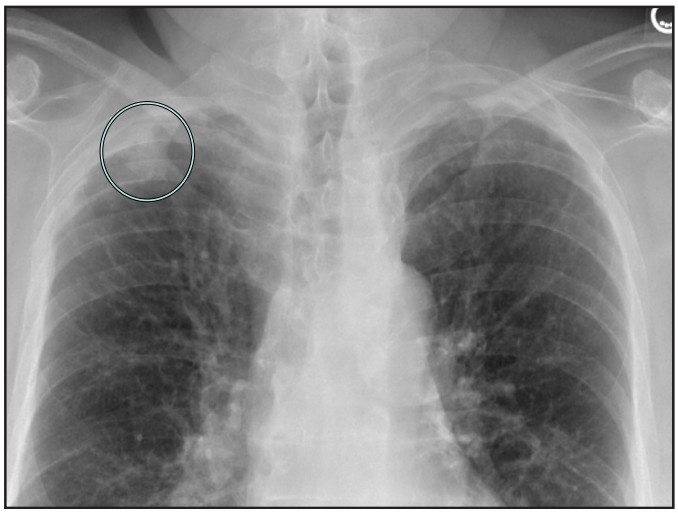
- PA
- AP (portable, supine, upright)
- Lateral
- Decubitus
- Apical lordotic
- Oblique
- Nipple markers

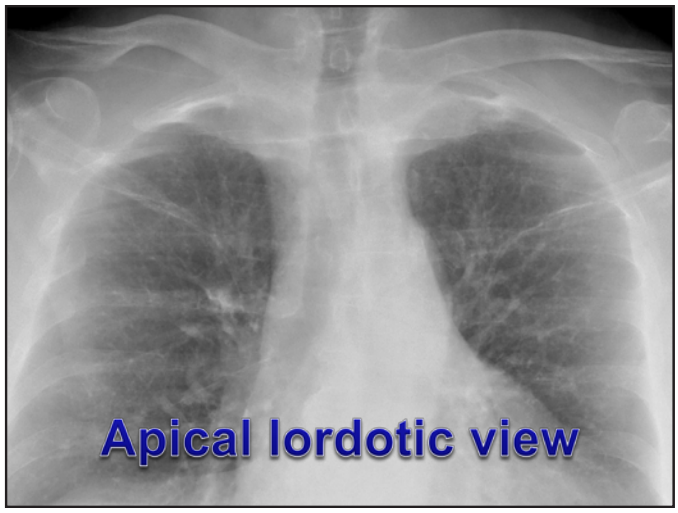


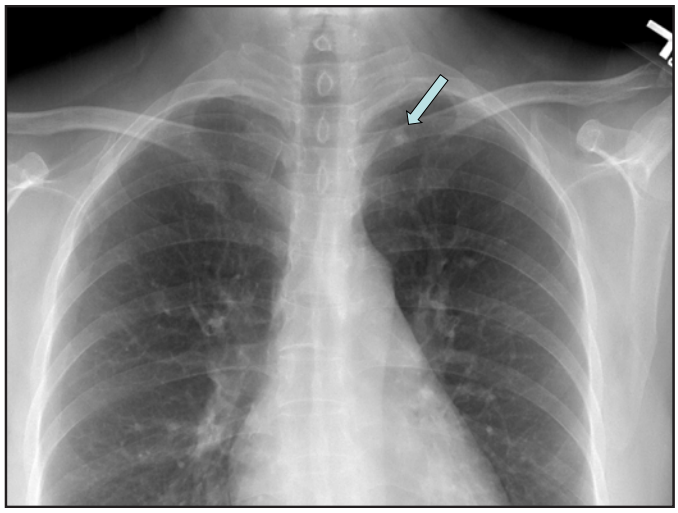


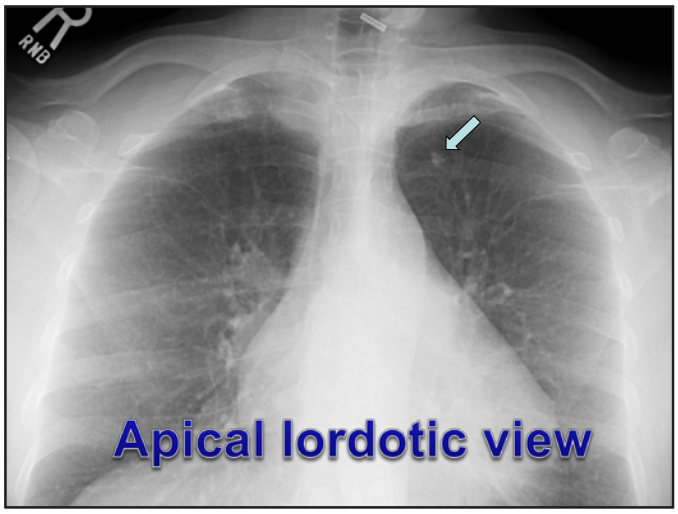


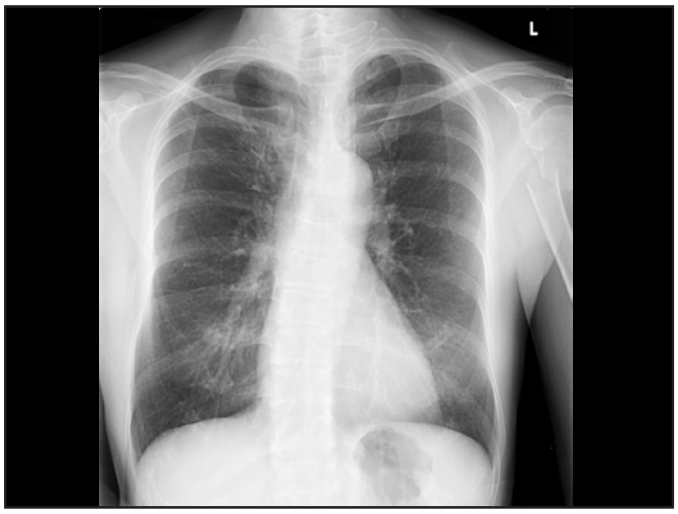


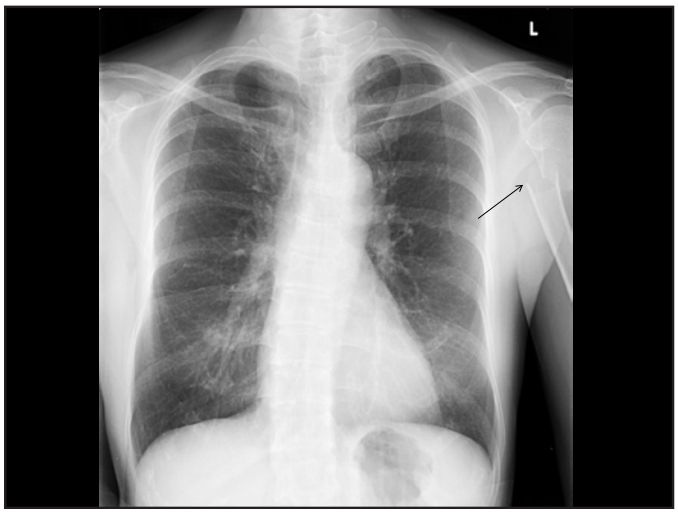


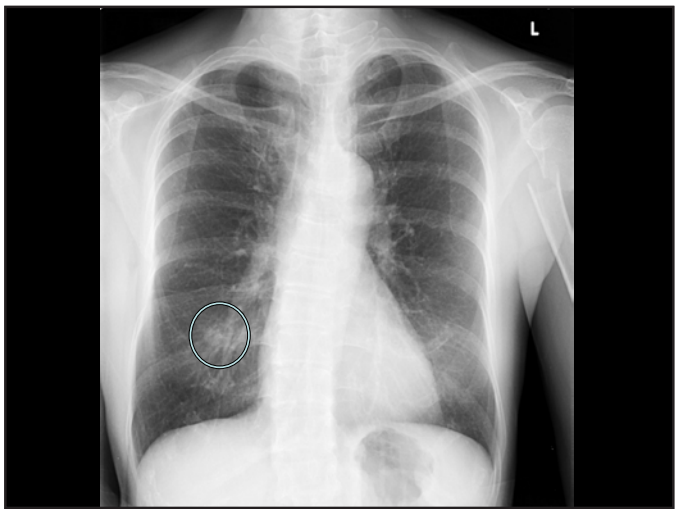

Apical lordotic view

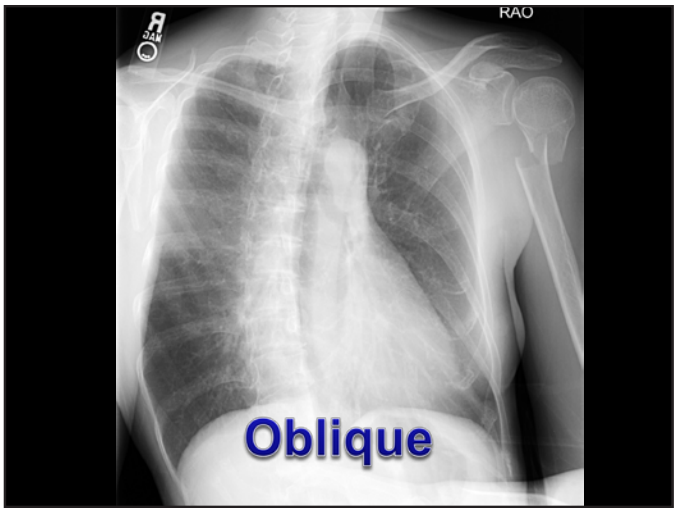


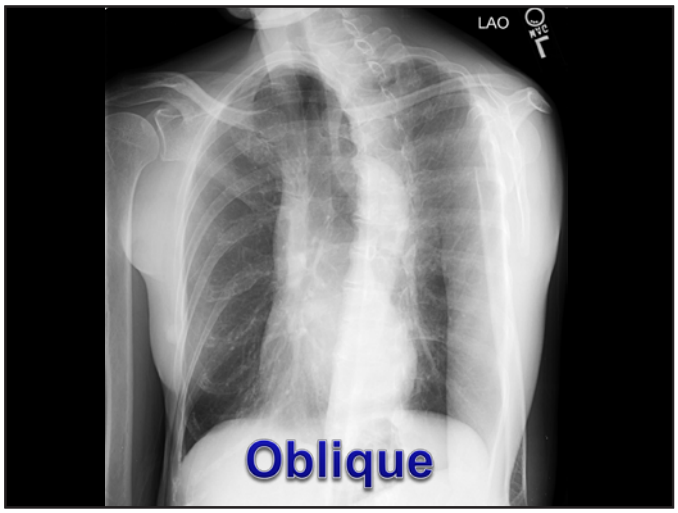

R
RND
Apical lordotic view

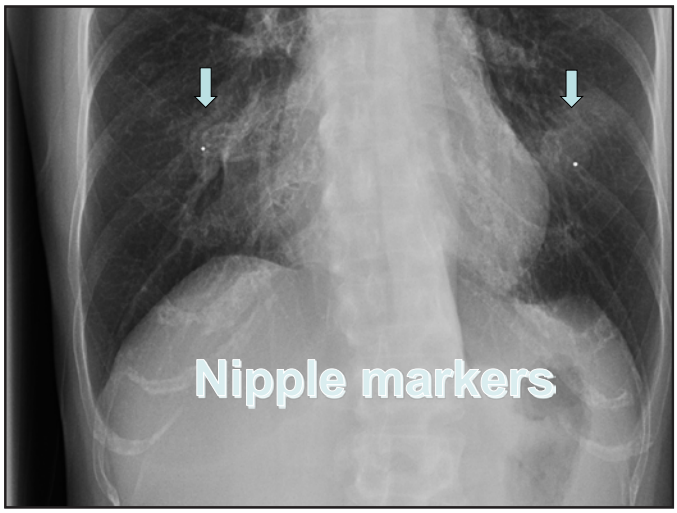

L


L


L

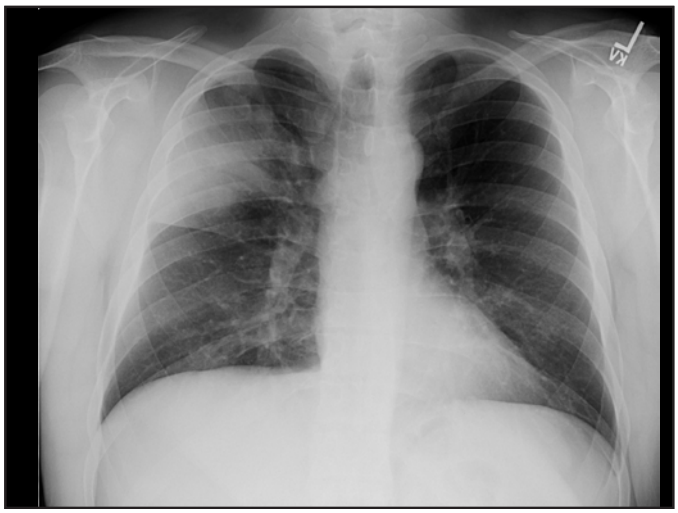


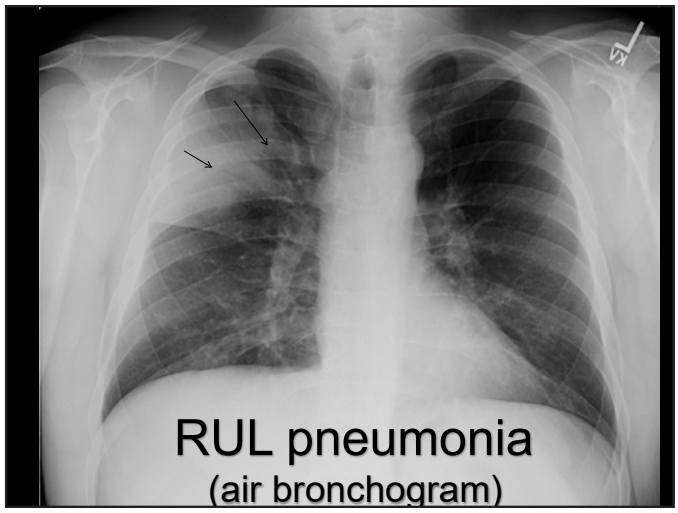


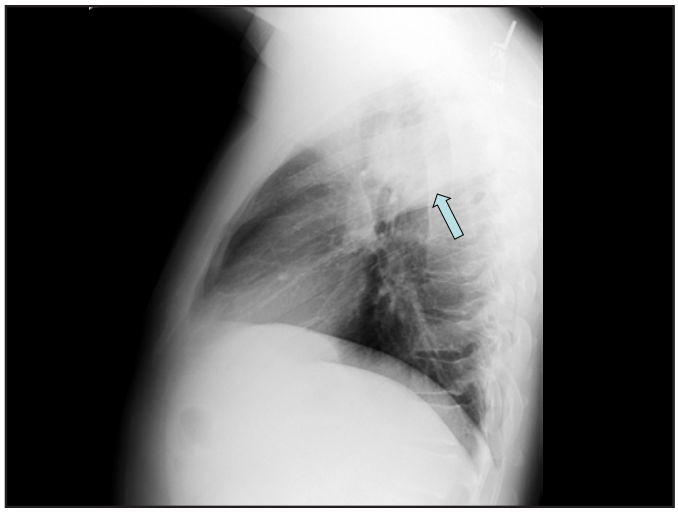


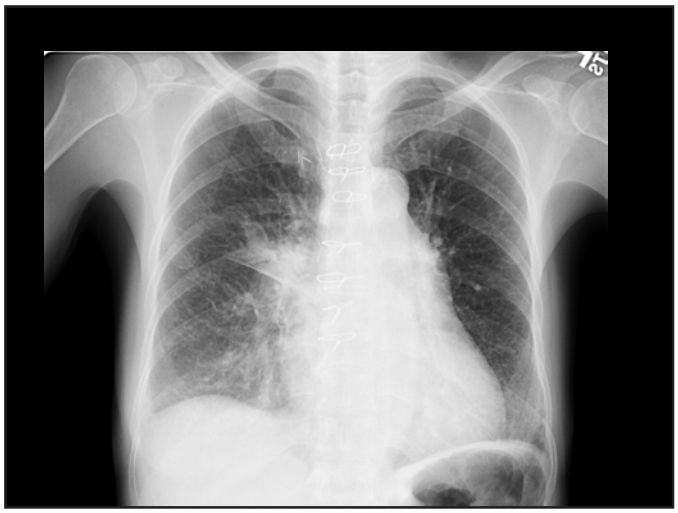
Pneumonia

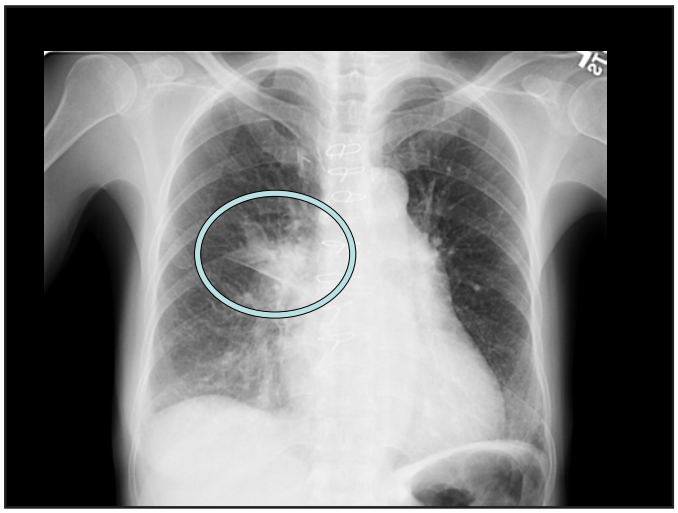
- Bacterial
- Mycobacterial
- Viral
- Miscellaneous
- ARDS

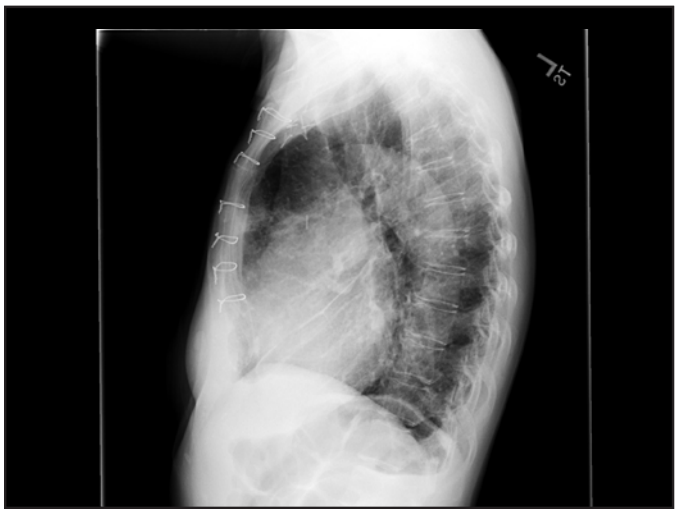


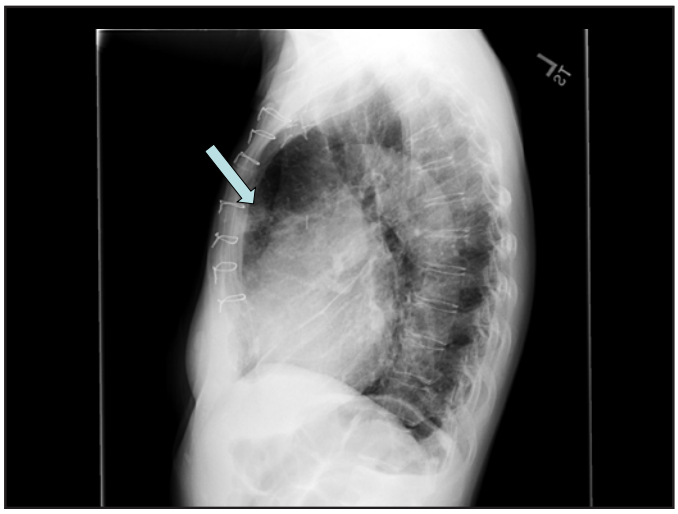

RUL pneumonia
(air bronchogram)

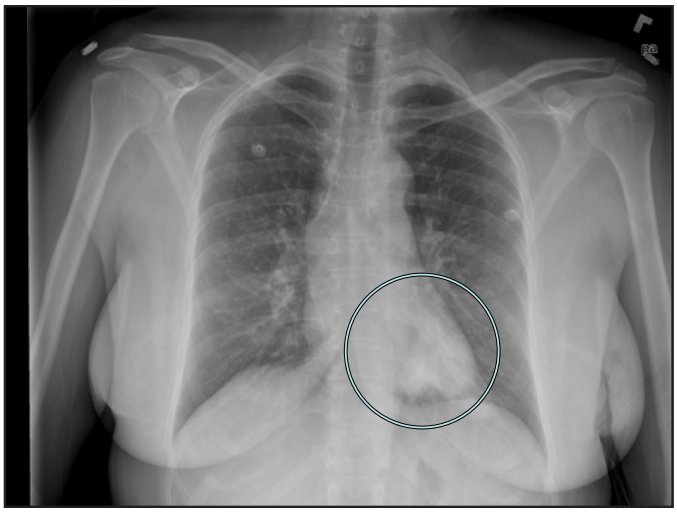


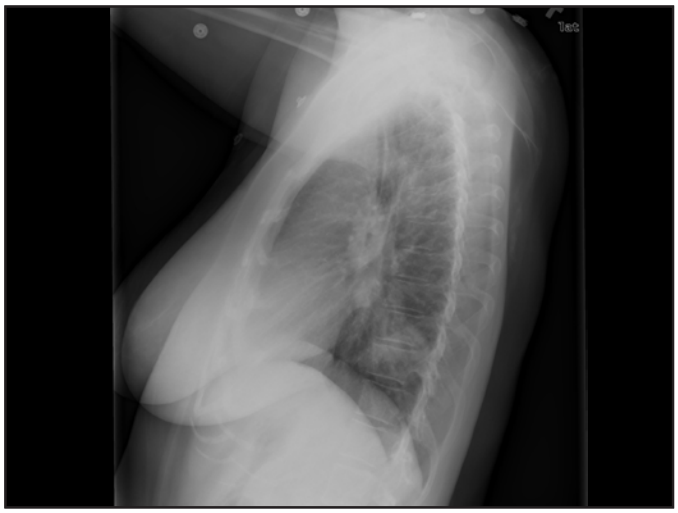


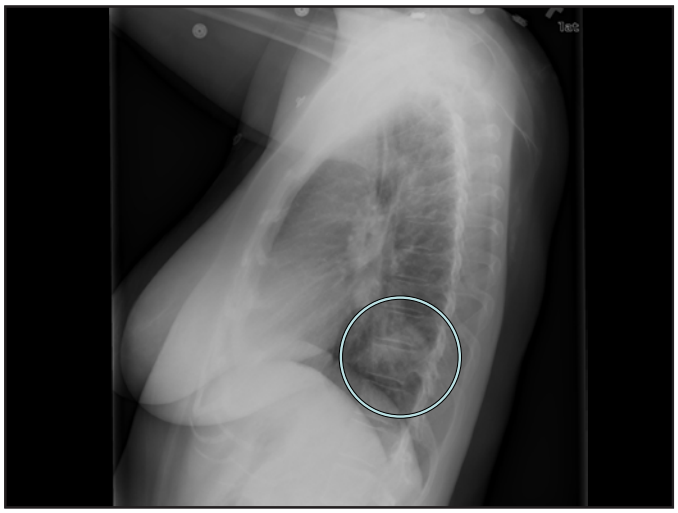


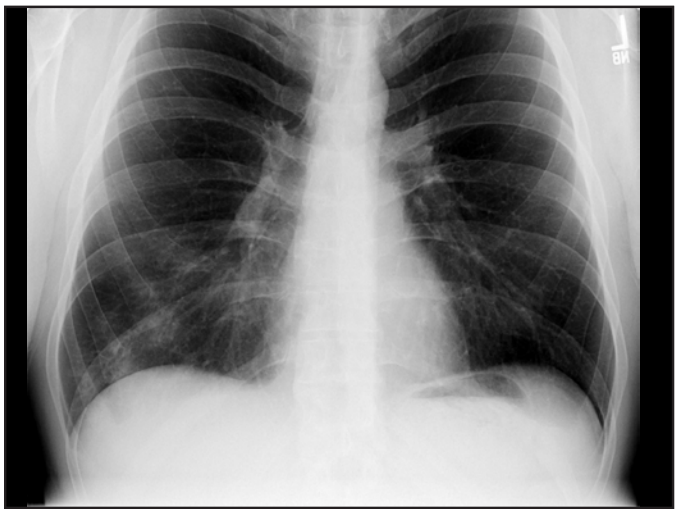


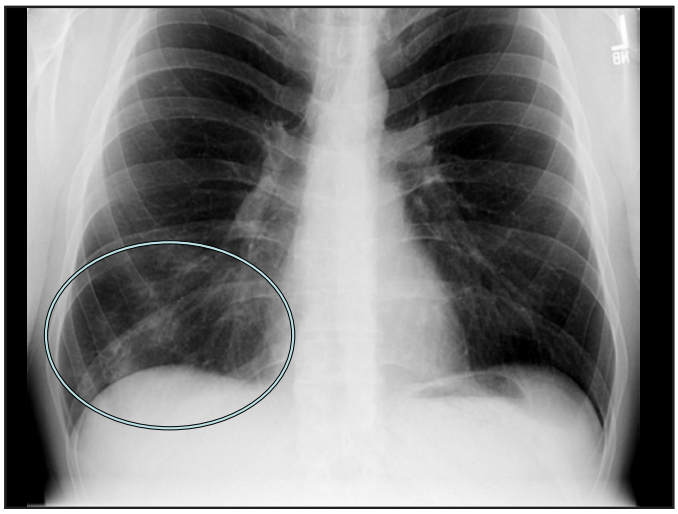


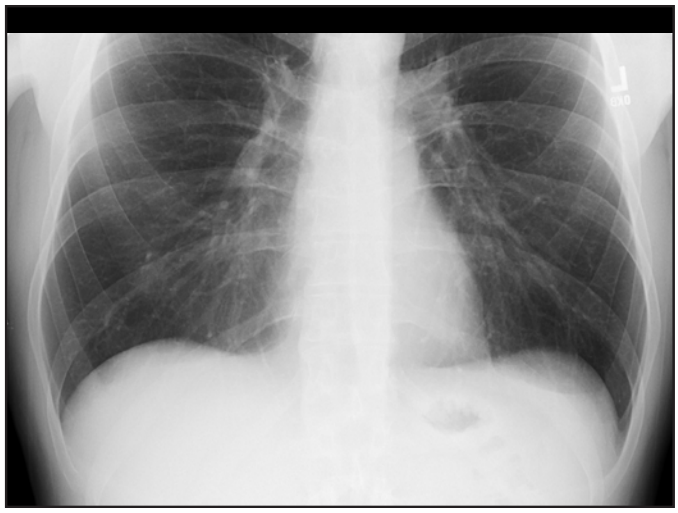


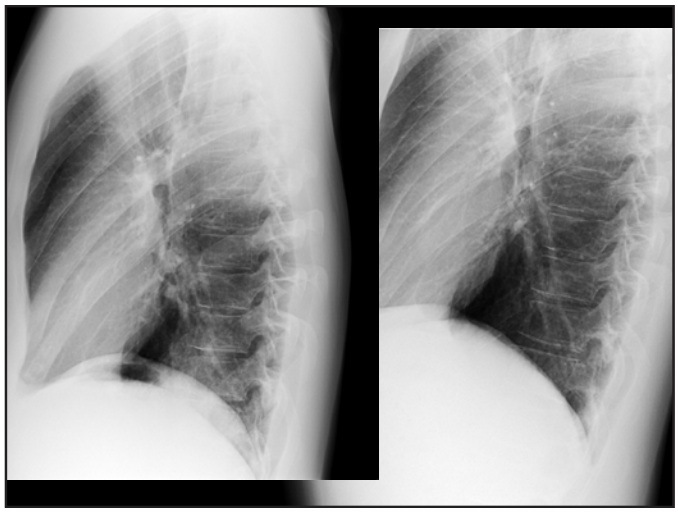


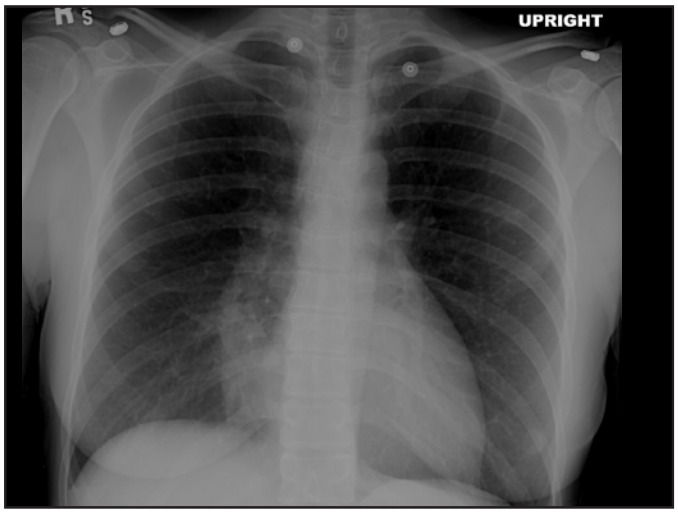


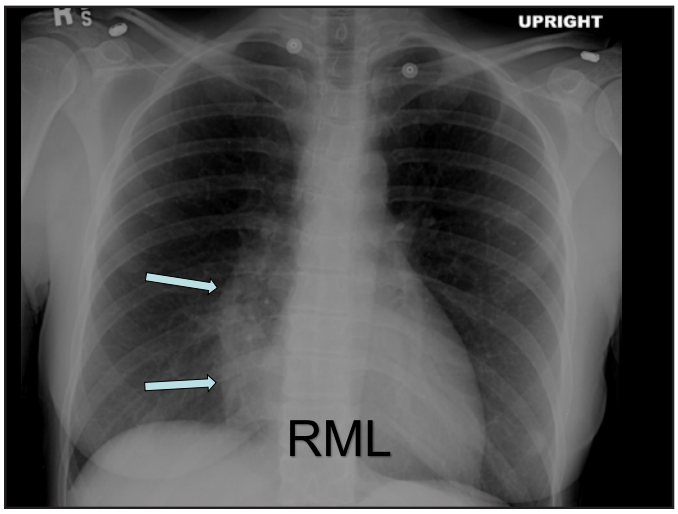


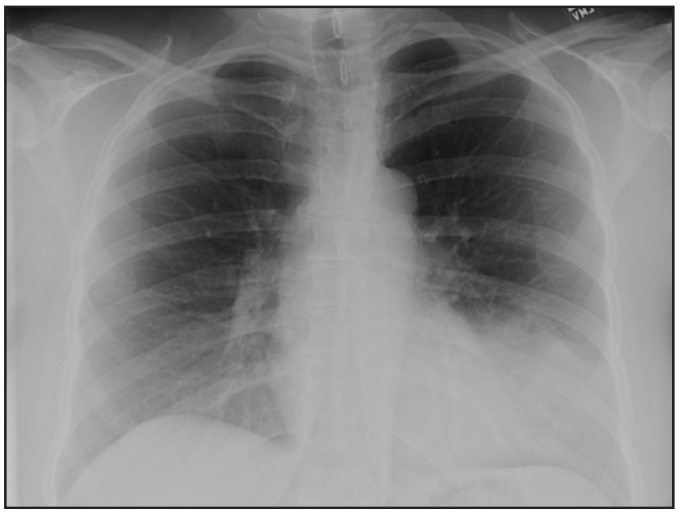


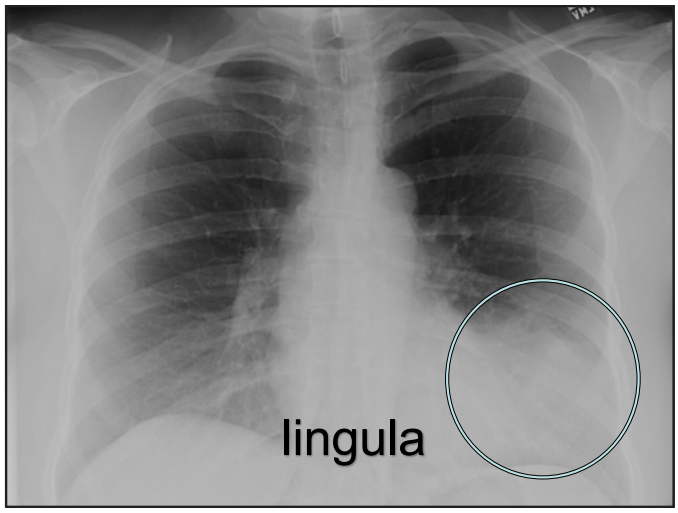


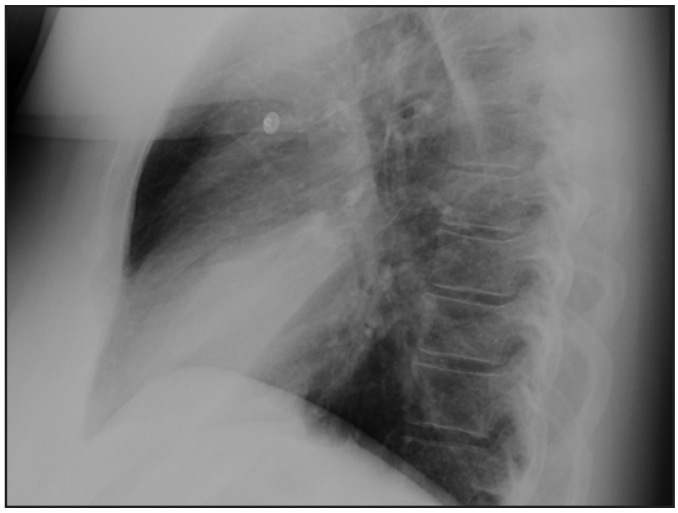


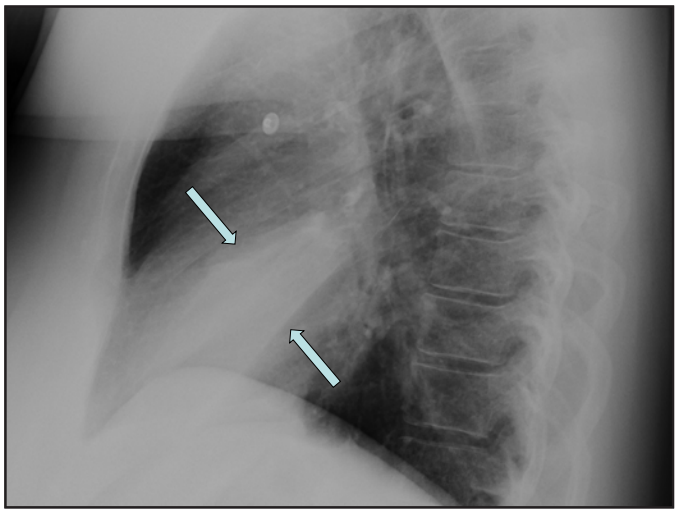

UPRIGHT

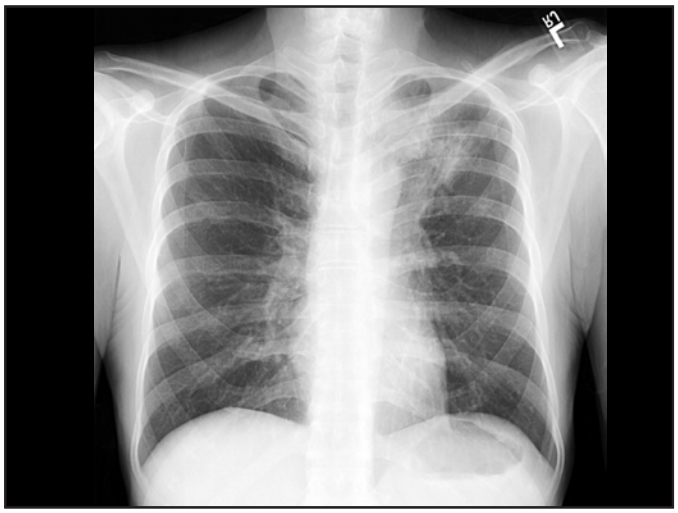

UPRIGHT
RML

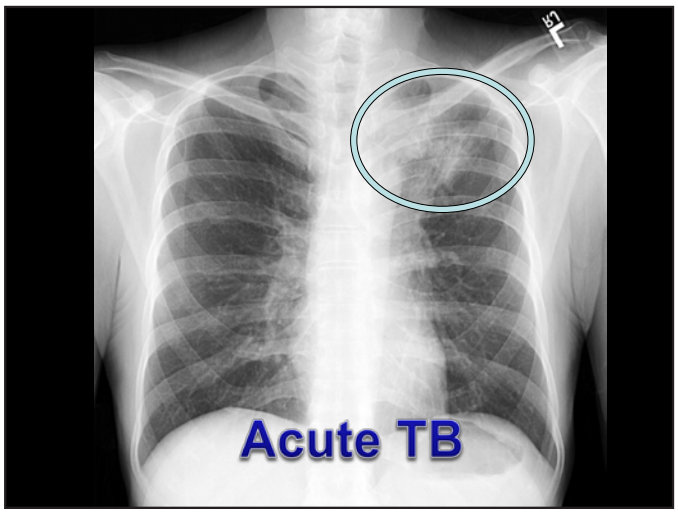


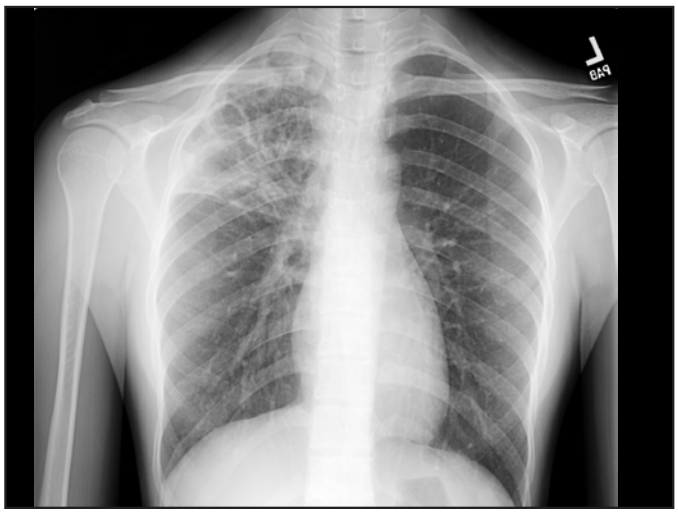

lingula

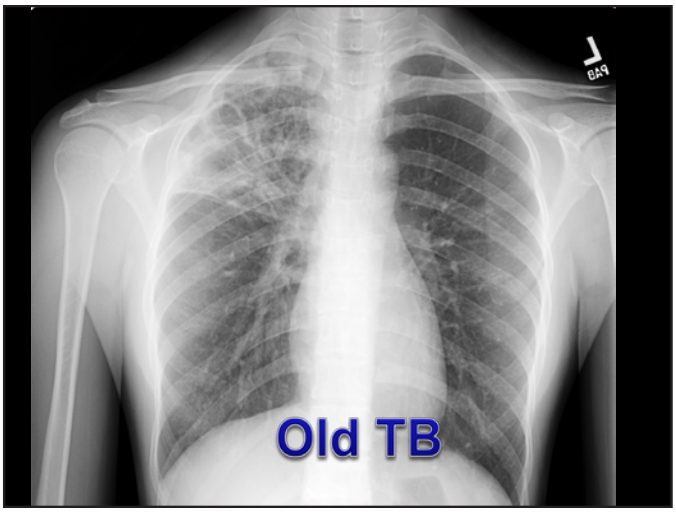


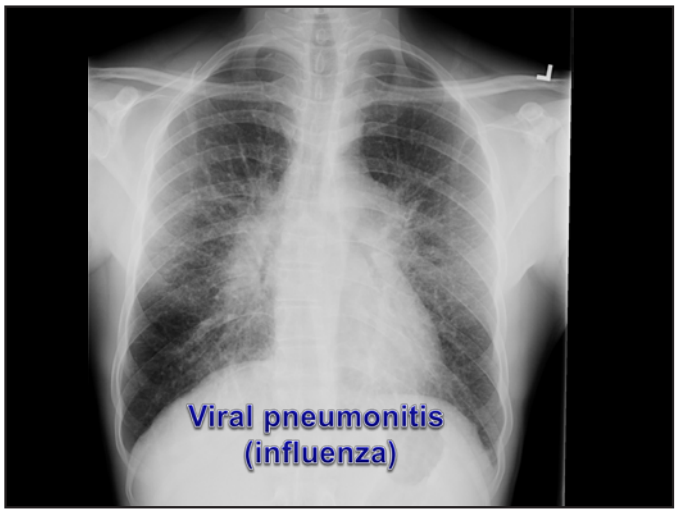


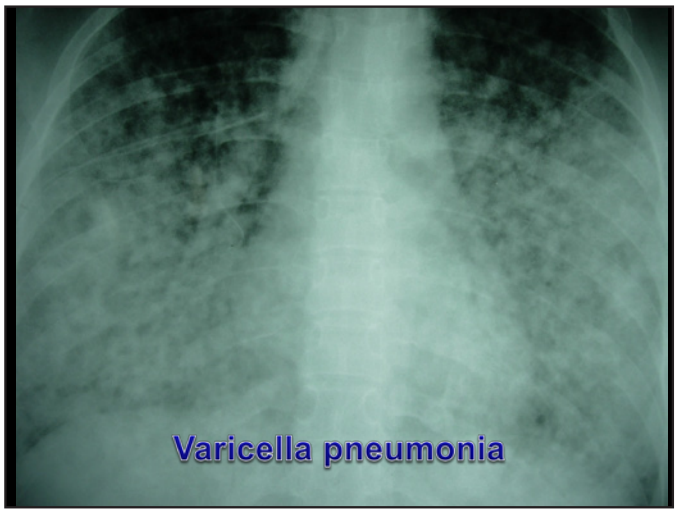


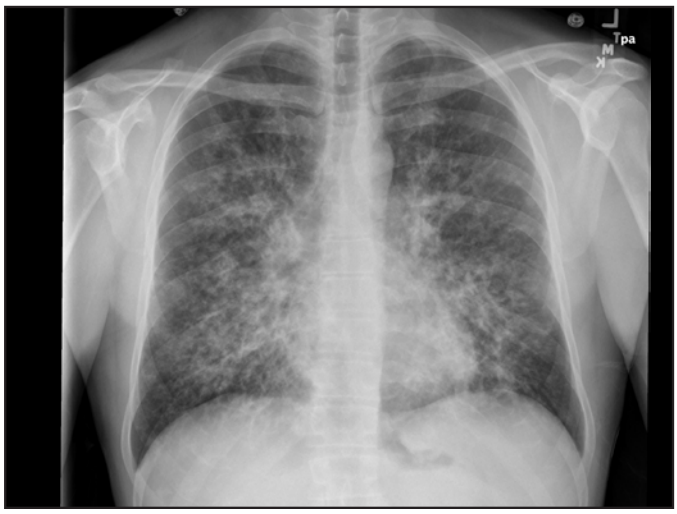

Acute TB

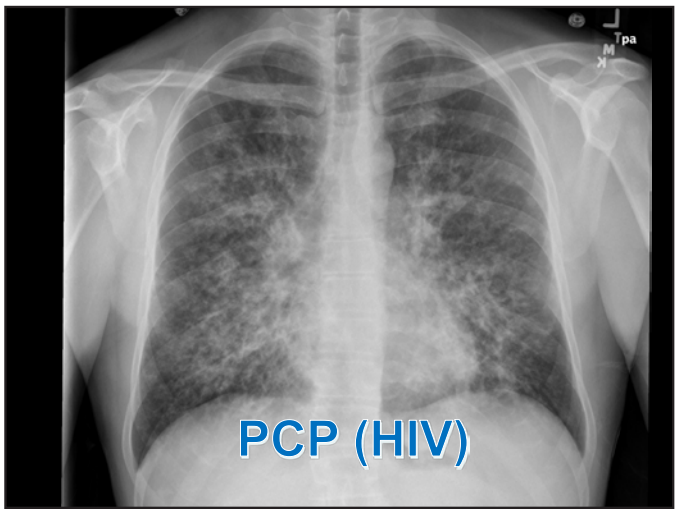


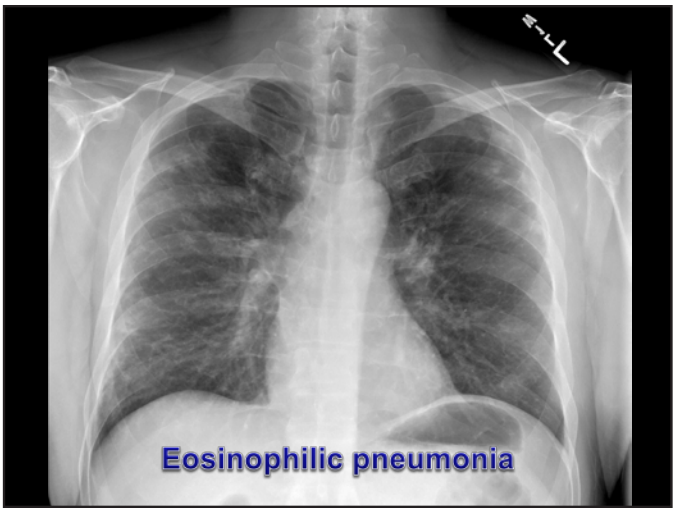

Old TB

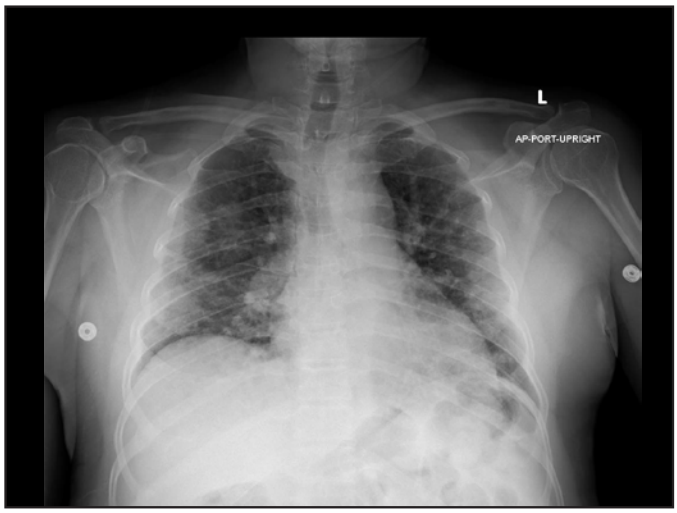

Viral pneumonitis
(influenza)

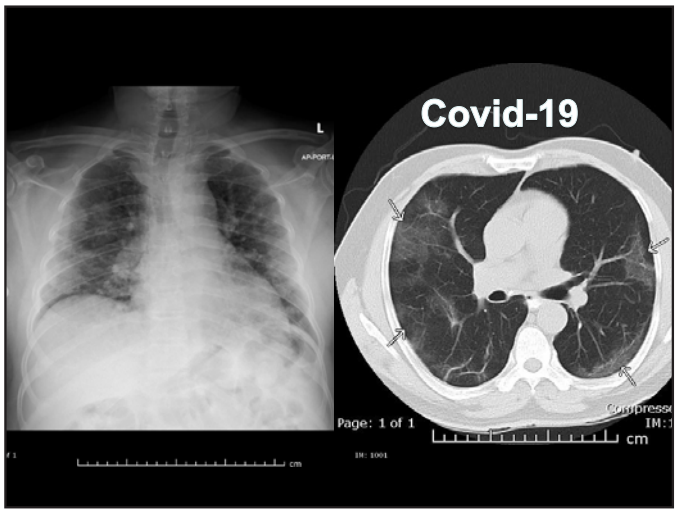

Varicella pneumonia

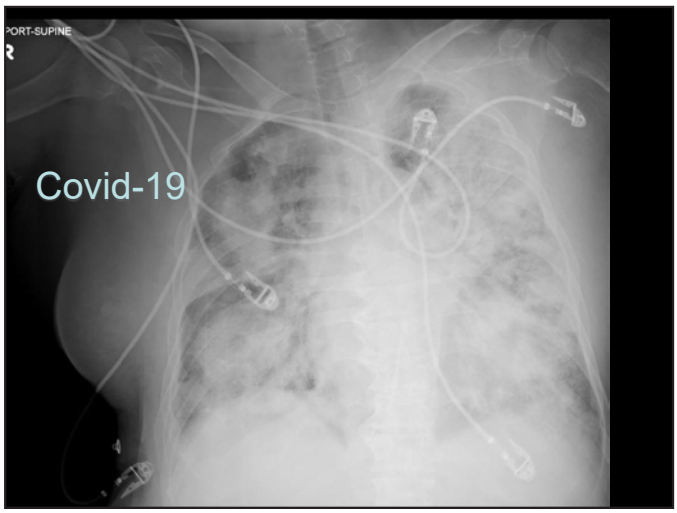


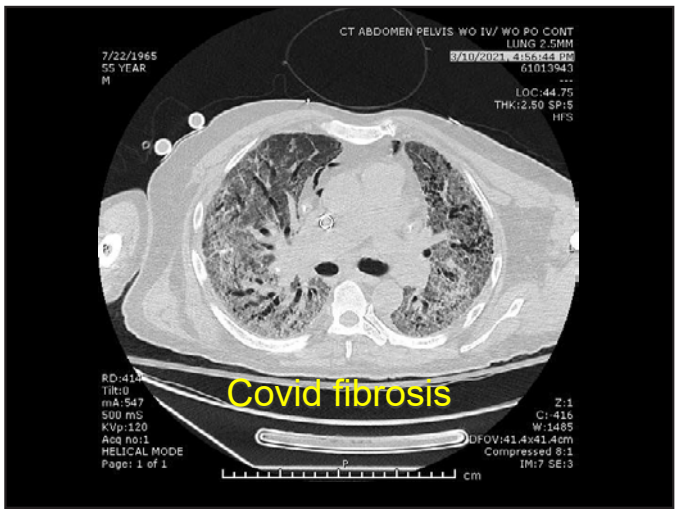

PCP (HIV)

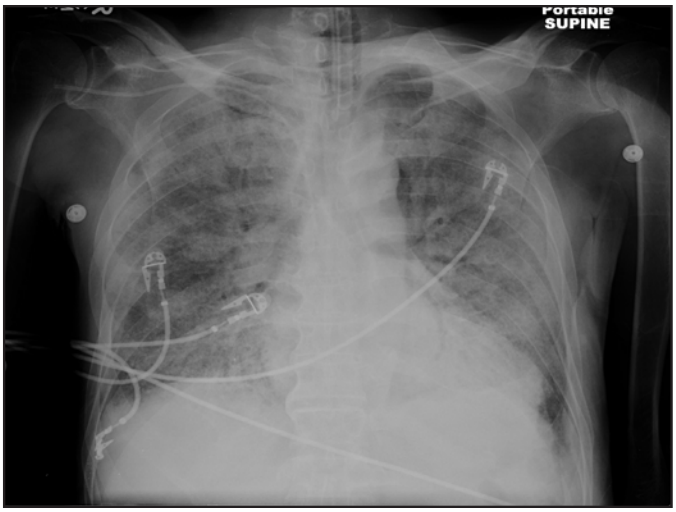

Eosinophilic pneumonia

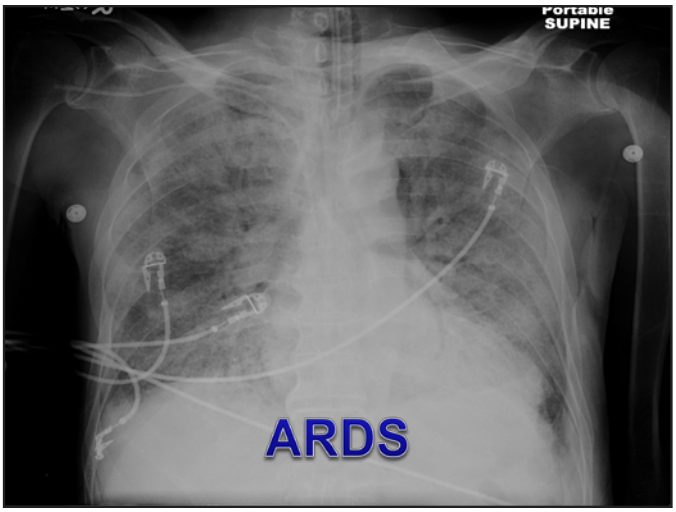

L
AP-PORT-UPRIGHT


Covid-19
Page: 1 of 1
cm

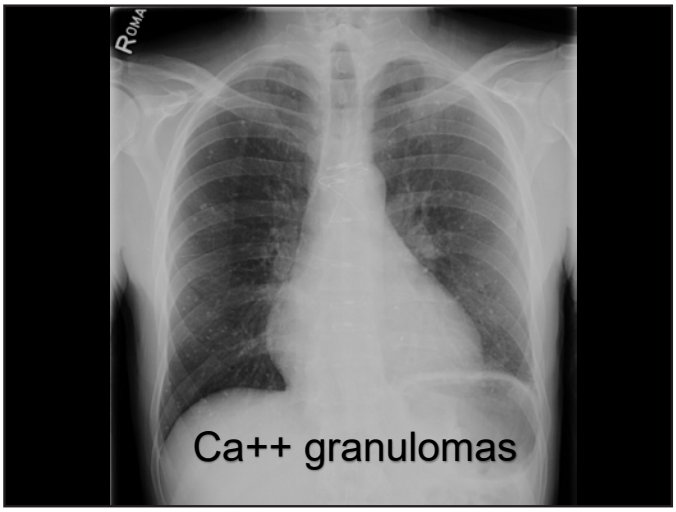

Covid-19

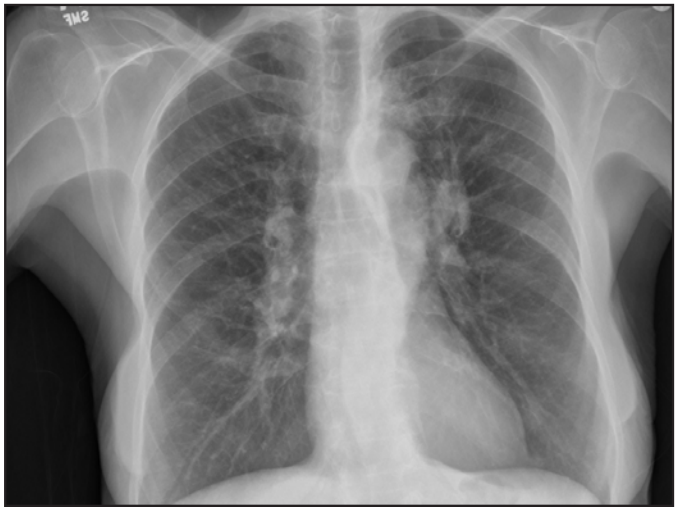

CT ABDOMEN PELVIS WO IV/ WO PO CONT
LUNG 2.5MM
7/22/1965
55 YEAR
M
Covid fibrosis
cm

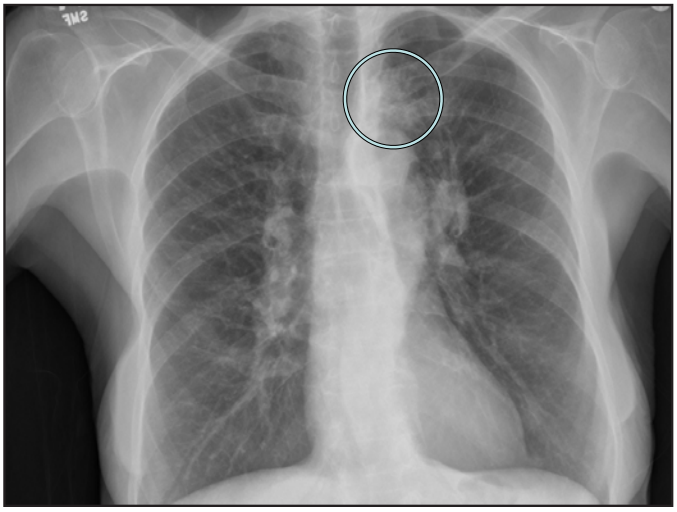


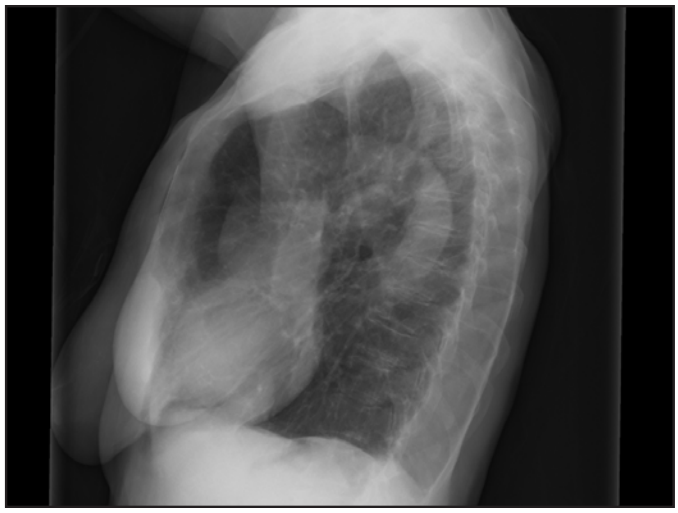


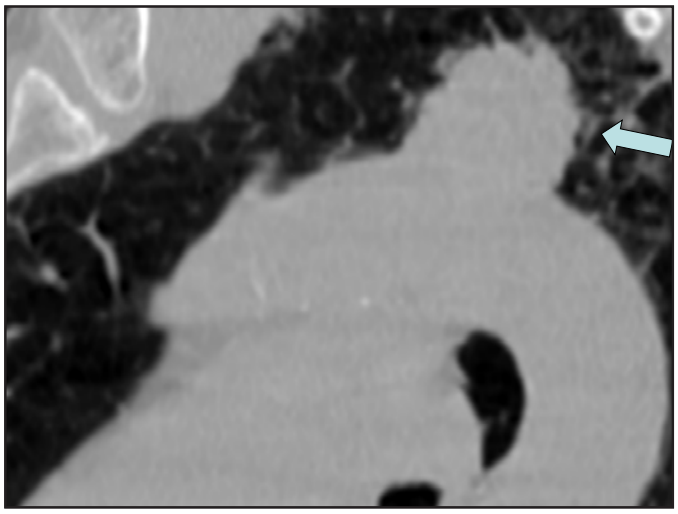
Lung Nodules

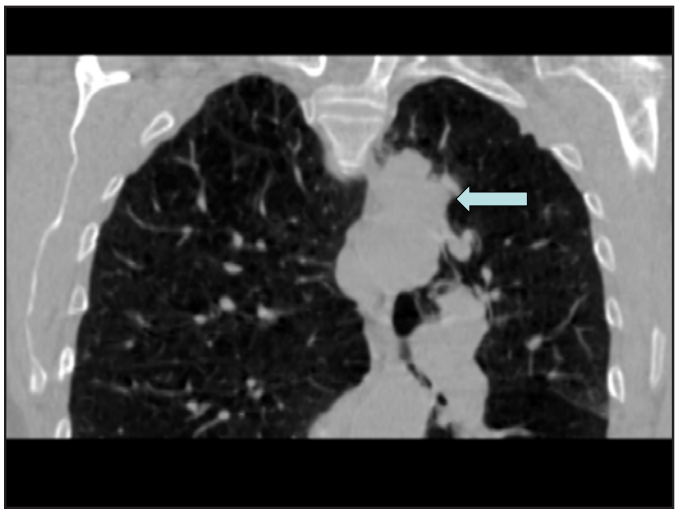


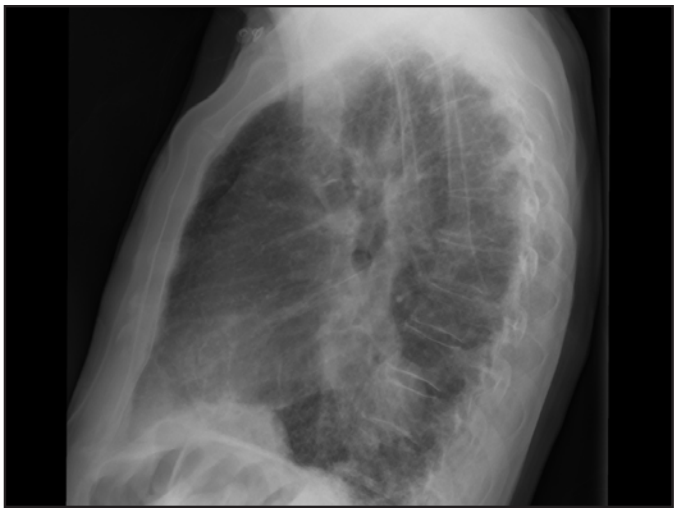


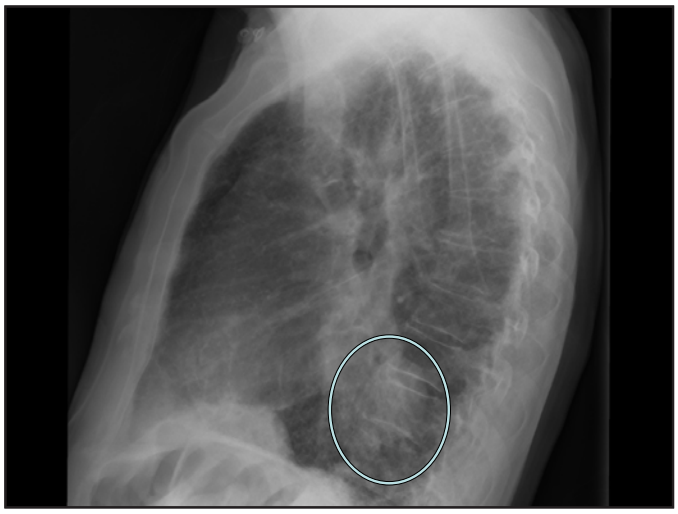


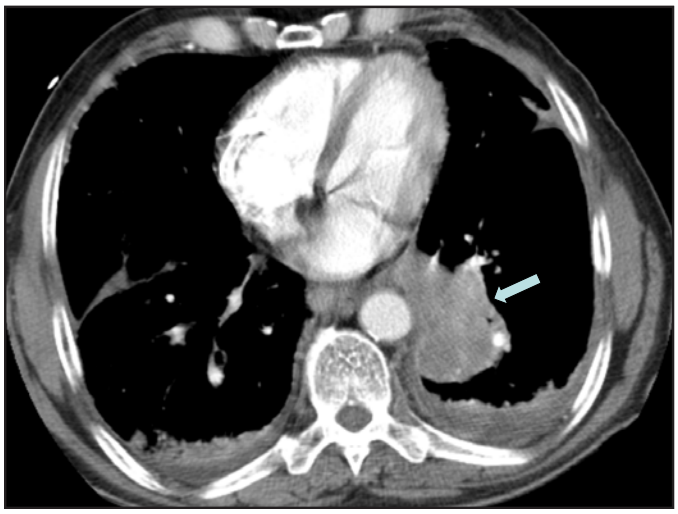


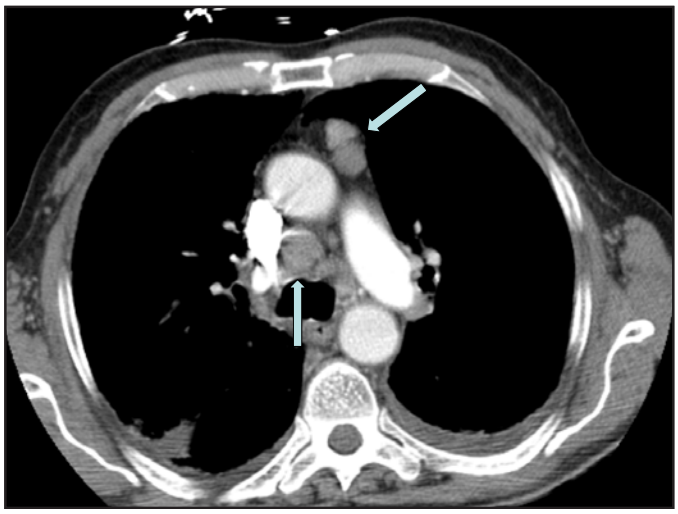


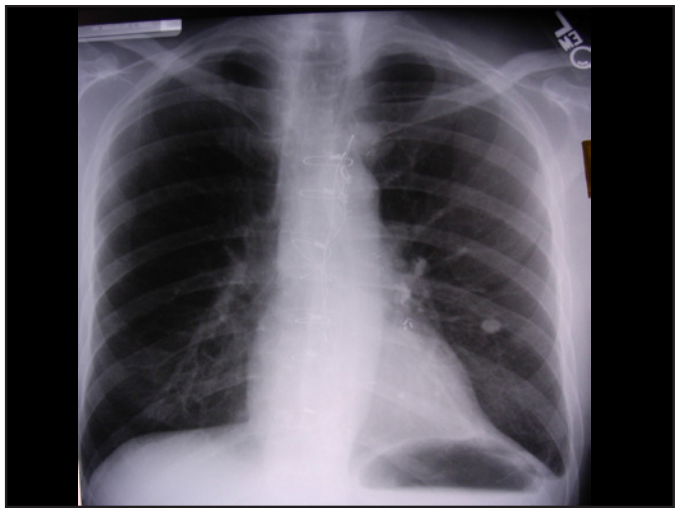


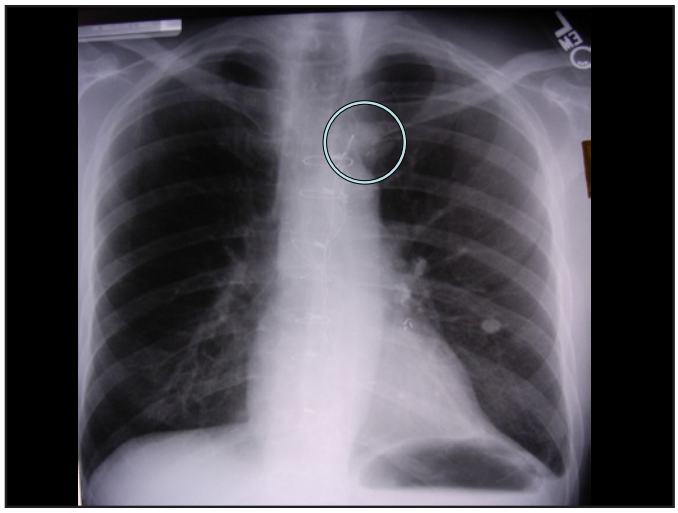


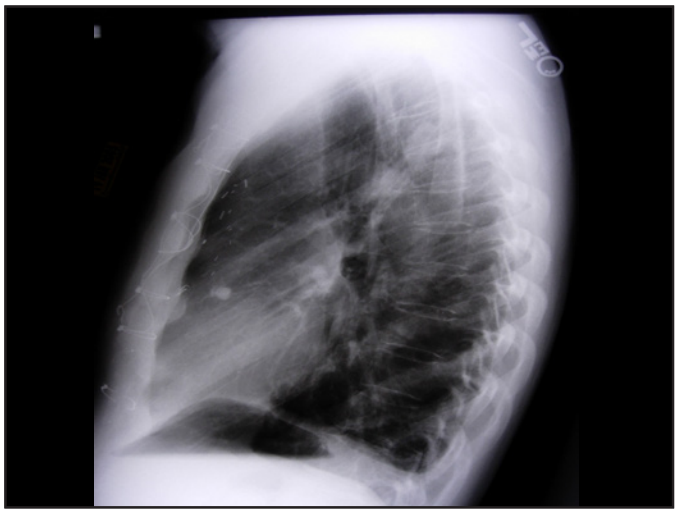


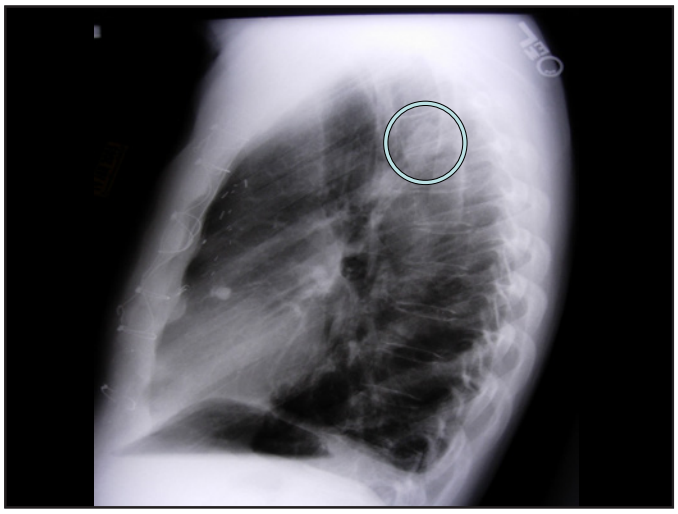


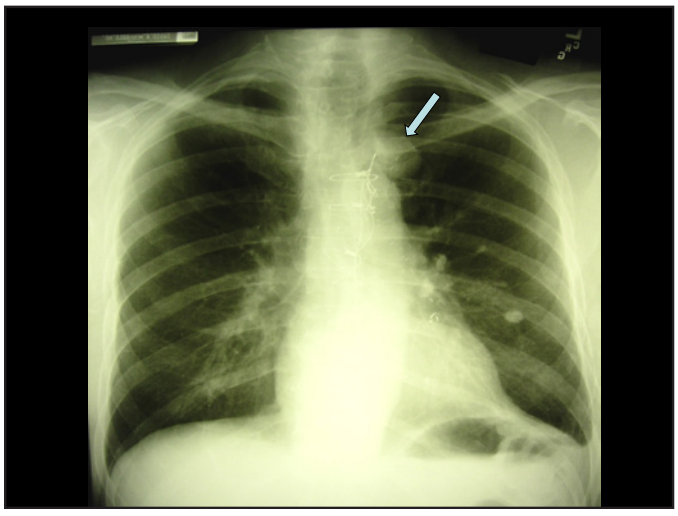


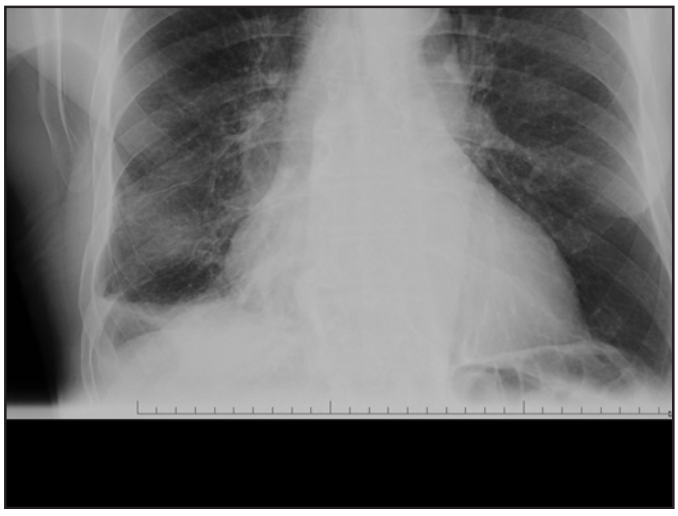


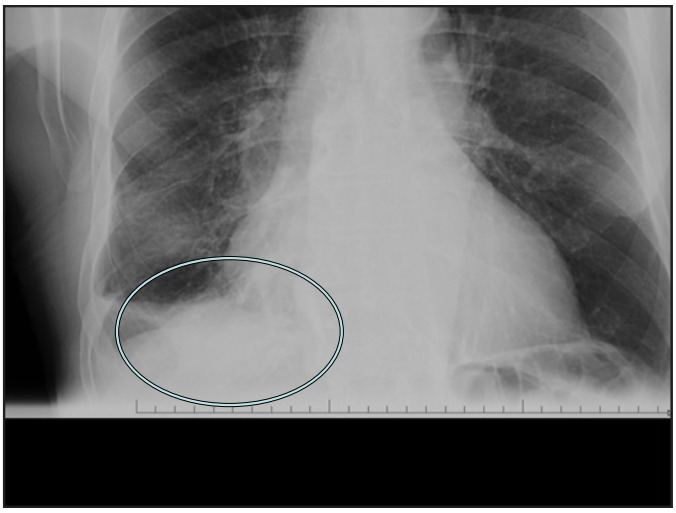


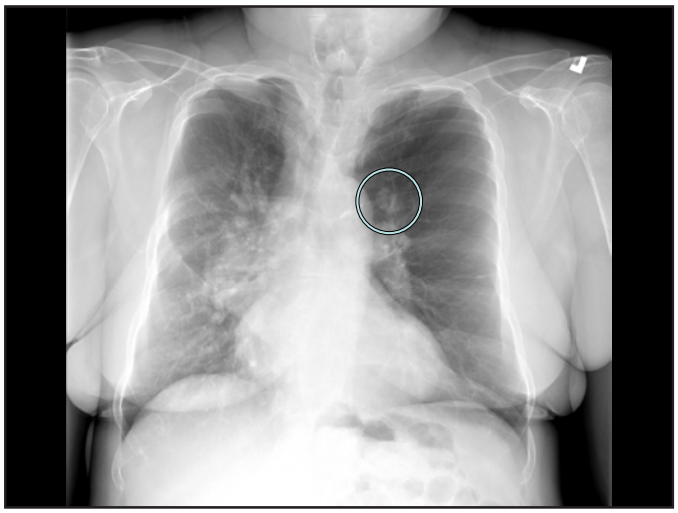


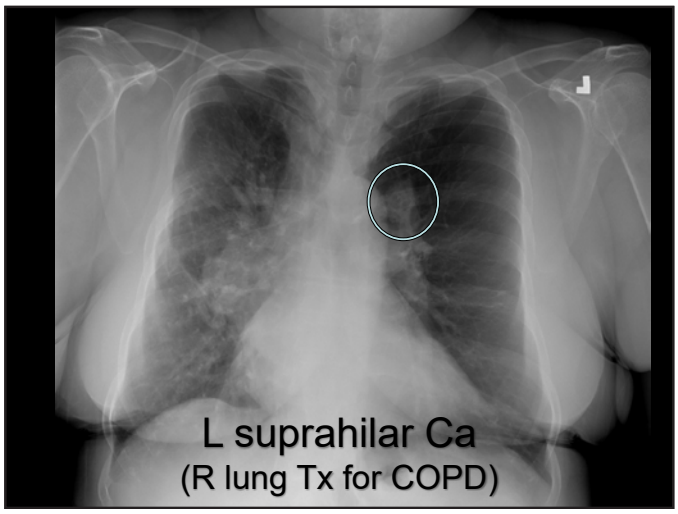


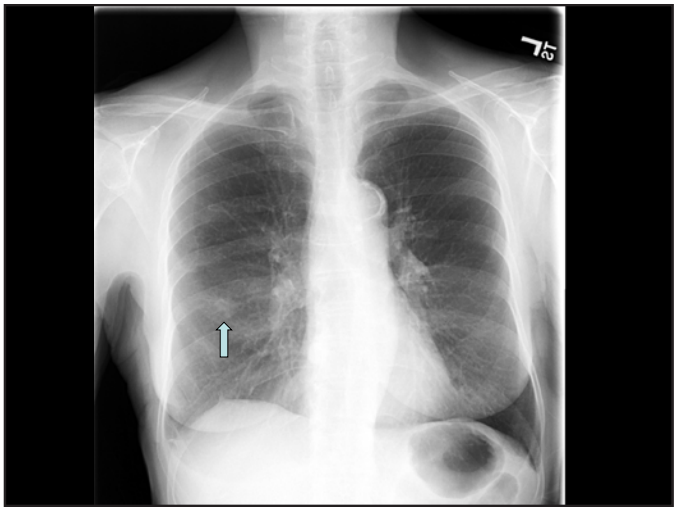


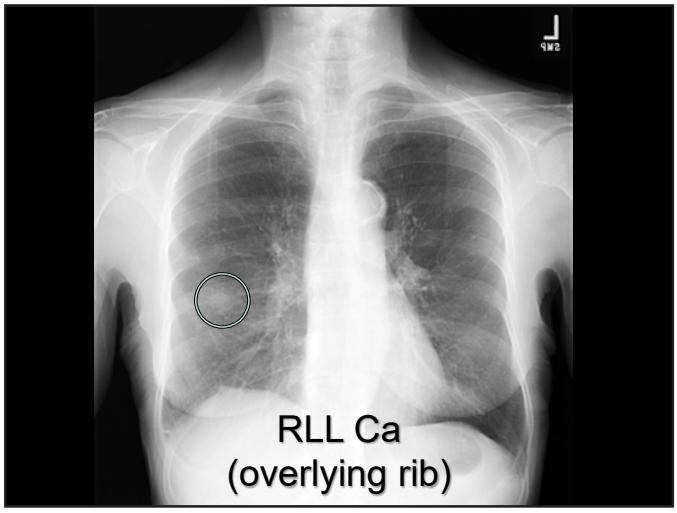


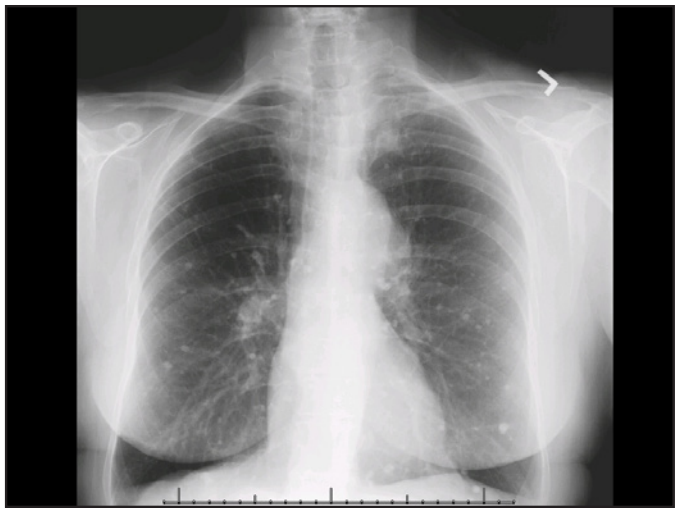


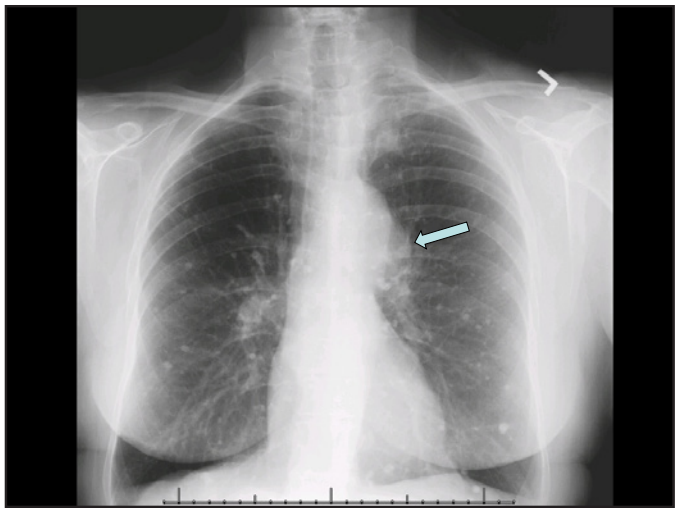


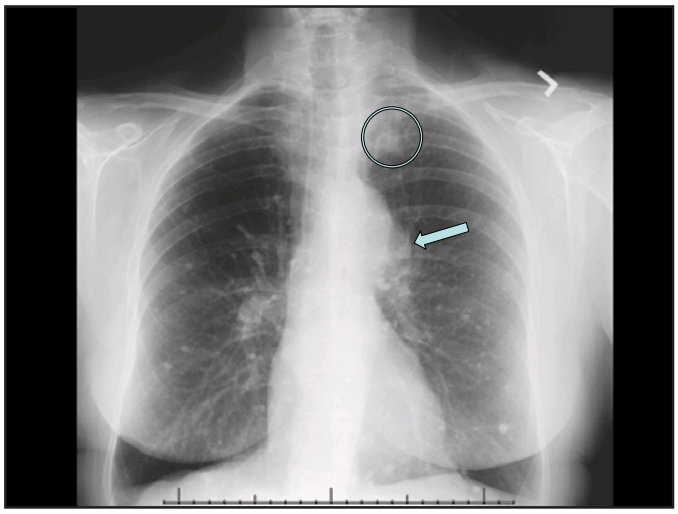

L suprahilar Ca
(R lung Tx for COPD)

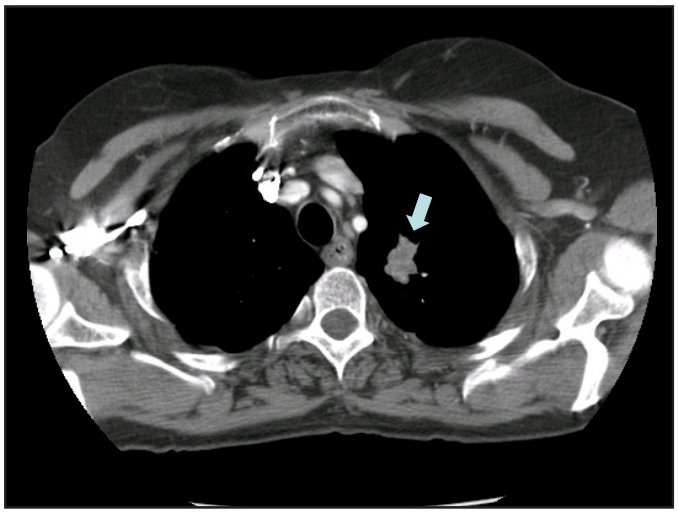


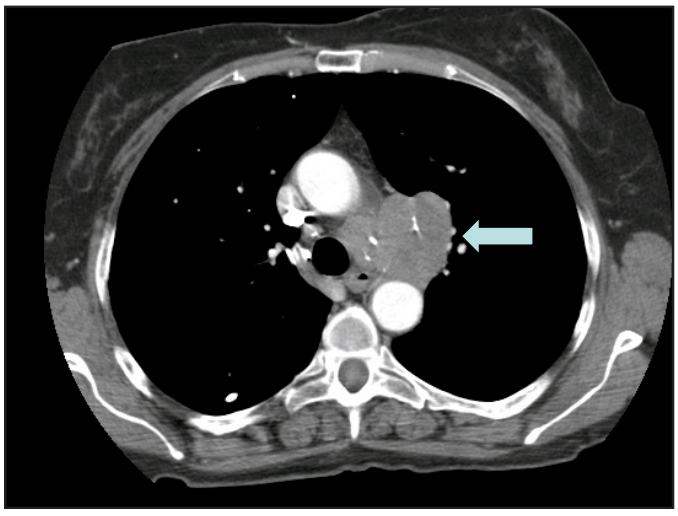

RLL Ca
(overlying rib)

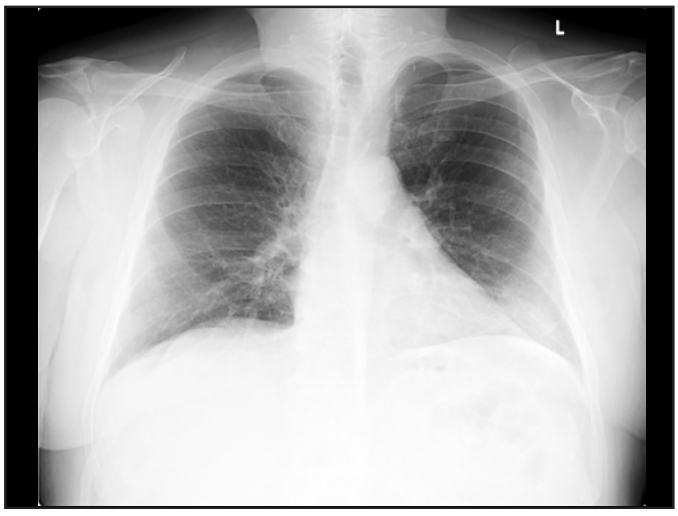


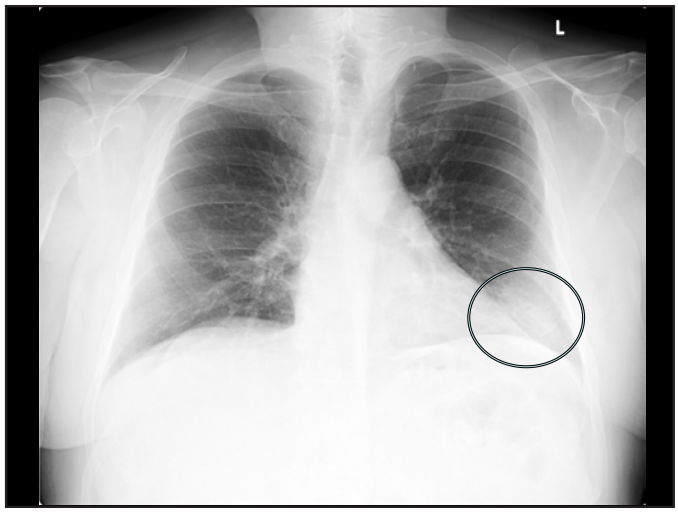


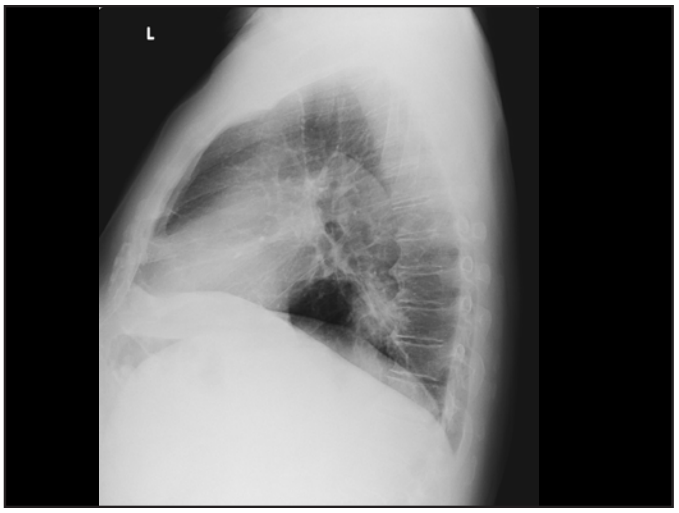


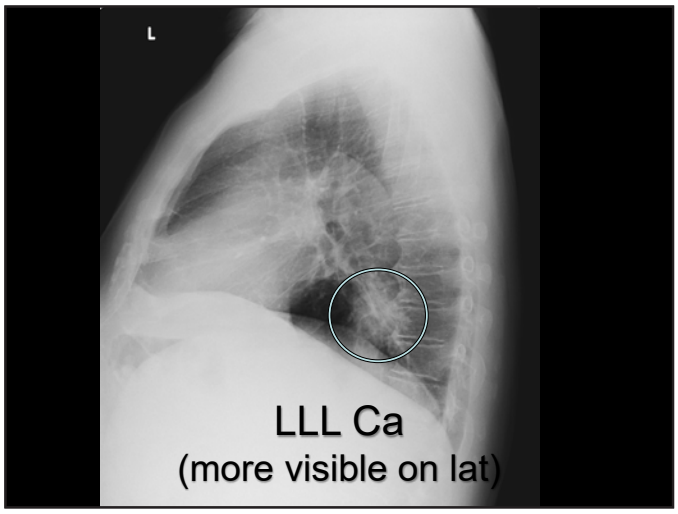


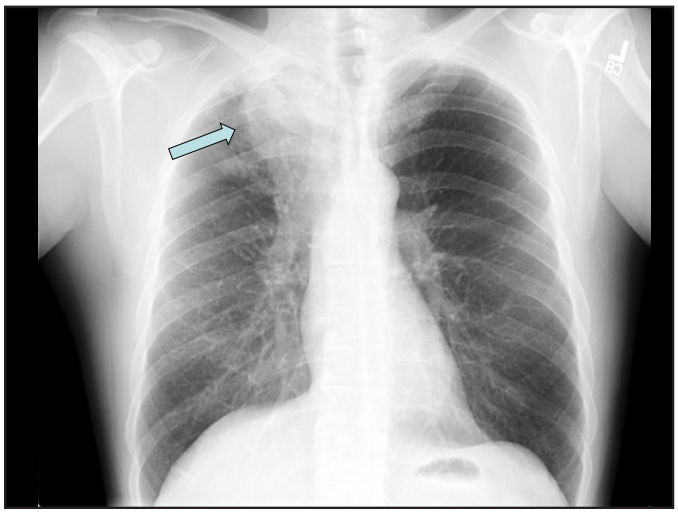


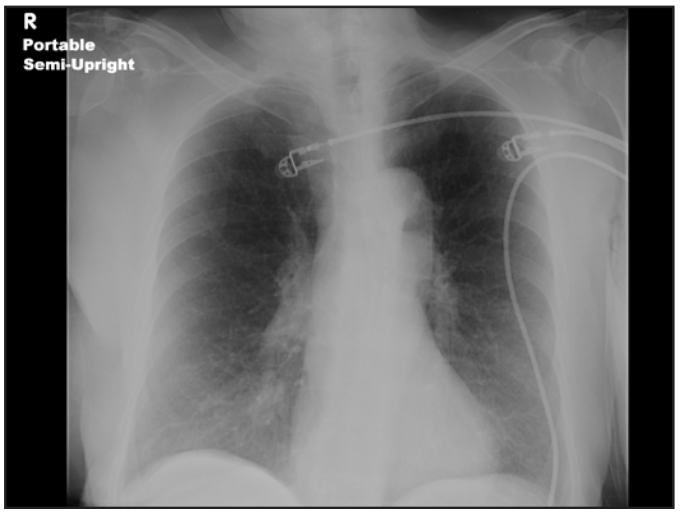

L

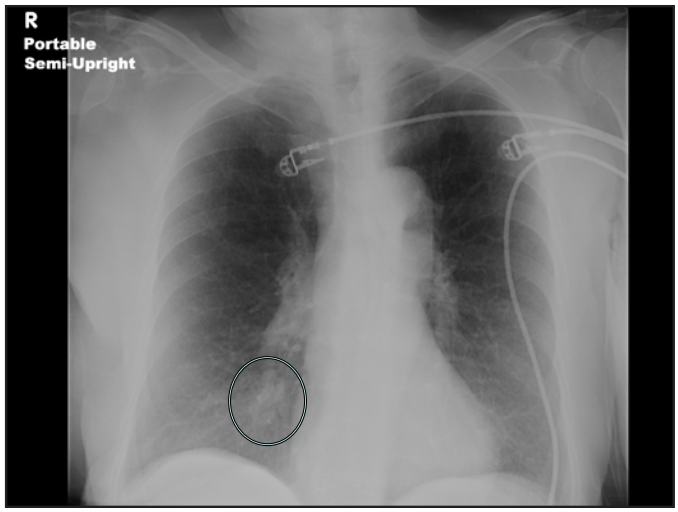

L

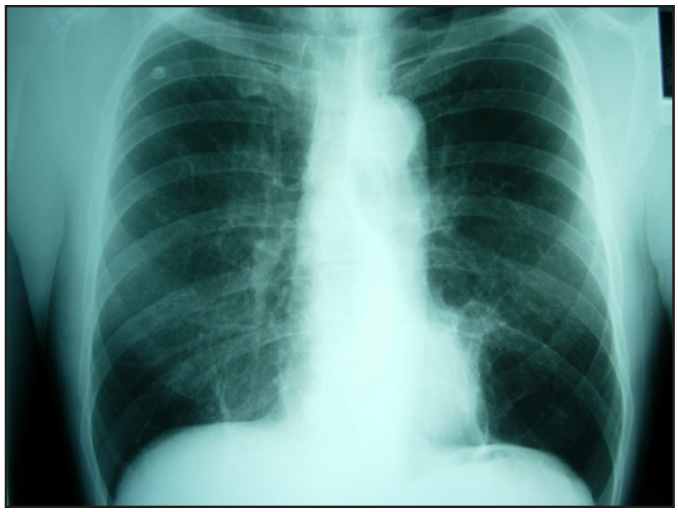

L

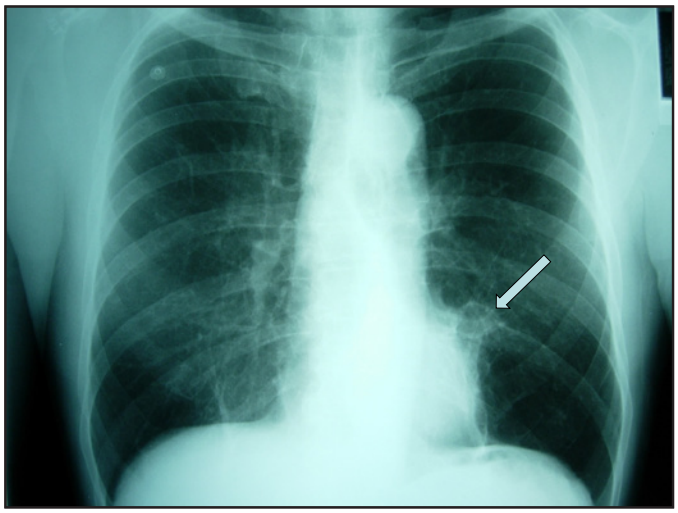

L
LLL Ca
(more visible on lat)

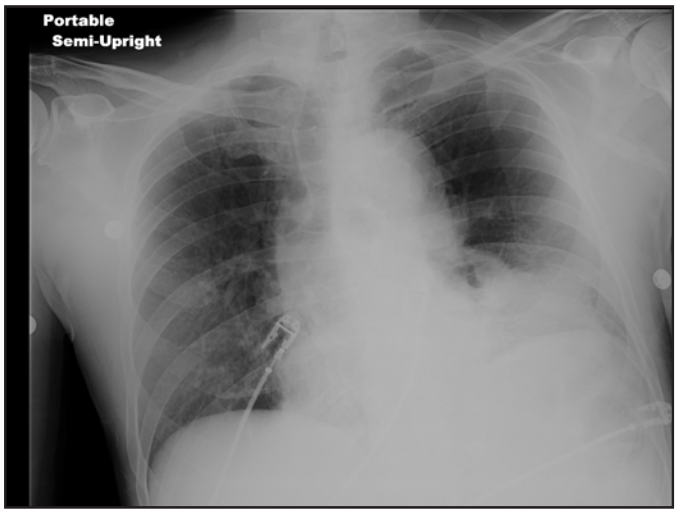


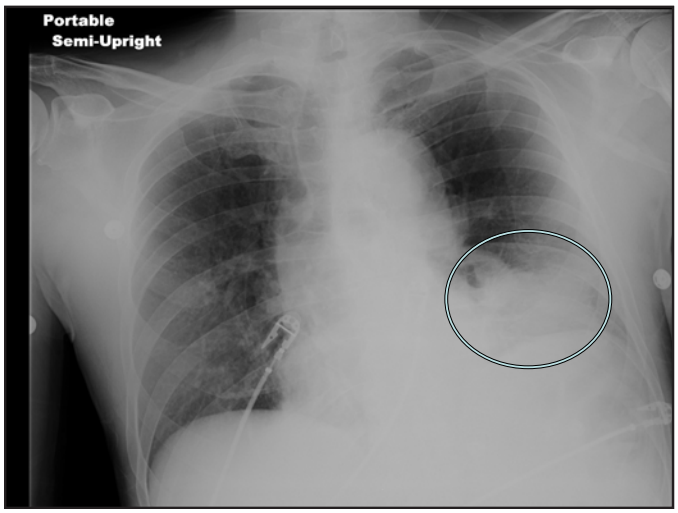

R
Portable
Semi-Upright

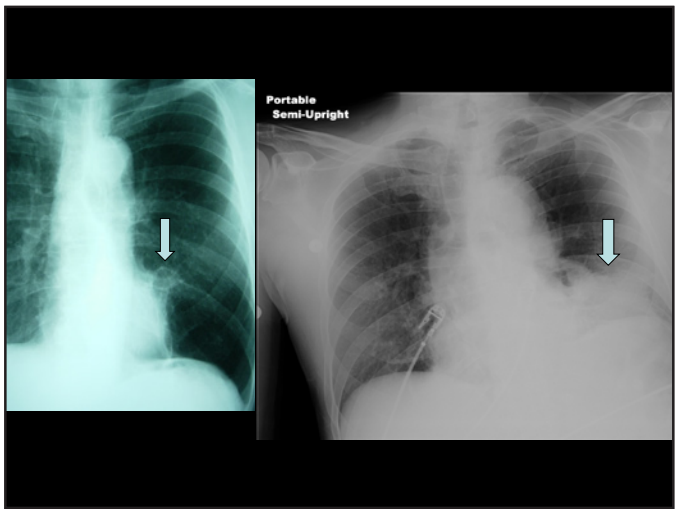

R
Portable
Semi-Upright

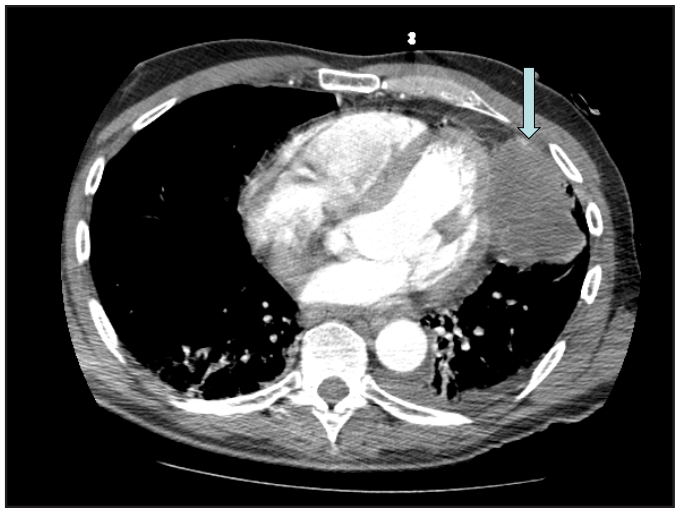


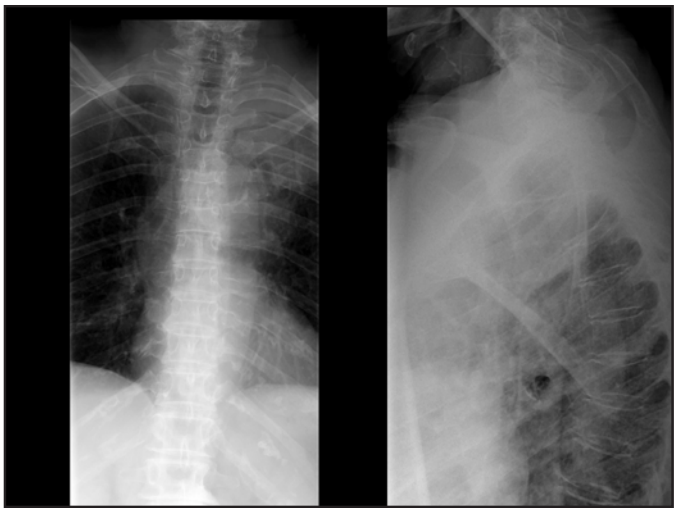


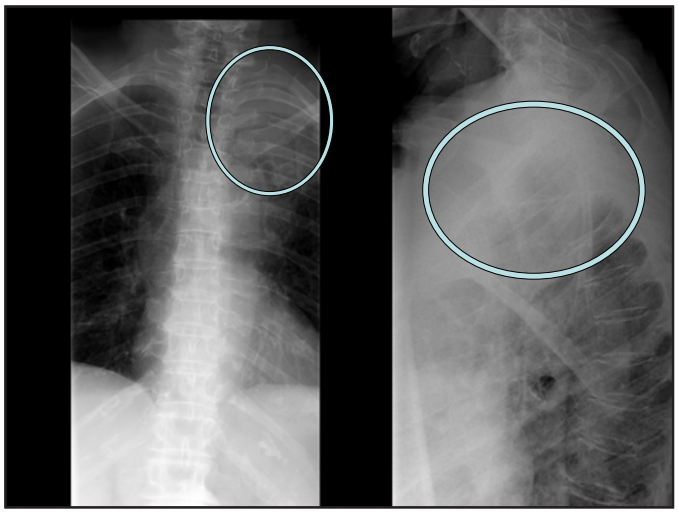

Portable
Semi-Upright


Portable
Semi-Upright


Portable
Semi-Upright

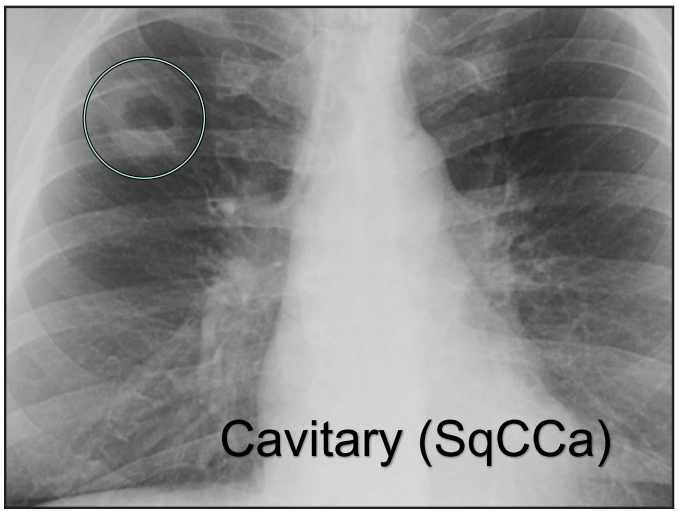


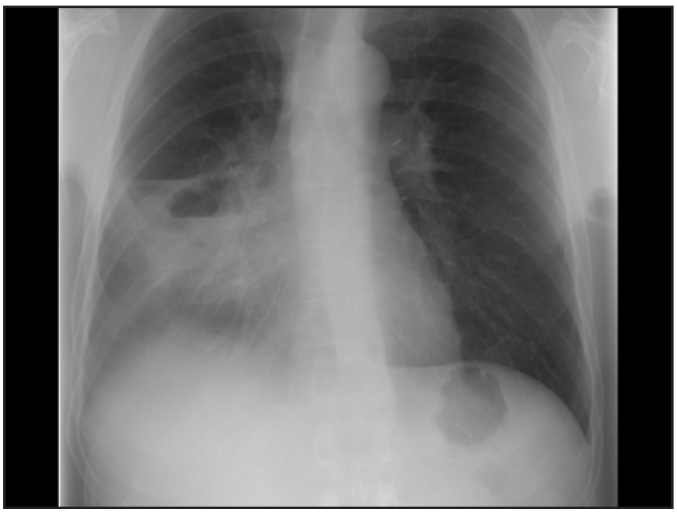


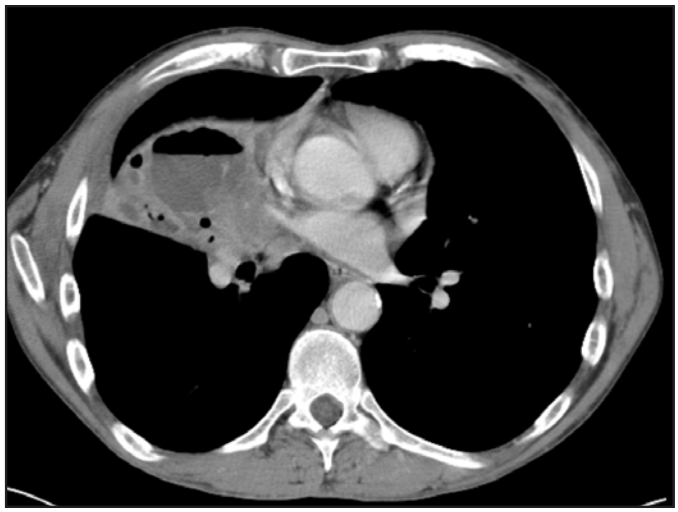


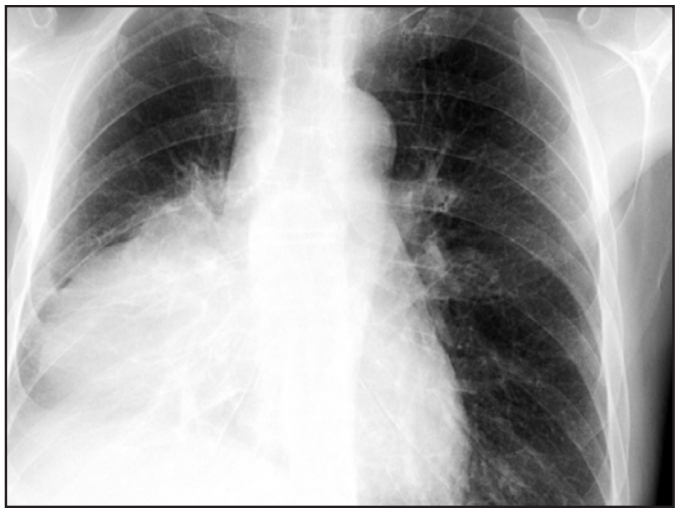
"Hidden" areas on CXR

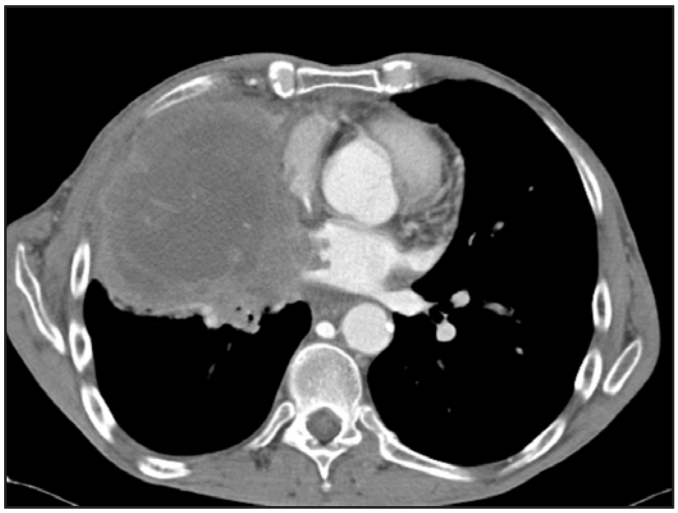
- Retrocardiac
- Apices
- Costophrenic sulci (lat. and post.)
- Hila, mediastinum

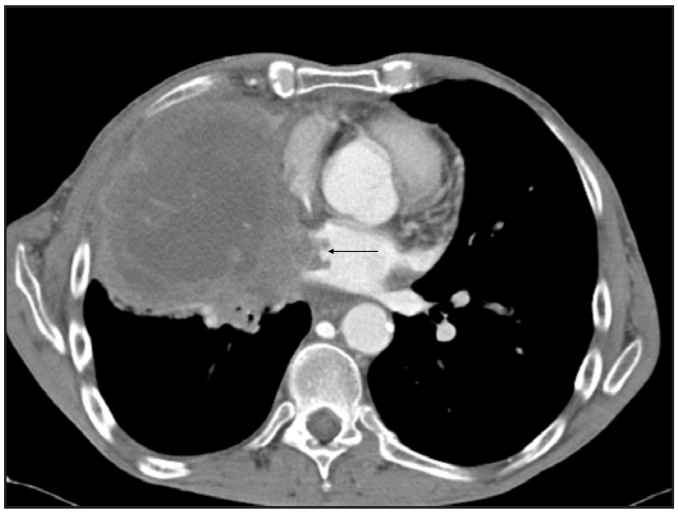


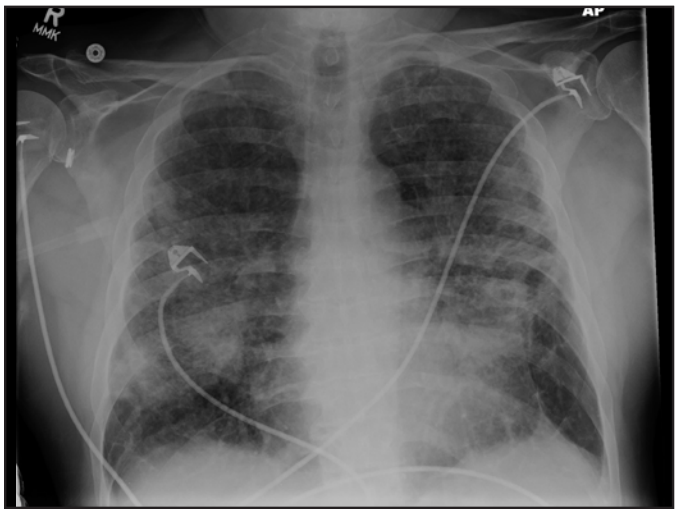


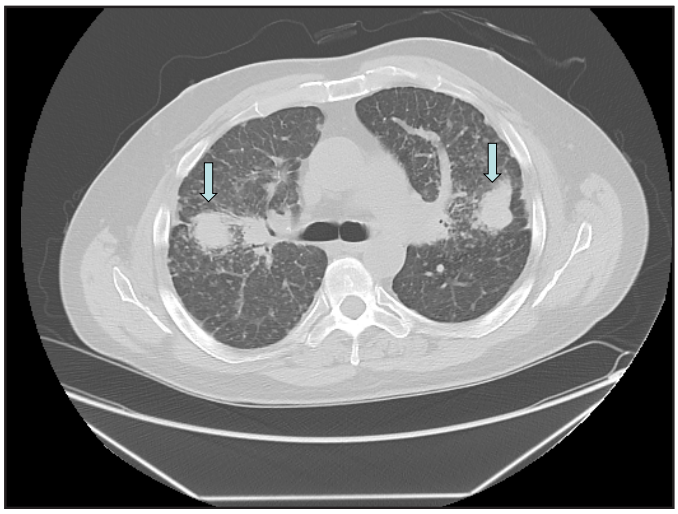


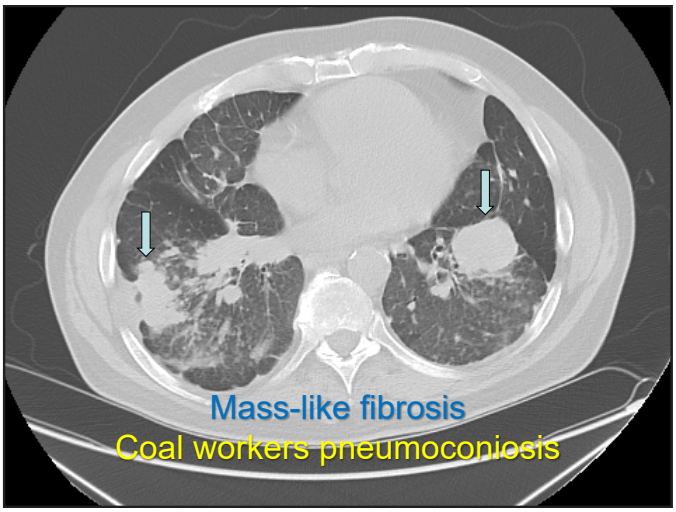




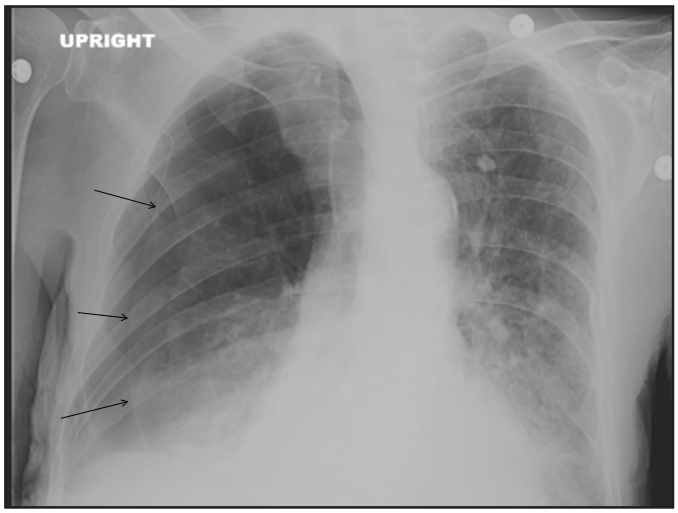


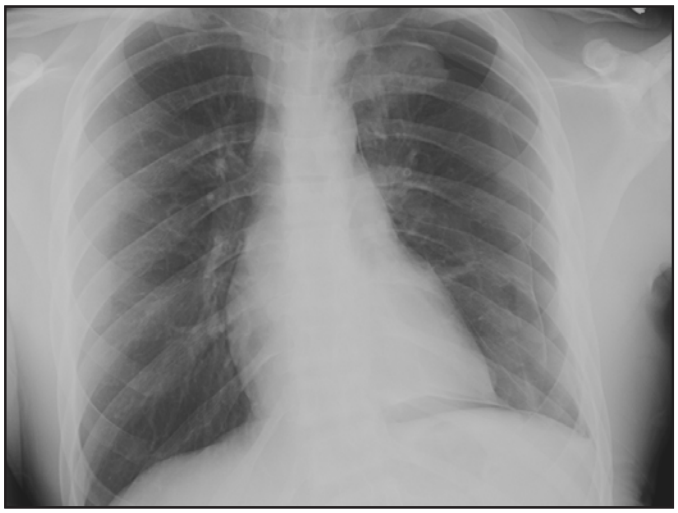


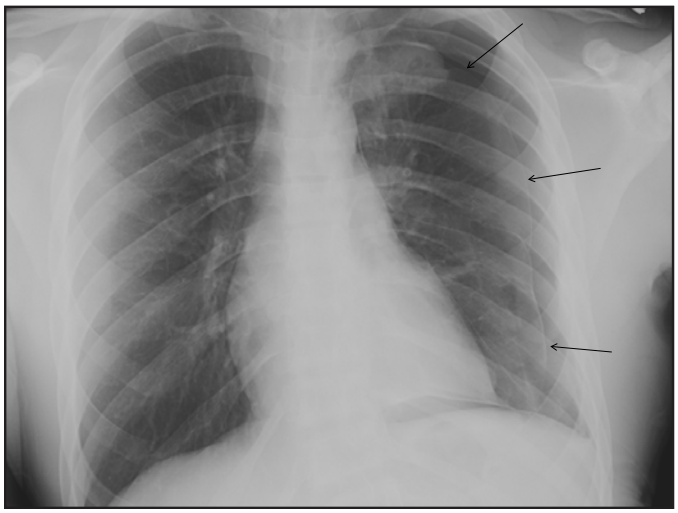


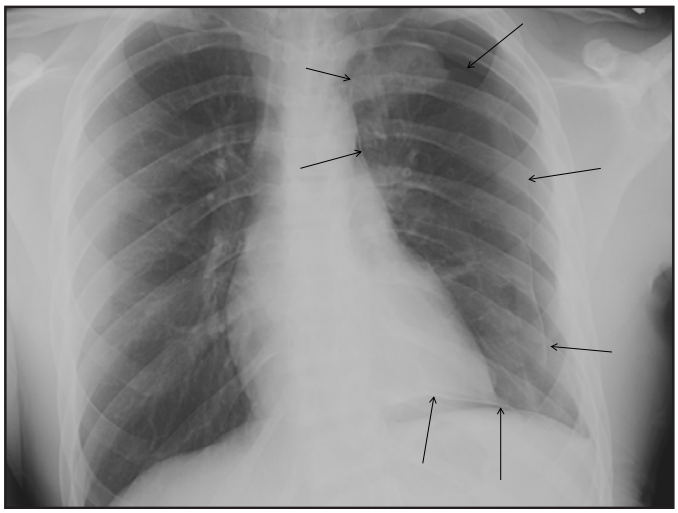


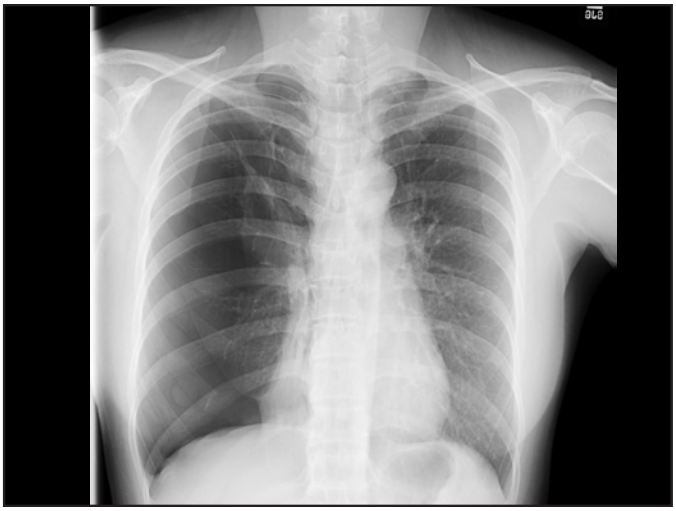
Pneumothorax

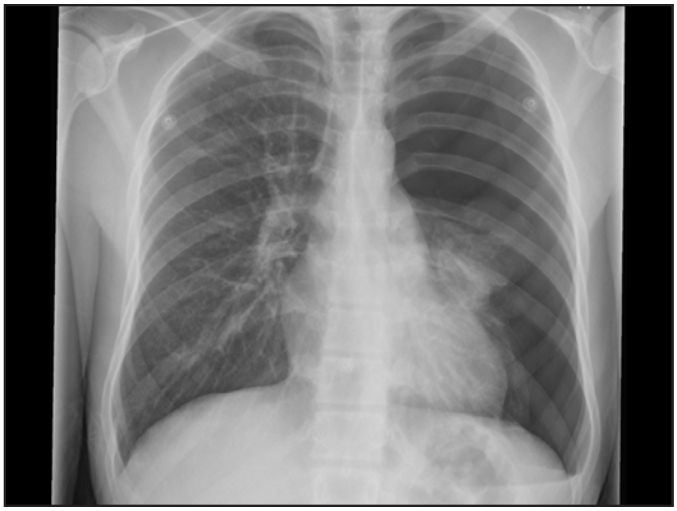


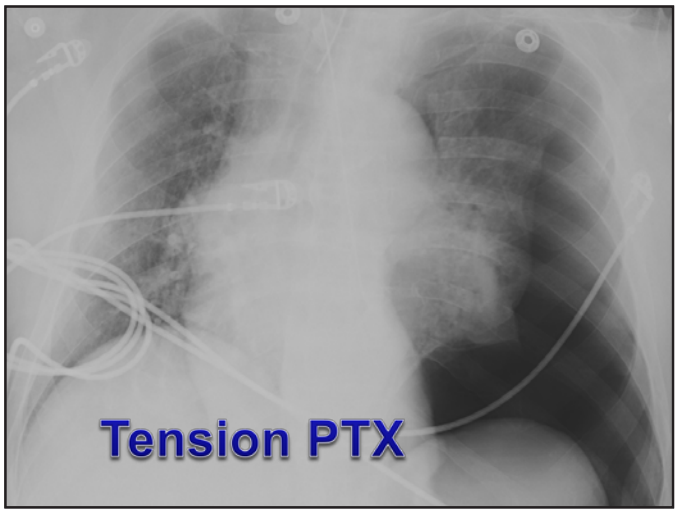


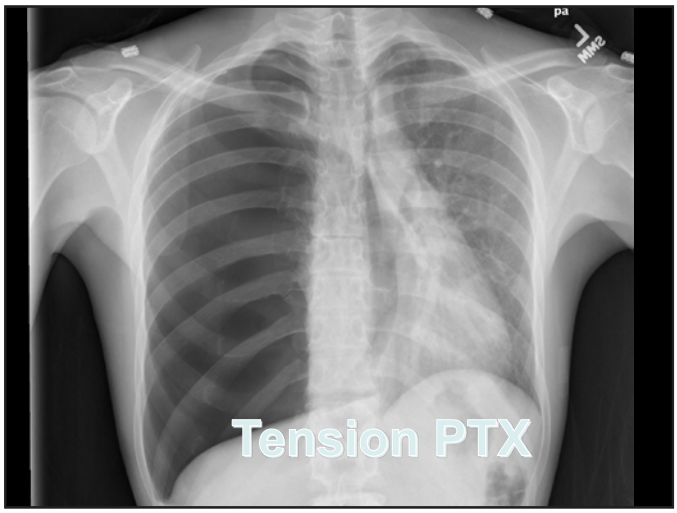


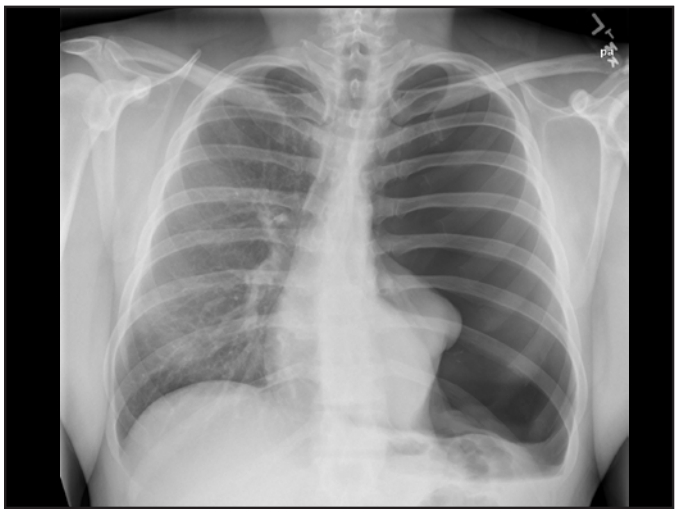


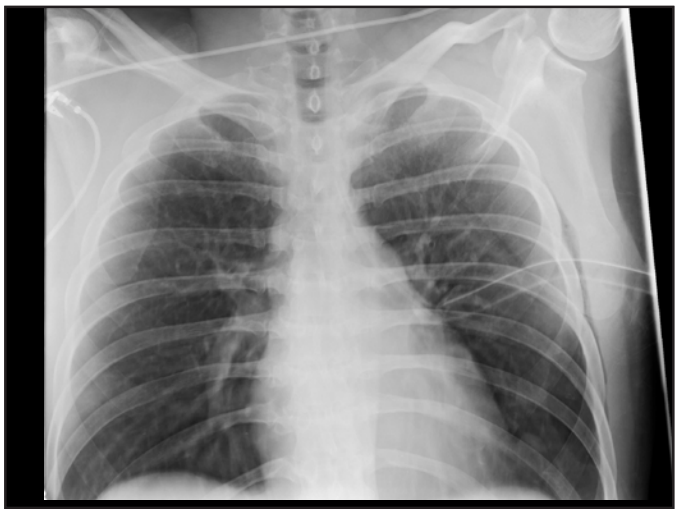


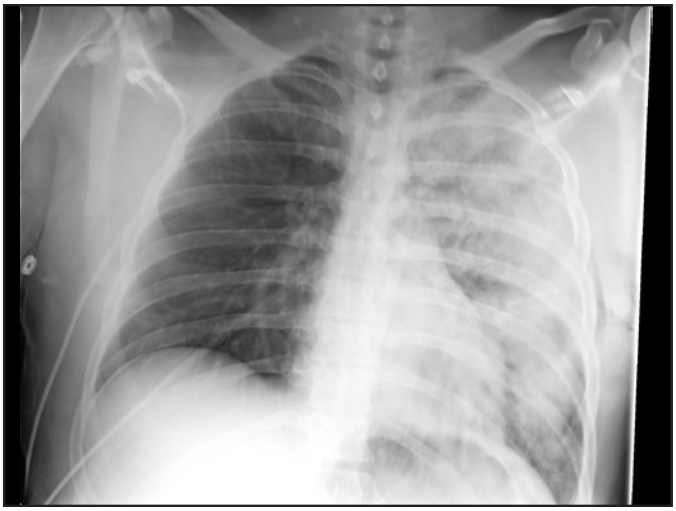


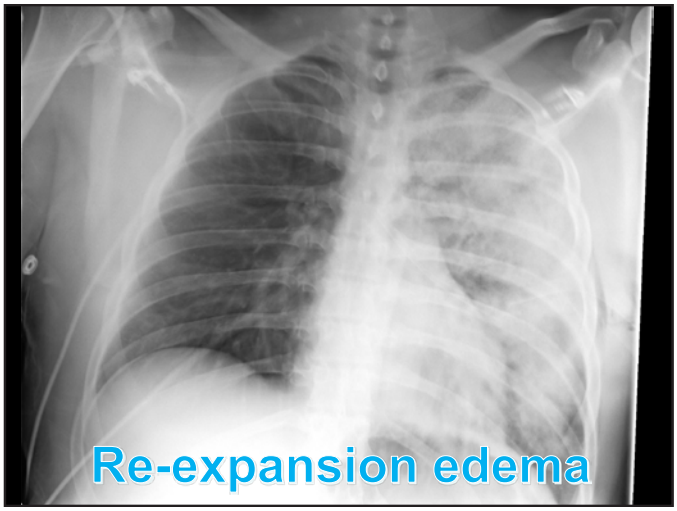

Tension PTX

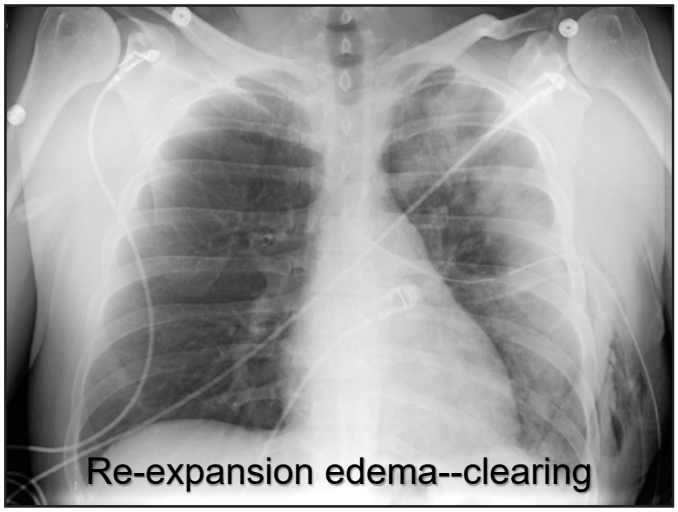

Tension PTX

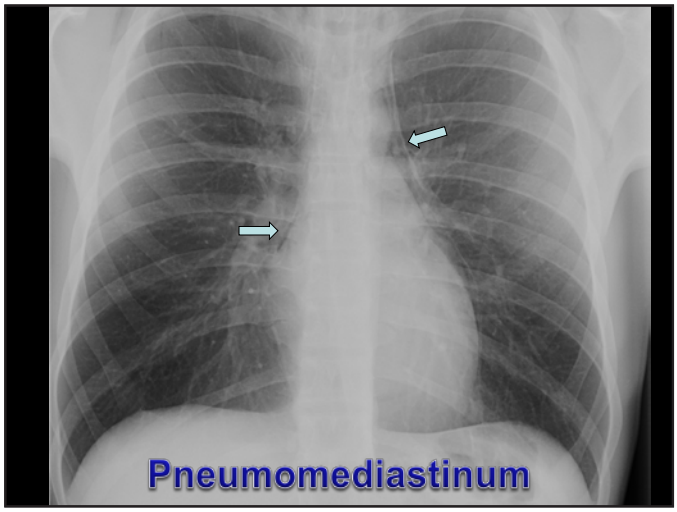


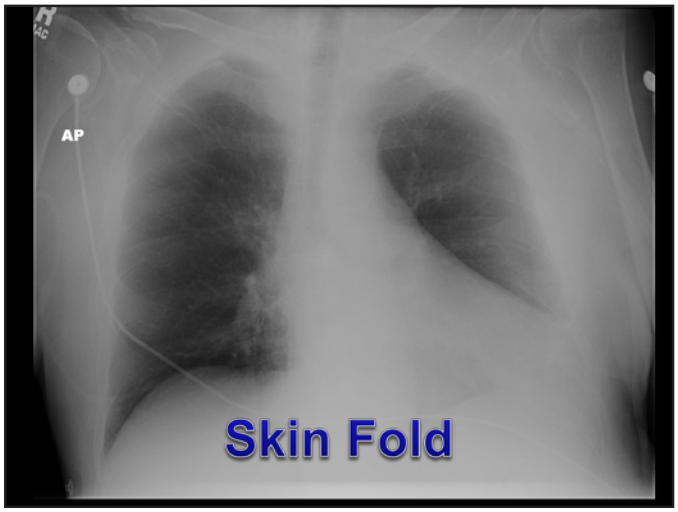


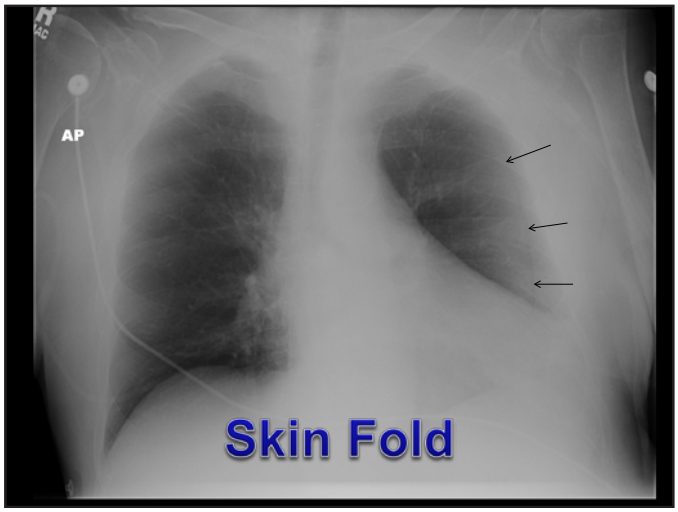


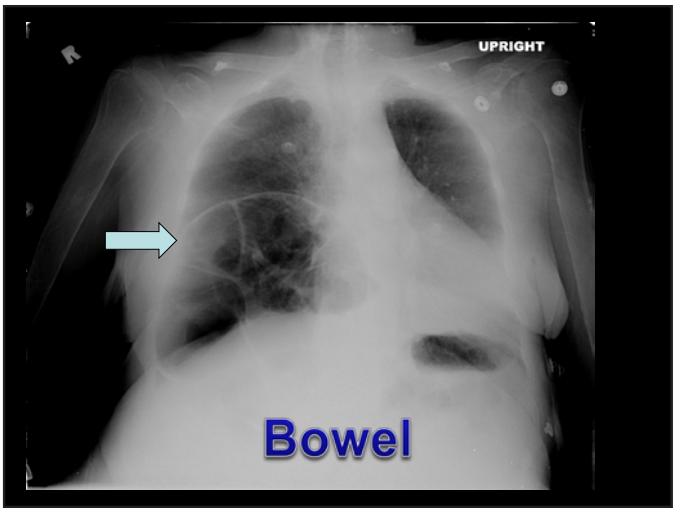

Re-expansion edema

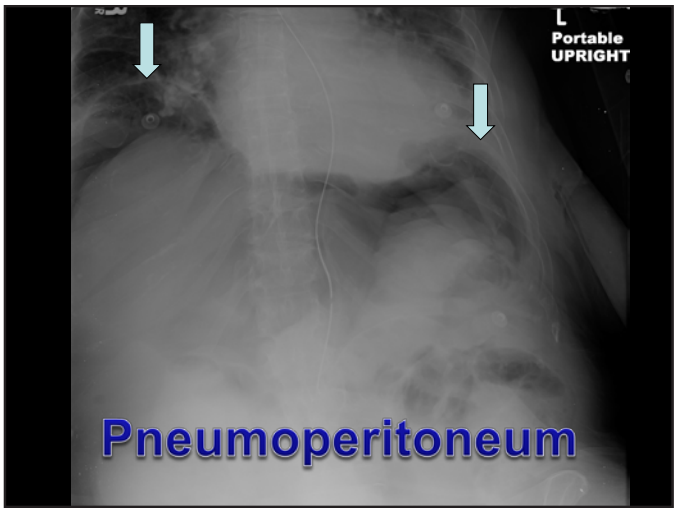

Re-expansion edema--clearing

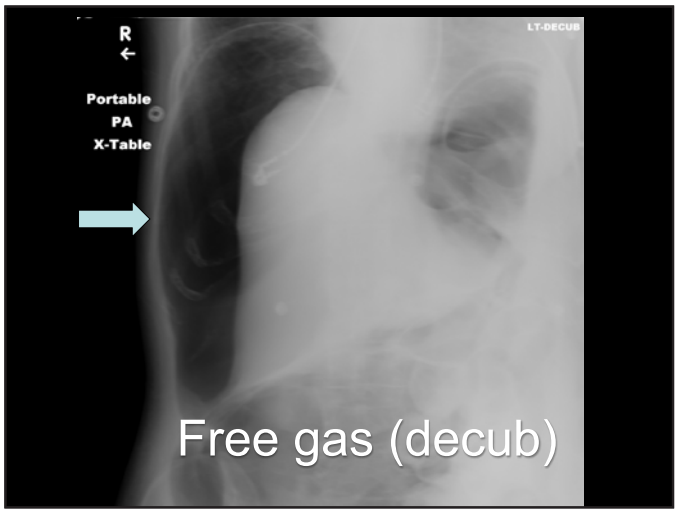

Pneumomediastinum

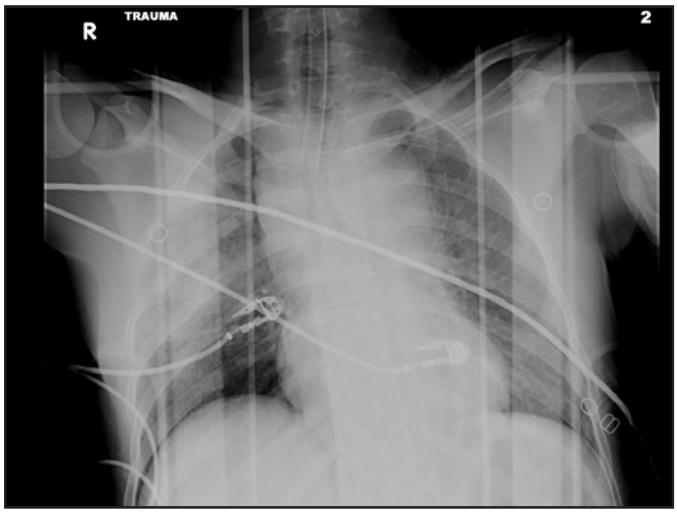

AP
Skin Fold

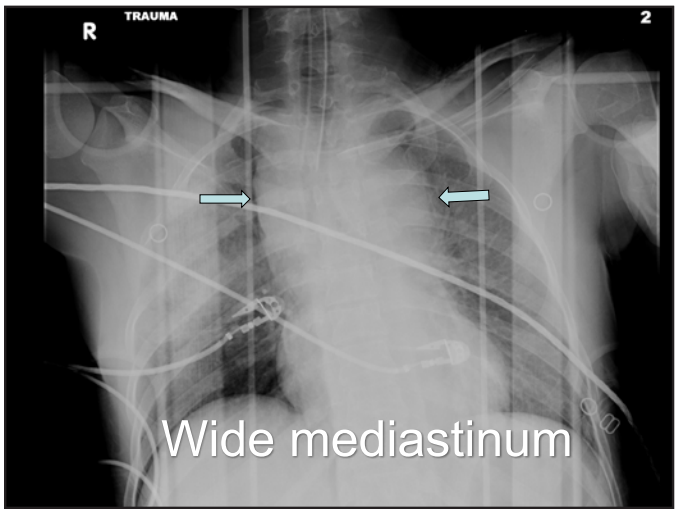

AP
Skin Fold

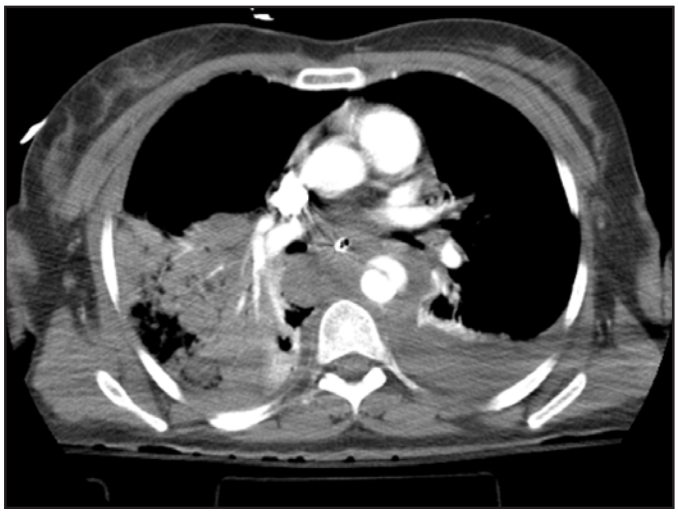

R
UPRIGHT
Bowel

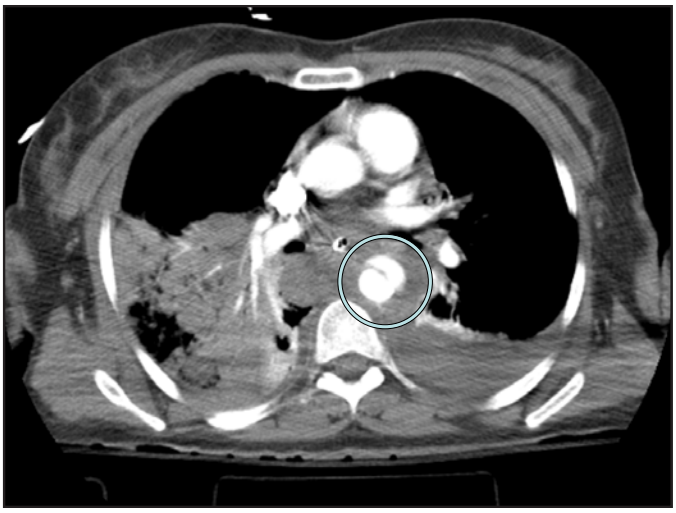

L
Portable
UPRIGHT
Pneumoperitoneum

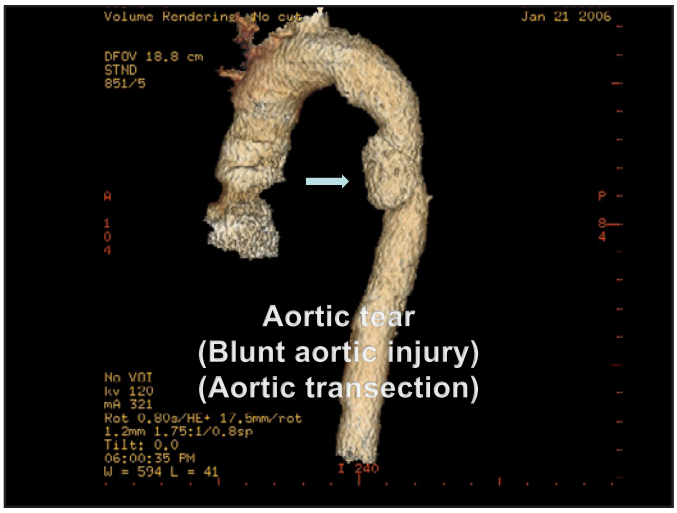

R
LT-DECUB
Portable
PA
X-Table
Free gas (decub)

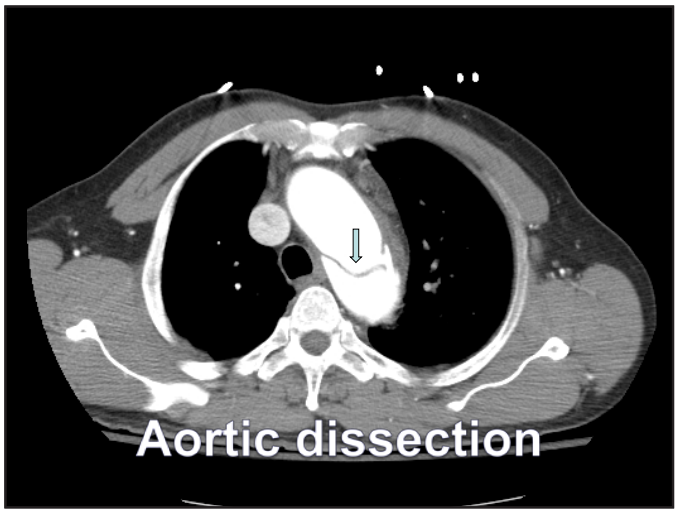

TRAUMA
R
2

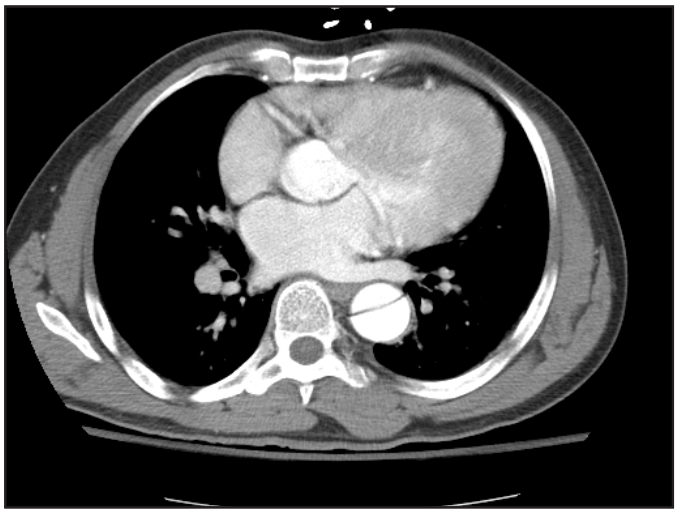

TRAUMA
R
2
Wide mediastinum

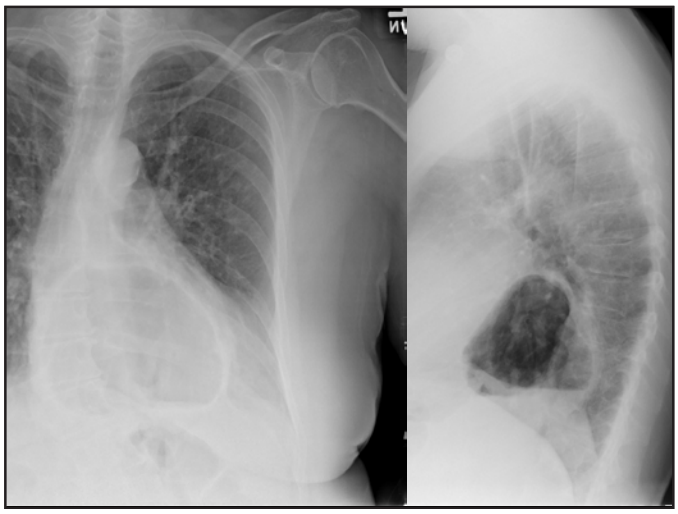


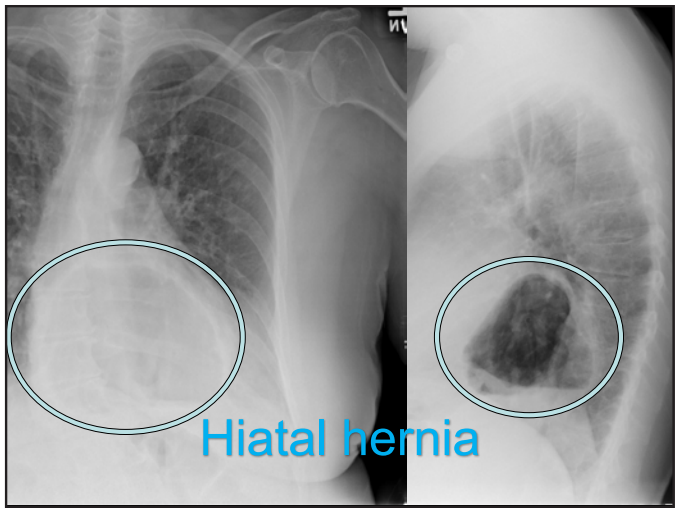


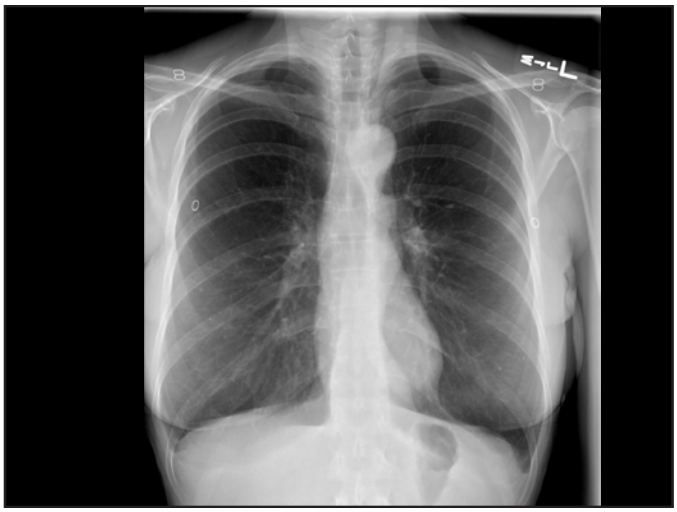

Volume Rendering No cut
Jan 21 2006
DFOV 18.8 cm
STND
851/5
Aortic tear
(Blunt aortic injury)
(Aortic transection)
No VOI
kv 120
mA 321
Rot 0.80s/HE+ 17.5mm/rot
1.2mm 1.75:1/0.8sp
Tilt: 0.0
06:00:35 PM
W = 594 L = 41

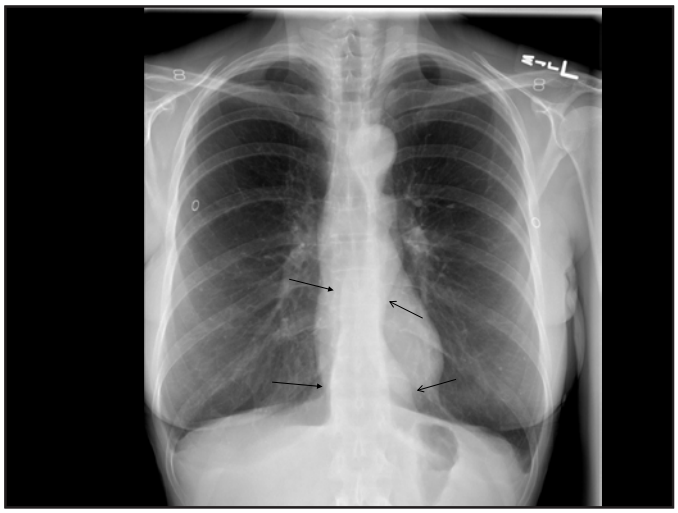

Aortic dissection

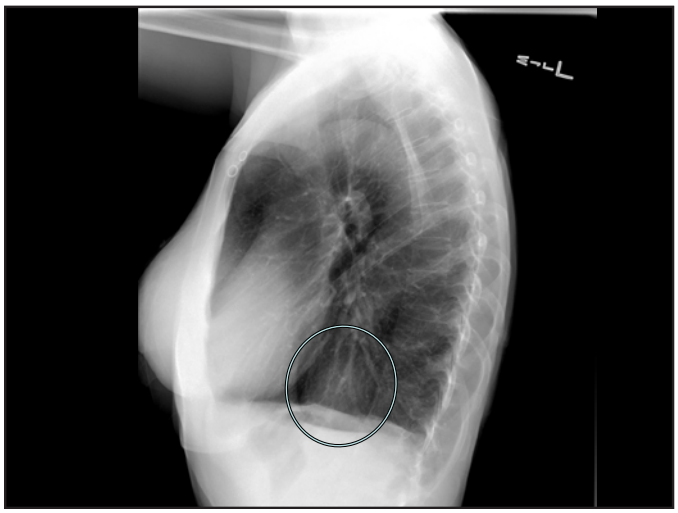


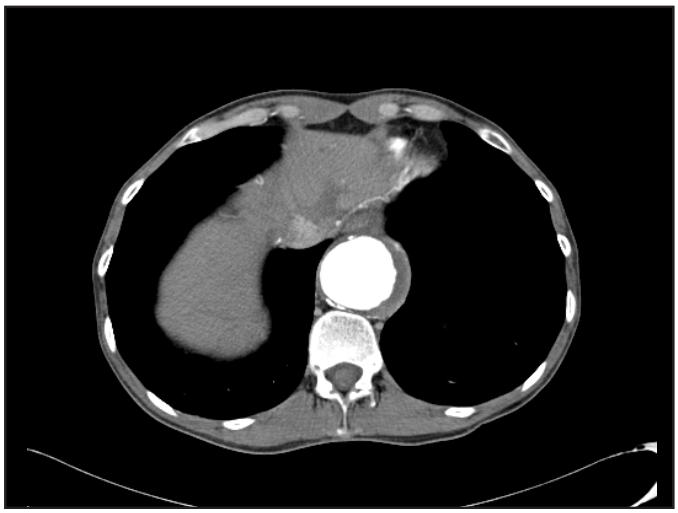


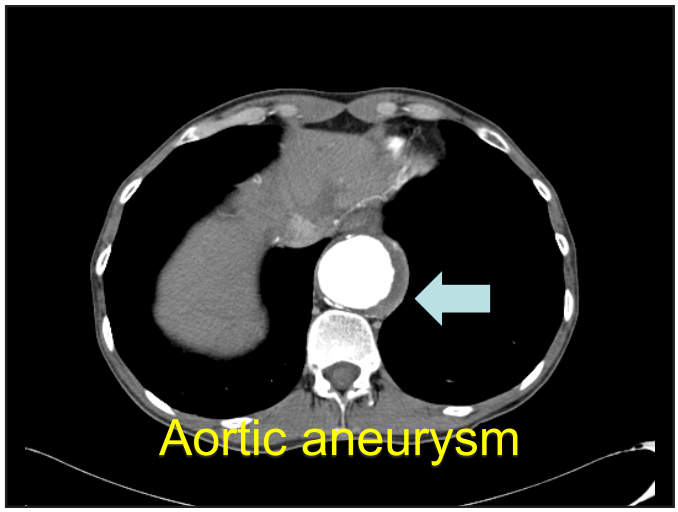

Hiatal hernia

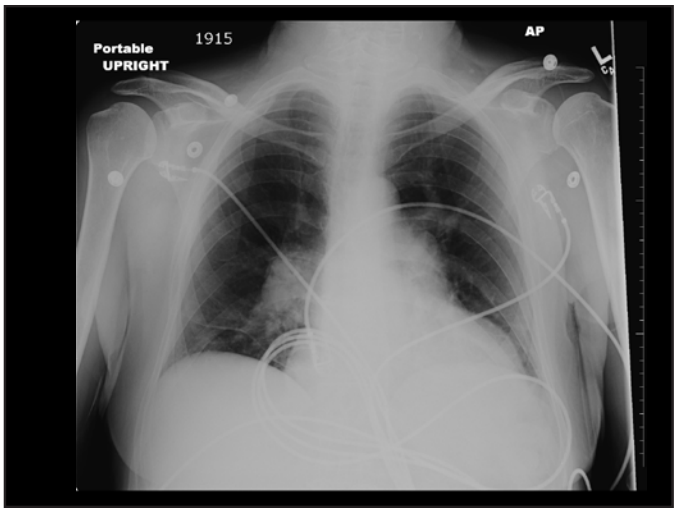


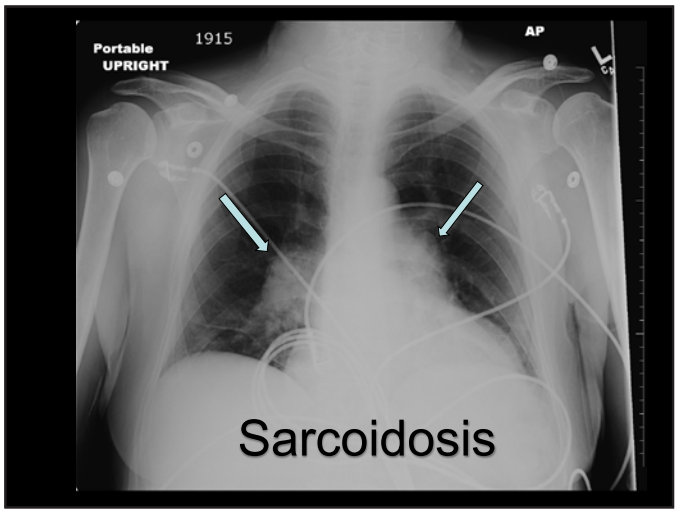


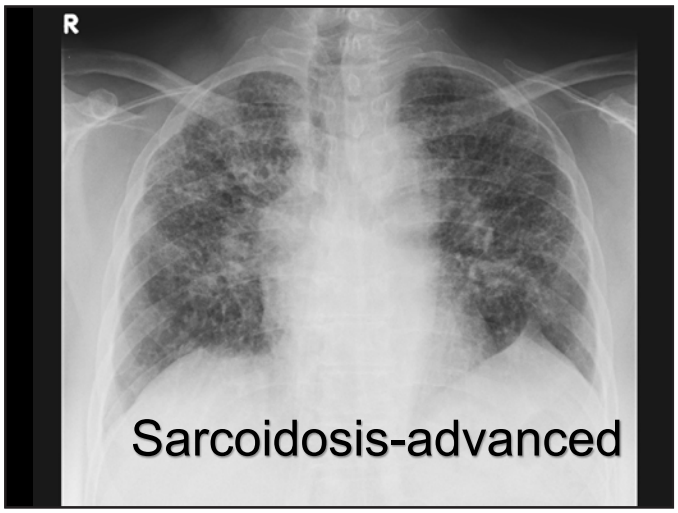


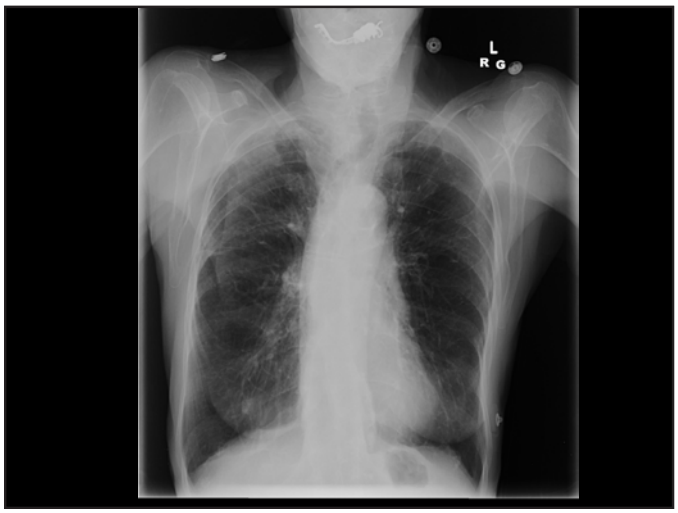


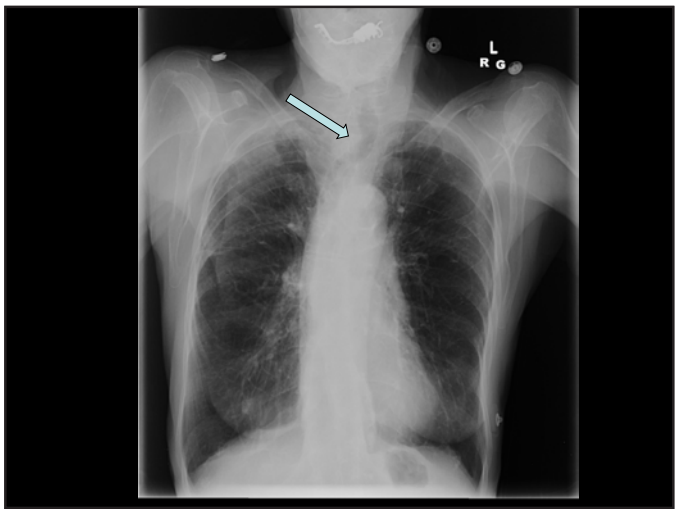

Aortic aneurysm

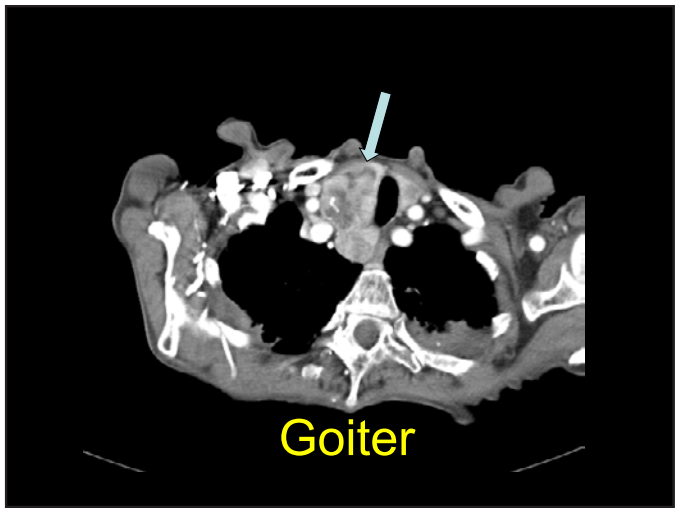

Portable
UPRIGHT
1915
AP

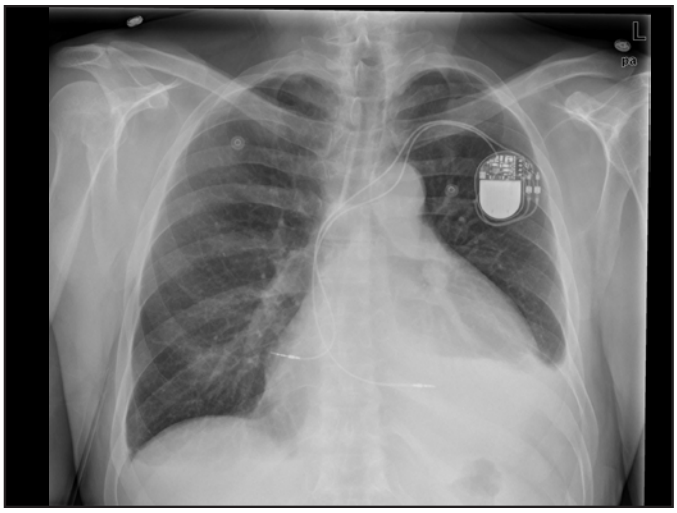

Portable
UPRIGHT
1915
AP
Sarcoidosis

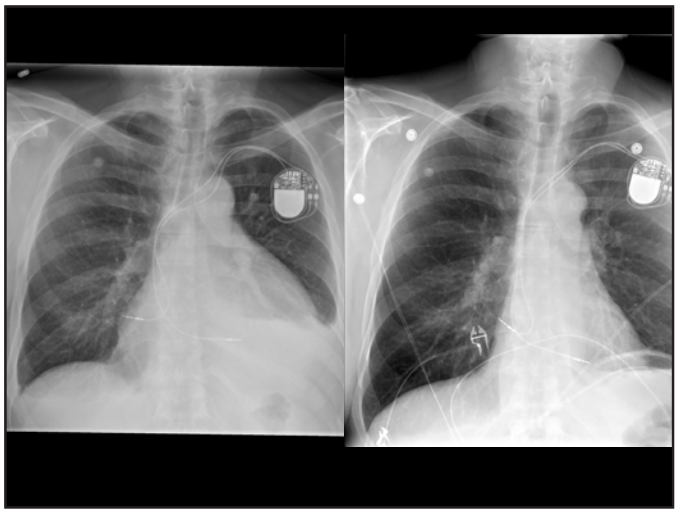

R
Sarcoidosis-advanced

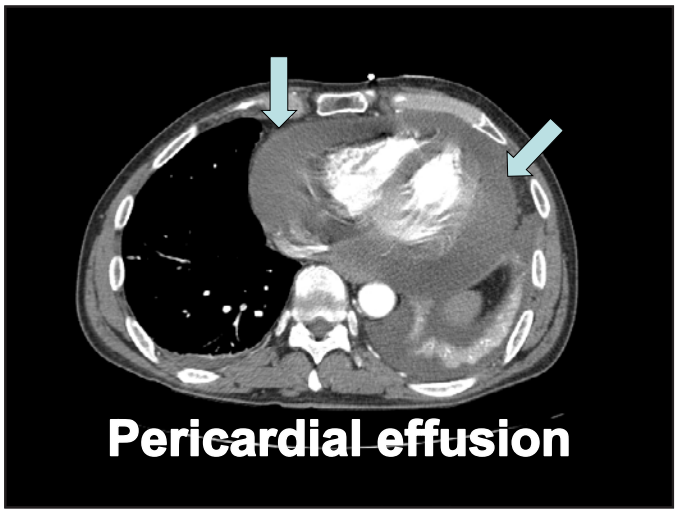

L
R G

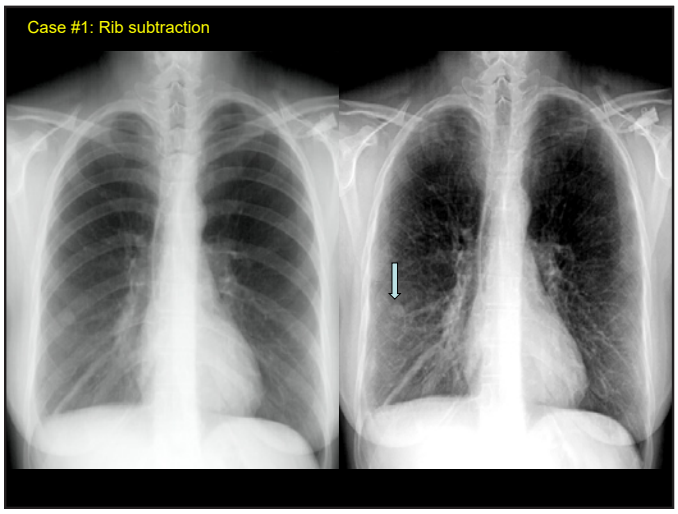

L
R G

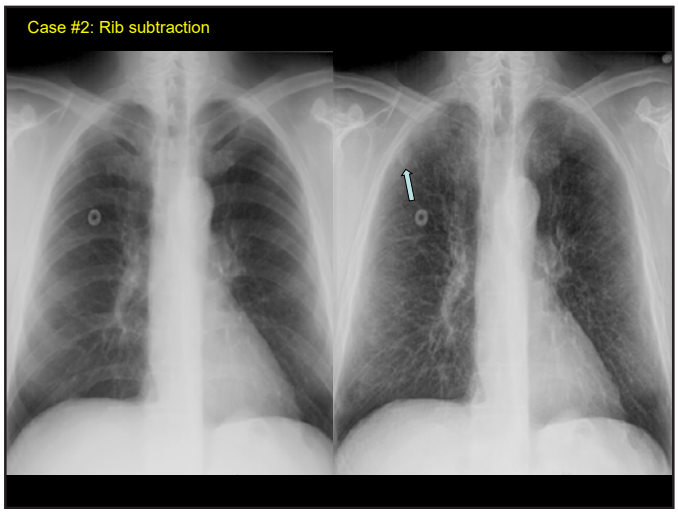

Goiter






Pericardial effusion


Case #1: Rib subtraction


Case #2: Rib subtraction

SELF EVALUATION

Chest X-ray Case Review

1. Familiarity with chest x-ray findings is clinically important in part because:

a. Chest x-ray studies remain very commonly used
b. Clinically significant findings can often be subtle
c. Findings may vary substantially depending not only on pathology, but also on patients' ages, body habitus, and other co-existing medical conditions
d. All of the above

2. Regions on chest images where abnormalities may be more obscured and harder to detect include:

a. Apices
b. Hilum and mediastinum
c. Retrocardiac
d. Costophrenic sulci
e. All of the above

3. T/F - Missed lung cancers on chest radiographs are a leading cause of litigation in medical imaging

4. The following general approaches to chest radiography typically improve the accuracy in interpreting chest radiographs:

a. Obtaining both frontal and lateral views whenever possible
b. Old film comparison
c. Added special views when warranted, including apical lordotic, decubitus, oblique, or repeat frontal view with nipple markers
d. All of the above

5. T/F - In addition to digital imaging replacing older film technique, newer available developments in chest radiography include software programs that digitally suppress rib markings, and computer-assisted detection software that increases the sensitivity of lung nodule detection

6. Depending on the scanner and technique, a chest CT scan may administer the radiation dose equivalent of how many single chest x-ray images?

a. 5-20
b. 20-50
c. 50-150
d. 150-400

Answer Key: 1. D, 2. E, 3. T, 4. D, 5. T, 6. C

Bert Orlov, MBA

Bert Orlov, MBA of New York City, New York, is a Managing Director of Eisner Amper Healthcare Consulting Group with 25 years of experience as a management consultant in the healthcare industry. Mr. Orlov earned his MBA from Yale School of Management and specializes in strategy, transactions, operations and project management for physician groups and hospital systems, as well as not-for-profits. Mr. Orlov has been published in many books and articles including the Beckers Hospital Review. He collaborates with the University of Pennsylvania on strategy for primary care practices.

You may contact Mr. Orlov with your questions or comments at 212-324-2297 or by email at bert.orlov@eisneramper.com.

EISNERAMPER
733 Third Avenue | New York, NY 10017 | 212.949.8700

Planning, Negotiating and Implementing a Practice Merger or Acquisition

Bert Orlov, MBA

Developing an Optimal Deal - Three-Step Framework

- With consolidation in the Physician Practice market moving ahead rapidly, a strategic/proactive approach is essential
- Practice success in crafting a strong deal depends on planning to improve Practice value (and thus deal value) and prevent a deal from unravelling late in the process
- The Three-Step Framework for evaluating and then conducting a PE transaction (or hospital network or other MD groups)

Private Equity: Overview

Industry Fundamentals

- Private Sector
  - Limited regulation
  - Multiple players
- PE Firms (Investors) seek growth, as money in the bank cannot generate profit
- Acquisition
  - Substantial equity investment
  - Payments to sellers may include cash and shares in PE entity
- Profitability Focus
  - Platform/Roll-up
  - Scrape
  - Second Bite
  - Unicorns

Typical Deal Structure

- Purchase
  - Valuation (EBITDA and QoE) times market multiple
  - Price
    - Cash and Terms
    - Stock in the PE entity itself, offering potential growth opportunity
- Ongoing Compensation
  - Productivity
  - Scrape / Profits to PE
- Management Services
- Profitability Enhancement

Private Equity: Growth Share Matrix

Source: BCG Matrix - Overview, Four Quadrants and Diagram

Private Equity: Deal Trends

- Private Equity deal activity has increased between 2012 and 2021
- After reaching its peak in 2021 activity decreased likely because of after-effects of COVID. Anecdotally, deal volume has grown in 2024
- PE firms are showing increasing interest in healthcare (especially physician practices)

2023 Healthcare Transactions

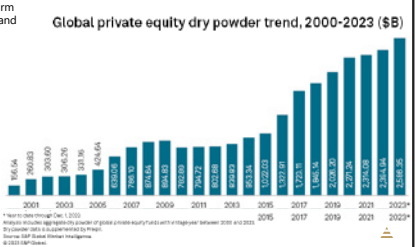
- 1135 unique deals
  - 148 buyouts
  - 259 growth/expansion investments
  - 728 add-on acquisitions

Sources: 1) Private Equity Report: 2022 Trends & 2023 Outlook | Cherry Bekaert (cbh.com) **2)** PESP_report_2023-Healthcare-Acquisitions_March-2024.pdf (pestakeholder.org)

Private Equity: "Dry Powder"

- **"Dry Powder" stands at an all time high at $2.5 trillion** – according to S&P Global
- Approximately $100 Billion is ear-marked for investment in the Healthcare sector

- PE investors seek to complement existing platform investments via acquisitions that increase scale and efficiencies in the following sectors:
  - Physician Practices
  - Healthcare Information Technology
  - BioPharma
  - Home Healthcare
  - Behavioral Health



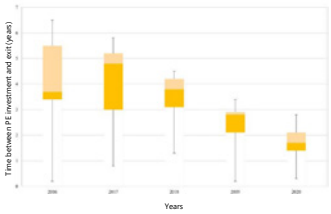
Private Equity: Practice Economics

- PE-driven industry changes flow from the consolidation of smaller practices into larger, better-capitalized groups

- PE Firms can add value to Practices through invest in:
  - Patient Panel Management
  - Patient Engagement
  - IT/Artificial Intelligence
  - Additional dentists
  - Leadership/Support staff
  - Marketing

Private Equity: Exits "Second Bite"

- PE generates profit by selling its investments ("Second Bite")
- In 2016, PE hold time typically lasts 3-8 years after the acquiring and growing physician practices through add-on consolidation
  - Hold times have been decreasing ever since
- According to a recent study published by Health Affairs Scholars
  - 807 acquisitions of PE acquired practices exited within 3 years of initial investment through secondary buyouts
  - Between investment and exit, PE firms increased the number of physician practices affiliated with the PE firm by an average of 595% in 3 years.



Private Equity: Potential Restrictions by State

- **Over the past two years, states have passed laws aimed to reduce healthcare mergers and acquisitions, especially PE ownership of hospitals (networks)**
- **Steward in MA represents a cautionary tale, from these States' viewpoint**

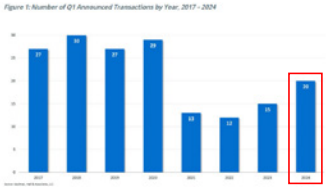
- **Massachusetts**
  - Legislature considering a bill that requires hospitals to disclose audited financial statements about their parent organization's out-of-operations, private equity investors, real estate investment trusts and management service organizations
- **Rhode Island**
  - Private equity (PE) firms that acquire healthcare companies are required to set aside funding to protect access to care, remove tax breaks that could incentivize corporate investors to strip hospital assets and require private equity firms to disclose their finances to the Health and Human Services (HHS) department. PE firms will also have to acquire a license from HHS to participate in healthcare transactions
- **Indiana**
  - Healthcare entities and private equity firms are required to notify state officials about pending mergers or acquisitions, and applies to any transaction with a healthcare entity that has at least $10 million in total assets
- **New York**
  - Requires a notification for any healthcare entity increasing its total in state revenues by at least $25 million within 12 months after a merger, acquisition, joint venture or partnership is completed
- **California**
  - Considering a measure to require a 90-day notice and attorney general's approval of healthcare transactions involving private equity groups or hedge funds, and would prevent private equity firms from controlling certain aspects of physician or psychiatric practices
- **Connecticut**
  - Considering legislation that would require state approval when a hospital sells more than 10% of its assets, including real estate

Private Equity: Adverse Case Study--Steward Health

- 2010, a private equity firm bought an unprofitable Massachusetts hospital chain
  - Hospitals are rebranded as Steward Health
  - Following PE firm acquisition spree, Steward becomes the country's largest private for-profit hospital chain w
- 2014, one of the hospitals closes, despite having pledged not to do so for at least 10 years after the acquisition, as part of the state regulatory approval process
- 2016, a $1.25 billion sale-leaseback agreement for its Mass. Properties was signed
- 2020, PE firm begins to exit
  - Agreeing to sell control in Steward to the hospitals' physicians in exchange for an interest-paying note
  - The physicians soon borrowed $335 million to buy back the note
  - PE firm generated around $800 million in profit via its Steward investment
- 2024, a federal investigation into private equity acquisitions of healthcare providers is initiated
  - A federal hearing was scheduled for April 3, 2024
  - Steward required to sell all 8 hospitals by the end of June 2024

Hospital Partner

- According to Kaufman Hall, Q1 2024 showed a significant uptick in M&A activity and represents the strongest Q1 since 2020
- A key highlight of the quarter was the diversity of transactions, showcasing a variety of trends that have been shaping the health care landscape:
  - Cross-Market Transactions
  - Community Health Systems seek larger partners
  - Portfolio realignment
  - A new partnership model
  - Academic health systems build community networks
- Since 2012, direct hospital employment of physicians has nearly doubled (as a % of physician workforce)



Practice to Practice: Overview

- According to the American Medical Association, In 2023, the U.S. physician group market size was estimated at $325 billion and expected to grow to $461 billion by 2030
  - Initiatives to improve revenue to physician groups
  - Shift towards value-based care
  - Growing trend of solo practitioners joining larger physician groups
- Practice Ownership (2012-2022)
  - The share of physicians working in private practices fell from 60.1% to 46.7%.
  - The share of physicians working in hospitals as direct employees or contractors increased from 5.6% to 9.6%
- Practice Size (2012-2022)
  - The share of physicians in small practices (10 or fewer physicians) shrank from 61.4 % to 51.8% between 2012 and 2022
  - Large practices (50 physicians or more) grew from 12.2% to 18.3%
  - Midsized practices (those with 11 – 49 physicians) remained stable
- Employment Status (2012-2022)
  - The share of physicians who were self-employed fell by 9 percentage points from 53.2% to 44%.
  - The share of physicians who were employed grew from 41.8% to 49.7%
  - The share of physicians under the age of 45 who were self-employed fell from 44.3% to 31.7%.

Practice to Practice: Consolidation

- According to the American Medical Association, the industry has seen a redistribution of physicians from small to large practices
  - In 2012, 61.4% of physician worked in practices with 10 Physicians or less – in 2022, the % declined by 9.6% to 51.8%
- According to the American Hospital Association, an overwhelming majority (94%) of physicians think it has become more financially and administratively difficult to operate a practice.
- Threats to independent practices includes – Low reimbursement rate, declining margins/profits, staffing shortages, and more.

Distribution of physicians by practice size (number of physicians in practice)

	2012	2014	2016	2018	2020	2022
Practice size						
Fewer than 5 physicians	40.0%	40.9%[a]	37.9%[a]	35.7%[a]	33.6%	32.8%[a]
5 to 10	21.4%[c]	19.8%	19.9%	20.8%	20.0%	19.0%[a]
11 to 24	13.4%[c]	12.1%	13.3%	12.7%	11.5%	12.1%
25 to 49	7.1%	6.3%[c]	7.4%	7.5%	7.8%	7.7%
50+ physicians	12.2%	13.5%	13.8%	14.7%[a]	17.2%	18.3%[a]
Direct hospital employee/contractor [‡]	5.8%[a]	7.4%	7.7%	8.5%[c]	9.7%	10.1%[a]
	100%	100%	100%	100%	100%	100%
N	3326	3388	3381	3339	3353	3329

Making a Deal: Deal Structure

Private Equity
- Purchase
  - Valuation
  - Price
    - Cash
    - Stock
- Ongoing Compensation
  - Productivity
  - "Scrape"
  - Profits to PE
- Management Services
- "Second Bite"

Hospitals/Networks
- Purchase
  - Rarely direct purchase
    - EBITDA or DCF, adjusted for future expectations
    - Assets only (e.g., F & F or ancillary business)
- Ongoing Compensation
  - Productivity
  - Stipends for academic or service activities
  - Quality metrics
- FMV limitations on not-for-profits
- Management Services

Practice to Practice
- Purchase
  - No direct purchase
    - Acquisition of shares in existing platform
    - Capitalization of new entity
- Ongoing Compensation
  - Productivity
  - Share of corporate profit
- Management Services
  - Consolidated leadership
  - Economies of scale
  - Improved rates

Making a Deal: Pros and Cons

Is PE (or Hospital) acquisition or merger with other Practices a good idea for your Practice?

Potential Benefits
- Substantial financial return
- Reduction in the burden of running a practice
- Operational support
- Support to grow the practice
- State regulation may prompt faster movement

Potential Risks
- Loss of autonomy
- Less financial attractiveness for younger doctors in out-years
- Uncertainty about the future of PE

Making a Deal: Three-Step Framework

I: Preparation → II: Negotiation → III: Implementation

- Develop realistic understanding of the practices' value and market dynamics
- Identify a means to increase market value
- Ensure Shareholder/Owner agreement on strategy

- Identify potential partners and select the best choice.
- Plan for the detailed components of negotiations
- Advance deal-making (including legal, financial, and tax review as well as proper due diligence on both sides)

- Detail essential seller and buyer responsibilities
- Navigate the often-convoluted closing process
- Facilitate the post-transition implementation for smooth transition for MDs, patients and new Owners

Phase I: SWOT Analysis

- Evaluating the strategic position of your practice

Strengths	**Opportunities**
Weaknesses	**Threats**

Phase I: Preparation

Potential Market Value
- Preliminary financial analysis of the Practice and QoE (Quality of Earnings report)
  - Overall financials
  - MD compensation
  - Ancillary products
- Market dynamics by specialty and geography
- Recent market transactions

Phase I: Preparation

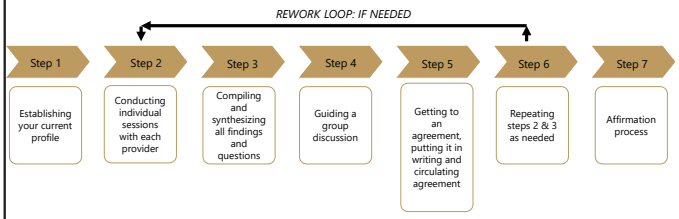
Potential EBITDA Improvement
- EBITDA equals practice earnings before interest, taxes, depreciation and amortization and represents the basis for calculating standard measurement of market value, typically based on a multiple of said EBITDA
- Core Analysis
  - Financials (revenues and expenses) with benchmarking
  - Productivity (and related profile in key MDs) with benchmarking
  - Referral sources
  - Patient throughput and efficiency
  - Market relationships (e.g., hospital linkages, shared coverage, etc.)
  - Coding accuracy
- Improvement Opportunities
  - Productivity growth, revenue cycle management, coding, staffing efficiencies and enhanced patient engagement, as well as potential ancillary development

Phase I: Preparation

Vision Alignment

- Discuss short- and long-term goals
  - Ensure all stakeholders are heard, especially for a Practice with divergent Shareholder profiles and extent of dependence on employed physicians
  - An independent, third-party facilitator can add objectivity and help prevent (or manage) internal conflict
- Articulate a strategy, forming the basis for deciding when and how to move forward
- Achieving a consensus amongst the group is a crucial step in deal development

Phase I: Strategy Consensus



Phase II: Negotiations

The Right partner

- Identify potential partners and contact those with relevant interests in your specialty, region, or organization type
- Develop a "pitch book" for outreach to potential partners and demonstration of your understanding of the market
- Pitch book should include:
  - Full scope quality of earnings (QoE) report
  - Relevant analyses to demonstrate value around productivity, cost effectiveness, and market strength

Phase II: Negotiations

Negotiating Process

- After signing a letter of intent, expect a "stand-still" period in which you can only negotiate with that one partner
- Use this time to gain a deeper understanding of the financial, strategic, operational, and organizational character of your potential partner
- Work out the deal terms *(see below)*
- Consider financial, legal and tax issues

Phase II: Negotiations

Deal Terms

- Secure and evaluate PE proposals
- Develop a clear matrix to evaluate proposals based on a set of key factors that can be "graded" to yield the top two or three candidates
  - Purchase price
  - Future compensation
  - Retention strategy
  - Guarantees of level of autonomy
  - Clarity on services provided
- Conduct due diligence on the finalists and select your preferred partner
- Negotiate optimal deal, guided by the evaluation matrix (above)

Phase III: Implementation

Division of Responsibilities

- Buyer:
  - System conversions (e.g., EHRs and IT)
  - Onboarding of staff/MDs
  - Marketing
- Seller:
  - AR run down
  - MD/staff productivity
  - Community outreach
- Mutual: usually a joint committee for oversight of the process
  - Especially for overlapping areas such as marketing to patients and the community

Phase III: Implementation

Strong Work Plan

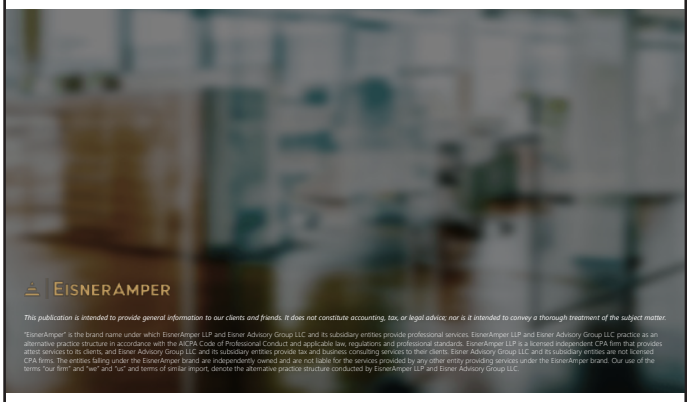
- Joint development of growth plans should begin
  - This allows the practice and PE partners/owners to immediately generate value for both PE firm and the partners/physicians (assuming they hold some equity)
- Monitor progress against the timeline and adjust as needed
  - Small delays are common, and it is generally better to nail down details than to rush into final signing
- Close the deal and transition operational management according to the ground rules established

Lessons Learned: Detail

- Without clear strategy and internal consensus: deals can fall apart at the very end of the process
- Wrong partner:
  - False expectations or mis-understandings, discovered too late
  - Disagreements on fundamentals, impeding deal structure and/or leading to a alck of mutual value added
- Who is in charge?
- Difficulty of un-wind, especially of third-party loans
- Trouble with old accounts receivable (AR)
- Trouble with smooth transition

Lessons Learned: Take-away

- If you are considering a private equity, hospital, or practice deal, there is tremendous value in following this summarized process with the appropriate support
- Even if no deal, Phase I: Strategy Planning is important



SELF EVALUATION

Planning, Negotiating and Implementing a Practice Merger or Acquisition

1. How much money is PE sitting on:

a. $10M
b. $100M
c. $1B
d. $20B

2. T/F - Should EVERY partner participate in the planning process for a deal?

3. T/F - The value of a practice equals its EBITDA ("Earnings before interest, taxes, depreciation and amortization)?

4. Which of the following should be reviewed during Phase II?

a. Revenue cycle management
b. How old is the practice
c. How nice is the office
d. Do the MDs have publicly-traded stock in healthcare companies

5. T/F - PE firms must meet FMV standards in paying for acquisitions

6. T/F - Hospitals typically pay market value in acquiring practices

7. Which elements are important in judging "fit" between a PE firm and a practice

a. Operational control over schedules
b. Capital available to PE
c. Future compensation model
d. Commitment to patient care
e. All of the above

8. What is the biggest risk factor in failed deals

a. Compensation offer
b. EBITDA multiple
c. Shareholder vesting rights
d. Lack of consensus
e. All of the above

Answer Key: 1. D, 2. T, 3. F, 4. A, 5. F, 6. F, 7. E, 8. E

Joel Kahn, MD

Joel Kahn, MD, of Detroit, Michigan, is a practicing cardiologist, and a clinical professor of medicine at Wayne State University School of Medicine. Known as "America's Holistic Heart Doc", Dr. Kahn is a diplomate of the American Board of Internal Medicine and maintains subspecialty board certification in cardiovascular medicine.

Dr. Kahn has authored scores of publications in his field including articles, book chapters, and monographs. He writes articles for Huffington Post, MindBodyGreen, and Reader's Digest and has five books in publication including *Your Whole Heart Solution*, *Dead Execs Don't Get Bonuses*, and *The Plant Based Solution*. He has had regular appearances on Dr. Phil, The Doctors TV Show, and Fox 2 News.

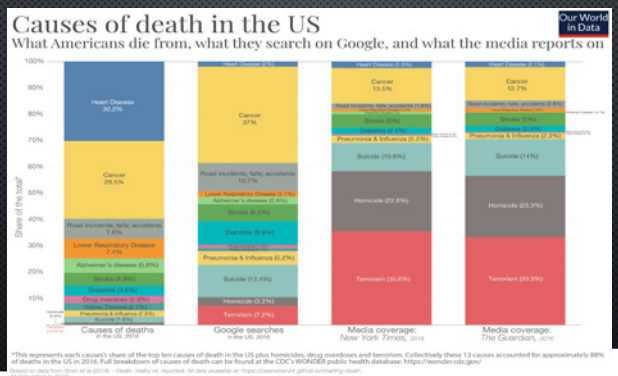
You may contact Dr. Kahn with any questions or comments at www.drjoelkahn.com.

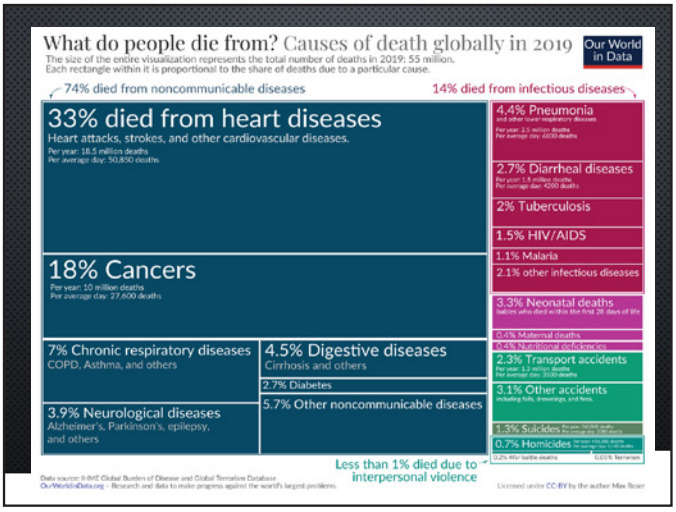
Joel Kahn, MD, FACC

Advanced Preventive Cardiology
Clinical Professor, Wayne State University
www.drjoelkahn.com
248-731-7412

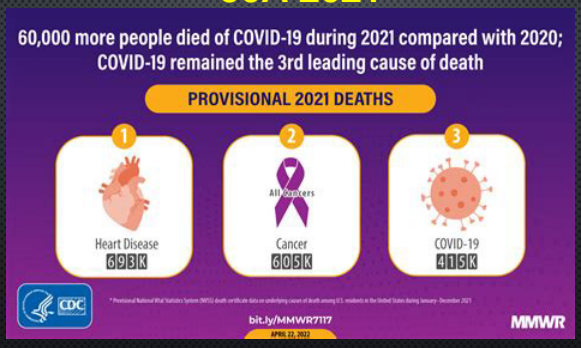
Heart Disease Prevention

Secret 1: Heart Disease is Still #1



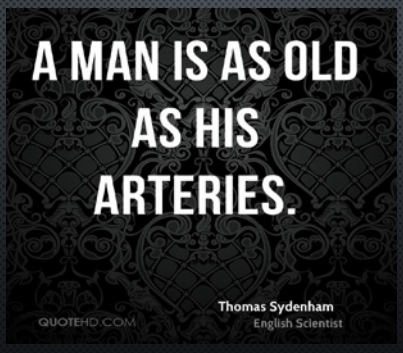


HEART DISEASE DEATHS: USA 2021

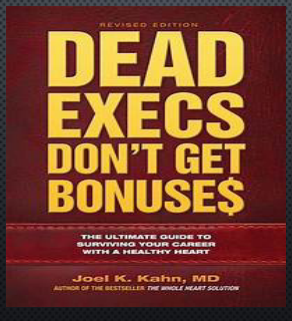


DON'T DIE OF HEART DISEASE: KNOW YOUR ARTERIAL AGE

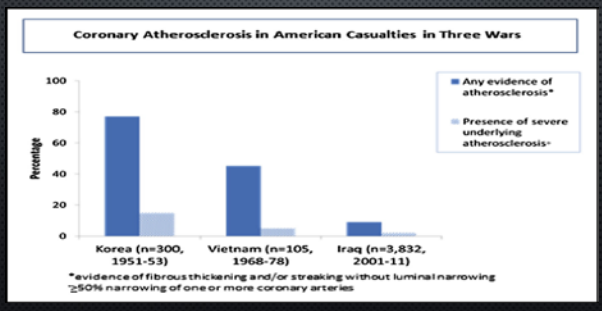
THOMAS SYDENHAM, MD 1624-1689

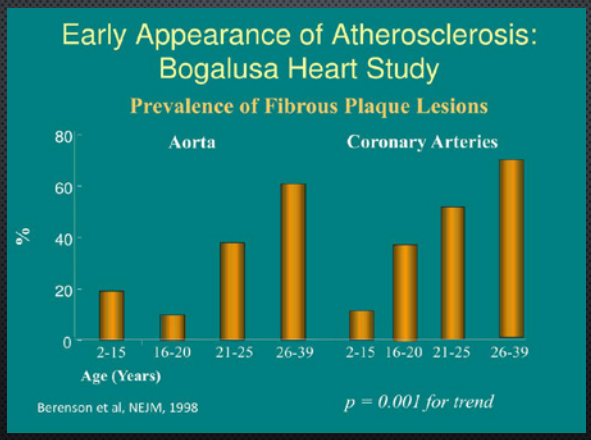


ACTION STEP 1: FOCUS ON HEART DISEASE

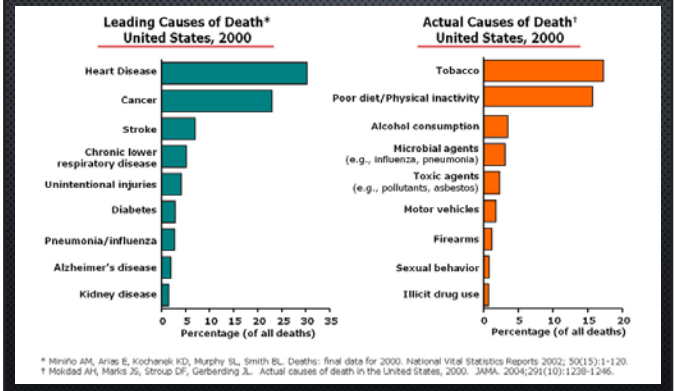


SECRET 2: HEART DISEASE STARTS YOUNG, SO YOU START EARLY





SECRET 3: WE KNOW WHY



Why Not Turn Off The Faucet?

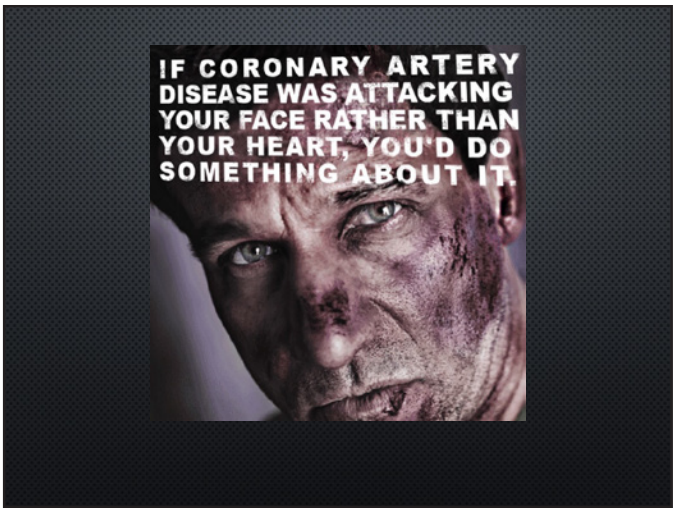
PREVENT 85% OF HEART ATTACKS

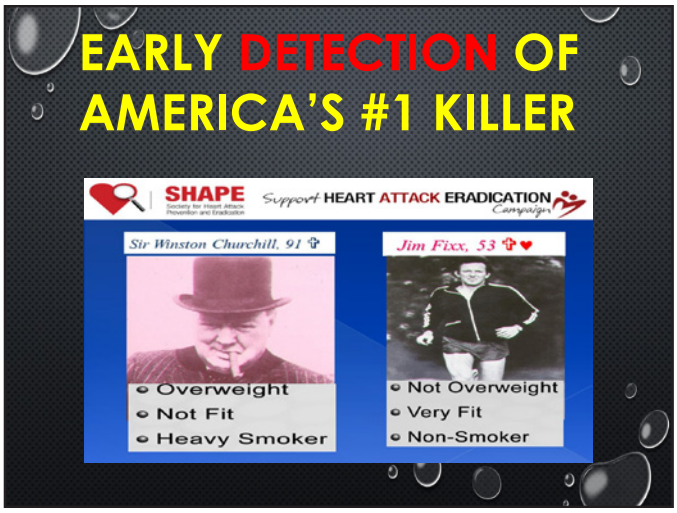
- DON'T SMOKE
- WALK 30-40 MINUTES DAILY
- EAT >5 SERVINGS OF FRUIT/VEG A DAY
- SLEEP 7 HOURS A NIGHT
- ENJOY A FEW ALCOHOLIC BEVERAGES A WEEK

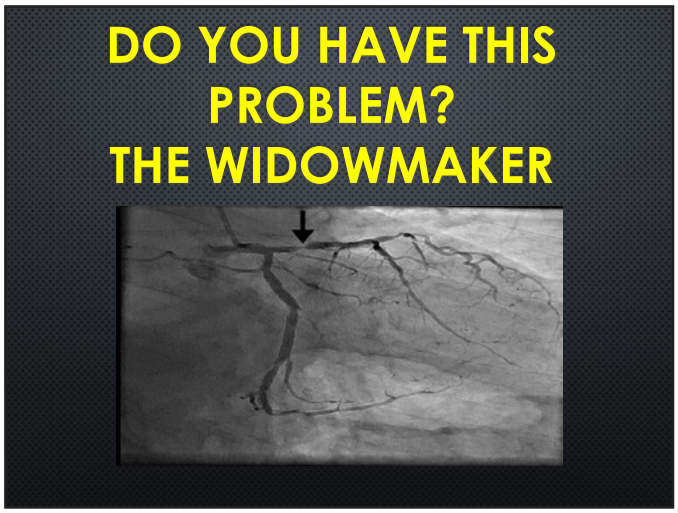
- MORGEN STUDY 2013 NETHERLANDS 17,887 MEN AND WOMEN
- KAROLINSKA STUDY 2014 SWEDEN 20,721 MEN

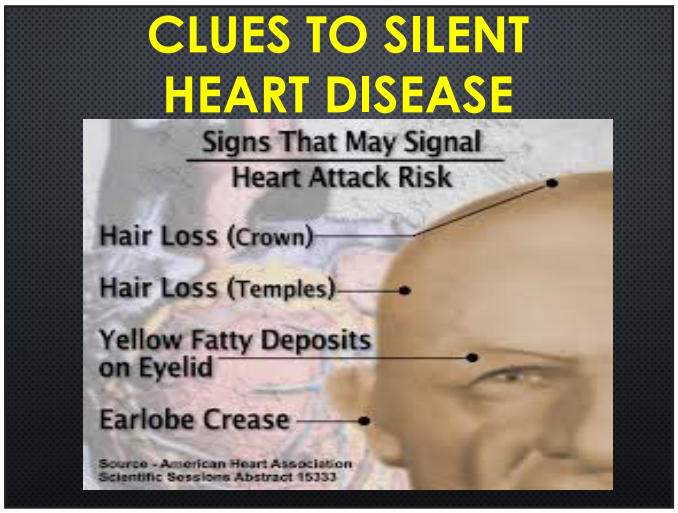
SECRET 4: TEST NOT GUESS

person
↓
A man is as old as his arteries.
Thomas Sydenham

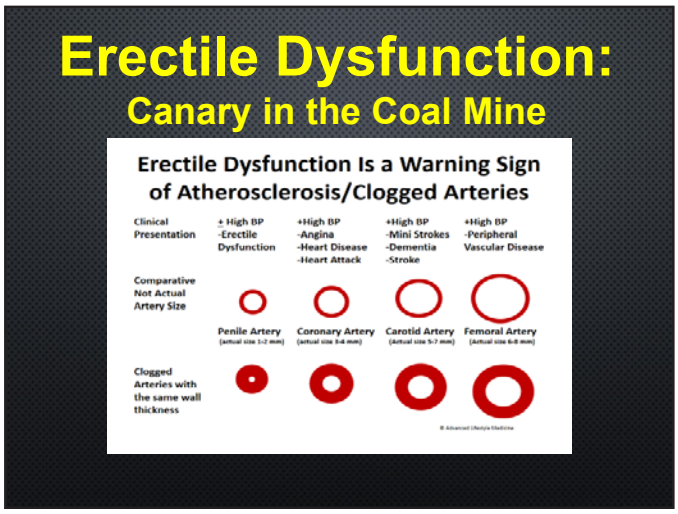

IF CORONARY ARTERY DISEASE WAS ATTACKING YOUR FACE RATHER THAN YOUR HEART, YOU'D DO SOMETHING ABOUT IT.


EARLY DETECTION OF AMERICA'S #1 KILLER
SHAPE
Support HEART ATTACK ERADICATION Campaign
Sir Winston Churchill, 91
Overweight
Not Fit
Heavy Smoker
Jim Fixx, 53
Not Overweight
Very Fit
Non-Smoker

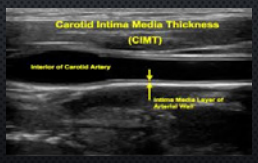

DO YOU HAVE THIS PROBLEM?
THE WIDOWMAKER


CLUES TO SILENT HEART DISEASE
Signs That May Signal Heart Attack Risk
Hair Loss (Crown)
Hair Loss (Temples)
Yellow Fatty Deposits on Eyelid
Earlobe Crease
Source - American Heart Association Scientific Sessions Abstract 15333


Diagonal EarLobe Crease: DELC


Erectile Dysfunction:
Canary in the Coal Mine
Erectile Dysfunction Is a Warning Sign of Atherosclerosis/Clogged Arteries
Clinical Presentation
+ High BP -Erectile Dysfunction
+High BP -Angina -Heart Disease -Heart Attack
+High BP -Mini Strokes -Dementia -Stroke
+High BP -Peripheral Vascular Disease
Comparative Not Actual Artery Size
Penile Artery
Coronary Artery
Carotid Artery
Femoral Artery
Clogged Arteries with the same wall thickness

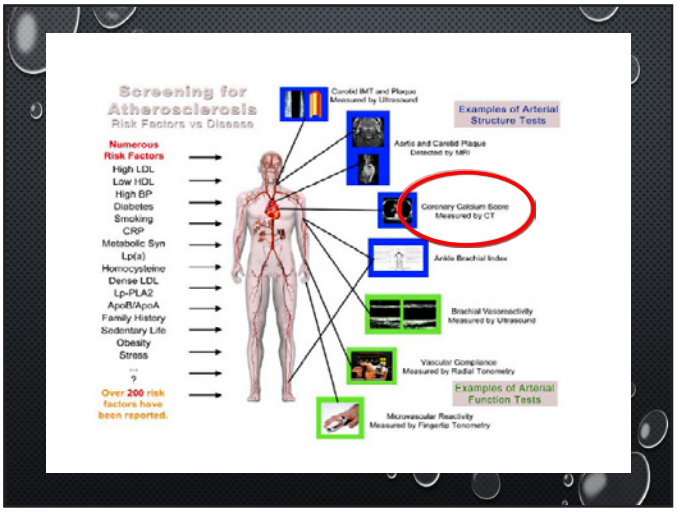
TOOLS OF THE HEART ATTACK PREVENTION SPECIALIST

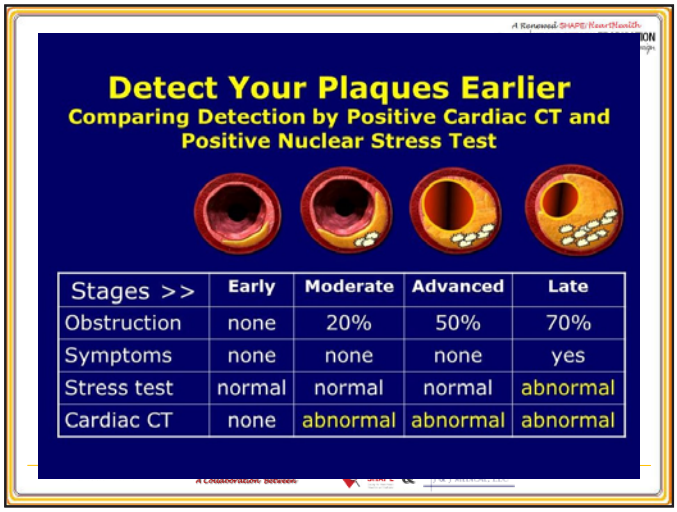


Common Sense

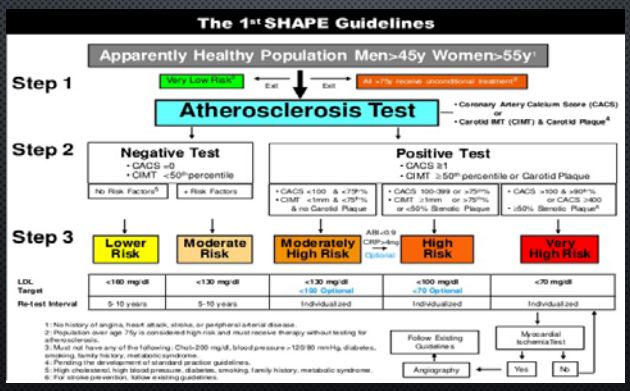
"The best test for prediction of the risk of atherosclerosis is the demonstration of atherosclerosis"

Dr. Ernest Schaeffer, Editor-in-Chief of Atherosclerosis





SHAPESOCIETY.ORG



CORONARY ARTERY CALCIUM SCORE (CACS)

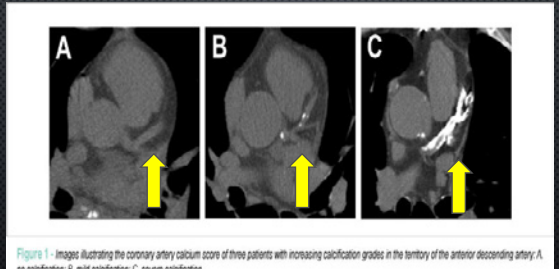


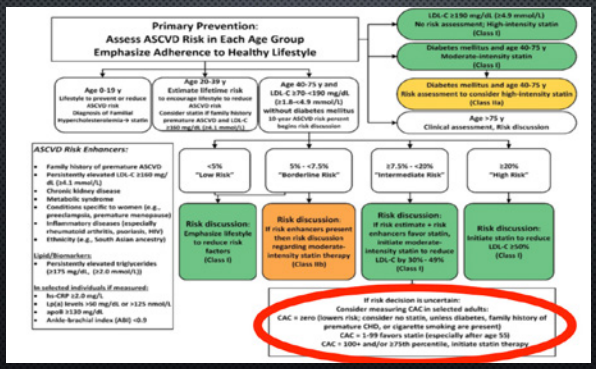
Figure 1 - Images illustrating the coronary artery calcium score of three patients with increasing calcification grades in the territory of the anterior descending artery: A, no calcification; B, mild calcification; C, severe calcification.

THE POWER OF A CACS OF ZERO

CALCIUM SCORE AND CARDIAC FINDINGS:

1. Left main coronary artery: 0
2. Left anterior descending coronary artery: 0
3. Left circumflex coronary artery: 0
4. Right coronary artery: 0
5. Total coronary calcium score: 0

CACS: MAINSTREAM 2019 AMERICAN HEART ASSOCIATION

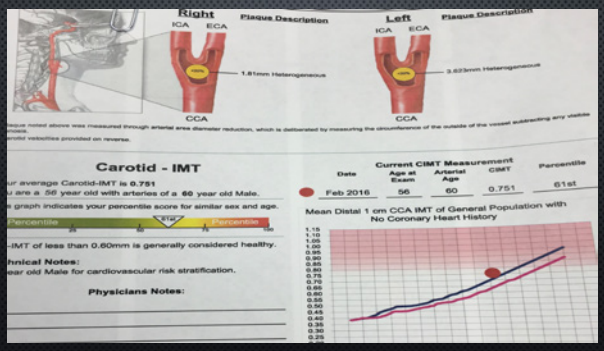


Carotid Intima Media Thickness (CIMT)

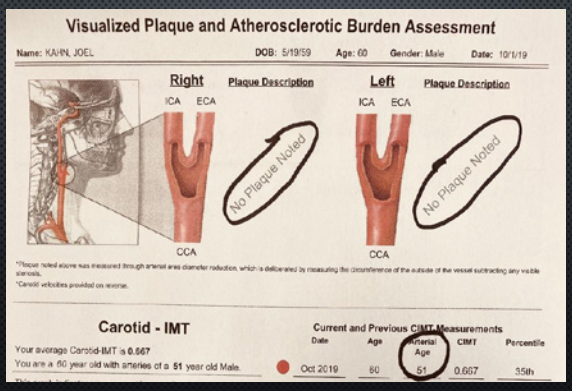
- Direct *in vivo* measurement of thickness of carotid artery wall by B-mode ultrasound
- Vessel wall thickness correlates with status of atherosclerosis and CV events
- Atherosclerosis is a systemic disorder
  - Atherosclerosis in the carotid artery is predictive of disease in other vascular beds

de Groot E, et al. *Circulation* (2004) 109[Suppl III] III-33-III-38.

CIMT: Carotid Intimal Medial Thickness Ultrasound



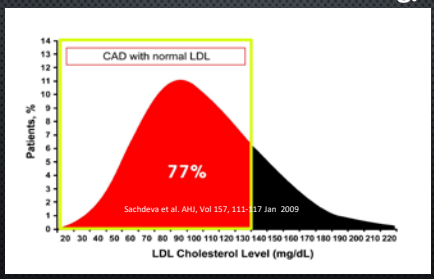
CIMT: A NORMAL

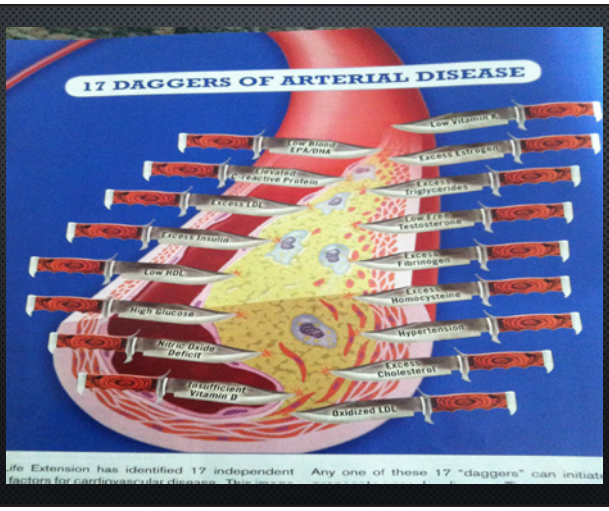


ACTION STEP

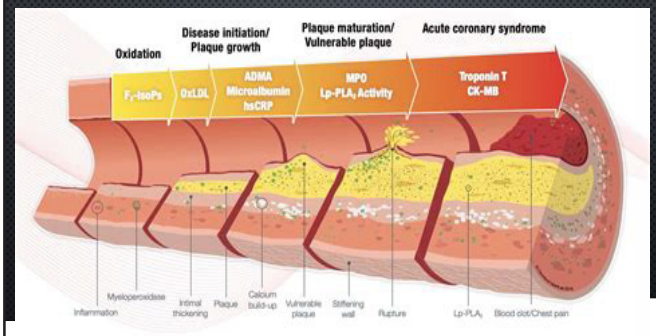
Secret 5: Routine Labs are NOT Adequate

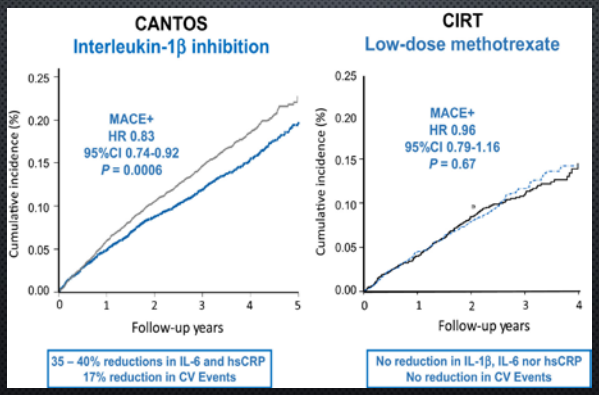
Of 136,905 patients hospitalized with CAD, 77% had LDL levels below 130 mg/dl

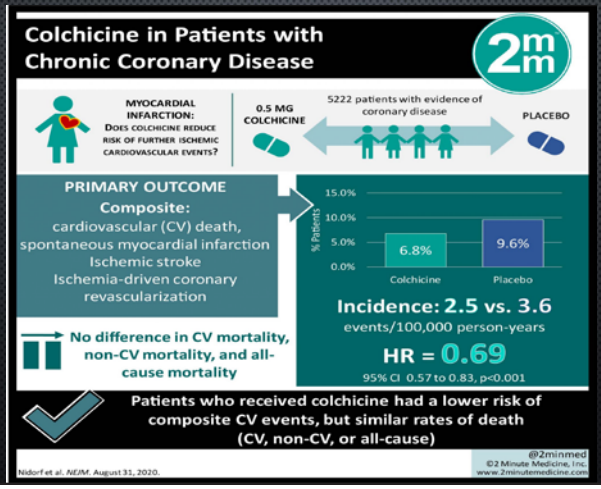




SECRET 6: INFLAMMATION LABS MATTERS

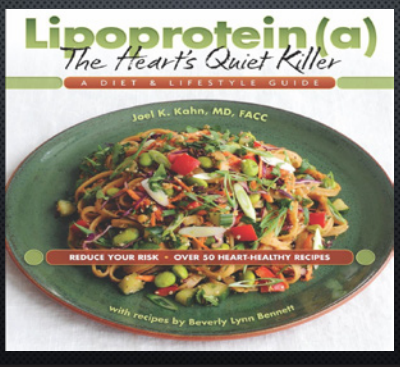


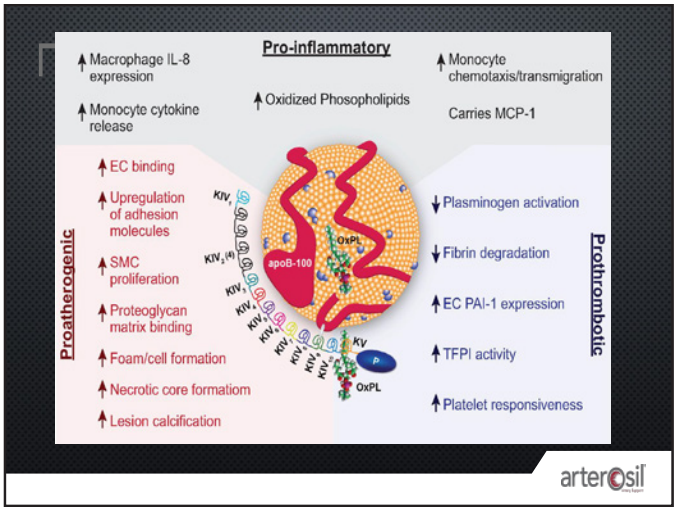


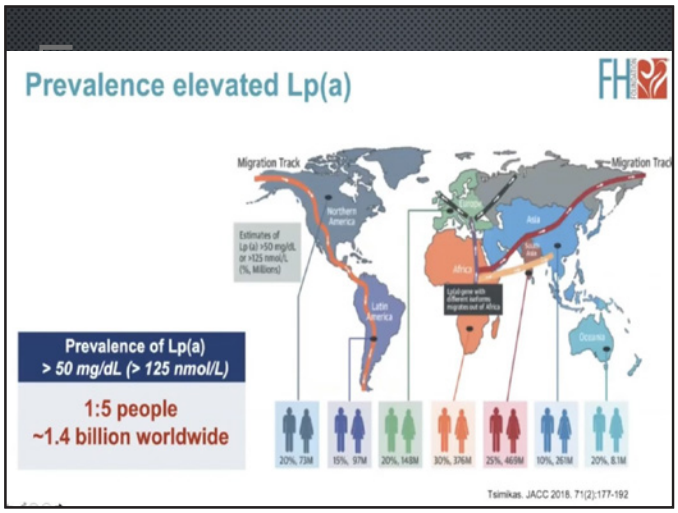


ACTION STEP: LABS

SECRET 7: LIPOPROTEIN(A) LAB

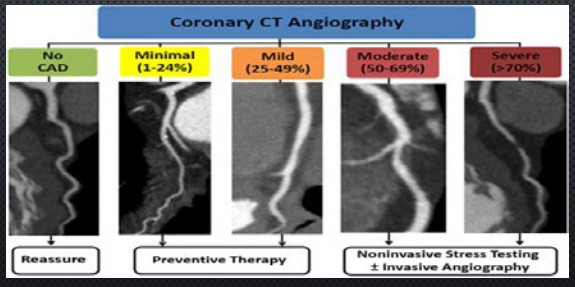




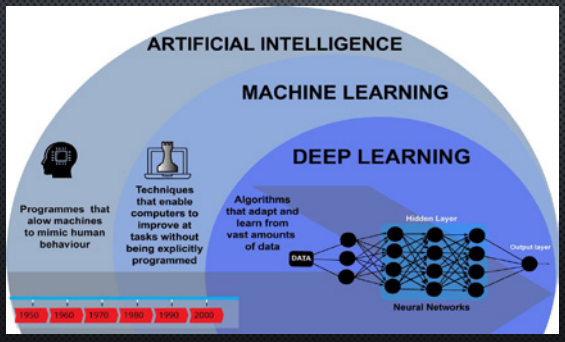


ACTION STEP: TEST NOT GUESS

SECRET 8: CORONARY CT ANGIOGRAPHY (CCTA)

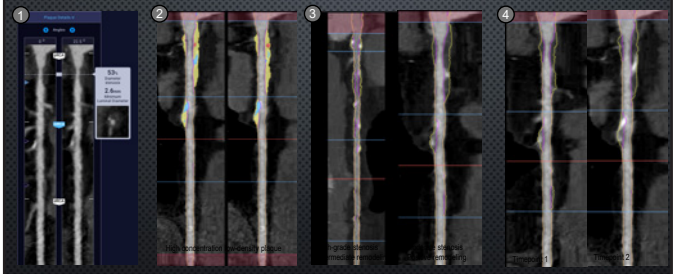


AI IN CARDIOLOGY



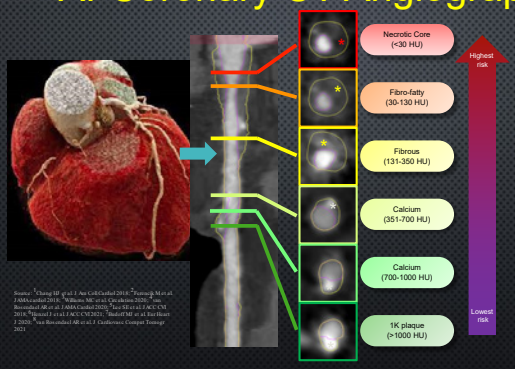
Coronary CCTA With AI Enables Comprehensive Evaluation of Individual Risk

The four (4) most important features of risk: CONFIRM, ICONIC, PARADIGM, PROMISE, SCOT-HEART, ISCHEMIA, PROSPECT, etc.



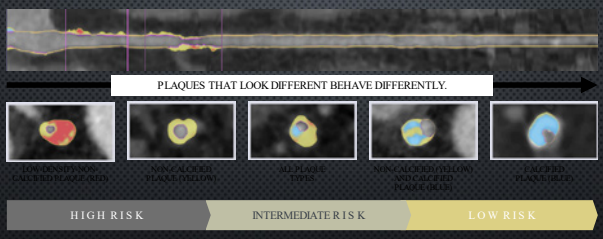
Plaque Burden | Plaque Composition | Vascular Morphology (Stenosis / Remodeling) | Plaque Progression

AI-Coronary CT Angiography



Dark Plaques Dangerous - strongest predictor of heart attack risk.[1-3]

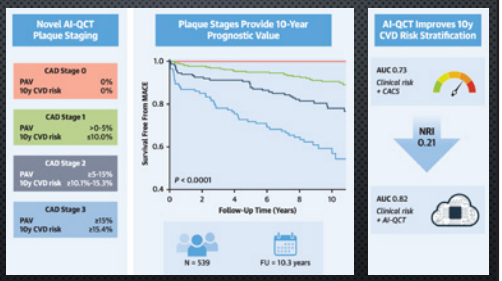
NOT ALL PLAQUES ARE THE SAME.



AI-CCTA: Improved CV Risk Assessment

MACE Prediction:

- CCTA Plaque Stage is a better predictor of short- and long-term MACE events than:
  - Risk Score (ASCVD etc.).
  - Agatston Score.
  - Stenosis presence



Nurmohamed et al JACC Imag 2023

Therapy Based on Plaque Stage

Freeman, A et al Am J Med 2022

Stage	Stenoses	Action	Rescan (until stable):
Stage 0: No Plaque	0	• GDMT / Consider de-escalation	4 years
Stage 1: Mild	<50%	• Statin, Ezetimibe	3 years
Stage 2: Moderate	<50%	Stage 1 Plus • Aspirin, Rivaroxaban • GLP1 if diabetic	2 years
Stage 3: Severe	<50%	Stage 2 plus • Consider PCSK9, Icosapent ethyl, Inclisirin, Bempedoic acid, Colchicine • GLP1 and SGLT2 if diabetic	1 year

CORONARY IMAGING AND CV OUTCOME TRIALS

Drug	CTA Progression	CVOT
Statin	+++ (Regression)	+++
Estrogen	Neutral	Neutral
Xarelto vs Warfarin	+ (slowed progression)	+
Fish Oil (EPA)	++ (slowed progression)	+++
Testosterone	Progression	Harmful
Eliquis vs Warfarin	+ (slowed progression)	+
Atorvastatin	+++ (regression)	+++
Colchicine	++ (mild regression)	++

CHANGES OF CCTA-MEASURED PLAQUE VOLUMES (IN MM³) OVER 12 MONTHS.

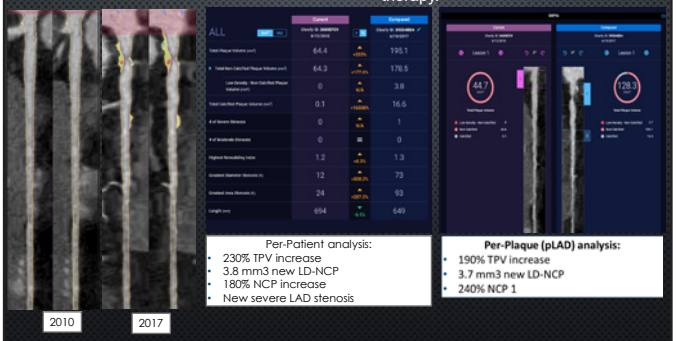
100 patients with serial CCTA over 1 year, 60 on statin therapy, 40 on placebo

Plaque Measures	Placebo (n=40)	Statin (n=60)	P Value
Total Plaque Volume	31.0	-33.3	0.0006
Non-calcified Plaque Volume	13.8	-47.7	<0.001
Low Attenuation Plaque	5.9	-12.2	<0.0001
Calcified Plaque Volume	29.3	10	0.133

ZEB - Atherosclerosis 2013

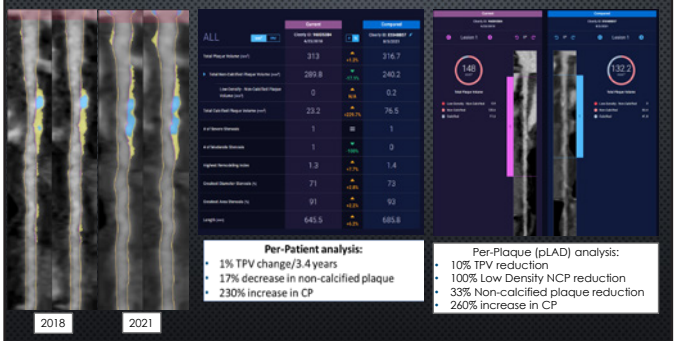
PLAQUE PROGRESSION.

60-year-old female not on medical therapy.



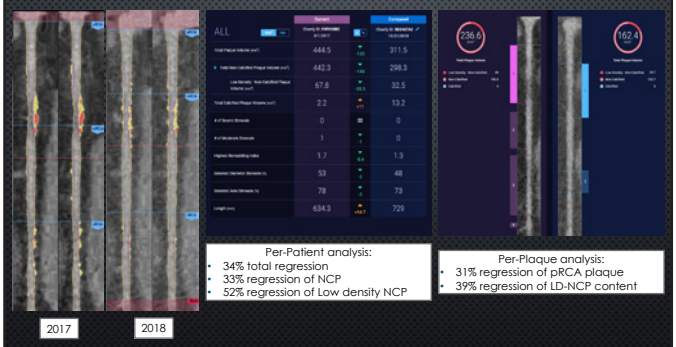
PLAQUE STABILIZATION.

56-year-old man on high intensity statin.

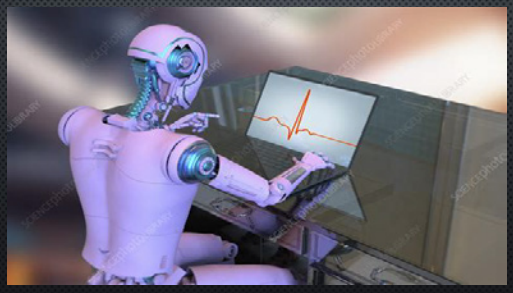


PLAQUE REGRESSION.

55-year-old man taking a PCSK9 inhibitor.



THE FUTURE OF PREVENTION IS BRIGHT



CONCLUSIONS

"All truth passes through three stages.
First, it is ridiculed.
Second, it is violently opposed.
Third, it is accepted as
being self-evident."
-Arthur Schopenhauer

SELF EVALUATION

Heart Disease Prevention

True/False

1. Atherosclerosis is never found in the arteries of 20 year olds.

2. Heart disease, also known as cardiovascular disease, is no longer the #1 killer in the USA.

3. Lifestyle measures including sleeping 7-8 hours predict the freedom from 85% of heart attacks.

4. The best way to identify atherosclerosis is a person without symptoms is an online calculator.

5. The coronary artery calcium CT scan requires sedation and intravenous contrast.

6. A coronary CT angiogram with artifical intelligence analysis can indicate the amount of both soft and hard plaque.

7. In studies using coronary CT angiography with AI imaging, statin medications like Lipitor have been shown to regress coronary plaque.

Answer Key: 1. F, 2. F, 3. T, 4. F, 5. F, 6. T, 7. T

David B. Mandell, JD, MBA

David B. Mandell, JD, MBA, of Ft. Lauderdale, Florida, is a practicing attorney in The Law Offices of David B. Mandell, PC, and a principal of the doctor focused wealth management firm OJM Group, LLC. He specializes in risk management, asset protection, and financial planning and has authored a number of books for doctors including his latest, *Wealth Strategies for Today's Physician: A Multi-Media Playbook*. His articles have appeared in over 100 publications, including over 30 medical specialty journals, and he has addressed many of the nation's leading medical conferences.

Mr. Mandell holds a bachelor's degree from Harvard University from which he graduated with honors, a law degree from the UCLA School of Law where he was awarded the "American Jurisprudence Award" for achievement in legal ethics and earned his MBA from UCLA'S Anderson School of Management.

You may contact Mr. Mandell with any questions or comments at (877) 656–4362 or by email at mandell@ojmgroup.com.

OJMGROUP
Integrity. Collaboration. Expertise.

CORPORATE HEADQUARTERS
8044 MONTGOMERY ROAD, SUITE 440
CINCINNATI, OH 45236
877.656.4362 866.913.4911 WWW.OJMGROUP.COM
Other offices in Arizona and Florida

Increasing Practice Financial Efficiency & Reducing Doctor Stress

David B. Mandell, JD, MBA

Today's Hot Topics in Financial Efficiency

1. Why reducing financial stress matters
2. Avoiding liability in a practice's qualified retirement plan
3. Finding a practice and personal financial advisor you can trust
4. Success factors in M&A for medical and dental practices

OJMGROUP

WHY REDUCING FINANCIAL STRESS MATTERS

OJMGROUP

Doctors Under Financial Stress*

1. 87 percent of respondents said they are moderately-to-severely stressed/burned out on an average day.
2. 63 percent said they were more stressed or burned out than they were three years ago.
3. The top three things that they felt would help them reduce stress:
   a. Better work hours and/or less call (32.5 percent)
   b. More or better work/life balance (30.7 percent)
   c. **Improved finances, compensation, reimbursement (29 percent)**

OJMGROUP

*Of 2,000 physicians as reports by Bouchard, Stephanie, "Impact of Physician Stress Underestimated," HealthCare Finance News, December 2, 2011

AVOIDING LIABILITY IN YOUR QUALIFIED PLAN

OJMGROUP

Are You Overpaying and Exposed?

- Parties involved in QRP administration
  - Recordkeeper
  - Third Party Administrator
  - Investment advisor
- "Bundled" services often lead to conflicts, kick-backs, expensive fund lineups
- Many small practice plans have not been reviewed
- As plan sponsor/trustee, you have fiduciary liability to employees
  - You can be sued for underperformance; high expense funds
    - U. of Chicago, MIT
    - MassMutual, Ameriprise, Nationwide settlements.
  - **Solution: have your plan audited independently with benchmarks**

OJMGROUP

Case Study: Plastic Surgeon Overpaying and Exposed

- Employees: 1 physician, 4 employees, including spouse
- Fees: 1.50% Investment Advisory
  - 2.41% across mutual fund expenses, TPA/Recordkeeping, and Investment Advisory
- This was a pooled investment account, meaning all participant investments are managed in the same manner. This can cause liability for the plan since not all participants will be comfortable taking the same level of risk.

Solution

- Plan design changed to allow each participant to direct his/her individual investments, including target-date retirement options.
- Per industry benchmarking, the advisory fee was dropped to 0.60% for the plan. Total fees dropped from 2.41% to 1.63%, which saved the plan $4,000 annually.

OJMGROUP

FINDING A PRACTICE AND PERSONAL FINANCIAL ADVISOR YOU CAN TRUST

OJMGROUP

Are Financial Advisors "Worth It"?

- Not for everyone
  - Fee drag is real
  - Some have the passion, time, dedication to DIY
- But.... studies show those with advisors benefit over time
  - **Vanguard's study *Quantifying Vanguard Advisor's Alpha*** looked at many factors: Behavioral coaching, appropriate asset allocation/diversification, cost effective implementation, rebalancing, asset location/utilizing accounts efficiently, spending strategy and withdrawal order
  - Additional alpha varied widely through the population, but Vanguard estimated advisors can **potentially add 3 percent in net returns—calculated retroactively on an annual basis.**
  - **Morningstar's study *Alpha, Beta and Now…Gamma*** focused on investing for retirement. Many of same factors: customized withdrawal plans during retirement; tax efficiency; total wealth asset allocation; guaranteed income efficiency and asset allocation predicated on future spending needs.
  - Concluded that retiree could expect "**an annual return increase of plus 1.59 percent**"
- For physicians and dentists, opportunity cost and "highest and best use"

OJMGROUP

When is a Good Time? Where to Find?

When? Anytime, but also…

- Practice: QRP review, interest in Non-Qualified plans, change in staff or partners
- Starting out/ Have funds to invest
- Key transition (new job, kids, move)
- Retirement "red zone"
- Other?

Where?

- Referrals from colleagues
- Research
- Specialization, expertise/publication
- Other?

OJMGROUP

What Can Advisor Help With Beyond Investments?

- **Practice issues**
  - QRP and Non-qualified plan design, execution
  - Tax reduction
  - Asset protection
  - Contacts on most other areas – billing/coding, financial management, healthcare law, tax preparation, M&A, etc.
- **Personal planning**
  - Debt repayment/budgeting
  - Tax reduction
  - Asset protection
  - Insurances
  - College education funding
  - Retirement planning
  - Charitable/estate planning

OJMGROUP

Why Is It Difficult to Determine If Your Advisor Is Working for You?

- "Financial Advisor" meaningless
  - Role of the financial professional is difficult to determine. Impossible to distinguish based on title
- Lack of transparency in the financial industry
- Difficult to determine what you are paying for advice and how you are charged
- Advisor's employing firm could be creating products under a different brand

OJMGROUP

Types of Advisors

- Brokers and Banks
- Insurance Agents
- Fee-Only Financial Advisors
- Automated Investment Management (Robo-Advisors)
- Registered Investment Advisors (RIAs)
- Strategy/Sleeve Advisors such as Private Equity, Hedge Funds

OJMGROUP

6 Questions to Ask Your Advisor/Prospective Advisor

1. Do you owe me a fiduciary duty as a client, or are you held only to a "suitability" standard?
2. Can you provide a detailed explanation of all the ways in which you are compensated?
3. Does your firm make money in other ways on my individual investments?
4. Do you use an outside custodian?
5. Do you utilize proprietary securities?
6. Does your firm engage in investment banking activities?

OJMGROUP

Trust Is #1

OJMGROUP

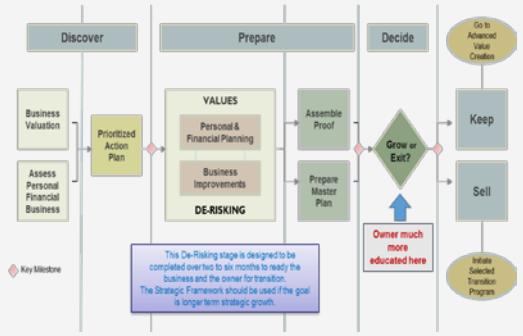
5 SUCCESS FACTORS IN PRACTICE M&A

OJMGROUP

#1: PREPARING THE PRACTICE FINANCIALLY
MAXIMIZING VALUE

OJMGROUP

Value Acceleration Process



OJMGROUP

Key Determinants of Value: Medical Practice

- Retention of key physicians and staff after transaction close
- A significant dollar amount of Adjusted EBITDA
  - Adjusted EBITDA = Practice Earnings Before Interest Expenses, Income Taxes, Depreciation and Amortization Expense + adding back non-recurring expenses + owner-related expenses + excess owner compensation
- Diversified sources of revenue (Medical & Ancillaries)
- Adjusted EBITDA margins that are consistently greater than 20%
- Highlighted growth opportunities (organic and add-on)

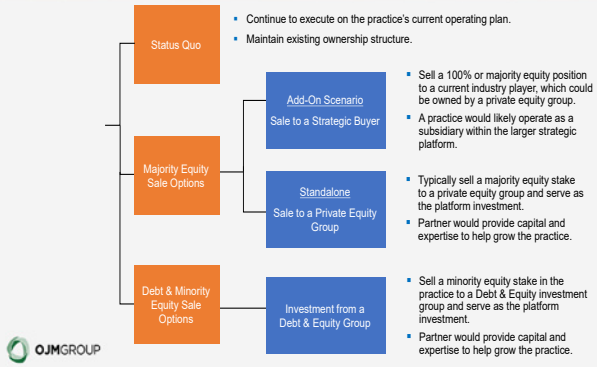
OJMGROUP

#2: DETERMINING THE RIGHT TRANSACTION FOR YOU

ONE SIZE DOES NOT FIT ALL

OJMGROUP

Strategic Options



OJMGROUP

#3: FINDING THE RIGHT ADVISOR TEAM

EXPERIENCE & EXPERTISE MATTER

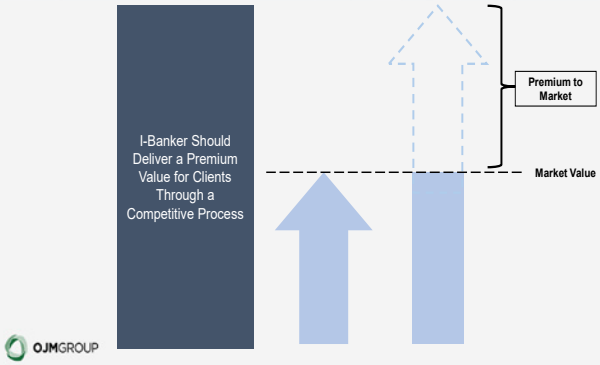
OJMGROUP

Finding the Right Team

- **Wealth Advisor** – how does a transaction impact future financial life?
- **Practice Accountant** – know the books
- **Transaction Accountant** – may be the practice accountant or one who has experience in deals
  - Identify strengths and weaknesses
  - Review/improve financials before going to market
- **Experienced M&A Attorney** – ideally within healthcare transactions; orthopedic deals
- **Investment Banker –** key to create maximum value in deal, field competitive offers, negotiate terms
  - Compensation should be tied to success/value creation
  - Better off, net of fee

OJMGROUP

What an Investment Banker Can Offer



OJMGROUP

#4: DEALING WITH PRIVATE EQUITY

OJMGROUP

Dealing with Private Equity (PE)

These tips come our podcast Episodes 4.10 and 4.1

Podcast Guests: Investment banker Clint Bundy and private equity firm founder Matt Ebbel

- For practices that will become a platform to acquire others, there will be considerable interaction with PE firm(s)
  - Reverse due diligence (RDD) is crucial – other deals, principals of portfolio firms, firm reputation, etc.
  - Time and effort with key players
- For practices joining an existing platform
  - Most physicians/practices will not interact much with PE firms directly
  - Still, RDD is crucial – but easier
    - Speak extensively with the platform principals about business plan and vision
    - Speak with physicians, staff, even vendors (pharma reps) in practices already acquired
- For both, a key adviser who knows the players (attorney, investment banker) can be invaluable

OJMGROUP

#5: PREPARING MENTALLY

UNDERSTAND & ACCEPT HOW THINGS WILL BE DIFFERENT

OJMGROUP

Preparing Mentally

- Motivation is the fundamental factor to any deal: the WHY?
- Are you prepared to become an employee? Have bosses?
- How will this impact your daily life as a physician in the practice – managerially, medically?
- How will this impact you financially?
  - Liquidity event
  - Lower annual income
- How does this jive/not jive with your life goals?

OJMGROUP

About OJM Group

- Specialized, fee-based wealth management firm
- 17 years in business; doctor clients in 48 states
- Multidisciplinary; three divisions
- Corporate and personal planning
- Goal: Reducing physician financial stress

OJMGROUP

How We Work With Physicians & Dentists

- **Investing**
  - RIA
  - Fiduciary, independent custodian
  - Tax-focused
- **Insurance and Benefits**
  - Life, disability, long term care insurance
  - Through partner firm, P&C coverages
  - Qualified and non-qualified plans
- **Consulting**

OJMGROUP

Personal Wealth Planning

- **Diagnostic vs. Treatment**
- **Advice and Expertise for a Flat Fee**
- **Building a Relationship**

OJMGROUP

Wealth Planning for the Modern Physician Podcast

- Physician wealth podcast hosted by David Mandell, JD, MBA
- Guests include physicians of all specialties and wealth management industry experts
- More than 75 episodes published to date
- Available on Apple Podcasts, Spotify and other popular podcast platforms
- Video versions of episodes now available on YouTube
- Scan the QR Code to listen and subscribe!

OJMGROUP

Wealth Strategies for Today's Physician: A Multi-Media Playbook

- New content from OJM: Our first book since 2020!
- Co-authored by OJM Group partners
- Innovative multi-media format includes more than 90 links to videos and podcast episodes that offer unique perspectives and real-world examples
- Videos to be periodically updated by OJM so that the Playbook remains current over time
- Crafted in six informative Strategies that can help physicians protect assets, reduce taxes, invest wisely and build wealth for retirement
- Bonus Strategy for medical practice owners and *doctorpreneurs*

Scan the QR Code to get a Free Copy!

OJMGROUP

Contact the Presenter

David B. Mandell, JD, MBA
OJM Group Partner

- 877.656.4362
- mandell@ojmgroup.com

OJMGROUP

Disclosure

OJM Group, LLC. ("OJM") is an SEC registered investment adviser with its principal place of practice in the State of Ohio. SEC registration does not constitute an endorsement of OJM by the SEC nor does it indicate that OJM has attained a particular level of skill or ability. OJM and its representatives are in compliance with the current notice filing and registration requirements imposed upon registered investment advisers by those states in which OJM maintains clients. OJM may only transact practice in those states in which it is registered or qualifies for an exemption or exclusion from registration requirements. For information pertaining to the registration status of OJM, please contact OJM or refer to the Investment Adviser Public Disclosure web site www.adviserinfo.sec.gov.

For additional information about OJM, including fees and services, send for our disclosure brochure as set forth on Form ADV using the contact information herein. Please read the disclosure statement carefully before you invest or send money.

This presentation contains general information that is not suitable for everyone. The information contained herein should not be construed as personalized legal or tax advice, or as a recommendation of any particular security or strategy. There is no guarantee that the views and opinions expressed in this article will be appropriate for your particular circumstances. Tax law changes frequently, accordingly, Information presented herein is subject to change without notice. You should seek professional tax and legal advice before implementing any strategy discussed herein.

OJMGROUP

SELF EVALUATION

Increasing Practice Financial Efficiency & Reducing Doctor Stress

1. According to the Healthcare Finance News survey referenced in the talk, the percentage of physicians surveyed who felt moderately-to-severely stressed was:

a. 17%
b. 37%
c. 47%
d. 87%

2. T/F - Many physicians in private practice are personally liable as fiduciaries for their practice's qualified retirement plan.

3. T/F - The Morningstar and Vanguard studies showed that most investors do not benefit from working with a professional advisor.

4. Which planning areas can professional advisors assist doctors with beyond investing:

a. Debt repayment/budgeting
b. Tax reduction
c. Asset protection
d. Insurances
e. All of the above.

5. T/F - The term "Financial Advisor" is standardized so that a physician or dentist working with a person with such a title knows exactly what their education and training will be.

6. T/F - "EBITDA" stands for "Earnings Before Interest Expenses, Income Taxes, Depreciation and Amortization Expense"

7. Which types of advisors are typically involved in a sale/merger of a medical or dental practice:

a. Personal Wealth Advisor
b. Practice Accountant
c. M&A Attorney
d. Investment Banker
e. All of the above

Answer Key: 1. D, 2. T, 3. F, 4. E, 5. F, 6. T, 7. E

C. Wayne Weart, Pharm.D., FASHP, FAPhA

C. Wayne Weart, PharmD, of Charleston, South Carolina, is professor emeritus of the Department of Clinical Pharmacy and Outcome Sciences at Medical University of South Carolina (MUSC) College of Pharmacy, as well as professor emeritus of Family Medicine in the College of Medicine, MUSC. Prior to MUSC he instructed at West Virginia University.

Dr. Weart has authored more than 100 publications, and he has presented hundreds of hours of lectures to numerous professional groups and societies, medical and house staffs at both West Virginia University and MUSC, and national pharmacy and medical seminar audiences across the country.

He has received numerous awards and honors in his field including: "Outstanding Teacher" awards at both West Virginia University and MUSC; "Hospital Pharmacist of the Year" in both South Carolina and West Virginia; and designation as a Fellow of the American Society of Health Systems Pharmacists. In 1991 Dr. Weart was among the first pharmacists to become a board-certified pharmacotherapy specialist.

You may contact Dr. Weart with any questions or comments by email at weartcw@musc.edu.

C. Wayne Weart, Pharm D, BCPS, FASHP, FAPhA

Professor of Clinical Pharmacy and Outcome Sciences
South Carolina College of Pharmacy
Professor of Family Medicine
Medical University of South Carolina
(843) 792-3606. weartcw@musc.edu

Management of Patients with Heart Failure

The 2023 AHA Statistical Update - Heart Failure

Circulation. 2023;147:e525-e536

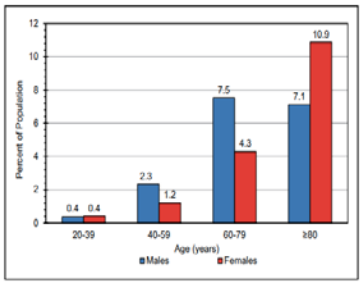


Chart 22-3. Prevalence of HF among US adults ≥20 years of age by sex and age (NHANES, 2017–2020).
https://www.cdc.gov/nchs/nhanes/

≈6.7 million Americans ≥20 years of age had HF, which is increased from ≈6.0 million according to NHANES 2015 to 2018

The lifetime risk for HF in the community ranges from 20% to 46% at 45 years of age and is higher in individuals with higher BP and BMI.

Incidence rates by HF subtype were as follows: **34.9 HFrEF cases, 26.9 HFpEF cases, and 6.7 HFmrEF cases per 10 000 person-years.** After HF onset, **all cause mortality rates were 459 events per 10 000 person-years among those with HFrEF, 394 events per 10 000 person-years in individuals with HFpEF, and 497 events per 10 000 person-years in those with HFmrEF**

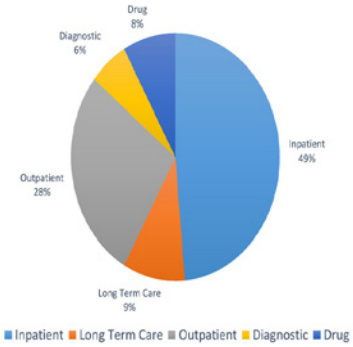
1

The 2023 AHA Statistical Update - Heart Failure

Circulation. 2023;147:e525-e536

- **In 2012, total cost for HF was estimated to be $30.7 billion (2010 dollars), of which more than two-thirds was attributable to direct medical costs. Projections suggest that by 2030 the total cost of HF will increase by 127%, to $69.8 billion**, amounting to ≈$244 for every US adult.
  - Circ Heart Fail. 2013;6:606–619. doi: 10.1161/HHF.0b013e318291329a
- In a systematic review of **HF-associated medical costs in the United States from 2014 to 2020, the annual median total cost was estimated at $24,383 per patient, with HF hospitalizations accounting for the majority ($15,879 per patient).**
  - Pharmacoeconomics. 2020;38:1219–1236. doi: 10.1007/s40273-020-00952-0

Breakdown of cost of care for patients with HF

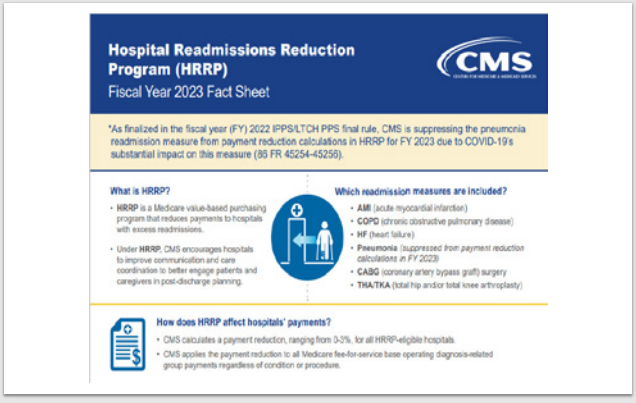


The breakdown of cost of care is shown for care types (2010 resource use). Because this study was performed, it is likely that care has shifted slightly to the outpatient setting.

Journal of Cardiac Failure 2022 28453-466DOI: (10.1016/j.cardfail.2021.12.017

Economic Issues in Heart Failure in the United States

- The **incidence is approximately 1,000,000 new patients with heart failure per year in the US. The annual cost of caring for a patient with heart failure is near $30,000 in the US and it is the second most common inpatient diagnosis billed to Medicare** and has among one of the highest 30-day readmission rates of any other medical or surgical condition.
- The **cumulative rate of all-cause hospitalization was 218.8 admissions per 100 person-years, and the median length of stay for HF-related, CV-related, and all-cause hospitalizations was 5 days**. Also, **22.3% of patients were readmitted within 30 days, 33.3% were readmitted within 60 days, and 40.2% were readmitted within 90 days.**
  - Journal of Cardiac Failure 2022 28453-466DOI: (10.1016/j.cardfail.2021.12.017



Heart Failure Mortality

- **Mortality associated with HF is substantial, such that ≈1 in 8 deaths in 2020 has HF mentioned on the death certificate. The number of underlying causes of deaths attributable to HF was 48.6% higher in 2020 (85,855) than in 2010 (57,757).**
  - https://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm
- Editorialists conclude: **"Ejection fraction does not appear to be an accurate biomarker for risk stratification after a patient has crossed the threshold to an HF admission.** These data should serve as another wake-up call to all providers to recognize the risk associated with HF."
  - Journal of the American College of Cardiology November 2017 DOI: 10.1016/j.jacc.2017.08.074

American Heart Association

AMERICAN COLLEGE of CARDIOLOGY FOUNDATION

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

Developed in partnership with the Heart Failure Society of America

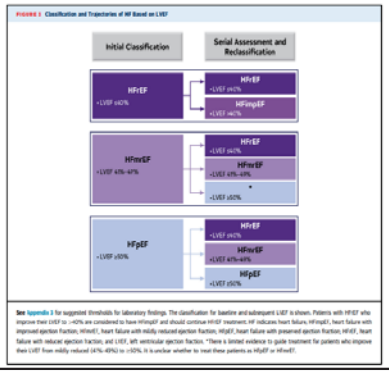
Published online ahead of print April 1, 2022, available at: Circulation.
https://www.ahajournals.org/doi/10.1161/CIR.0000000000001063 and
Journal of the American College of Cardiology published online ahead of print April 1, 2022.
https://www.jacc.org/doi/10.1016/j.jacc.2021.12.012 and
Journal of Cardiac Failure Volume 28 Issue 5 Pages 878-880 (May 2022) DOI:
https://doi.org/10.1016/j.cardfail.2022.02.010

Revised Classification of HF by LVEF

HFrEF	HFimpEF	HFmrEF	HFpEF
• LVEF ≤40%	• Previous LVEF ≤40% and follow-up measurement of LVEF >40%	• LVEF 41-49%	• LVEF ≥50%
		Evidence of spontaneous or provokable increase LV filling pressures (e.g., elevated NP, noninvasive and invasive hemodynamic measurement)	

J Cardiac Fail 2021;27:387-413 | Circulation. 2022;145:00-00. DOI: 10.1161/CIR.0000000000001063

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines



https://www.jacc.org/doi/10.1016/j.jacc.2021.12.012

The 2023 AHA Statistical Update - Heart Failure

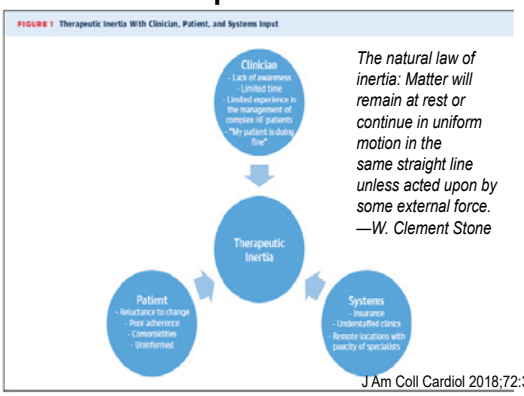
Circulation. 2023;147:e525-e536

- **Initiation of contemporary guideline-directed medical therapy for HFrEF (quadruple therapy with ARNIs, β-blockers, mineralocorticoid receptor antagonists, and SGLT-2 inhibitors) is estimated to reduce the hazard of cardiovascular death or HF hospitalization by up to 62%** (HR, 0.38 [95% CI, 0.30–0.47]) **compared with limited conventional therapy, resulting in an estimated 1.4 to 6.3 additional years alive.**
  - Lancet 2020;396:121–128. doi: 10.1016/S0140-6736(20)30748-0

How many patients with HFrEF are receiving Guideline Directed Medical Therapy?

- **The CHAMP-HF (Change the Management of Patients with Heart Failure) registry** included outpatients in the United States with chronic HFrEF receiving at least 1 oral medication for management of HF.
- **3,518 patients from 150 primary care and cardiology practices were incl**uded. Mean age was 66 +/- 13 years, 29% were female, and mean EF was 29 +/- 8%.
- Among eligible patients, **27%, 33%, and 67% were not prescribed ACEI/ARB/ARNI, beta-blocker, and MRA therapy, respectively.**
- **When medications were prescribed, few patients were receiving target doses of ACEI/ARB (17%), ARNI (14%), and beta-blocker (28%), whereas most patients were receiving target doses of MRA therapy (77%).**
- **Among patients eligible for all classes of medication, 1% were simultaneously receiving target doses of ACE/ARB/ARNI, beta-blocker, and MRA.**
  - In adjusted models, older age, lower blood pressure, more severe functional class, renal insufficiency, and recent HF hospitalization generally favored lower medication utilization or dose.
  - (J Am Coll Cardiol 2018;72:351–66)

Therapeutic Inertia



The natural law of inertia: Matter will remain at rest or continue in uniform motion in the same straight line unless acted upon by some external force. —W. Clement Stone

J Am Coll Cardiol 2018;72:367–69

Cost Barriers

- The current study involved **all 4068 Medicare prescription drug plans implemented in 2020.** Study authors analyzed cost sharing, prior authorization, and step therapy. Here are the key findings:
  - **Tier ≥3 cost sharing was required by 99.1% of plans for ARNI and 98.5% for at least 1 SGLT2 inhibitor.**
  - Only ARNI required prior authorization (24.3% of plans), and step therapy was required only for SGLT2 inhibitors (5.4%) and eplerenone (0.8%).
  - The **median 30-day standard coverage out-of-pocket cost of quadruple therapy was $94 (IQR: $84-$100), including $47 (IQR: $40-$47) for ARNI and $45 (IQR: $40-$47) for SGLT2 inhibitors.**
  - **The median annual out-of-pocket cost of quadruple therapy was $2217** (IQR: $1956-$2579) compared with $1319 (IQR: $1067-$1675) when excluding SGLT2 inhibitors, and $1322 (IQR: $1025-$1588) when including SGLT2 inhibitors and substituting an ACE inhibitor or angiotensin receptor blocker for ARNI therapy.
  - **The median 30-day out-of-pocket cost of generic regimens was $3** (IQR: $0-$9).

Barriers to Access

- **For high-value drugs, placing the burden of payment on patients may inappropriately decrease therapy rates and worsen clinical outcomes.** Sacubitril-valsartan is an example of a cost-effective drug that is unaffordable for many patients with heart failure, contributing to inadequate sacubitril-valsartan use and adherence, increasing heart failure morbidity and mortality. (Circ Heart Fail. 2018; 11e004302) **Copays and deductibles should be minimal for high-value therapies like sacubitril-valsartan and SGLT-2 inhibitors with current out-of-pocket costs covered by the insurance plan**. (Circulation. 2021; 143: 1073-1075) Prioritizing the affordability of high-value drugs is critical to maximize population health outcomes for diseases such as heart failure.
  - Economic Issues in Heart Failure in the United States HEART FAILURE SOCIETY OF AMERICA REVIEW| VOLUME 28, ISSUE 3, P453-466, MARCH 01, 2022

HFrEF Quadruple Treatment

ARNi	BB	MRA	SGLT2i
• Recommended in NYHA II-III to reduce M&M (1 A) • Replace ACEi or ARB with ARNI in NYHA II-III (1 B-R) • ACEi is beneficial to reduce M&M when ARNi not feasible (1 A)	• Metoprolol succinate, carvedilol, or bisoprolol recommended to reduce mortality & hospitalizations (1 A)	• Recommended in NYHA II-IV to reduce M&M, if eGFR >30 ml/min/1.73m² and serum K <5 mEq/L (1 A)	• Recommended to reduce HHF and CV mortality, irrespective of the presence of T2DM (1 A)

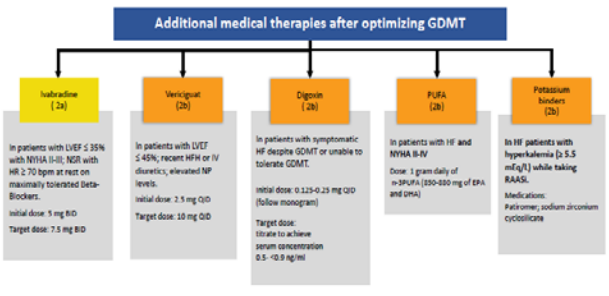
CV, cardiovascular; HHF, hospitalization for HF; M&M, morbidity & mortality; T2DM, type 2 diabetes

Circulation. 2022;145:00–00. DOI: 10.1161/CIR.0000000000001063

Clinical Implications?

- Asked about the plethora of available drug options—beta blockers, sacubitril/valsartan, potassium-sparing diuretics (spironolactone/eplerenone), and SGLT2 inhibitors—for patients with HFrEF, **Dr. Milton Packer** (member of Executive Comm Emperor Reduced Trial) said one of the ways he likes to frame the question is to imagine himself as a patient. **"If I was just given the diagnosis of heart failure with reduced ejection fraction, I would want my physician to initiate therapy with all four classes of drugs within the first 4 to 6 weeks after they made my diagnosis,"** he said. "That means I'm recommending **concomitant, nearly simultaneous initiation of therapy—not on the same day**—but within a reasonably short period of time."

Additional Therapies After GDMT Optimization



Circulation. 2022;145:00–00. DOI: 10.1161/CIR.0000000000001063

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

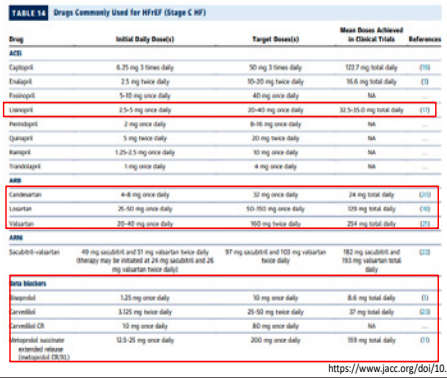


TABLE 16 Drugs Commonly Used for HFrEF (Stage C HF)

Drug	Initial Daily Dose(s)	Target Dose(s)	Mean Doses Achieved in Clinical Trials	References
ACEi				
Captopril	6.25 mg 3 times daily	50 mg 3 times daily	122.7 mg total daily	(19)
Enalapril	2.5 mg twice daily	10–20 mg twice daily	16.6 mg total daily	(3)
Fosinopril	5–10 mg once daily	40 mg once daily	NA	
Lisinopril	2.5–5 mg once daily	20–40 mg once daily	32.5–35.0 mg total daily	(15)
Perindopril	2 mg once daily	8–16 mg once daily	NA	
Quinapril	5 mg twice daily	20 mg twice daily	NA	
Ramipril	1.25–2.5 mg once daily	10 mg once daily	NA	
Trandolapril	1 mg once daily	4 mg once daily	NA	
ARB				
Candesartan	4–8 mg once daily	32 mg once daily	24 mg total daily	(20)
Losartan	25–50 mg once daily	50–150 mg once daily	129 mg total daily	(16)
Valsartan	20–40 mg once daily	160 mg twice daily	254 mg total daily	(21)
ARNI				
Sacubitril-valsartan	49 mg sacubitril and 51 mg valsartan twice daily (therapy may be initiated at 24 mg sacubitril and 26 mg valsartan twice daily)	97 mg sacubitril and 103 mg valsartan twice daily	182 mg sacubitril and 193 mg valsartan total daily	(22)
Beta blockers				
Bisoprolol	1.25 mg once daily	10 mg once daily	8.6 mg total daily	(1)
Carvedilol	3.125 mg twice daily	25–50 mg twice daily	37 mg total daily	(23)
Carvedilol CR	10 mg once daily	80 mg once daily	NA	
Metoprolol succinate extended release (metoprolol CR/XL)	12.5–25 mg once daily	200 mg once daily	159 mg total daily	(1)

https://www.jacc.org/doi/10.1016/j.jacc.2021.12.012

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

Mineralocorticoid receptor antagonists				
Spironolactone	12.5–25 mg once daily	25–50 mg once daily	36 mg total daily	(6)
Eplerenone	25 mg once daily	50 mg once daily	42.6 mg total daily	(13)
SGLT2i				
Dapagliflozin	10 mg once daily	10 mg once daily	9.8 mg total daily	(8)
Empagliflozin	10 mg once daily	10 mg once daily	NR	(9)
Isosorbide dinitrate and hydralazine				
Fixed dose combination	20 mg isosorbide dinitrate and 37.5 mg hydralazine 3 times daily	40 mg isosorbide dinitrate and 75 mg hydralazine 3 times daily	90 mg isosorbide dinitrate and ~175 mg hydralazine total daily	(10)
Isosorbide dinitrate and hydralazine	20–30 mg isosorbide dinitrate and 25–50 mg hydralazine 3–4 times daily	120 mg isosorbide dinitrate total daily in divided doses and 300 mg hydralazine total daily in divided doses	NA	(24)
I_f Channel inhibitor				
Ivabradine	5 mg twice daily	7.5 mg twice daily	12.8 total daily	(25 27)
Soluble guanylate cyclase stimulator				
Vericiguat	2.5 mg once daily	10 mg once daily	9.2 mg total daily	(28)
Digoxin	0.125–0.25 mg daily (modified according to monogram)	Individualized variable dose to achieve serum digoxin concentration 0.5~0.9 ng/mL	NA	(29,30)

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CR, controlled release; CR/XL, controlled release/extended release; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; NA, not applicable; NR, not reported; and SGLT2i, sodium glucose cotransporter 2 inhibitor.

https://www.jacc.org/doi/10.1016/j.jacc.2021.12.012

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

TABLE 15 Benefits of Evidence-Based Therapies for Patients With HFrEF (3-6,8,10-14,23,31-42)

Evidence-Based Therapy	Relative Risk Reduction in All-Cause Mortality in Pivotal RCTs, %	NNT to Prevent All-Cause Mortality Over Time*	NNT for All-Cause Mortality (Standardized to 12 mo)	NNT for All- Cause Mortality (Standardized to 36 mo)
ACEI or ARB	17	22 over 42 mo	77	26
ARNI†	16	36 over 27 mo	80	27
Beta blocker	34	28 over 12 mo	28	9
Mineralocorticoid receptor antagonist	30	9 over 24 mo	18	6
SGLT2i	17	43 over 18 mo	63	22
Hydralazine or nitrate‡	43	25 over 10 mo	21	7
CRT	36	12 over 24 mo	24	8
ICD	23	14 over 60 mo	70	23

*Median duration follow-up in the respective clinical trial.
†Benefit of ARNI therapy incremental to that achieved with ACEI therapy. For the other medications shown, the benefits are based on comparisons to placebo control.
‡Benefit of hydralazine-nitrate therapy was limited to African American patients in this trial.

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor neprilysin inhibitor; CRT, cardiac resynchronization therapy; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; NNT, number needed to treat; RCT, randomized controlled trial; and SGLT2i, sodium-glucose cotransporter 2 inhibitor.

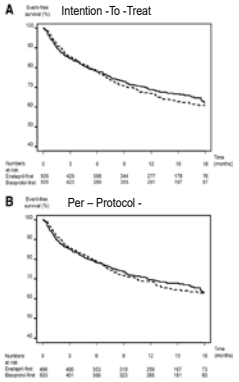
https://www.jacc.org/doi/10.1016/j.jacc.2021.12.012

Initial Medication Choice BB or ACEI/ARB?

- In a patient with new-onset HFrEF, a common question is whether to initiate a beta blocker or ACEI/ARB first. **Initiation of ACEI or ARB is often better tolerated when the patient is still congested ("wet"; when renin-angiotensin-aldosterone system activation is less), whereas beta blockers are better tolerated when the patient is less congested ("dry") with adequate resting heart rate.**
- **Data from the randomized CIBIS (Cardiac Insufficiency Bisoprolol) III trial suggest that either is safe.**
  - JACC 2018; 71:201-30

Effect on Survival and Hospitalization of Initiating Treatment for Chronic Heart Failure With Bisoprolol Followed by Enalapril, as Compared With the Opposite Sequence
(Cardiac Insufficiency Bisoprolol Study (CIBIS) III. Circulation. 2005; 112:2426–35)

Randomized 1010 patients with mild to moderate CHF and left ventricular ejection fraction ≤35%, who were not receiving ACE inhibitor, β-blocker, or angiotensin receptor blocker therapy, to open-label monotherapy with either bisoprolol (target dose 10 mg QD; n=505) or enalapril (target dose 10 mg BID; n=505) for 6 months, followed by their combination for 6 to 24 months. The 2 strategies were blindly compared with regard to the combined primary end point of all-cause mortality or hospitalization and with regard to each of these end point components individually. **Bisoprolol-first treatment was noninferior to enalapril-first treatment**



Bisoprolol solid line; enalapril dashed line

Doses of Beta-blockers in HF

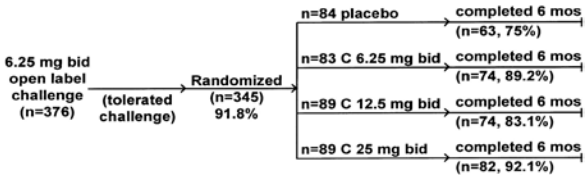
- **Bisoprolol (Cardio-selective) - initial dose 1.25mg QD titrated as tolerated to a target dose of 10mg QD (10 mg ~ $20.00/30)**
  - **CIBIS II trial - NYHA Class III and IV, 15 months, 34% reduction in all cause mortality NNT=20**
- **Extended-release metoprolol (Cardio-selective) – initial dose 12.5 -25 mg QD titrated to a target dose of 200mg QD (200 mg ~ $15-30.00/30)**
  - **MERIT-HF trial – NYHA Class II and III, 21 months, 34% reduction in total mortality NNT=27**

Doses of Beta-Blockers in HF

- **Carvedilol (Non-selective and alpha blocking) – initial dose 3.125 mg BID titrated to a target dose of 25 mg BID (50 mg BID for patients >85 Kg) (25 mg ~ $4-35.00/60)**
  - **COPERNICUS trial – NYHA Class III and IV, 10.4 months, 35% reduction in total mortality NNT=14**
  - **COMET trial – NYHA Class II and III, 58 months, 17% reduction in total mortality NNT=18 (trial compared BID carvedilol to 50mg BID generic metoprolol at less than recommended doses)**

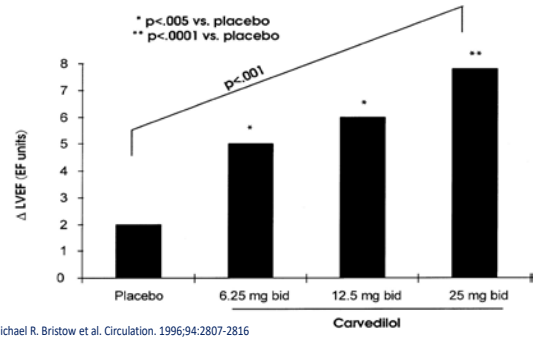
Study design and overall outcome of the MOCHA trial

(dose response of carvedilol in chronic heart failure, protocol 220).



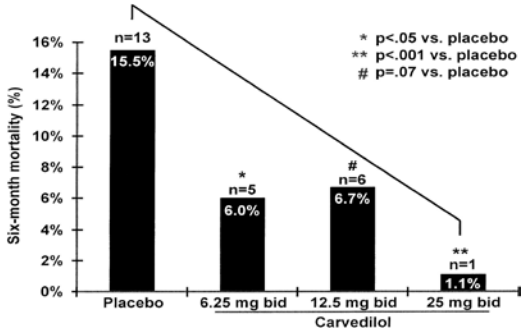
Michael R. Bristow et al. Circulation. 1996;94:2807-2816

Carvedilol protocol 220 (MOCHA): LVEF data at end of 6-month maintenance period as change (Δ) from baseline values.



Michael R. Bristow et al. Circulation. 1996;94:2807-2816

Carvedilol protocol 220 (MOCHA): six-month crude mortality as deaths per randomized patients×100.



Michael R. Bristow et al. Circulation. 1996;94:2807-2816

Beta-blockers in Patients with COPD/Asthma?

- **Bisoprolol** has data for use in heart failure and coronary artery disease and **has a beta-1/2 receptor selectivity ratio of 14:1, which is higher than either atenolol (5:1) or metoprolol (2:1)** [Br J Pharmacol 2005; 144: 317–322].
- **In a cross-over study of 51 patients with COPD and heart failure, directly comparing 6 weeks of bisoprolol, metoprolol and carvedilol** [J Am Coll Cardiol 2010; 55: 1780–1787], **FEV1 was lowest with carvedilol and highest with bisoprolol with metoprolol in between.**

β-Blocker Therapy and Risk of Chronic Obstructive Pulmonary Disease – A Danish Nationwide Study of 1·3 Million Individuals

- A total of 301,542 new users of β-blockers and 1,000,633 new users of any other antihypertensive drugs aged 30–90 years without any history of COPD hospitalizations were included in the present study and followed in the Danish National Patient Registry for incident admissions for COPD and COPD death between 1995 and 2015.
- **People treated with β-blockers continuously for more than 6 months had a 19.7% lower risk of COPD hospitalization during follow-up compared to people treated with any other antihypertensive drugs** (adjusted hazard ratio 0·80, 95% CI 0·79–0·82). Risk of COPD hospitalization was lowered in the groups treated with β-blockers among patients with ischemic heart disease (0·72, 0·69–0·75), cardiac arrhythmias (0·76, 0·72–0·80), asthma (0·69, 0·61–0·79), hypertension (0·91, 0·86–0·96), and diseases of the pulmonary circulation (pulmonary embolism and cor pulmonale) (0·72, 0·59–0·87). **All-cause mortality as well as risk of COPD death during follow-up was 44% lower in the group treated with β-blockers compared to the group treated with any other antihypertensive drugs** (0·56, 0·53–0·59). https://doi.org/10.1016/j.eclinm.2019.01.007

ATLAS STUDY DESIGN

Circulation 1999;100:2312-2318

- **3,164 patients with moderate to severe congestive heart failure**
- randomized 5-year double-blind trial
- **lisinopril**
  2.5 - 5 mg/day vs. 32.5 - 35 mg/day
  – **Lisinopril 40 mg ~ $0-10.00/30**

ATLAS RESULTS

Circulation 1999;100:2312-2318

Outcomes at 3 yrs	Hazard ratio (95% CI)	Number Needed to Treat (NNT)
Mortality plus hospitalization	0.88 (0.82-0.96)	26
Mortality plus HF hospitalization	0.85 (0.78- 0.93)	17
CV mortality plus CV hospitalization	0.91 (0.84-0.99)	30
Mortality plus CV hospitalization	0.92 (0.84-0.99)	34

Total mortality was 8% lower and CV mortality was 10% lower with the high dose vs. low dose lisinopril but did not reach statistical significance

ATLAS RESULTS

Circulation 1999;100:2312-2318

- **Cough - the major reason for drug discontinuation - occurred more often in the low-dose group, probably because their CHF was not as well controlled**
- **90% of patients randomized to high-dose therapy achieved target dose**
- **Resulted in an estimated 250,000 fewer hospitalizations / yr at an annual savings of $2 billion**

ARB's in Heart Failure

- **Elite II no benefit in morbidity and mortality with losartan 50mg QD over captopril 50mg TID, but when dosed at 150 mg QD in the HEAAL Trial reduced CV hospitalization for HF in patient's intolerant to ACEI vs. losartan 50 mg (100 mg ~ $10-44.00/45)**
  - **Hospitalization for heart failure 6/100 pt-yrs vs. 7/100 pt-yrs (HR 0·87; 95% CI 0·76-0.98; P=0·025)**
  - **All-cause mortality 7.6/100 pt-yrs vs. 8.2/100 pt-yrs (HR 0·94; 99% CI 0·84-1.04; P=0·24)**
- **Val-Heft IV valsartan 160mg BID was not better than ACEI plus BB unless the patient was not on an ACEI (IE ACEI intolerant patients) (160 mg ~ $20-67.00/60)**
- **CHARM candasartan 32mg QD was better than ACEI plus BB alone in the CHARM Added Trial and especially in ACEI intolerant patients including patients with angioedema (90% of this group was able to tolerate the ARB) The CHARM Alternative Trial (32 mg ~ $23-50.00/30)**

Can we use an ARB in Patients with angioedema on an ACE inhibitor?

- A nationwide retrospective registry-based cohort study of the Danish population during the period 1994 to 2016, and it uses Danish health registries.
- A total of 1,106,024 ACEi users were identified. In total, **5,507 (0.5%) of these patients had experienced angioedema during ACEi treatment and were included in the study.** The highest risk of angioedema recurrence was associated with continued ACEi use at an adjusted hazard ratio of 1.45 (95% CI, 1.19 to 1.78). An inverse association was found between **AT2s and angioedema (adjusted hazard ratio, 0.39**; 95% CI, 0.30 to 0.51) compared with **other antihypertensives (adjusted hazard ratios, 0.77 to 0.97).**
- CONCLUSIONS: **Compared with other antihypertensive drugs, AT2s do not increase the incidence of angioedema in patients with previous ACEi-related angioedema.**
  - J Intern Med. 2019;285(5):553. Epub 2019 Jan 8.

ARNI (Angiotensin Receptor Neprilysin Inhibitor) - Valsartan/Sacubitril - Entresto

- **FDA approved 7-8-2015 indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction.**
- It is usually administered in conjunction with other heart failure therapies including an evidence-based beta blocker and when appropriate an aldosterone antagonist and replaces the ACE inhibitor or other ARB.

Film-coated tablets (sacubitril/valsartan): **24/26 mg; 49/51 mg; 97/103 mg for BID dosing**

Cost: $600-700.00/mo GoodRx.com

Valsartan/Sacubitril - Entresto

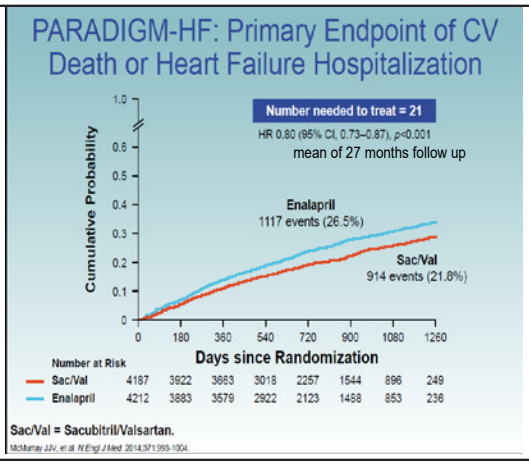
- **If switching from an ACE inhibitor to (sacubitril/valsartan) allow a washout period of 36 hours between administration of the two drugs**
- **The recommended starting dose is 49/51 mg (sacubitril/valsartan) twice-daily.**
- **Double the dose of after 2 to 4 weeks to the target maintenance dose of 97/103 mg (sacubitril/valsartan) twice-daily, as tolerated by the patient.**
- **Reduce the starting dose to 24/26 mg (sacubitril/valsartan) twice-daily for:**
  - **patients not currently taking an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) or previously taking a low dose of these agents**
  - **patients with severe renal impairment**
  - **patients with moderate hepatic impairment**

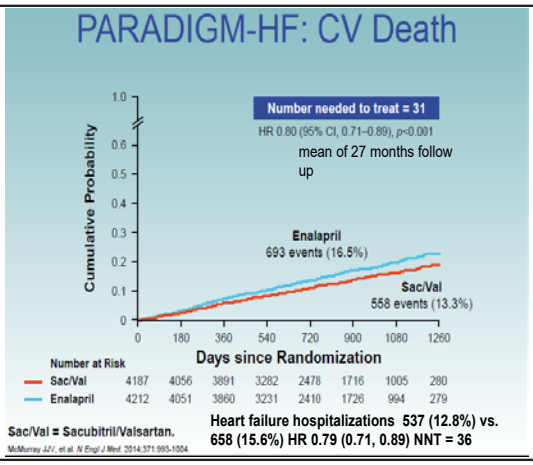
Valsartan/Sacubitril - Entresto

- In the **double-blind period of PARADIGM-HF, 0.5% of patients treated with (valsartan/sacubitril) and 0.2% of patients treated with enalapril had angioedema.**
  - Note all patients had to tolerate enalapril in an open label lead-in phase before randomization
  - associated with a higher rate of angioedema in Black than in non-Black patients
    - N Engl J Med 2014; 371:993-1004 DOI: 10.1056/NEJMoa1409077

PARADIGM-HF Trial

- **Compared the angiotensin-neprilysin inhibitor LCZ696 (200 mg BID) with the angiotensin converting enzyme inhibitor enalapril (10 mg BID) in 8399 patients with heart failure and reduced ejection fraction (<35%, NYHA Class II-IV)** able to tolerate ACEI or ARB and also on stable doses of beta blocker/mineralocorticoid antagonist unless not tolerated, in a double-blind trial. (NOTE **only 5% of pts were black and <10% from North America)**
- **200 mg of LCZ696 delivers the equivalent of 160 mg of valsartan** (evidence-based dose of valsartan in HF and post MI)
  - N Engl J Med 2014; 371:993-1004 DOI: 10.1056/NEJMoa1409077





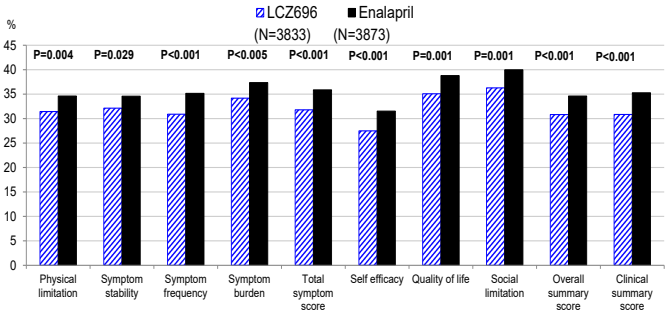
Valsartan/Sacubitril – Entresto in PARADIGM - HF

- **Mean daily doses achieved were LCZ696 375 mg and enalapril 18.9 mg**; 76% and 75% of LCZ696 and enalapril patients, respectively, maintained the target dose through the end of the study.
- **Incidence of symptomatic hypotension was 14% with LCZ696 and 9.2% with enalapril (P < 0.001); number needed to harm (NNH) with LCZ696 was 21**.
- **Incidence of serum creatinine elevated to at least 2.5 mg/dL was 3.3% with LCZ696 and 4.5% with enalapril (P = 0.007); NNH with enalapril was 84**.
- **Incidence of serum potassium greater than 6 mmol/L was 4.3% with LCZ696 and 5.6% with enalapril (P = 0.007); NNH with enalapril was 77.**
- **Incidence of cough was 11.3% with LCZ696 and 14.3% with enalapril (P < 0.001); NNH with enalapril was 34.**
  - N Engl J Med 2014; 371:993-1004 DOI: 10.1056/NEJMoa1409077

Valsartan/Sacubitril – Entresto in PARADIGM - HF

- **Estimating the Long-Term Treatment Benefits of Sacubitril–Valsartan** (N Engl J Med 2015; 373:2289-2290)
- Using actuarial estimates from the PARADIGM-HF trial, and assuming that the protective effects of sacubitril–valsartan remain consistent with long-term use, we extrapolated from the available short-term follow-up data to **estimate that treatment with sacubitril–valsartan would result in a projected benefit of 1 to 2 years of increased life expectancy and survival free from heart failure for patients (45 to 75 years of age) such as those in the PARADIGM-HF trial.**

PARADIGM-HF: Percentage of patients with at least 5 points deterioration in KCCQ (Kansas City Cardiomyopathy Questionnaire) scores at month 8



Clinical summary score based on the physical limitation and total symptom score domains. Death imputed as zero. The analysis included all patients with at least one KCCQ data point

Valsartan/Sacubitril – Entresto Safety Concern

- The **November 1, 2017 edition of ISMP QuarterWatch, a publication from the Institute for Safe Medication Practices, reports that a so-called "drug safety signal"** has been detected recently **for valsartan/sacubitril (Entresto) as regards hypotension** being a serious side effect which warrants more attention — and, perhaps, and an increased warning.
- Relying upon "New data from 2017 Q1" of the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS), this leading drug safety publication ends its recent report on valsartan/sacubitril (Entresto) with these statements in the final Conclusions section:

Valsartan/Sacubitril – Entresto Safety Concern

- **Nov 2017 ISMP (Institute for Safe Medication Practices) identified 1,684 adverse event reports indicating a hypotension-related event (ranging from dizziness to blackouts with some requiring hospitalization)**, more than for any other cardiovascular drug we monitored over the 12 months ending in 2017 Q1. **They occurred in older patients (median age 70 years), and although there were 69 reported deaths, in two-thirds of the cases, the health consequences were not severe.**
- **The FDA has not yet made any label changes.**
- **CAUTION PATIENTS!!!**

AHA/ACC/HFSA Recommendations

- **"In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality.' (COR 1/LOE B-R)**
- **"ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor."** (COR III Harm/LOE B-R)
- **"ARNI should not be administered to patients with a history of angioedema"** (COR III harm/LOE EO)
  - Journal of the American College of Cardiology (2016), doi: 10.1016/j.jacc.2016.05.011.

Pharmacologic Therapy: Aldosterone Antagonists

Recommendations for Mineralocorticoid Receptor Antagonists (MRAs)
Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	RECOMMENDATIONS
1	A	1. In patients with HFrEF and NYHA class II to IV symptoms, an MRA (spironolactone or eplerenone) is recommended to reduce morbidity and mortality, if eGFR is >30 mL/min/1.73 m^2 and serum potassium is <5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely monitored thereafter to minimize risk of hyperkalemia and renal insufficiency (1-3).
Value Statement: High Value (A)		2. In patients with HFrEF and NYHA class II to IV symptoms, MRA therapy provides high economic value (4-7).
3: Harm	B-NR	3. In patients taking MRA whose serum potassium cannot be maintained at <5.5 mEq/L, MRA should be discontinued to avoid life-threatening hyperkalemia (8,9).

–Spironolactone 25 mg ~ $ 3-10.00/30)

–Eplerenone 25 mg ~ $20-36.00/30)

–Endocrine side effects of spironolactone (gynecomastia, breast pain, menstrual irregularities, impotence, and decreased libido) result from nonselective binding to androgen and progesterone receptors. Eplerenone has greater specificity for the mineralocorticoid receptor, resulting in a lower incidence of endocrine side effects (1 versus 10 percent)

Table 2. Aldosterone Antagonists in Heart Failure: Evidence From Randomized Controlled Trials

Trial	n	Population	Primary Endpoint	Mean Length of Follow-up (Months)	ACE inhibitor or ARB, %	β-blocker, n (%)	All-cause Mortality, n (%) RR (95% CI)	Death or HF Hospitalization, n (%) RR (95% CI)	Serious Hyperkalemia, n (%)
RALES[7]	822 S 841 P	NYHA Class III/IV (IV within 6 months prior) (SCr >2.5 mg/dL or serum potassium >5 mmol/L excluded)	All-cause mortality	24	95% S 94% P	11% S 10% P	284 (35) S 386 (46) P 0.7 (0.60–0.82), $P < .001$ $P < .001$ **NNT=9**	CV death or CV hospitalization 0.68 (0.59–0.78), $P < .001$	≥6 mmol/L 14 (2) S 10 (1) P $P = .42$
EPHESUS[8]	3319 E 3313 P	AMI, LVEF ≤40, and HF symptoms (SCr >2.5 mg/dL or serum potassium >5 mmol/L excluded)	Co-primary: Time to death from any cause Time to CV death or first CV hospitalization	16	86% E 87% P	75% E 75% P	478 (14.4) E 554 (16.7) P 0.85 (0.75–0.96), $P = .008$ **NNT=44**	CV death or CV hospitalization 885 (26.7%) E 993 (30%) P 0.87 (0.79–0.95), $P = .002$ **NNT=25**	≥6 mmol/L 180 (5.5) E 126 (3.9) P $P = .002$
EMPHASIS-HF[11]	1364 E 1373 P	NYHA Class II (NYHA III/IV, eGFR <30 mL/min, serum potassium >5 mmol/L excluded)	CV death or first HF hospitalization	21 (median)	94% E 93% P	87% E 87% P	171 (12.5) E 213 (15.5) P 0.76 (0.62–0.93), $P = .008$ **NNT=33**	CV death or HF hospitalization (primary endpoint) 249 (18.3) E 336 (25.9) P HR 0.63 (0.54–0.74), $P < .001$ **NNT=14**	>6 mmol/L 33 (2.5) E 25 (1.9) P, $P = .20$ >5.5 mmol/L 158 (11.8) E 96 (7.7) P, $P < .001$

ACE, angiotensin-converting enzyme; AMI, acute MI; CV, cardiovascular; E, eplerenone; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; S, spironolactone; P, placebo; RALES, Randomized Aldactone Evaluation study; SCr, serum creatinine.

Aldosterone Antagonists and Renal Function

- **Aldosterone antagonists are not recommended when:**
  - **Creatinine > 2.5mg/dL (or clearance < 30 mL/min)**
  - **Serum potassium> 5.0 mmol/L**
  - **Therapy includes other potassium-sparing diuretics**

  Strength of Evidence = A
- **It is recommended that potassium be measured at baseline, then 1 week, 1 month, and every 3 months**

  Strength of Evidence = A
- Supplemental potassium is not recommended unless potassium is < 4.0 mmol/L

  Strength of Evidence = A

–2017 ACC/AHA/HFSA Heart Failure Focused Update

Spironolactone in Patients with HFpEF

- **The TOPCAT trial randomly assigned 3445 patients with symptomatic HF and LVEF ≥45 percent to receive either spironolactone or placebo. The composite primary outcome (death from cardiovascular causes, aborted cardiac arrest, or hospitalization for HF) was lower, but not statistically different, with spironolactone compared to placebo (18.6 and 20.4 percent,** respectively; hazard ratio [HR] 0.89, 95% CI 0.77-1.04). **Hospitalization for HF was less frequent in the spironolactone group (12.0 percent) compared with the placebo group (14.2 percent; HR 0.83, 95% CI 0.69-0.99),** but other components of the primary outcome occurred at similar rates in the two treatment groups. **Total deaths and total hospitalizations were similar in spironolactone and placebo groups.** (N Engl J Med. 2014;370(15):1383)
- New: patients with HFpEF (preserved EF)(>/=45%), elevated BNP levels or hospitalization in last year and eGFR > 30ml/min, Cr < 2.5 mg/dl, potassium <5.0 mmol/L might be added to reduce hospitalizations.
  - 2017 ACC/AHA/HFSA Heart Failure Focused Update

DAPA HF Trial

- **Patients with HFrEF (irrespective of diabetes status) were randomized to dapagliflozin 10 mg daily (n = 2,373) versus placebo (n = 2,371). 20 countries and 410 sites. Duration of follow-up: 18.2 months. Mean patient age: 66 years; Percentage female: 24%; Percentage with diabetes: 42%.**
- Inclusion criteria:
  - **Symptomatic heart failure**
  - Left ventricular ejection fraction **(LVEF) ≤40% (Mean 31%) (~ 64-70% NYHA Class II, 29-35% Class III, 1% Class IV)**
  - N-terminal pro–B-type natriuretic peptide ≥600 pg/ml (if hospitalized for heart failure within last 12 months ≥400 pg/ml; if atrial fibrillation/flutter ≥900 pg/ml) (Median >1400 pg/ml)
- Exclusion criteria:
  - **Estimated glomerular filtration rate <30 ml/min/1.73 m2 (Mean eGFR 63-68)**
  - Symptomatic hypotension or systolic blood pressure <95 mm Hg (Mean SBP 120-123 mm Hg)
  - Type 1 diabetes mellitus
- **Primary outcome: composite of an episode of worsening heart failure or cardiovascular death**

JAMA. 2020;323(14):1353-1368. doi:10.1001/jama.2020.1906

DAPA HF Trial

- Among **participants without diabetes**, the **primary outcome occurred in 171 of 1298 (13.2%) in the dapagliflozin group and 231 of 1307 (17.7%) in the placebo group (hazard ratio, 0.73**[95%CI,0.60-0.88]). **ARR = 4.5%, NNT = 23**
- In **patients with diabetes, the primary outcome occurred in 215 of 1075 (20.0%) in the dapagliflozin group and 271 of 1064 (25.5%) in the placebo group (hazard ratio, 0.75**[95%CI,0.63-0.90])(P value for interaction=.80). **ARR = 5.5%, NNT = 19**
  - JAMA.2020;323(14):1353-1368.doi:10.1001/jama.2020.1906 Published online March 27,2020.

DAPA HF Trial

Secondary outcomes:

- **Cardiovascular death: 9.6% with dapagliflozin vs. 11.5% with placebo (HR 0.82; 95% CI 0.69-0.98 NNT = 53)**
- **Hospitalization for heart failure: 9.7% with dapagliflozin vs. 13.4% with placebo (HR 0.70; 95% CI 0.59-0.83 NNT = 27)**
- Worsening of renal function: 1.2% with dapagliflozin vs. 1.6% with placebo (p = 0.17)
- **No major effects on A1c in either patients with or without diabetes vs. placebo**
  - N Engl J Med 2019; 381:1995-2008

DAPA HF Trial

Adverse events of interest — no./total no. (%)

	Dapagliflozin	Placebo	
• Volume depletion	178/2368 (7.5)—	162/2368 (6.8)—	—0.40
• Renal adverse event	153/2368 (6.5)—	170/2368 (7.2)—	—0.36
• Fracture	49/2368 (2.1) —	50/2368 (2.1)—	—1.00
• Amputation	13/2368 (0.5)—	12/2368 (0.5)—	—1.00
• Major hypoglycemia	**4/2368 (0.2)—	4/2368 (0.2)—	—NA
• Diabetic ketoacidosis	††3/2368 (0.1)—	0—	—NA
• Fournier's gangrene	0—	1/2368 (<0.1)—	—NA

– ** requiring treatment by another person; †† only occurred in patients with diabetes N Engl J Med 2019; 381:1995-2008

DAPA HF Trial

Dapagliflozin and baseline medication use:

- **Angiotensin-converting enzyme (ACE) inhibitor/angiotensin-receptor blocker (ARB) target dose <50%: HR 0.78**
- **ACE inhibitor/ARB target dose ≥50%: HR 0.64 (38% of pts)**(p for interaction = 0.21)
- **Beta-blocker target dose <50%: HR 0.71**
- **Beta-blocker target dose ≥50%: HR 0.44 (52% of pts)** (p for interaction = 0.76)
- Mineralocorticoid receptor antagonist (MRA) target dose <50%: HR 0.71
- MRA target dose ≥50%: HR 0.74 (p for interaction = 0.82)
  - European Heart Journal, ehaa183, https://doi.org/10.1093/eurheartj/ehaa183 Published: 28 March 2020

DAPA HF Trial

Limitations?

- Only 11% of patients were taking an ARNI but they did appear to benefit
- Almost no patients with NYHA Class IV heart failure
- Only 5% of patients were black
- Small number of patients were very elderly with multiple concurrent conditions

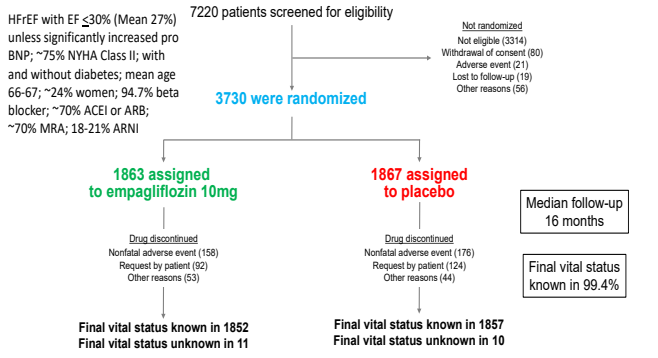
Dapagliflozin and HFrEF

- **May 5, 2020 The FDA following classification as a Priority Review (6 mo vs. 12 mo Standard Review) approved Farxiga (dapagliflozin) oral tablets for adults with heart failure with reduced ejection fraction to reduce the risk of cardiovascular death and hospitalization for heart failure.** Dapagliflozin is the first agent in this particular drug class, sodium-glucose co-transporter 2 (SGLT2) inhibitors, to be **approved to treat adults with New York Heart Association's functional class II-IV** heart failure with reduced ejection fraction.
  - Norman Stockbridge, M.D., Ph.D., director of the Division of Cardiology and Nephrology in the FDA's Center for Drug Evaluation and Research. "This approval provides patients with heart failure with reduced ejection fraction an additional treatment option that can improve survival and reduce the need for hospitalization."

April 2021 FDA Approved Indications for Dapagliflozin

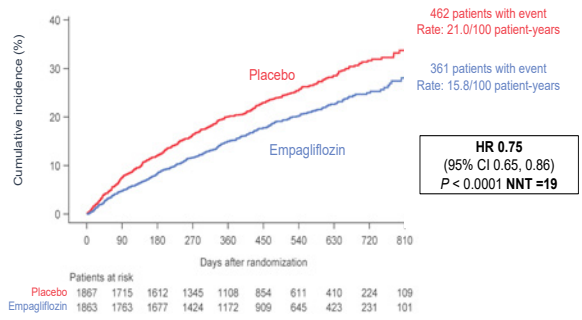
- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and either established cardiovascular disease or multiple cardiovascular risk factors.
- to **reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure with reduced ejection fraction (NYHA class II-IV).**
- to reduce the risk of sustained eGFR decline, end stage kidney disease cardiovascular death and hospitalization for heart failure in adults with chronic kidney disease at risk of progression.

EMPEROR-Reduced: Patient Disposition



DOI: 10.1056/NEJMoa2022190 on-line 8-29-2020

EMPEROR-Reduced: Time to Cardiovascular Death or Hospitalization for Heart Failure (Primary Endpoint)



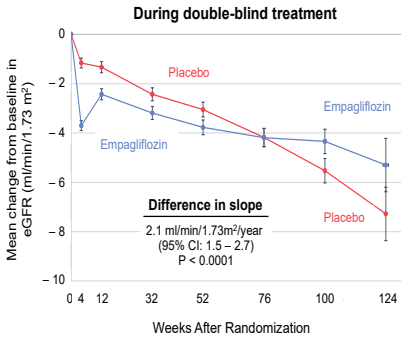
DOI: 10.1056/NEJMoa2022190 on-line 8-29-2020

EMPEROR-Reduced: Effect on Individual Components of the Primary Endpoint

	Empagliflozin (n=1863)		Placebo (n=1867)		Hazard ratio (95% CI)	P value
	Number of events (%)	Events/100 patient-yr	Number of events (%)	Events/100 patient-yr		
Primary composite outcome	361 (19.4%)	15.8	462 (24.7%)	21.0	0.75 **NNT 19** (0.65 – 0.86)	<0.0001
First hospitalization for heart failure	246 (13.2%)	10.7	342 (18.3%)	15.5	0.69 **NNT 20** (0.59 – 0.81)	
Cardiovascular death	187 (10.0%)	7.6	202 (10.8%)	8.1	0.92 (0.75 – 1.12)	

DOI: 10.1056/NEJMoa2022190 on-line 8-29-2020

EMPEROR-Reduced: Slope of Decline in Glomerular Filtration Rate — Hierarchical Endpoint #3



In 966 patients, eGFR was reassessed at the end of the trial 23-42 days after the withdrawal of double-blind therapy, thus allowing unconfounded assessment of the effects of treatment. Over 16 months, eGFR deteriorated by

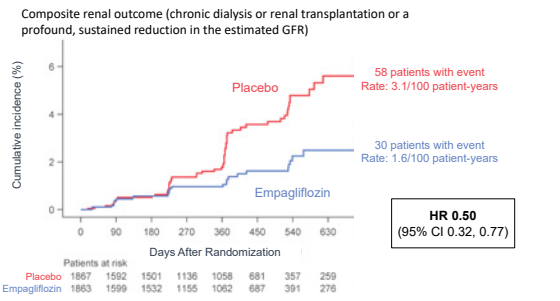
– 4.2 ml/min/1.73 m² on placebo

– 0.9 m/min/1.73 m² on empagliflozin

P < 0.0001

DOI: 10.1056/NEJMoa2022190 on-line 8-29-2020

EMPEROR-Reduced: Composite Renal Endpoint



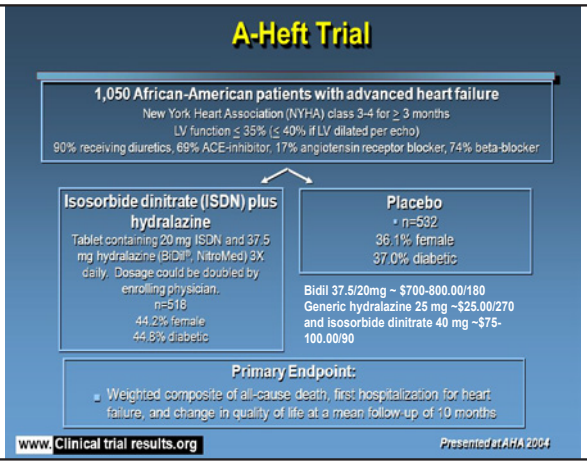
DOI: 10.1056/NEJMoa2022190 on-line 8-29-2020

Empagliflozin and HFrEF

- **8/18/2021 The FDA approved empagliflozin (Jardiance) for treating heart failure with reduced ejection fraction (HFrEF)**, Boehringer Ingelheim and Eli Lilly announced.
- **The 10-mg once-daily dose of the SGLT2 inhibitor was okayed for the reduction of risk of cardiovascular death and hospitalization for heart failure based on the EMPEROR-Reduced trial** (At randomization, 75% of patients were NYHA class II, 24% were class III and 0.5% were class IV. The mean LVEF was 28%).

Clinical Implications?

- Asked about the plethora of available drug options—beta blockers, sacubitril/valsartan, potassium-sparing diuretics (spironolactone/eplerenone), and SGLT2 inhibitors—for patients with HFrEF, **Dr. Milton Packer** (member of Executive Comm Emperor Reduced Trial) said one of the ways he likes to frame the question is to imagine himself as a patient. **"If I was just given the diagnosis of heart failure with reduced ejection fraction, I would want my physician to initiate therapy with all four classes of drugs within the first 4 to 6 weeks after they made my diagnosis,"** he said. "That means I'm recommending **concomitant, nearly simultaneous initiation of therapy—not on the same day**—but within a reasonably short period of time."



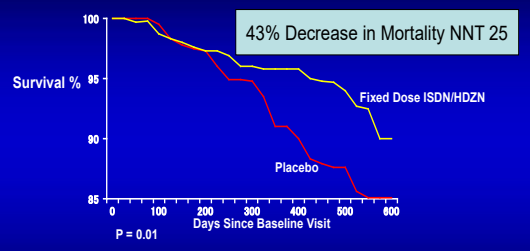
A-HeFT Outcomes

End point	ISDN-HDZN (n=518)	Placebo (n=532)	p	NNT
Primary end point composite score	-0.1	-0.5	0.01	
All-cause mortality (%)	6.2	10.2	0.02	25
1st HF hospitalization (%)	16.4	24.4	0.001	13
Change in quality-of-life score at 6 months**	-5.5	-2.7	0.02	

Taylor AL et al. N Engl J Med 2004; 351;2049-57

Heart Failure Society of America

A-HeFT All-Cause Mortality



Taylor AL et al. N Engl J Med 2004;351:2049-57

Heart Failure Society of America

Ivabradine – Corlanor

by Amgen

- **April 15, 2015 The FDA approved ivabradine (Corlanor, Amgen) for reducing the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction of 35% or less, who are in sinus rhythm with resting heart rate of 70 bpm or more, and either are on maximally tolerated doses of beta blockers or have a contraindication to beta-blocker use.** The drug acts by blocking the hyperpolarization-activated cyclic nucleotide–gated channel responsible for the cardiac pacemaker.
- FDA granted Ivabradine expedited approval and did not hold an FDA Cardiovascular Advisory Committee Meeting.
- The drug has been available for several years in Europe, where it is sold by Servier under the brand names of Corlentor and Procoralan

Ivabradine – Corlanor

- **Ivabradine causes a dose-dependent reduction in heart rate.** The size of the effect is dependent on the baseline heart rate (i.e., greater heart rate reduction occurs in subjects with higher baseline heart rate). At recommended doses, heart rate reduction is approximately 10 bpm at rest and during exercise. Analysis of heart rate reduction vs. dose indicates a plateau effect at doses > 20 mg twice daily.
- **Ivabradine does not have negative inotropic effects.**

Ivabradine – Corlanor

SHIFT Trial

- The Systolic Heart failure treatment with the *If* inhibitor ivabradine Trial **(SHIFT) was a randomized, double-blind trial comparing Ivabradine and placebo in 6558 adult patients with stable NYHA class II to IV (primarily II and III) heart failure, left ventricular ejection fraction ≤ 35%, and resting heart rate ≥ 70 bpm**. Patients had to have been clinically **stable for at least 4 weeks on an optimized and stable clinical regimen, which included maximally tolerated doses of beta-blockers and, in most cases, ACE inhibitors or ARBs, spironolactone, and diuretics,** with fluid retention and symptoms of congestion minimized. Patients had to have been hospitalized for heart failure within 12 months prior to study entry.
  - Lancet. 2010;376:875–885

Ivabradine – Corlanor

- All subjects were initiated on ivabradine 5 mg (or matching placebo) twice daily and the dose was increased to 7.5 mg twice daily or decreased to 2.5 mg twice daily to maintain the resting heart rate between 50 and 60 bpm, as tolerated.
- The primary endpoint was a composite of the first occurrence of either hospitalization for worsening heart failure or cardiovascular death.
  - **89% of patients were taking beta-blockers, with 26% on guideline-defined target daily doses**. The main reasons for not receiving the target beta-blocker doses at baseline were hypotension (45% of patients not at target), fatigue (32%), dyspnea (14%), dizziness (12%), history of cardiac decompensation (9%), and bradycardia (6%).
  - **91% of patients were taking either an ACEI or ARB**
  - **83% of patients were taking diuretics and 60% aldosterone antagonists**
    - Lancet. 2010;376:875–885

Ivabradine – Corlanor

Endpoint	Ivabradine N=3241 N	%	Placebo N=3264 N	%	HR 95% CI	P-value	ARR/NNT
Primary composite of time to first hospitalization for HF and CV death	793	24.5%	937	28.7%	0.82 (0.75-0.90)	<0.0001	4.2%/24
Hospitalization for worsening HF	505	15.6%	660	20.2%	0.74 (0.66-0.83)	<0.0001	4.6%/24
CV death as first event	288	8.9%	277	8.5%			

Mean follow-up 23 months. Ivabradine's benefit on the primary endpoint in SHIFT appeared to decrease as the dose of beta-blockers increased, with little if any benefit demonstrated in patients taking guideline-defined target doses of beta-blockers. Lancet. 2010;376:875–885

Ivabradine – Corlanor

Adverse Effects from SHIFT Trial:

Bradycardia	10%	2.2%
Hypertension	8.9%	7.8%
Atrial Fibrillation	8.3%	6.6%
Phosphenes, visual brightness*	2.8%	0.5%

*Phosphenes are phenomena described as a transiently enhanced brightness in a limited area of the visual field, halos, image decomposition (stroboscopic or kaleidoscopic effects), colored bright lights, or multiple images (retinal persistency).

Postmarketing reports: syncope, hypotension, angioedema, erythema, rash, pruritus, urticaria, vertigo, diplopia, and visual impairment. Lancet. 2010;376:875–885

Ivabradine – Corlanor

Dosage Adjustment Table

Heart Rate	Dose Adjustment
> 60 BPM	Increase dose by 2.5 mg BID up to a maximum dose of 7.5 mg BID
50-60 BPM	Maintain the dose
< 50 BPM	Decrease the dose by 2.5 mg BID, if current dose is 2.5 mg BID discontinue therapy

Available as a scored 5 mg tablet and 7.5 mg unscored tablet
Cost is reported to be ~$550.00 per month GoodRx.com

Vericiguat – Verquvo by Merck

- 1-19-2021 FDA approved **to reduce the risk of cardiovascular death and heart failure hospitalization following a hospitalization for heart failure or need for outpatient IV diuretics, in adults with symptomatic chronic HF and ejection fraction less than 45%.**
- **Vericiguat is a stimulator of soluble guanylate cyclase (sGC), an important enzyme in the nitric oxide (NO) signaling pathway.** When NO binds to sGC, the enzyme catalyzes the synthesis of intracellular cyclic guanosine monophosphate (cGMP), a second messenger that plays a role in the regulation of vascular tone, cardiac contractility, and cardiac remodeling. **Heart failure is associated with impaired synthesis of NO and decreased activity of sGC, which may contribute to myocardial and vascular dysfunction. By directly stimulating sGC, vericiguat augments levels of intracellular cGMP, leading to smooth muscle relaxation and vasodilation.**
  - **Concomitant use of vericiguat with PDE-5 inhibitors is not recommended because of the potential for hypotension**

Vericiguat - Verquvo

- **BLACK BOX WARNING: EMBRYO-FETAL TOXICITY**
  - **Do not administer vericiguat to a pregnant female because it may cause fetal harm.** Females of reproductive potential: Exclude pregnancy before the start of treatment.
- **Dosage: The recommended starting dose of vericiguat is 2.5 mg orally once daily with food. Double the dose approximately every 2 weeks to reach the target maintenance dose of 10 mg once daily, as tolerated by the patient.**
  - Tablets may be crushed and mixed with water for patients who have difficulty swallowing.
  - The half-life of vericiguat is 30 hours in patients with heart failure.
  - Renal dosing: No dosage adjustment of vericiguat is recommended in patients with estimated glomerular filtration rate (eGFR) ≥15 mL/min/1.73m2 who are not on dialysis. Vericiguat has not been studied in patients with eGFR <15 mL/min or on dialysis.

Victoria Trial

- **VICTORIA** was a randomized, parallel-group, placebo-controlled, double-blind, event-driven, multi-center **trial comparing vericiguat titrated to 10 mg QD and placebo in 5,050 adult patients with symptomatic chronic heart failure (New York Heart Association class II 59%; III 40%; IV 1%) and left ventricular ejection fraction (LVEF) less than 45% following a worsening heart failure event.** A worsening heart failure event was defined as heart failure hospitalization within 6 months before randomization or use of outpatient IV diuretics for heart failure within 3 months before randomization.
  - The primary endpoint was a composite of time to first event of CV death or hospitalization for heart failure. The median follow-up for the primary endpoint was 11 months.
  - At baseline, 93% of patients were on a beta blocker, 73% were on an ACEI or ARB, 15% were on an ARNI, 70% were on a mineralocorticoid receptor antagonist, 28% of patients had an implantable cardiac defibrillator, and 15% had a biventricular pacemaker. Ninety-one percent of patients were treated with 2 or more heart failure medications (beta blocker, any renin-angiotensin system [RAS] inhibitor or MRA) and 60% of patients were treated with all 3. At baseline, 6% of patients were on ivabradine and 3% of patients were on a sodium glucose co-transporter 2 (SGLT2) inhibitor.
    - N Engl J Med 2020; 382:1883-1893

Victoria Trial

Table 2: Treatment Effect for the Primary Composite Endpoint and the Secondary Endpoints of Cardiovascular Death and Heart Failure Hospitalization

	VERQUVO N=2,526		Placebo N=2,524		Treatment Comparison		
	n (%)	Event rate: % of patients per year*	n (%)	Event rate: % of patients per year*	Hazard Ratio (95% CI)†	p-value‡	ARR§
Primary endpoint							
Composite of cardiovascular death or heart failure hospitalization¶	897 (35.5)	33.6	972 (38.5)	37.8	0.90 (0.82, 0.98)	0.019	4.2 NNT = 24 at 11 mo.
Secondary endpoints							
Cardiovascular death	414 (16.4)	12.9	441 (17.5)	13.9	0.93 (0.81,1.06)		
Heart failure hospitalization	691 (27.4)	25.9	747 (29.6)	29.1	0.90 (0.81,1.00)		

* Total patients with an event per 100 patient years at risk.
† Hazard ratio (VERQUVO over Placebo) and confidence interval from a Cox proportional hazards model.
‡ From the log-rank test.
§ Absolute risk reduction, calculated as difference (Placebo-VERQUVO) in event rate per 100 patient years.
¶ For patients with multiple events, only the first event contributing to the composite endpoint is counted.
N=Number of patients in Intent-to-Treat (ITT) population; n=Number of patients with an event.

The Kaplan-Meier curve (Figure 2) shows time to first occurrence of the primary composite endpoint of CV death or heart failure hospitalization.

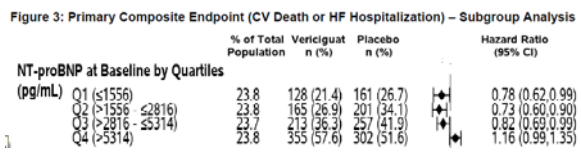
Most common adverse reactions reported in ≥5% are hypotension 16% and anemia 10%.

Cost: 2.5, 5 and 10 mg tabs ~$600-700.00 per 30 tabs

N Engl J Med 2020; 382:1883-1893

Vericiguat - Verquvo

Figure 3: Primary Composite Endpoint (CV Death or HF Hospitalization) – Subgroup Analysis



– N Engl J Med 2020; 382:1883-1893

- NT-proBNP at randomization was related to both the rate of clinical events as well as associated with the treatment efficacy of vericiguat.
- Patients with **a NT-proBNP <4000 pg/ml had an even further enhanced benefit on the CVD and HF hospitalization.**
  – J Am Coll Cardiol Heart Fail. 2020 Nov, 8 (11) 940–942

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

Recommendation for HF With Improved Ejection Fraction
Referenced studies that support the recommendation are summarized in the Online Data Supplements.

COR	LOE	RECOMMENDATION
1	B-R	1. In patients with HFimpEF after treatment, GDMT should be continued to prevent relapse of HF and LV dysfunction, even in patients who may become asymptomatic (1).

In an **open-label RCT, phased withdrawal of HF medications in patients with previous dilated cardiomyopathy** (DCM)—**who were now asymptomatic, whose LVEF had improved from <40% to ≥50%,** whose left ventricular end-diastolic volume (LVEDV) had normalized, and who had an NT-proBNP concentration <250 ng/L—**resulted in relapse of cardiomyopathy and HF in 40% of the patients within 6 months.** Relapse was defined by at least 1 of these: 1) a reduction in LVEF by >10% and <50%; 2) an increase in LVEDV by >10% and to higher than the normal range; 3) a 2-fold rise in NT-proBNP concentration and to >400 ng/L; or 4) clinical evidence of HF. **Treatment was withdrawn successfully in only 50% of patients**. Secondary analyses showed worsening Kansas City Cardiomyopathy Questionnaire scores, a substantial reduction in LVEF, and nonsignificant increases in NT-proBNP and LV volumes with withdrawal of HF medications. **Lancet 2019;393:61-73**

https://www.jacc.org/doi/10.1016/j.jacc.2021.12.012

New Recommendations in HFmrEF (LVEF 41-49%)

SGLT2i
- Can be beneficial in decreasing HHF and CV mortality

2a B-R

ARNi, ACEi, or ARB; MRA; BB
- May be considered to reduce risk of HHF and CV mortality, particularly among patients with LVEF on lower end of this spectrum

2b B-NR

CV, cardiovascular; HHF, hospitalization for HF

Circulation. 2022;145:00–00. DOI: 10.1161/CIR.0000000000001063

New Recommendations in HFpEF (LVEF ≥50%)

SGLT2i
- Can be beneficial in decreasing HHF and CV mortality

2a B-R

MRA
- May be considered in selected patients to decrease HHF, particularly among patients with LVEF on lower end of this spectrum

2b B-R

ARNi
- May be considered in selected patients to decrease HHF, particularly among patients with LVEF on lower end of this spectrum

2b B-R

CV, cardiovascular; HHF, hospitalization for HF

Circulation. 2022;145:00–00. DOI: 10.1161/CIR.0000000000001063

EMPEROR-Preserved: Empagliflozin Outcome Trial in Patients with Chronic Heart failure with Preserved Ejection Fraction

Purpose:

Evaluate the effects of SGLT2 inhibitor (Empagliflozin) on cardiovascular death and heart failure hospitalizations in patients with heart failure with a preserved ejection fraction (HFpEF), with or without diabetes.

Trial Design: N=5998, International multicenter (622 centers in 23 countries) randomized placebo controlled, double-blind, event-driven study. Symptomatic HFpEF patients (LVEF>40%) received empagliflozin (10mg once daily) or placebo, in addition to usual therapy. Median follow up period was 26 months.

Primary Endpoint: Composite of CV death or heart failure hospitalization.

Secondary Endpoints: Heart Failure hospitalizations(including first and recurrent events), rate of decline in eGFR during treatment.

	Empagliflozin n=2997	Placebo n=2991	HR (95% CI)	P-value
Primary Composite Outcome: Composite of CV death or HF hospitalization	415 (13.8%)	511 (17.1%)	0.79 (0.69-0.90)	< 0.001
HF hospitalization	259 (8.6%)	352 (11.8%)	0.71 (0.60-0.83)	
Cardiovascular Death	219 (7.3%)	244 (8.2%)	0.91 (0.76-1.09)	
Secondary Outcomes specified in hierarchical testing procedure				
Total number of HF hospitalizations	407	541	0.73 (0.61-0.88)	< 0.001
eGR mean slope change per year (ml/min/1.73m²)	-1.25±0.11	-2.62±0.11	1.36 (1.06-1.66)	< 0.0001

Results: Empagliflozin reduced the combined risk of cardiovascular death or heart failure hospitalization in patients with HFpEF by 21%, regardless of the presence or absence of diabetes. This benefit was consistent across pre-specified EF subgroups. Empagliflozin reduced total (first and recurrent) hospitalizations for HF by 27%.

Presented by: Stefan Anker ESC 2021, The Digital Experience

Results reflect the data available at the time of presentation.

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

CLINICAL TRIAL

Design: A multicenter, double-blind, randomized, placebo-controlled trial examined the effects of the SGLT2 inhibitor empagliflozin in patients with heart failure and a preserved ejection fraction.

Intervention: 5988 adults with New York Heart Association functional class II–IV chronic heart failure and a left ventricular ejection fraction >40% were randomly assigned to receive empagliflozin (10 mg once daily) or placebo, in addition to their usual treatment. The primary outcome was a composite of cardiovascular death or hospitalization for heart failure.

RESULTS

Efficacy: During a median follow-up of 26.2 months, a primary composite outcome event occurred significantly less often in the empagliflozin group than in the placebo group, largely owing to a decrease in hospitalizations for heart failure with empagliflozin. The benefit of empagliflozin appeared similar in patients with or without diabetes.

Safety: Serious adverse events occurred in 47.9% of patients in the empagliflozin group and in 51.6% of those in the placebo group. Uncomplicated genital and urinary tract infections and hypotension were more common with empagliflozin.

LIMITATIONS AND REMAINING QUESTIONS

- In this trial, empagliflozin did not significantly reduce the incidence of cardiovascular death alone.

CONCLUSIONS

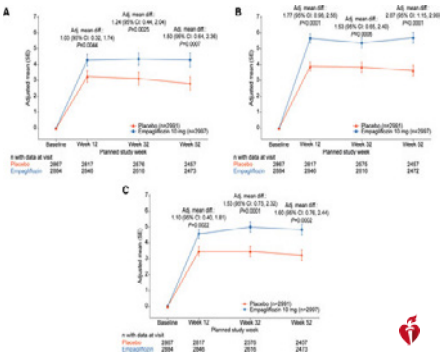
In patients with heart failure and a preserved ejection fraction, the SGLT2 inhibitor empagliflozin lowered the risk of a composite of cardiovascular death or hospitalization for heart failure, mainly owing to a reduction in hospitalizations for heart failure.

N Engl J Med 2021; 385:1451-1461

Figure 2. Effects of empagliflozin versus placebo on mean KCCQ scores. Changes in (A) Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score, (B) Total Symptom Score, and (C) Overall Summary Score from baseline to 12, 32, and 52 weeks for empagliflozin versus placebo. Adj. mean diff indicates adjusted mean difference.

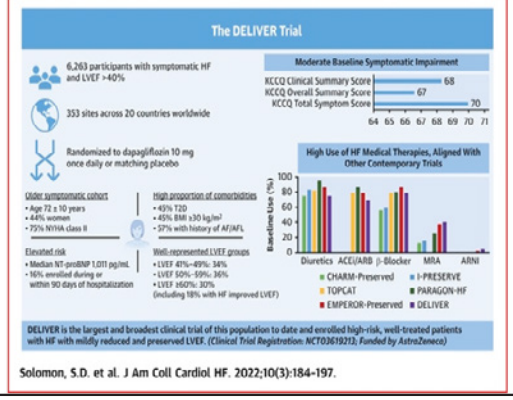
Conclusions

Treatment with empagliflozin reduced the risk for cardiovascular death or HF hospitalization across the range of baseline HRQoL scores in patients with HFpEF. **Empagliflozin also significantly improved HRQoL in patients with HFpEF, and this improvement was seen early and was sustained for at least 1 year.**



Javed Butler. Circulation. Empagliflozin, Health Status, and Quality of Life in Patients With Heart Failure and Preserved Ejection Fraction: The EMPEROR-Preserved Trial, Volume: 145, Issue: 3, Pages: 184-193, DOI: (10.1161/CIRCULATIONAHA.121.057812)

CENTRAL ILLUSTRATION: Baseline Characteristics of Participants Enrolled in DELIVER



Solomon, S.D. et al. J Am Coll Cardiol HF. 2022;10(3):184-197.

Dapagliflozin in HFpEF - DELIVER Trial

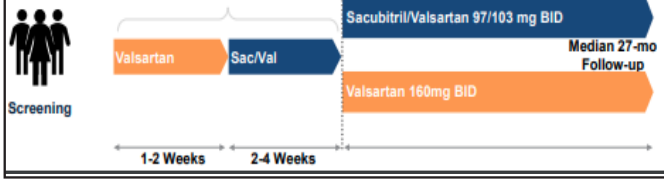
- **6263 patients with heart failure and a left ventricular ejection fraction of more than 40% to receive dapagliflozin (at a dose of 10 mg once daily) or matching placebo, in addition to usual therapy.** The **primary outcome was a composite of worsening heart failure** (which was defined as either an unplanned hospitalization for heart failure or an urgent visit for heart failure) **or cardiovascular death**, as assessed in a time-to-event analysis.
- RESULTS: Over a **median of 2.3 years, the primary outcome occurred** in 512 of 3131 patients **(16.4%) in the dapagliflozin group** and in 610 of 3132 patients **(19.5%) in the placebo group (hazard ratio, 0.82**; 95% confidence interval [CI], 0.73 to 0.92; P<0.001). **ARR 3.1%, NNT 33**
- **Worsening heart failure occurred in** 368 patients **(11.8%) in the dapagliflozin group** and in 455 patients **(14.5%) in the placebo group (hazard ratio, 0.79**; 95% CI, 0.69 to 0.91) **ARR 2.7%, NNT 37**; **cardiovascular death occurred in** 231 patients **(7.4%)** and 261 patients **(8.3%),** respectively (**hazard ratio, 0.88; 95% CI, 0.74 to 1.05**).
  - **Results were similar among patients with a left ventricular ejection fraction of 60% or more and those with a left ventricular ejection fraction of less than 60%, and results were similar in prespecified subgroups, including patients with or without diabetes.**
  - NEJM August 27, 2022 DOI: 10.1056/NEJMoa2206286

PARAGON-HF Study Design

Key Eligibility Criteria
- Age ≥50 years
- EF ≥45%
- Elevated Natriuretic Peptides
- Structural Heart Disease

Minimum NT-proBNP for Inclusion
- >200 pg/ml with HF hospitalization
- >300 pg/ml without hospitalization
- 3-fold increase in AF

N=4,796

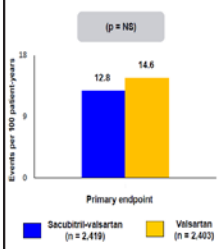


PARAGON-HF

#ESCCongress

AMERICAN COLLEGE of CARDIOLOGY

Trial Description: Patients with heart failure with preserved ejection fraction were randomized to sacubitril-valsartan 97/103 mg twice daily versus valsartan 160 mg twice daily.



RESULTS
- Primary efficacy endpoint: rate of cardiovascular deaths or hospitalizations for heart failure was 12.8 events per 100 patient-years in the sacubitril-valsartan group vs. 14.6 events per 100 patient-years in the valsartan group (p = NS)
- NYHA class improvement: 15.0% in the sacubitril-valsartan group vs. 12.6% in the valsartan group (p < 0.05)

CONCLUSIONS
- Among patients with heart failure with preserved ejection fraction, sacubitril-valsartan was not effective at reducing the incidence of cardiovascular death or hospitalization for heart failure compared with valsartan

Solomon SD, et al. N Engl J Med 2019;Sep 1:[Epub]

Sacubitril/Valsartan – Entresto Update

- 2-16-2021 Entresto's odyssey ends with an FDA indication, more than a year after a highly anticipated PARAGON-HF study fell just short of hitting its primary end point. However, in **December 2020, FDA's Cardiovascular and Renal Drugs Advisory Committee found that Entresto was worthy of some indication based on the PARAGON-HF trial, which studied patients with left ventricular ejection fraction (LVEF) of ≥45%**. The panel discussed the fact that **HFpEF is something of a misnomer and that LVEF above 40% but below 57% may constitute its own range.**
- The language in the announcement reflected that discussion. Novartis stated that FDA had approved an expanded indication **"to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure," and that, "Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal."**

Treatment Of Preserved Cardiac Function Heart Failure with an Aldosterone anTagonist (TOPCAT)

TOPCAT — Funded by the NHLBI

- **Objective**
  - To determine if treatment with spironolactone can produce a clinically meaningful reduction in the composite endpoint of cardiovascular mortality, aborted cardiac arrest, or hospitalization for the management of heart failure, compared with placebo, in adults with HF-Preserved EF.
- **Inclusions:**
  Symptomatic Heart Failure, Age ≥ 50, LVEF ≥ 45%, stratified according to:
  - Hospitalization within the past year for management of heart failure, or
  - Elevated natriuretic peptides (BNP ≥100 pg/mL or NT-proBNP ≥360 pg/mL)
- **Major Exclusions:**
  eGFR<30 mL/min/1.7m², serum potassium ≥5 mmol/L, uncontrolled hypertension, AF with rate > 90/min, recent ACS, restrictive, infiltrative, or hypertrophic cardiomyopathy

Rationale and design: (A. Desai, Am Heart J 2011)

- **3345** HFpEF with HF hospitalization in past year or elevated NP past 30 day
  - LVEF > 45%
  - at least 1 sign + 1 symptom
- Spironolactone 15 – 45 mg Daily or placebo
- Composite Outcome: HF hospitalization, aborted cardiac arrest, CV death

Followed for 3.3 years
North (US, Can) and South America (Arg and Bra) and Eastern Europe (Rus and Geo)

TOPCAT Trial

Table 2. Incidence Rates of the Primary Composite Outcome, Its Components, and Additional Secondary Outcomes.*

Outcome	Spironolactone (N=1722)		Placebo (N=1723)		Hazard Ratio with Spironolactone (95% CI)†	P Value
	Participants with Event	Incidence Rate	Participants with Event	Incidence Rate		
	no. (%)	no./100 person-yr	no. (%)	no./100 person-yr		
Primary outcome	320 (18.6)	5.9	351 (20.4)	6.6	0.89 (0.77–1.04)	0.14
Components of the primary outcome						
Death from cardiovascular causes	160 (9.3)	2.8	176 (10.2)	3.1	0.90 (0.73–1.12)	0.35
Aborted cardiac arrest	3 (0.2)	0.05	5 (0.3)	0.09	0.60 (0.14–2.50)	0.48
Hospitalization for heart failure	206 (12.0)	3.8	245 (14.2)	4.6	0.83 (0.69–0.99)	0.04
Additional secondary outcomes						
Death from any cause	252 (14.6)	4.2	274 (15.9)	4.6	0.91 (0.77–1.08)	0.29
Hospitalization for any reason	766 (44.5)	18.8	792 (46.0)	20.0	0.94 (0.85–1.04)	0.25
Myocardial infarction	65 (3.8)	1.2	64 (3.7)	1.1	1.00 (0.71–1.42)	0.98
Stroke	57 (3.3)	1.0	60 (3.5)	1.1	0.94 (0.65–1.35)	0.73

* Some participants had more than one component of the primary outcome and are included once for the primary outcome and once for each component they had.
† Shown are unadjusted hazard ratios calculated with the use of Cox proportional-hazards models.

NEJM 2014;370:1383-1392

TOPCAT Results??

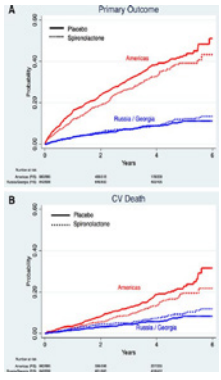
Outcome	Spironolactone (N = 1722)	Placebo (N = 1723)	Hazard Ratio (95% CI) p-value
Primary Outcome	320 (18.6%) 5.9/100pt-yr	351 (20.4%) 6.6/100pt-yr	0.89 (0.77-1.04) P=0.138
Primary Components			
CV Mortality	160 (9.3%) 2.8/100pt-yr	176 (10.2%) 3.1/100pt-yr	0.90 (0.73-1.12) P=0.354
Aborted Cardiac Arrest	3 (<1%) 0.05/100pt-yr	5 (<1%) 0.09/100pt-yr	0.60 (0.14-2.50) P=0.482
Hospitalization for Heart Failure	206 (12.0%) 3.8/100pt-yr	245 (14.2%) 4.6/100pt-yr	0.83 (0.69-0.99) P=0.042

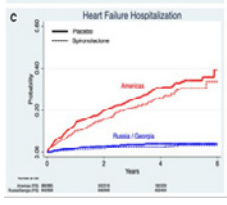
Outcome	Americas (USA CAN ARG BRA) (N=1,767)			Eastern Europe (RUS GEO) (N=1,678)		
	Number and % of Participants with Event, and Incidence Rate per 100 person-years		Unadjusted Model	Number and % of Participants with Event, and Incidence Rate per 100 person-years		Unadjusted Model
	Spironolactone (N = 886)	Placebo (N = 881)	HR(1 vs. 2), 95% CI, p-value	Spironolactone (N = 836)	Placebo (N = 842)	HR(1 vs. 2), 95% CI, p-value
Primary Outcome	242 (27.3%) 10.4 per 100 person-years	280 (31.8%) 12.6 per 100 person-years	0.82 (0.69-0.98) 0.026	78 (9.3%) 2.5 per 100 person-years	71 (8.4%) 2.3 per 100 person-years	1.10 (0.79-1.51) 0.576

Primary reason for reanalysis?

N Engl J Med 2014; 370:1383-1392

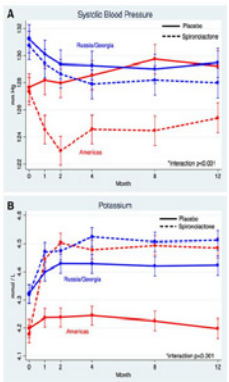
TOPCAT Reanalysis





In a **post hoc analysis of this trial, an unusually large (≈4-fold) difference was identified in the placebo group primary event rate of the patients randomized from Russia and Georgia** (Russia/Georgia) compared with those enrolled from the United States, Argentina, Brazil, and Canada (the Americas)
This **post hoc analysis demonstrated greater potassium and creatinine changes and possible clinical benefits with spironolactone in patients with heart failure and preserved ejection fraction from the Americas** Circulation. 2015;131:34–42

TOPCAT Reanalysis



- This **post hoc analysis demonstrated greater blood pressure, potassium and creatinine changes and possible clinical benefits with spironolactone in patients with heart failure and preserved ejection fraction from the Americas**
- Circulation. 2015;131:34–42

TOPCAT Trial Inconsistencies?

BMJ 2017;357:j2218

- Blood tests taken from a sample of **patients in Russia and stored since the trial ended showed that 30% of them had no sign of an active metabolite of the drug spironolactone (canrenone) which would have been present if they had taken it. Among patients in Argentina, Brazil, Canada, and the US only 3% showed no evidence of the metabolite. N Engl J Med 2017; 376:1690-1692**
- In the New England Journal of Medicine, Marc Pfeffer, of Brigham and Women's Hospital in Boston, and colleagues said that **the evidence raised questions about how the trial was conducted in Russia and, by implication, in Georgia. Half the trial participants came from these two countries.**
- **The trial was conducted by an international CRO (Contract Research Organization) which may have let some of the data go unverified?**

ARB's in Patients with HFpEF

- In the **CHARM-Preserved (Candesartan in patients with chronic HF and preserved left-ventricular ejection fraction) trial, patients with LVEF >40% were randomized to an ARB, candesartan, or to placebo. The primary endpoint (cardiovascular death or HF hospitalization) was not significantly different between the 2 groups (HR, 0.89;** 95% CI, 0.77–1.03, P=0.118; covariate-adjusted HR, 0.86; P=0.051). **Cardiovascular mortality was identical in the 2 groups**; **HF hospitalizations were lower in the candesartan arm,** with borderline statistical significance on the covariate-adjusted analysis only (HR, 0.84; 95% CI, 0.70–1.00; P=0.047). The number of individuals hospitalized for HF was lower in the candesartan group than placebo (230 versus 279). Lancet 2003;362:777-81.
- A post hoc analysis of the CHARM trials showed that improvement in outcomes with candesartan was greater at the lower end the LVEF spectrum. Eur J Heart Fail. 2018;20:1230–1239
- In a meta-analysis of 7694 patients with HFpEF in 4 trials evaluating ARB, there was no signal for benefit on cardiovascular mortality (HR, 1.02), all-cause mortality (HR, 1.02), or HF hospitalization (HR, 0.92; 95% CI, 0.83–1.02). Heart 2019;105:1533–1535.

SELF EVALUATION

Management of Patients with Heart Failure

1. Which beta-blocker would you recommend in a patient with HFrEF and mixed COPD/asthma?
    a. Carvedilol 25-50 mg BID
    b. Metoprolol succinate 100 mg QD
    c. Bisoprolol 10 mg QD
    d. No beta blocker

2. Which of the following medications is probably safest to consider as part of the Guideline Directed Medical Therapy (GDMT)for patients with reduced eject ion fraction heart failure (HFrEF) who has a history of ACE inhibitor angioedema?
    a. Lisinopril
    b. An ARNI Valsartan/sacubitril (Entresto)
    c. An angiotensin 2 inhibitor (i.e., losartan, candesartan)
    d. None of the above

3. According to the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure which SGLT-2 inhibitors are evidence-based and recommended for the treatment of patients with reduced ejection fraction heart failure (HFrEF)?
    a. Dapagliflozin 10 mg daily
    b. Empagliflozin 10 mg daily
    c. Canagliflozin 100 mg daily
    d. A and b are both recommended

4. According to the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure which medications are recommended based upon limited evidence for the treatment of patients with preserved ejection fraction heart failure HFpEF?
    a. An SGLT-2 inhibitor (i.e., dapagliflozin or empagliflozin)
    b. An ARNI valsartan/sacubitril (Entresto)
    c. An MRA spironolactone
    d. All of the above

5. T/F - According to the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure patients with heart failure with improved ejection fraction (HFimpEF) after treatment, GDMT for HFrEF should be continued to prevent relapse of heart failure and LV dysfunction, even in patients who may be asymptomatic.

Answer Key: 1. C, 2. C, 3. D, 4. D, 5. T

Erin King-Mullins, MD

Dr. Erin King-Mullins of Atlanta, GA, is a double board-certified general and colorectal surgeon working in private practice at the Colorectal Wellness Center. With several presentations and publications to her credit, Dr. King-Mullins is passionate about improving patient access, clinical research and the empowering her colleagues in colorectal surgery. She is an active participant and leader in several national organizations including the American Society of Colon and Rectal Surgeons, the National Medical Association, the Association of Women Surgeons, the Society of American Gastrointestinal and Endoscopic Surgeons, the American College of Surgeons, and more.

You may contact Dr. King-Mullins with your questions or comments by email at ekmullins@golowellness.com.

Colorectal Wellness Center
1275 Hwy 54 West, Suite 205
Fayetteville, GA 30214

Phone: (770) 325-2275

Colorectal Cancer Screening, Treatment and Surveillance

Erin King-Mullins, MD

Objectives

- To provide medical professionals with an overview of colorectal cancer (CRC) screening including:
  - Epidemiology of colon cancer
  - Cost of Colorectal cancer
  - Colorectal cancer basics
  - Screening methods
  - Screening guidelines
  - Colorectal cancer treatment
  - Surveillance
  - Benefits of screening

Epidemiology of Colorectal Cancer

- 3rd most commonly diagnosed cancer in both men and women in the U. S. , slight male predominance
  - 1/23 men
  - 1/25 women
- 2nd leading cause of cancer-related deaths in the US

Epidemiology of Colorectal Cancer

- The American Cancer Society's estimates for the number of colorectal cancers in the United States for 2024 are:
  - About 106,590 new cases of colon cancer
    - 54,210 in men and 52,380 in women
  - About 46,220 new cases of rectal cancer
    - 27,330 in men and 18,890 in women

Cancer.org

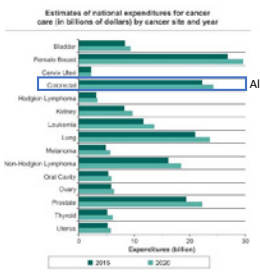
Epidemiology of Colorectal Cancer

- Rates of CRC have been decreasing in older persons for several decades
- In persons <55 years of age, rates have increased 1% per year since the mid 2000s

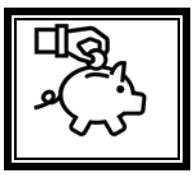
Epidemiology of Colorectal Cancer
Special note on young colorectal cancer patients

- By 2030 11% of colon cancers and 23% of rectal cancers will be in patients <50
- Comparison of SEER data 2000-2002 and 2014-2016
  - Sharpest rise in metastatic colon cancer in ages 30-39
  - Sharpest rise in metastatic rectal cancer in ages 20-29

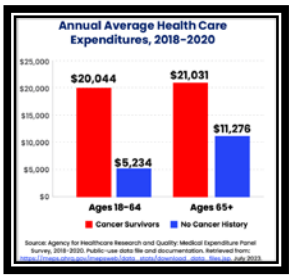
Epidemiology of Colorectal Cancer
Cost:



Almost $25 billion



Epidemiology of Colorectal Cancer Cost:

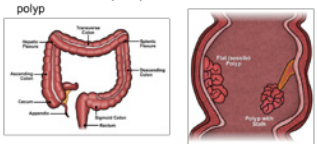


the-costs-of-colorectal-cancer.pdf (fightcancer.org)

Colorectal Cancer Basics

- Polyp - benign neoplasm that grows and develops into cancer

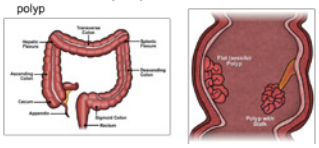
- Colorectal cancer (CRC) starts in the colon or rectum as a polyp



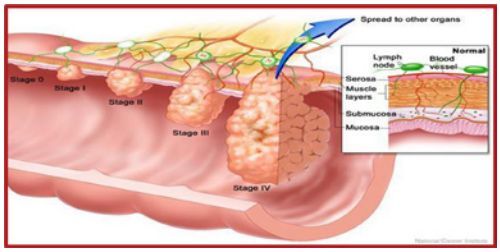
Colorectal Cancer Basics

- Types (in order of increased risk of malignant transformation)
  - Hyperplastic – no malignant potential
  - Tubular adenoma
  - Villous adenoma
  - Tubulovillous adenoma
  - Serrated adenoma

- Colorectal cancer (CRC) starts in the colon or rectum as a polyp



Colorectal Cancer Basics - Staging



Colorectal Cancer Basics- Risk Factors

- Non-modifiable:
  - Age
  - Family history colorectal cancer or polyps
  - Genetic syndrome
  - Personal history of Ulcerative Colitis or Crohn's disease

Colorectal Cancer Basics- Risk Factors

- Non-modifiable:
  - Age
  - Family history colorectal cancer or polyps
  - Genetic syndrome
  - Personal history of Ulcerative Colitis or Crohn's disease

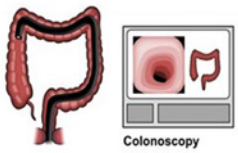
- Modifiable:
  - Diet (high red meat, low fiber, processed foods)
  - Sedentary lifestyle
  - Obesity
  - Habits (tobacco use, alcohol consumption)

Colorectal Cancer Basics- Signs and Symptoms

- Many people have no symptoms
- Symptoms could include:
  - A change in bowel movements (diarrhea, constipation, never feeling "relieved", narrower stools)
  - Blood in the stool (either bright or dark red)
  - Abdominal discomfort
  - Weight loss for no known reason
  - Constant fatigue
  - Vomiting

Screening Modalities

- Colonoscopy – gold standard
  - visual examination of the colon and rectum
  - Diagnostic and therapeutic, allows for biopsy and removal of polyps



fascrs.org

Screening Modalities

- Invasive
  - Colonoscopy – gold standard
  - Flexible sigmoidoscopy – visualization of rectum and left colon
- Non-invasive
  - Stool based studies
    - Fecal immunochemical test (FIT) detects hidden blood in stool
    - Cologuard®– looks for abnormal DNA and blood in stool
  - Imaging – requires bowel prep
    - Barium enema
    - CT colonography

Screening Guidelines

- Average risk individuals should begin screening at 45 years of age
  - U.S. Preventive Services Taskforce updated in 2021
- High risk individuals:
  - Family history of colorectal cancer or precancerous polyps – begin 10 yrs... prior to the age of diagnosis of youngest affected persons
    - First degree relative or multiple 2nd degree relatives

Screening Guidelines

- High risk individuals (continued):
  - Personal history of Inflammatory bowel disease
  - Genetic Syndrome – varies
    - Lynch Syndrome (HNPCC) every 1-2 yrs... starting at 20-25 yrs... of age
    - Familial Adenomatous Polyposis (FAP) annually starting at 10-12 yrs... of age

Screening Guidelines Frequency

- Normal screening, average risk →
  - Colonoscopy every 10 yrs..
  - Sigmoidoscopy +/- FOBT every 5 yrs..
  - CT colonography every 5 yrs..
  - Barium enema every 5 yrs..
  - Stool based studies
    - FIT – annually
    - Cologuard – 3-5 yrs..
    - FOBT alone – annually

Screening Guidelines - Frequency

- Normal screening, increased risk individuals*** →
  - Family history colorectal cancer/precancerous polyps – 5 years
  - Personal history of polyps – 3-5 years depending on size, number, type of polyp
  - Genetic Syndrome – varies by disease

Treatment

- Surgery
- Chemotherapy
- Radiation

Mainstays of Therapy

Treatment

- Surgery
- Chemotherapy
- Radiation
- Other options:
  - Immunotherapy
  - Biologic Therapy
  - Clinical trials

Mainstays of Therapy

Treatment

Surgery

Mainstay of treatment when possible

Goal is to remove as much of the cancer as possible

Treatment

Surgery

Mainstay of treatment when possible

Goal is to remove as much of the cancer as possible

Chemotherapy

Adjuvant & Neoadjuvant

- Given after surgery vs before surgery

Maintenance

Treatment

Radiation

Targeted to tumor itself or the tumor bed after removal

Also for targeting certain areas of metastasis

Liver, Lung, Bone, Brain

Treatment

Radiation

Targeted to tumor itself or the tumor bed after removal

Also for targeting certain areas of metastasis

Liver, Lung, Bone, Brain

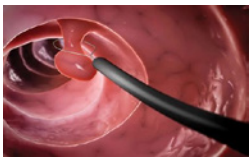
Chemoradiation

Chemotherapy and radiation given during the same time period

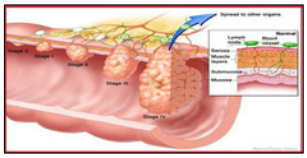
The chemotherapy is designed to make the tumor more sensitive to the radiation

Surveillance for polyps

- 5 years
  - <3 polyps
  - No polyps > 1 cm
- 3 years
  - >3 polyps
  - Any polyp > 1cm
  - Serrated adenoma



Surveillance for Colorectal Cancer



- Stage I – local disease
  - Colonoscopy at 1 year after surgery
  - If advanced adenoma, repeat in 1 year
  - If no advanced adenoma, repeat in 3 years, then every 5 years

NCCN Guidelines 2024

Surveillance for Colorectal Cancer

- Stage II-IV
  - History and physical examination every 3–6 mo. for 2 years, then every 6 months for a total of 5 years
  - CEA every 3–6 months for 2 years, then every 6 months for a total of 5 years
  - Chest/Abdomen/Pelvis CT every 6–12 months from date of surgery for a total of 5 years
  - Colonoscopy in 1 y after surgery
    - If advanced adenoma, repeat in 1 year
    - If no advanced adenoma repeat in 3 years, then every 5 years

NCCN Guidelines 2024

Benefits of Screening

- Detection of polyps – remove polyps to prevent malignant transformation
- Reduction in Mortality – regular screening reduces the rate of death from colorectal cancer by earlier detection

Benefits of Early Detection

5-year relative survival rates for colon cancer

These numbers are based on people diagnosed with cancers of the colon between 2013 and 2019.

SEER stage	5-year relative survival rate
Localized	91%
Regional	73%
Distant	13%
All SEER stages combined	63%

Cancer.org

Benefits of Early Detection

5-year relative survival rates for rectal cancer

These numbers are based on people diagnosed with cancers of the rectum between 2012 and 2018.

SEER stage	5-year relative survival rate
Localized	90%
Regional	74%
Distant	18%
All SEER stages combined	67%

Cancer.org

Conclusions

- While the rates of colorectal cancer in the older population is decreasing, it is increasing in the younger populations
- By 2030 11% of colon cancers and 23% of rectal cancers will be in patients <50
- Screening decreases mortality via early detection

Conclusions

- Colonoscopy is the gold standard in screening as it is diagnostic and therapeutic
- Treatment for colorectal cancer is a tremendous cost burden for patients and the healthcare system

Patient scenarios

- 45 y.o male presents to the office for rectal pain and bleeding. You find out he has a family history of colorectal cancer in a maternal grandmother. You also find out his mother had colon polyps on her colonoscopy at the age of 50

Patient scenarios

- 45 y.o male presents to the office for rectal pain and bleeding. You find out he has a family history of colorectal cancer in a maternal grandmother. You also find out his mother had colon polyps on her colonoscopy at the age of 50
  - History and physical
    - Normal abdominal exam and DRE, no gross blood
    - Colonoscopy reveals a 5 cm mass in the sigmoid colon
  - Biopsy reveals moderately differentiated adenocarcinoma

Patient scenarios

- 45 y.o male presents to the office for rectal pain and bleeding. You find out he has a family history of colorectal cancer in a maternal grandmother. You also find out his mother had colon polyps on her colonoscopy at the age of 50
  - History and physical
    - Normal abdominal exam and DRE, no gross blood
    - Colonoscopy reveals a 5 cm lesion in the sigmoid colon
  - Biopsy reveals moderately differentiated adenocarcinoma
  - CT c/a/p reveals no signs of distant disease and no positive lymph nodes

Patient scenarios

- 45 y.o male presents to the office for rectal pain and bleeding. You find out he has a family history of colorectal cancer in a maternal grandmother. You also find out his mother had colon polyps on her colonoscopy at the age of 50
  - Treatment: He underwent a robotic assisted sigmoid colectomy
  - Final pathology: Stage 2 moderately differentiated adenocarcinoma
    - No further treatment required

Patient scenarios

- 64-year-old woman presents with lower abdominal discomfort and anemia
  - PMHx of HTN and DM
  - Last colonscopy > 10 yrs.. ago
  - No known family history of colorectal cancer

Patient scenarios

- 64-year-old woman presents with lower abdominal discomfort and anemia
  - PMHx of HTN and DM
  - Last colonoscopy > 10 yrs.. ago
  - No known family history of colorectal cancer
  - CT abdomen and pelvis was performed and revealed a 12 cm mass invading the uterus
    - Follow up colonoscopy revealed a mass in the ascending colon
    - Biopsies inconclusive

Patient scenarios

- 64-year-old woman presents with lower abdominal discomfort and anemia
  - Surgery: open right colectomy in conjunction with gyn oncology who simultaneously removed the uterus.
  - Final pathology, Stage 3 colon cancer, with local invasion to uterus and 3 positive lymph nodes
  - Referred to oncology for adjuvant chemotherapy

Patient scenarios

- 35-year-old woman presents on recommendation from her gyn for colonoscopy because her father had colon polyps found on his colonoscopy at age 45
  - Screening colonoscopy demonstrated 2 polyps: 1 in the transverse colon and 1 in the descending colon

Patient scenarios

- 35-year-old woman presents on recommendation from her gyn for colonoscopy because her father had colon polyps found on his colonoscopy at age 45
  - Screening colonoscopy demonstrated 2 polyps: 1 in the transverse colon and 1 in the descending colon
  - Final pathology 1 cm tubular adenoma and 0.5 cm serrated adenoma
    - Her next colonoscopy will be in 3 years
    - Her children will begin screening at age 25

Patient scenarios

- 35-year-old woman presents on recommendation from her gyn for colonoscopy because her father had colon polyps found on his colonoscopy at age 45
  - Screening colonoscopy demonstrated 2 polyps: 1 in the transverse colon and 1 in the descending colon
  - Final pathology 1 cm tubular adenoma and 0.5 cm serrated adenoma
    - Her next colonoscopy will be in 3 years
    - Her children will begin screening at age 25
    - She will be referred for genetics counseling for a deep dive into her family history

Patient scenarios

- 47-year-old man presents on recommendation from his PCP for colonoscopy because he just learned of the updated guidelines
  - Colonoscopy was performed and a 0.5 cm polyps was found in the rectum
  - Pathology : well differentiated rectal cancer

Patient scenarios

- 47-year-old man presents on recommendation from his PCP for colonoscopy because he just learned of the updated guidelines
  - Colonoscopy was performed and a 0.5 cm polyp was found in the mid rectum
  - Pathology : well differentiated rectal cancer

  - CT c/s/p negative for distant disease
  - MRI pelvis + lymph nodes
  - Patient underwent neoadjuvant chemoradiation therapy

Patient scenarios

- 47-year-old man presents on recommendation from his PCP for colonoscopy because he just learned of the updated guidelines

  - CT c/s/p negative for distant disease
  - MRI pelvis + lymph nodes
  - Patient underwent neoadjuvant chemoradiation therapy

  - Patient underwent robotic assisted low anterior resection to remove rectum and a temporary diverting ileostomy
  - He is recovering well awaiting his next set of scans

SELF EVALUATION

Colorectal Cancer Screening, Treatment and Surveillance

1. At what age does the American Cancer Society recommend average-risk individuals begin colorectal cancer screening?

a. 40 years old
b. 45 years old
c. 50 years old
d. 55 years old

2. Which screening method is considered the gold standard for detecting colorectal cancer?

a. Sigmoidoscopy
b. Fecal immunochemical test (FIT)
c. Colonoscopy
d. CT colonography

3. How often should an average-risk individual undergo colonoscopy for CRC screening?

a. Every 5 years
b. Every 10 years
c. Every 15 years
d. Every 20 years

4. Which factor does NOT increase the risk of colorectal cancer?

a. Age
b. Family history of CRC
c. Regular physical activity
d. Inflammatory bowel disease

5. Which condition is considered a high-risk factor for early CRC screening?

a. Irritable bowel syndrome
b. Familial adenomatous polyposis
c. Lactose intolerance
d. Peptic ulcer disease

6. T/F - The primary goal of CRC screening is the early detection of colorectal cancer

7. T/F - The primary treatment for early-stage colorectal cancer is chemotherapy.

8. T/F - The average age of onset of CRC is getting younger.

Answer Key: 1. B, 2. C, 3. B, 4. C, 5. B, 6. T, 7. F, 8. T

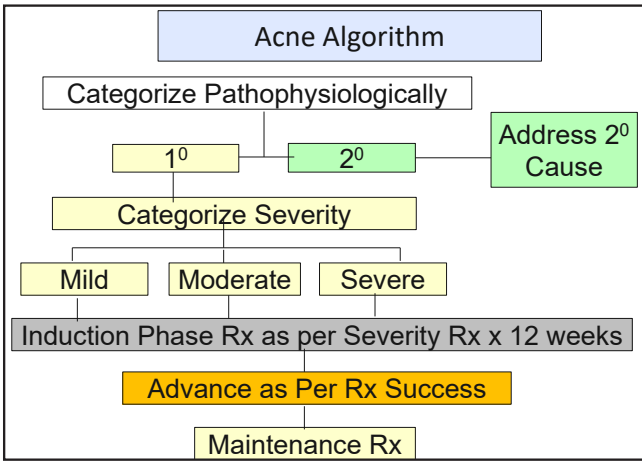
LOUIS KURITZKY, MD
4510 NW 17th Place
GAINESVILLE, FL 32605
(352) 377-3193 LKuritzky@aol.com

Managing Adult and Adolescent Acne

Goals

- Review recent acne guidelines
- Become familiar with recommended pharmacotherapies for acne within the spectrum of 1^0 care
- Be cognizant of current data on the relationship between diet and acne

Acne Algorithm



FROM THE ACADEMY

Guidelines of care for the management of acne vulgaris

Work Group: Andrea L. Zaenglein, MD (Co-Chair),[a] Arun L. Pathy, MD (Co-Chair),[b] Bethanee J. Schlosser, MD, PhD,[c] Ali Alikhan, MD,[d] Hilary E. Baldwin, MD,[e] Diane S. Berson, MD,[f,g] Whitney P. Bowe, MD,[e] Emmy M. Graber, MD,[h,i] Julie C. Harper, MD,[j] Sewon Kang, MD,[k] Jonette E. Keri, MD, PhD,[l,m] James J. Leyden, MD,[n] Rachel V. Reynolds, MD,[o,p] Nanette B. Silverberg, MD,[q,r] Linda F. Stein Gold, MD,[s] Megha M. Tollefson, MD,[t] Jonathan S. Weiss, MD,[u] Nancy C. Dolan, MD,[c] Andrew A. Sagan, MD,[v] Mackenzie Stern,[c] Kevin M. Boyer, MPH,[w] and Reva Bhushan, MA, PhD[w]
Hershey and Philadelphia, Pennsylvania; Centennial, Colorado; Chicago and Schaumburg, Illinois; Cincinnati, Ohio; New York, New York; Boston, Massachusetts; Birmingham, Alabama; Baltimore, Maryland; Miami, Florida; Detroit, Michigan; Rochester, Minnesota; and Atlanta, Georgia

Zaenglein AL, et al *J Am Acad Dermatol* 2016;74:945-73

NICE National Institute for Health and Care Excellence

Royal College of Obstetricians & Gynaecologists

BRITISH ASSOCIATION OF DERMATOLOGISTS

NICE guideline

Acne vulgaris: management

NICE guideline
Published: 25 June 2021
www.nice.org.uk/guidance/ng198

Practical management of acne for clinicians: An international consensus from the Global Alliance to Improve Outcomes in Acne

Diane M. Thiboutot, MD, Chair,[a] Brigitte Dréno, MD, PhD, Co-Chair,[b,c,d] Abdullah Abanmi, MD,[e] Andrew F. Alexis, MD, MPH,[f] Elena Araviiskaia, MD, PhD,[g] Maria Isabel Barona Cabal, MD,[h] Vincenzo Bettoli, MD,[i] Flordeliz Casintahan, MD,[j] Steven Chow, MD,[k] Adilson da Costa, MD, MSc, PhD,[l] Tam El Ouazzani, MD,[m] Chee-Leok Goh, MD,[n] Harald P. M. Gollnick, MD,[o] Minerva Gomez, MD,[p] Nobukazu Hayashi, MD, PhD,[q] Maria Isabel Herane, MD,[r] Juan Honeyman, MD,[s] Sewon Kang, MD,[t] Lajos Kemeny, MD, PhD,[u] Raj Kubba, MD,[v] Julien Lambert, MD, PhD,[w] Alison M. Layton, MB ChB,[x] James J. Leyden, MD,[y] Jose Luis López-Estebaranz, MD, PhD,[z] Nopadon Noppakun, MD,[aa,bb] Falk Ochsendorf, MD,[cc] Cristina Oprica, MD, PhD,[dd] Beatriz Orozco, MD,[ee] Montserrat Perez, MD,[ff] Jaime Piquero-Martin, MD, MSc,[gg] Jo-Ann See, MD,[hh] Dae Hun Suh, MD, PhD,[ii] Jerry Tan, MD,[jj] Vicente Torres Lozada, MD,[kk] Patricia Troielli, MD,[ll] and Leihong Flora Xiang, MD, PhD[mm]

Thiboutot DM et al *J Am Acad Dermatol* 2018;78(2-Suppl):s1-s24

And When They Say **GLOBAL** Alliance….

USA	Italy	Singapore	Hungary
France	Philippines	Germany	India
Saudi Arabia	Malaysia	Mexico	Belgium
Russia	Brazil	Japan	UK
Columbia	Morocco	Chile	Spain
Thailand	Sweden	Venezuela	Australia
Korea	Canada	Argentina	China

Thiboutot DM et al *J Am Acad Dermatol* 2018;78(2-Suppl):s1-s24

Test Question #1

- Clinical Guidelines are
  - ❑ **THE** correct way to do things
  - ☒ **A** correct way to do things

Guidelines NOT Intended to be the Standard of Care

"…these guidelines should not be interpreted as setting a standard of care…nor exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the propriety of any specific therapy…must be made … in light of all the circumstances presented by the individual patient, and the known variability and biologic behavior of the disease.

Zaenglein AL et al *J Am Acad Dermatol* 2016;74:945-73

ACNE: Why Bother?

"Acne is a chronic inflammatory skin disease that is estimated to affect approximately 85% of the population at some point in their lives. "

Thiboutot DM et al *J Am Acad Dermatol* 2018;78(2-Suppl):s1-s24

ACNE: Why Bother?

"Although acne is a very common disease, little time is spent on it in medical curricula….more than half of American medical schools teach <10 hours of dermatology"

Thiboutot DM et al *J Am Acad Dermatol* 2018;78(2-Suppl):s1-s24

The Problem: Major League

Thiboutot DM et al *J Am Acad Dermatol* 2018;78(2-Suppl):s1-s24

The Problem: 'Minor' League

Closed Comedone ('whitehead')

Open Comedone ('blackhead')

Incidental Acne

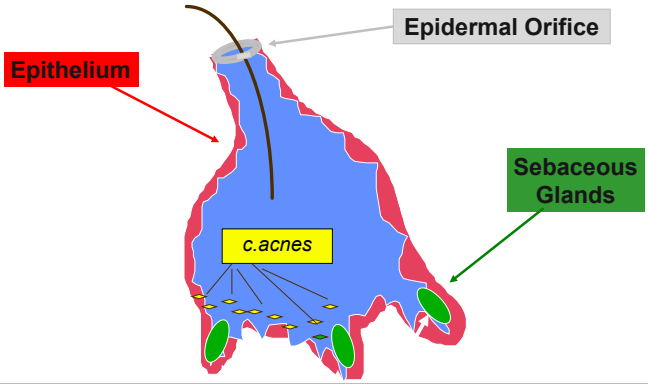
The Culprits

- Testosterone
- Pilosebaceous Hyperkeratinization
- Dysseborrhea
- *Cutibacterium Acnes*

The Players

- **Retinoids** Topical Systemic
- **Benzoyl Peroxide**
- **Antibiotics** Topical Systemic
- **Cleansing Agents**
- **Hormonal Agents** COC Spironolactone
- **Diet**
- **Azelaic Acid**
- **Dapsone** Topical
- **Corticosteroids**
- **Phototherapy**

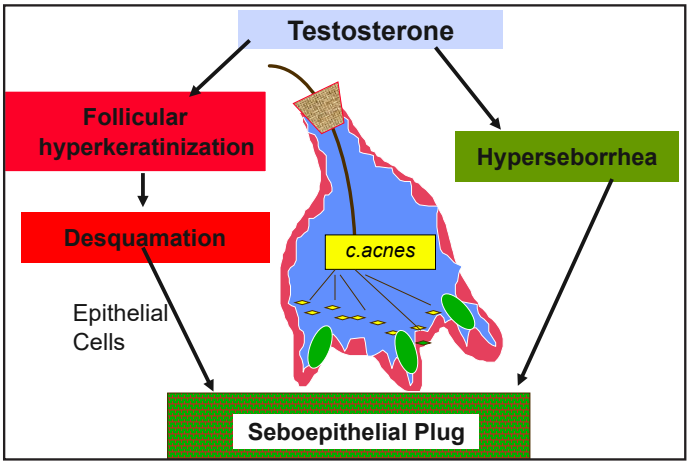
Pilosebaceous Unit



Acne Pathophysiology

- Follicular Hyperkeratinization
- ↑Sebum production
- Pilosebaceous Unit Obstruction (Sebo-epithelial Plug)
- *Cutibacterium acnes* Infection

Chien AL *J Drugs Dermatol* 2018;17(12 Suppl):s51-s56



Treatment

Acne Treatment Path

- Assess Severity
- Pharmacotherapy:
  - Induction Phase: severity-concordant GDMT
  - Maintenance Phase
- Diet
- Skin Hygiene
- Maintenance

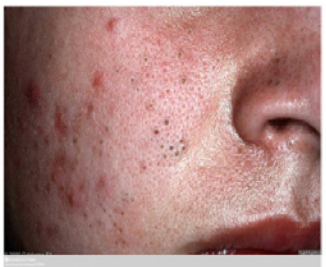
Acne Severity Grading

Acne Severity Grading

"Several systems for grading acne exist; most employ lesion counting combined with some type of global assessment of severity (eg, mild, moderate, severe) that represents a synthesis of the #, size, and extent of lesions."

Strauss JS, et al *J Am Acad Dermatol* 2007;56:651-63

Grading is Simple: Just Count the Lesions?



Thiboutot DM et al *J Am Acad Dermatol* 2018;78(2-Suppl):s1-s24

ACNE: Severity Assessment

"There is no standardized acne grading or classification system; however, acne is often categorized by an overall gestalt as mild, moderate, and severe…"

Thiboutot DM et al *J Am Acad Dermatol* 2018;78(2-Suppl):s1-s24

Grading Acne Severity

"Currently, no universal acne grading/classifying system can be recommended."

Zaenglein AL et al *J Am Acad Dermatol* 2016;74:945-73

How To Measure Treatment Success

- Reduction in Lesions:
  - Excellent: ≥75% ↓
  - Good: 50-74% ↓
  - Fair: 25-49% ↓
  - Poor: <25% ↓

Lyons RE *Pharmacol Therapeutics* 1978;17(3):246-251

Pharmacologic Rx

The Players

Retinoids Topical Systemic

Benzoyl Peroxide

Antibiotics Topical Systemic

Azelaic Acid

Hormonal Agents COC Spironolactone

Diet

Cleansing Agents

Dapsone Topical

Corticosteroids

Phototherapy

Mild Acne: 1st Line Rx

(t) = topical

Benzoyl Peroxide (t) or Retinoid (t)
Benzoyl Peroxide (t) + Retinoid (t)
Benzoyl Peroxide (t) + Antibiotic (t)
Benzoyl Peroxide(t) + Retinoid(t) + Antibiotic(t)

Alternatives: Alternative Retinoid (t), Dapsone(t)

Zaenglein AL et al *J Am Acad Dermatol* 2016;74:945-73

Moderate Acne: 1st Line Rx

(t) = topical

Benzoyl Peroxide (t) + Antibiotic (t)
Benzoyl Peroxide (t) + Retinoid (t)
Benzoyl Peroxide(t) + Retinoid(t) + Antibiotic(t)
Benzoyl Peroxide(t) + Retinoid(t) + Antibiotic(po)
Benzoyl Peroxide(t) + Retinoid(t) + Antibiotic (t+po)

Alternative: COC, spironolactone, isotretinoin, Δ Oral antibiotic

Zaenglein AL et al *J Am Acad Dermatol* 2016;74:945-73

Severe Acne: 1st Line Rx

Benzoyl Peroxide (t) + Antibiotic (t+po)
Benzoyl Peroxide (t) + Retinoid (t) + Antibiotic (po)
Benzoyl Peroxide (t) + Antibiotic (t)
Benzoyl Peroxide(t) + Retinoid(t) + Antibiotic(t+po)
Isotretinoin

Alternatives: COC, Spironolactone, Δ Oral Antibiotic

Zaenglein AL et al *J Am Acad Dermatol* 2016;74:945-73

'Traditional' Antibiotics For Acne

Did you notice anything in GDMT that differs from what primary care clinicians have often done?

'Traditional' Antibiotics For Acne

Did you notice anything in GDMT that differs from what primary care clinicians have often done?

NO ANTIBIOTICS-ONLY REGIMENS

Acne Global Alliance Consensus Statement 2

"The role of antibiotics in acne Rx has changed. Neither topical nor systemic antibiotics should be used as monotherapy for acne treatment."

Thiboutot DM et al *J Am Acad Dermatol* 2018;78(2-Suppl):s1-s24

Acne: GDMT

What was included as a1st-line Therapy at EVERY SEVERITY LEVEL of of GDMT?

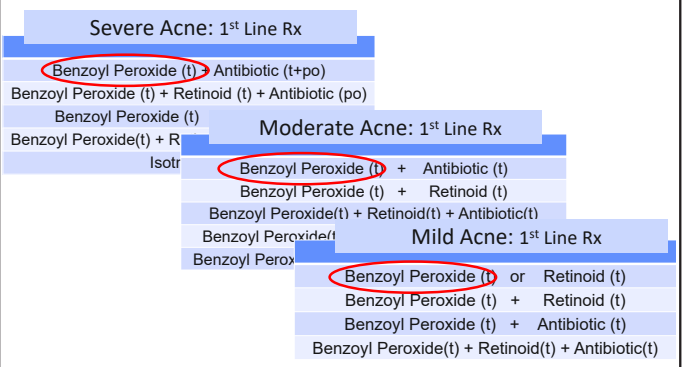
Acne: GDMT

What was included as a1st-line Therapy at Every Severity Level of of GDMT?

Benzoyl Peroxide

Benzoyl Peroxide

Acne: BPO Rules!!



Zaenglein AL et al *J Am Acad Dermatol* 2016;74:945-73

Benzoyl Peroxide
Nobody Told Me it Was an Antibiotic

- Very lipophilic → ↑↑pilosebaceous penetration
- 1^0 Activity: antibacterial
  - Intradermal conversion → benzoic acid
  - Benzoic acid converted to cysteine
  - Cysteine → free-radical O_2 species
  - Free radical O_2 → *C. acnes* cell wall lysis
- 2^0 activity: mildly comedolytic

Benzoyl Peroxide

- Bacteriocidal to *C. acnes*
  - MOA: release of free O_2 radicals
  - Mildly comedolytic
  - No development of bacterial resistance
- Prompt response time: as soon as 5 days
- If poor tolerance: use ↓concentration (2.5%-5%), H_20-based products

Zaenglein AL et al *J Am Acad Dermatol* 2016;74:945-73

Benzoyl Peroxide

"Benzoyl peroxide….combinations with antibiotics are a key element of topcal acne Rx, as the bactericidal effect of benzoyl peroxide can synergstically prevent bacterial resistance to antibiotics."

Bramman C, Muller-Goymann CC *Int J Pharmaceutics* 2020;578:1-13

Benzoyl Peroxide: How Supplied

- BPO Monocomponent 2.5% -10%: OTC
- When combined with retinoid, antibiotic: Rx

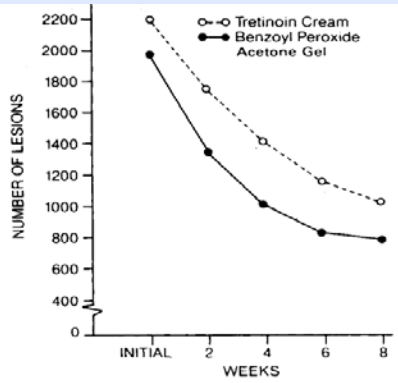
Bramman C, Muller-Goymann CC *Int J Pharmaceutics* 2020;578:1-13

Benzoyl Peroxide vs Retinoid

- PRCT mild-moderate acne (n=147)
- Rx
  - BPO 5% qd-b.i.d. X 4 weeks, then BPO 10%
  - Tretinoin cream 0.1% qd-b.i.d.
- Outcome (at 8 weeks)
  - Comdeones (open & closed)
  - Papules
  - Pustules

Lyons RE *Pharmacol Therapeutics* 1978;17(3):246-251

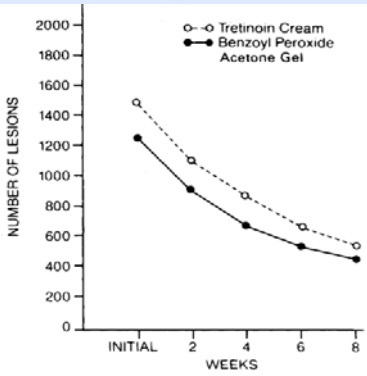
Benzoyl Peroxide vs Retinoid: Total Lesions



n =147 p = NS

Lyons RE *Pharmacol Therapeutics* 1978;17(3):246-251

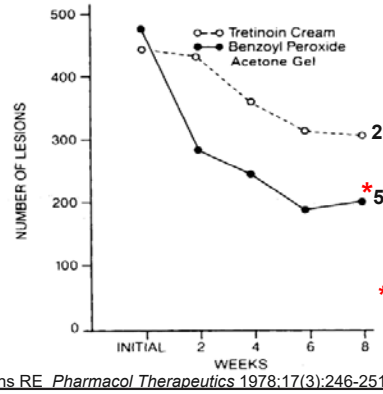
Benzoyl Peroxide vs Retinoid: Comedones



n =147 p = NS

Lyons RE *Pharmacol Therapeutics* 1978;17(3):246-251

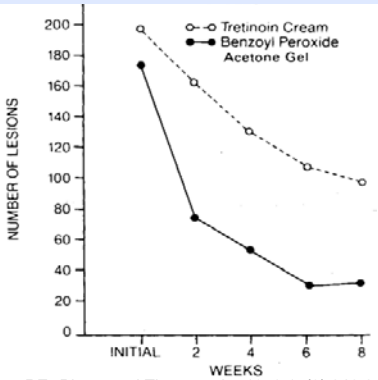
Benzoyl Peroxide vs Retinoid: Papules



n =147 * p = <0.02

Lyons RE *Pharmacol Therapeutics* 1978;17(3):246-251

Benzoyl Peroxide vs Retinoid: Pustules



n =147 p = NS

Lyons RE *Pharmacol Therapeutics* 1978;17(3):246-251

Benzoyl Peroxide vs Retinoid: Tolerability

"Burning and erythema were noted in 10/55 patients Rx with tretinoin. No side effects were noted in patients Rx with the benzoyl peroxide gel formulations."

Lyons RE *Pharmacol Therapeutics* 1978;17(3):246-251

Benzoyl Peroxide Adverse Effects

- Itching
- Redness
- Peeling
- Drying
- Dose related
- Diminish with time
- Bleaching/discoloration of clothing, sheets

Bramman C, Muller-Goymann CC *Int J Pharmaceutics* 2020;578:1-13

Azelaic Acid

Azelaic Acid

- Anti-inflammatory (IL-6, TNF)
- Antibacterial
  - *C. acnes, S. epidermidis,* MRSA
  - No known resistant strains
- Antifungal: *M. furfur*
- Keratinolytic
- ↓ Postinflammatory hyperpigmentation (blocks tyrosinase)
- No photosensitivity

Sieber MA, Hegel JKE *Skin Pharmacol Physiol* 2014;27(suppl1):9-17

What is Azelaic Acid

- Naturally occurring substance: wheat, barley, rye
- Antikeratinizing, antibacterial, antiinfllammatory
- As Monotherapy = BPO 5%, erthryomycin 2%, tretinoin 0.05%
- No skin irritation
- No sun sensitivity
- No induction of bacterial resistance

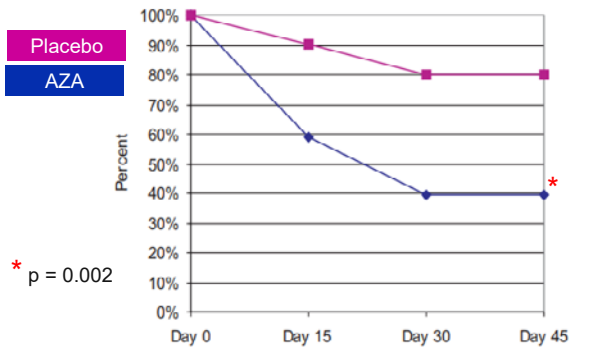
Dinulos JGH *Habif's Clinical Dermatology 2021*

Acne: Azelaic Acid

- Study: Prospective open label (n=46)
- Inclusion:
  - Age >14
  - Mild-severe acne (Cunliffe score I-III/IV)
- Rx azelaic acid cream 20% qd X 7 then b.i.d x 23 weeks

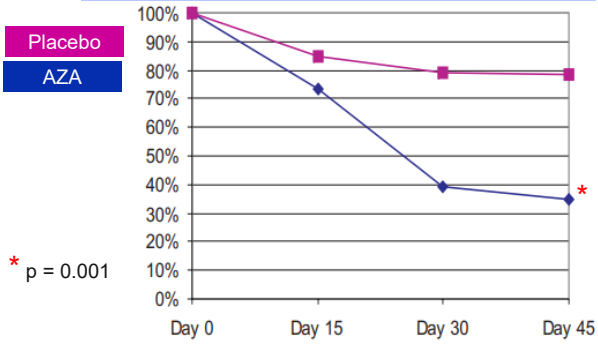
Shemer A, et al J Europ Acad Dermaol Vernerol 2002;16:171-188

Azelaic Acid for Acne: Lesion Count



Iraji F et al, Indian J Dermatol Venereol Leprol 2007;73(2):94-96

Azelaic Acid for Acne: Acne Severity Index



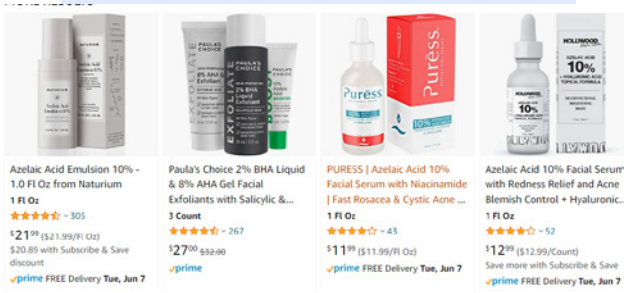
Iraji F et al, Indian J Dermatol Venereol Leprol 2007;73(2):94-96

Azelaic Acid: Acne Global Alliance Consensus Statement 7

"azelaic acid cream 20% or gel 15% is a useful acne treatment in pregnant women and patients with acne and PIH .

Thiboutot DM et al *J Am Acad Dermatol* 2018;78(2-Suppl):s1-s24

Azelaic Acid OTC



Amazon.com June-5, 2022

Azelaic Acid Rx

The Retinoids

So What Are Retinoids?

- Structural or Functional Vit A Analogues
- Bind to intranuclear retinoic acid receptors (RAR-β, RAR-γ)
  - →Follicular keratinization normalization
  - →↓Follicular occlusion
- Immunomodulation
  - →↓inflammation
  - →↓Postinflammatory hyperpigmentation
- Enhance epidermal penetration of other topicals

Bell KA et al *Annals Pharmacotherapy* 2021;55(1):111-116

Why Is Vitamin A Confusing?

"Vitamin A is a… **group** of organic compounds that includes retinol, retinal (AKA retinaldehyde), retinoic acid, and several provitamin A carotenoids (most notably β-carotene)."

Wikipedia accessed 6/2/22

Acne Global Alliance Consensus Statement 1

"Retinoids have an essential role in Rx of acne. For most patients with inflammatory acne, comedonal acne, or both, a topical retinoid plus BPO is first-line therapy."

Thiboutot DM et al *J Am Acad Dermatol* 2018;78(2-Suppl):s1-s24

'Generations' of Retinoids

	Generic	Trade	Form	Indication
1st	tretinoin	Retin-A	Topical	Acne
	isotretinoin	Accutane	PO	Severe Acne
2nd	acitretin	Soriatane	PO	Psoriasis
3rd	adapalene	Differin	Topical	Acne
	tazarotene	Tazorac	Topical	Acne
4th	trifarotene	Aklief	Topical	Acne

Chien AL *J Drugs Dermatol* 2018;17(12 Suppl):s51-s56

Acne: The Players

Retinoids	Trade	Form	Dose
Adapalene	Differin	Cream 0.1%	
		Gel 01.%, 0.3%	
		Lotion 0.1%	
Tretinoin	Retin-A	Cream 0.025%, 0.05%, 0.1%	
		Gel 0.01%, 0.025%, 0.05%	
		Gel Microsphere 0.04%,0.1%	
Tazarotene	Fabior	0.1% Foam	QHS
	Tazorac	Cream 0.05%, 0.1%	
Trifarotene	Aklief	Cream 0.005%	

Topical Retinoids

adapalene, tazarotene, tretinoin. [trifarotene]

- Good for maintenance Rx (post systemics)
- Benzoyl peroxide co-administration may inactivate retinoids
- HS application recommended
- AEs: drying, peeling, erythema, irritation
- Efficacy: clinical trial limitations preclude definitive statement. Maybe:
  - Tazarotene > adapalene > tretinoin

Zaenglein AL et al *J Am Acad Dermatol* 2016;74:945-73

Tips To Enhance Retinoid Use

- Elicit past tolerability issues
- Apply fingertip amount, thin layer
- Use vehicle as per skin type
  - Dry/sensitive: creams, lotions, aqueous gels
  - Oily: gels or foam
- Initial Rx phase (2-4 weeks)
  - Appy q.o.d.
  - Short contact (wash off after 30-60 mins)
  - Add noncomedogenic moisturizer

Thiboutot DM et al *J Am Acad Dermatol* 2018;78(2-Suppl):s1-s24

Topical Retinoids
adapalene, tazarotene, tretinoin

- Evidence of Efficacy: Level A
- Derived from Vitamin A
- Site of action: retinoic acid receptors
  - 3 distinct receptor classes (α,β,γ)
  - Each retinoid works on different receptors
- MOA: ↓ follicle obstruction
  - comedolytic
  - anti-inflammatory

Zaenglein AL et al *J Am Acad Dermatol* 2016;74:945-73

Postinflammatory Hyperpigmentation

Postinflammatory Hyperpigmentation

Ebuluk N, et al *Am J Clin Dermatol* 2021;22:829-836

4th Generation Retinoid: Trifarotene
Post-Inflammatory Hyperpigmentation

"Inflammatory acne is often accompanied by post-inflammatory hyperpigmentation, especially in Black and Asian subjects. The rapid in vivo anti-pigmenting activity of trifarotene is therefore another useful characteristic of this molecule."

Aubert K, et al *Brit J Dermatol* 2018:179(2):442-456

Skin Care

Don't Forget the Syndet

1.2 Skin Care Advice

1.2.1 "Advise people with acne to use a non-alkaline (skin pH neutral or slightly acidic) synthetic detergent (syndet) cleansing product twice daily on acne-prone skin."

Acne Vulgaris Management *NICE Guideline* 2021

Don't Forget the Syndet

Synthetic Detergent (syndet)

"A synthetic detergent (syndet) is a blend of synthetic surfactants and is formulated to have neutral to slightly acidic pH similar to the skin. It is widely available in both solid and liquid forms as a skin cleanser."

Acne Vulgaris Management *NICE Guideline* 2021

https://www.chagrinvalleysoapandsalve.com/blog/posts/what-are-syndets/ accessed 6/4/22

Syndets

- "Although the word syndet may be new to many people, the first syndet bar, Dove, was introduced in 1955."
- " A syndet is the name given to a cleansing bar or liquid made with synthetic surfactants."
- "Syndet bars cannot really call themselves 'soap', because the word "Soap" actually has a legal definition provided by the FDA.
- Since syndets are made with synthetic surfactants they do not meet the legal definition of soap.

https://www.chagrinvalleysoapandsalve.com/blog/posts/what-are-syndets/ accessed 6/4/22

An Example Syndet Bar

Diet

What Does NICE Say About Diet?

1.3

1.3.1 Advise people that there is not enough evidence to support specific diets for treating acne

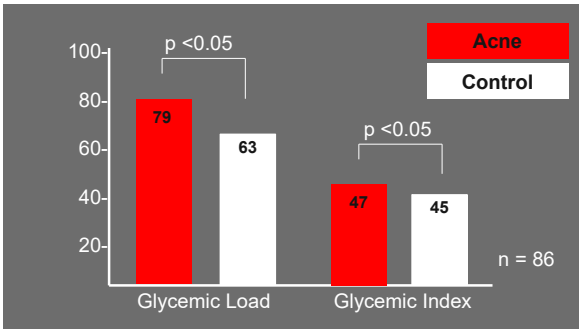
Acne Vulgaris Management 2021 NICE Guideline #198

High Glycemic Index & Acne: WHY?

High glycemic Index
↓
Hyperinsulinemia
↓
↑ Androgens

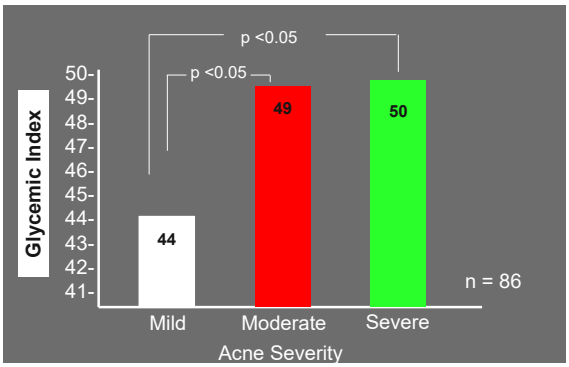
Cerman AA et al *J Am Acad Dermatol* 2016;75:155-162

Glycemic Index & Acne



Cerman AA et al *J Am Acad Dermatol* 2016;75:155-162

Glycemic Index vs Acne Severity



Cerman AA et al *J Am Acad Dermatol* 2016;75:155-162

The impact of chocolate consumption on acne vulgaris in college students: A randomized crossover study

Gregory R Delost, DO, Maria E Delost, PhD, Jenifer Lloyd DO

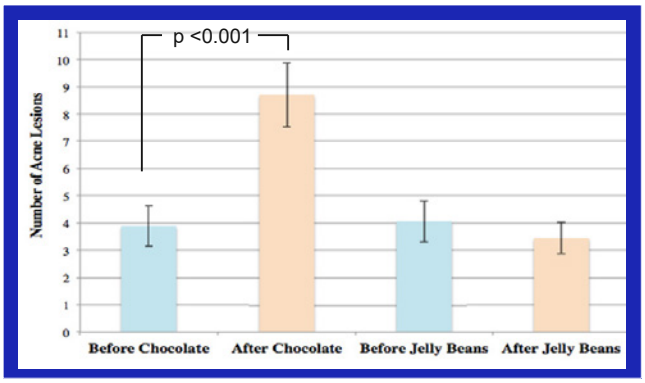
J Am Acad Dermatol 2016:75(1):220-222

Chocolate & Acne

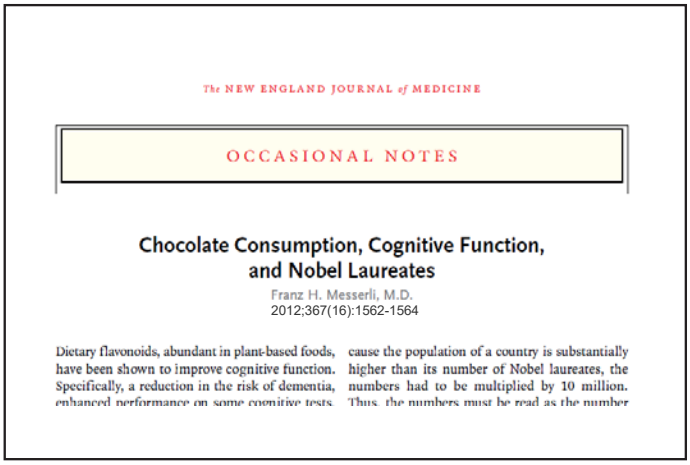
- Study: SBXO Youngstown State University students with acne (n= 54)
- Rx: Hersheys' milk chocolate bar (43 g CHO) vs equivalent Jelly Beans (JB: 15 beans)
- Method:
  - Baseline photo
  - Ingest Hershey Bar or Jelly Beans
  - 48 hr post 'Rx' f/u photo & lesion count
  - 4 week washout
  - XO & repeat

Delost GR et al *J Am Acad Dermatol* 2016;75(1):220-222

Acne: Chocolate Vs Jelly Beans



Delost GR et al *J Am Acad Dermatol* 2016;75(1):220-222



The NEW ENGLAND JOURNAL of MEDICINE

OCCASIONAL NOTES

Chocolate Consumption, Cognitive Function, and Nobel Laureates

Franz H. Messerli, M.D.
2012;367(16):1562-1564

Dietary flavonoids, abundant in plant-based foods, have been shown to improve cognitive function. Specifically, a reduction in the risk of dementia, enhanced performance on some cognitive tests, cause the population of a country is substantially higher than its number of Nobel laureates, the numbers had to be multiplied by 10 million. Thus, the numbers must be read as the number

Maintenance Phase Rx

Acne: Maintenance Phase

"An effective maintenance therapy should prevent acne recurrence by targeting the early stages of comedogenesis and the precursor of mature acne lesions, the microcomedo. At present, the most effective comedolytic agents are oral isotretinoin and topical retinoids."

Thiboutot DM et al *Arch Dermatol* 2006;142:597-602

Acne Global Alliance Consensus Statement 6

": most patients with acne should receive maintenance Rx with a topical retinoid with or without BPO. Topical antibiotics should not be used as acne maintenance therapy.

Thiboutot DM et al *J Am Acad Dermatol* 2018;78(2-Suppl):s1-s24

STUDY

Comparison of Tazarotene and Minocycline Maintenance Therapies in Acne Vulgaris

A Multicenter, Double-blind, Randomized, Parallel-Group Study

James Leyden, MD; Diane M. Thiboutot, MD; Alan R. Shalita, MD; Guy Webster, MD, PhD; Kenneth Washenik, MD, PhD; Bruce E. Strober, MD, PhD; Jerome Shupack, MD

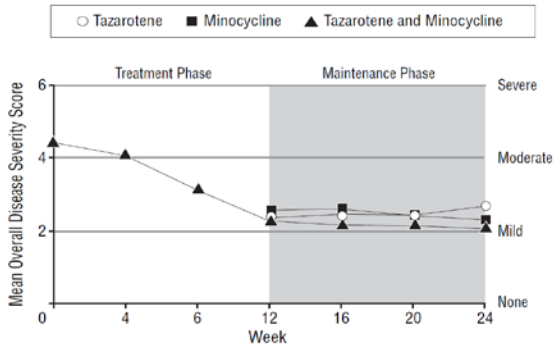
Arch Dermatol 2006;142:605-612

Acne *Maintenance* Rx Tazarotene vs Minocycline vs Both

- Study: DBRCT mod severe-severe acne
- Subjects: Responders (n=110) to 12 weeks combo Rx (≥75% clearing)
- Rx (x additional 12 weeks)
  - 0.1% tazarotene gel QHS
  - 100 mg minocycline b.i.d.
  - Both

Leyden J et al *Arch Dermatol* 2006;142:605-612

Acne *Maintenance* Rx
Tazarotene vs Minocycline vs Both



Leyden J et al *Arch Dermatol* 2006;142:605-612

Acne *Maintenance* Rx
Tazarotene vs Minocycline vs Both

RESULTS

"At week 24, >80% of patients in each group had maintained ≥50% global improvement from baseline, and >50% had maintained a ≥ 75% global improvement."

Leyden J et al *Arch Dermatol* 2006;142:605-612

Acne *Maintenance* Rx
Tazarotene vs Minocycline vs Both

Conclusions

"A high percentage of patients with moderately severe to severe acne can maintain improvement in their condition with topical retinoid *monotherapy**."

*emphasis added

Leyden J et al *Arch Dermatol* 2006;142:605-612

STUDY

Adapalene Gel, 0.1%, as Maintenance Therapy for Acne Vulgaris

A Randomized, Controlled, Investigator-Blind Follow-up of a Recent Combination Study

Diane M. Thiboutot, MD; Alan R. Shalita, MD; Paul S. Yamauchi, MD, PhD; Catherine Dawson; Nabil Kerrouche; Stéphanie Arsonnaud; Sewon Kang, MD

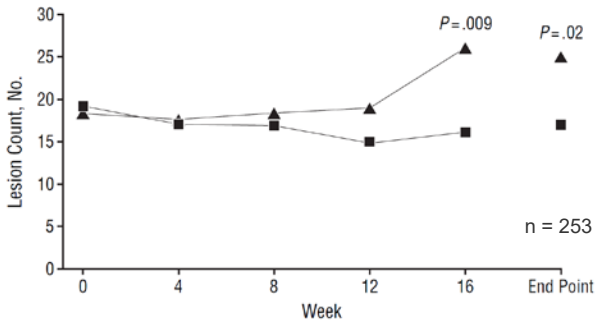
Arch Dermatol 2006;142:597-602

Adapalene Maintenance

- Study: RDBPCT severe acne Rx-responders (≥50% improvement post 12 weeks of doxycycline 100 mg qd ± adapalene 1% gel qhs) n = 253
- Rx: adapalene 1% gel vs vehicle qhs x 16 weeks
- Outcomes:
  - lesion count
  - pt satisfaction

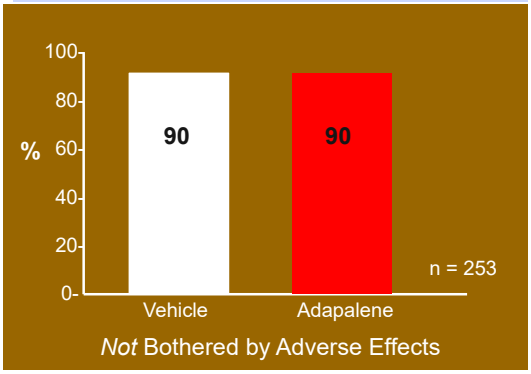
Thiboutot DM et al *Arch Dermatol* 2006;142:597-602

Adapalene 1% gel Maintenance Rx



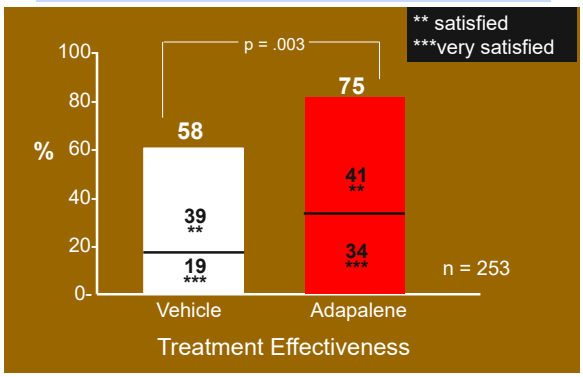
Thiboutot DM et al *Arch Dermatol* 2006;142:597-602

Adapalene 1% Gel Maintenance



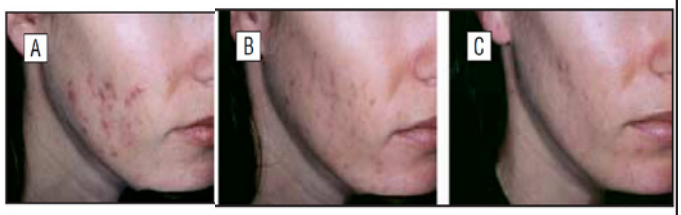
Thiboutot DM et al *Arch Dermatol* 2006;142:597-602

Adapalene 1% Gel Maintenance



Thiboutot DM et al *Arch Dermatol* 2006;142:597-602

Adapalene 1% Gel Maintenance



baseline | **adapalene + doxycycline 12 weeks** | **adapalene 16 weeks**

Thiboutot DM et al *Arch Dermatol* 2006;142:597-602

Combo to Mono Transition

Minocycline + Tazarotene to Tazarotene Alone

Leyden J et al Arch Dermatol 2006;142:605-612

DOI: 10.1111/jdv.12823 JEADV

ORIGINAL ARTICLE

A randomized investigator-blind parallel-group study to assess efficacy and safety of azelaic acid 15% gel vs. adapalene 0.1% gel in the treatment and maintenance treatment of female adult acne

A. Thielitz,[1,*] A. Lux,[2] A. Wiede,[1] S. Kropf,[2] E. Papakonstantinou,[1] H. Gollnick[1]

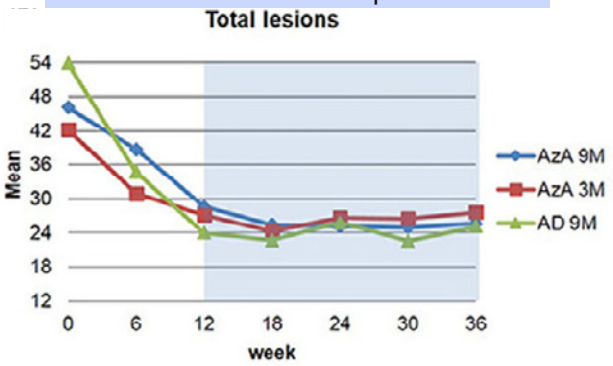
Thielitz A, et al *J Eur Assoc Dermatol Venereol* 2014;29(4):789-796

Acne Maintenance Rx
Azelaic Acid vs Adapalene

- Study: RSBT Adults mild-mod Acne
- Rx (n= 55 adult ♀):
  - Azelaic acid b.i.d. X 3 months
  - Azelaic acid b.i.d. X 9 months
  - Adapalene gel qd X 9 months
- Outcomes (9 months)
  - Lesion counts
  - Lesion severity
  - Relapse rate

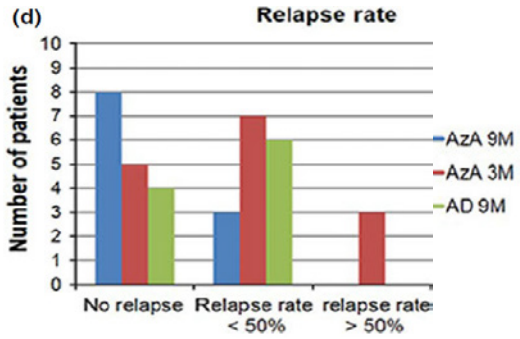
Thielitz A, et al *J Eur Assoc Dermatol Venereol* 2014;29(4):789-796

Acne Maintenance Rx
Azelaic Acid vs Adapalene



Thielitz A, et al *J Eur Assoc Dermatol Venereol* 2014;29(4):789-796

Acne Maintenance Rx
Azelaic Acid vs Adapalene



Thielitz A, et al *J Eur Assoc Dermatol Venereol* 2014;29(4):789-796

Acne Maintenance Rx
Azelaic Acid vs Adapalene

"Azelaic acid 15% gel is a safe and effective Rx and maintenance Rx of female adult acne with non-inferior efficacy to adapalene 0.1% gel…."

Thielitz A, et al *J Eur Assoc Dermatol Venereol* 2014;29(4):789-796

Hormonal Rx

Androgen Evaluation: Who?

"Routine endocrinologic evaluation…is not indicated….Laboratory evaluation is indicated for patients who have… additional signs of androgen excess."*

*Emphasis added

Strauss JS, et al "Guidelines of care for acne vulgaris management" *J Am Acad Dermatol* 2007;56:651-63

Combined Oral Contraceptives: MOA

- ↓Ovarian androgen production
- ↑SHBG
- Testosterone receptor blockade
- Direct progestational anti-androgen effect

Zaenglein AL et al *J Am Acad Dermatol* 2016;74:945-73

Combined OCs FDA-Approved for Acne

Generic	Trade
Ethinyl estradiol + norgestimate	Ortho Tri-Cyclen
Ethinyl estradiol + norethindrone	Estrostep
Ethinyl estradiol + drospirenone	Yaz
Ethinyl estradiol + drospirenone	Beyza

Zaenglein AL et al *J Am Acad Dermatol* 2016;74:945-73

Spironolactone MOA

- Antiandrogen:
- Direct androgen receptor antagonist
- ↓ovarian TsT production
- ↓ ovarian and adrenal androstenedione
- ↑TsT clearance
- Effects dose- related (most hirsute pts require ± 200 mg/d)

Lobo R *Ob & Gyn Clin of N America* 1987;14(4):955-967

Spironolactone for resistant acne

- 8 females, failed 6 months erythromycin + 5% benzoyl peroxide
- Rx : 200 mg spironolactone QD X 3 months
- 6/8 patients → significant improvement (mean overall ↓ 52%)
- Sebum excretion rate ↓maximally by 30 days and maintained

Burke B *Br J Derm* 1984:124-125

Topical Antibiotics

Topical Antibiotics

- Clindamycin 1%
  - Gel, Solution, Ointment
- Erythromycin 1.5%-4%
  - Gel, Solution, Ointment
- Minocycline
  - Foam 4% (Amzeeq)

Acne: No Topical Antibiotic Monotherapy Regimens!

"…it should be noted that monotherapy with a topical antibiotic is advised against in current guidelines and recommendations because of the potential for antimicrobial resistance."

Thiboutot DM et al *J Am Acad Dermatol* 2018;78(2-Suppl):s1-s24

Systemic Antibiotics

Systemic Antibiotics: Evidence-Based Rxs

- Tetracycline
- Doxycycline
- Minocycline
- Trimethoprim
- TMP/SMX
- Erythromycin
- Azithromycin
- Amoxicillin
- Cephalexin

Zaenglein AL et al J Am Acad Dermatol 2016;74:945-73

Systemic Antibiotics: Key Points

- Primarily for mod-severe acne or failed topicals
- Monotherapy: NOT
- Efficacy: Doxycycline = minocycline > tetracycline
- Azithromycin: for tetracycline intolerant or pregnancy
- Erythromycin: NOT 1st line (resistance issues)
- TMP-SMX: for tetracycline intolerant or Rx-resistant
- Start with 2–3-month Rx then maintain with topicals

Zaenglein AL et al *J Am Acad Dermatol* 2016;74:945-73

Systemic Antibiotics: Tetracyclines to Start

"The tetracycline class of antibiotics should be considered first-line therapy in moderate to severe acne, except when contraindicated because of other circumstances (ie, pregnancy, ≤8 years of age, or allergy)."

Zaenglein AL et al J Am Acad Dermatol 2016;74:945-73

Clinical Question #3

- You have decided to Rx acne in this 19 y.o. male patient with doxycycline. What is the 'right' dose?
  - doxycycline 100 mg b.i.d.
  - doxycycline 500 mg b.i.d.
  - doxycyline 20 mg b.i.d.

Subantimicrobial-Dose Doxycycline

- Study: DBRPCT (n=51) adults with acne
- Inclusion: Moderate severity
- Rx: doxycycline hyclate 20 mg b.i.d. (Periostat) vs placebo x 6 months

Skidmore R *Arch Derm* 2003;139:459-464

Subantimicrobial-Dose Doxycycline

Outcomes:

- *Primary*: Δ from baseline # inflammatory, noninflammatory, and total acne lesions
- *Secondary*:
  - Δ from baseline # papules, pustules, nodules
  - Physician and Patient global assessment

Skidmore R *Arch Derm* 2003;139:459-464

Subantimicrobial-Dose Doxycycline Results: p < 0.05

Results (all p <0.05 favor Rx)

- % reduction # comedones, inflammatory, noninflammatory lesions
- Total inflammatory lesions
- Clinician's global assessment
- No change in bacterial count

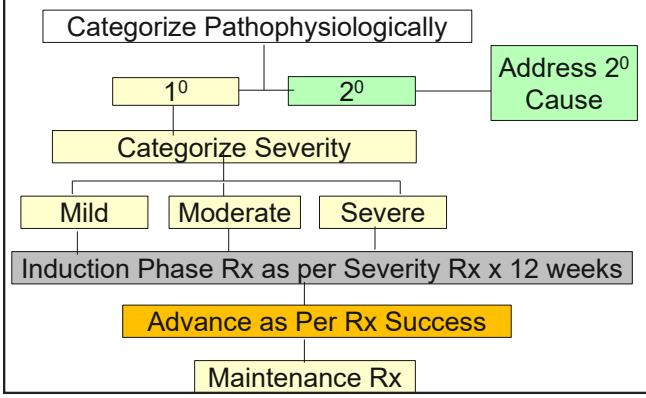
Skidmore R *Arch Derm* 2003;139:459-464

Subantimicrobial-Dose Doxycycline Conclusions

"Twice-daily subantimicrobial-dose doxycycline treatment significantly ↓ the # of inflammatory and noninflammatory lesions in patients with moderate facial acne, was well tolerated, had no detectable antimicrobial effect on the skin flora, and did not result in any increase in the number or severity of resistant organisms."

Skidmore R *Arch Derm* 2003;139:459-464

Acne Algorithm



SELF EVALUATION

Managing Adult and Adolescent Acne

1. Combined oral contraceptives are usually beneficial for acne. Which mechanisms account for this?
    a. Increases in Sex Hormone Binding Globulin (SHBG) bind up free testosterone
    b. Direct antagonism of testosterone by estrogen
    c. Estrogenic effects of progestins
    d. A and B
    e. B and C

2. According to Guideline Directed Medical Therapy, which treatment is not appropriate as initial therapy for mild acne?
    a. Benzoyl peroxide
    b. A topical retinoid (e.g., tazarotene)
    c. A systemic antibiotic (e.g., tetracycline)
    d. Topical azelaic acid

3. The PRIMARY mechanism of action of benzoyl peroxide is?
    a. Antibacterial, without inducing resistance
    b. Keratinolytic
    c. Decreased sebum production
    d. Exfoliative

4. Some persons are burdened with postinflammatory hyperpigmentation subsequent to acne. Which agent below is associated with less postinflammatory hyperpigmentation?
    a. Benzoyl peroxide
    b. Minocycline
    c. Azelaic Acid
    d. Boric Acid

5. What is the impact of diet on acne?
    a. A high glycemic load and high glycemic index foods have been associated with worse acne
    b. Compared to an equivalent caloric load of jelly beans, chocolate has been demonstrated to worsen acne
    c. There is not enough scientific data to make strong statements about diet and acne
    d. All of the above

Answer Key: 1. D, 2. C, 3. A, 4. C, 5. D

David M. Ottenwess | Ottenwess Law, PLC
3000 Town Center, Suite 2500 | Southfield, MI 48075 |P 313.965.2121 | F 313.965.7680 | D 313.788.7030
dottenwess@ottenwesslaw.com | www.ottenwesslaw.com

Avoiding Malpractice Pitfalls: Advice from the Front

AVOIDING MALPRACTICE LITIGATION

- It's hard to avoid litigation these days
- With today's practice, there is too much to oversee
  - Mid-levels
  - EMRs
  - Knowledgeable internet-savvy patients
- It is easy to lose track of information and keep staff under control as today's practices expand

TWO POTENTIAL PITFALLS

- Spot problems in the office
  - Engage with the staff
  - Make sure you are on the same page
- Clinical
  - Physician to Physician
  - You know this: write notes!
  - Be proactive without being accusatory

OFFICE

- Know what policies are in place for staff.
- Be sure you and your staff understand the importance of communication and what is being communicated.
- Instruct staff to be respectful and polite – it could actually save you.

OFFICE COMMUNICATION EXAMPLES

Q. So just going back to the April 2018 CTA study and the pulmonary aspect of the study, you understand it showed or [redacted] reported abnormalities in the base of the right lung; is that correct?
A. I saw that for the first time in 2020.

[redacted], you had learned by April 2018, please confirm this, that if there were abnormalities in a diagnostic study that were significant an individual, a professional such as you would be called by the medical professional who determined an abnormality existed and that abnormality would be reported to you,

Q. So when you opened it in -- is that the October date, 2019?
A. Yes, but I didn't read the report and I -- I had made a -- my inbox is quite full. I had a physician comment on it so I emptied everything from 2018 under the assumption that it was a shared result system, when I would put a physician name with mine that they also reviewed these tests, so I kept everything from 2019 to review but I did not read a report at that time from 2018 pertaining to [redacted] I never read the report until 2020.

A. Yes, especially something to that degree. There's abnormalities found in incidental findings but that is a huge red flag, I mean, that suggests cancer and that's always -- it should be communicated, yes, that's my experience.

OFFICE COMMUNICATION EXAMPLES

Q. And you've seen plenty of nodules, pulmonary nodules on the images that you've reviewed; correct?
A. Yes.
Q. And you know that nodules are a fairly common finding, relatively speaking, on pulmonary studies?
A. Correct.

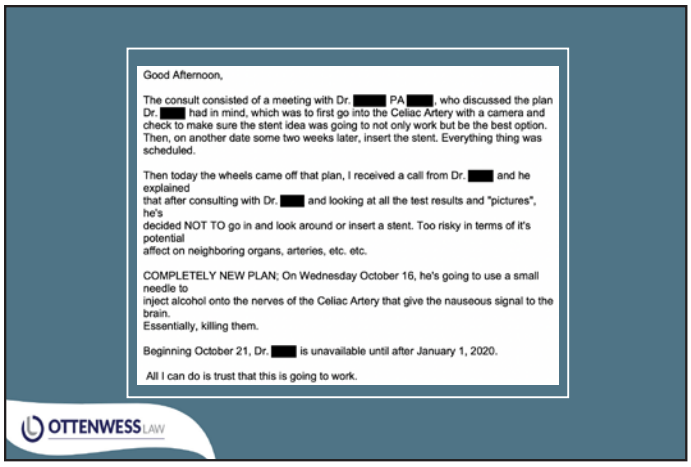
Q. Sure. I assume that the PAs had an understanding that there was an expectation on the part of the physicians that they would open up any test studies that appeared in their in-basket in a timely fashion; correct?
A. See, again, I don't know that, because [redacted] -- or [redacted] didn't know that.

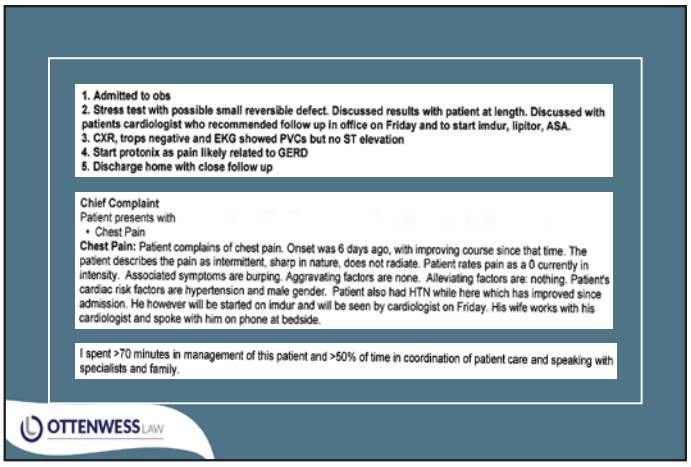
A. Hang on, hang on. I order a coronary CTA. The hospital decides that they want me to see two reports. Okay? I don't -- I don't need the -- let me rephrase it.
It's a coronary CTA that I ordered. The hospital is throwing in a thoracic read as part of that test. It's a cardiac test, it's not a thoracic test. If I wanted a thoracic test, I would order a CAT scan, a dedicated CAT scan with and without IV contrast.
Q. Okay. Are you finished?
A. Yes, I am.
Q. Okay. I think as you've already indicated to [redacted] irrespective of what you want or what you're looking at, the fact of the matter is, when the test is ordered, you're obligated to look at the results of the entire test, are you not?
A. First of all, are you saying tests, plural? Because you're asking me to read two tests. So if it's -- but the answer is, if I order it, if I order it, then I'm absolutely obligated to look at both parts, --

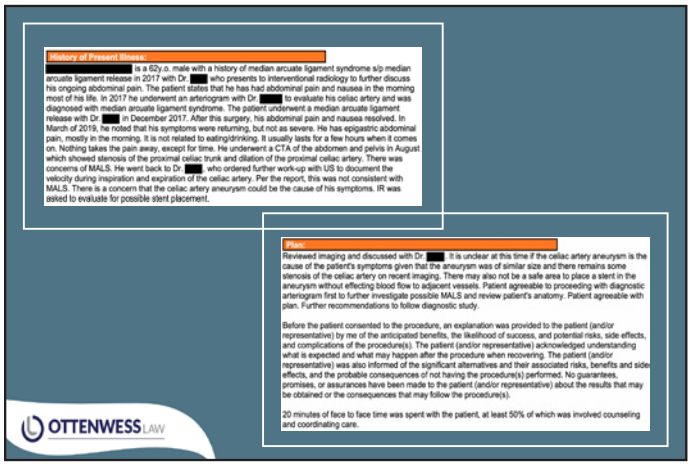
Q. Okay. She had an obligation to look at her in-basket while she was at [redacted], correct?
[redacted]
A. Correct.

CLINICAL

- If it is not written, it didn't happen.
  - If it is not written completely or correctly, good luck!
- Be cautious but be sure you are getting information into the record that explains your actions.
- Examples


Good Afternoon,
The consult consisted of a meeting with Dr. [redacted] PA [redacted], who discussed the plan Dr. [redacted] had in mind, which was to first go into the Celiac Artery with a camera and check to make sure the stent idea was going to not only work but be the best option. Then, on another date some two weeks later, insert the stent. Everything thing was scheduled.
Then today the wheels came off that plan, I received a call from Dr. [redacted] and he explained
that after consulting with Dr. [redacted] and looking at all the test results and "pictures", he's
decided NOT TO go in and look around or insert a stent. Too risky in terms of it's potential
affect on neighboring organs, arteries, etc. etc.
COMPLETELY NEW PLAN; On Wednesday October 16, he's going to use a small needle to
inject alcohol onto the nerves of the Celiac Artery that give the nauseous signal to the brain.
Essentially, killing them.
Beginning October 21, Dr. [redacted] is unavailable until after January 1, 2020.
All I can do is trust that this is going to work.
OTTENWESS LAW


1. Admitted to obs
2. Stress test with possible small reversible defect. Discussed results with patient at length. Discussed with patients cardiologist who recommended follow up in office on Friday and to start imdur, lipitor, ASA.
3. CXR, trops negative and EKG showed PVCs but no ST elevation
4. Start protonix as pain likely related to GERD
5. Discharge home with close follow up
Chief Complaint
Patient presents with
• Chest Pain
Chest Pain: Patient complains of chest pain. Onset was 6 days ago, with improving course since that time. The patient describes the pain as intermittent, sharp in nature, does not radiate. Patient rates pain as a 0 currently in intensity. Associated symptoms are burping. Aggravating factors are none. Alleviating factors are: nothing. Patient's cardiac risk factors are hypertension and male gender. Patient also had HTN while here which has improved since admission. He however will be started on imdur and will be seen by cardiologist on Friday. His wife works with his cardiologist and spoke with him on phone at bedside.
I spent >70 minutes in management of this patient and >50% of time in coordination of patient care and speaking with specialists and family.
OTTENWESS LAW


History of Present Illness:
[redacted] is a 62y.o. male with a history of median arcuate ligament syndrome s/p median arcuate ligament release in 2017 with Dr. [redacted] who presents to interventional radiology to further discuss his ongoing abdominal pain. The patient states that he has had abdominal pain and nausea in the morning most of his life. In 2017 he underwent an arteriogram with Dr. [redacted] to evaluate his celiac artery and was diagnosed with median arcuate ligament syndrome. The patient underwent a median arcuate ligament release with Dr. [redacted] in December 2017. After this surgery, his abdominal pain and nausea resolved. In March of 2019, he noted that his symptoms were returning, but not as severe. He has epigastric abdominal pain, mostly in the morning. It is not related to eating/drinking. It usually lasts for a few hours when it comes on. Nothing takes the pain away, except for time. He underwent a CTA of the abdomen and pelvis in August which showed stenosis of the proximal celiac trunk and dilation of the proximal celiac artery. There was concerns of MALS. He went back to Dr. [redacted] who ordered further work-up with US to document the velocity during inspiration and expiration of the celiac artery. Per the report, this was not consistent with MALS. There is a concern that the celiac artery aneurysm could be the cause of his symptoms. IR was asked to evaluate for possible stent placement.
Plan:
Reviewed imaging and discussed with Dr. [redacted]. It is unclear at this time if the celiac artery aneurysm is the cause of the patient's symptoms given that the aneurysm was of similar size and there remains some stenosis of the celiac artery on recent imaging. There may also not be a safe area to place a stent in the aneurysm without effecting blood flow to adjacent vessels. Patient agreeable to proceeding with diagnostic arteriogram first to further investigate possible MALS and review patient's anatomy. Patient agreeable with plan. Further recommendations to follow diagnostic study.
Before the patient consented to the procedure, an explanation was provided to the patient (and/or representative) by me of the anticipated benefits, the likelihood of success, and potential risks, side effects, and complications of the procedure(s). The patient (and/or representative) acknowledged understanding what is expected and what may happen after the procedure when recovering. The patient (and/or representative) was also informed of the significant alternatives and their associated risks, benefits and side effects, and the probable consequences of not having the procedure(s) performed. No guarantees, promises, or assurances have been made to the patient (and/or representative) about the results that may be obtained or the consequences that may follow the procedure(s).
20 minutes of face to face time was spent with the patient, at least 50% of which was involved counseling and coordinating care.
OTTENWESS LAW

SELF EVALUATION

Avoiding Malpractice Pitfalls: Advice from the Front

True/False

1. Your office staff may be your biggest exposure to a lawsuit.

2. Direct communication with patients is not that important as long as you are a meticulous note-taker.

3. Writing complete and accurate notes in the patient's chart is probably the best way to avoid litigation.

4. Failing to write a note describing your actions is okay because you can always rely on "habit and custom" to "fill in the blanks."

5. You can always avoid being named in a medical malpractice case simply by practicing great medicine.

Answer Key: 1. T, 2. F, 3. T, 4. F, 5. F

C. Wayne Weart, Pharm D, BCPS, FASHP, FAPhA

Professor of Clinical Pharmacy and Outcome Sciences
South Carolina College of Pharmacy
Professor of Family Medicine
Medical University of South Carolina
(843) 792-3606. weartcw@musc.edu

Current Cholesterol Guidelines and Medications

LDL-C and Atherosclerotic CV Disease: Cause or Surrogate Marker?

- Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A **consensus statement from the European Atherosclerosis Society Consensus Panel. 4/25/2017**
- **Conclusion: "Consistent evidence from numerous and multiple different types of clinical and genetic studies unequivocally establishes that LDL causes ASCVD."**
- **LDL-C should no longer be considered a surrogate marker for ASCVD.**
  - European Heart Journal (2017) 0, 1–14 doi:10.1093/eurheartj/ehx144

Low-density lipoprotein (LDL) as a causal factor for atherosclerotic cardiovascular disease: key implications

- **Cumulative LDL arterial burden is a central determinant for the initiation and progression of atherosclerotic cardiovascular disease.**
- **The lower the LDL cholesterol (LDL-C) level attained by agents that primarily target LDL receptors, the greater the clinical benefit accrued.**
- **Both proportional (relative) risk reduction and absolute risk reduction relate to the magnitude of LDL-C reduction.**
- **Lowering LDL-C in individuals at high cardiovascular risk earlier rather than later appears advisable, especially in those with familial hypercholesterolaemia.**
  - European Heart Journal (2017) 0, 1–14 doi:10.1093/eurheartj/ehx144

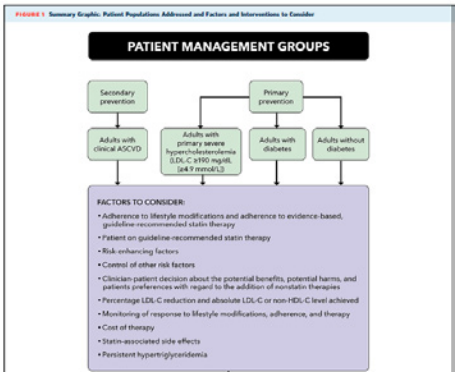
2022 ACC Expert Consensus Decision Pathway on the Role of Non statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Solution Set Oversight Committee

Expert Consensus Decision Pathway

Writing Committee, Donald M. Lloyd-Jones, Pamela B. Morris, Christie M. Ballantyne, Kim K. Birtcher

Endorsed by the National Lipid Association

J Am Coll Cardiol. 2022 Oct, 80 (14) 1366–1418



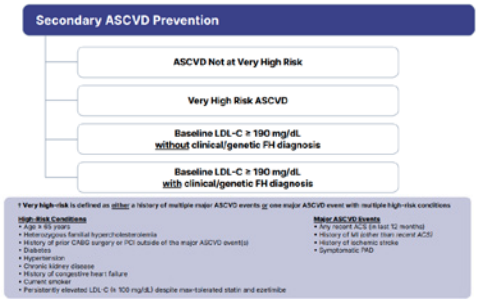
High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL–C on average, by approximately ≥50%	Daily dose lowers LDL–C on average, by approximately 30% to <50%	Daily dose lowers LDL–C on average, by <30%
Atorvastatin (40†)–80 mg **Rosuvastatin 20** *(40)* **mg**	**Atorvastatin 10** *(20)* **mg** **Rosuvastatin** (*5*) **10 mg** **Simvastatin 20–40 mg‡** **Pravastatin 40** *(80)* **mg** **Lovastatin 40 mg** *Fluvastatin XL 80 mg* **Fluvastatin 40 mg bid** *Pitavastatin 2–4 mg*	*Simvastatin 10 mg* **Pravastatin 10–20 mg** **Lovastatin 20 mg** *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

Specific statins and doses are noted in bold that were evaluated in RCTs.

2022 ACC Expert Consensus Decision Pathway on the Role of Non statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Solution Set Oversight Committee J Am Coll Cardiol 2022; 80:1366-1418.



Adults With Clinical ASCVD at Very High Risk on Statin Therapy for Secondary Prevention

In view of the favorable net clinical benefit of the addition of non-statin therapies in patients with clinical ASCVD at very high risk on high-intensity statin therapy and lifestyle management and the very low levels of LDL-C achieved in RCTs of non-statin therapies, a lower LDL-C threshold of LDL->55 mg/dL (or non–HDL >85 mg/dL) is recommended by the writing committee. There is evidence from clinical trials that individuals who achieve LDL-C <55 mg/dL experience lower event rates than those with higher LDL-C. Preference should be given to therapies with demonstrated cardiovascular outcomes benefits. Prospective and observational trials demonstrate a direct and significant relationship between LDL-C level and atherosclerosis progression and ASCVD event risk, and absolute LDL-C reduction is directly associated with ASCVD risk reduction**. There appears to be no LDL-C level below which benefit ceases. Current evidence indicates that lifelong very low LDL-C levels in the range of 15-30 mg/dL in patients with hypobetalipoproteinemia or PCSK9 loss-of-function mutations and in shorter-term lipid-lowering clinical trials are associated with a lower incidence of ASCVD without adverse effects.**

2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Solution Set Oversight Committee
J Am Coll Cardiol 2022; 80:1366-1418.

2022 American College of Cardiology Foundation

JACC

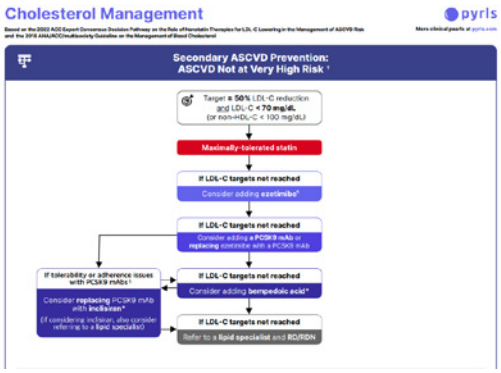
Adults With Clinical ASCVD at Very High Risk on Statin Therapy for Secondary Prevention

If additional LDL-C lowering is warranted (patient has achieved <50% reduction in LDL-C or LDL->55 mg/dL or non–HDL->85 mg/dL) despite maximally tolerated statin therapy, ezetimibe, and a PCSK9 mAb, the addition of bempedoic acid may be considered. Clinicians may also consider the use of Inclisiran in place of a PCSK9mAb. Although there **are currently no outcome studies for bempedoic acid, this agent may be beneficial for further LDL-C reduction or if evidence-based agents are contra-indicated or not tolerated. Considerations that may favor the addition of bempedoic acid include the need for further LDL-C reduction (with a mean expected reduction of approximately 17%), documented statin intolerance,** and ease of use for patients who prefer to avoid injectable medications. **Bempedoic acid should be used with caution in patients who have a history of gout or tendon rupture.** At the current time, a PCSK9 mAb is preferred as the initial PCSK9 inhibitor of choice in view of its demonstrated safety, efficacy, and cardiovascular outcomes benefits in FOURIER and ODYSSEY Outcomes. **The ORION-4 and VICTORION-2P cardiovascular outcomes trials with inclisiran are currently in progress and are anticipated to be completed in 2026 and 2027, respectively.** However, in view of the twice-yearly dosing regimen, **inclisiran may be considered in patients with demonstrated poor adherence to PCSK9 mAbs. Patients with adverse effects from both PSCK9 mAbs or those who may be unable to self-inject** may also be considered for therapy with inclisiran.

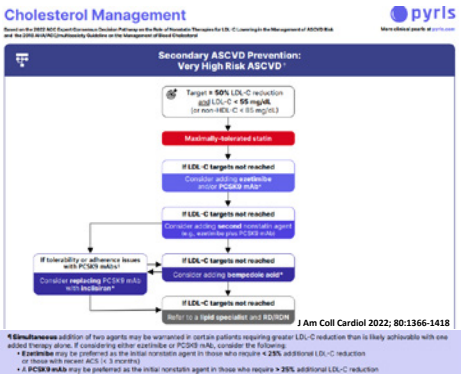
2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Solution Set Oversight Committee ***J Am Coll Cardiol*** **2022; 80:1366-1418.**

2022 American College of Cardiology Foundation

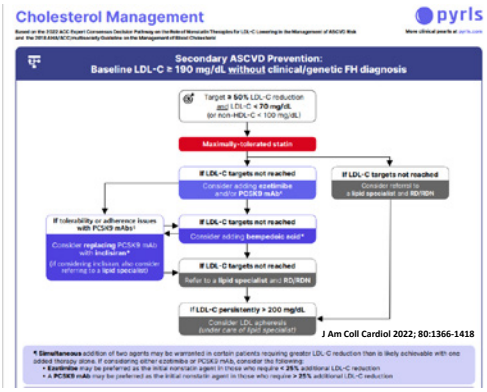
JACC



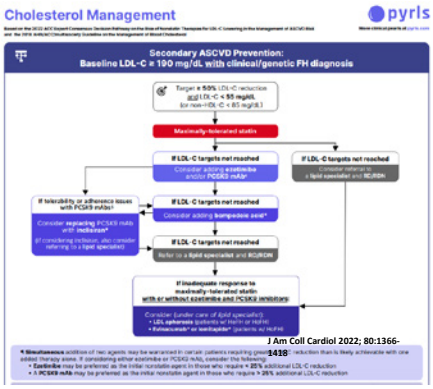
J Am Coll Cardiol 2022; 80:1366-1418.



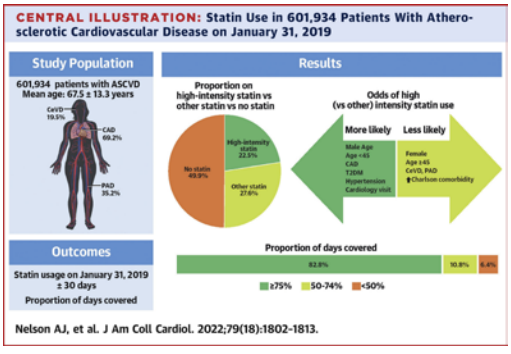
J Am Coll Cardiol 2022; 80:1366-1418



J Am Coll Cardiol 2022; 80:1366-1418



J Am Coll Cardiol 2022; 80:1366-1418



Secondary Prevention Trials

Trial/Drug/Dose	N/Duration	Primary Outcome	RRR/ARR/NNT
4-S Trial Simva 20-40 mg vs. Placebo	4,444 pts (MI/angina) Age 35-69 5.4 years	Total Mortality 8.2% 11.5%	30%/3.3%/31
CARE Trial Prava 40 mg vs. Placebo	4159 pts (s/p MI) Age 21-75 5 years	CV death, NF-MI 10.2% 13.2%	24%/3.0%/33
LIPID Trial Prava 40 mg vs. Placebo	9014 pts (s/p MI) Age 31-75 6.1 years	CV death 6.4% 8.3%	24%/1.9%/53
Heart Protection Simva 40 mg vs. Placebo	20,536 pts (MI,PVD,DM) Age 40-80 5 years	Mort/Vasc events 19.8% 25.2%	24%/5.4%/19
Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Atorva 80 mg vs. Placebo	4731 patients 1-6 months post CVA/TIA and no CHD 60% male, mean age 63 years 4.9 years	Any Nonfatal or Fatal Stroke 11.2% 13.1%	16%/1.9%/53

SPARCL Trial

- **Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) NEJM 2006;355:549-59**
- **4731 patients 1-6 months post CVA/TIA and no CHD**
  - 60% male, mean age 63 years, 62% hypertensive (BP mean 138/82 mm Hg), 19% current and 40% previous smokers and ~17% DM
  - **~67% ischemic stroke, ~30% TIA and ~2% hemorrhagic stroke**
  - **Atorvastatin 80 mg vs. placebo for 4.9 yrs**
  - **Baseline LDL 100-190mg/dl, mean 132 mg/dl baseline and 73 vs. 129mg/dl at end of the trial**
  - **87% on antiplatelet therapy and 6% on warfarin**
  - **Less than 3% on statin at baseline**
    - NEJM 2006;355:549-59

SPARCL: Main results

Type of stroke	Hazard ratio with atorvastatin @5 yrs
Any	0.84 ARR 2.2% NNT 46
Fatal	0.57
Nonfatal	0.87 NS
Ischemic	0.78
Hemorrhagic	1.66 (no difference in fatal hemorrhagic stroke)

Welch M et al. 15th European Stroke Conference; May 16-19, 2006; Brussels, Belgium.

NEJM 2006;355:549-59

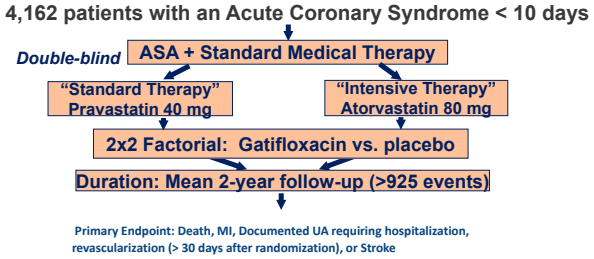
SPARCL: Results Cont.

- **Major cardiovascular events were reduced by 20% with an ARR 3.5% NNT 29**
- **No difference in total mortality (P=0.98)**
- Rates of serious adverse events were also not significantly different but increased AST/AST>3x's ULN was more common in the atorvastatin group 2.2% vs. 0.5%
  - NEJM 2006;355:549-59

Intensity of Statin Therapy: High vs. Lower Potency/Dose?

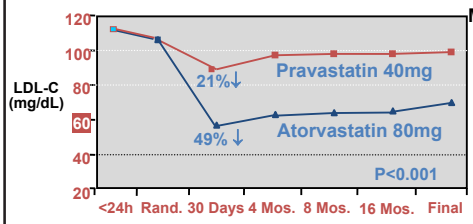
PROVE IT - TIMI 22: Study Design

N Engl J Med 2004;350:1495-504



Changes from (Post-ACS) Baseline in Median LDL-C

N Engl J Med 2004;350:1495-504

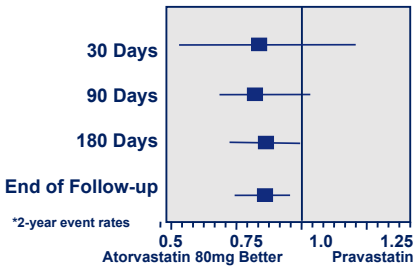


Median LDL-C (Q1, Q3)
95 (79, 113)
62 (50, 79)

Note: Changes in LDL-C may differ from prior trials:
- 25% of patients on statins prior to ACS event
- ACS response lowers LDL-C from true baseline

Primary Endpoint Over Time

N Engl J Med 2004;350:1495-504



	RR	Events Rates Atorva 80	Prava 40
30 Days	17%	1.9%	2.2%
90 Days	18%	6.3%	7.7%
180 Days	14%	12.2%	14.1%
End of Follow-up	16%	22.4%*	26.3%*
		NNT 26	

TNT Trial

10,003 patients with stable coronary heart disease
Age 35-75 years, LDL between 130 and 250 mg/dL, triglyceride ≤ 600 mg/dL
19% female, mean age 60.3 years
All received atorvastatin 10 mg during 8 week open-label run-in period

Atorvastatin 80 mg n=4,995

Atorvastatin 10 mg n=5,006

Primary Endpoint: Major cardiovascular event defined as coronary heart death (CHD) , nonfatal MI, resuscitated cardiac arrest, and fatal or nonfatal stroke at a mean follow-up of 4.9 years.

Secondary Endpoint: Major coronary events, cerebrovascular events, hospitalization for congestive heart failure (CHF), all-cause mortality, peripheral artery disease, any cardiovascular event, any coronary event

Presented at ACC 2005

TNT: Primary efficacy outcomes

Outcome	Atorvastatin 10 mg (n=5006)	Atorvastatin 80 mg (n=4995)	Hazard ratio/NNT (95% CI)	p
Total major cardiovascular events (%)	10.9	8.7	0.78/46 (0.69-0.89)	<0.001
▪Death from coronary heart disease (%)	2.5	2.0	0.80 (0.61-1.03)	0.09
▪Nonfatal MI (%)	6.2	4.9	0.78/77 (0.66-0.93)	0.004
▪Resuscitation after cardiac arrest (%)	0.5	0.5	0.96 (0.56-1.67)	0.89
▪Fatal or nonfatal stroke (%)	3.1	2.3	0.75/125 (0.59-0.96)	0.02

LaRosa JC et al. *N Engl J Med* 2005;352:1425-35 http://www.nejm.org.

TNT: Key CV End Points in At-Risk Subpopulations

Patient subpopulation:	Atorvastatin 80 mg (n)	Atorvastatin 10 mg (n)	Outcome measure	Relative risk reduction (RRR)
Diabetes	748	753	Time to first major CV event	- 25% (P= .026) HR=0.75 (CI, 0.58–0.97) ARR=4.1% NNT 25
CKD	1602	1505	Time to first major CV event	- 32% (P= .0003) HR=0.68 (CI, 0.55–0.84) ARR=4.1% NNT 25
Prior HF	377	404	Risk of hospitalization for heart failure	- 41% (P= .000) HR=0.59 (CI, 0.40–0.86) ARR=6.7% NNT 15
≥65 y	1937	1872	Time to first major CV event	-19% (P= .032) HR=0.81 (CI, 0.67-0.98) ARR=2.3% NNT 44

1. Shepherd J et al. *Diabetes Care.* 2006;29(6):1220-1226. 2. Shepherd J et al. *J Am Coll Cardiol.* 2006;51(15):1448-1454. 3. Khush KK et al. *Circulation.* 2007;115(5):576-583. 4. LaRosa JC et al. *N Engl J Med.* 2005;352(14):1425-1435. 5. Wenger NK et al. *Ann Intern Med.* 2007;147(1):1-9.

VII. Managing Statin Intolerance and Safety

Statin-Associated Muscle Symptoms	
Definition	Bilateral muscle symptoms (eg, pain, weakness, cramps, stiffness) with onset of statin use, relief with discontinuation, and recurrence with rechallenge with same and/or 2 other statins
Incidence	5-20% in clinical studies; rhabdomyolysis (CK >10 ULN) rare: ~1/10,000 patient-years
Risk factors	Older (>75 years), female, low BMI, East Asian, history of muscle symptoms, impaired renal and/or hepatic function, diabetes, HIV, some medications (eg, fibrates, erythromycin, fluconazole), statin type and dose, low vitamin D, hypothyroidism, acute infection
Prevention	Assess pre-existing symptoms, reinforce that benefits of statins outweigh the risks Consider lower doses in patients at risk
Treatment	• Acknowledge patient's symptoms and, if considered significant, stop the statin • When symptoms resolve, if myopathy not severe, rechallenge; may try lower dose, less frequent dosing (1-3/week); different statin (at least 2; consider pitavastatin or fluvastatin) • Consider normalizing a low vitamin D and/or adding CoQ10 • As needed add nonstatin therapies
Other Disorders	
Increased risk of new onset diabetes	Statins may minimally increase hyperglycemia but not enough to offset the benefits of reduced cardiovascular morbidity and mortality
No risk	No evidence of effects on liver, kidney, cognition, or eyes

Abbreviations: BMI = body mass index; CK = creatine kinase; CoQ10; coenzyme Q10; ULN = upper limit of normal.

Effect of statin therapy on muscle symptoms: an individual participant data meta-analysis of large-scale, randomized, double-blind trials
Cholesterol Treatment Trialists' Collaboration

- **Among 19 placebo-controlled trials (mean age 63 years, with 34 533 [27·9%] women, 59 610 [48·1%] participants with previous vascular disease, and 22 925 [18·5%] participants with diabetes), during a weighted average median follow-up of 4·3 years**, 16 835 (27·1%) allocated statin versus 16 446 (26·6%) allocated placebo reported muscle pain or weakness (rate ratio [RR] 1·03; 95% CI 1·01–1·06). **During year 1, statin therapy produced a 7% relative increase in muscle pain or weakness** (1·07; 1·04–1·10), corresponding to an **absolute excess rate of 11 (6–16) events per 1000 person-years**, which indicates that **only one in 15** ([1·07–1·00]/1·07) **of these muscle-related reports by participants allocated to statin therapy were actually due to the statin. After year 1, there was no significant excess in first reports of muscle pain or weakness** (0·99; 0·96–1·02).
- **For all years combined, more intensive statin regimens (ie, 40–80 mg atorvastatin or 20–40 mg rosuvastatin once per day) yielded a higher RR than less intensive or moderate-intensity regimens (1·08** [1·04–1·13] **vs 1·03** [1·00–1·05]) compared with placebo, and a small excess was present (1·05 [0·99–1·12]) for more intensive regimens after year 1. There was no clear evidence that the RR differed for different statins, or in different clinical circumstances. Statin therapy yielded a small, clinically insignificant increase in median creatine kinase values of approximately 0·02 times the upper limit of normal.
  - The Lancet 2022 400832-845DOI: (10.1016/S0140-6736(22)01545-8)

Benefit accrual with cardiovascular disease prevention and effects of discontinuation: a modelling study

- **Statin treatment benefits, measured in QALYs gained, accrue over lifetime. The majority of benefits accrue later in life. Men accumulate larger benefits and earlier than women.** The pattern of benefits accrual is similar for participants with and without previous CVD. The higher the participants' CVD risk, the larger and earlier the benefits, with younger participants accruing larger benefits. **Compared with lifelong prevention, stopping treatment at 80 years of age leads to large reductions in overall benefits, especially in women and those at lower CVD risk. For example, compared to lifelong therapy, people without previous CVD who initiate therapy in their 50s, would lose 47% of QALYs benefit (if men), 66% (if women), 73% (if with CVD risk <5%), and 35% (if with CVD risk ≥20%), respectively, if they stop treatment when they reach 80 years of age.** Five-year delay of statin therapy initiation in people under 45 years of age reduces their benefits by about 4% on average, though the loss is somewhat larger in people at higher CVD risk.
- **Conclusion Benefits from lifelong cardiovascular prevention accrue over peoples' lifespan with large share of benefits accruing at older age. Stopping treatment earlier substantially reduces benefits.**
  - European Heart Journal, Volume 43, Issue Supplement_2, October 2022, ehac544.2850, https://doi.org/10.1093/eurheartj/ehac544.2850

IMPROVE-IT: Results

- The results of IMPROVE-IT (AHA 11/17/2014 Scientific Sessions). **The study included more than 18 000 patients from 39 countries who were stable following ACS (<10 days).** Patients were randomized to one of two treatment strategies**: simvastatin 40 mg alone or simvastatin 40 mg plus ezetimibe 10 mg.** They were followed for a minimum of 2.5 years or until the study investigators accrued 5250 clinical events.
- At baseline, the mean LDL-cholesterol level among the ACS patients was 95 mg/dL in both treatment arms. With **simvastatin 40 mg, LDL-cholesterol levels were reduced to 69.9 mg/dL at 1 year. The addition of ezetimibe 10 mg to simvastatin further lowered LDL-cholesterol levels, to 53.2 mg/dL at 1 year**. Over 7 years, there remained a significant difference between the two treatments in the achieved LDL-cholesterol levels.
  - N Engl J Med 2015;372:2387-97

IMPROVE-IT

Primary End Point and Individual Components (7-Year Event Rates)

Clinical Outcomes	Simvastatin, n=9077 (%)	Ezetimibe/Simvastatin, n=9067 (%)	*P*
Primary end point (Cardiovascular death, MI, unstable angina, coronary revascularization, or stroke)	34.7	32.7	0.016
All-cause death	15.3	15.4	0.782
MI	14.8	13.1	0.002
Stroke	4.8	4.2	0.052
Ischemic stroke	4.1	3.4	0.008
Unstable angina	1.9	2.1	0.618
Coronary revascularization	23.4	21.8	0.107

Primary combined endpoint at 7 years: RRR 6.4%; ARR 2.0%; NNT 50
MI at 7 years: ARR 1.7%; NNT 59
Ischemic stroke at 7 years: 0.7%; NNT 142

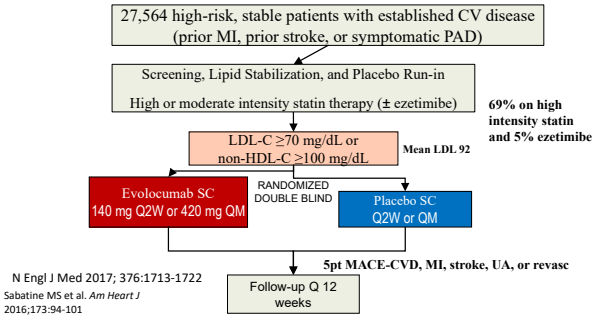
'Modest' Benefit When Adding Ezetimibe to Statins in Post-ACS Patients. *Medscape*. Nov 17, 2014.

PCSK-9 Inhibitor: Evolocumab – Repatha

by Amgen

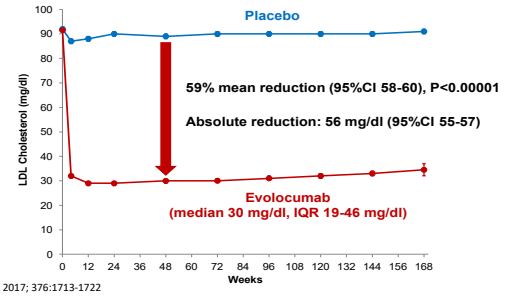
- **FDA approved 8-27-2015 a PCSK9 (proprotein convertase subtilisin kexin type 9) inhibitor antibody indicated as an adjunct to diet and: for the treatment of patients with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low-density lipoprotein cholesterol(LDL-C).**
- **Patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C when other LDL-C lowering therapies are not adequate (e.g., statins, ezetimibe, LDL apheresis).**

Fourier Trial Design



N Engl J Med 2017; 376:1713-1722
Sabatine MS et al. *Am Heart J* 2016;173:94-101

LDL Cholesterol



N Engl J Med 2017; 376:1713-1722

Types of CV Outcomes

Endpoint	Evolocumab (N=13,784)	Placebo (N=13,780)	HR (95% CI)
	3-yr Kaplan-Meier rate		
5pt MACE-CVD, MI, stroke, UA, or revasc	12.6	14.6	0.85 (0.79-0.92) NNT 50
CV death, MI, or stroke	7.9	9.9	0.80 (0.73-0.88) NNT 50
Cardiovascular death	2.5	2.4	1.05 (0.88-1.25)
MI	4.4	6.3	0.73 (0.65-0.82) NNT 53
Hosp for unstable angina	2.2	2.3	0.99 (0.82-1.18)
Coronary revasc	7.0	9.2	0.78 (0.71-0.86) NNT 46
Urgent	3.7	5.4	0.73 (0.64-0.83)
Elective	3.9	4.6	0.83 (0.73-0.95)
Death from any cause	4.8	4.3	1.04 (0.91-1.19)

N Engl J Med 2017; 376:1713-1722

Long-Term Evolocumab in Patients With Established Atherosclerotic Cardiovascular Disease – Fourier-Ole open label extension trial

- The parent FOURIER trial randomized **27,564 patients with atherosclerotic cardiovascular disease and LDL-C ≥70 mg/dL on statin to evolocumab versus placebo.** Patients completing FOURIER at participating sites were eligible to receive evolocumab in **2 open-label extension studies (FOURIER-OLE [FOURIER Open-Label Extension]) in the United States and Europe**; primary analyses were pooled across studies. The **primary end point was the incidence of adverse events. Lipid values and major adverse cardiovascular events** were prospectively collected.
- A total of **6635 patients were enrolled in FOURIER-OLE (3355 randomized to evolocumab and 3280 to placebo in the parent study)**. **Median follow-up in FOURIER-OLE was 5.0 years; maximum exposure to evolocumab in parent plus FOURIER-OLE was 8.4 years.**
  - Circulation. 2022;146:1109–1119. DOI: 10.1161/CIRCULATIONAHA.122.061620

Long-Term Evolocumab in Patients With Established Atherosclerotic Cardiovascular Disease – Fourier-Ole open label extension trial

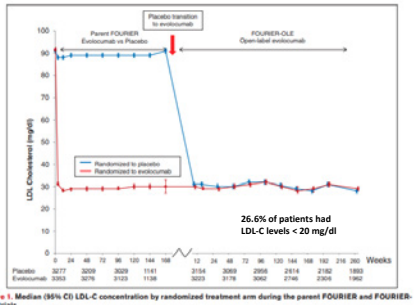


Figure 1. Median (95% CI) LDL-C concentration by randomized treatment arm during the parent FOURIER and FOURIER-OLE trials.

Circulation. 2022;146:1109–1119. DOI: 10.1161/CIRCULATIONAHA.122.061620

Long-Term Evolocumab in Patients With Established Atherosclerotic Cardiovascular Disease – Fourier-Ole open label extension trial

- **Incidences of serious adverse events, muscle-related events, new-onset diabetes, hemorrhagic stroke, and neurocognitive events with evolocumab long term did not exceed those for placebo treated patients during the parent study and did not increase over time.**
- **During the FOURIER-OLE follow-up period**, patients originally randomized in the parent trial to **evolocumab versus placebo had a 15% lower risk of cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina or coronary revascularization** (hazard ratio, 0.85 [95% CI, 0.75–0.96]; P=0.008); a **20% lower risk of cardiovascular death, myocardial infarction, or stroke** (hazard ratio, 0.80 [95% CI, 0.68–0.93]; P=0.003); and a **23% lower risk of cardiovascular death** (hazard ratio, 0.77 [95% CI, 0.60–0.99]; P=0.04).
  - Circulation. 2022;146:1109–1119. DOI: 10.1161/CIRCULATIONAHA.122.061620

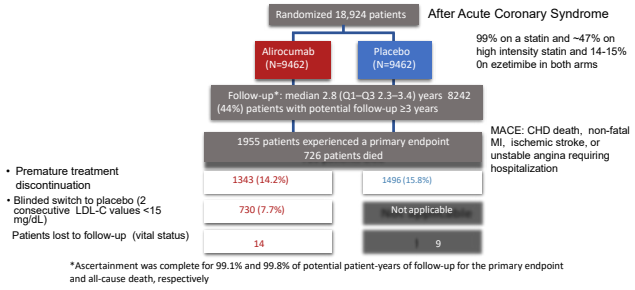
PCSK-9 Inhibitor: Alirocumab-Praluent

by Regeneron and Sanofi

FDA Approved Indications: (4/2021)

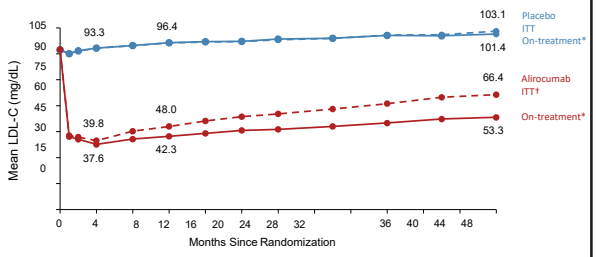
- **To reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease.**
- **As an adjunct to diet, alone or in combination with other low density lipoprotein cholesterol (LDL-C)-lowering therapies, in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH), to reduce LDL-C.**
- **As an adjunct to other LDL-C-lowering therapies in adult patients with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C.**

ODYSSEY OUTCOMES Trial Patient Disposition



*Ascertainment was complete for 99.1% and 99.8% of potential patient-years of follow-up for the primary endpoint and all-cause death, respectively

LDL-C: ITT and On-Treatment Analyses

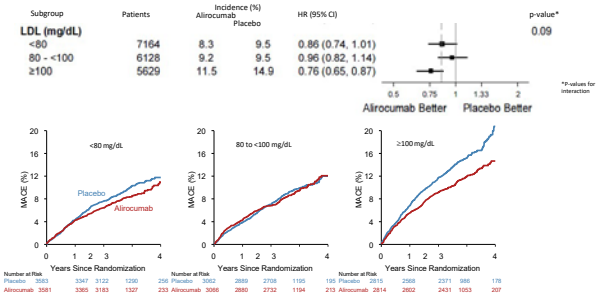


*Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo
†All LDL-C values, including those after premature treatment discontinuation, blinded down titration, or blinded switch to placebo

Primary Efficacy and Components

Endpoint, n (%)	Alirocumab (N=9462)	Placebo (N=9462)	HR (95% CI)	Log-rank P-value
MACE	**903 (9.5)**	**1052 (11.1)**	**0.85 (0.78, 0.93)** **NNT 59**	**0.0003**
CHD death	**205 (2.2)**	**222 (2.3)**	0.92 (0.76, 1.11)	0.38
Non-fatal MI	**626 (6.6)**	**722 (7.6)**	0.86 (0.77, 0.96) **NNT 100**	**0.006**
Ischemic stroke	**111 (1.2)**	**152 (1.6)**	0.73 (0.57, 0.93) **NNT 250**	**0.01**
Unstable angina	**37 (0.4)**	**60 (0.6)**	0.61 (0.41, 0.92)	0.02

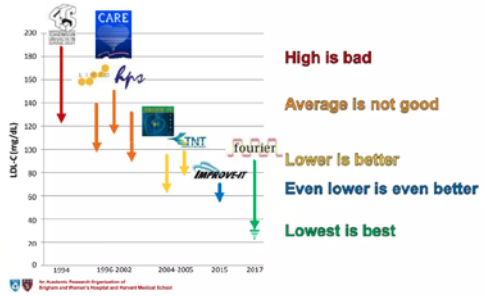
Primary Efficacy in Main Prespecified Subgroups



Efficacy: Subgroup with Baseline LDL-C ≥100 mg/dL (Median Baseline LDL-C 118 mg/dL)

Endpoint, n (%)	Alirocumab (N=2814)	Placebo (N=2815)	Absolute risk reduction (%)/NNT	HR (95% CI)
MACE	324 (11.5)	420 (14.9)	**3.4/30**	**0.76** (0.65, 0.87)
CHD death	69 (2.5)	96 (3.4)	**1.0/100**	**0.72** (0.53, 0.98)
CV death	81 (2.9)	117 (4.2)	**1.3/77**	**0.69** (0.52, 0.92)
All-cause death	114 (4.1)	161 (5.7)	**1.7/59**	**0.71** (0.56, 0.90)

A Quarter of a Century of Treating LDL-C



Bempedoic Acid – Nexletol by Esperion

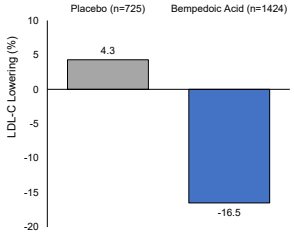
- Approved February 2020 as an adjunct to diet and maximally tolerated statin therapy in heterozygous FH or established ASCVD for additional LDL-C reduction
- Dose: **180 mg orally daily with or without food**
- **Available as bempedoic acid alone (Nexletol) or as a fixed-dose combination with ezetimibe (Nexlizet)**
- Adverse effects
  - **Hyperuricemia (0.8 mg/dL uric acid increase), tendon rupture**
  - Others reported (e.g., atrial fibrillation, anemia, hepatic transaminases, creatine kinase)
- **Drug-drug interaction with simvastatin (restrict dose to 20 mg) and pravastatin (restrict dose to 40 mg)**

Ballantyne CM, et al. Cardiovasc Drugs Ther. 2021;35:853-864
Nexletol (bempedoic acid) [package insert]. Ann Arbor,MI: Esperion Therapeutics, Inc.; 2020

Bempedoic Acid: Clinical Efficacy

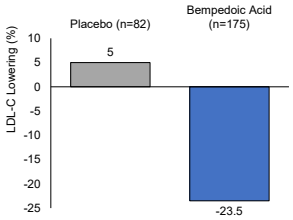
CLEAR Harmony

On maximally tolerated statin



CLEAR Tranquility

On ezetimibe, statin intolerant



Ray KK, et al. N Engl J Med. 2019;380:1022–1032.
Ballantyne CM, et al. Atherosclerosis. 2018;277:195-203.

Bempedoic Acid

- **CLEAR Outcomes Trial**
  - Randomized, double-blind, placebo-controlled clinical trial
  - **14,014 patients** included patients with all of the following:
    - **Established ASCVD or have a high risk of developing ASCVD; documented statin intolerance; LDL-C ≥100 mg/dL on maximally tolerated lipid-lowering therapy**
    - NOTE: **22.4% of statin intolerance patients tolerate a low dose statin** (rosuvastatin <5 mg, atorvastatin <10 mg, simvastatin<10 mg, lovastatin <20 mg, pravastatin <40 mg, fluvastatin <40 mg or pitavastatin <2 mg)
    - Estimated duration is 3.75 years; completion date is December 2022
  - **Dec. 07, 2022 -- Esperion announced** that the landmark Cholesterol Lowering via Bempedoic acid, an ACL-Inhibiting Regimen (CLEAR) **Outcomes trial met its primary endpoint, demonstrating statistically significant risk reduction in MACE-4 in patients treated with 180 mg/day bempedoic acid compared to placebo**.
    - Scheduled for Late-Breaking Clinical Trial sessions in New Orleans during the ACC.23/WCC on March 4, 2023.

Nicholls, SJ, et al. Am Heart J. 2021;235:104-112. https://clinicaltrials.gov/ct2/show/NCT02993406

Inclisiran – Leqvio by Novartis

- **Dec 22, 2021, the FDA approved Inclisiran-Leqvio** a small interfering RNA directed to **block synthesis/production of PCSK9** (proprotein convertase subtilisin kexin type 9) mRNA which **increases LDL receptors and lowers LDL-C**, indicated **as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C).**
- **Limitations of Use: The effect of inclisiran on cardiovascular morbidity and mortality has not been determined but is being studied in the ongoing ORION 4 Trial in ~15,000 patients with ASCVD an on max tolerated statin dose. Expected 2026**
  (https://www.clinicaltrials.gov/ct2/show/NCT03705234?term=ORION+4&draw=2&rank=1)

Inclisiran – Leqvio

- **ORION-11**, (NCT03400800) was a multicenter, double-blind, randomized, placebo-controlled **18month trial in which 1414 adults with ASCVD were randomized 1:1 to receive subcutaneous injections of either LEQVIO 284 mg (n = 712) or placebo (n = 702) on Day 1, Day 90, Day 270, and Day 450.** Patients were taking a **maximally tolerated dose of statin with or without other lipid modifying therapy,** and required additional LDL-C reduction. Patients were stratified by country and by current use of statins or other lipid-modifying therapies. **Patients taking PCSK9 inhibitors were excluded from the trial.**
  - The mean age at baseline was 65 years (range: 35 to 88 years), 56% were ≥ 65 years old, 25% were women, 98% were White, 1% were Black, < 1% were Asian, and 1% identified as Hispanic or Latino ethnicity. Thirty-one percent (31%) of patients had diabetes at baseline. The **mean baseline LDL-C was 101 mg/dL. At the time of randomization, 96% of patients were receiving statin therapy and 80% were receiving high-intensity statin therapy.**

Inclisiran – Leqvio

Table 3: Changes in Lipid Parameters in Patients with ASCVD on Maximally Tolerated Statin Therapy (Mean % Change from Baseline to Day 510 in Study 2)

Treatment Group	LDL-C	Total Cholesterol	Non-HDL-C	ApoB
Day 510 (mean percentage change from baseline)				
Placebo (n = 702)	4	2	2	1
LEQVIO (n = 712)	+46	+28	+42	+39
Difference from placebo (LS Mean) (95% CI)	-51 (-54, -47)	-30 (-32, -28)	-44 (-47, -41)	-40 (-42, -37)

ApoB = apolipoprotein B. CI = confidence interval. HDL-C = high-density lipoprotein cholesterol. LDL-C = low-density lipoprotein cholesterol

ORION-11, (NCT03400800) was a multicenter, double-blind, randomized, placebo-controlled 18month trial in which 1414 adults with ASCVD were randomized 1:1 to receive subcutaneous injections of either LEQVIO 284 mg (n = 712) or placebo (n = 702)

- Change in **median triglyceride level at day 510: −12%** in the inclisiran group and −5% in the placebo group; treatment difference was −7%.
- Change in **median lipoprotein(a) at day 540: −18.6%** in the inclisiran group, with no change in the placebo group; treatment difference was −18.6%.
- Change in **HDL-C at day 510: +10.2%** in the inclisiran group and +4.1% in the placebo group; treatment difference was +6.1%.
- Change in median hsCRP at day 540 (safety population): **Median hsCRP was unchanged** in the inclisiran group and was −8.9% in the placebo group; treatment difference was +8.9%.

Inclisiran – Leqvio

Table 1: Adverse Reactions Occurring in Greater Than or Equal to 3% of LEQVIO-treated Patients and More Frequently than with Placebo (Studies 1, 2, and 3)

Adverse Reactions	Placebo (N = 1822) %	LEQVIO (N = 1833) %
Injection site reaction†	1.8	8.2
Arthralgia	4.0	5.0
Urinary tract infection	3.6	4.4
Diarrhea	3.5	3.9
Bronchitis	2.7	4.3
Pain in extremity	2.6	3.3
Dyspnea	2.6	3.2

†includes related terms such as: injection site pain, erythema and rash

Immunogenicity: As with all oligonucleotides, there is potential for immunogenicity. In the placebo-controlled clinical trials, 1830 patients had samples tested for anti-drug antibodies. Confirmed positivity was detected in 33 (1.8%) patients prior to dosing and in 90 (4.9%) patients during the 18 months of treatment with inclisiran. There was no evidence that the presence of anti-drug binding antibodies impacted the pharmacodynamic profile, clinical response, or safety of inclisiran, but the long-term consequences of continuing inclisiran treatment in the presence of anti-drug binding antibodies are unknown.

Inclisiran – Leqvio

- **DOSING:** Inclisiran is for administration via **subcutaneous injection** by a health care provider **during the initial visit, at 3 months, then every 6 months thereafter.** In clinical trials, the **inclisiran sodium dose used was 300 mg (which corresponds to an inclisiran free acid dose of 284 mg).** Patient should remain in the clinic for observation for at least 30 minutes after the injection.
- Injection: 284 mg/1.5 mL (189 mg/mL) of inclisiran as a clear, and colorless to pale yellow solution in a single-dose prefilled syringe.
- **Cost: ~$3,250.00/dose or $6,500.00/year**

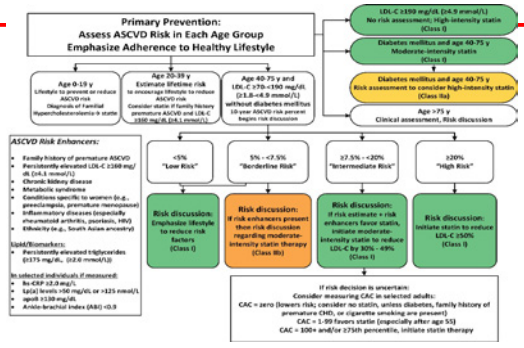
Store at controlled room temperature

Combination of Inclisiran and a PCSK9 mAb?

- There is currently **no evidence or mechanistic plausibility for additional efficacy in LDL-C lowering or cardiovascular outcomes benefit for combination therapy with a PSCK9 mAb and inclisiran when added to maximally tolerated statin therapy** with or without ezetimibe or bempedoic acid; therefore, **if inclisiran is to be used, it should be in place of a PCSK9 mAb and not added to a PCSK9 mAb.**
  - J Am Coll Cardiol 2022; 80:1366-1418

Inclisiran – Leqvio

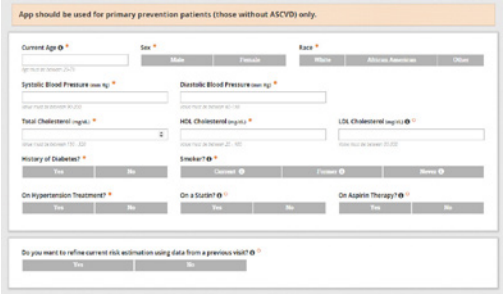
- **Inclisiran is being launched as a "buy-and-bill" therapy, the first of its kind in cardiology. Under this model, it would be purchased by the healthcare provider and/or system then be administered to the patient in the office.**
- As a healthcare provider-administered drug, inclisiran will be **covered by the medical benefit pathway (as opposed to the pharmacy benefit** pathway), which differs from other medications, including alirocumab and evolocumab. Novartis is hopeful this will reduce hurdles around access, particularly for Medicare fee-for-service patients. Under this pathway, Novartis says that 70% of patients eligible for inclisiran would have zero co-pays.
- For doctors who don't want to set up buy-and-bill services within their center or office, **Novartis has developed a network of roughly 1,000 alternative injection centers that will acquire and administer inclisiran.**



J Am Coll Cardiol. 2019 Jun, 73 (24) e285–e350.
https://doi.org/10.1016/j.jacc.2018.11.003

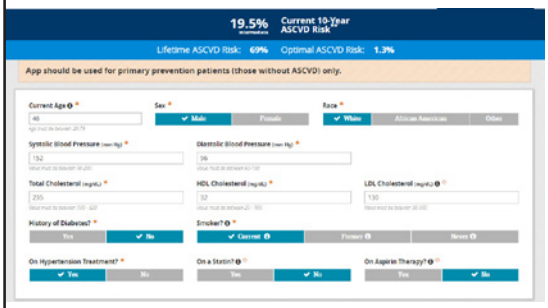
AMERICAN COLLEGE of CARDIOLOGY

ASCVD Risk Plus Estimator



AMERICAN COLLEGE of CARDIOLOGY

ASCVD Risk Plus Estimator



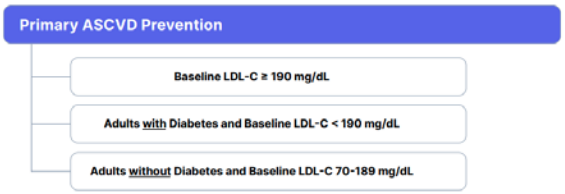
Based on the data entered (assuming no clinical ASCVD, age 40-75 and LDL-C 70-189mg/dl)

Example
46 y/o white male;
BP 152/96;
TC 235, HDL 32, LDL 130;
Diabetes - No;
Smoker - Yes;
BP Treatment - Yes;
Statin - Yes;
Low Dose Aspirin - No

AMERICAN COLLEGE of CARDIOLOGY

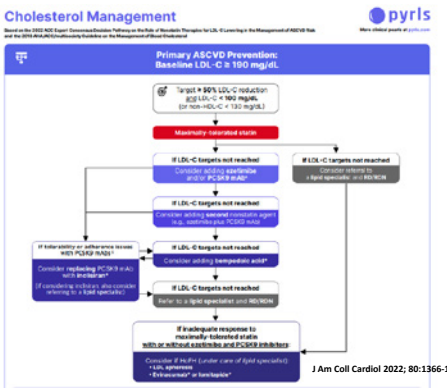
56

2022 ACC Expert Consensus Decision Pathway on the Role of Non statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Solution Set Oversight Committee



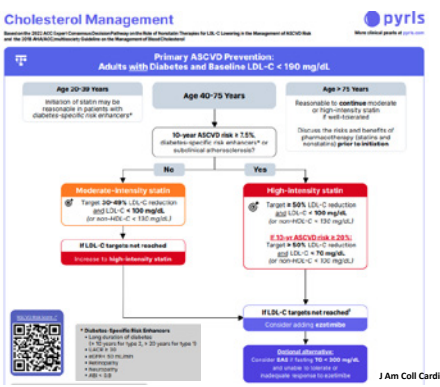
J Am Coll Cardiol 2022; 80:1366-1418.

Cholesterol Management



J Am Coll Cardiol 2022; 80:1366-1418

Cholesterol Management



J Am Coll Cardiol 2022; 80:1366-1418

Cholesterol Management

Risk-enhancing factors Medical History/Demographics
- Family history of premature ASCVD (males < 55 years; females < 65 years)
- Primary hypercholesterolemia (LDL-C 160-189 mg/dL)
- Chronic kidney disease (with or without albuminuria)
- Metabolic syndrome
- History of premature menopause (before age 40) or preeclampsia
- Chronic inflammatory disorders (e.g., psoriasis, RA, HIV/AIDS)
- High-risk race/ethnicities (e.g., South Asian ancestry)

Biomarkers
- Persistently elevated, primary hypertriglyceridemia (≥ 175 mg/dL)
- CRP ≥ 2.0 mg/dL
- Lp(a) level ≥ 50 mg/dL (or >125 nmol/L)
- apoB ≥ 130 mg/dL
- Ankle-brachial index (ABI) <0.9

J Am Coll Cardiol 2022; 80:1366-1418

Primary Prevention Trials

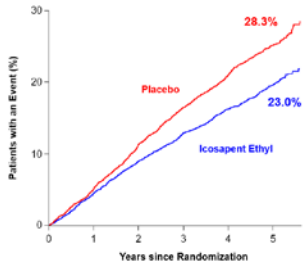
Trial/Drug/Dose	N/Duration	Primary Outcome	RRR/ARR/NNT
WESCOPS Prava 40 mg vs. placebo	6,595 pts Age 45-64 4.9 years	CV death + NF-MI 5.5% 7.9%	31%/2.4%/42
PROSPER Prava 40 mg vs. Placebo	5,804 pts Age 70-82 3.2 years	CV death, NF-MI, CVA 14.1% 16.2%	15%/2.1%/48
ASCOT (LLA) Atorva 10 mg vs. Placebo	10,305 pts Age 40-79 3.3 years	CV death + NF-MI 1.9% 3.0%	36%/1.1%/90
AFCAPS/TexCAPS Lova 20-40 mg vs. Placebo	6605 pts 45-73 M/55-73F 5.2 years	CV death, NF-MI, UA 6.8% 10.9%	37%/4.1%/25
JUPITER (CRP > 2.0) Rosuva 20 mg vs. Placebo	17,802 M>/=55, F>/=65 1.9 years	MI, CVA, UA, Revasc, CV Death 0.77% 1.36%	44%/ 0.59%/84

REDUCE-IT Trial with Icosapent ethyl (EPA, Vascepa)

- September 2018 Amarin/Kowa announced the topline results of the **Reduce-It Trial a cardiovascular (CV) outcomes study of icosapent ethyl (VASCEPA) capsules** met its **pre-specified primary composite endpoint (4-point MACE of CV death, nonfatal myocardial infarction (MI, including silent MI), nonfatal stroke, coronary revascularization, and unstable angina requiring hospitalization**) in the intent – to - treat population:
- Randomized **8,179 patients on** a 1:1 basis to **statin plus VASCEPA 4g/day or statin plus placebo** and compared the incidence of MACE between treatment arms over a **median period of 4.9 years.**
- **Baseline LDL-C controlled to between 41-100 mg/dL (median baseline 75 mg/dL)** by statin therapy and with various cardiovascular risk factors including **persistent elevated TGs between 150-499 mg/dL (median baseline 216 mg/dL) and either established cardiovascular disease (secondary prevention) or diabetes mellitus and at least one other CV risk factor (primary prevention)**
- Showed reduction in a composite of major adverse cardiovascular events (MACE) of approximately 25% – P value <0.001 (highly statistically significant)
  - N Engl J Med 2019; 380:11-22

Primary End Point:

CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med*. 2018. Bhatt DL. AHA 2018, Chicago.

Prespecified Hierarchical Testing

Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	RRR	P-value
Primary Composite (ITT)	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)	25%▼	<0.001
Key Secondary Composite (ITT)	459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65–0.83)	26%▼	<0.001
Cardiovascular Death or Nonfatal Myocardial Infarction	392/4089 (9.6%)	507/4090 (12.4%)	0.75 (0.66–0.86)	25%▼	<0.001
Fatal or Nonfatal Myocardial Infarction	250/4089 (6.1%)	355/4090 (8.7%)	0.69 (0.58–0.81)	31%▼	<0.001
Urgent or Emergent Revascularization	216/4089 (5.3%)	321/4090 (7.8%)	0.65 (0.55–0.78)	35%▼	<0.001
Cardiovascular Death	174/4089 (4.3%)	213/4090 (5.2%)	0.80 (0.66–0.98)	20%▼	0.03
Hospitalization for Unstable Angina	108/4089 (2.6%)	157/4090 (3.8%)	0.68 (0.53–0.87)	32%▼	0.002
Fatal or Nonfatal Stroke	98/4089 (2.4%)	134/4090 (3.3%)	0.72 (0.55–0.93)	28%▼	0.01
Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke	549/4089 (13.4%)	690/4090 (16.9%)	0.77 (0.69–0.86)	23%▼	<0.001
Total Mortality	274/4089 (6.7%)	310/4090 (7.6%)	0.87 (0.74–1.02)	13%▼	0.09

0.4 1.0 1.4
Icosapent Ethyl Better | Placebo Better
RRR denotes relative risk reduction

Bhatt DL. AHA 2018, Chicago. Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med*. 2018.

STRENGTH Trial

JAMA Cardiol. Published online May 16,2021.doi:10.1001/jamacardio.2021.1157

- **Optimal statin-treated patients with dyslipidemia (TG 1175-499 mg/dl) and high cardiovascular risk were randomized to omega-3 CA (Epanova EPA+DHA by AZ) 4 g/day (n = 6,539) versus placebo (n = 6,539).**
  - **Total number of enrollees: 13,078**
  - **Duration of follow-up: Median 42 months**
  - Mean patient age: 63 years
  - Percentage female: 35%
  - Percentage with diabetes: 70%
- **The trial was terminated early due to interim analysis revealing low probability for benefit with omega-3 CA. The primary outcome of cardiovascular death, myocardial infarction, stroke, coronary revascularization, or hospitalization for unstable angina occurred in 12.0% of the omega-3 CA group compared with 12.2% of the placebo group (p = 0.84).**

Cardiovascular Disease and Risk Management

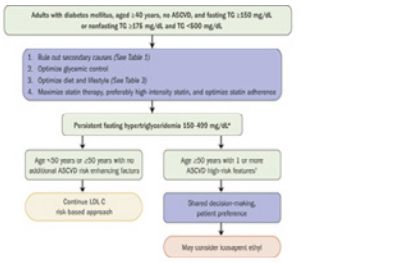
Treatment of Other Lipoprotein Fractions or Targets

10.28 For individuals with fasting triglyceride levels ≥500 mg/dL, evaluate for secondary causes of hypertriglyceridemia and consider medical therapy to reduce the risk of pancreatitis. C

10.29 In adults with moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175–499 mg/dL), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that raise triglycerides. C

10.30 **In individuals with atherosclerotic cardiovascular disease or other cardiovascular risk factors on a statin with controlled LDL cholesterol but elevated triglycerides (135–499 mg/dL), the addition of icosapent ethyl can be considered to reduce cardiovascular risk. A**

Diabetes Care 2023;46(Suppl. 1):S158-S190



Salim S. Virani et al. *J Am Coll Cardiol* 2021;

SELF EVALUATION

Current Cholesterol Guidelines and Medications

1. T/F - A consensus statement from the European Atherosclerosis Society Consensus Panel concludes that consistent evidence from numerous and multiple different types of clinical and genetic studies unequivocally establishes that LDL causes ASCVD.

2. According to the 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk the goal LDL-C for patients with a history of previous ASCVD (i.e.. post MI, post CVA) is ?
    a. <100 mg/dl
    b. <70 mg/dl
    c. <55 mg/dl
    d. None of the above

3. According to the 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk patients with ASCVD or very high risk should be treated with a high intensity statin and if needed to achieve the LDL-C goal should have which medications added in order the get to goal LDL-C?
    a. Ezetimibe followed by a PCSK-9 inhibitor
    b. Ezetimibe followed by bempedoic acid
    c. PCSK-9 inhibitor followed by bempedoic acid
    d. Ezetimibe followed by Inclisiran

4. T/F - Recent data suggests that the benefits from lifelong cardiovascular prevention from a statin accrue over peoples' lifespan with large share of benefits accruing at older age. Stopping treatment earlier substantially reduces benefits.

5. According to the ADA and the ACC individuals with atherosclerotic cardiovascular disease or other cardiovascular risk factors on a statin with controlled LDL cholesterol but elevated triglycerides (135–499 mg/dL), the addition of _____ ethyl can be considered to reduce cardiovascular risk.
    a. OTC omega 3 fatty acids (fish oil)
    b. Prescription Icosapent ethyl (EPA)
    c. Fenofibrate
    d. Ezetimibe

Answer Key: 1. T, 2. C, 3. A, 4. T, 5. B

John F. Dombrowski, MD

Dr. Dombrowski, of Washington, DC, is a practicing anesthesiologist with a special interest in pain and addiction. He is board certified in both anesthesiology, and pain medicine and addiction medicine, is principle of the Washington Pain Center and medical director of several Medication Assistant treatment programs. Dr. Dombrowski is president of the DC and Maryland Society of Addiction Medicine, and a frequent speaker and commentator on pain management and addiction treatments.

You may contact Dr. Dombrowski at (202) 362-4787, or by email at jfdmdpc@gmail.com.

John F. Dombrowski, MD, PC

Board certified in Anesthesiology and Pain Medicine
A Specialist in Pain Medicine
Thewashingtonpaincenter.com

3301 New Mexico Avenue NW
Washington, DC 20016

Telephone: 202-362-4787
Email: Drjohn@dcpaindoc.com

Managing Patient Pain while Preventing Addiction

GOALS

- Correctly identifying patients for risk factors for substance use disorder.
- Properly writing and documenting opiate management therapy for either acute or chronic pain settings.
- Red flag warnings where the patient should be counseled and seek other treatment.
- Referring the patient to a higher level of care treatment options.

REASON FOR OPIOIDS

- An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in such terms ***International Association of the Study of Pain***

ACUTE PAIN

- Surgery
- Injury
- Acute inflammation of chronic disease

BARRIERS TO EFFECTIVE PAIN MANAGEMENT

- Reluctance to report pain.
- Many patient silently tolerate unrelieved pain due to a cultural or societal reason.
- Reluctance to take pain medications.
- Lack of adequate education regarding the availability of pain relief remedies medication or otherwise

Agency for health care policy and research publication number 94-0592.

American pain Society. Principles of analgesic use in the treatment of acute pain and cancer pain fourth edition Greenview, IL: American pain Society; 1999.

MANAGEMENT OF PAIN

- 3.5-6,000,000 cancer pain sufferers needlessly (World Health Organization)
- 23 million surgical patient suffer with chronic pain (American Hospital Association)
- 53 million injured pain sufferers - Newton
- 50-70% of primary care visits have an underlying pain complaint
- Physicians will tell patients to learn to live with their pain and accepted in normal.
- 1000 patient's weekly wanted Dr. Kevorkian's help/the right to die movement

MANAGEMENT OF PAIN - FACTS

- 30% of the US population has either acute or chronic pain 4% of these patients are elderly and a good majority are disabled.
- Opiates are the most commonly prescribed class of medication in the United States.
- In 2014 260 million opiate prescriptions are written
- 65% of these medications for less than three weeks only 4% were for chronic opiate analgesic treatment(COAT)

ACUTE PAIN

- This is protective,
- It is usually time-limited
- It is a sign or symptom not the problem
- Aggressive treatment of acute pain can prevent establishment of chronic pain

"Acute pain is a type of pain that typically lasts less than 3 to 6 months, or pain that is directly related to soft tissue damage such as a sprained ankle or a paper cut. ... Acute pain is distinct from chronic pain and is relatively more sharp and severe."

ACUTE PAIN TREATMENT

Reasons for treatment

- Limit suffering

- Preserve hope

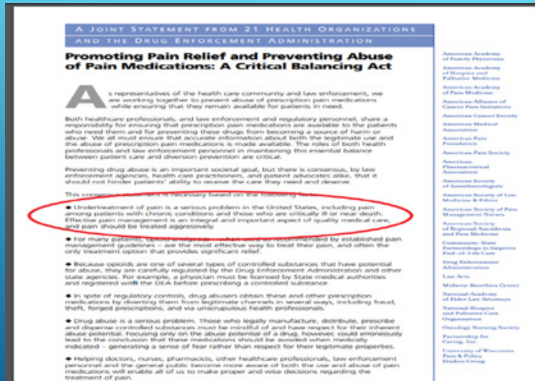
- Prevent debilitation

- Improve treatment compliance

- Prevent loss of work pleasure role in the family or society

INADEQUATE PAIN RELIEF AND THE CONSEQUENCES.

- Physical
  - -Increase pulsed, increase blood pressure, increase respirations
  - -decreased activity decreased mobility decreased actives a daily living
  - -decreased oxygen to tissues
  - -decreased recovery due to limited ambulation.
- Psychological
  - -anorexia, fatigue, sleep disorders, anxiety, depression
- Social economic
  - - decreased productivity due to lost days at work increase cost to the medical system.



A JOINT STATEMENT FROM 21 HEALTH ORGANIZATIONS AND THE DRUG ENFORCEMENT ADMINISTRATION

Promoting Pain Relief and Preventing Abuse of Pain Medications: A Critical Balancing Act

As representatives of the health care community and law enforcement, we are working together to prevent abuse of prescription pain medications while ensuring that they remain available for patients in need.

Both healthcare professionals, and law enforcement and regulatory personnel, share a responsibility for ensuring that prescription pain medications are available to the patients who need them and for preventing these drugs from becoming a source of harm or abuse. We all must ensure that accurate information about both the legitimate use and the abuse of prescription pain medications is made available. The roles of both health professionals and law enforcement personnel in maintaining this essential balance between patient care and diversion prevention are critical.

Preventing drug abuse is an important societal goal, but there is consensus, by law enforcement agencies, health care practitioners, and patient advocates alike, that it should not hinder patients' ability to receive the care they need and deserve.

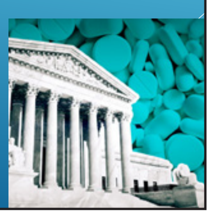
This consensus statement is necessary based on the following facts:

- Undertreatment of pain is a serious problem in the United States, including pain among patients with chronic conditions and those who are critically ill or near death. Effective pain management is an integral and important aspect of quality medical care, and pain should be treated aggressively.
- For many patients, opioid analgesics – when used as recommended by established pain management guidelines – are the most effective way to treat their pain, and often the only treatment option that provides significant relief.
- Because opioids are one of several types of controlled substances that have potential for abuse, they are carefully regulated by the Drug Enforcement Administration and other state agencies. For example, a physician must be licensed by State medical authorities and registered with the DEA before prescribing a controlled substance.
- In spite of regulatory controls, drug abusers obtain these and other prescription medications by diverting them from legitimate channels in several ways, including fraud, theft, forged prescriptions, and via unscrupulous health professionals.
- Drug abuse is a serious problem. Those who legally manufacture, distribute, prescribe and dispense controlled substances must be mindful of and have respect for their inherent abuse potential. Focusing only on the abuse potential of a drug, however, could erroneously lead to the conclusion that these medications should be avoided when medically indicated – generating a sense of fear rather than respect for their legitimate properties.
- Helping doctors, nurses, pharmacists, other healthcare professionals, law enforcement personnel and the general public become more aware of both the use and abuse of pain medications will enable all of us to make proper and wise decisions regarding the treatment of pain.

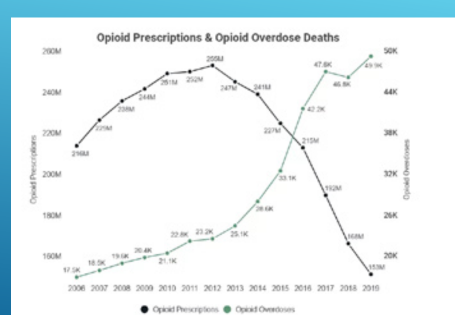
HEALTH
Fight over opioid prescribing — and when it turns criminal — heads to Supreme Court Stat News
Andrew Joseph
By Andrew Joseph Feb. 11, 2022

Doctors have wide latitude to prescribe drugs, including potentially dangerous ones, but even they face limits. The question is, what threshold do physicians have to cross — and what sort of intent do they need to have — for their prescribing to be considered a crime?

It's an issue headed to the Supreme Court next month, in a case concerning two physicians who were convicted of unlawfully dispensing opioid painkillers.



ADDICTION IN AMERICA



https://drugabusestatistics.org/prescription-drug-abuse-statistics/

GREENSPUN SHAPIRO PC
ATTORNEYS AT LAW
Call: **703-352-0100**

HOME | PRACTICE AREAS | ABOUT US | RESOURCE CENTER | CASE RESULTS | CONTACT US

Overprescribing Pain Medications Can Lead to Serious Criminal Charges

Providing patients with medications for controlling their pain when they suffer an injury or after surgery is an important duty of a doctor. In some cases, this involves prescribing powerful narcotic and opioid drugs. The main pain-relieving drug in these prescriptions are opium and codeine. While these drugs can relieve pain, they come with serious risks. Patients can become addicted to these drugs. In addition, the prescribing of these medications can lead to a patient's drug overdose and death.

Overuse of powerful opioids, such as Dilaudid, Percocet, Vicodin, and OxyContin (oxycodone), has become a national crisis and is regularly spotlighted in the news. This has led to an increased focus and prosecution of doctors who prescribe these medications to their patients. In some cases, physicians who prescribe these medications can be unfairly charged with committing a crime. These charges can be extremely serious and have long-term consequences on a doctor's life—such as loss of his medical license, dramatically higher insurance premiums, loss of employment, and a permanent criminal record. If you have been charged with a crime associated with prescribing pain medications, our experienced criminal defense attorneys are here to help you build a strong defense that may result in the charges against you being dismissed or reduced to a less serious offense.

Get Help Now

Vision. Experience. Imagination.

Name *
Phone *
Email *
Tell us more.
SUBMIT

All of these matters discussed fall on YOU

- Everyone is at risk.
- *Must the document* and appropriate history and physical exam.
- Must document risk assessment tool.
- Must actively engage patient with respect to medication risk and benefit.
- Must consider other therapies outside of narcotic management.

MORE THAN JUST PAIN MEDICINES

- 3.3 million people were currently misusing opiate medications.
- 2 million people were misusing tranquilizers.
- 1.7 million people were misusing stimulants.
- 497,000 people were misusing sedative hypnotics.
- In total 6 million Americans are misusing prescription-based medications all of which **are more than the total number of people abusing cocaine, heroin, hallucinogens, inhalation drugs**.

Drug enforcement agency. Practitioners manual; section 2. 2015; HTTP://www.thatDEAdiversion.USDOJ.gov/P UBS/manuals/practice/section 2. H TM. June 13, 2015

PATIENT WITH THESE RISK FACTORS TEND TO BE AT HIGHER RISK

- Exaggerated pain/hysteria/catastrophizing
- Young age
- Personal history/family history of abuse medications-physical
- Poor social support
- Multifactorial biopsychosocial

Weber LR, predicting a Baird behaviors in opiate treatment patients; preliminary validation of the opiate risk tool. Pain medicine. 2005; 6(6): 432 – 442

PATIENTS AT RISK OF OVERDOSE

- Middle-age
- Polypharmacy-opiates-antidepressants-benzodiazepines
- Unemployment
- High opiate use
- Recent release from Prison

Weber LR, predicting a Baird behaviors in opiate treatment patients; preliminary validation of the opiate risk tool. Pain medicine. 2005; 6(6): 432 – 442

OTHER RISKY BEHAVIOR

- 39% of patients increase their dose without direction from a HCP.
- 26% engage in purposeful over sedation.
- 20% drank alcohol concurrent with opiate use.
- 18% used opiates - other than relieving pain.
- 18% obtained extra opiate medications from other physicians.

Fleming space MF substance use disorders in a primary care sample receiving daily opiate therapy. Journal pain. 2007; 8 (seven): 537-582.

CHARTING STAYS OUT OF TROUBLE

- ► Establish and measure goals for improved pain and function.
- ► Discuss benefits, risks, and availability of nonopioid therapies with patient.
- ► Assess pain intensity, functional impairment, and quality of life.

https://www.cdc.gov/opioids/healthcare-admins/pdf/quality-improvement-care-coordination-508.pdf

RISK ASSESSMENT TOOL

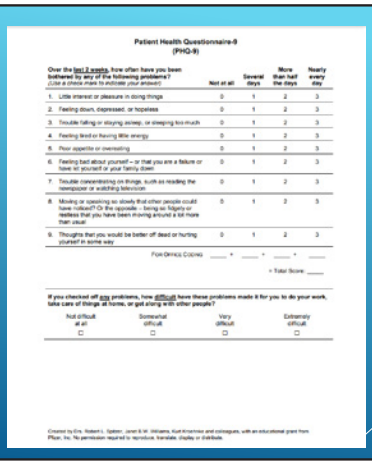
Opioid Risk Tool

This tool should be administered to patients upon an initial visit prior to beginning opioid therapy for pain management. A score of 3 or lower indicates low risk for future opioid abuse, a score of 4 to 7 indicates moderate risk for opioid abuse, and a score of 8 or higher indicates a high risk for opioid abuse.

Mark each box that applies	Female	Male
Family history of substance abuse		
Alcohol	1	3
Illegal drugs	2	3
Rx drugs	4	4
Personal history of substance abuse		
Alcohol	3	3
Illegal drugs	4	4
Rx drugs	5	5
Age between 16—45 years	1	1
History of preadolescent sexual abuse	3	0
Psychological disease		
ADD, OCD, bipolar, schizophrenia	2	2
Depression	1	1
Scoring totals		

MORE ASSESSMENTS

- The Patient Health Questionnaire (PHQ) is a self-report version of the Primary Care Evaluation of Mental Disorders (PRIME-MD) diagnostic tool for common mental disorders. The PHQ-9 is a brief, 9-item scale that includes only the depression-related items from the PHQ. The PHQ-9 has been validated for use in primary care settings and can be used to make a tentative diagnosis of depression and to monitor depression severity and response to treatment in the past 2 weeks.



Patient Health Questionnaire-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? (Use a check mark to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or hurting yourself in some way	0	1	2	3

FOR OFFICE CODING ____ + ____ + ____ + ____

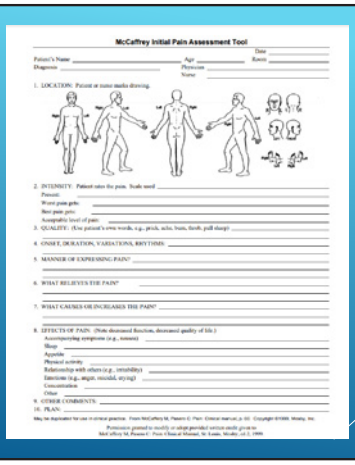
= Total Score ____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Created by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer, Inc. No permission required to reproduce, translate, display or distribute.

FORM FOR DOCUMENTATION OF PAIN ACUTE AND CHRONIC



HISTORY AND PHYSICAL EXAM

- **Pain Evaluation Questions**
- **Character** - A description of how the pain feels (dull, pinching, pounding, sharp, shooting, throbbing, pounding, stinging, burning).
- **Radiation** - Does the pain move anywhere?
- **Site** - Where is the pain? Where does it hurt?
- **Onset** - When did the pain start?
- **Progression** - Has the pain gotten worse or better since it started?
- **Duration** - For how long have you had the pain? Is it episodic?
- **Severity** - What is the pain severity (1 to 10)?
- **Aggravating factors** - Does anything make it worse, such as movement or a position?
- **Relieving factors** - Does anything you do or not do make the pain better? What treatments have you tried?
- **Associative factors** - Other relevant questions from a review of systems based on the patient complaint.

- ▶ Use immediate-release opioids when starting.
- ▶ Start low and go slow.
- ▶ When opioids are needed for acute pain, prescribe no more than needed.
- ▶ Do not prescribe ER/LA opioids for acute pain.
- ▶ Follow-up and re-evaluate risk of harm; reduce dose or taper if needed.

https://www.cdc.gov/opioids/healthcare-admins/pdf/quality-improvement-care-coordination-508.pdf

- ▶ Check PDMP for high dosages and prescriptions from other providers.
- ▶ Use urine drug testing to identify prescribed substances and undisclosed use.
- ▶ Avoid concurrent benzodiazepine and opioid prescribing.
- ▶ Arrange treatment for OUD if needed.

https://www.cdc.gov/opioids/healthcare-admins/pdf/quality-improvement-care-coordination-508.pdf

USE OF OPIOIDS ACUTE PAIN 0-6 WEEKS

- Help the patient set reasonable expectations about recovery
- Reserve opioids for pain from severe injuries or medical conditions, surgical procedures or when alternatives are ineffective. If prescribed, shortest duration and lowest necessary dose
- For minor surgical procedures (eg, impacted wisdom tooth)-prescribe no more than 1-3 days
  short acting opioid
- Consider tapering off opioids by 6 weeks as acute episode resolved or if CMIF (clinical meaningful improvement of function)hasn't occurred

SUB ACUTE MANAGEMENT 6-12 WEEKS

- Do NOT prescribe opioids if use during acute phase doesn't lead to CMIF
- Screen for depression, anxiety and opioid risk using validated tools
- Avoid prescribing new benzodiazepines and sedative-hypnotics
- Discontinue opioids if there is no CMIF, treatment resulted in severe adverse outcome or patient has a current substance use disorder or a history of opioid use disorder

THE OPIOID PRESCRIPTION SHOULD INCLUDE DOCUMENTED INFORMED CONSENT AND A TREATMENT AGREEMENT ADDRESSING:

- Drug interactions
- Physical dependence
- Side effects
- Tolerance
- Psychologic dependence
- Driving and motor skill impairment
- Limited evidence of long-term benefit
- Addiction, dependence, misuse
- Risk/benefit profile of the drug prescribed
- Signs/symptoms of overdose

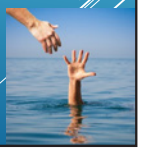
https://www.ncbi.nlm.nih.gov/books/NBK537318/#article-40661.s8

BEHAVIORS SUGGESTING OPIOID DRUG USE DISORDER

- Aggressive demand for more drugs
- Forging prescriptions
- Increased alcohol use and lack of control
- Increasing dose without permission
- Injecting or inhaling drugs prescribed for oral use
- Obtaining drugs from illegitimate sources
- Obtaining opioids from other providers
- Prescription loss
- Refusing to decrease pain medication dosage when stabilized
- Resisting medication change
- Requesting early refills
- Requesting specific medications
- Selling drugs
- Sharing prescriptions
- Stockpiling medications
- Using illegal drugs

HAVING A PLAN TO REFER OUT

- This is no sign of weakness
- Quickly realize that the patient NOT getting better or is becoming problematic
- Obtain a consult with a pain medicine physician, psychiatrist, addiction medicine physician
- You to have an obligation to treat however this obligation cannot be taken advantage of.



SELF EVALUATION

Managing Patient Pain while Preventing Addiction

True/False

1. Treating patients in a medical practice with narcotic therapy is highly controversial and the drug enforcement agency has made a statement stating this very fact.

2. The number of prescriptions written, and the number of opiate deaths correlates with one another.

3. In a addition to being concerned about the use of opioids one should also be concerned about misuse of other medication such as sedative hypnotics, stimulants and tranquilizers.

4. A patient presenting with a history of hysteria with respect to their pain, or with bipolar disorder and a poor social network is nonetheless a candidate for opiate management.

5. One way of preventing patients from receiving medications from multiple physicians would be querying the pharmacy database. This should be done before writing any medication for a patient.

6. One opiate risk tool assessment scoring tool would be early consensual sexual relations.

Answer Key: 1. F, 2. F, 3. T, 4. T, 5. T, 6. F

LOUIS KURITZKY, MD
4510 NW 17th Place
GAINESVILLE, FL 32605
(352) 377-3193 LKuritzky@aol.com

Engaging the Mediterranean Diet in the Clinical Practice Setting

Mediterranean Diet

- Only a very small percent of adults in America at high risk for CVD have been advised to or are using the Mediterranean diet. The primary reason for this is

a) Smoking Cessation is much more effective
b) Rx of dyslipidemia is much more effective
c) The diet itself lacks proven efficacy
d) Clinicians are not well informed on easy methods to successfully employ the diet

Mediterranean Diet: Premise

SIMPLE & CONVINCING
Why

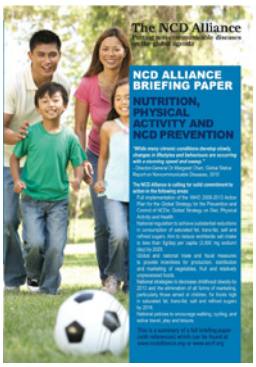
\+

SIMPLE & CONVINCING
How

Success

Nutrition, physical activity and NCD prevention

- Up to **80% of heart disease, stroke and type 2 diabetes** and over a third of the most common cancers **could be prevented** by eliminating obesity, unhealthy diets and physical inactivity
- Call for commitments at the global and national level to address these risk factors including:
  - Control food supply, food information and marketing and promotion of energy-dense, nutrient-poor foods that are **high in saturated, trans-fat, salt or refined sugars**

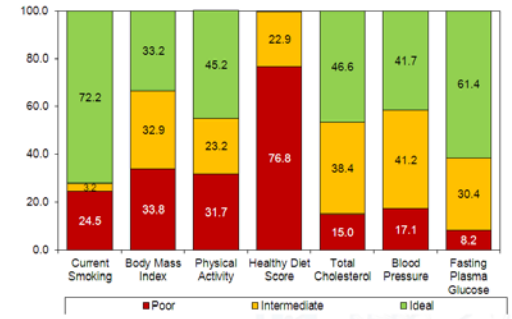


State of the Union
AHA 2020 USA CV Health Goals

- The 7 metrics that comprise the AHA 2020 health goals are: smoking, BMI, exercise, diet, cholesterol, BP, and fasting glucose. Which of these has the highest level of adults scoring 'poor' in goal attainment ?

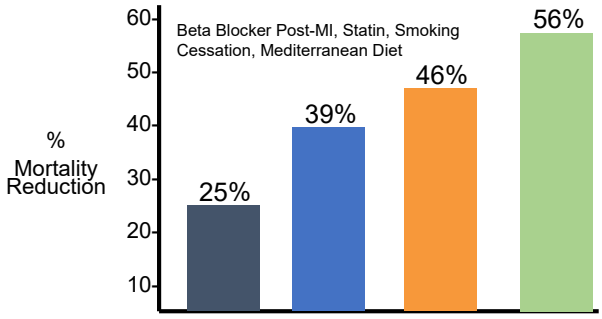
a) Smoking
b) BMI
c) Healthy Diet
d) BP

Age-standardized prevalence estimates for poor, intermediate and ideal cardiovascular health for each of the seven metrics of cardiovascular health in the AHA 2020 goals, among US adults >20 years of age, NHANES 2005-2006 (baseline available data as of January 1, 2010).



Roger VL et al. Published online in *Circulation* Dec. 15, 2010

How Much Cluck for Your Buck?
All-Cause Mortality Reduction



de Lorgeril M, et al *Circulation*. 1999;99:779-785 (Mediterannean Diet)
Kezerashvili A, et al et al *Current Cardiology Reviews*, 2012, *8*, 77-84 (beta blocker)
Stenestrand U, et al JAMA 2001;285:430-436 (Statin)
Wilson K et al Arch Int Med 2000;160:939-944 (Smoking)

From Whence Cometh the Mediterranean Diet?

"The concept of the Mediterranean diet originated from the Seven Countries Study initiated by Ancel Keys in the 1950s."

Hu FB *NEJM* 2003;348(26):2595-2596

Whence Cometh the Mediterranean Diet?

"The study showed that, despite a high fat intake, the population of the island of Crete in Greece had very low rates of CHD and certain types of cancer and had a long-life expectancy."

Hu FB *NEJM* 2003;348(26):2595-2596

Whence Cometh the Mediterranean Diet?

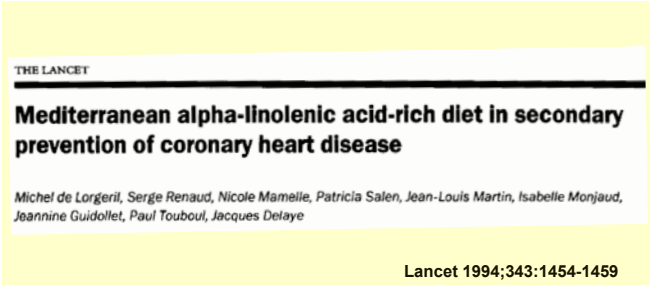
" The traditional dietary patterns….were considered to be largely responsible…."

Hu FB *NEJM* 2003;348(26):2595-2596

Mediterranean Diet

- The Lyon Heart Study was a RCT of diet vs placebo post MI. After 5 years, compared to control, the effect of Mediterranean diet on subsequent survival without future MI was

a) No different than control
b) Statistically significantly > control but of questionable clinical relevance
c) Only effective in subgroups with poor diet at baseline
d) Markedly superior to control


THE LANCET

Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease

Michel de Lorgeril, Serge Renaud, Nicole Mamelle, Patricia Salen, Jean-Louis Martin, Isabelle Monjaud, Jeannine Guidollet, Paul Touboul, Jacques Delaye

Lancet 1994;343:1454-1459

Mediterranean Diet: 2^0 Prevention

- Study: 2^0 MI prevention (n = 605)
- Intervention: Mediterranean diet (oleic acid and α-linolenic acid enriched) vs control
- Inclusion:
  - age <70
  - MI within 6 months

de Lorgeril M, Renaud S *Lancet* 1994:343:1454-1459

Mediterranean Diet: The Dietary Intervention Content

"…adopt a Mediterranean-type diet: more bread, more root vegetables and green vegetables, more fish, less meat (beef, lamb and pork to be replaced with poultry), no day without fruit, and butter and cream to be replaced with margarine."

de Lorgeril M, Renaud S *Lancet* 1994:343:1454-1459

Mediterranean Diet: The Dietary Intervention Oil Content

- "Because the patients would not accept olive oil…as the only fat, a rapeseed (canola) oil-based margarine…was supplied free for the whole family…comparable to olive oil with 15% saturated fatty acids, 48% oleic acid."
- "The oils recommended for salads and food preparation were rapeseed and olive oils exclusively."

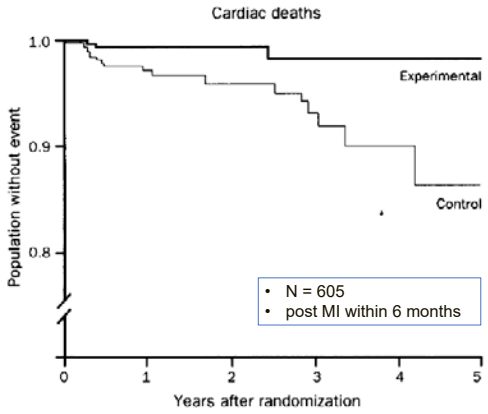
de Lorgeril M, Renaud S *Lancet* 1994:343:1454-1459

Mediterranean Diet: 2^0 Prevention

- Exclusions
  - NYHF Stage III-IV
  - HTN >180/100 mm Hg
  - Stable
- Outcomes (at mean f/u 27 months):
  - CHD Deaths: 3 vs 16 (RR = 0.19, p <0.002)
  - Non-fatal MI: 5 vs 17
  - Combined endpoint: RR = 0.27, p <0.001
  - All-cause mortality: 8 vs 20 (RR 0.30, p = 0.02)

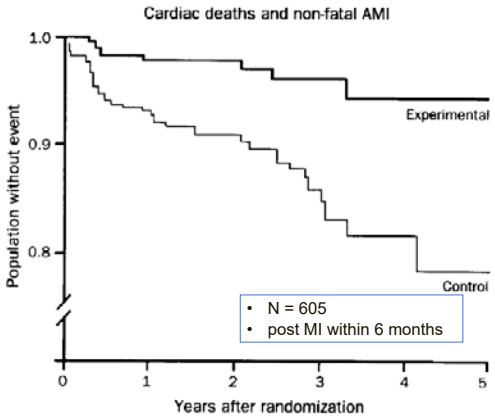
de Lorgeril M, Renaud S *Lancet* 1994:343:1454-1459

Mediterranean Diet



de Lorgeril M, Renaud S *Lancet* 1994:343:1454-1459

Mediterranean Diet



de Lorgeril M, Renaud S *Lancet* 1994:343:1454-1459

Mediterranean Diet WHY Did It Work?

Risk Factor	Mediterranean (M) vs Control (C)
Total Cholesterol	M = C
Triglycerides	M = C
HDL	M = C
LDL	M = C
Apo A_1, ApoB	M = C
BMI	26.1 vs 26.2
BP mm Hg	126/78 vs 129/79
α-linolenic acid	↑ M (68%)
linoleic acid	↓ M (7%)

de Lorgeril M, Renaud S *Lancet* 1994:343:1454-1459

Mediterranean Diet
WHY Did It Work?

"Whether it is the α-linolenic acid that plays a protective part cannot be determined by this study; it is one of the most striking differences between the experimental and control groups and already present at 8 weeks."

De Lorgeril M, Renaud S *Lancet* 1994:343:1454-1459

Mediterranean Diet:
The Dietary Interventions

- Control
  - "To avoid between-group contamination, control patients received no dietary advice apart from that of hospital dieticians or attending physicians."
- Intervention: 1-hr session (dietician & research cardiologist)

de Lorgeril M, Renaud S *Lancet* 1994:343:1454-1459

Mediterranean Diet, Traditional Risk Factors, and the Rate of Cardiovascular Complications After Myocardial Infarction

Final Report of the Lyon Diet Heart Study

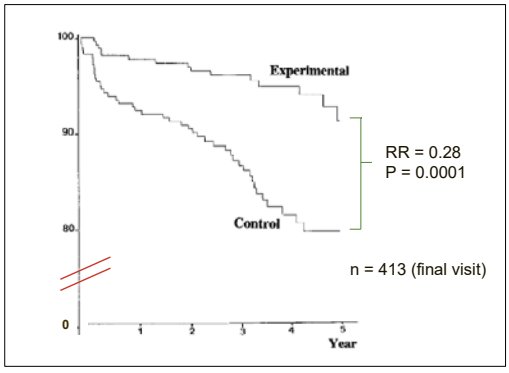
De Lorgeril M, et al Circulation 1999;99:779-785

The Lyon Diet Heart Study

- Study: RSBCT post MI pts (n=423)
- Inclusion:
  - 1st MI
  - Age <70
  - Clinically stable
  - Willingness to follow diet x 5 yrs
  - No contraindication to diet
- Rx: Mediterranean vs 'prudent' diet

De Lorgeril M, et al *Circulation* 1999;99:779-785

Lyon Diet Heart Study
Survival Without MI



De Lorgeril M, et al *Circulation* 1999;99:779-785

Lyon Diet Heart Study
3 Major Composite Outcomes

Endpoint	Components	HR
C01	Survival & no MI	0.28 (0.15-0.53)
C02	CO1 + unstable angina, HF, CVA, PE, peripheral embolism	0.33 (0.21-0.52)
C03	CO2 + recurrent stable angina, restenosis, revascularization, thrombophlebitis	0.53 (0.38-0.74)

De Lorgeril M, et al *Circulation* 1999;99:779-785

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JUNE 26, 2003 VOL. 348 NO. 26

Adherence to a Mediterranean Diet and Survival in a Greek Population

Trichopoulou A et al *NEJM* 2003;348:2599-2608

Mediterranean Diet Study Mortality

- Study: Prospective Observational (n = 22,043)
- Metric: Mediterranean Diet Scale
- Age: 45% > 55 years
- Endpoints (at 44 months):
  - All-cause Mortality
  - CHD mortality
  - CA Mortality
- Endpoints adjusted for age, sex, BMI, physical activity, other confounders

Trichopoulou A et al *NEJM* 2003;348:2599-2608

Mediterranean Diet Score 9 Items: 0-1 point/item

Fish	0	1
Vegetables	<median	>median
Legumes	< median	>median
Fruits and Nuts	< median	>median
Grains	<median	>median
Fish	<median	>median
MU Fats/Sat Fats	<median	>median
Red meats , Poultry	>median	<median
Dairy	>median	<median
Alcohol g/d MEN	<10 or >50	10-50
WOMEN	<5 or >25	5-25

Ortola R , et al. *Am J Med* 2019;132:1091-1102

Mediterranean Diet: Mortality Study
Hazard Ratio per 2 Point ↑MDS

Variable	#	Hazard Ratio (CI)
All-cause mortality	275	0.75 (0.64-0.87)*
CHD mortality	54	0.67 (0.47-0.94)*
CA mortality	97	0.76 (0.59-0.98)*

*p <0.05 *p <0.001

Trichopoulou A et al *NEJM* 2003;348:2599-2608

Mediterranean Diet: Mortality Study Bottom Line

"A two-point increment in the Mediterranean diet score was associated with a 25% reduction in total mortality (P<0.001)"

Trichopoulou A et al *NEJM* 2003;348:2599-2608

ORIGINAL CONTRIBUTION

N = 2,339

Mediterranean Diet, Lifestyle Factors, and 10-Year Mortality in Elderly European Men and Women
The HALE Project

JAMA 2004;292:1433-1439

Kim T. B. Knoops, MSc
Lisette C. P. G. M. de Groot, PhD
Daan Kromhout, PhD
Anne-Elisabeth Perrin, MD, MSc
Olga Moreiras-Varela, PhD
Alessandro Menotti, MD, PhD
Wija A. van Staveren, PhD

Context Dietary patterns and lifestyle factors are associated with mortality from all causes, coronary heart disease, cardiovascular diseases, and cancer, but few studies have investigated these factors in combination.

Objective To investigate the single and combined effect of Mediterranean diet, being physically active, moderate alcohol use, and nonsmoking on all-cause and cause-specific mortality in European elderly individuals.

Design, Setting, and Participants The Healthy Ageing: a Longitudinal study in Europe (HALE) population, comprising individuals enrolled in the Survey in Europe on Nutrition and the Elderly: a Concerted Action (SENECA) and the Finland, Italy, the Netherlands, Elderly (FINE) studies, includes 1507 apparently healthy men and 822 women, aged 70 to 90 years in 11 European countries. This cohort study was conducted between 1988 and 2000.

THE NUMBER OF OLDER PEOPLE IS growing rapidly worldwide. More than 380 million people

Conclusion Among individuals aged 70 to 90 years, adherence to a Mediterranean diet and healthful lifestyle is associated with a more than 50% lower rate of all-causes and cause-specific mortality.

Mediterranean Diet: The HALE Project
Healthy Aging A Longitudinal Study in Europe

- Study: Prospective 10-year Observational Study (n = 2,339)
- Subjects:
  - Multinational European Men & Women
  - age 70-90 at baseline (mean = 74)
- Outcomes: CHD, CVD events, CA, All-cause mortality

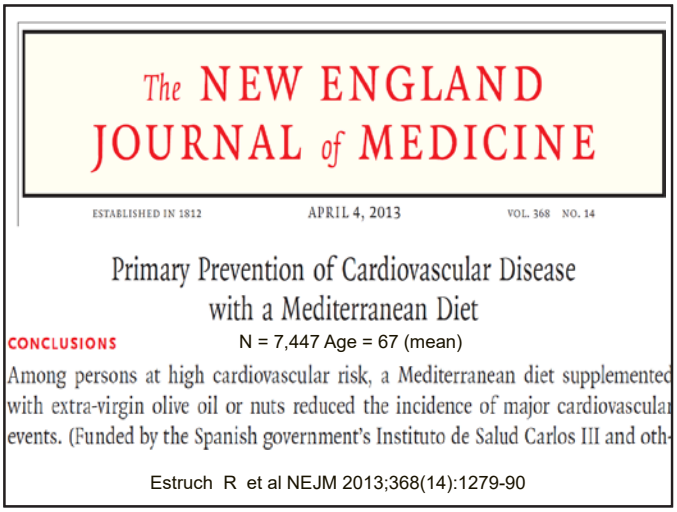
Knoops KTB, de Groot LCPCM, et al *JAMA* 2004;292:1433-1439

Mediterranean Diet: The HALE Project
Healthy Aging A Longitudinal Study in Europe

10 Yr Mortality HR

Factor	All Cause	CHD	CVD	CA
Mediterranean Diet	0.77* (0.68-.88)	0.61* (0.43-0.88)	0.71* (0.58-0.88)	0.90 (0.70-1.17)
Physical Activity	0.63* (0.55-0.72)	0.72 (0.48-1.07)	0.65* (0.52-0.81)	0.64* (0.48-0.84)
Nonsmoking	0.65* (0.57-0.75)	0.80 (0.54-1.17)	0.68* (0.54-0.85)	0.47* (0.36-0.62)

Knoops KTB, de Groot LCPCM, et al *JAMA* 2004;292:1433-1439


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 4, 2013 VOL. 368 NO. 14

Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

CONCLUSIONS

Among persons at high cardiovascular risk, a Mediterranean diet supplemented with extra-virgin olive oil or nuts reduced the incidence of major cardiovascular events. (Funded by the Spanish government's Instituto de Salud Carlos III and oth-

N = 7,447 Age = 67 (mean)

Estruch R et al NEJM 2013;368(14):1279-90

Mediterranean Diet: The PREDIMED Study
Prevencio con Dieta Mediterranea

- Study: PRCT high risk CV patients (n=7,447)
- Interventions:
  - Mediterranean diet + Extra Virgin Olive Oil
  - Mediterranean diet + Nuts
  - Control (low fat diet)
- 1⁰ Outcome: MI, Stroke, or CV death

Estruch R et al NEJM 2013;368(14):1279-1290

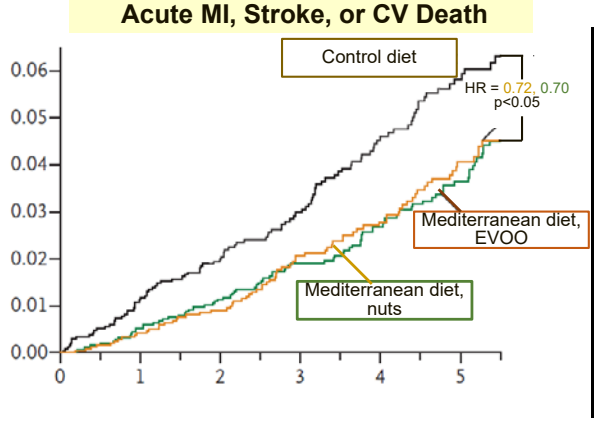
Mediterranean Diet: The PREDIMED Study
Prevencio con Dieta Mediterranea

- Inclusion:
  - Age 55-80
  - High CV Risk
  - No evident CV endpoints at baseline
  - T2DM

  or
  - ≥3: smoking, HTN, ↑LDL, ↓HDL, BMI > 27, + FH premature CHD

Estruch R et al *NEJM* 2013;368(14):1279-1290

1⁰ Endpoint:
Acute MI, Stroke, or CV Death



Estruch R et al *NEJM* 2013;368(14):1279-90

Research

N = 447
Mean age = 67 years

JAMA *Intern Med* 2015;175(7):1094-1103

Original Investigation

Mediterranean Diet and Age-Related Cognitive Decline
A Randomized Clinical Trial

Cinta Valls-Pedret, MSc; Aleix Sala-Vila, DPharm, PhD; Mercè Serra-Mir, RD; Dolores Corella, DPharm, PhD; Rafael de la Torre, DPharm, PhD; Miguel Ángel ... Jordi Salas-S...

CONCLUSIONS AND RELEVANCE In an older population, a Mediterranean diet supplemented with olive oil or nuts is associated with improved cognitive function.

Mediterranean Diet: Cognitive Decline
A PREDIMED Substudy

- Study: PRCT cognitively intact high CV risk older patients (n=680, mean age = 67)
- Interventions:
  - Mediterranean diet + Extra Virgin Olive Oil
  - Mediterranean diet + Nuts
  - Control (low fat diet)
- 1^0 Outcome: Cognitive Δ/time (mean 4.1 yrs)

Valls-Pedret C et *al* *JAMA Intern Med* 2015;175(7):1094-1103

Mediterranean Diet: The PREDIMED Study
Prevencio con Dieta Mediterranea

- Inclusion:
  - Age 55-80
  - High CV Risk
  - No evident CV endpoints at baseline
  - T2DM

    or
  - ≥3: smoking, HTN, ↑LDL, ↓HDL, BMI > 27, + FH premature CHD

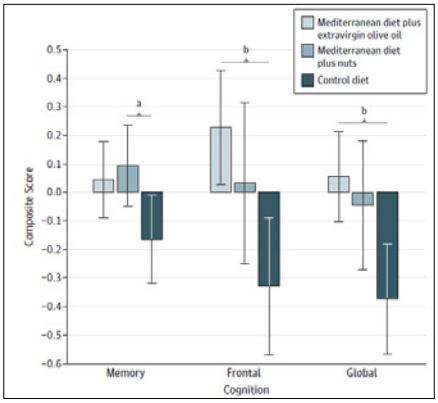
Estruch R et al *NEJM* 2013;368(14):1279-1290

Mediterranean Diet: Cognition

"In a PREDIMED substudy, we assessed cognitive performance by various neuropsychological tests at baseline and after a median follow-up of 4.1 years."

Valls-Pedret C et *al* *JAMA Intern Med* 2015;175(7):1094-1103

Mediterranean Diet: Cognition



Valls-Pedret C et *al* *JAMA Intern Med* 2015;175(7):1094-1103

Mediterranean Diet: Cognition

"Results revealed cognitive improvement in participants allocated the Mediterranean diet and cognitive decline in those allocated the control diet."

*emphasis added

Valls-Pedret C et *al* *JAMA Intern Med* 2015;175(7):1094-1103

Mediterranean Diet: Cognition

"The benefit of the Mediterranean diet was independent of sex, age, energy intake, and cognition related variables….."

Valls-Pedret C et *al* *JAMA Intern Med* 2015;175(7):1094-1103

Mediterranean Diet: Cognition

"These findings are novel because, to our knowledge, no prior long-term clinical trial has assessed cognitive changes in response to dietary patterns."

Valls-Pedret C et *al* *JAMA Intern Med* 2015;175(7):1094-1103

Review

The Mediterranean Diet Slows Down the Progression of Aging and Helps to Prevent the Onset of Frailty: A Narrative Review

Cristiano Capurso *, Francesco Bellanti, Aurelio Lo Buglio and Gianluigi Vendemiale

Department of Medical and Surgical Sciences, University of Foggia, Viale Pinto 1, 71122 Foggia, Italy; francesco.bellanti@unifg.it (F.B.); aurelio.lobuglio@unifg.it (A.L.B.); gianluigi.vendemiale@unifg.it (G.V.)
* Correspondence: cristiano.capurso@unifg.it

Capurso C et al *Nutrients* 2020, 12, 35; doi:10.3390/nu12010035

Fried's Frailty Index

Characteristics of Frailty	
• Unintentional weight loss	Baseline: > 4,5 Kg (10 lbs) lost unintentionally in prior year
• Weakness	Hand Grip: <5,85 Kg (12,89 lbs) for males; <3,37 Kg (7,43 lbs) for females
• Exhaustion	Self-reported: at least 3 days / week
• Slowness	> 7 seconds to travel 4.57 m (15 feet) on a known route
• Low activity	Assessed using the Physical Activity Scale for the Elderly (PASE); or Kcals/week: < 383 Kcals/week for males, < 270 Kcals/week for females
Presence of Frailty	
Frailty phenotype: ≥ 3 criteria present	
Intermediate or pre-frail: 1 or 2 criteria present	

Capurso C et al *Nutrients* 2020;12(35):e1-e34

Mediterranean Diet Aging & Frailty

"Most authors agree that the Mediterranean diet is the best… to maintain health, or to get old with a lower incidence of frailty syndrome, or disability…."

Capurso C et al *Nutrients* 2020;12(35):e1-e34

Harnessing the Benefits of the Mediterranean Diet

When Is It TOO LATE To Make A Life Choice Change?

CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE

Influence of Changes in Diet Quality on Unhealthy Aging: The Seniors-ENRICA Cohort

Rosario Ortolá, MD, PhD[a,b], Esther García-Esquinas, MD, PhD[a,b], Giselle García-Varela, MSc[a], Ellen A Struijk, PhD[a,b], Fernando Rodríguez-Artalejo, MD, PhD[a,b], Esther López-García, PhD[a,b,c]

[a]Department of Preventive Medicine and Public Health, Universidad Autónoma de Madrid and Idipaz, Madrid, Spain; [b]CIBER of Epidemiology and Public Health (CIBERESP), Madrid, Spain; [c]IMDEA Food Institute, CEI UAM+CSIC, Madrid, Spain.

Ortola R , et al. *Am J Med* 2019;132:1091-1102

Mediterranean Diet Initiated Late in Life
The Seniors-ENRICA Cohort

- Study: Prospective Observational Study adults ≥60 (n=2042)
- Method (phone interview + 2 home visits)
  - Wave 0 (2008-2010)
  - Wave 1 (2012)
  - Wave 2 (2015)
- Metrics (all 3):
  - MEDAS (Mediterr Diet Adherence Screener)
  - MDS (Mediterranean Diet Score)
  - AHEI-2010 (Alternate Healthy Eating Index)

Ortola R , et al. *Am J Med* 2019;132:1091-1102

The Seniors-ENRICA Cohort: MEDAS

s/d or s/w(servings/day or week)	0	1
Olive Oil for Cooking	No	Yes
Olive Oil (g/d)	<36	≥36
Vegetables s/day	<2	≥2
Fruit s/day	<3	≥3
Red meat s/d	0.8	<0.8
Butter, margarine,cream s/day	≥0.8	<0.8
Sugar Sweetened Drinks s/day	1	<1
Wine s/week	1	<1
Legumes s/week	<3	≥3
Seafood s/week	<3	≥3
Pastries s/day	2	<2
Nuts s/week	<2	≥2
Prefer white > red meat	No	Yes
Dishes w/ tomato, garlic, onion. leek, olive oil sauce s/week	<2	≥2

Ortola R , et al. *Am J Med* 2019;132:1091-1102 [adapted]

Mediterranean Diet Initiated Late in Life
Conclusions

Improvement in diet…was associated with less deficit accumulation….particularly functional deterioration, suggesting that disability could be prevented or delayed by adopting a better diet, specifically by ↓ …red/processed meat and sugar-sweetened beverages, and ↑… fish. Although improving diet quality should start early in life, it seems to be effective even in late life."

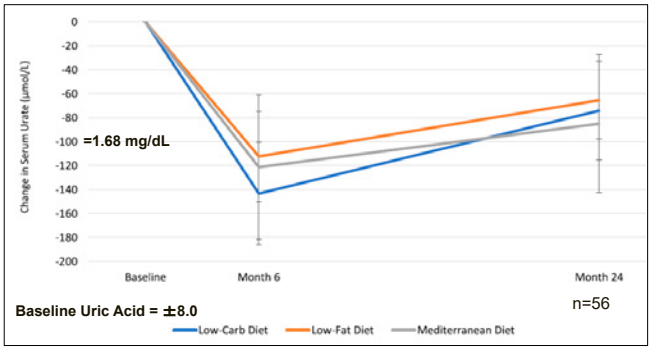
Ortola R , et al. *Am J Med* 2019;132:1091-1102

Mediterranean Diet
Might Make Your Big Toe Hurt Less

Effects of Low-Fat, Mediterranean, or Low-Carbohydrate Weight Loss Diets on Serum Urate and Cardiometabolic Risk Factors

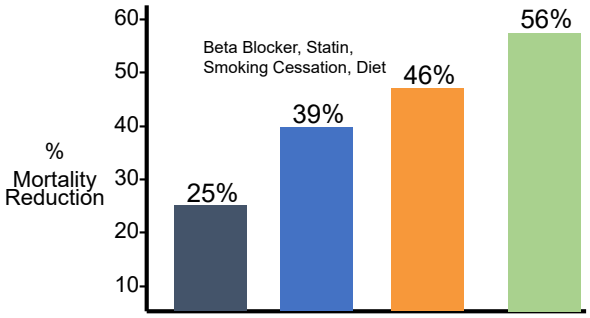
Yokose C et al Diabetes Care 2020;43(11):2812-282

Mediterranean Diet
Impact on Hyperuricemia



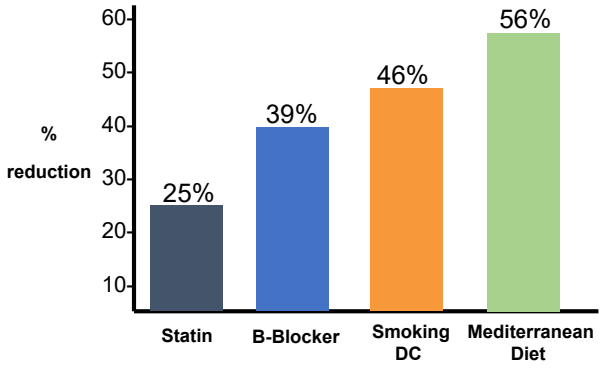
Yokose C et al *Diabetes Care* 2020 Nov; 43(11): 2812-2820

How Much Cluck for Your Buck?
All-Cause Mortality Reduction



de Lorgeril M, et al *Circulation*. 1999;99:779-785 (Mediterannean Diet)
Kezerashvili A, et al et al *Current Cardiology Reviews*, 2012, *8*, 77-84 (beta blocker)
Stenestrand U, et al JAMA 2001;285:430-436 (Statin)
Wilson K et al Arch Int Med 2000;160:939-944 (Smoking)

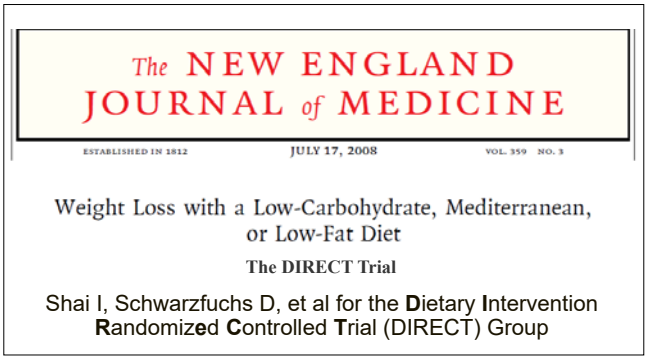
How Much Cluck for Your Buck?
Post-MI All-Cause Mortality Reduction



Mediterranean Diet: Obesity

- Low carb and low-fat diets are most popularly advised by clinicians for weight loss. A randomized trial of each of these vs Mediterranean diet for weight loss showed

a) Low fat was the best
b) Low carb was the best
c) Low carb and Mediterranean were similarly effective, and both outperformed low fat


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 17, 2008 VOL. 359 NO. 3

Weight Loss with a Low-Carbohydrate, Mediterranean, or Low-Fat Diet

The DIRECT Trial

Shai I, Schwarzfuchs D, et al for the **D**ietary **I**ntervention **R**andomize**d** **C**ontrolled **T**rial (DIRECT) Group

Obesity
Low Carb vs Mediterranean vs Low Fat Diet

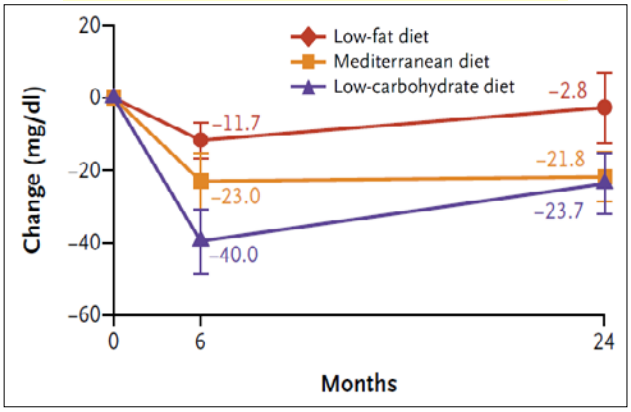
- Study: obese adults (n=322)
- Inclusion
  - Age 40-65 (Mean age = 52)
  - BMI > 27 (Mean BMI = 31)
  - Gender: 86% men
- Rx: Diet plus dietician counseling (90 min sessions) weeks 1, 3, 5, 7, and then q6 weeks) = 18 sessions

Shai I et al *NEJM* 2008;359:229-241

Weight Loss Over 2 Years

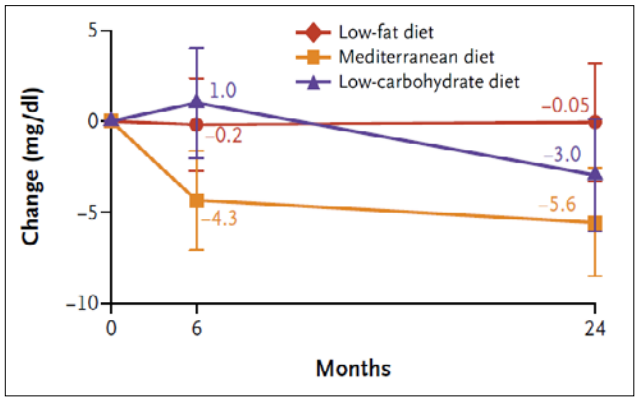
Shai I et al *NEJM* 2008;359:229-241

Triglycerides Over 2 Years



Shai I et al *NEJM* 2008;359:229-241

LDL Over 2 Years



Shai I et al *NEJM* 2008;359:229-241

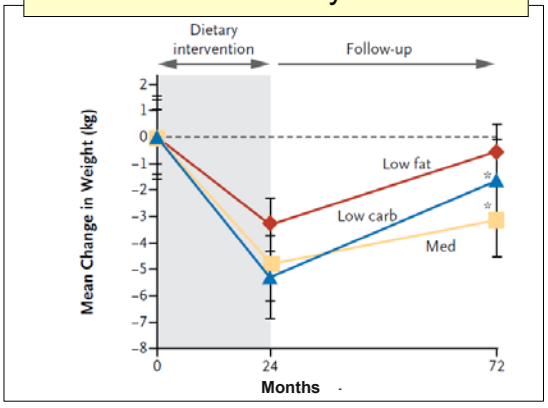
DIRECT
Dietary Intervention Randomized Controlled Trial

Four-Year Follow-up after Two-Year Dietary Interventions

TO THE EDITOR: Data from trials that compare the effectiveness of weight-loss diets are frequently limited to the intervention period. In our 2-year workplace-based study, called the Dietary Intervention Randomized Controlled Trial (DIRECT),[1,2] we randomly assigned 322 moderately obese

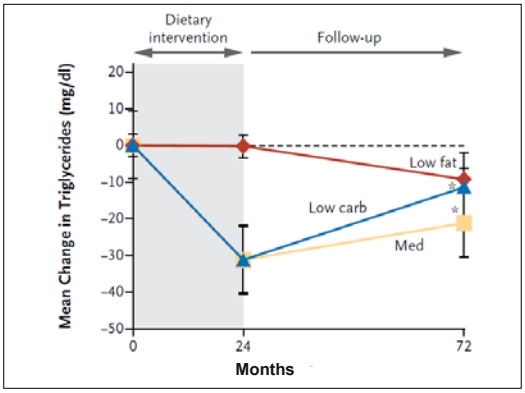
Schwarzfuchs D, Golan R, Shai I
NEJM 2012;367;14:1373-1374

4 Yr F/U after 2-year Diet



Schwarzfuchs D, Golan R, Shai I *NEJM* 2012;367;14:1373-1374

4 Yr F/U after 2-year Diet



Schwarzfuchs D, Golan R, Shai I *NEJM* 2012;367;14:1373-1374

Mediterranean Diet

Maybe an Impact on
PROSTATE CANCER?

Oncology: Prostate/Testis/Penis/Urethra

Mediterranean Dietary Pattern is Associated with Low Risk of Aggressive Prostate Cancer: MCC-Spain Study

Adela Castelló,* Elena Boldo, Pilar Amiano, Gemma Castaño-Vinyals, Nuria Aragonés, Inés Gómez-Acebo, Rosana Peiró, Jose Juan Jimenez-Moleón, Juan Alguacil, Adonina Tardón, Lluís Cecchini, Virginia Lope, Trinidad Dierssen-Sotos, Lourdes Mengual, Manolis Kogevinas, Marina Pollán and Beatriz Pérez-Gómez on behalf of MCC-Spain Researchers

J Urology 2018;199:430-437

Diet & Prostate CA: The MCC-Spain Study
(Multicase-Control Study on Common Tumors in Spain)

- Study: Case-control study (n = 2,031)
- Subjects: Bx-proven prostate CA (n= 754) vs controls (n=1,277) in men age 38-85
- Outcome: relationship between tumor aggressiveness and diet

Castello A et al *J Urology* 2018;199:430-437

Diet & Prostate CA: The MCC-Spain Study
(Multicase-Control Study on Common Tumors in Spain)

Relative Risk of Gleason > 6
as per Quartile of Mediterranean Diet Adherence

	RR	p for trend
Q3 vs Q1	0.66 (0.46-0.96)	0.023
Q4 vs Q1	0.68 (0.46-1.01)	

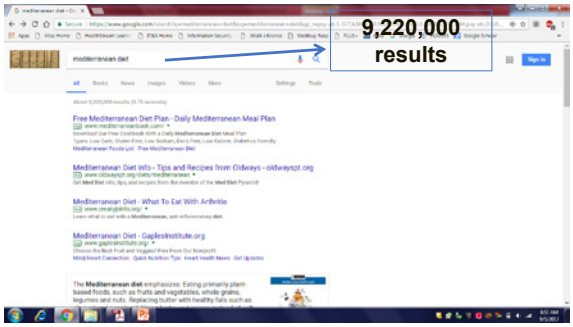
"We found important differences between the Mediterranean dietary pattern, which was associated with a lower risk of aggressive prostate cancer, and Western and prudent dietary patterns, which had no relationship with prostate cancer risk."

Castello A et al *J Urology* 2018;199:430-437

SIMPLE
How

NOT SIMPLE….

This ISN'T Going to Be Simple



Will the REAL Mediterranean Diet Please Stand?

"There is no single 'Mediterranean diet'. More than 15 countries border the Mediterranean Sea, and their dietary habits, the types of food produced, and their cultures vary considerably."

Hu FB *NEJM* 2003;348(26):2595-2596

Mediterranean Diet: Definition?

"Although there is no uniform definition of a Mediterranean diet, it generally consists of…"

http://www.acc.org/latestincardiology/articles/2014/07/18/18/28/primarypreventionofcvdwithamediterraneandiet

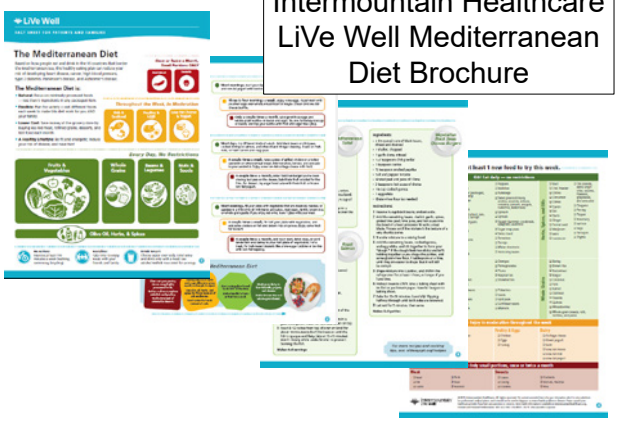
Mediterranean Diet: Definition?

"Although there is no uniform definition…."	
Unrestricted Fat	Cereals (Bread, Pasta, Rice)
Abundant Vegetables	Moderate wine with meals
Legumes	Aromatic Herbs & Spices
Fresh Fruits	Frequent Fish
Tree Nuts	Low meat/animal products
Low simple sugars	Low milk/milk products

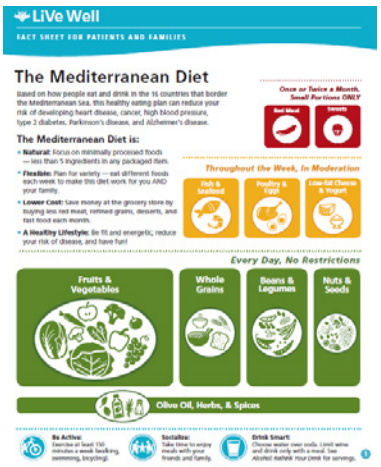
http://www.acc.org/latestincardiology/articles/2014/07/18/18/28/primarypreventionofcvdwithamediterraneandiet

Really
SIMPLE….

Intermountain Healthcare LiVe Well Mediterranean Diet Brochure



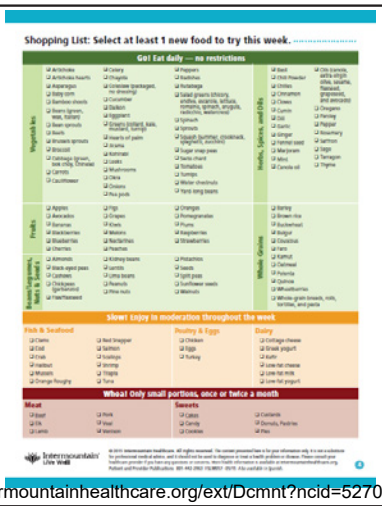
https://intermountainhealthcare.org/ext/Dcmnt?ncid=527023066



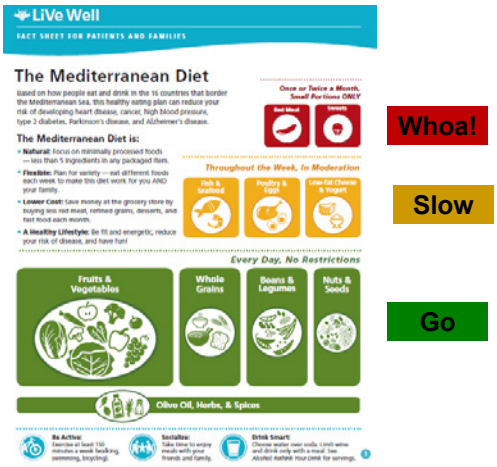
https://intermountainhealthcare.org/ext/Dcmnt?ncid=527023066

https://intermountainhealthcare.org/ext/Dcmnt?ncid=527023066

https://intermountainhealthcare.org/ext/Dcmnt?ncid=527023066

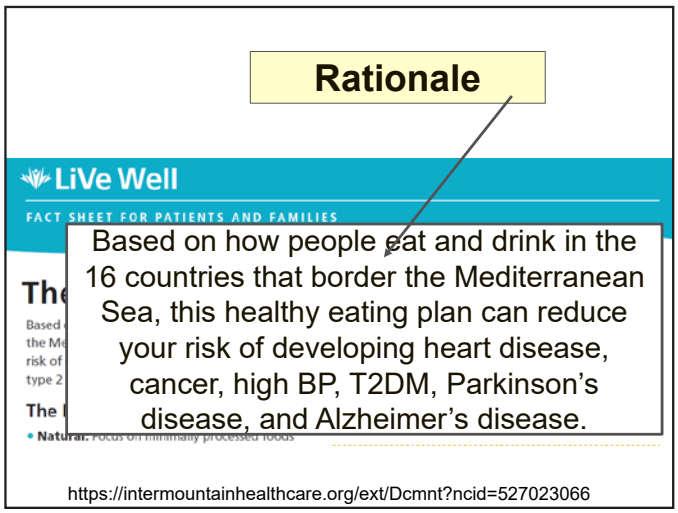


https://intermountainhealthcare.org/ext/Dcmnt?ncid=527023066



https://intermountainhealthcare.org/ext/Dcmnt?ncid=527023066

https://intermountainhealthcare.org/ext/Dcmnt?ncid=527023066

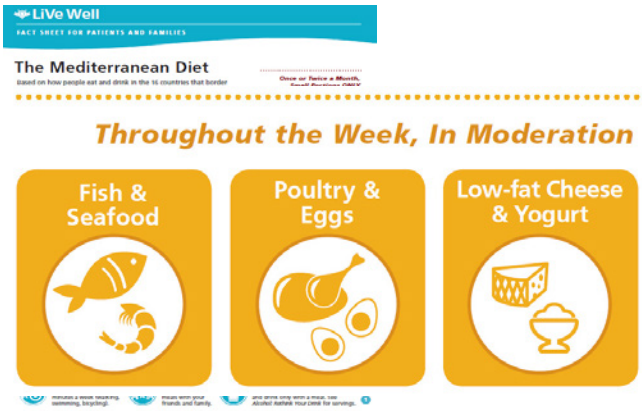


https://intermountainhealthcare.org/ext/Dcmnt?ncid=527023066

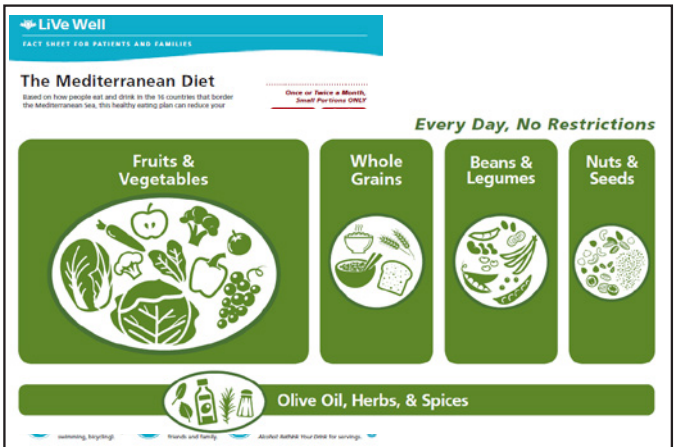
Countries Bordering the Mediterranean Sea
(Wikipedia Accessed 017-Aug-30)

- Akrotiri & Dhekelia
- Albania
- Algeria
- Bosnia & Herzegovina
- Croatia
- Cyprus
- Egypt
- France
- Gibraltar
- Greece
- Israel
- Italy
- Lebanon
- Libya
- Malta
- Monaco
- Montenegro
- Morocco
- Slovenia
- Spain
- Syria
- Tunisia
- Turkey

https://intermountainhealthcare.org/ext/Dcmnt?ncid=527023066

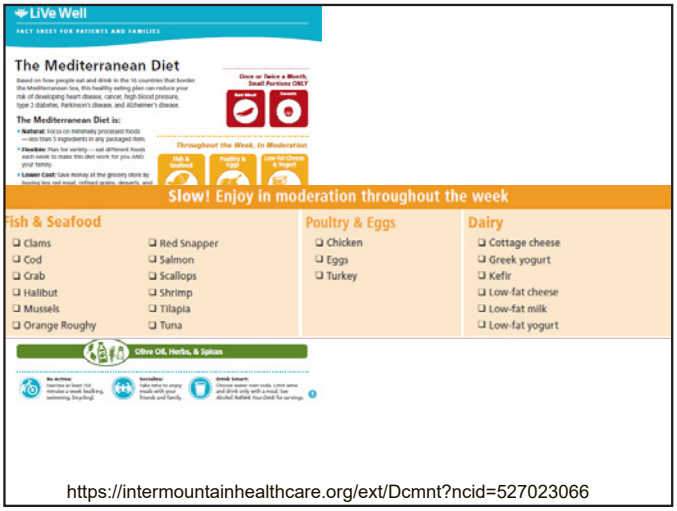


https://intermountainhealthcare.org/ext/Dcmnt?ncid=527023066

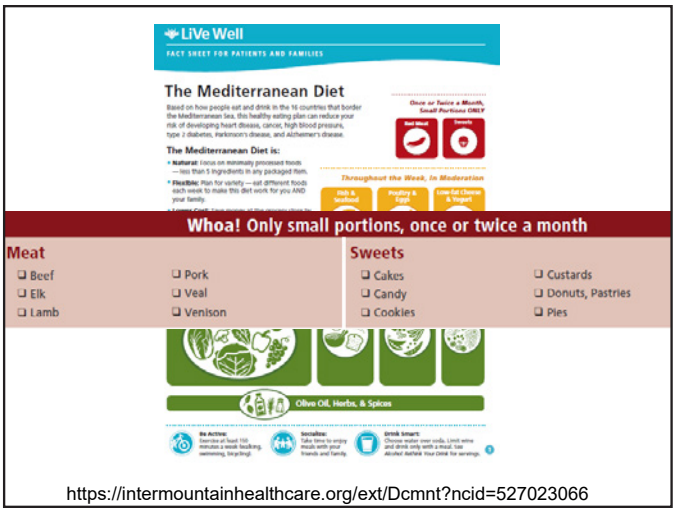


https://intermountainhealthcare.org/ext/Dcmnt?ncid=527023066

https://intermountainhealthcare.org/ext/Dcmnt?ncid=527023066



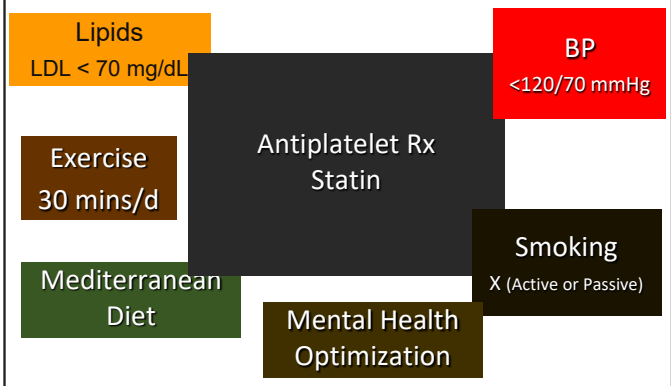
https://intermountainhealthcare.org/ext/Dcmnt?ncid=527023066



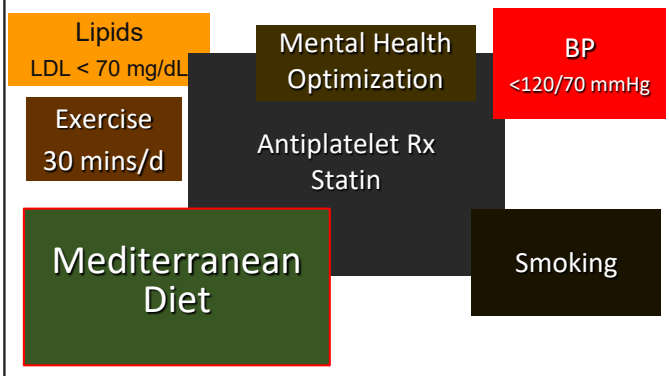
How to Locate the Intermountain Healthcare LiVeWell Mediterranean Diet Brochure

https://intermountainhealthcare.org/ext/Dcmnt?ncid=527023066

The Vasculopath:
Agendas for the Primary Care Clinician



The Atherosclerotic Vasculopath:
Agendas for the Primary Care Clinician



SELF EVALUATION

Engaging the Mediterranean Diet in the Clinical Practice Setting

1. Of the “7 metrics for healthy living” advocated by the American Heart Association, which component demonstrates the poorest performance by Americans?

a. Cholesterol
b. Blood Pressure
c. Smoking
d. Healthy Diet

2. The Lyon Heart Study was a RCT of diet vs placebo post MI. After 5 years, compared to control, the effect of Mediterranean diet on subsequent survival without future MI was

a. No different than control
b. Statistically significantly > control but of questionable clinical relevance
c. Only effective in subgroups with poor diet at baseline
d. Markedly superior to control

3. After the remarkable success in reducing CV endpoints in the Lyon Heart Study, which blood chemistry element improvement was suspected of being potentially causal?

a. Cholesterol
b. Triglycerides
c. Linoleic acid
d. ApoB

4. A large trial (n > 7,000) of the Mediterranean diet for PRIMARY PREVENTION of CVD was performed and reported in the New England Journal of Medicine in 2013. The primary composite outcome of the trial (MI, Stroke, or CV Death) at 5 years was, compared to control:

a. Unchanged
b. Statistically significantly increased by ±10%
c. Statistically significantly decreased by ±30%
d. Statistically significantly decreased by over 50%

5. In a 4 year PREDIMED substudy of the Mediterranean Diet versus control upon cognitive function

a. Cognitive function decline was less with the Mediterranean diet than control
b. There was no difference in cognitive decline between Mediterranean diet and control
c. Cognitive decline was worse with Mediterranean diet than control

Answer Key: 1. D, 2. D, 3. C, 4. C, 5. A

OJMGROUP
Integrity. Collaboration. Expertise.

CORPORATE HEADQUARTERS
8044 MONTGOMERY ROAD, SUITE 440
CINCINNATI, OH 45236
877.656.4362 866.913.4911 WWW.OJMGROUP.COM
Other offices in Arizona and Florida

Planning for Retirement After the Consolidated Appropriations Act of 2023

Carole C. Foos, CPA

Topics we will Cover

- New Required Minimum Distribution (RMD) Rules
- Catch-Up Contributions for High Income Earners
- Tax Diversification Strategies
- Using Non-Qualified and Defined Benefit Plans in Retirement Planning

OJMGROUP

Changes to Required Minimum Distributions

- Previous age for RMD = 72
- New law increases
  - 73 for those born 1951-1959
  - 75 for those born 1960 and later
- Qualified Charitable Distribution stays at 70 ½
- RMD penalty drops to 25% (from 50%)
- Eliminates RMD's for Roth 401(k) and 403(b) – same as Roth IRA beginning 2024

OJMGROUP

How to Plan for RMD Changes

- Individuals with more $$ than they will need in retirement account will need to decide: take RMD's earlier or wait until required?
  - Spread out tax burden, potentially maintain a lower tax bracket
  - Reduce future RMD's to minimize impact on future tax
  - Increase flexibility in financial planning (pay off debt, charitable endeavors, add to after-tax investment accounts)
  - Estate planning – heirs may be in a higher tax bracket than you will be in retirement
  - Hedge against future tax changes and investment performance potentially increase diversity
  - Fund charitable giving

OJMGROUP

How to Plan for RMD Changes

- Acceleration of tax liability - timing as well as potentially higher tax bracket
- Impact on Retirement Income – reduction in account balance diminishes future availability
- Loss of tax-deferred growth
- Loss of asset protection
- Reduced inheritance for beneficiaries
- Potential to miss investment opportunities

OJMGROUP

Catch-Up Contributions for High Income Earners

- Beginning 2026 (IRS Notice 2023-62) if wages from sponsoring employer exceeded $145,000 previous year , catch-up must be to Roth for 401(k), 403(b), governmental 457(b)
- May not apply if job change
- Does not apply to IRA catch-up including SIMPLE IRA
- Limit applies based on FICA wages (somewhat unclear regarding SE income)
- This means catch-up will be made with after tax dollars
- If plan does not have Roth option and there are participants in this category, no one will be allowed catch up contributions
- Beginning after 2024, catch-ups indexed for inflation

OJMGROUP

Catch-Up Contribution Example

- Dr Jones, age 55, earns $300,000 in W2 income from ABC Orthopedics in 2025
- Wants to maximize 401(k) salary deferrals and a catch-up in 2026
- Assuming same limits as 2024, she can defer $23,000 into traditional 401(k) in 2026 but $7,500 catch-up must be to Roth
- $23k pre-tax; $7,500 after-tax
- If she changes jobs and works for XYZ Ortho in 2026, can presumably make all with pre-tax dollars

OJMGROUP

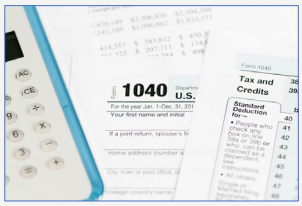
Additional Catch-Up ages 60-63

- Beginning in 2025, those aged 60-63 can make increased catch-up contributions
- Applicable to 401(k)'s and similar plans as well as SIMPLE IRA's
- For qualified plans, additional limit will be > of 150% of regular catch-up amount for the year OR $10,000 (150% of current catch-up = $11,250 so limit would be $11,250)
- For SIMPLE plans, additional limit is greater of 150% of regular catch-up OR $5,000
- Catch-up amounts indexed for inflation beginning in 2024

OJMGROUP

Tax Diversification Strategies

- Maintain a mix of tax-deferred, tax-free and taxable accounts
- Tax-Deferred includes traditional 401(k) and 403(b) and IRA's
- Tax-Free includes Roth 401(k), Roth IRA and permanent life insurance
- Taxable accounts include after-tax brokerage accounts and real estate investments



OJMGROUP

Tax Diversification Strategies

- Tax-Deferred
  - Pre-tax contributions reduce current tax liability
  - Contribute in years when in higher tax brackets
  - Manage withdrawals in retirement to minimize tax / control tax bracket
- Tax-Free
  - After-tax contributions but tax-free growth and distributions
  - Contribute in years of lower tax brackets
  - Contribute at least partially for diversification / tax hedge
- Taxable
  - After-tax contributions / investments
  - Subject to current rates on income and gains
  - Flexibility in terms of liquidity and penalty-free withdrawals
  - Can utilize tax loss harvesting and LTCG treatment

OJMGROUP

Tax Diversification

ORDINARY INCOME	CAPITAL GAINS	TAX FREE
37.0% FEDERAL + 6.6% STATE + 3.8% ACA (47.4% TAX)	20% FEDERAL + 6.6% STATE + 3.8% ACA (30.4% TAX)	(0% TAX)
WITHDRAWAL: $100,000	WITHDRAWAL: $100,000	WITHDRAWAL: $100,000
LESS TAX: $47,400	LESS TAX: $30,400	LESS TAX: $0
NET AFTER TAX: $52,600	NET AFTER TAX: $69,600	NET AFTER TAX: $100,000

OJMGROUP

Addition of Non-Qualified and DB Plans

- Non-Qualified Plans
  - In addition to qualified plan
  - Higher contribution limits
  - Flexibility on who participates and to what extent
  - Flexibility on timing of distributions
- Defined Benefit Plans
  - In addition to defined contribution plan
  - Specific retirement benefit based on years of service and compensation
  - Fully funded by employer

OJMGROUP

Non-Qualified Plans

- Generally offered to key executives / owners
- Participation at discretion of employer
- Often specific benefit amount or formula-based income stream
- Employer contributions (depending on type of plan and where assets held, could be subject to creditors of employer)
- Vesting schedules permitted
- Contributions can be greater as long as reasonable compensation
- Tax implications for practices as contributions likely don't provide tax deduction until benefit paid

OJMGROUP

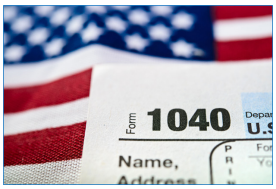
Defined Benefit Plans

- Actuarially determined contribution amount
- May be able to contribute $200k plus annually
- Tax deductible contributions, tax-deferred growth
- Asset protection
- Employee costs can be high
- Penalties for underfunding or termination
- Can be a tool for attracting / retaining talent
- Distributions taxed at ordinary income tax rates

OJMGROUP

Miscellaneous Provisions

- Employer non-forfeitable matching and non-elective contributions can be made to Roth's effective immediately
- SIMPLE and SEP contributions can be made to Roth's starting in 2023



OJMGROUP

529 to Roth IRA Transfer

- Beginning 2024, 529 plan balances can be transferred to Roth IRA's
  - Roth account must be in name of 529 beneficiary
  - 529 plan must have been maintained at least 15 years
  - No transfer of contributions made within last 5 years and their earnings
  - Lifetime max transfer $35,000
  - Annual transfer limit = IRA contribution limit for that year less contributions already made
  - Beneficiary will need to have earned income to contribute
  - Change beneficiary restart 15 year????

OJMGROUP

Employer Provisions

- Beginning 2024 employee student loan payments treated as elective deferrals for purpose of matching
  - Based on employee certification of payments
  - Vesting and matching rules must be same as if loan payment were employee deferral
- New Starter 401(k) for businesses that don't currently offer retirement plans (2024)
  - Would include automatic enrollment
  - Contribution limits = IRA contribution limits
- New plans required to have auto enrollment
- Part-time employees can participate if age 21 or completed 12 months and >1,000 hours OR 2 12-month periods of >500 hours

OJMGROUP

Conclusion

- Understand changes and how they affect your current plans and your future funding
- Work with your financial advisor to implement a tailored strategy in order to optimize your retirement readiness
- Key to secure retirement is informed decision making and proactive financial planning

OJMGROUP

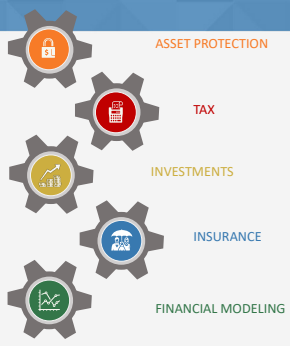
PERSONAL
WEALTH
PLANNING

DIAGNOSTIC vs. TREATMENT

ADVICE & EXPERTISE
FOR A FLAT FEE

BUILDING A RELATIONSHIP

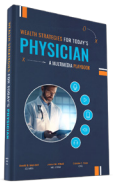
OJMGROUP



Wealth Strategies for Today's Physician: A Multi-Media Playbook

- New content from OJM: Our first book since 2020!
- Co-authored by OJM Group partners
- Innovative multi-media format includes more than 90 links to videos and podcast episodes that offer unique perspectives and real-world examples
- Videos to be periodically updated by OJM so that the Playbook remains current over time
- Crafted in six informative Strategies that can help physicians protect assets, reduce taxes, invest wisely and build wealth for retirement
- Bonus Strategy for medical practice owners and *doctorpreneurs*

Scan the QR Code to get a Free Copy!



OJMGROUP

Learn More

Contact the Presenter

Carole C. Foos, CPA
OJM Group Partner
877.656.4362
carole@ojmgroup.com

Schedule a Free Consultation

OJMGROUP

Disclosure

OJM Group, LLC. ("OJM") is an SEC registered investment adviser with its principal place of practice in the State of Ohio. SEC registration does not constitute an endorsement of OJM by the SEC nor does it indicate that OJM has attained a particular level of skill or ability. OJM and its representatives are in compliance with the current notice filing and registration requirements imposed upon registered investment advisers by those states in which OJM maintains clients. OJM may only transact practice in those states in which it is registered or qualifies for an exemption or exclusion from registration requirements. For information pertaining to the registration status of OJM, please contact OJM or refer to the Investment Adviser Public Disclosure web site www.adviserinfo.sec.gov.

For additional information about OJM, including fees and services, send for our disclosure brochure as set forth on Form ADV using the contact information herein. Please read the disclosure statement carefully before you invest or send money.

This presentation contains general information that is not suitable for everyone. The information contained herein should not be construed as personalized legal or tax advice, or as a recommendation of any particular security or strategy. There is no guarantee that the views and opinions expressed in this article will be appropriate for your particular circumstances. Tax law changes frequently, accordingly, Information presented herein is subject to change without notice. You should seek professional tax and legal advice before implementing any strategy discussed herein.

OJMGROUP

SELF EVALUATION

Planning for Retirement After the Consolidated Appropriations Act of 2023

1. The age for required minimum distributions for someone born in 1958 is:

a. 70.5
b. 72
c. 73
d. 75

2. One benefit of taking distributions before required age is:

a. Delaying payment of tax
b. Spreading out tax burden to maintain a lower tax bracket
c. Maximize tax-deferred growth
d. Better asset protection outside retirement plan

3. Wage earners earning above $145,000 must make catch up contributions to A Roth account beginning in

a. 2024
b. 2025
c. 2026
d. Never

4. In 2025 workers aged 60-63 can make catch up contributions to a 401k plan of :

a. $7,500
b. Zero
c. > 150% of current catch up contribution amount or $10,000
d. > 150% of current catch up contribution amount or $5,000

5. Tax Deferred accounts generally have:

a. After tax contributions and tax-free growth and distributions
b. After-tax contributions and capital gains rates on distributions
c. Pre-tax contributions and ordinary taxes when distributed
d. After-tax contributions and ordinary tax when distributed

6. T/F - A non-qualified plan must cover all employees in the same manner without discrimination.

7. T/F - A 529 plan can be rolled over to a Roth IRA of the same beneficiary if the account has been maintained for at least 15 years.

Answer Key: 1. C, 2. B, 3. C, 4. C, 5. C, 6. F, 7. T

The New Age of Sleep Medicine

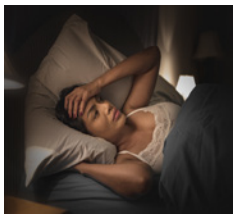
Contents

The Growing Demand for Sleep Health

Undiagnosed Sleep Disorders

80-85% of people with Obstructive Sleep Apnea are undiagnosed

Only 13% of those with insomnia will ever see a health care provider



Watson, et al. JCSM 2019

Consumer Health Technologies

"Quantifiable Self"

Fitness tracking

Sleep tracking

Calorie tracking

Moods

Oxygen and glucose levels

Prevalence of Consumer Sleep Trackers

350 million wearable devices sold worldwide in 2020

25% of US adults have monitored their sleep with a wearable device or an "app"

Liu, 2019; Syngene Research, 2019; Moar, 2018; Kunst, 2017

Consumer Sleep Trackers—Options

Smart Watches

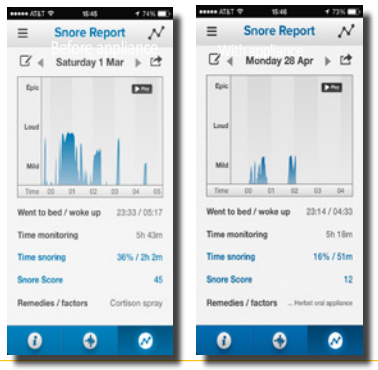
Smart Rings

Smart Mattresses

Smart Pajamas

Snore Sensors

Liu, 2019; Syngene Research, 2019; Moar, 2018; Kunst, 2017



Consumer Sleep Trackers

Advantages

- Lower cost
- Daily data
- Wireless and Blue tooth connections
- Sensors—autonomic (heart rate or HRV), sound, full body movement

Chinoy, et al. 2021; Grandner, et al. 2021

How Consumer Sleep Trackers Compare

- Most studies were industry funded
- Most investigators were industry funded
- Device algorithms considered intellectual property and rarely disclosed

Chinoy, et al. 2021; Grandner, et al. 2021

Independent Study on CSTs

Stone, et al. Nature and Sci of Sleep 2020; 12:821-42

- Using 8 different sleep trackers
- Data tracking over 98 nights
- Data compared to HST (Sleep Profiler)

Independent Study on CSTs

Stone, et al. Nature and Sci of Sleep 2020; 12:821-42

Table 2 Sleep Assessment Variables by Device

Device	TST	TWT	SE	Light Time	DeepTime	REM Time
Beddit	Yes	Yes	Yes	No	No	No
Fatigue Science	Yes	Yes	Yes	No	No	No
Fitbit	Yes	Yes	Yes	Yes	Yes	Yes
Garmin	Yes	Yes	Yes	Yes	Yes	Yes
Oura	Yes	Yes	Yes	Yes	Yes	Yes
Polar	Yes	Yes	Yes	No	No	No
Sleep++	Yes	No	No	No	No	No
SleepWatch	Yes	No	No	No	No	No
WHOOP	Yes	Yes	Yes	Yes	Yes	Yes

Independent Study on CSTs

Stone, et al. Nature and Sci of Sleep 2020; 12:821-42

Conclusions:

- Oura and Fitbit most accurate for non-staging sleep metrics (TST, TWT, SE)
- Whoop accurate for TST but not TWT

Independent Study on CSTs

Stone, et al. Nature and Sci of Sleep 2020; 12:821-42

Conclusions:

No devices accurately reported sleep stages

Whoop most accurate in reporting light and deep sleep duration

Tracker performance deteriorates with sleep fragmentation.

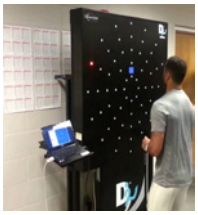
i.e. people with sleep disorders.

Sleep Supplements

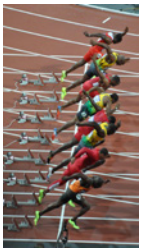
- Melatonin
- Magnesium
- CBD
- THC
- Valerian root
- Lavender
- Passionflower
- Glycine
- And many, many more…

Sleep and Athletic Performance

- Reaction Time Before and After Sleep Training



The Game Changing Value of Better Sleep

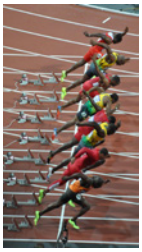


Reaction Times

Errors

(Wikimedia Commons)

The Game Changing Value of Better Sleep

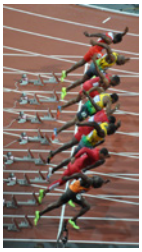


Reaction Times ↓

Errors

(Wikimedia Commons)

The Game Changing Value of Better Sleep



Reaction Times ↓

Errors ↓

(Wikimedia Commons)

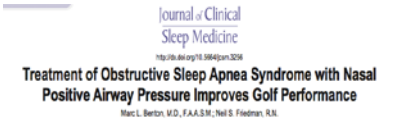
The Game Changing Value of Better Sleep

(Wikimedia Commons)

Maintain Core Body Temperature (avoid hyperthermia)

Sustained peak cardiac output

Sustained peak mental performance



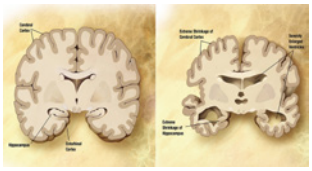
Controlled Study Using Golfers recently diagnosed with OSA

- Correction with CPAP resulted in a mean drop in handicap from 12.4 to 11.0
  - Greater response amongst skilled golfers: 9.2 to 6.3

(Benton et al 2013)

Sleep and Alzheimer's Disease

- Clinical trial data
  - Cross sectional as well as longitudinal studies (average of 10 year follow up) showed that sleep disturbances associated with dementia in general and Alzheimer's disease in particular.



Wikimedia Commons

(Bubu et al 2017, Shi et al 2018, Livingston et al 2020)

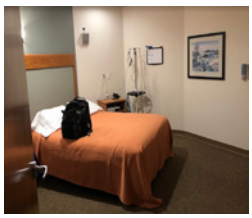
Glymphatic Clearance

(Wikimedia Commons)

(Xie 2013, Lucke-Wold et al 2015)

The Limitations of Conventional Sleep Medicine

Brick and Mortar Sleep Centers

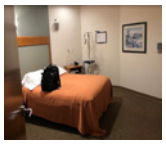


M Health Fairview Sleep Center-Edina

Brick and mortar Sleep Centers

- 2,500 sleep centers in the United States
  - Maybe perform 2 million in-lab sleep studies a year.
  - But there are 40+ million people right now with sleep apnea.
  - + sleep disorders that need laboratory testing
    - REM sleep Behavior Disorder-4 million patients
    - Narcolepsy and other hypersomnias-500,000

M Health Fairview Sleep Center-Edina



In lab sleep studies

- Polysomnography
  - EEG
  - EOG
  - Chin EMG
  - Limb EMG
  - EKG
  - Ventilatory effort
  - O2 saturation.
  - Airflow

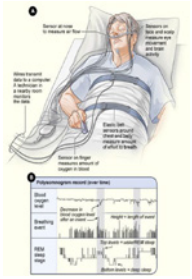
Resistance to sleep testing

Challenges:

-Unfamiliar sleep environment

-Expensive

-Time consuming for patient/staff



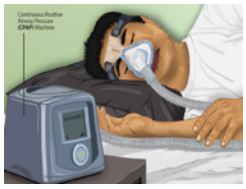
Resistance to CPAP

Continuous Positive Airway Pressure:

-Seals over nose/mouth

-Pneumatically splints the airway open

-50% long term success rate



New Approaches for the Management of Sleep Disorders: Sleep Apnea

Home Sleep Apnea Testing

Home Sleep Apnea Testing (HSAT)

Acceptable alternative to PSG for diagnosing OSA for patients with high pre-test probability

Less night-to-night variability

Better patient acceptance

Lower cost

Home Sleep Apnea Testing (HSAT)

Watch PAT

More Treatment Options

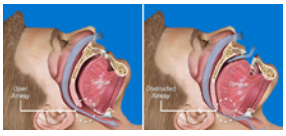
What is Obstructive Sleep Apnea (OSA)?

- Caused by a decrease in upper airway size and patency during sleep
- Hypoxemia
- Repeated arousals from sleep
- Hyperadrenergic
- Apnea - cessation of airflow
  - Hypopnea - decrease in airflow

Dempsey JA, Xie A, Patz DS, Wang D. Physiology in Medicine: Obstructive sleep apnea pathogenesis and treatment – considerations beyond airway anatomy. *J. Appl Physiol* 116: 1, 2014.

OSA Prevalence

- 40-70 million Americans
  - OSA is our most common chronic, non-communicable disease

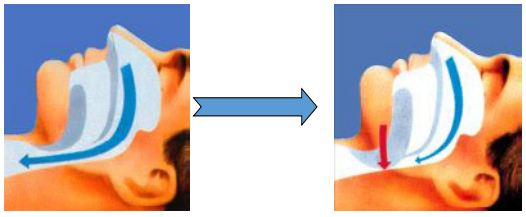


(Wikimedia Commons)

1. Price of Fatigue Report 2011 Source: McKinsey & Company analysis; Harvard Medical School, 2010 Young et al j Am Med Ass 2004
2. Paul E. Peppard, Terry Young, Jodi H. Barnet, Mari Palta, Erika W. Hagen, and Khin Mae Hla. *Am J Epidemiol.* 2013;177(9):1006-1014

Continuum of Obstruction

Normal Snorers Mild **OSA** Moderate OSA Severe **OSA**



Apnea Hypopnea Index-AHI

	AHI
NORMAL	< 5
MILD	5 - 15
MODERATE	15 - 30
SEVERE	> 30

Apnea Hypopnea Index-AHI

	AHI
NORMAL	< 5
MILD	5 - 15
MODERATE	15 - 30
SEVERE	> 30

Average AHI for adults > 40 yo

⬇

(Young et al 2002)

Apnea Hypopnea Index-AHI

	AHI
NORMAL	< 5
MILD	5 - 15
MODERATE	15 - 30
SEVERE	> 30

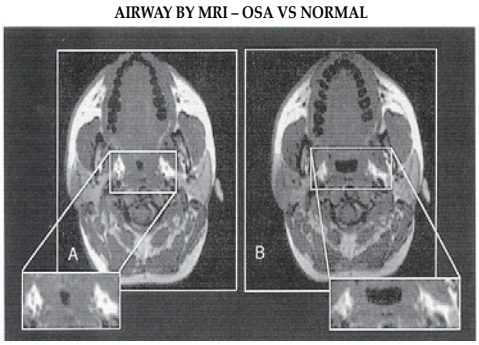
Average AHI for adults > 40 yo

⬇

8.8

(Young et al 2002)

OSA Airway



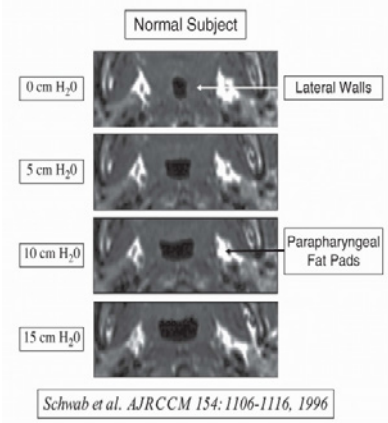
OSA-mechanical problem in need of a mechanical solution

- Positive Airway Pressure (PAP) Therapy
  - Seals over the nose or mouth/nose.
  - Acts as a pneumatic splint to the upper airway.
- Adherence challenges
  - Works very well about 50% of the time.

(Wikimedia Commons)

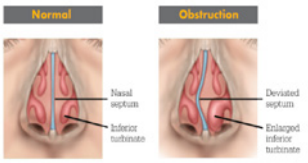
(Gottlieb et al 2020)

CPAP Mechanism of Action



OSA-what to do when PAP is not working

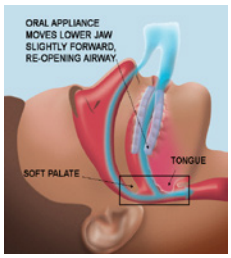
- Evaluate for possible nasal obstruction
  - Nasal endoscopy
- Relieve nasal obstruction-three benefits
  - Directly decreases AHI
  - Improve PAP and other OSA treatmen adherence
  - Improved nasal breathing during the day



(Wikimedia Commons)

(Gottlieb et al 2020)

Oral Appliance Therapy



(Wikimedia Commons)

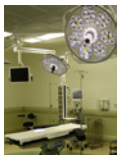
Cardiovascular Benefits of Oral Appliance Therapy

- Improvement in blood pressure, endothelial function and left ventricular function are proven in several independent studies.

Gilles Van Haesendonck, BSc; Marijke Dieltjens, MBS, et al. *JDSM.* Cardiovascular Benefits of Oral Appliance Therapy in Obstructive Sleep Apnea: A Systematic Review. Vol. 2, No. 1 2015, 9-14.

Surgical treatments for OSA

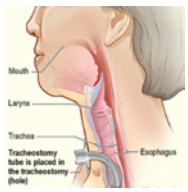
- First published treatment for OSA was surgical



(Wikimedia Commons)

Surgical treatments for OSA

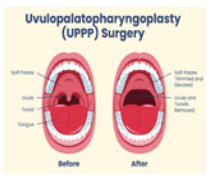
- First published treatment for OSA was surgical
  - Tracheostomy

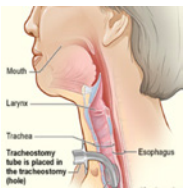


(Wikimedia Commons)

Surgical treatments for OSA

- First published treatment for OSA was surgical
  - Tracheostomy
- Follow up procedures
  - Uvulopalatopharyngoplasty
  - Maxillomandibular advancement

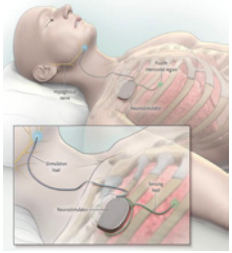




(Wikimedia Commons)

Hypoglossal Nerve Stimulation

- Stimulation of the hypoglossal nerve (CN XII).
  - Permanent pacemaker for the tongue
  - Moderate to Severe OSA
  - BMI < 40
  - Approximately 70% reduction of AHI.
  - Inspire and multiple devices in development.



Inspire System

(Gottlieb et al 2020)

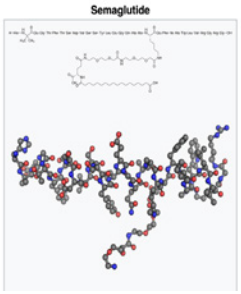
Weight Loss and OSA

- 70% of OSA patients are obese (BMI > 30)
- Bariatric surgery significantly reduces AHI
  - Bariatric surgery can result in 40-60% reduction in AHI.
- Glucagon-like Peptide-1 Receptor Agonists (GLP-1s)
  - Semiglutide, tirzepatide, exenatide,
  - increase pancreatic release of insulin
  - Also activate GLP 1 receptors in Central Nervous System
  - Promotes satiety driving weight loss

Am J Med2009 Jun;122(6):535-42 Effects of surgical weight loss on measures of obstructive sleep apnea: a meta-analysis. Greenburg DL et al

GLP-1's and OSA

- Approximately 3% drop in AHI for each 1% drop in BMI
  - BMI drop typically 10-20% so can expect 30-60% drop in AHI.
- Complications
  - > 50% intolerance rate
  - Loss of lean body tissue (approximately 40% of total weight loss)
    - Muscle/tendon
    - Bone
    - Recommend following with DEXA scans
    - ? Effect upon upper airway muscle tone.



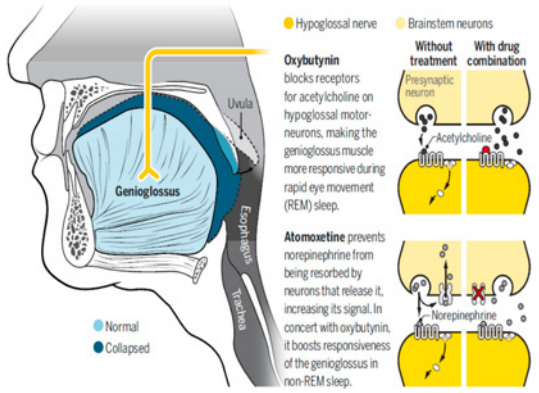
(Wikimedia Commons)

(McCrimmon et al 2020, Wilding et al 2021, Prime Therapeutics 2023)

Therapy Targeting Muscle Tone

- Medications targeting upper airway dilating musculature
  - Many OSA patients have weak upper airways.
- Atomoxetine and Oxybutynin combination therapy
  - Both agents have been FDA approved for decades
  - Short term studies demonstrate 50-60% reduction in AHI
  - 63% reduction in AHI

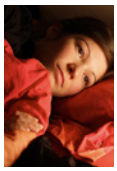
(Montemurro et al 2019, Aishah et al 2023)



New Approaches for the Management of Sleep Disorders: Insomnia

Insomnia-a conditioned response

- Trying to sleep becomes an insomnia trap
  - Despite feeling tired the act of climbing into bed is an alerting not sedating response. Psychophysiological Insomnia develops as a conditioned response.
- Feel tired and sleepy outside of the bedroom
  - Alert once an insomniac climb into bed.
  - May sleep better in hotel's and out of the typical sleeping environment.

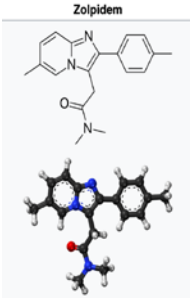


(Wikimedia Commons)

(Mitchel et al 2019)

CNS hypervigilant Insomnia Treatment-Pharmacotherapies

- Sedating antidepressants
  - Trazodone, quetiapine, mirtazapine
  - Lack of efficacy data
- Benzodiazepines
  - Temazepam, diazepam
  - Morning sedation, balance difficulties, cognitive impairment, dependence
- Benzodiazepine receptor agonists
  - Zolpidem, eszopiclone
  - Morning sedation, balance difficulties, cognitive impairment, dependence



(Wikimedia Commons)

CNS hypervigilant Insomnia Treatment-Pharmacotherapies

- Gold Standard Therapy
  - Cognitive Behavioral Therapy for Insomnia (CBT-I)
    - Best chance of curing insomnia
    - Administered by a licensed psychologist
    - Unfortunately, at most only 1% of patients who could benefit from CBT-I see an CBT-I specialist.

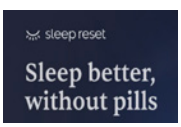
(Wikimedia Commons)

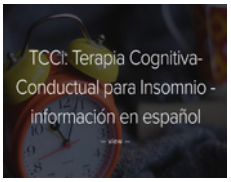
(Mitchel et al 2019)

Population Delivery of Cognitive Behavioral Therapy

Tools for wider CBT-I delivery

- Online tools, both synchronous and asynchronous, provide the best opportunity to deliver CBT-I to a large audience across language barriers.





Cognitive Behavioral Therapy for Insomnia

- Two Rules:

Cognitive Behavioral Therapy for Insomnia

- Two Rules:
  - Get out of bed if you are not sleeping.

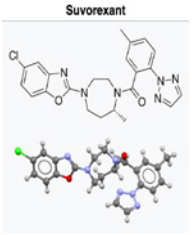
Cognitive Behavioral Therapy for Insomnia

- Two Rules:
  - Get out of bed if you are not sleeping.
  - Don't sleep outside of the bedroom.

Insomnia-
New Pharmacotherapies

Insomnia Treatment-Pharmacotherapies

- Orexin antagonists
  - Sleep promoting agents
    - Block the wake promoting neurotransmitter orexin
  - Morning sedation, imbalance
  - Does not suppress respiration
  - May help prevent neurodegenerative pathology

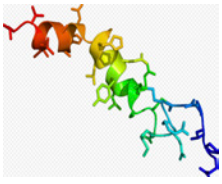


(Wikimedia Commons)

(Mitchel et al 2019)

Orexin as a possible driver of neurodegeneration

- Orexin: wake promoting neuropeptide
  - Increased orexin levels are associated with decreased sleep and propagates the Alzheimer's disease pathological cascade of both tau based neurofibrillary tangles and insoluble beta amyloid-beta (Aβ) plaques.
  - Among patients with AD, CSF orexin levels increase in tandem with both sleep disruption and the clinical progression of dementia.



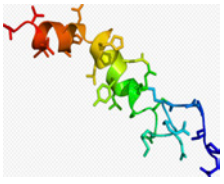
Orexin A

(Wikimedia Commons)

(Kang et al 2009, Liguori et al 2014, Deuschle et al 2014, Osorio et al 2016, Gao et al 2021)

Orexin as a possible driver of neurodegeneration

- Elderly patients with Narcolepsy Type 1, who are orexin deficient, have a lower amyloid burden as measured by PET and a delayed appearance of amyloid plaques.



Orexin A

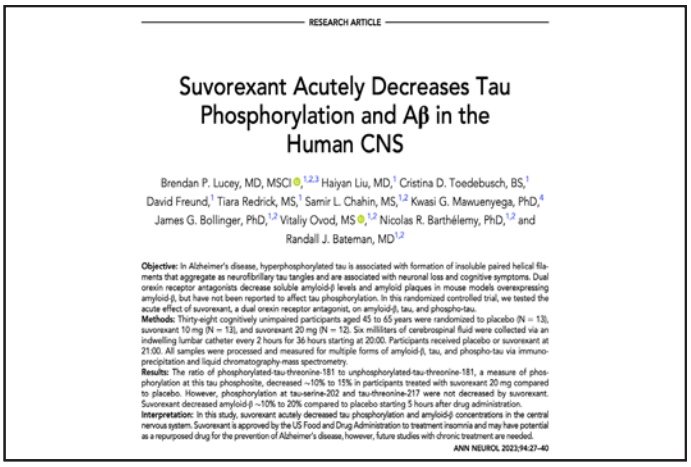
(Wikimedia Commons)

(Ma et al 2016, Gabelle et al 2018)

Can orexin blockers prevent dementia

- These findings suggest that the treatment of insomnia, in particular with orexin blocking agents, might be a unique opportunity to delay, halt or potentially reverse AD pathology.
- FDA approved agents
  - Suvorexant
  - Lemborexant
  - Daridorexant

(Gao et al 2021)



RESEARCH ARTICLE

Suvorexant Acutely Decreases Tau Phosphorylation and Aβ in the Human CNS

Brendan P. Lucey, MD, MSCI,[1,2,3] Haiyan Liu, MD,[1] Cristina D. Toedebusch, BS,[1] David Freund,[1] Tiara Redrick, MS,[1] Samir L. Chahin, MS,[1,2] Kwasi G. Mawuenyega, PhD,[4] James G. Bollinger, PhD,[1,2] Vitaliy Ovod, MS,[1,2] Nicolas R. Barthélemy, PhD,[1,2] and Randall J. Bateman, MD[1,2]

Objective: In Alzheimer's disease, hyperphosphorylated tau is associated with formation of insoluble paired helical filaments that aggregate as neurofibrillary tau tangles and are associated with neuronal loss and cognitive symptoms. Dual orexin receptor antagonists decrease soluble amyloid-β levels and amyloid plaques in mouse models overexpressing amyloid-β, but have not been reported to affect tau phosphorylation. In this randomized controlled trial, we tested the acute effect of suvorexant, a dual orexin receptor antagonist, on amyloid-β, tau, and phospho-tau.

Methods: Thirty-eight cognitively unimpaired participants aged 45 to 65 years were randomized to placebo (N = 13), suvorexant 10 mg (N = 13), and suvorexant 20 mg (N = 12). Six milliliters of cerebrospinal fluid were collected via an indwelling lumbar catheter every 2 hours for 36 hours starting at 20:00. Participants received placebo or suvorexant at 21:00. All samples were processed and measured for multiple forms of amyloid-β, tau, and phospho-tau via immunoprecipitation and liquid chromatography-mass spectrometry.

Results: The ratio of phosphorylated-tau-threonine-181 to unphosphorylated-tau-threonine-181, a measure of phosphorylation at this tau phosphosite, decreased ~10% to 15% in participants treated with suvorexant 20 mg compared to placebo. However, phosphorylation at tau-serine-202 and tau-threonine-217 were not decreased by suvorexant. Suvorexant decreased amyloid-β ~10% to 20% compared to placebo starting 5 hours after drug administration.

Interpretation: In this study, suvorexant acutely decreased tau phosphorylation and amyloid-β concentrations in the central nervous system. Suvorexant is approved by the US Food and Drug Administration to treatment insomnia and may have potential as a repurposed drug for the prevention of Alzheimer's disease, however, future studies with chronic treatment are needed.

ANN NEUROL 2023;94:27–40

Orexin antagonism as possible neuroprotection

- Suvorexant: Acutely decreases tau phosphorylation and Ab in the CSF of healthy middle aged human adults.
- Clinical trials are currently ongoing with several orexin blocking medications.

(Lucey et al 2023)

SELF EVALUATION

The New Age of Sleep Medicine

True/False

1. The majority of patients with Obstructive Sleep Apnea in the United States have been diagnosed

2. Improved sleep leads to fewer errors and longer reaction times.

3. Sleep deprivation leads to hypothermia with sustained aerobic exercise

4. Addressing sleep apnea could reasonable be expected to improve a patient's golf game.

5. Glymphatic flow removing metabolic wastes from the brain peaks during NREM sleep.

6. Long term CPAP adherence rates range from 80-90%.

7. Once an OSA patient fails CPAP there are no other treatment options.

8. Orexin antagonists represent a new approach for treating insomnia.

Answer Key: 1. F, 2. F, 3. F, 4. T, 5. T, 6. F, 7. F, 8. T

EISNERAMPER
733 Third Avenue | New York, NY 10017 | 212.949.8700

Practice Optimization for Sale, Merger, or Continued Independence

Bert Orlov, MBA

Developing an Optimal Deal - Three-Step Framework

- With consolidation in the Physician Practice market moving ahead rapidly, a strategic/proactive approach is essential
- The three-step framework for evaluating and then conducting a PE transaction, employment by Hospital/Network or M&A with other MD groups
- Even if strategy does NOT focus on a deal, the Phase I: Preparation has tremendous value

I: Preparation → II: Negotiation → III: Implementation

Private Equity: Overview

Industry Fundamentals

- Private Sector
  - Limited regulation
  - Multiple players
- PE Firms (Investors) seek growth, as money in the bank cannot generate profit
- Acquisition
  - Substantial equity investment
  - Payments to sellers may include cash and shares in PE entity
- Profitability Focus
  - Platform/Roll-up
  - Scrape
  - Second Bite
  - Unicorns

Typical Deal Structure

- Purchase
  - Valuation (EBITDA and QoE) times market multiple
  - Price
    - Cash and Terms
    - Stock in the PE entity itself, offering potential growth opportunity
- Ongoing Compensation
  - Productivity
  - Scrape / Profits to PE
- Management Services
- Profitability Enhancement

Private Equity: Growth Share Matrix

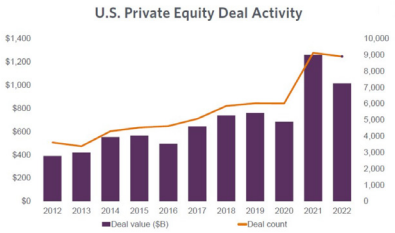
Source: BCG Matrix - Overview, Four Quadrants and Diagram

Private Equity: Deal Trends

- Private Equity deal activity has increased between 2012 and 2021
- After reaching its peak in 2021 activity decreased likely because of after-effects of COVID. Anecdotally, deal volume has grown in 2024
- PE firms are showing increasing interest in healthcare (especially physician practices)

2023 Healthcare Transactions

- 1135 unique deals
  - 148 buyouts
  - 259 growth/expansion investments
  - 728 add-on acquisitions



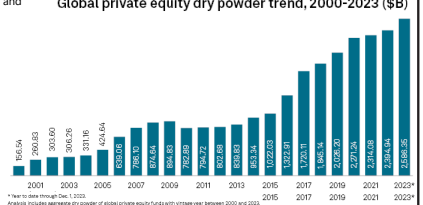
Sources: 1) Private Equity Report: 2022 Trends & 2023 Outlook | Cherry Bekaert (cbh.com) **2)** PESP_report_2023-Healthcare-Acquisitions_March-2024.pdf (pestakeholder.org)

Private Equity: "Dry Powder"

- **"Dry Powder" stands at an all time high at $2.5 trillion** – according to S&P Global
- Approximately $100 Billion is ear-marked for investment in the Healthcare sector

- PE investors seek to complement existing platform investments via acquisitions that increase scale and efficiencies in the following sectors:
  - Physician Practices
  - Healthcare Information Technology
  - BioPharma
  - Home Healthcare
  - Behavioral Health

Global private equity dry powder trend, 2000-2023 ($B)



* Year to date through Dec. 1, 2023.
Analysis includes aggregate dry powder of global private equity funds with vintage year between 2000 and 2023.
Dry powder data is supplemented by Preqin.
Source: S&P Global Market Intelligence.
© 2023 S&P Global.

Hospital Partner

- According to Kaufman Hall, Q1 2024 showed a significant uptick in M&A activity and represents the strongest Q1 since 2020
- A key highlight of the quarter was the diversity of transactions, showcasing a variety of trends that have been shaping the health care landscape:
  - Cross-Market Transactions
  - Community Health Systems seek larger partners
  - Portfolio realignment
  - A new partnership model
  - Academic health systems build community networks
- Since 2012, direct hospital employment of physicians has nearly doubled (as a % of physician workforce)

2024 Q1

Practice to Practice: Overview

- According to the American Medical Association, In 2023, the U.S. physician group market size was estimated at $325 billion and expected to grow to $461 billion by 2030
  - Initiatives to improve revenue to physician groups
  - Shift towards value-based care
  - Growing trend of solo practitioners joining larger physician groups
- Practice Ownership (2012-2022)
  - The share of physicians working in private practices fell from 60.1% to 46.7%.
  - The share of physicians working in hospitals as direct employees or contractors increased from 5.6% to 9.6%
- Practice Size (2012-2022)
  - The share of physicians in small practices (10 or fewer physicians) shrank from 61.4 % to 51.8% between 2012 and 2022
  - Large practices (50 physicians or more) grew from 12.2% to 18.3%
  - Midsized practices (those with 11 – 49 physicians) remained stable
- Employment Status (2012-2022)
  - The share of physicians who were self-employed fell by 9 percentage points from 53.2% to 44%.
  - The share of physicians who were employed grew from 41.8% to 49.7%
  - The share of physicians under the age of 45 who were self-employed fell from 44.3% to 31.7%.

Practice to Practice: Consolidation

- According to the American Medical Association, the industry has seen a redistribution of physicians from small to large practices
  - In 2012, 61.4% of physician worked in practices with 10 Physicians or less – in 2022, the % declined by 9.6% to 51.8%
- According to the American Hospital Association, an overwhelming majority (94%) of physicians think it has become more financially and administratively difficult to operate a practice.
- Threats to independent practices includes – Low reimbursement rate, declining margins/profits, staffing shortages, and more.

Distribution of physicians by practice size (number of physicians in practice)

	2012	2014	2016	2018	2020	2022
Practice size						
Fewer than 5 physicians	40.0%	40.9%[b]	37.9%[c]	35.7%[c]	33.6%	32.8%[a]
5 to 10	21.4%[c]	19.8%	19.9%	20.8%	20.0%	19.0%[a]
11 to 24	13.4%[c]	12.1%	13.3%	12.7%	11.5%	12.1%
25 to 49	7.1%	6.3%[c]	7.4%	7.6%	7.8%	7.7%
50+ physicians	12.2%	13.5%	13.8%	14.7%[a]	17.2%	18.3%[a]
Direct hospital employee/contractor [2]	5.8%[a]	7.4%	7.7%	8.5%[c]	9.7%	10.1%[a]
	100%	100%	100%	100%	100%	100%
N	3326	3388	3381	3339	3353	3328

Making a Deal: Pros and Cons

Is PE (or Hospital) acquisition or merger with other Practices a good idea for your Practice?

Potential Benefits

- Substantial financial return
- Reduction in the burden of running a practice
- Operational support
- Support to grow the practice
- State regulation may prompt faster movement

Potential Risks

- Loss of autonomy
- Less financial attractiveness for younger doctors in out-years
- Uncertainty about the future of PE

Developing an Optimal Deal - Three-Step Framework

I: Preparation

- Develop realistic understanding of the practices' value and market dynamics,
- Identify a means to increase market value.
- Ensure Shareholder/Owner agreement on strategy

II: Negotiation

- Identify potential partners and select the best choice.
- Plan for the detailed components of negotiations.
- Advance deal-making (including legal, financial, and tax review as well as proper due diligence on both sides)

III: Implementation

- Detail essential seller and buyer responsibilities
- Navigate the often-convoluted closing process.
- Facilitate the post-transition implementation for smooth transition for DDS/DMDs, patients and new Owners

Phase I: SWOT Analysis

- Evaluating the strategic position of your practice

Strengths	**Opportunities**
Weaknesses	**Threats**

Phase I: Strategy Planning—Vision Alignment

- Discuss short- and long-term goals
- Build consensus among owners (advisor supported)
- Outcomes
  - SWOT analysis to drive strategy
  - Financial projections and preliminary valuation estimate
  - Prevents wasted time if not all together or last-minute deal collapse
  - Enables selection of right partner and informs negotiation strategy
- EVEN IF NO DEAL, this EFFORT guides strategy and performance improvement

Phase I: Strategy Planning—Improvement Opportunities

Revenue Side

- Productivity
- Scheduling and Patient Flow
- Growth Strategies (including strategic collaborations, e.g., with hospitals or payors for value-based contracts
- Revenue Cycle Management Opportunity (one-time and ongoing)
- Managed Care Rates
- Referral Network and Leakage (referrals)

Operations Side

- Coding
- Staffing and Non-Labor Overhead reductions
- Patient Engagement
- Managing Value-Based Contracts
- Ancillary Service Profitability (Opportunity)
- Compliance and Risk Management

Improvement Opportunities: Productivity & Compensation

- Following assessments for productivity and capacity, equitable compensation modeling should be performed, and marketing enhancements considered

Compensation Modeling

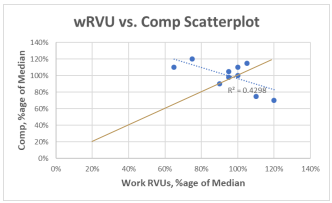
- Compensation Models should be reviewed to ensure providers production is adequately compensated relative to industry benchmarks and to prevent the risk of provider departure
- Provider incentives should be aligned with industry standards

DHS Services

- Strict rules govern the distribution of DHS (Designated Health Services, aka ancillaries)
- Non-compliance can result in civil and even criminal penalties

Provider Schedule Development

- Optimizing provider schedules through Capacity Reviews can increase productivity and patient visits



Improvement Opportunities: RCM Assessment

Revenue Cycle Management Assessments

- Net Margin
- Clean Claim Rates
- Charge Lag Time
- Collection Rates
- Collections/wRVU
- Aging Accounts Receivable & Average Days in AR
- Denial Rates & Reasons

RCM Assessment		
	2022	Benchmark
Clean Claim Rate	99%	95%
Denial Rate (First Time Pass)	14%	8%
DOS to Charge Lag Time	18 Days	4 Days
Collections	$367M	-
Collection Rate	96%	98%
Average Days in AR	38 Days	46 Days
Total AR 120+ Days	9%	12%

Improvement Opportunities: RCM Opportunity

Opportunity Area	Value Range Estimate
One Time Opportunity:	
AR Push Effort	**$0.9M - $1.6M**
Ongoing Opportunities:	
RCM Performance / Net Collection Rate	$3.7M - $9.2M
Billing Costs	Limited, costs appear in line
Subtotal Ongoing	**$3.7M – $9.2M**

Capturing Opportunity

- One-time AR push effort to collect at risk aging AR
  - Aging AR: likelihood of collections falls over time (esp. patient portion), as well as the inherent risk of "aging out"
  - Prioritization: when working AR, clear segmentation is critical
    - Size of claim
    - Age
    - Payor
    - Cause of denial
  - Potential need for SWAT team/extra staff
- Ongoing net collection rate improvement via process improvement & best practice implementations

Improvement Opportunities: RCM Assessment & Opportunity

Revenue Cycle Management Assessments

- Net Margin
- Clean Claim Rates
- Charge Lag Time
- Collection Rates
- Collections/wRVU
- Aging Accounts Receivable & Average Days in AR
- Denial Rates & Reasons

Revenue Cycle Management Opportunity

- One-time AR push effort to collect at risk aging AR
- Ongoing net collection rate improvement via process improvement & best practice implementations

RCM Assessment		
	2022	Benchmark
Clean Claim Rate	99%	95%
Denial Rate (First Time Pass)	14%	8%
DOS to Charge Lag Time	18 Days	4 Days
Collections	$367M	-
Collection Rate	96%	98%
Average Days in AR	38 Days	46 Days
Total AR 120+ Days	9%	12%

Improvement Opportunities: Managed Care Rates

Rate Reviews

- Annual reviews should be performed for reimbursement rates of payor contracts
  - Compare current rates to Medicare and across carriers
  - Focus on CPTs that drive highest volume and revenue per unit
  - Identify under-performing contracts and push negotiations
  - Do not rule out potential (threat) of contract cancellation, depending of course on your market power and importance of a given payor
- Contractual allowance reviews should be performed to ensure the validity of accounts/AR on a regular basis
  - These procedures reduce practice exposure to underpayments and improper write-offs

Improvement Opportunities: Growth and Marketing

Growth Strategies

- Create new services (specialties or ancillaries), as well as internal growth in provider capacity (assuming solid productivity)
- Develop partnerships with selected providers
  - Other practices (potential referral sources or "preferred vendors")
  - Collaborative development of ancillary services (e.g., ambulatory surgery or diagnostics)
  - Hospital relationships, including PSAs or coverage and stipend agreements
  - Engage in risk-sharing with hospitals, such as management contracts in surgical specialties
- M&A
  - Target potential partners, based on both geography and specialty, considering complementarity or market dominance
  - Conduct outreach to test interest, the explore possibilities
  - Remember that deals take time investment to develop
- Value-based plans

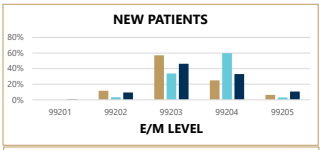
Marketing

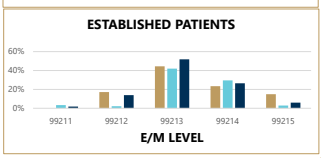
- Marketing practices should be reviewed for potential enhancement to increase patient visits
- Expand referral network
- Considering the following can all enhance your practices' marketing capability:
  - Improving advertising strategies
  - Leveraging digital marketing tools
  - Optimizing search engine presence
  - Traditional MD outreach techniques
    - Internal: prevent leakage of referrals (esp. procedures and chronic patients) to other MDs
    - External: outreach to potential referral sources, as well as speaking and publishing

Improvement Opportunities: Coding Reviews

Coding Reviews

- A smart private equity group will ask about coding
- This is a useful defensive tool for practices to consider
- Encounter documentation, coding reviews, & education should be performed annually as recommended by the OIG for an effective compliance plan
  - Ensures providers/charge posters/coders are not placing the practice at risk by over coding
  - Identifies under coding and opportunities for increased revenue





Improvement Opportunities: Staffing

Staffing

- Clinical & Administrative head count and expenses should be tracked and regularly reviewed
- Findings should be compared to industry benchmarks for a group of similar size
- This ensures the group is in line with industry expectations and identifies areas for cost savings

Clinic Staffing Summary						
Employee Type	**Total Salary**	**Total FTE**	**Adjusted FTE**	**MGMA Median Per Provider**	**Implied FTE**	**Variance**
Physician	$104,205k	190	190	-	-	-
NP/PA	$17,172k	138	69	-	-	-
Therapists	$21,308k	243	121	-	-	-
Admin Support	$30,584k	570	-	1.44	548	22
Clinical Support	$26,211k	490	-	1.28	487	3
Ancillary	$6,932k	112	-	0.32	122	-9
Other	$11,025k	151	-	-	-	-

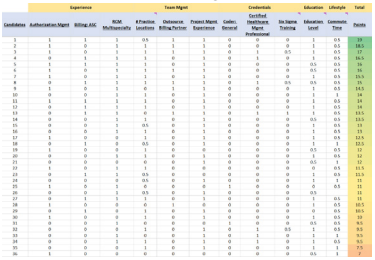
***Example:** Organization is overstaffed for Administrative Support and slightly understaffed for Ancillary Support compared to benchmarks*

Improvement Opportunities: Executive/Talent Management

Recruitment

- Identifying the right talent for an executive team or adding new physicians to a roster can be a challenging and time-consuming effort
- Recruiting, advertising, and screening initiatives to identify a narrow pool of credible candidates should be performed
- Candidate scoring matrices allow the creation of a pipeline of qualified candidates for critical roles

Candidate Scoring Matrix



Improvement Opportunities: Patient Engagement

Patient Engagement & Retention

- Patient engagement can be enhanced through more personalized and improved communication or loyalty programs to keep patients engaged with their care plans

Leakage

- Implementing patient navigation services, more convenient patient scheduling, improved patient education, practice feedback mechanisms, and telehealth services can help address leakage

Referrals

- Streamlining your referral process can ensure patients are promptly and smoothly transitioned to appropriate specialists or services without long wait times
- Implementing efficient referral processes can be accomplished via referral management systems and enhanced care coordination

Improvement Opportunities: Risk Management

- Managing Risk effectively can help your organization ensure stability, and sustain growth while maintaining high standards of patient care

Wind-Down / Retirement / Succession Planning

- Comprehensive plans for the smooth transition of responsibilities and patient care is important as key staff members retire, developing detailed documentation of roles, patient handover protocols, training programs, leadership development initiatives, can all support succession planning and staff changes

Market Competition / Consolidations

- Staying competitive can be accomplished by analyzing market trends, providing consolidation resources and forming partnership alliances through mergers and acquisitions support, expanding service lines, leveraging economies of scale while still providing high-quality care at lower costs

Patient Safety Initiatives

- Implementing robust patient safety programs to reduce errors and enhance quality of care using technology to monitor and improve patient safety metrics

Cybersecurity Measures

- Protecting patient data and organizational information from cyber threats through advanced cybersecurity protocols and HIPPA Security Assessments

Crisis Management Planning

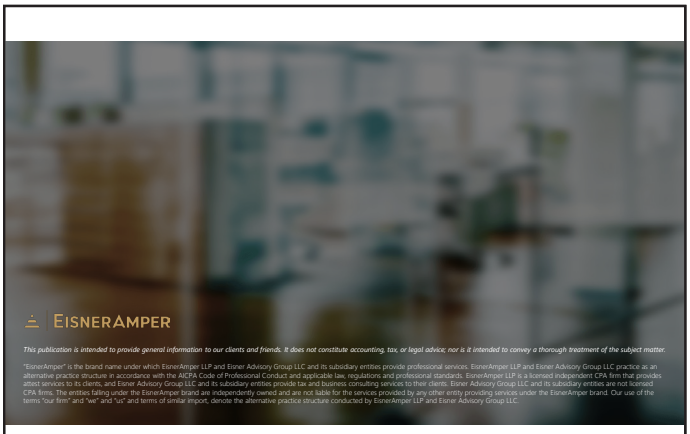
- Developing and regularly updating crisis management plans for emergencies such as natural disasters, pandemics, EHR failure, or other unforeseen events, this includes communication strategies, resource allocations, and continuity of operations plans

Improvement Opportunities: Compliance

- Under ACA, government and carriers increasingly depend both the existence of and monitoring of performance
  - Fraud, Waste & Abuse (FWA)
  - Coding and Billing
  - HIPAA and IT security
  - Communications
    - Internal
    - External to patients and other physicians/providers
  - Education and training
  - Enforcement
    - Monitoring
    - Re-education
    - Penalties

Lessons Learned

- If NO GO… Phase I improve performance and mitigate risks when remaining independence
- If GO… Phase I improves EBITDA (market value) and prepares the Practice for a transaction
- IF GO, THEN this Strategy Process prevents
  - Deal falling apart at the last minute due to mis-aligned expectations
  - Under valuing the practice and thus both purchase price and future compensation
  - Potentially entering the wrong deal, in terms of personal and organizational goals



SELF EVALUATION

Practice Optimization for Sale, Merger, or Continued Independence

1. How much money is PE sitting on:

a. $10M
b. $100M
c. $1B
d. $20B

2. T/F - EVERY partner should participate in the planning process for a deal?

3. Which of the following is not part of RCM

a. Patient scheduling
b. EMR close-out
c. Managed care contract negotiations
d. Patient balance billing

4. T/F - Gross collection rate is a better metric than net collections in measuring performance

5. T/F - Both the EBITDA of the practice and the multiple thereof paid by a buyer are critical

6. Which links with other practices are critical to PE firms' evaluation of a practice

a. Referral patterns
b. Location in the same building
c. Admitting to the same hospital
d. Many staff know each other

7. T/F - If a PE firms acquires a practice, then the practice must terminate all existing hospital relationships

8. Buyers consider the age of the providers in assessing the attractiveness of the deal, because:

a. Age drives short-term priorities (e.g., purchase cash vs. long-term compensation
b. The likely viability of the practice depends on patient loyalty, which diminishes as given doctors leave a practice
c. Should an older physician drive referral relationships, then his/her potential retirement poses risks
d. All of the Above

9. T/F - Coding warrants review

Answer Key: 1. D, 2. T, 3. C, 4. F, 5. T, 6. A, 7. F, 8. D, 9. T