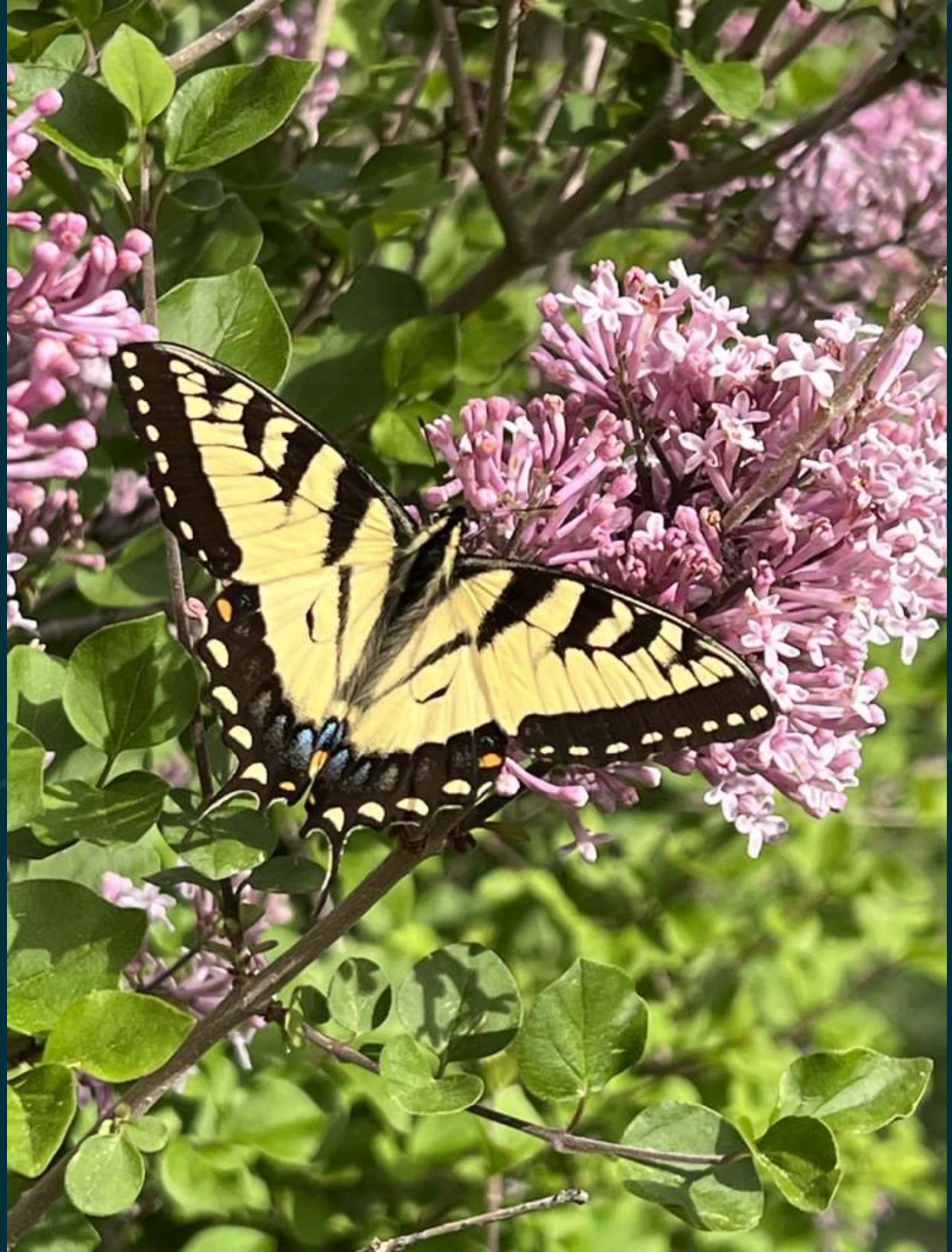


CardioVascular Disease & Wellness Symposium

Oct '22

Updates:

A Journey That Covers The Distance

Alex Schabauer, MD, FSVMB, FACC

Consultant in Cardiac and Vascular Medicine

MONUMENT HEALTH

Disclosures

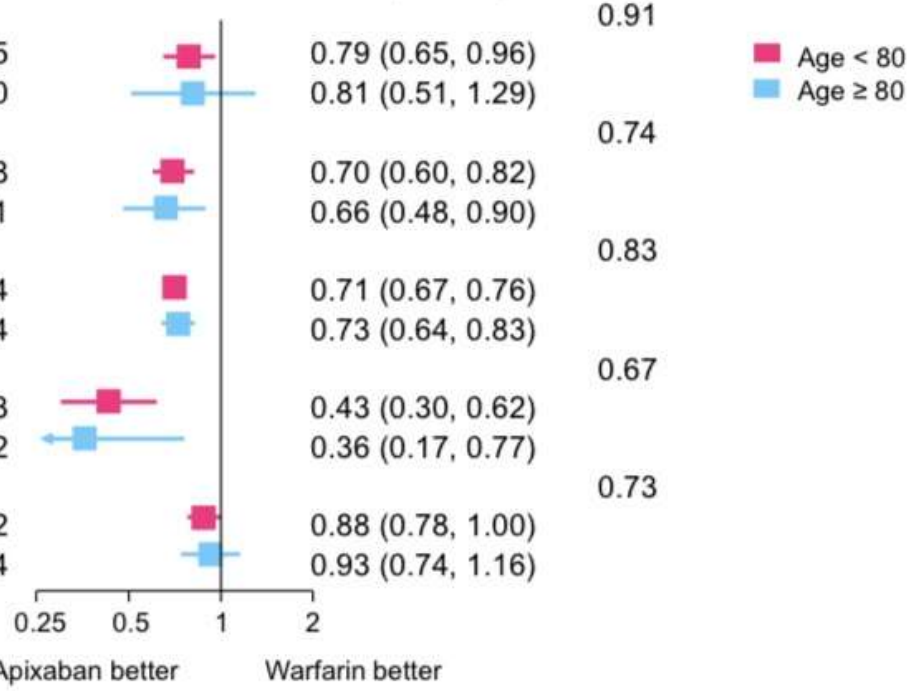
- Nihil
- Nichts
- Nic
- Nada
- Niente
- Aucun
- Ingenting
- Intet
- Semmi

CardioVascular Disease and Wellness Symposium Committee:

- CoDirectors: Alex Schabauer, MD; Drew Purdy, MD
- Committee:
- Diane Schabauer, CNP
- Fawzi Ameer, MD
- Cee Cee Thompson
- Judith Blair
- Karlee Bauman
- Crystal Gruetzmacher
- Jocelyn Palacios
- Jacob Staley
- Theresa Ferdinand
- Julie Symes

Apixaban vs. warfarin in patients ≥ 80 (n=2,436) vs. < 80 years

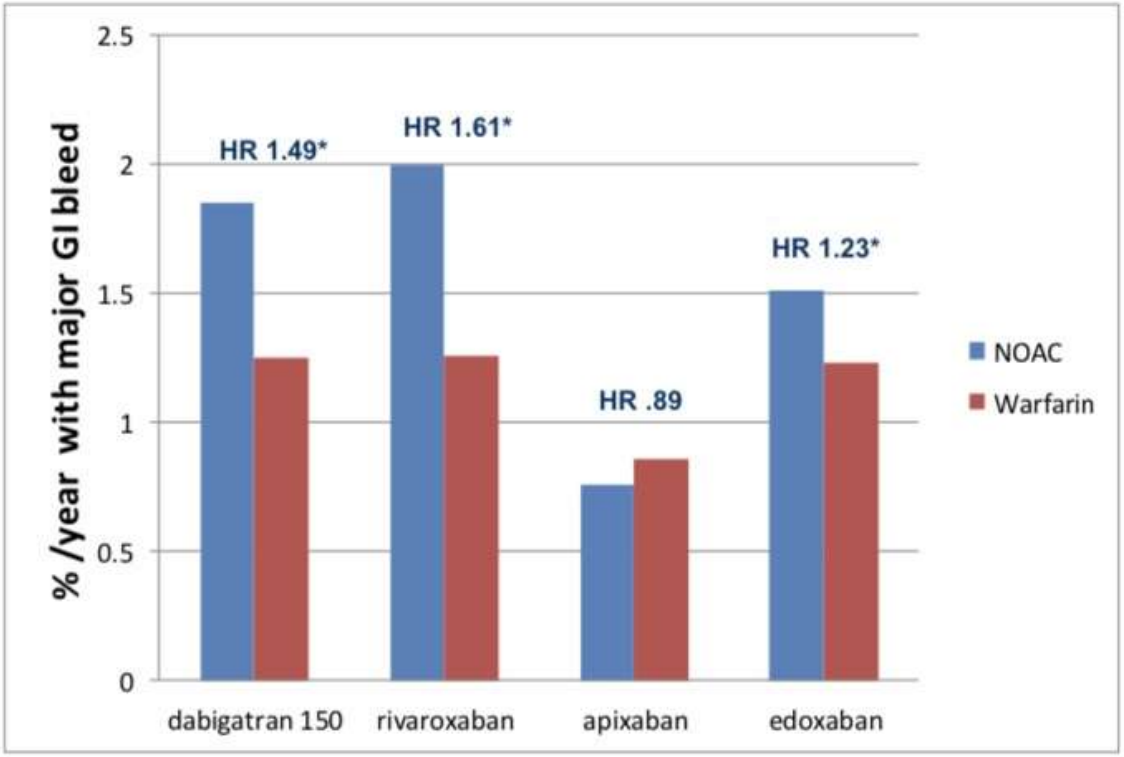
	Event Rate (%/year) Apixaban	Warfarin	HR (95% CI)	Interaction P-value
Stroke/Systemic Embolism				0.91
Age < 80	1.23	1.55	0.79 (0.65, 0.96)	
Age ≥ 80	1.53	1.90	0.81 (0.51, 1.29)	
Major Bleeding				0.74
Age < 80	1.93	2.78	0.70 (0.60, 0.82)	
Age ≥ 80	3.55	5.41	0.66 (0.48, 0.90)	
All Bleeding				0.83
Age < 80	17.0	24.4	0.71 (0.67, 0.76)	
Age ≥ 80	26.4	37.4	0.73 (0.64, 0.83)	
Intracranial Bleeding				0.67
Age < 80	0.32	0.73	0.43 (0.30, 0.62)	
Age ≥ 80	0.47	1.32	0.36 (0.17, 0.77)	
All-cause Mortality				0.73
Age < 80	3.03	3.42	0.88 (0.78, 1.00)	
Age ≥ 80	6.86	7.44	0.93 (0.74, 1.16)	



Duke Clinical Research Institute

Halvorsen S, et al. Eur Heart 2014

GI Bleeding: Most common site of major bleeding, and higher with NOACs than warfarin



HR 1.09 for dabi 110 v warfarin

Duke Clinical Research Institute

1. Connolly S, et al. *NEJM*. 2009. **2.** Patel M, et al. *NEJM*. 2011. **3.** Granger CB, et al. *NEJM*. 2011 4. Guiliano R NEJM.

Choosing Antithrombotic Therapy for Elderly Patients With Atrial Fibrillation Who Are at Risk for Falls

Malcolm Man-Son-Hing, MD, MSc, FRCPC; Graham Nichol, MD, MPH, FRCPC; Anita Lau; Andreas Laupacis, MD, MSc, FRCPC

- Among older patients, falling is common (about 30% fall at least once a year), and subdural hematomas are uncommon

"… persons taking warfarin must fall about 295 times in 1 year for warfarin to not be the optimal therapy."

- In ARISTOTLE, among patients with history of falls, there was an 80% lower rate of ICH with apixaban vs warfarin
  - » Of 375 patients with falling on apixaban, 0 had subdural hematoma

Duke Clinical Research Institute

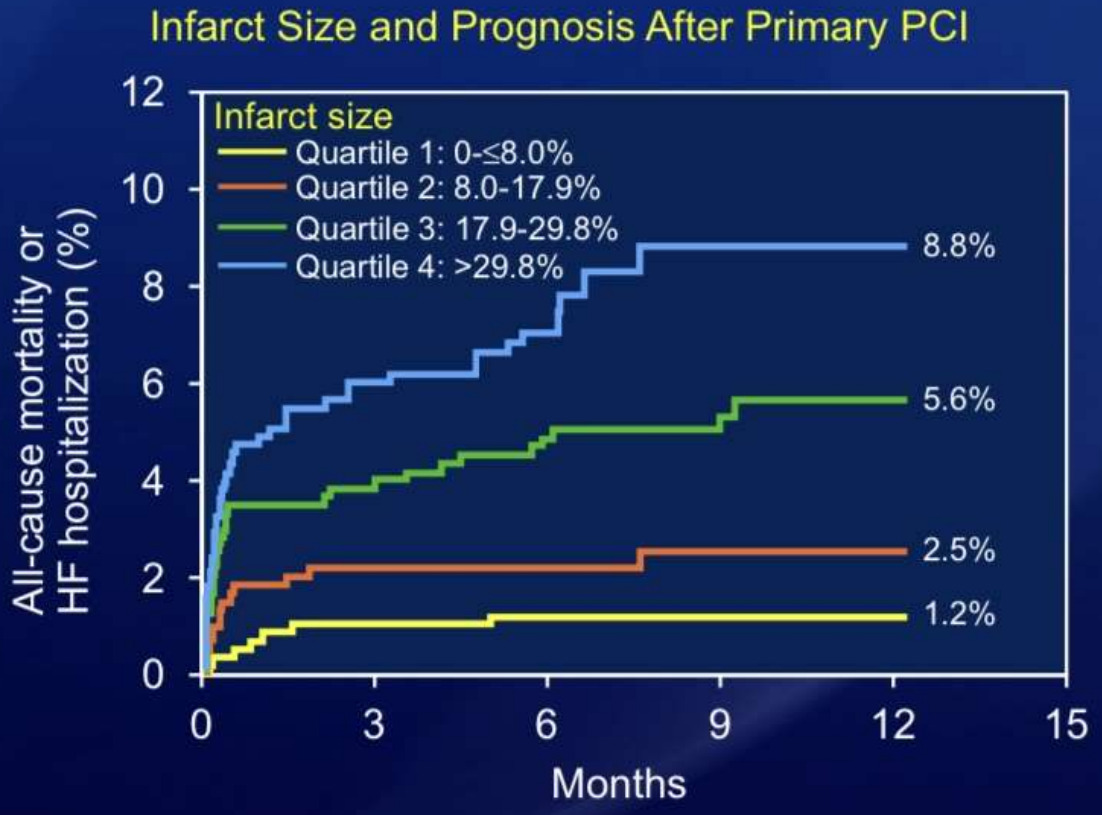
Arch Intern Med 1999;159:677-685
Rao M et al. Am J Med 2017

Aspirin nearly doubles the risk of bleeding for patients on OAC

Duke Clinical Research Institute

Relationship Between Infarct Size and Outcomes Following PPCI

- 10 randomized trials
- 2,632 pts
- Infarct size
  - MRI (21.8%)
  - SPECT (28.2%)



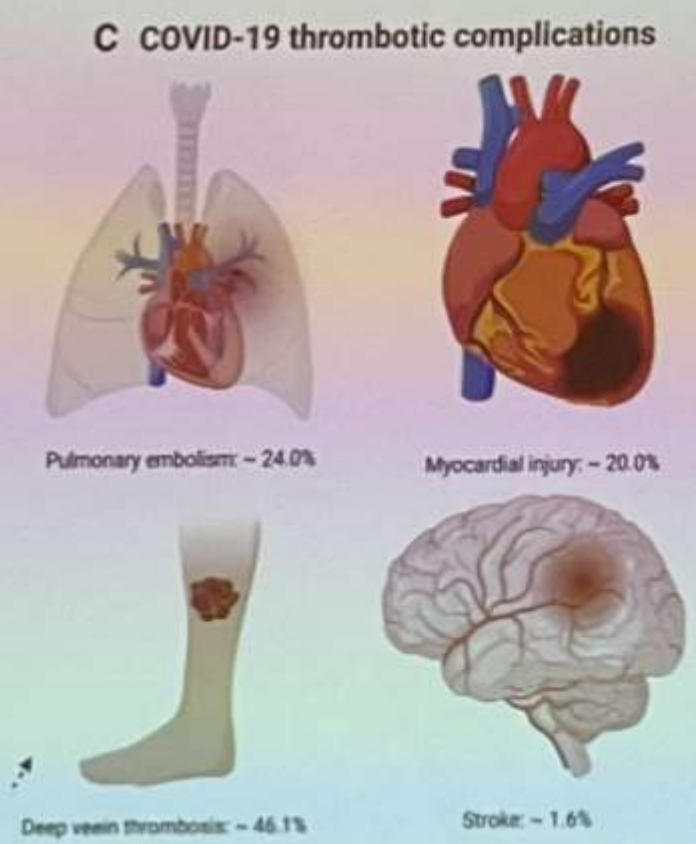
Stone: JACC, 2015

MAYO CLINIC

Common macrothrombotic clinical presentations

- VTE most common

- Less common:
  - <5%
    - – Stroke
    - – Acute MI
    - – Acrocyanosis
    - – Ischemic limb



rnier Mayo Clinic Proc 2020, 96; 295-303
ega-Paz JAHA 2021, 10; 1-9.

Incidence of Thrombosis in COVID-19

Author	Country	Number of Patients	VTE Rate	Other Rates
Zhang	China	143	46.1% (DVT only)	
Middledorp	Netherlands	198 (75 ICU)	42% (25% symptomatic)	59% ICU 9.2% Floor
Klok	Netherlands	184 (all ICU)		All TE 49%
Longchamp	Switzerland	25 (all ICU)	32%	
Chui	China	81 (all ICU)	25%	
Al-Samkari	USA	400 (144 ICU)	4.8%	All TE 9.5%
Lodigiani	Italy	388 (61 ICU)	4.4% (8.3% ICU)	All TE 7.7%
Moll	USA	210 (102 ICU)	4.3%	
Helms	France	150 (all ICU)	16.7% (PE)	OR 6.2 vs. non-COVID ARDS
Bilaloglu	USA	3334 (829 ICU)	11.5% (non-ICU) 29.4% (ICU)	All TE 16.0%

NIH National Heart, Lung, and Blood Institute

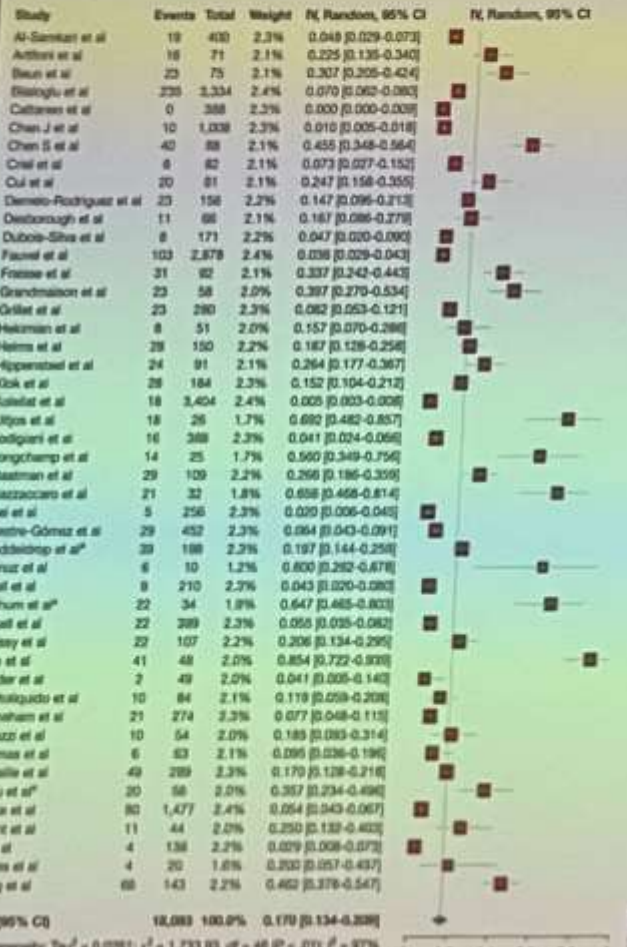
10.1161/circulationaha.120.046702
10.1111/jth.14888. 10.1016/j.thromres.2020.04.041
10.1002/rth2.12376
10.1182/blood.2020006520
10.1016/j.thromres.2020.04.024
10.1016/j.chest.2020.07.031
10.1111/jth.14830
10.1001/jama.2020.13372
10.1007/s00134-020-06062-x

c. G.Barnes

Slide

NIH National Heart, Lung, and Blood Institute

Covid and VTE risk



Meta-analysis: 47 studies, 18,093 patients

VTE Risk: 17.0% (range 0-85.4%)

- Floor – 7.1%
- ICU – 27.9%
- Screening – 33.1%
- Clinical diagnosis – 9.8%

Bleeding Risk: 7.8% (range 2.7-21.6%)

Chest 2020;159:1182-1196

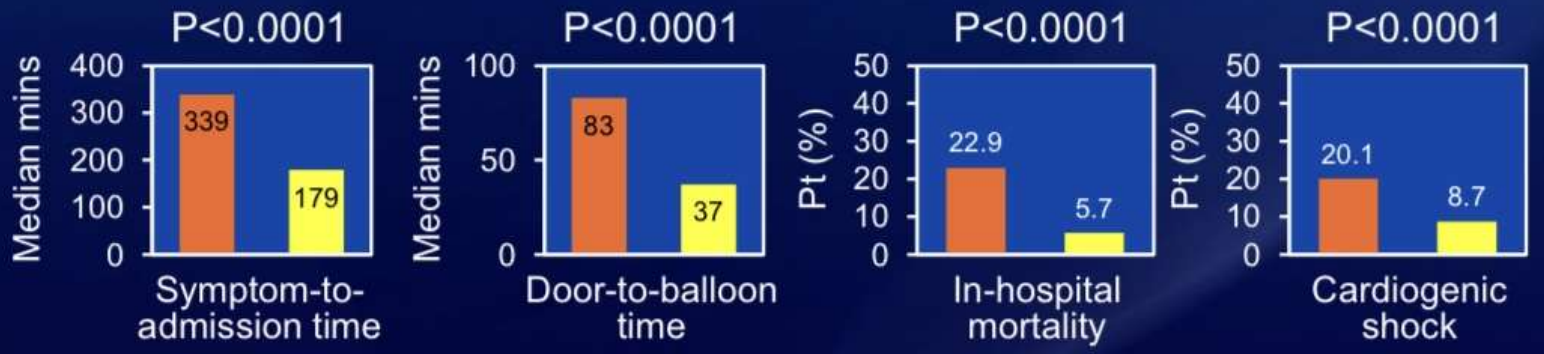
L CARDIOVASCULAR CENTER

Impact of COVID-19 on ACS Patients Undergoing an Invasive Strategy

Collateral Damage

- Prospective registry
- 55 interventional centers
- 265 pts — STEMI – 145; NSTE-ACS – 121 } COVID-19 confirmed or high index of clinical suspicion
- Comparison with 2 UK large databases pre COVID

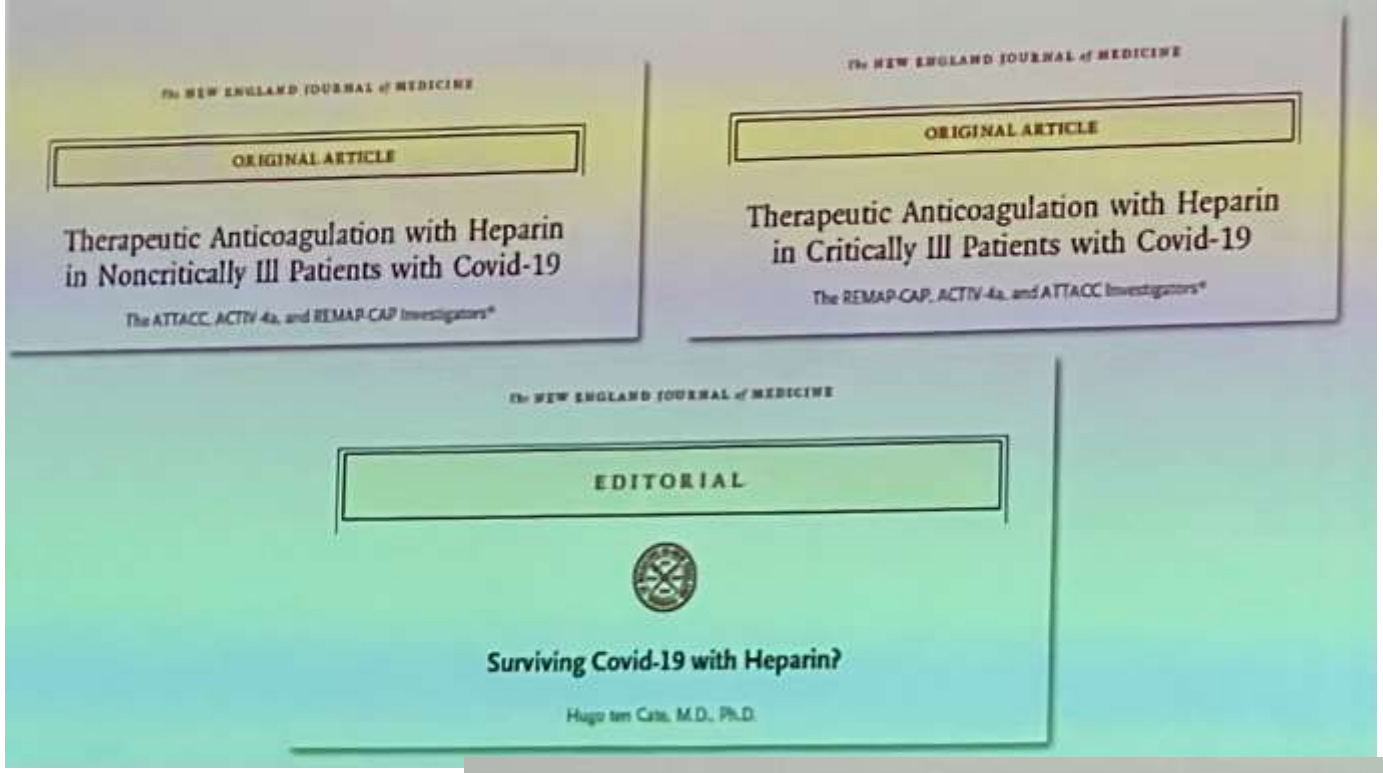
STEMI Subgroup



Redrawn from: Kite and Gershlick JACC, 2021

MAYO CLINIC

MONUMENT HEALTH



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19

The ATTACC, ACTIV-4a, and REMAP-CAP Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

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Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19

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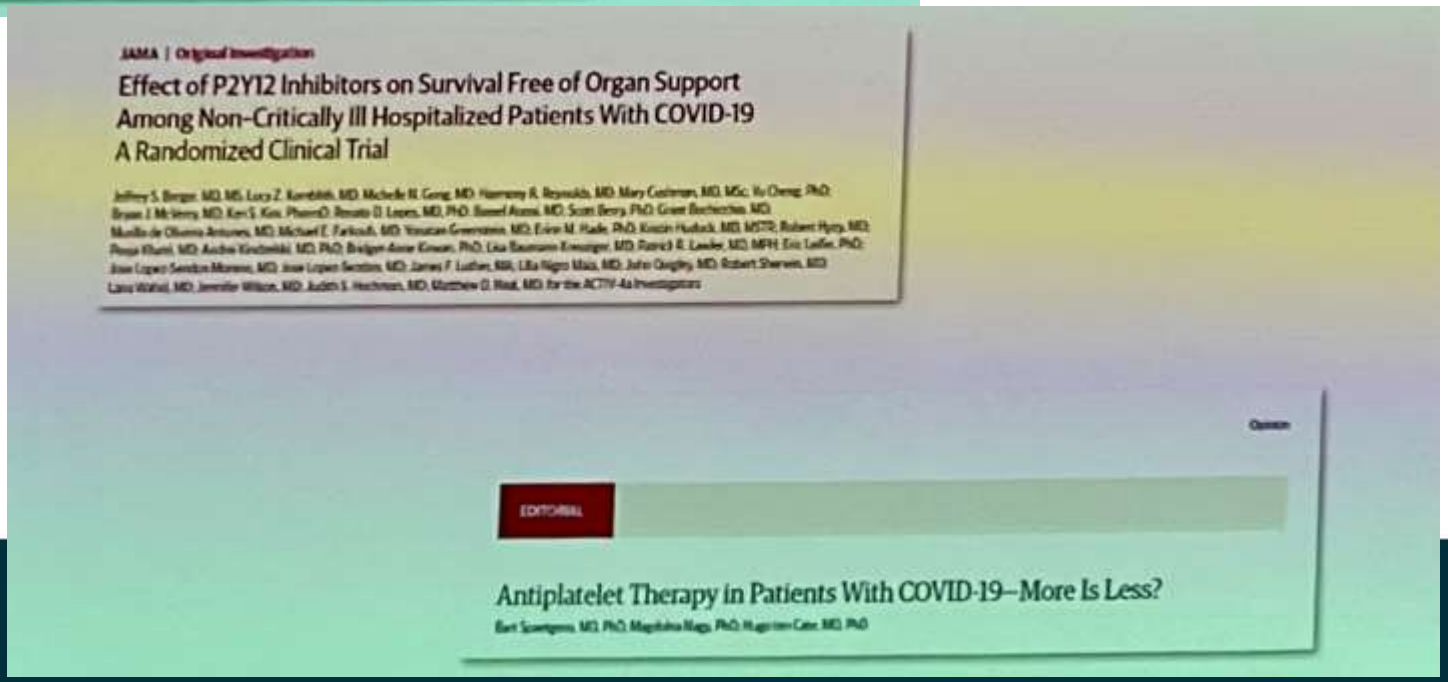
The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

Surviving Covid-19 with Heparin?

Hugo ten Cate, M.D., Ph.D.



JAMA | Original Investigation

Effect of P2Y12 Inhibitors on Survival Free of Organ Support Among Non-Critically Ill Hospitalized Patients With COVID-19 A Randomized Clinical Trial

Opinion

EDITORIAL

Antiplatelet Therapy in Patients With COVID-19—More Is Less?

COVID-19 Outpatient Thrombosis Prevention Trial

A Randomized Double-Blind Placebo-Controlled Adaptive-Design Platform Trial of 45 Days of Assigned Treatment (and 30 additional days of safety follow-up) Comparing Prophylactic Dose Apixaban (2.5 mg po bid), to Therapeutic Dose Apixaban (5.0 mg po bid), to Aspirin (81mg po qd), to Placebo (po bid) among Symptomatic PCR-Confirmed COVID-19 Patients who have Elevated Thrombotic and Inflammatory Risk (D-dimer >ULN and hsCRP >10mg/L), Yet Who Are Not Admitted to Hospital as Cardio-Pulmonary Status is Currently Stable and Uncompromised

Ridker 8.7.

NIH National Heart, Lung, and Blood Institute

MONUMENT HEALTH

JAMA | Original Investigation

Effect of Antithrombotic Therapy on Clinical Outcomes in Outpatients With Clinically Stable Symptomatic COVID-19
The ACTIV-4B Randomized Clinical Trial

Jean M. Connors, MD; Maria M. Brooks, PhD; Frank C. Sciurba, MD; Jerry A. Krishnan, MD; Joseph R. Bledsoe, MD; Andrei Kindzelski, MD; Amanda L. Baucom, MS; Bridget-Anne Kirwan, PhD; Heather Eng, BA; Deborah Martin, BA; Elaine Zaharris, BA; Brendan Everett, MD; Lauren Castro, MS; Nancy L. Shapiro, PharmD; Janet Y. Lin, MD; Peter C. Hou, MD; Carl J. Pepine, MD; Eileen Handberg, PhD; Daniel O. Haight, MD; Jason W. Wilson, MD; Sarah Majercik, MD; Zhuxuan Fu, MS; Yongqi Zhong, PhD; Vidya Venugopal, PhD; Scott Beach, PhD; Steve Wisniewski, PhD; Paul M Ridker, MD; for the ACTIV-4B Investigators

Opinion

EDITORIAL

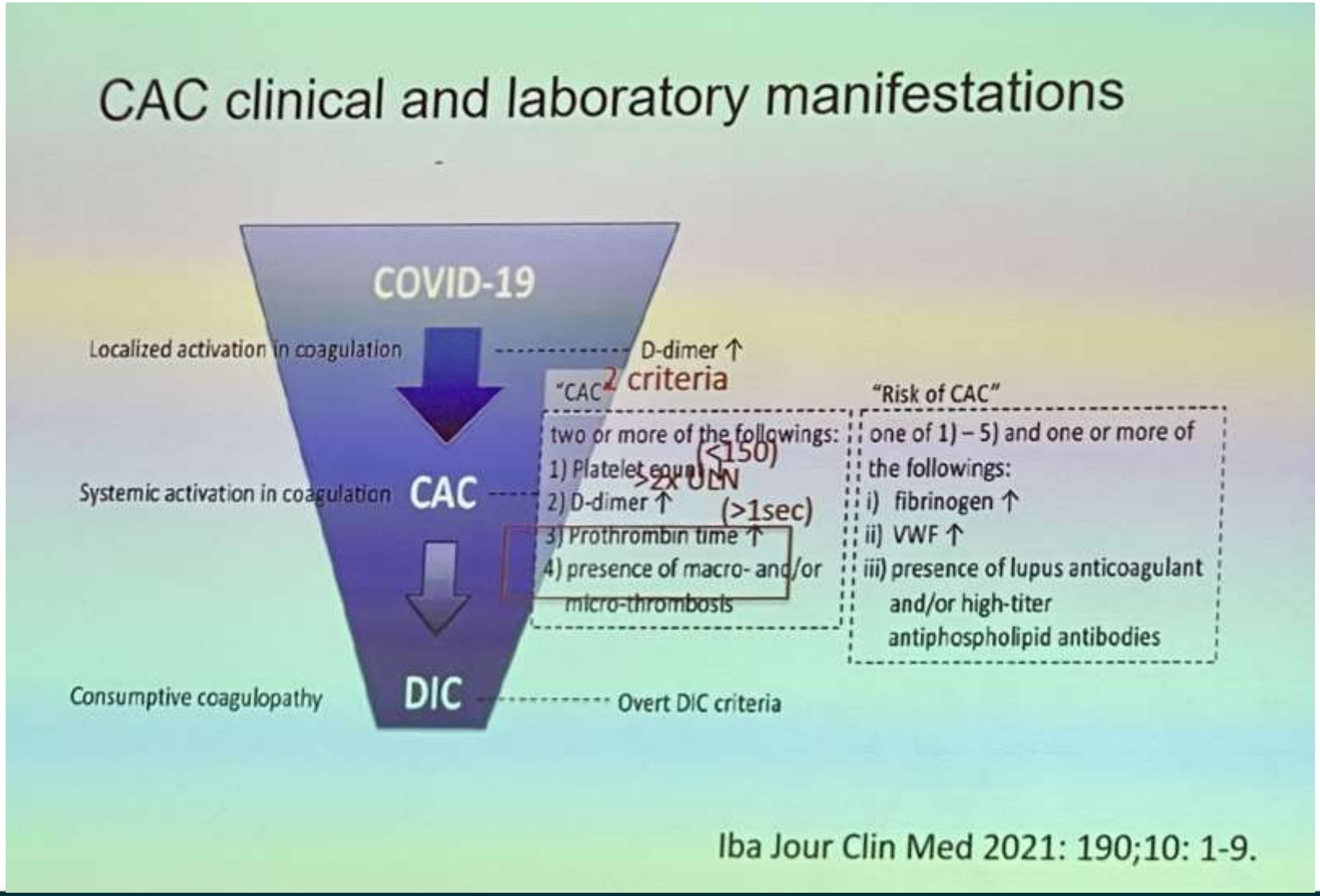
Antithrombotic Therapy for Outpatients With COVID-19
Implications for Clinical Practice and Future Research

Otavio Berwanger, MD, PhD

NIH National Heart, Lung, and Blood Institute

MONUMENT HEALTH

Covid Associated Coagulopathy



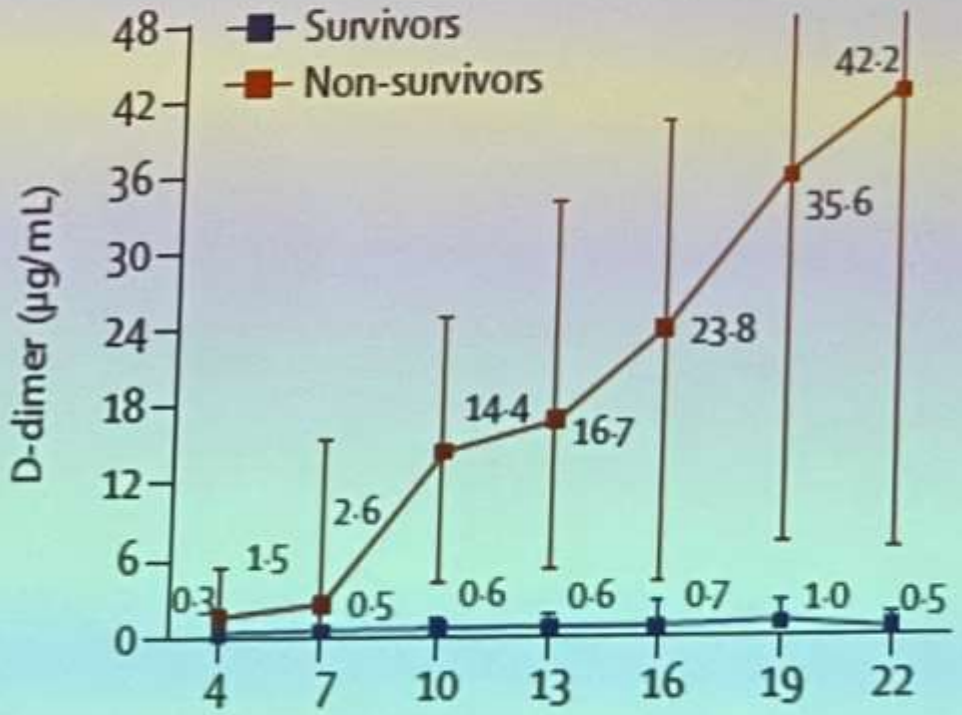
Key features of CAC

Summary of findings
1. Coagulopathy is manifest as elevated fibrinogen, elevated D-dimers, and minimal change in PT, aPTT, and platelet count in early stages of infection
2. Increasing IL-6 levels are correlated with increasing fibrinogen levels
3. Coagulopathy appears to be related to severity of illness and resultant thromboinflammation and not intrinsic viral activity
4. Elevated D-dimer at admission is associated with increased mortality
5. Rising D-dimer after admission precedes multiorgan failure and overt DIC a. Noted to start at 4 d after admission in nonsurvivors b. Longer duration of hospital stay associated with increasing D-dimer and development of sepsis physiology
6. Bleeding manifestations are not common despite coagulopathy

Connors and Levy. Blood, 2020, 135: 2033-2039

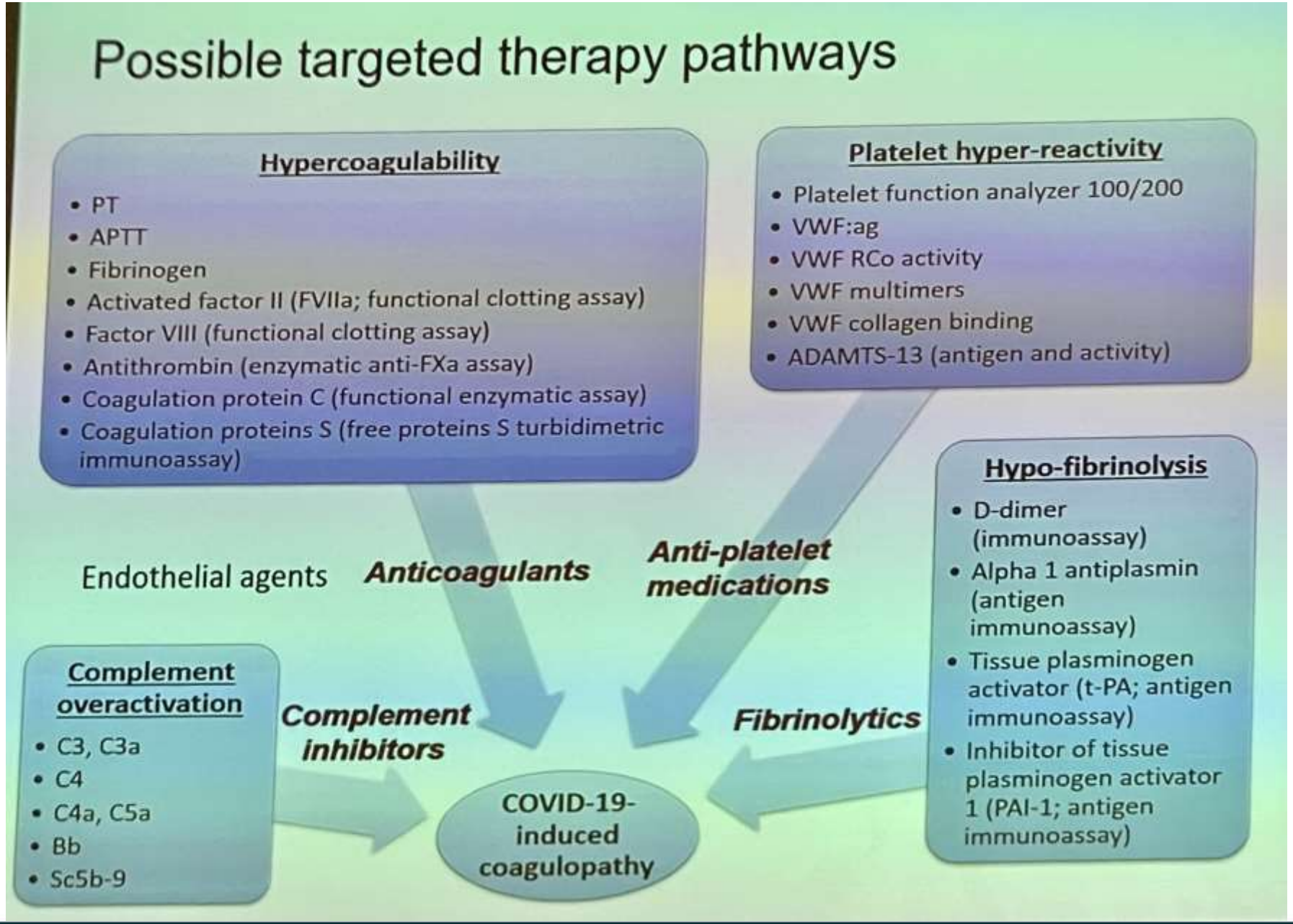
D dimer is a marker of disease severity and mortality

- Diagnostic hallmark of COVID-DIC is a rapidly rising D-dimer
- **High D-dimer is a strong prognostic factor for poor outcome.**
- **D-dimer > 1ug/ml associated with nearly 20-fold increased death rate.**



Lancet 2020; 395: 1054-62

Possible targeted therapy pathways



Summary -- timing is key

- The hallmark of severe COVID19 infection is endothelial damage and hypercoaguability leading to micro and macrovascular thrombosis.
- Covid coagulopathy has features unique from DIC.
- AC is now better defined, with benefit in non critically ill patients
- There is a pressing need to study the long term effects of CAC and to target additional pathways.

VTE is a Highly Prevalent and Major cause of Hospital Morbidity and Mortality

- > 900,000 patients Diagnosed with VTE annually in the US
- 60,000-100,000 deaths
- 33-50% will have long term complication of the lower extremity (PTS)
- 1/3rd will have a recurrence within 10 years
- $10B total US economic burden

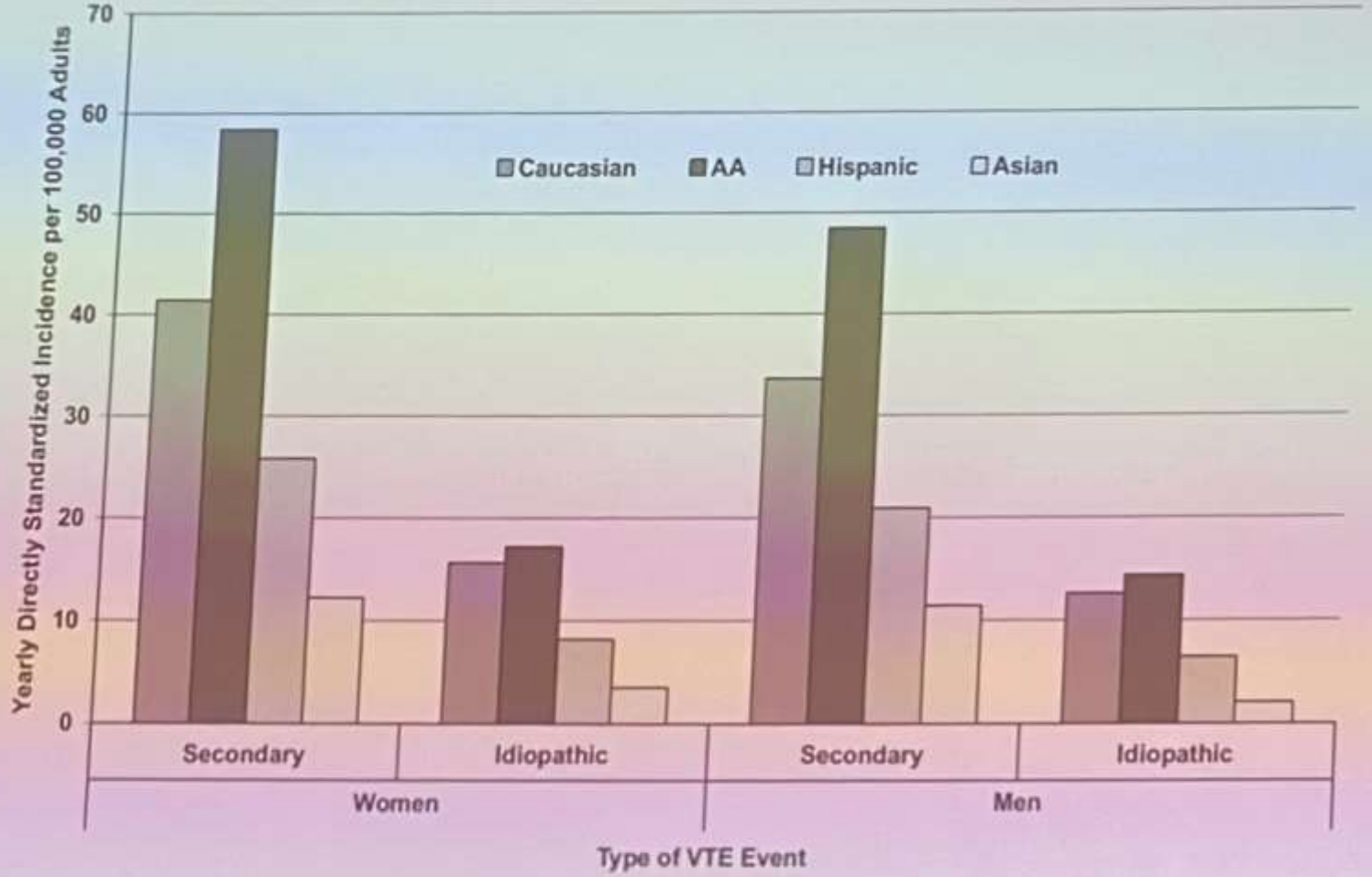


Fig. 3. Directly standardized incidence in 1996 of idiopathic and secondary venous thromboembolism in men and women of the principal racial/ethnic groups in California. (Copyright approval from Current Opinion in Pulmonary Medicine.)

- In New York City 578 consecutive out of hospital PE cases underwent examination
- Race adjusted incidence was per 100,000, Blacks 3.73, whites 1.15 and Hispanics 0.93
- Thrombophilia more common in whites per CDC (14.7% vs 1.5% of blacks)

Table 1. Nature

Race
Genetic predisposition for hypercoagulability (factor V Leiden, prothrombin gene mutation)
Acquired predisposition for hypercoagulability (antiphospholipid antibody syndrome)
Inflammation (nature, nurture, or both?)
Hypercholesterolemia (nature, nurture, or both?)
Diabetes mellitus (nature, nurture, or both?)

Table 2. Nurture

Obesity
Hypertension (nurture, nature, or both?)
Cigarette smoking
Immobility
Healthcare disparities

Conclusion

- African Americans have higher rates of VTE based on multiple studies.
- Female gender seems to have a lot of conflicting information, and there are some inherent risk factors that can confound this
- High Income Countries have higher incidence of deep venous disease

Background

- Chronic Venous Insufficiency (CVI) affects up for 40% of the US population
- Accounts for 1% of US healthcare budget
- Treatment for CEAP 2-6 disease improves long term QOL by alleviating the physical and psychological burden of longstanding CVI
- Mainstay treatment:
  - Compression therapy
  - Venous Intervention
    - Surgical (high ligation or stripping)
    - Thermal ablation (RFA or EVLA)
    - Non-thermal ablation (Clarivein™, Varithena™, VenaSeal™)

2020 Appropriate Use Criteria for Chronic Lower Extremity Venous Disease

American Venous Forum | SVS Society for Vascular Surgery | Multi-Society Document | American Vein & Lymphatic Society | Society of Interventional Radiology

Great Saphenous Vein (GSV) ablation	
CEAP 2-6*	Appropriate
Below-knee in CEAP 4-6*	Appropriate

Small Saphenous Vein (SSV) ablation	
CEAP 2-6* when reflux directed to affected area	Appropriate
CEAP 4-6* when reflux to GSV or thigh veins	Appropriate

Anterior Accessory Saphenous Vein (AASV) ablation	
CEAP 2, 4-6* when reflux directed to affected area	Appropriate

Ablation of any vein	
CEAP 1-2 for *asymptomatic* disease and visible veins	Rarely Appropriate
NO reflux	Never Appropriate

Perforator vein treatment	
CEAP 4-6*, with high outward flow and large diameter directed toward affected area	Appropriate
CEAP 1-2*, with high outward flow and large diameter directed toward affected area	Rarely Appropriate
CEAP 1-2 in asymptomatic patient	Never Appropriate

Iliac vein or inferior vena cava (IVC) stenting	
CEAP 4-6,* for obstructive disease *without* superficial truncal reflux	Appropriate
CEAP 3 (edema),* for obstructive disease *with or without* superficial truncal reflux	May Be Appropriate
In asymptomatic patient for iliac vein compression (such as May-Thurner compression), found as incidental finding by imaging, with or without teleangiectasia (CEAP 1)	Never Appropriate

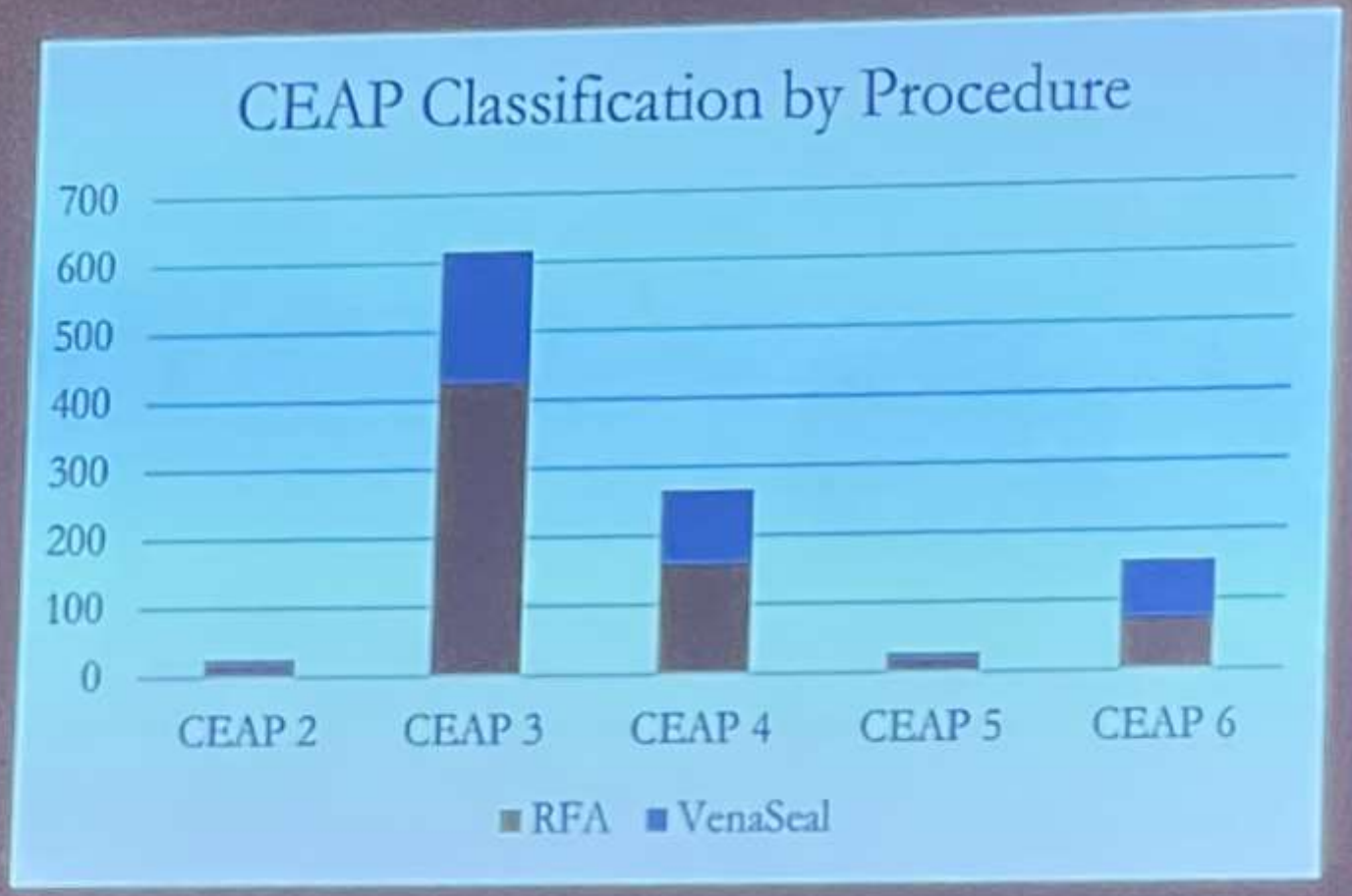
*in symptomatic patients

JVS-VL Journal of Vascular Surgery Venous and Lymphatic Disorders

Masuda et al. *J Vasc Surg Venous Lymphat Disord, July 2020*

@JVascSurg @TheJVascSurg

Classification of Venous Disease Treated



Changes in the Iliac Veins with Position

Boston Scientific

- 41 women (age 44 ± 10.3 years) with PVD
- Posture-dependent stenosis
- Significant stenosis (CSA reduction > 60%)
  - Supine: 26 patients (63.4%)
  - Lying on left side: 8 patients (19.5%)
  - Standing: 10 patients (24.4%)
- Only 5 (12.2%) concordant positive
- Maximal CSA also showed changes
  - Supine: 149.6 mm^2
  - Lying on left side: 192.3 mm^2
  - Standing: 192.6 mm^2

rzanowski M. et al. J Vasc Surg Venous Lymphat Disord. 2019 Nov;7(6):845-852.

Stenosis Assessment – True or False Lesion?

Boston Scientific

LCIV

Supine

Left-Side Lying

Standing

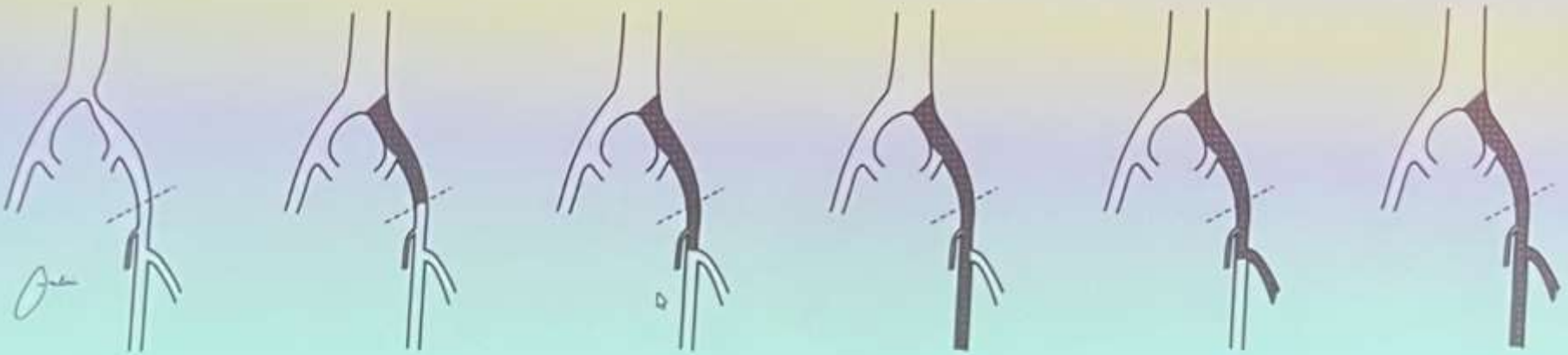
Anatomic — versus — Pathologic

Positional — versus — Fixed

Left CIV Compression — versus — May-Thurner Syndrome

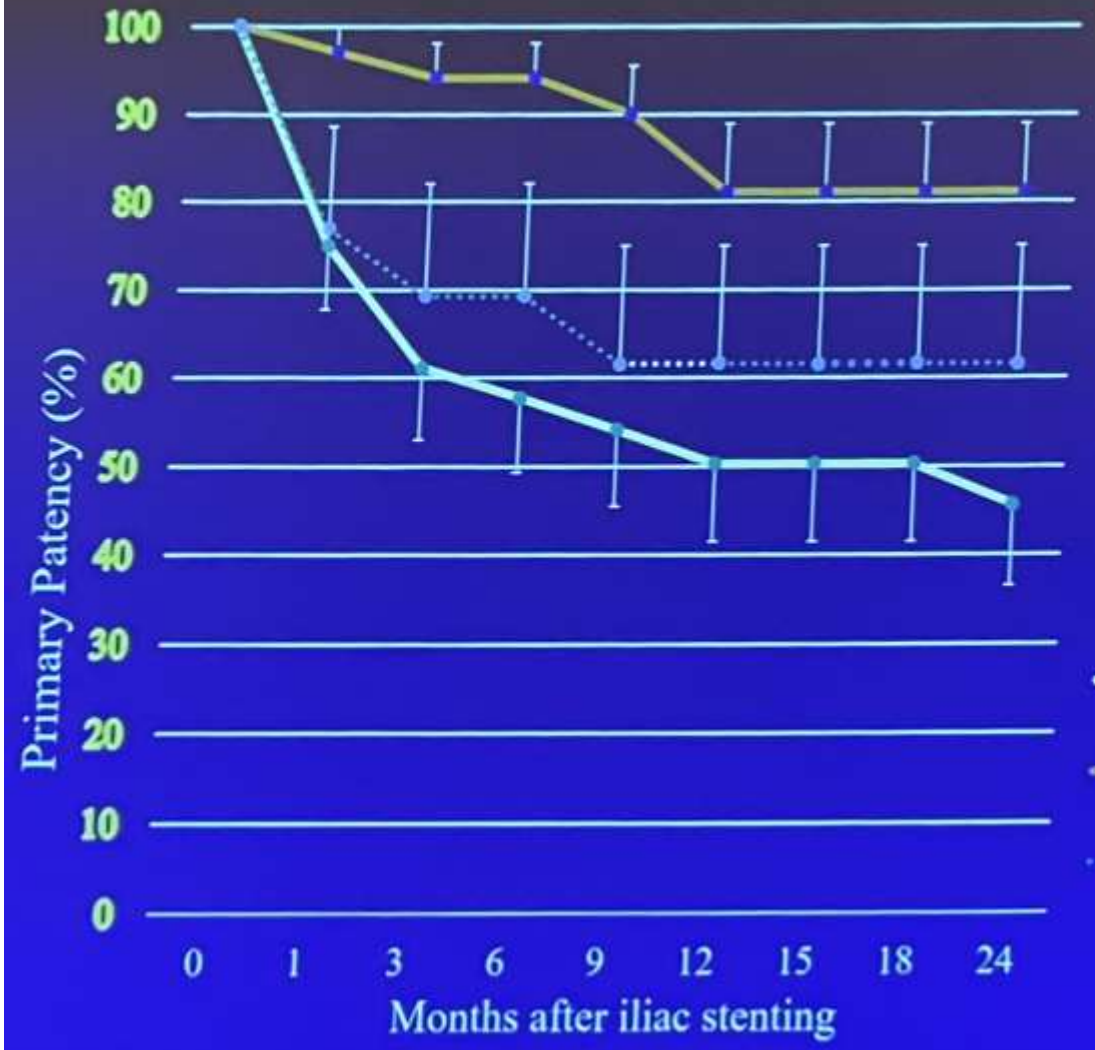
Classification

- Classification based on anatomical expansion of the postthrombotic trabeculation (> 50 % lumen narrowing)



I	II	III	IV a	IV b	V
Endovascular	Endovascular	Endovascular	1) Endovascular + Endophlebectomy 2) Endovascular + Stenting into the DFV/ cranial to DFV	1) Endovascular + Endophlebectomy 2) Endovascular + Stenting into the FV / cranial to DFV	1) Contrainidcation (conservative) 2) Endovascular + Recanalization of the FV down to PV

Primary patency by anticoagulation



LMWH 81% @ 2 yrs

Warfarin 62% @ 32yrs

Factor Xa 47% @ 2 yrs

Factor Xa (n=39)

LMWH > 10 days (n=41)

Warfarin (n=12)

Risk factors for early thrombosis

Variable	Thrombosis at 3 mos	P val
Hypercoagulable state	47.8% with 19.3% without	0.02
Severity of occlusion	34.9% for Type IV 11.6% for Type III	0.007
Type of anticoagulation	38.9% Factor Xa inhib 4.9% LMWH > 10 days	0.004

Summary

- Patients with most severe form of ilio-caval venous obstruction are a separate subset
  - More severe symptoms
  - More difficult to recanalize
  - Higher stent thrombosis after intervention
- Likely inflammatory response to recanalization of chronically scarred channel
- Need system to classify these separately from less severely disease cases

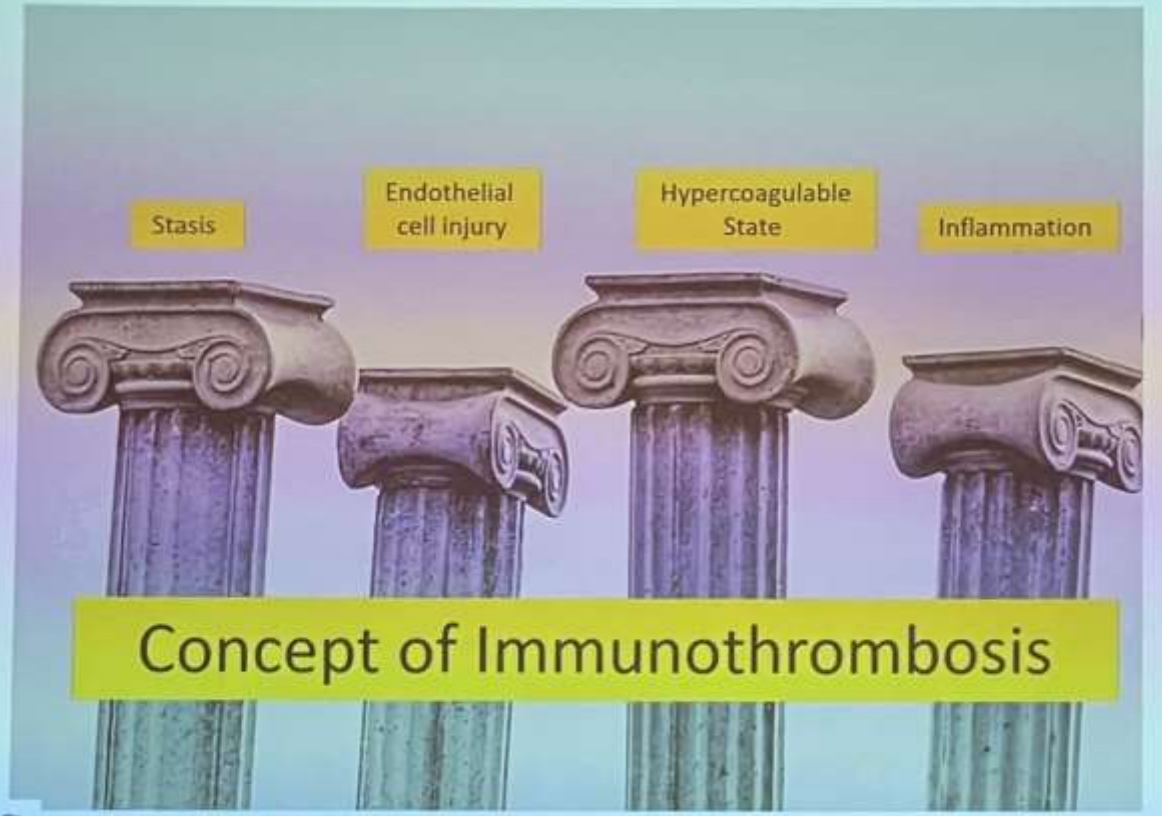
Summary

- Re-thrombosis occurs more often if occlusion is more extensive and in patients with known hypercoagulable state
- Anticoagulation type matters
  - LMWH better for initial 3-4 weeks
- Inflow critical – need better way to identify it

This group needs frequent follow-up and reintervention to achieve excellent long-term patency

Making A Case for Low Molecular Weight Heparin

Virchow's Triad is more likely now a Quartet



Coagulation

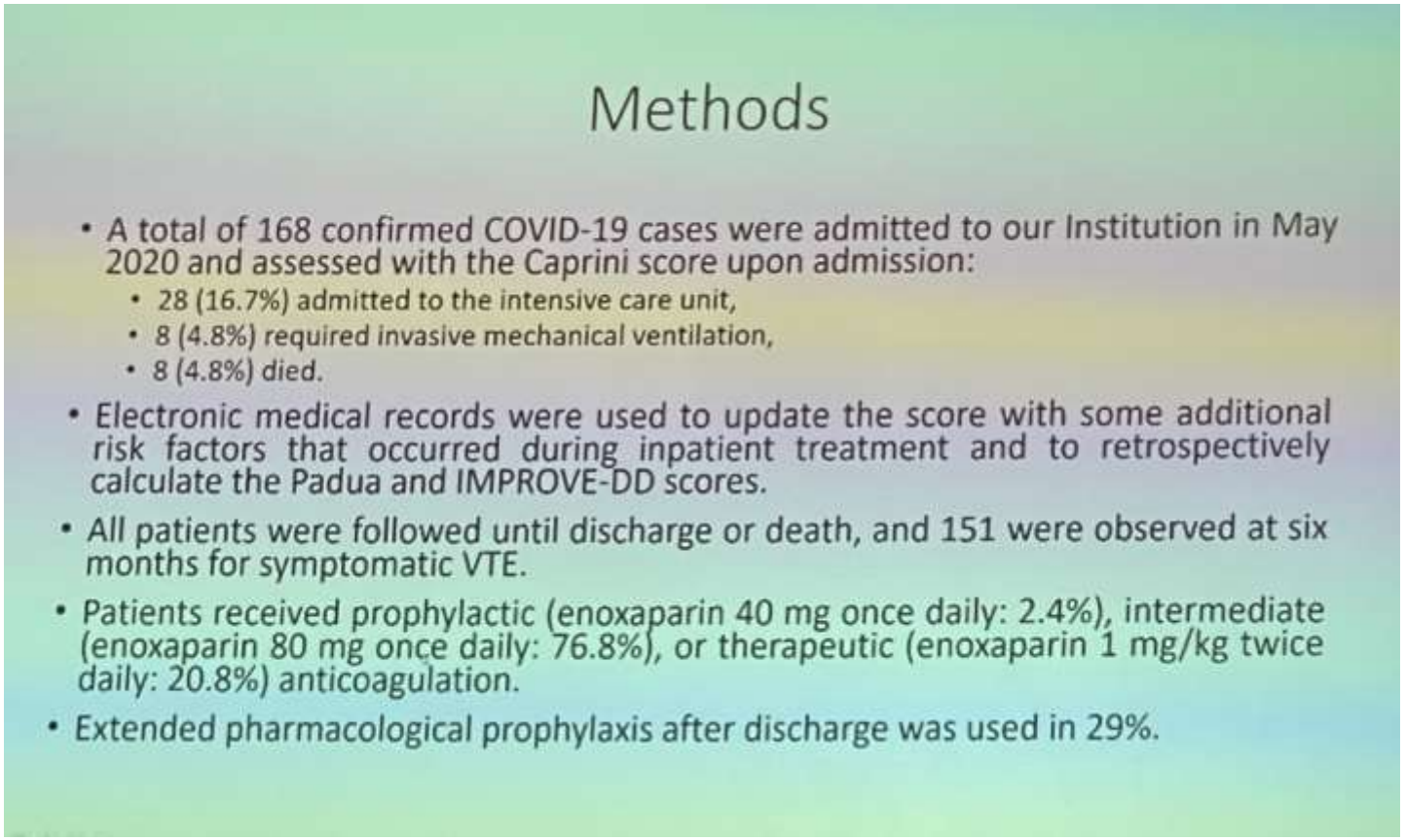
Inflammation

- Surgery
- Trauma
- Cancer
- Obesity
- Inflammatory bowel disease
- Antiphospholipid syndrome
- Systemic infection

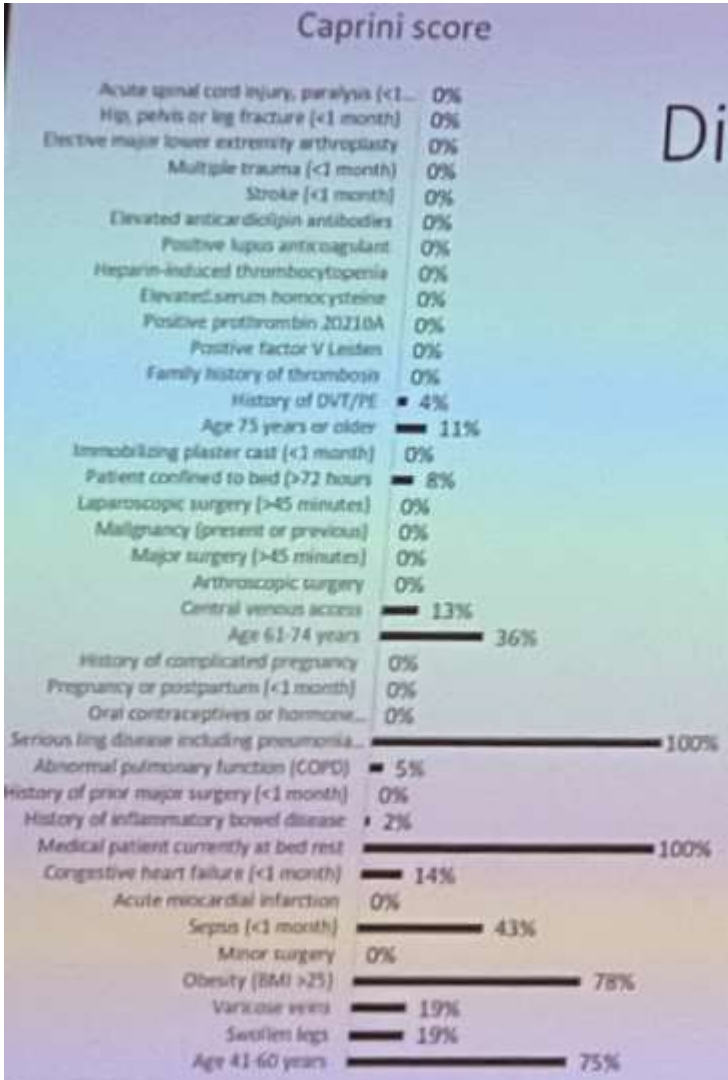
@adityasharmamd

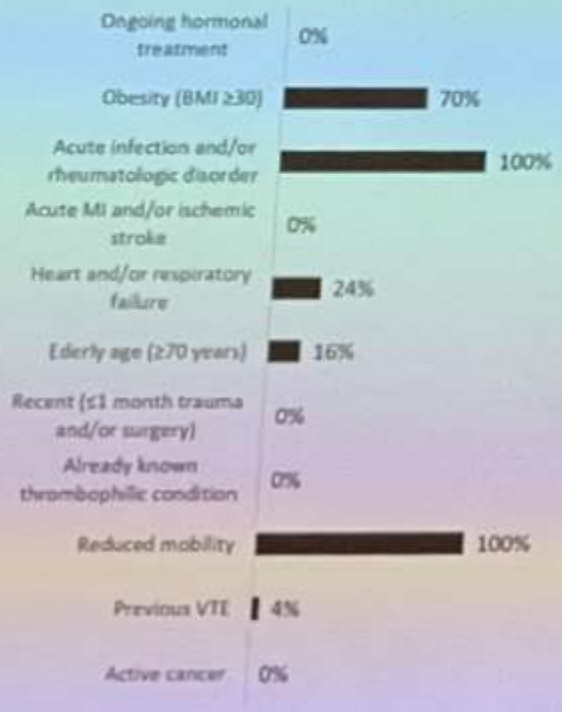
Hematology. 2019;24(1):742–750.

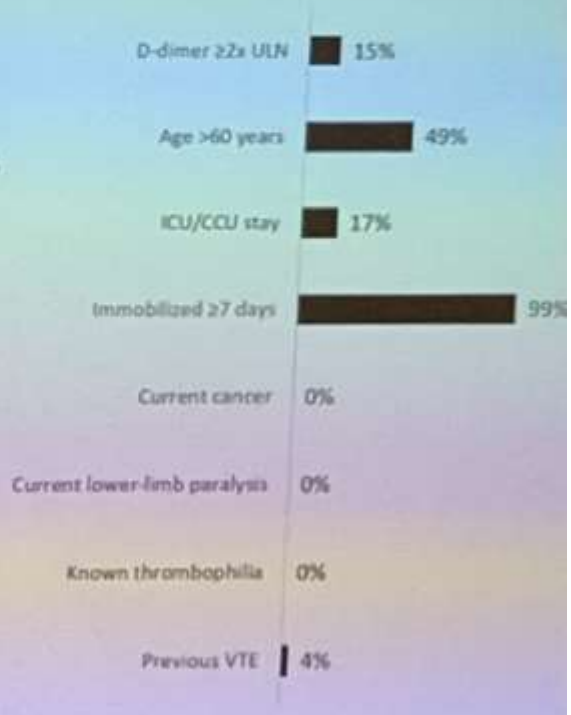
CoVid and VTE Risk scores



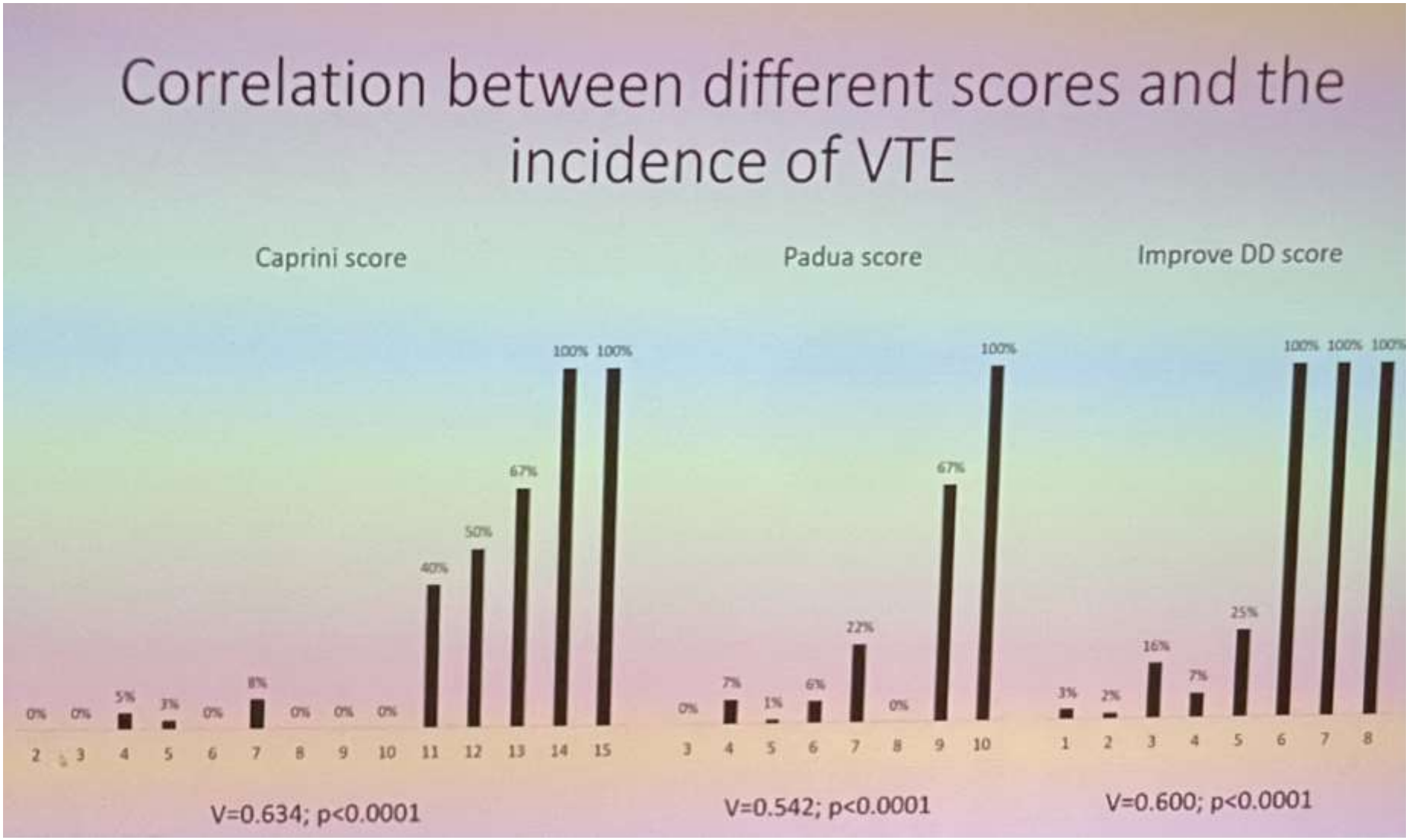
Distribution of the risk factors







Correlation between different scores and the incidence of VTE



VTE in high-risk group

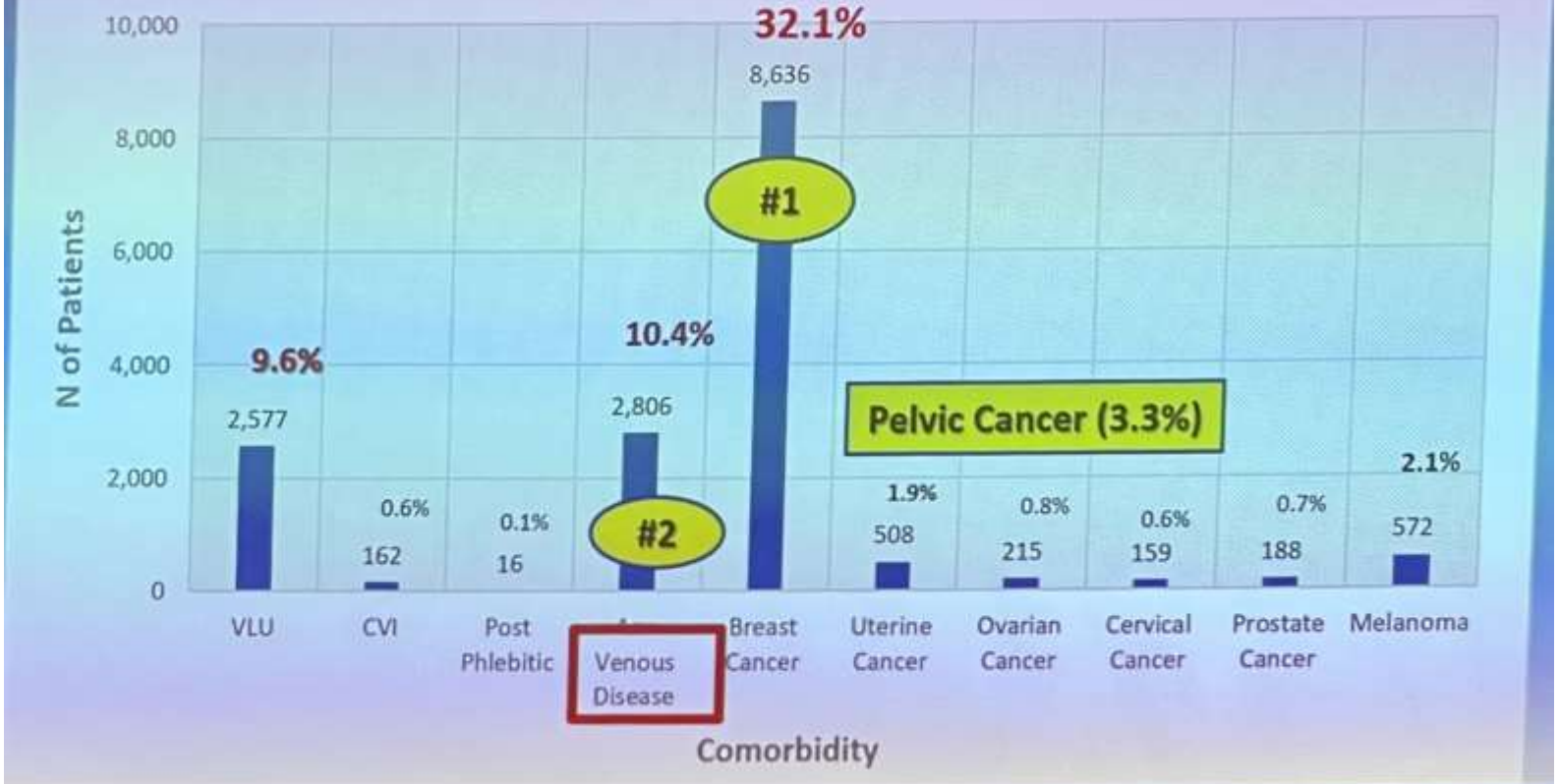
	Non-high-risk group	High-risk group	P-value
Caprini score	2/58 (3,4%)	10/110 (9,1%)	0,221
Padua score	0/1 (0%)	12/167 (7,2%)	0,999
Improve DD score	6/146 (4,1%)	6/22 (27,3%)	0,001

Conclusion

- Caprini and IMPROVE-DD scores can equally predict symptomatic VTE in COVID-19 patients.
- The standard thresholds for the high-risk group are not accurate for COVID-19 patients undergoing pharmacological prophylaxis.
- Revised thresholds are needed to predict VTE in this patient group.

*Distribution of LED etiologies in the BHI study sample

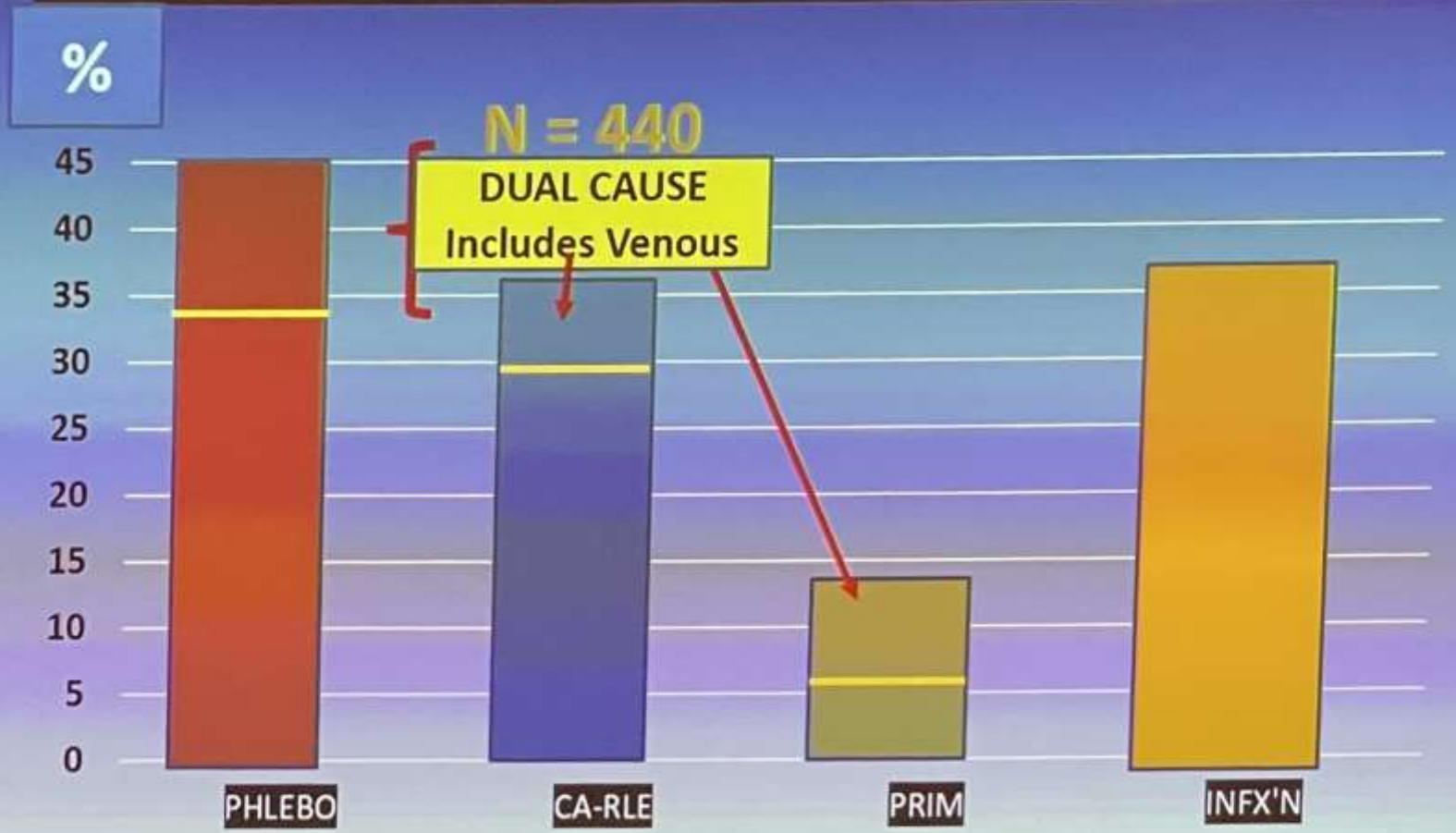
(Lymphedema Population, n = 26,902 Patients)



*Son A, et al. J Vasc Surg Ven and Lym Dis 2019; 7:724–730

*CAUSES OF LYMPHEDEMA

[Dean S, et al. J Vasc Surg V&LD e PUB 1/25/2020]



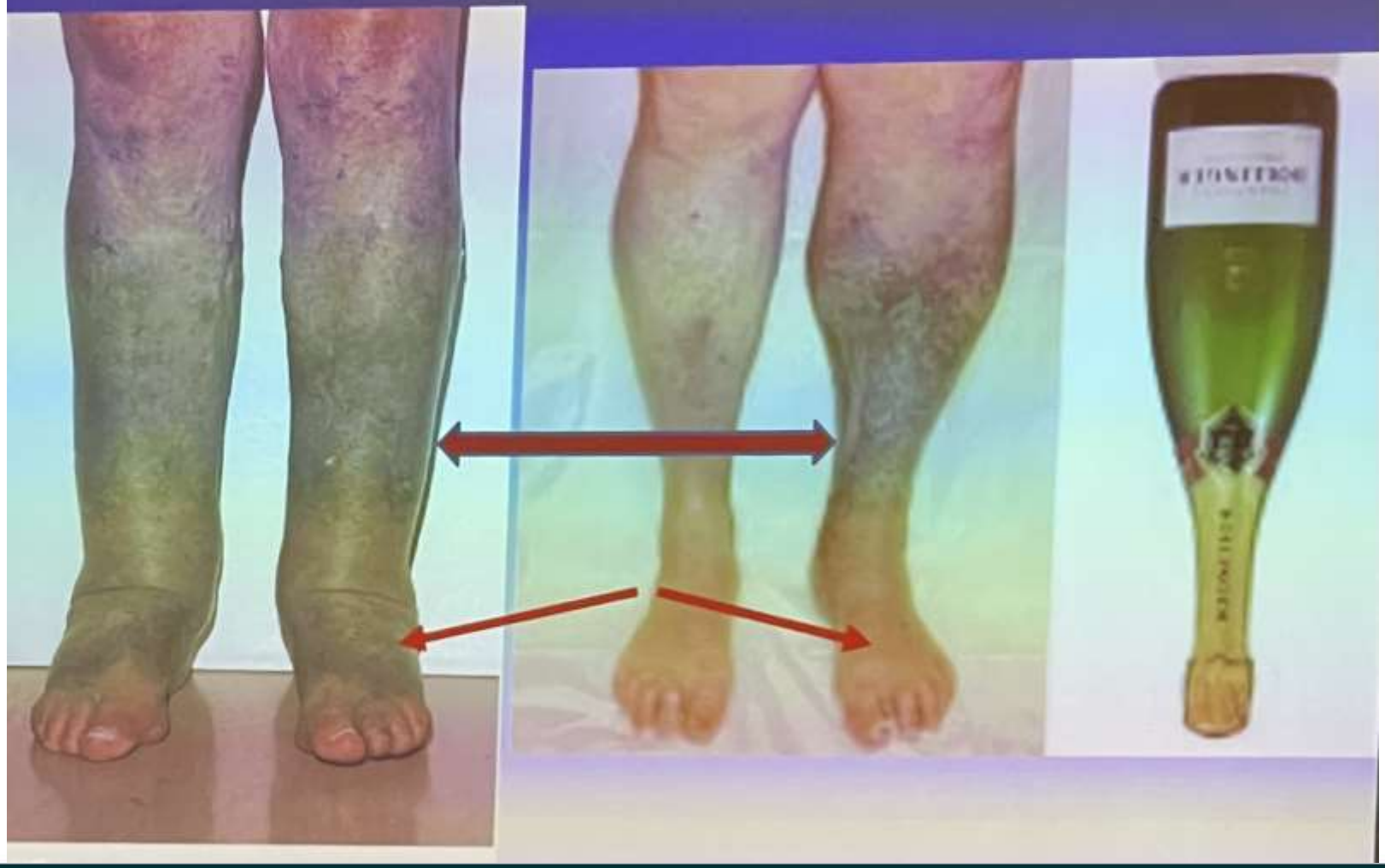
DIAGNOSIS OF PHLEBOLYMPHEDEMA

→CLINICAL

"rests primarily on clinical impression (ie, suggestive history and characteristic findings at physical examination)."

[Witte C, et al. Radiographics 2000;20:1709 – 1720]

PHYSICAL FINDINGS OF PHLEBOLYMPHEDEMA



CONCLUSIONS PHLEBOLYMPHEDEMA

- Underdiagnosed and Undertreated
- Dual Pathophysiology must be recognized for successful Rx
- Lymphatic Dysfunction Important

20 years later, PE mortality remains high

After 20 years, **mortality is still high** in PE patients

		1999 ICOPER[1]	2018 MGH PERT data[2]	2020 PERT Consortium data[3]
30-day	**Mortality** (High-Risk / Massive)	~51.0%	34.8%	25.9%
	Mortality (Intermediate-risk / Sub-massive	~11.0%	8.2%	6.1%
	Major Bleeding	10.5%*	11.5%	5%

* 90-day major bleeding rate

1. Kucher et al., Massive pulmonary embolism. Circulation. 2006;113(4):577-582. 2. Secemsky et al., Contemporary Management and Outcomes of Patients with Massive and Submassive Pulmonary Embolism, The American Journal of Medicine (2018), doi: https://doi.org/10.1016/j.amjmed.2018.07.035 3. PERT Consortium® Registry Data; October 2020

@mcbunte

Costs of Conservative Management

18.1%

have ongoing RV dysfunction[1]

33.2%

have moderate or severe functional impairment[1]

24.4%

30-day all-cause readmission[2]

5th percentile

6-minute walk test score (vs. population norms)[1]

1. Sista AK, et al. Persistent right ventricular dysfunction, functional capacity limitation, exercise intolerance, and quality of life impairment following pulmonary embolism: Syste meta-analysis. Vasc Med. 2017 Feb;22(1):37-43
2. PERT Consortium Registry Data. Interim results on 3,400 Patients presented at PERT Symposium October 2020

@mcbunte

MONUMENT HEALTH

AMERICAN VEIN & LYMPHATIC SOCIETY

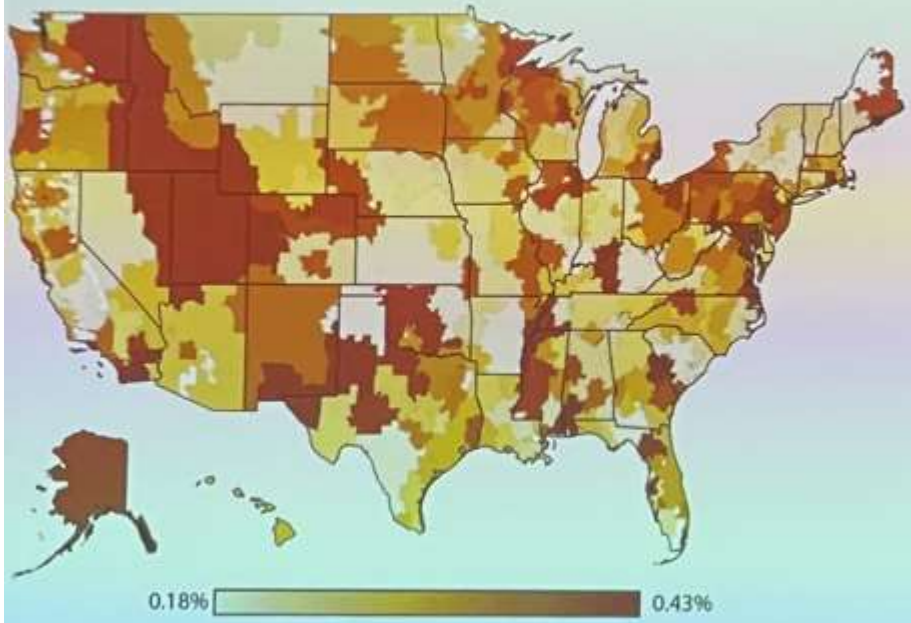
Task Force Findings

The following characteristics were identified that needed attention:

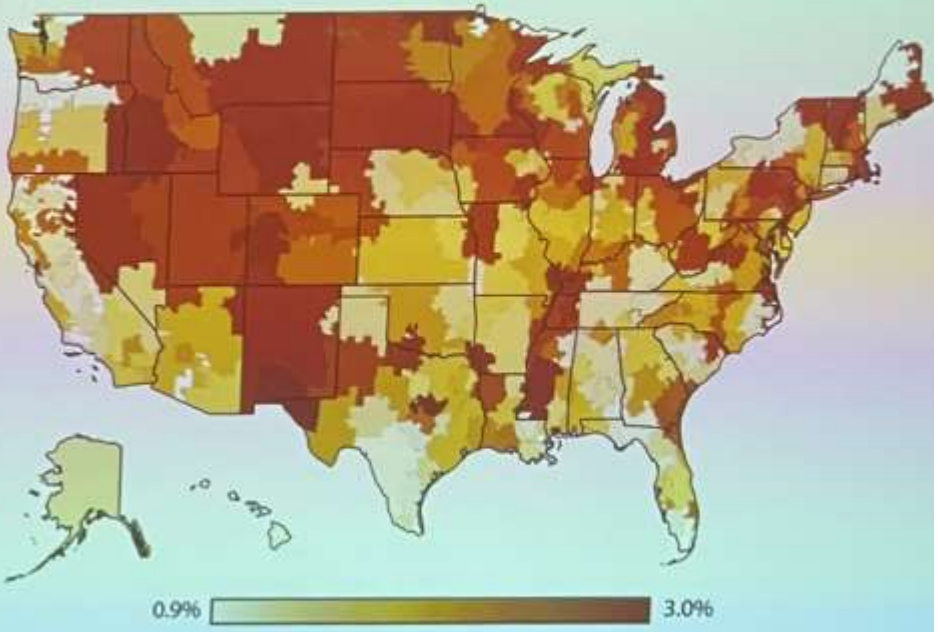
1. Wound centers providers often do not recognize venous pathology;
2. Wound centers are disincentivized to send early referrals for vascular evaluation;
3. We have Level I evidence that early intervention accelerates ulcer healing & is cost effective
4. There is an extraordinary education gap that needed to be filled

Rate of Postoperative VTE

Risk-Adjusted Pre-Discharge VTE Rate



90-day Risk-adjusted Post-Discharge VTE Rate



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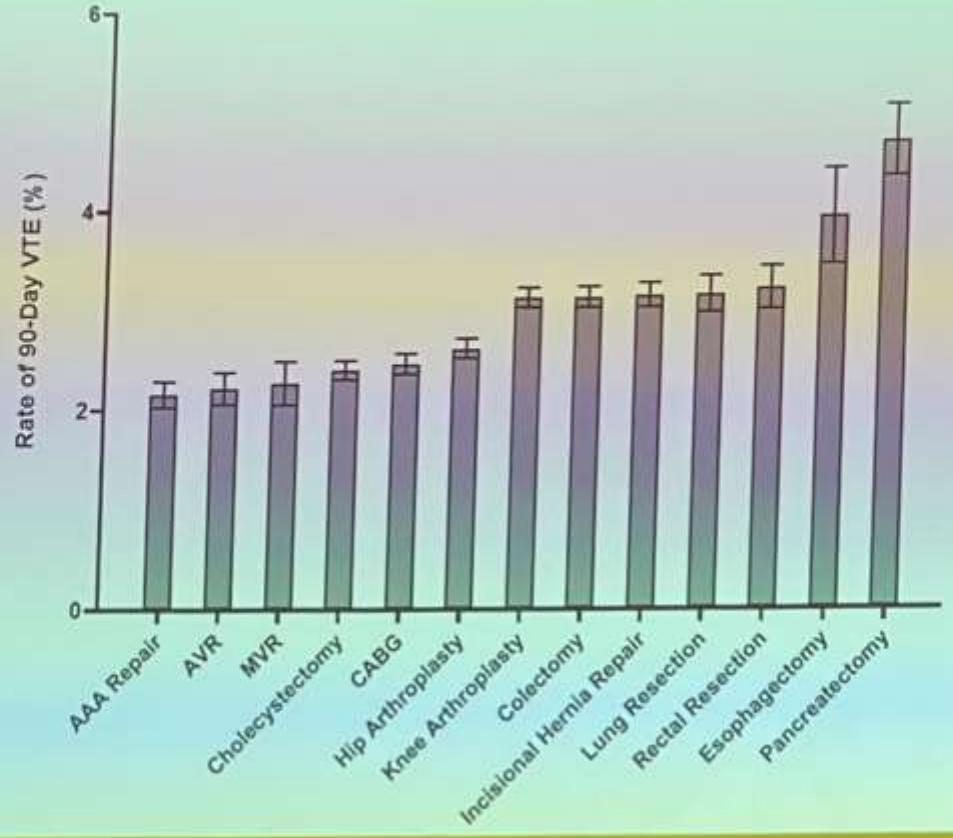
Rate of Post-operative VTE by Surgery Type



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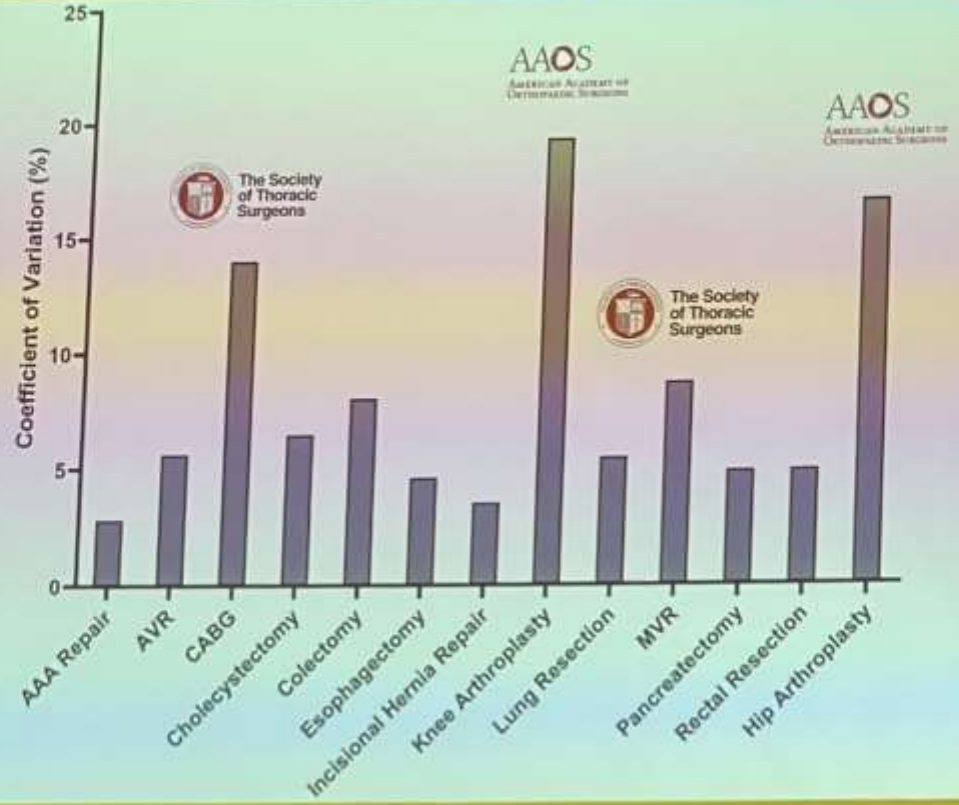
Coefficient of Variation Across Hospitals by Surgery Type



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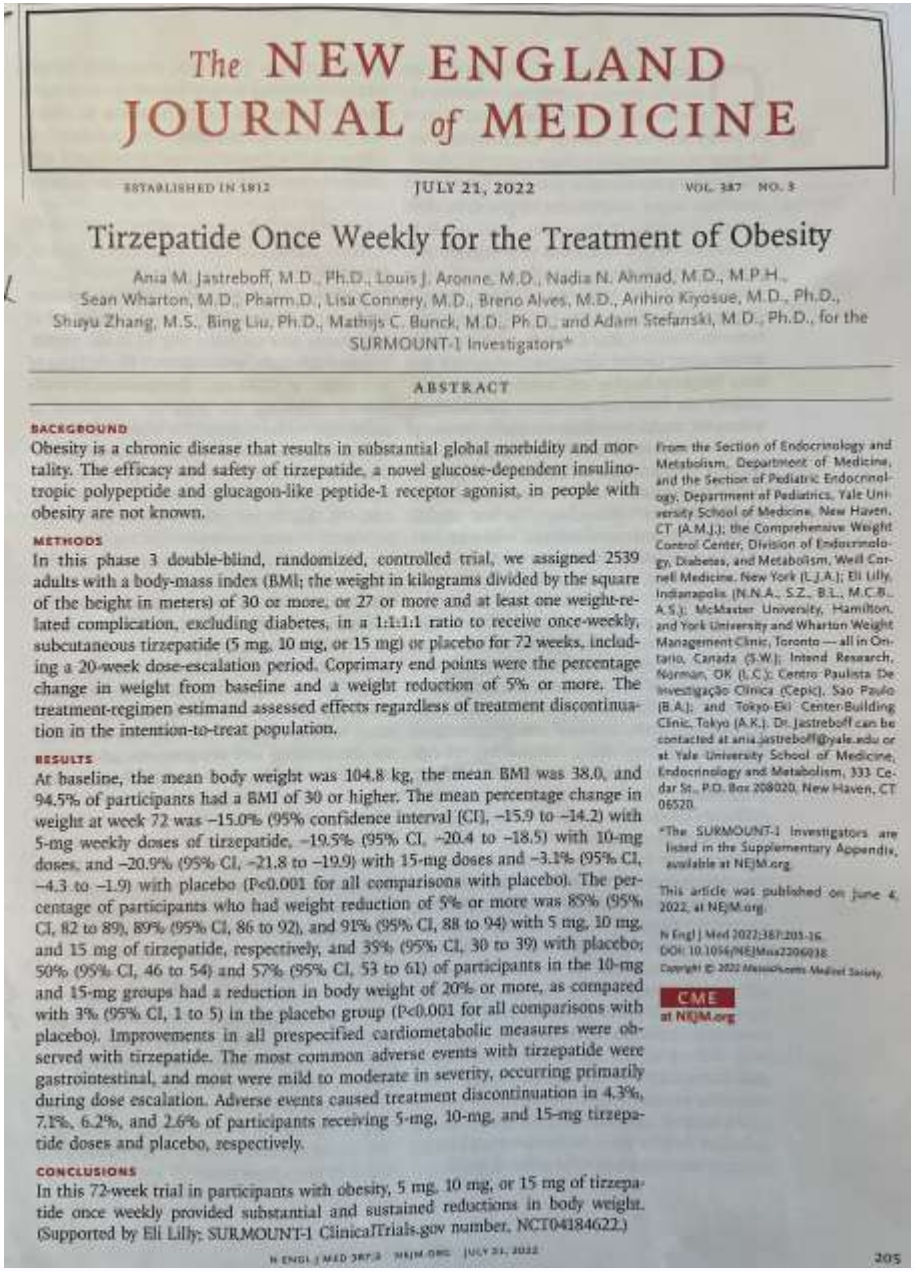
Conclusions

While post-operative VTE rates are dropping, there is still substantial variation across geographic regions, hospitals, and surgical procedures

Post-discharge VTE represents the majority of VTE post-operatively

There is substantially more variation in post-op VTE rates for most highly scrutinized surgeries

Identification of factors leading to this variation can be targets for quality improvement



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 21, 2022 VOL. 387 NO. 3

Tirzepatide Once Weekly for the Treatment of Obesity

Ania M. Jastreboff, M.D., Ph.D., Louis J. Aronne, M.D., Nadia N. Ahmad, M.D., M.P.H., Sean Wharton, M.D., Pharm.D., Lisa Connery, M.D., Breno Alves, M.D., Arihiro Kiyosue, M.D., Ph.D., Shuyu Zhang, M.S., Bing Liu, Ph.D., Mathijs C. Bunck, M.D., Ph.D., and Adam Stefanski, M.D., Ph.D., for the SURMOUNT-1 Investigators*

ABSTRACT

BACKGROUND

Obesity is a chronic disease that results in substantial global morbidity and mortality. The efficacy and safety of tirzepatide, a novel glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, in people with obesity are not known.

METHODS

In this phase 3 double-blind, randomized, controlled trial, we assigned 2539 adults with a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 30 or more, or 27 or more and at least one weight-related complication, excluding diabetes, in a 1:1:1:1 ratio to receive once-weekly, subcutaneous tirzepatide (5 mg, 10 mg, or 15 mg) or placebo for 72 weeks, including a 20-week dose-escalation period. Coprimary end points were the percentage change in weight from baseline and a weight reduction of 5% or more. The treatment-regimen estimand assessed effects regardless of treatment discontinuation in the intention-to-treat population.

RESULTS

At baseline, the mean body weight was 104.8 kg, the mean BMI was 38.0, and 94.5% of participants had a BMI of 30 or higher. The mean percentage change in weight at week 72 was −15.0% (95% confidence interval [CI], −15.9 to −14.2) with 5-mg weekly doses of tirzepatide, −19.5% (95% CI, −20.4 to −18.5) with 10-mg doses, and −20.9% (95% CI, −21.8 to −19.9) with 15-mg doses and −3.1% (95% CI, −4.3 to −1.9) with placebo (P<0.001 for all comparisons with placebo). The percentage of participants who had weight reduction of 5% or more was 85% (95% CI, 82 to 89), 89% (95% CI, 86 to 92), and 91% (95% CI, 88 to 94) with 5 mg, 10 mg, and 15 mg of tirzepatide, respectively, and 35% (95% CI, 30 to 39) with placebo; 50% (95% CI, 46 to 54) and 57% (95% CI, 53 to 61) of participants in the 10-mg and 15-mg groups had a reduction in body weight of 20% or more, as compared with 3% (95% CI, 1 to 5) in the placebo group (P<0.001 for all comparisons with placebo). Improvements in all prespecified cardiometabolic measures were observed with tirzepatide. The most common adverse events with tirzepatide were gastrointestinal, and most were mild to moderate in severity, occurring primarily during dose escalation. Adverse events caused treatment discontinuation in 4.3%, 7.1%, 6.2%, and 2.6% of participants receiving 5-mg, 10-mg, and 15-mg tirzepatide doses and placebo, respectively.

CONCLUSIONS

In this 72-week trial in participants with obesity, 5 mg, 10 mg, or 15 mg of tirzepatide once weekly provided substantial and sustained reductions in body weight. (Supported by Eli Lilly; SURMOUNT-1 ClinicalTrials.gov number, NCT04184622.)

From the Section of Endocrinology and Metabolism, Department of Medicine, and the Section of Pediatric Endocrinology, Department of Pediatrics, Yale University School of Medicine, New Haven, CT (A.M.J.); the Comprehensive Weight Control Center, Division of Endocrinology, Diabetes, and Metabolism, Weill Cornell Medicine, New York (L.J.A.); Eli Lilly, Indianapolis (N.N.A., S.Z., B.L., M.C.B., A.S.); McMaster University, Hamilton, and York University and Wharton Weight Management Clinic, Toronto — all in Ontario, Canada (S.W.); Intend Research, Norman, OK (L.C.); Centro Paulista De Investigação Clínica (Cepic), Sao Paulo (B.A.); and Tokyo-Eki Center-Building Clinic, Tokyo (A.K.). Dr. Jastreboff can be contacted at ania.jastreboff@yale.edu or at Yale University School of Medicine, Endocrinology and Metabolism, 333 Cedar St., P.O. Box 208020, New Haven, CT 06520.

*The SURMOUNT-1 Investigators are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on June 4, 2022, at NEJM.org.

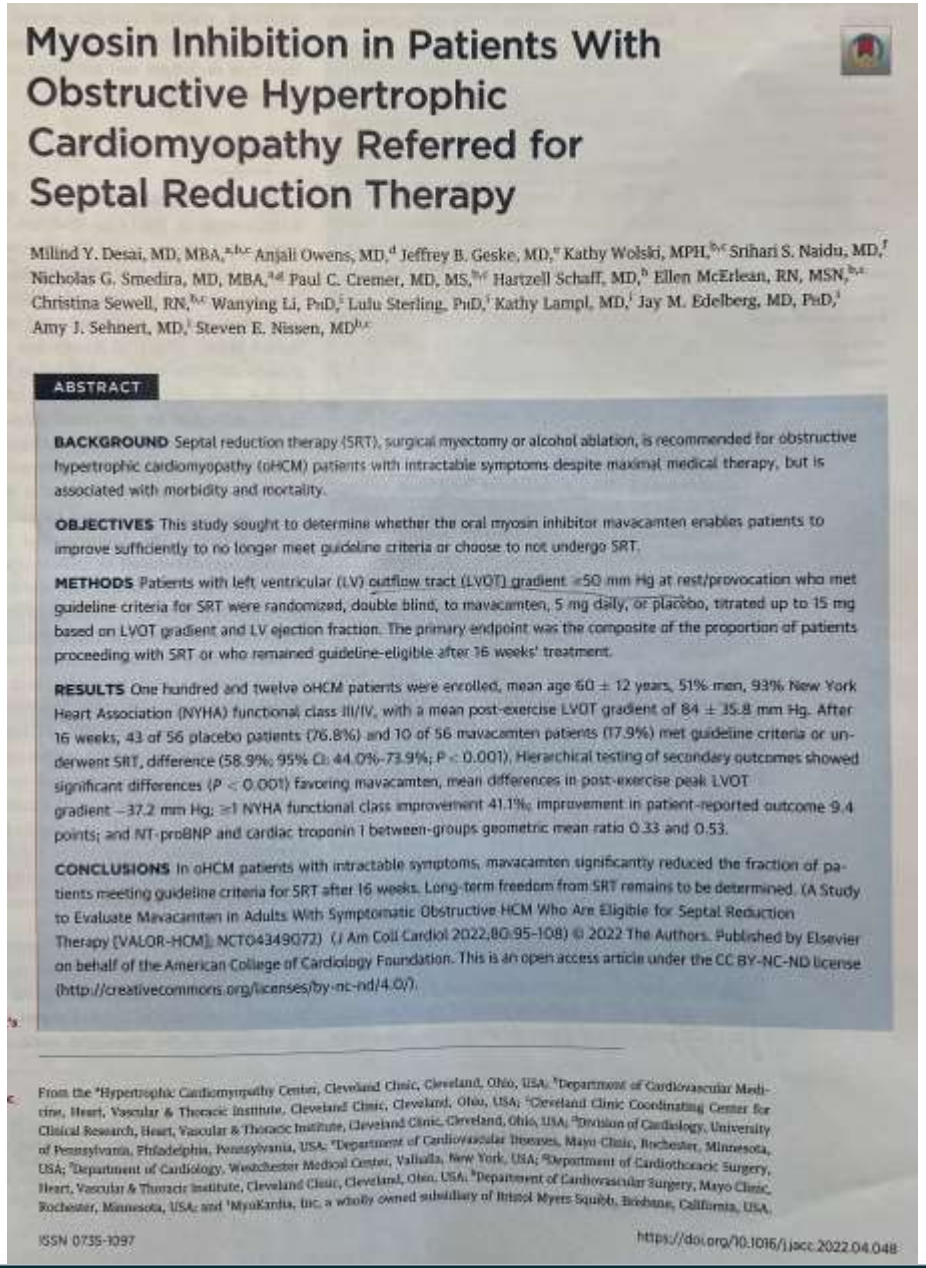
N Engl J Med 2022;387:205-16.
DOI: 10.1056/NEJMoa2206038

CME at NEJM.org

Mounjaro / tirzepatide

- Escalating doses
- SQ weekly
- Novel glucose-dependent insulinotropic polypeptide AND glucagon-like peptide-1 receptor agonist

- 10 & 15 mg doses had ≥ 20% weight reduction (baseline BMI 38)



Myosin Inhibition in Patients With Obstructive Hypertrophic Cardiomyopathy Referred for Septal Reduction Therapy

Milind Y. Desai, MD, MBA,[a,b,c] Anjali Owens, MD,[d] Jeffrey B. Geske, MD,[e] Kathy Wolski, MPH,[b,c] Srihari S. Naidu, MD,[f] Nicholas G. Smedira, MD, MBA,[a,d] Paul C. Cremer, MD, MS,[b,c] Hartzell Schaff, MD,[b] Ellen McErlean, RN, MSN,[b,c] Christina Sewell, RN,[b,c] Wanying Li, PhD,[g] Lulu Sterling, PhD,[g] Kathy Lampl, MD,[g] Jay M. Edelberg, MD, PhD,[g] Amy J. Sehnert, MD,[g] Steven E. Nissen, MD[b,c]

ABSTRACT

BACKGROUND Septal reduction therapy (SRT), surgical myectomy or alcohol ablation, is recommended for obstructive hypertrophic cardiomyopathy (oHCM) patients with intractable symptoms despite maximal medical therapy, but is associated with morbidity and mortality.

OBJECTIVES This study sought to determine whether the oral myosin inhibitor mavacamten enables patients to improve sufficiently to no longer meet guideline criteria or choose to not undergo SRT.

METHODS Patients with left ventricular (LV) outflow tract (LVOT) gradient ≥50 mm Hg at rest/provocation who met guideline criteria for SRT were randomized, double blind, to mavacamten, 5 mg daily, or placebo, titrated up to 15 mg based on LVOT gradient and LV ejection fraction. The primary endpoint was the composite of the proportion of patients proceeding with SRT or who remained guideline-eligible after 16 weeks' treatment.

RESULTS One hundred and twelve oHCM patients were enrolled, mean age 60 ± 12 years, 51% men, 93% New York Heart Association (NYHA) functional class III/IV, with a mean post-exercise LVOT gradient of 84 ± 35.8 mm Hg. After 16 weeks, 43 of 56 placebo patients (76.8%) and 10 of 56 mavacamten patients (17.9%) met guideline criteria or underwent SRT, difference (58.9%; 95% CI: 44.0%-73.9%; $P < 0.001$). Hierarchical testing of secondary outcomes showed significant differences ($P < 0.001$) favoring mavacamten, mean differences in post-exercise peak LVOT gradient −37.2 mm Hg; ≥1 NYHA functional class improvement 41.1%; improvement in patient-reported outcome 9.4 points; and NT-proBNP and cardiac troponin I between-groups geometric mean ratio 0.33 and 0.53.

CONCLUSIONS In oHCM patients with intractable symptoms, mavacamten significantly reduced the fraction of patients meeting guideline criteria for SRT after 16 weeks. Long-term freedom from SRT remains to be determined. (A Study to Evaluate Mavacamten in Adults With Symptomatic Obstructive HCM Who Are Eligible for Septal Reduction Therapy (VALOR-HCM); NCT04349072) (J Am Coll Cardiol 2022;80:95-108) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation.

From the [a]Hypertrophic Cardiomyopathy Center, Cleveland Clinic, Cleveland, Ohio, USA; [b]Department of Cardiovascular Medicine, Heart, Vascular & Thoracic Institute, Cleveland Clinic, Cleveland, Ohio, USA; [c]Cleveland Clinic Coordinating Center for Clinical Research, Heart, Vascular & Thoracic Institute, Cleveland Clinic, Cleveland, Ohio, USA; [d]Division of Cardiology, University of Pennsylvania, Philadelphia, Pennsylvania, USA; [e]Department of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota, USA; [f]Department of Cardiology, Westchester Medical Center, Valhalla, New York, USA; [g]Department of Cardiothoracic Surgery, Heart, Vascular & Thoracic Institute, Cleveland Clinic, Cleveland, Ohio, USA; [h]Department of Cardiovascular Surgery, Mayo Clinic, Rochester, Minnesota, USA; and [i]MyoKardia, Inc. a wholly owned subsidiary of Bristol Myers Squibb, Brisbane, California, USA.

ISSN 0735-1097 https://doi.org/10.1016/j.jacc.2022.04.048

Camzyos / mavacamten

- Oral myosin inhibitor
- Monthly escalating doses
- Lots of echos
- Significant ↓ in LVOT gradient
-Significant drop in pts qualifying for septal reduction therapy

Effect of Empagliflozin on Heart Failure Outcomes

	EMPEROR-Reduced EF ≤ 40%	EMPEROR-Preserved EF > 40%
Cardiovascular death or hospitalization for heart failure	0.75 (0.65 – 0.86) [823 events]	0.79 (0.69 – 0.90) [926 events]
Time to first heart failure hospitalization	0.69 (0.59 – 0.81) [588 events]	0.71 (0.60 – 0.83) [611 events]
Time to cardiovascular death	0.92 (0.75 – 1.12) [389 events]	0.91 (0.76 – 1.09) [463 events]
Total (first and recurrent) hospitalizations for heart failure	0.70 (0.58 – 0.85) [941 events]	0.73 (0.61 – 0.88) [948 events]

Packer M et al. *N Engl J Med 2020;* Anker SD et al. *N Engl J Med 202*

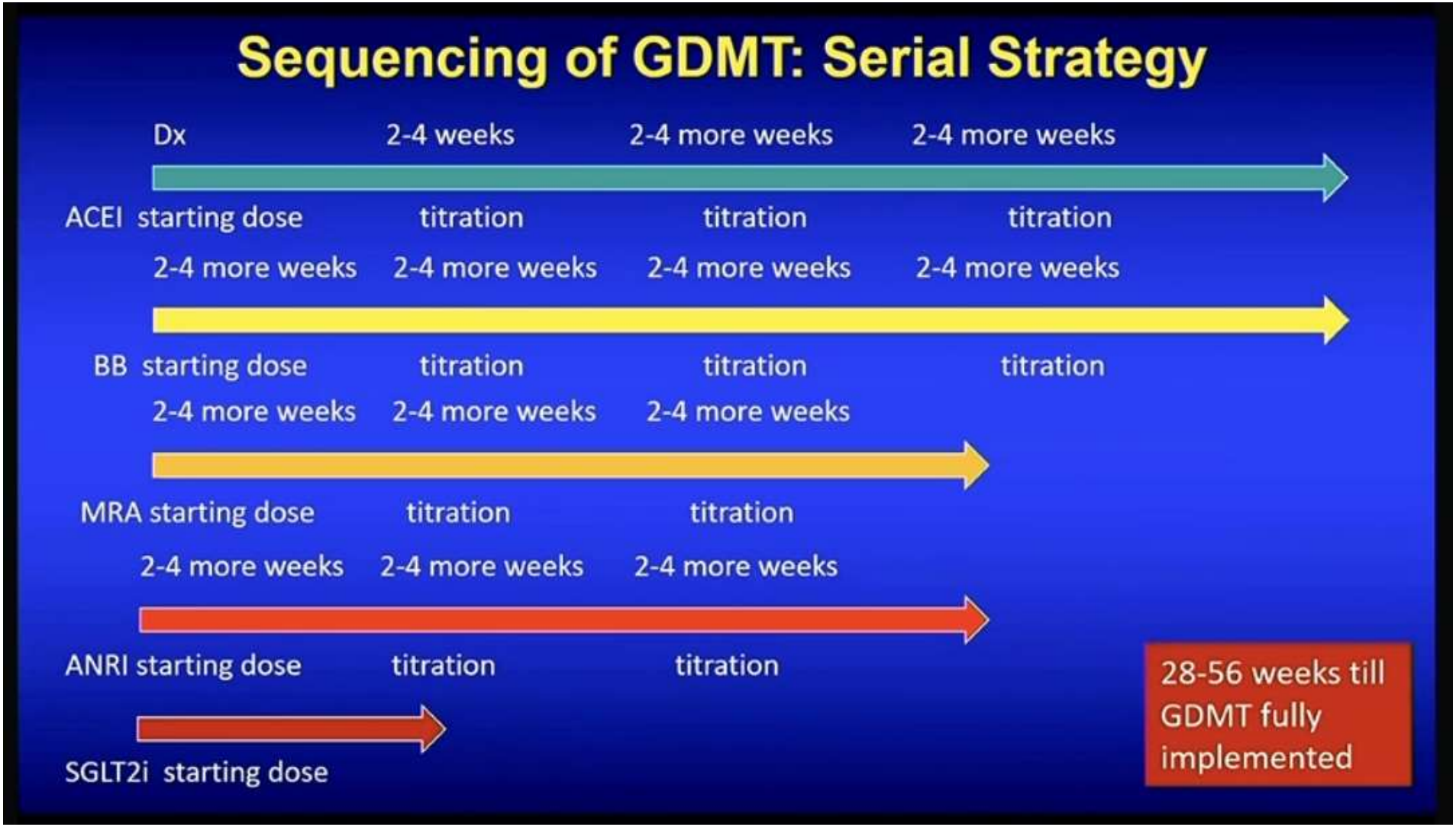
Cumulative Impact of Evidence-Based Heart Failure with Reduced EF Medical Therapies

	Relative-risk	2 yr Mortality
None	- -	35%
ACEI or ARB	↓ 23%	27%
Beta Blocker	↓ 35%	18%
Aldosterone Ant	↓ 30%	13%
ARNI (replacing ACEI/ARB)	↓ 16%	10.9%
SGLT2 inhibitor	↓ 17%	9.1%

Cumulative risk reduction if all evidence-based medical therapies are used:
Relative risk reduction 74.0%, Absolute risk reduction: 25.9%, NNT = 3.9

Updated from Fonarow GC, et al. Am Heart J 2011;161:1024-1030 and Lancet 2008;372:1195-1196.

Sequencing of GDMT: Serial Strategy



GDMT: Simultaneous/Rapid Sequence Strategy

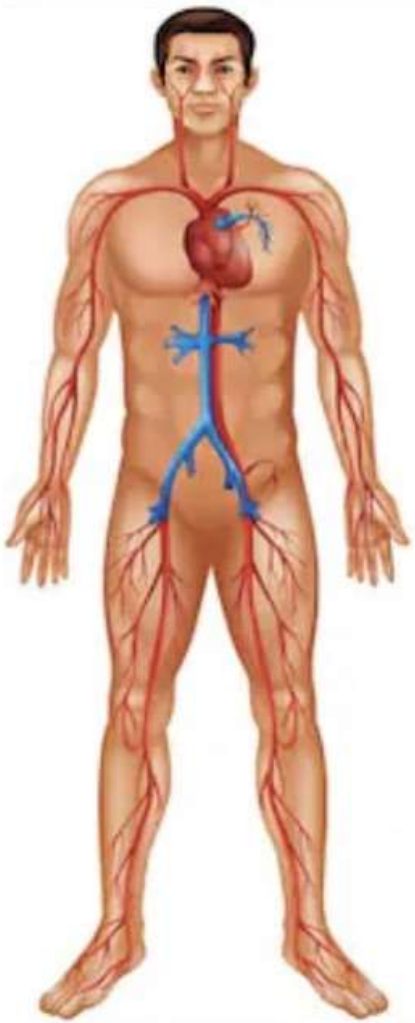
Comprehensive disease-modifying medical therapy (CDMMT) from Day 1

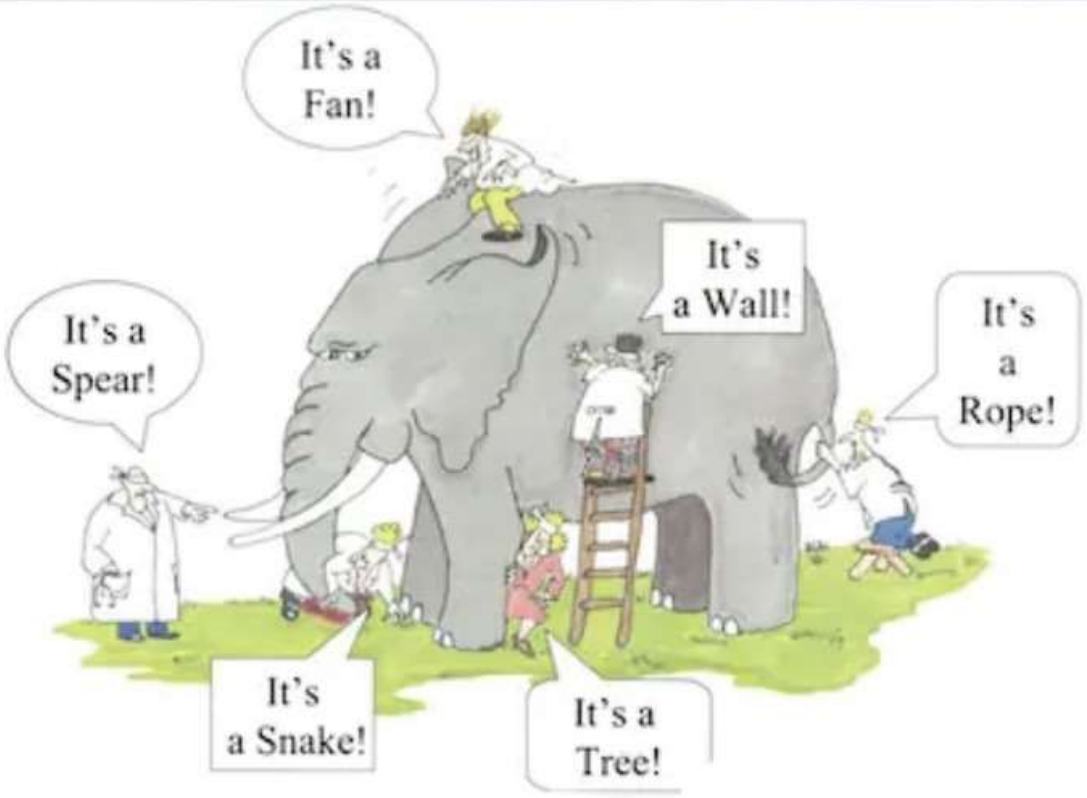
Hospitalized or outpatient

Day 1	Day 7-14	Day 14-28	Day 21-42	Beyond
ARNI	…	(Titrate, as tolerated)	Titrate, as tolerated	• Maintenance / further optimization of foundational therapies • Consideration of EP device therapies/Mitraclip • Consideration of add-on therapies or advanced therapies, if refractory • Manage comorbidities
BB	Titrate, as tolerated	Titrate, as tolerated	Titrate, as tolerated	
MRA	…	Titrate, as tolerated	…	
SGLT2i	…	…	…	
Low starting doses Prioritize beta-blocker titration	Benefits of each Rx demonstrated within 30 days of initiation Cumulative benefits within 30 days (>75% relative risk reduction)			Focus on complete set of CDMMT being implemented

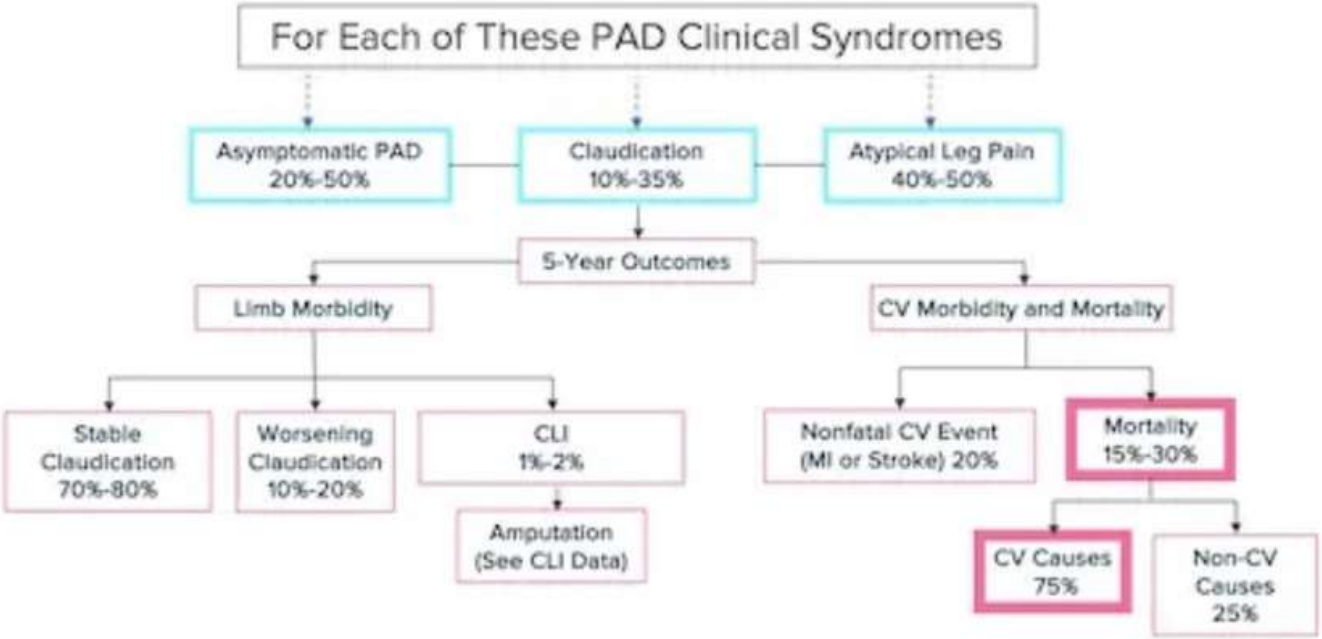
Greene, Butler, Fonarow. *JAMA Cardiology* 2021 doi:10.1001/jamacardio.2021.0496.

We must see the *WHOLE PICTURE*





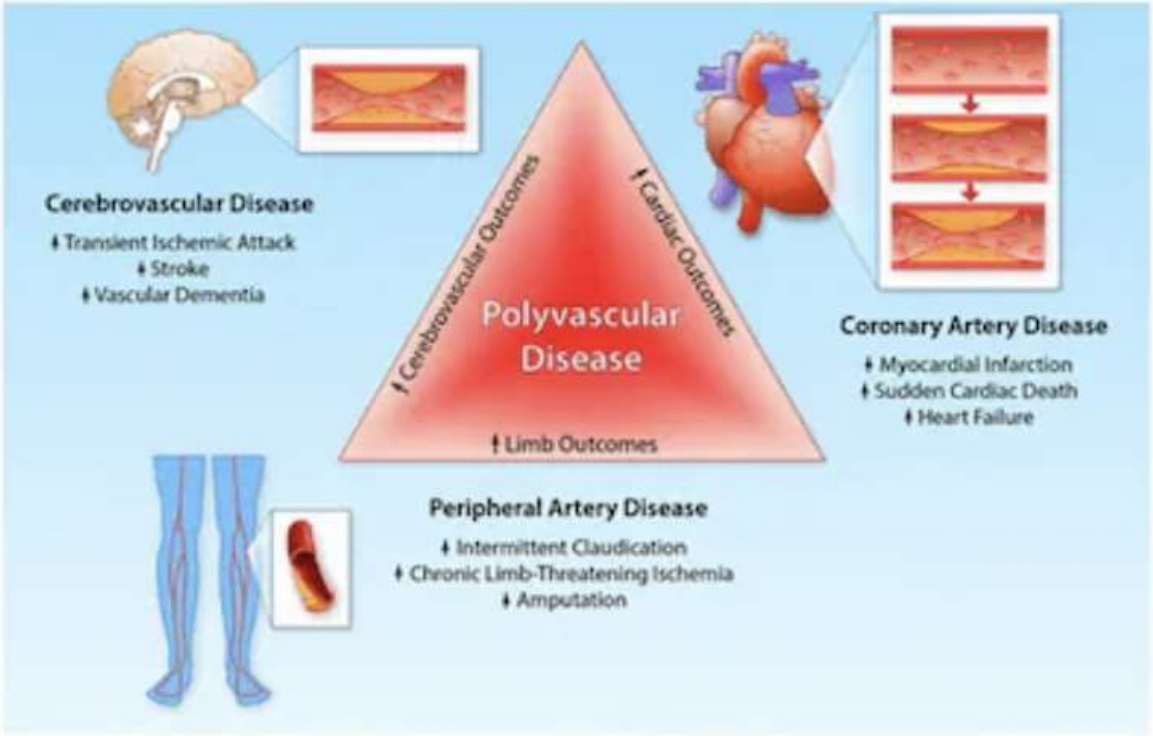
Natural History of Atherosclerotic Lower-Extremity PAD



CLI, critical limb ischemia; CV, cardiovascular; MI, myocardial infarction.
Hirsch AT, et al. Circulation. 2006;113:e463-e654.

Polyvascular Disease

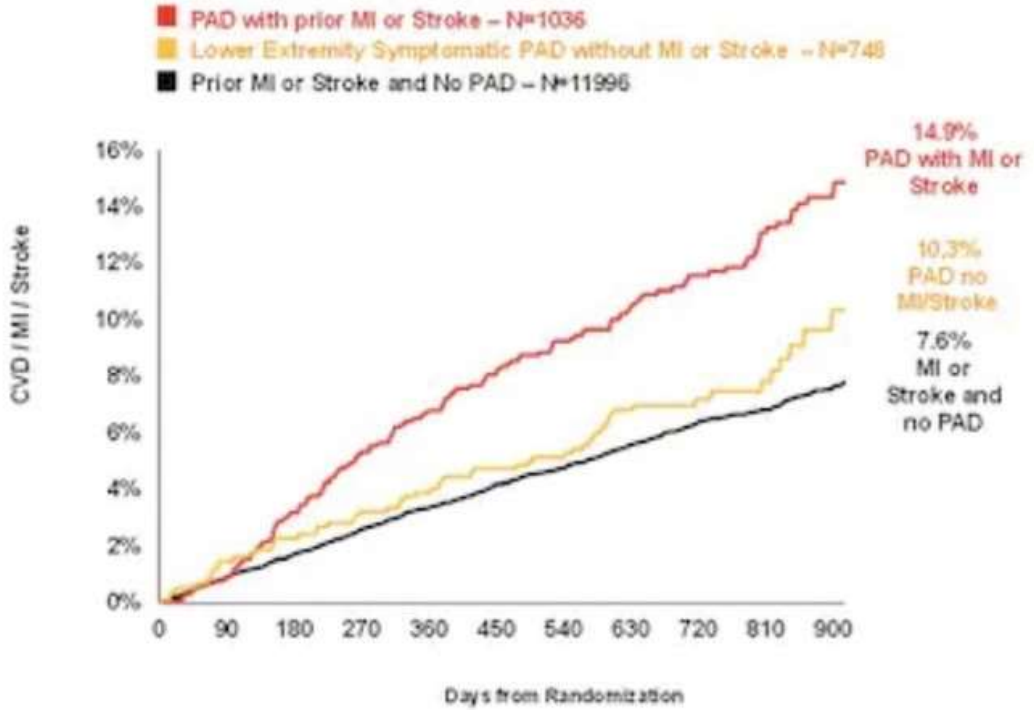
Atherosclerotic Disease in ≥ 2 Arterial Beds, Typically Symptomatic or Resulting in Significant (> 50%) Vessel Stenosis



Aday AW, et al. Circ Res. 2021;128:1818-1832.

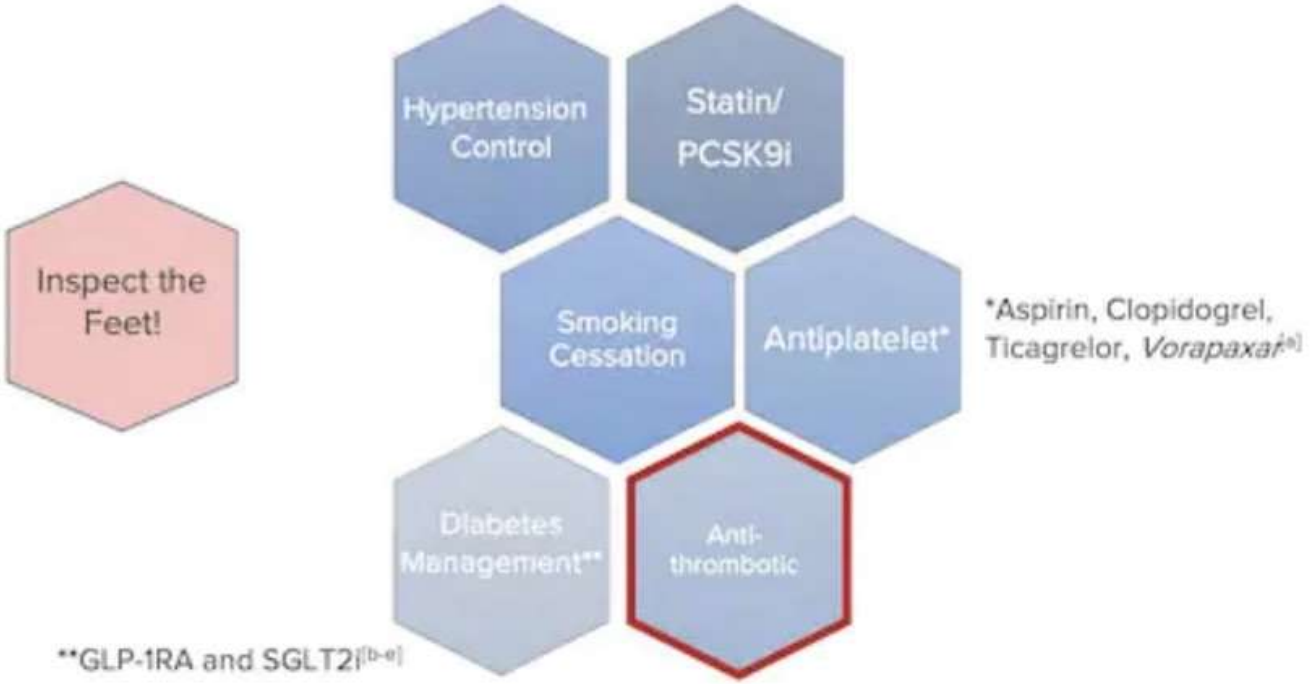
Polyvascular Disease and the Risk of MACE in Patients With PAD

Major Adverse Cardiovascular Events in Placebo Patients by Disease State



Bonaca MP, et al. Circulation. 2018;137:338-350.

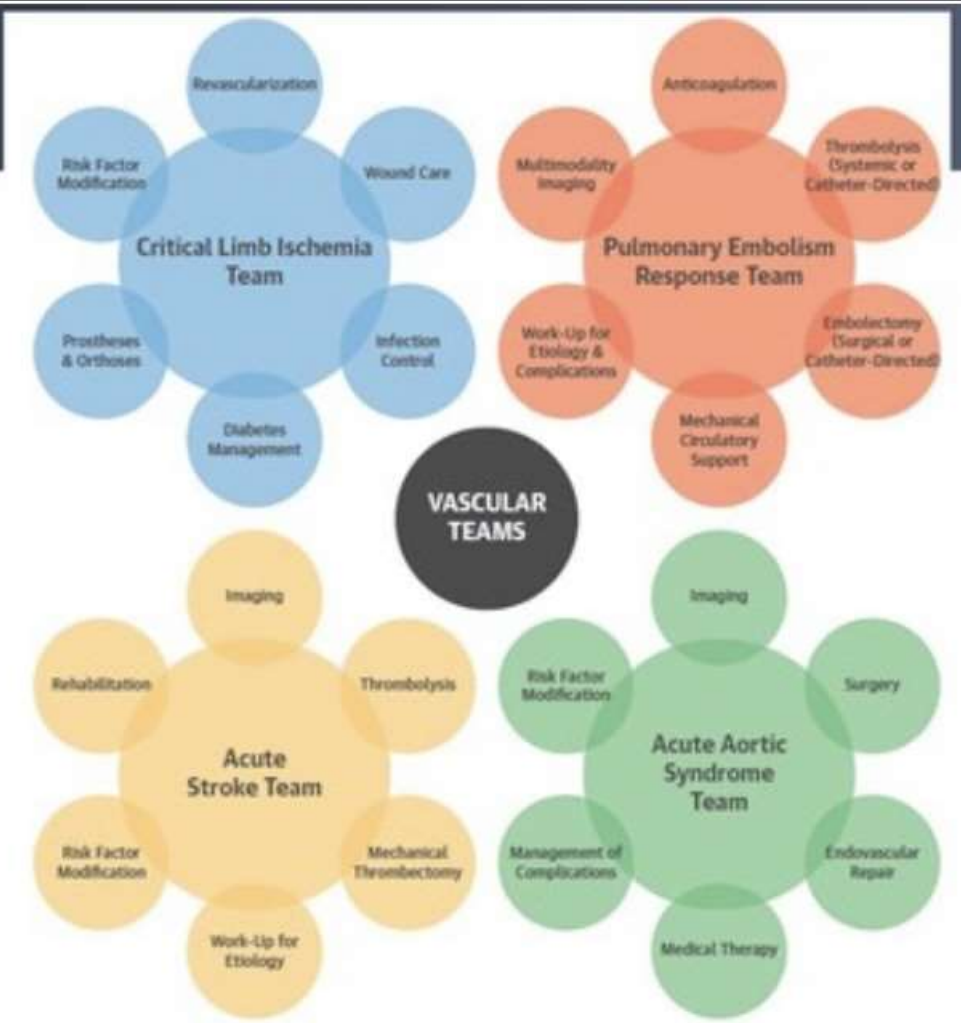
Preventing MACE/MALE in Patients With PAD



GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium/glucose cotransporter-2 inhibitor.

a. Hiatt WR, et al; EUCLID Trial Steering Committee and Investigators. New Engl J Med. 2017;376:32-40; b. Verma S, et al. Circulation. 2018;137:405-407; c. Bonaca MP, et al. Circulation. 2020;142:734-747; d. Verma S, et al; LEADER Publication Committee on behalf of the LEADER Trial Investigators. Circulation. 2018;137:2179-2183; e. Dhatariya K, et al; LEADER Publication Committee on behalf of the LEADER Trial Investigators. Diabetes Care. 2018;41:2229-2235.

Vascular Teams



Kolte D, et al. J Am Coll Cardiol. 2019;73:2477-2486

Levels of Evidence

- **Tier 1** – synthesized evidence supporting implementation in practice
- **Tier 2** – synthesized evidence not adequate to support routine implantation in practice; may still be useful in selective use strategies/decision making
- **Tier 3** – synthesized evidence supporting recommendations against use, or no relevant synthesized evidence

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Fundamental Tenets of Evidence-Based Medicine (EBM)

Awareness of best available evidence required for best decision making

EBM helps us understand how trustworthy the evidence is

Evidence, on its own, is never sufficient to make a clinical decision

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In summary
Trust your team
Continually reassess all data
Frequent communication from trusted stakeholders
Involve all levels of the team in your structure
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Missed Opportunities for Better Cardiovascular Health

4.1 M[1] not taking aspirin as recommended

67.8 M[2] with uncontrolled BP (≥ 130/80 mm Hg)

37.4 M[3] not taking statins as recommended

52.5 M[4] combustible tobacco users

\+ **69.7 M**[5] who are physically inactive

~ **231.5 M** missed opportunities

illion Hearts®

1. Wall HK, et al. Vital Signs: Prevalence of Key Cardiovascular Disease Risk Factors for Million Hearts 2022 — 2011–2018. MMWR. 2018;67(35):983-991.
2. Centers for Disease Control and Prevention (CDC). Hypertension Cascade: Hypertension Prevalence, Treatment and Control Estimates Among US Adults Aged 18 Y... Older Applying the Criteria From the American College of Cardiology and American Heart Association's 2017 Hypertension Guideline—NHANES 2015–2018. Atlanta, GA: Department of Health and Human Services; 2019. https://millionhearts.hhs.gov/data-reports/hypertension-prevalence.html. Accessed August 21, 2021.
3. Thompson-Paul AM, et al. Recommended and Observed Statin Use among U.S. Adults – National Health and Nutrition Examination Survey, 2011-2018. JACC. In submiss...
4. Internal analysis of 2019 National Survey on Drug Use and Health data.
5. Preliminary results from internal analysis of 2020 National Health Interview Survey data.

Million Hearts® 2027 Priorities

Building Healthy Communities
Decrease Tobacco Use
Decrease Physical Inactivity
Decrease Particle Pollution

Optimizing Care
Improve Appropriate Aspirin or Anticoagulant Use
Improve Blood Pressure Control
Improve Cholesterol Management
Improve Smoking Cessation
Increase Use of Cardiac Rehabilitation

Focusing On Health Equity

- Pregnant and Postpartum People with Hypertension
- People from Racial/Ethnic Minority Groups
- People with Behavioral Health Issues Who Use Tobacco
- People with Lower Incomes
- People Who Live in Rural Areas or Other 'Access Deserts'

Strategies to Reduce/Neutralize Implicit Bias

1. **Common identity formation.** Ask interviewee questions about interests and activities that you share (focus on a shared, common identity betwee YOU and the interviewee).
2. **Perspective taking.** (Take the perespecitve of a member of the group against which you have the unconcious bias).
3. **"Consider the oppostie".** (When data seem to poin to one conclusion, breifly look for the data supporting the opposite conclusion before making a final decision).
4. **Counter-stereotypical exemplars.** (Spend time with or focus on individuals you admire from groups against which you have bias).