MHIF FEATURED STUDY:

COVID-PACT

OPEN AND ENROLLING:

EPIC message: *Research MHIF Patient Referral*

CONDITION:
Critically-ill patients hospitalized with COVID-19

PI:
Retu Saxena, MD

RESEARCH CONTACT:
Stephanie Ebnet, RN
Stephanie.Ebnet@allina.com | 612-863-6286

SPONSOR:
TIMI Study Group

DESCRIPTION:

Phase 2/3, randomized, open-label strategy trial to evaluate the efficacy and safety of antithrombotic therapy for prevention of arterial and venous thrombotic complications in critically-ill patients with COVID-19. Subjects are randomized to standard dose prophylactic versus therapeutic dose anticoagulation (Heparin or Lovenox) and antiplatelet (Plavix) versus no antiplatelet therapy. Subjects are followed for 28 days or until discharge (whichever occurs first). Several trials of anticoagulant intensity in COVID-19 have been completed, but the results of these trials have not yet resolved the uncertainty regarding the optimal dosing of anticoagulant therapy and not led to changes in professional society guidelines from those in place.

CRITERIA LIST/ QUALIFICATIONS:

Inclusion:

- ≥ 18 years old
- Acute infection with SARS-CoV2
- Currently admitted to the ICU or receiving ICU level cares ≤ 96 hours

Exclusion:

- Ongoing (>48 hours) or planned full-dose anticoagulation
- Ongoing or planned treatment with dual antiplatelet therapy
- Contraindication to antithrombotic therapy or high risk of bleeding
- History of heparin-induced thrombocytopenia
- Ischemic stroke within the past 2 weeks
- Pregnancy

Evolution of the ABC's of CVD Prevention: The Kevin Graham Lecture

Roger S. Blumenthal, MD, FACC, FAHA

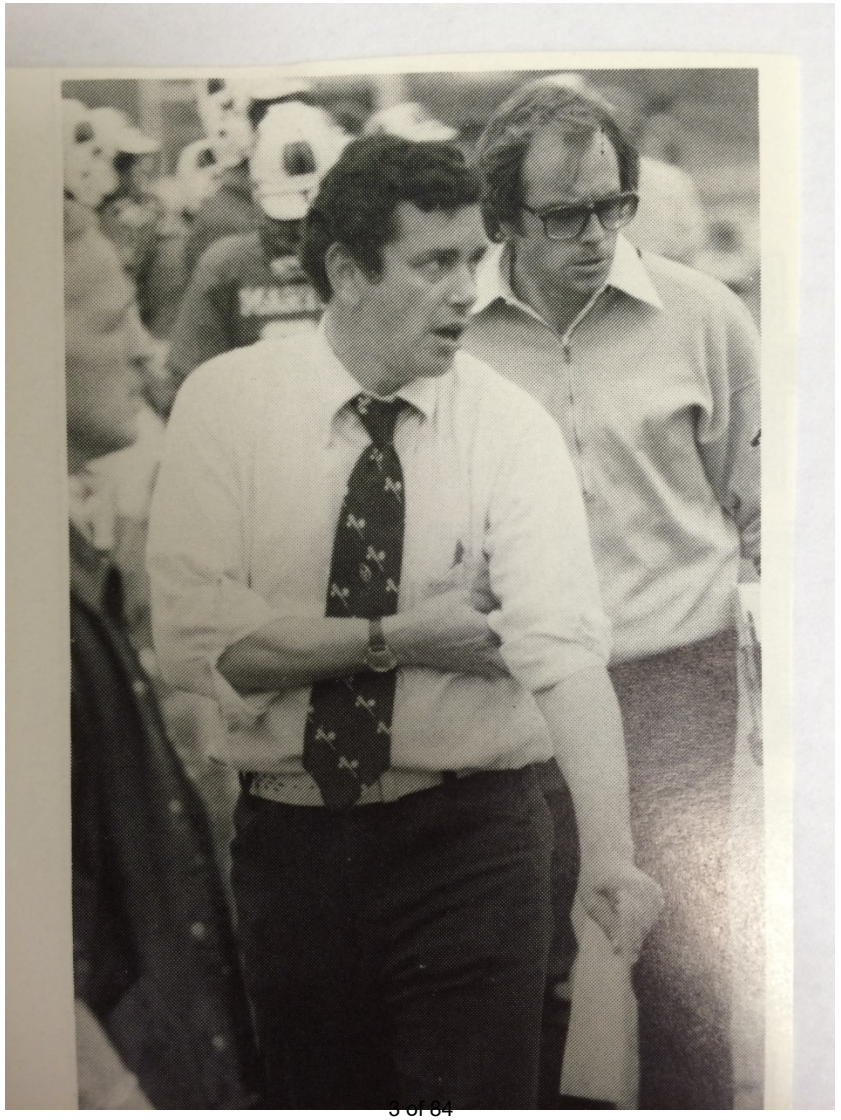
The Kenneth Jay Pollin Professor of Cardiology

Director, The Johns Hopkins Ciccarone Center for the Prevention of Heart Disease

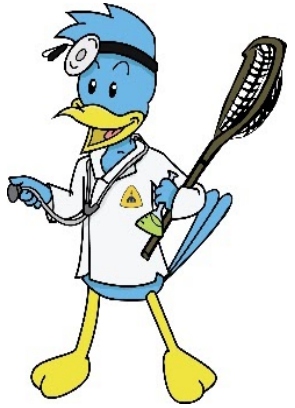
Disclosures: None

JOHNS HOPKINS
MEDICINE

Intense Coaches in NCAA Lacrosse Championship Game



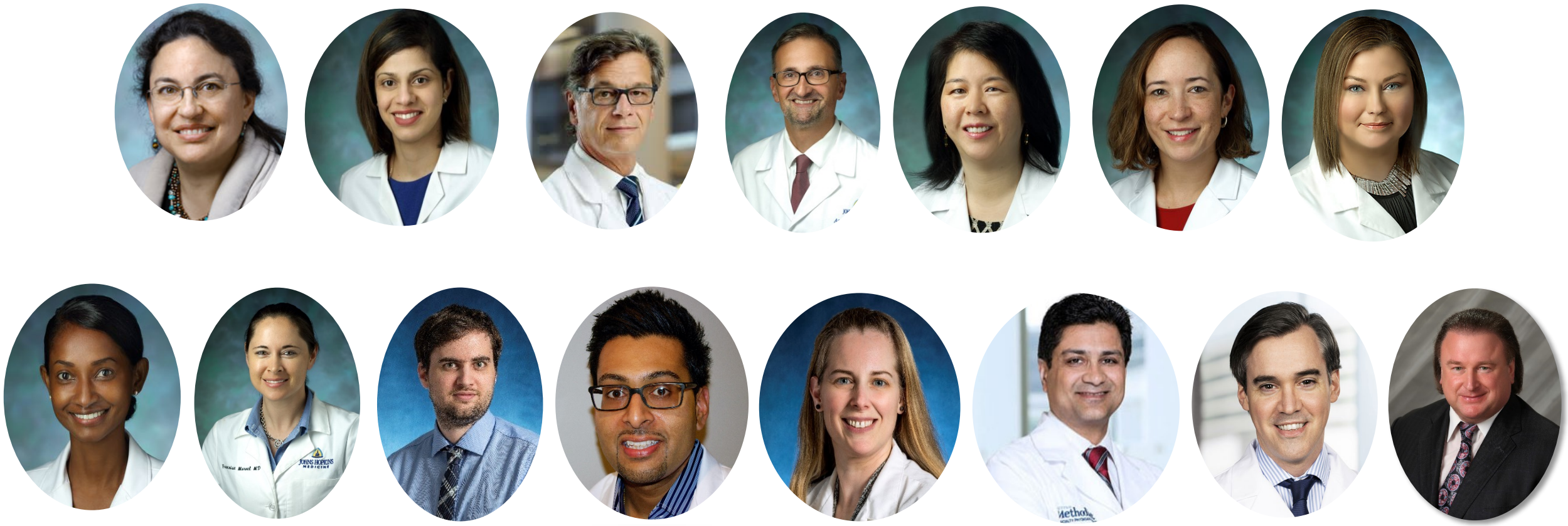
The Ciccarone Center for the Prevention of CV Disease



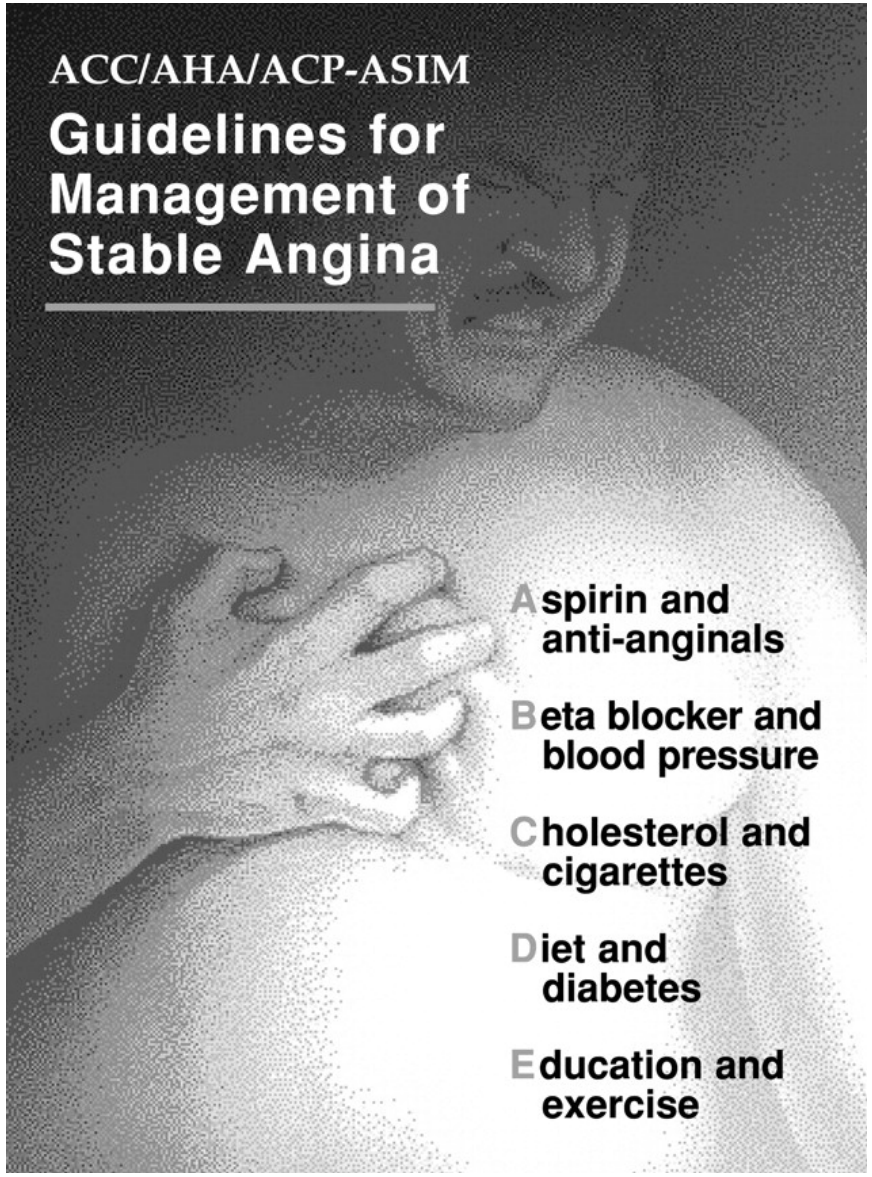
@CiccaroneCenter

Focused on the prevention of ASCVD, HF, AFIB, PAD

Ciccarone Team (Cont.)



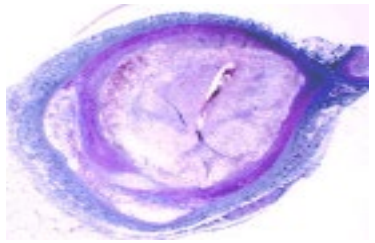
ABC Approach for Angina (1999)

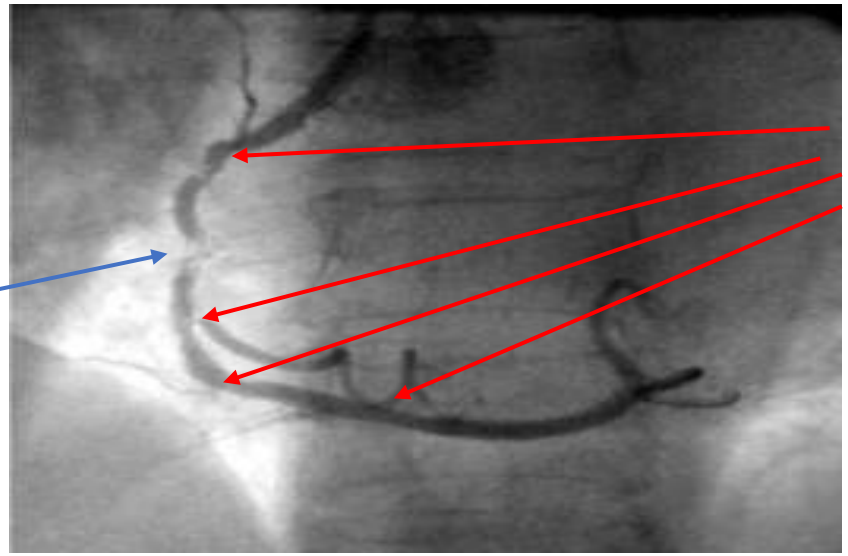


A paradigm that suggests why randomized trials have not demonstrated a survival benefit for revascularization in SIHD

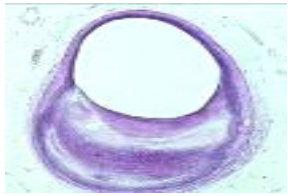
Severe Obstruction (angina, no rupture) vs Mild Obstruction (no angina, likely to rupture)

Severe fibrotic plaque
- **Severe obstruction**
- **No lipid**
- **Fibrosis, Ca^{2+}**





Vulnerable plaque
- **Minor obstruction**
- **Eccentric plaque**
- **Lipid pool**
- **Thin cap**

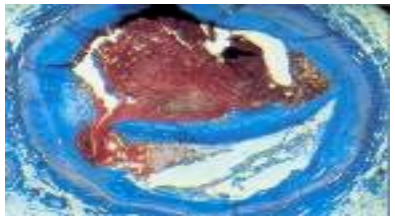


Plaque rupture
- **Acute MI**
- **Unstable angina**
- **Sudden death**

Exertional angina
- **(+) ETT**

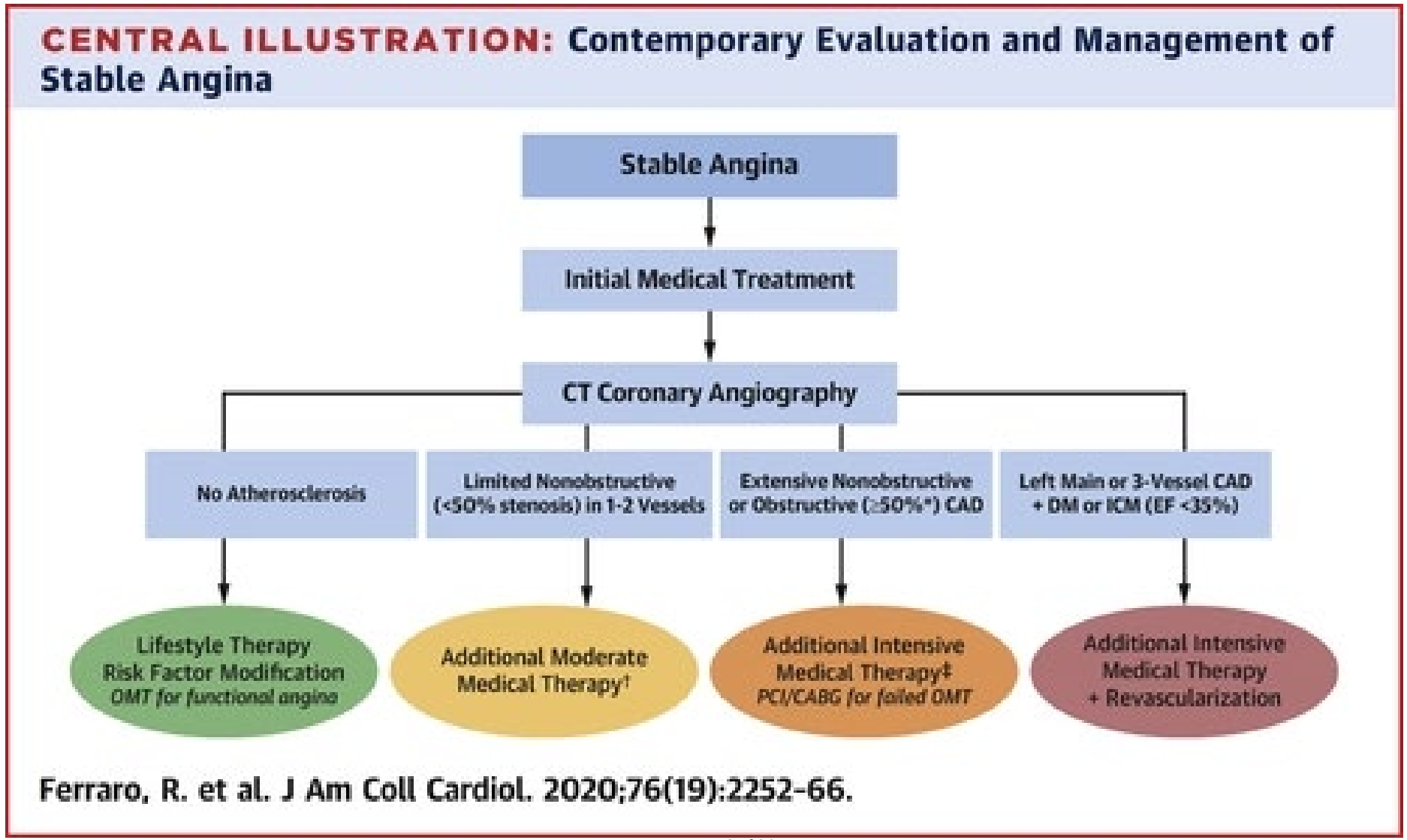
Revascularization
Anti-anginal Rx

Pharmacologic stabilization
Early identification of high-risk?

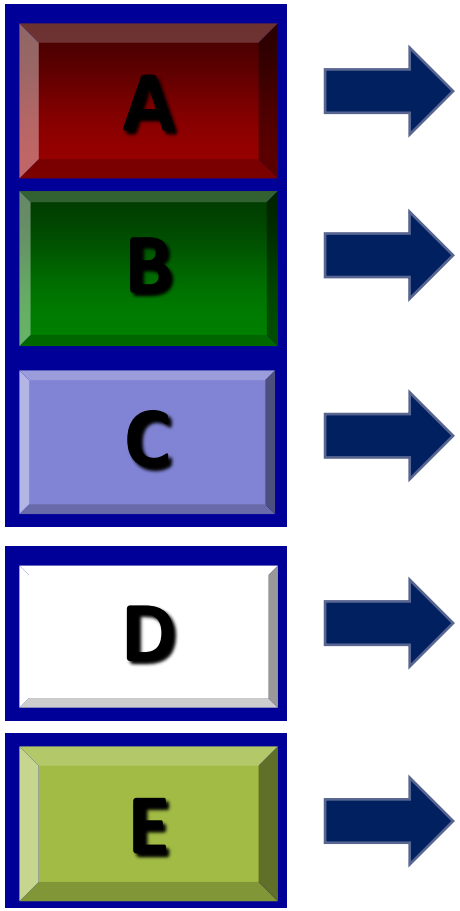


Courtesy of PH Stone, MD.

Management of Stable Angina/ASCVD in 2020



"ABCs" of CVD Prevention & Management



Cholesterol
Cigarette Cessation

Diabetes/Glucose Management
Diet/Weight

Exercise/Education

2019 ACC/AHA CVD Prevention Guideline Writing Committee

- Routine use of an ‘ABCDEF’ approach for management to track of latest prevention-related guidelines.

Donna K. Arnett, PhD, MSPH, FAHA, *Co-Chair*

Roger S. Blumenthal, MD, FACC, FAHA, *Co-Chair*

Michelle A. Albert, MD, MPH
Andrew B. Buroker, Esq†
Zachary D. Goldberger, MD
Ellen J. Hahn, PhD, RN*
Cheryl D. Himmelfarb, PhD, RN,
Amit Khera, MD, MSc,
Donald Lloyd-Jones, MD,
J. William McEvoy, MBBCh, MEd,
Erin D. Michos, MD, MHS
Michael D. Miedema, MD,
Daniel Muñoz, MD, MPA,
Sidney C. Smith, Jr, MD, MACC
Salim S. Virani, MD, PhD
Kim A. Williams, Sr, MD
Joseph Yeboah, MD, MS,
Boback Ziaeian, MD, PhD

ACC/AHA CLINICAL PRACTICE GUIDELINE

2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

TOP 10 TAKE-HOME MESSAGES FOR THE PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE

1. The most important way to prevent atherosclerotic vascular disease, heart failure, and atrial fibrillation is to promote a healthy lifestyle throughout life.

Arnett, D. K., Blumenthal, R. S., Albert, M. A., Buroker, A. B., Goldberger, Z. D., Hahn, E. J., ... & Ziaeian, B. (2019). 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology*, *74*(10), e177-e232.

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Assessment of CVD Risk

Shared Decision Making

Team-Based Approach to Prevention

Social Determinants of Health

- Socioeconomic factors: limit effectiveness of recommendations
- Socioeconomic disadvantages: not captured by existing CVD risk estimators
- Medicare/Medicaid developed 5 domain screening tool:

A – Assess Risk

Toolbox

JOHNS HOPKINS MEDICINE

Toolbox for Estimating ASCVD Risk

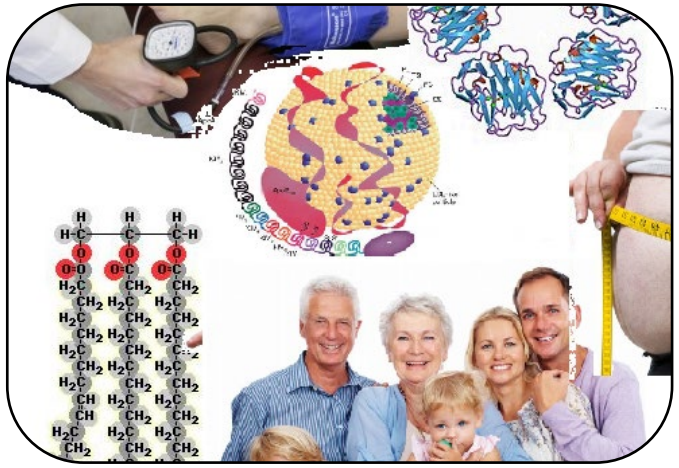
AMERICAN COLLEGE of CARDIOLOGY

ASCVD PLUS

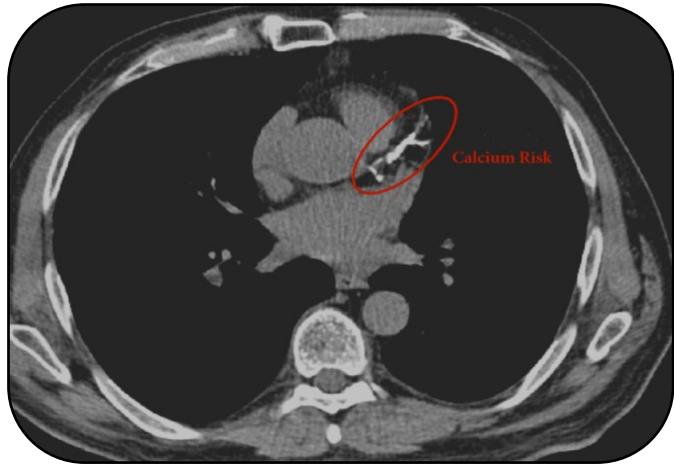
ASCVD Risk Estimator Plus

PCE: (Class I)

30-yr ASCVD risk: (Class IIb)



Risk-Enhancing Factors: (Class IIa)



CAC Score: (Class IIa)

A – Assess Risk

Risk Enhancing Factors

Recent Updates

- Risk calculator still begins risk discussion; now use **risk-enhancing factors** to personalize approach
- *When* to use?
  - **Uncertainty** of PCE estimate OR
  - If **further** risk stratification needed
- *Whom* to use in?
  - **Borderline** (5% to <7.5%) OR
  - **Intermediate** (≥7.5% to <20%) 10-yr ASCVD risk

Table. ASCVD risk enhancers

- Family history of premature ASCVD
- Primary hypercholesterolemia (LDL-C ≥160)
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (e.g. preeclampsia, premature menopause)
- Chronic inflammatory conditions (especially rheumatoid arthritis, psoriasis, HIV)
- High risk race/ethnicity (e.g. south Asian ancestry)

Lipid/Biomarkers:

- Persistently elevated triglycerides (≥175 mg/dL)

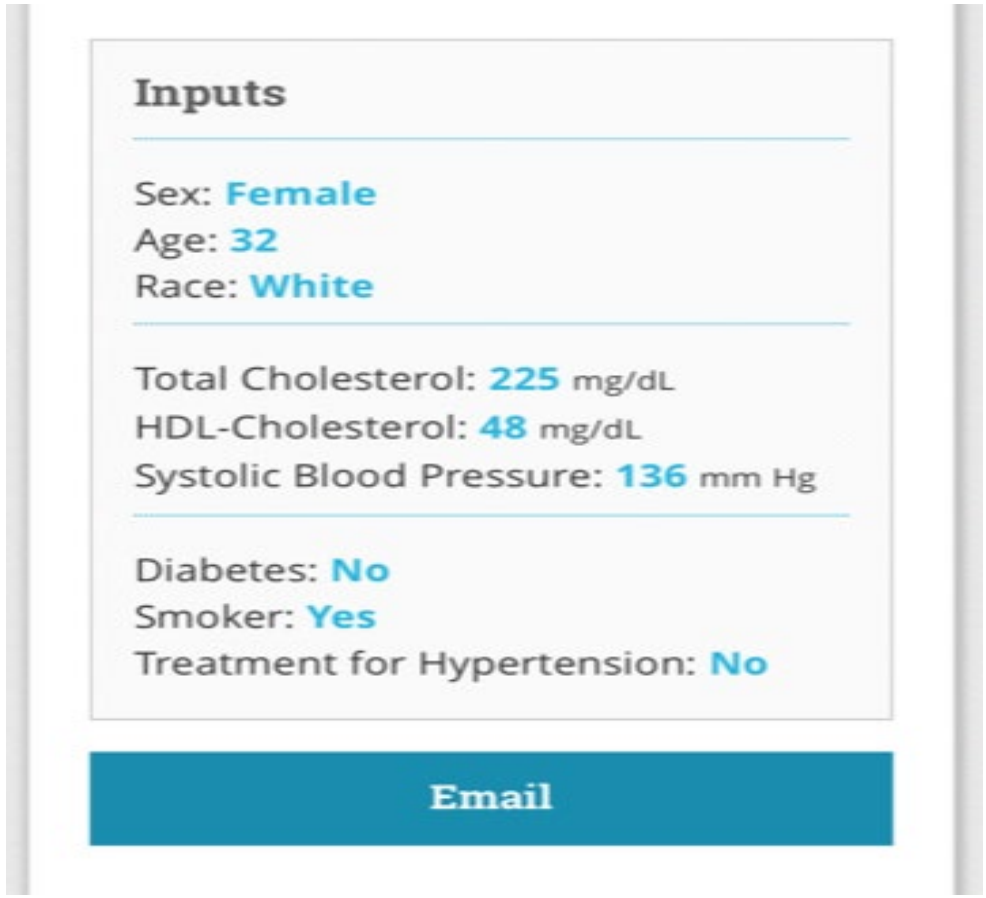
In selected individuals if measured:

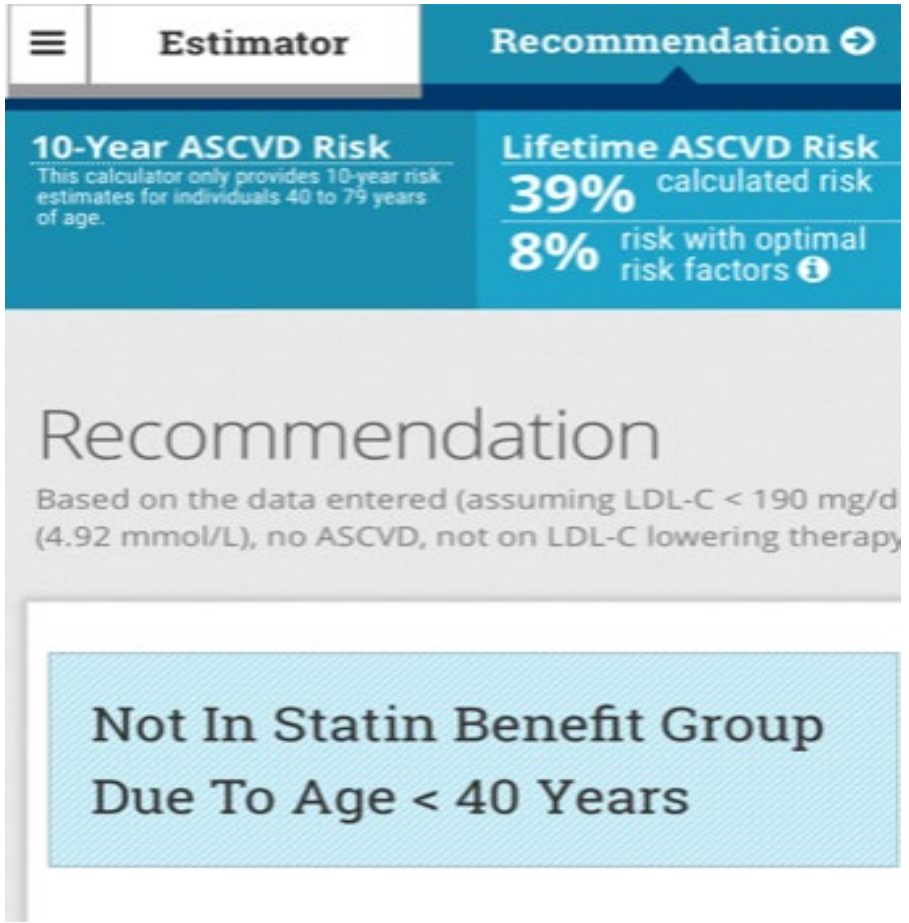
- hsCRP ≥2 mg/L
- Lp(a) levels ≥50 mg/dL or ≥125 nmol/L
- ApoB levels ≥130 mg/dL
- Ankle-brachial index <0.9

Assessment of Cardiovascular Risk

ASSESSMENT		
COR	**LOE**	**Recommendations**
IIa	B-NR	4. In adults at intermediate risk (≥7.5% to <20% 10-yr ASCVD risk) or selected adults at borderline risk (5% to <7.5%), if risk-based decisions for preventive interventions (e.g., statin Rx) remain uncertain, it is reasonable to measure a coronary artery calcium score to guide risk discussion.
IIb	B-NR	5. For adults 20-39 y/o and for those 40-59 y/o who have <7.5% 10-yr risk, estimating lifetime or 30-yr risk may be considered.

Lifetime Risk Estimate – ASCVD Risk Estimator Plus





From Lloyd-Jones D et al Risk Assessment Nov 2018

A – Assess Risk

Pooled Cohort Equations

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Recommendation

- Calculate 10-year ASCVD risk using the Pooled Cohort Equations (PCE)

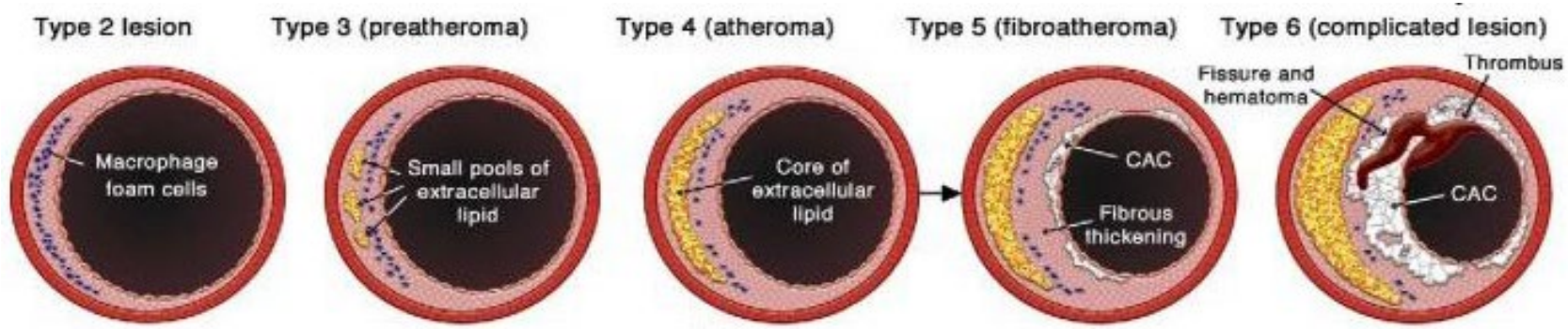
2013 ACC/AHA (U.S; 40-79 yrs)

Gender	Male
Age	years
Race	Non-Black
Total Cholesterol	mg/dL
HDL Cholesterol	mg/dL
Systolic BP	mmHg
Receiving treatment for high blood pressure (if SBP > 120 mmHg)	Yes
Diabetes	Yes
Smoker	Yes

A – Assess Risk

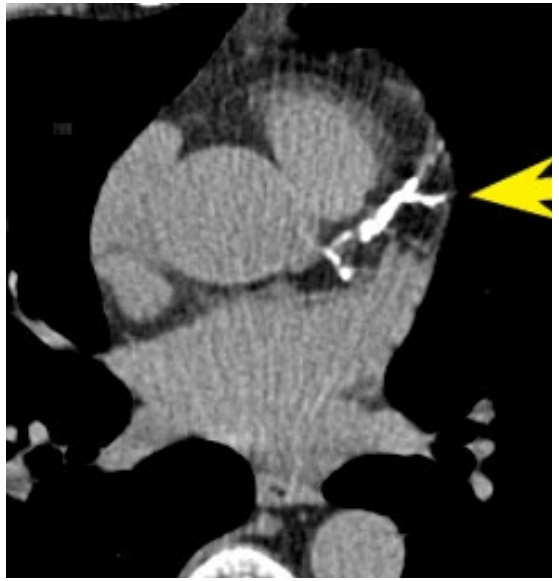
Coronary Artery Calcium Score

Background



CAC 1-100 **CAC >100**

- CAC: subclinical atherosclerosis
- Highly predictive of incident CHD/CVD
  - CAC ≥300: ~10x increased CHD risk



[1] Whelton SP, et al. *JACC Imaging*. 2015.
[2] Detrano R, et al. *NEJM*. 2008.

2009: Origin of Power of Zero

JACC: CARDIOVASCULAR IMAGING
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ISSN 1936-878X/09/$36.00
DOI:10.1016/j.jcmg.2009.03.009

Absence of Coronary Artery Calcification and All-Cause Mortality

Michael Blaha, MD, MPH,* Matthew J. Budoff, MD,† Leslee J. Shaw, PHD,‡ Faisal Khosa, MD,§ John A. Rumberger, MD, PHD,‖ Daniel Berman, MD,¶ Tracy Callister, MD,# Paolo Raggi, MD,‡ Roger S. Blumenthal, MD,* Khurram Nasir, MD, MPH**

Baltimore, Maryland; Torrance and Los Angeles, California; Atlanta, Georgia; Boston, Massachusetts; Princeton, New Jersey; and Hendersonville, Tennessee

CONCLUSIONS In appropriately selected asymptomatic patients, the absence of CAC predicts excellent survival with 10-year event rates of approximately 1%. A finding of 0 CAC might be used as a rationale to emphasize lifestyle therapies rather than pharmacotherapy and to forgo repeated imaging studies. Individuals with low CAC score (CAC 1 to 10) are at increased risk above individuals with a 0 score and could be considered a distinct risk group by physicians and investigators. (J Am Coll Cardiol Img 2009;2:692–700) © 2009 by the American College of Cardiology Foundation

Cardiovascular Perspectives

Understanding the Utility of Zero Coronary Calcium as a Prognostic Test

A Bayesian Approach

Michael J. Blaha, MD, MPH; Roger S. Blumenthal, MD;
Matthew J. Budoff, MD; Khurram Nasir, MD, MPH

- The PIONEERS of this approach since 2011:

Risk Prediction: The Power of Zero

- CAC is the best tie-breaker if Uncertainty
- Personalization: identify very low risk group
- Decision aid, not screening tool
- Focus Rx on those who will benefit the most

A – Assess Risk

Coronary Artery Calcium Score

Recent Updates

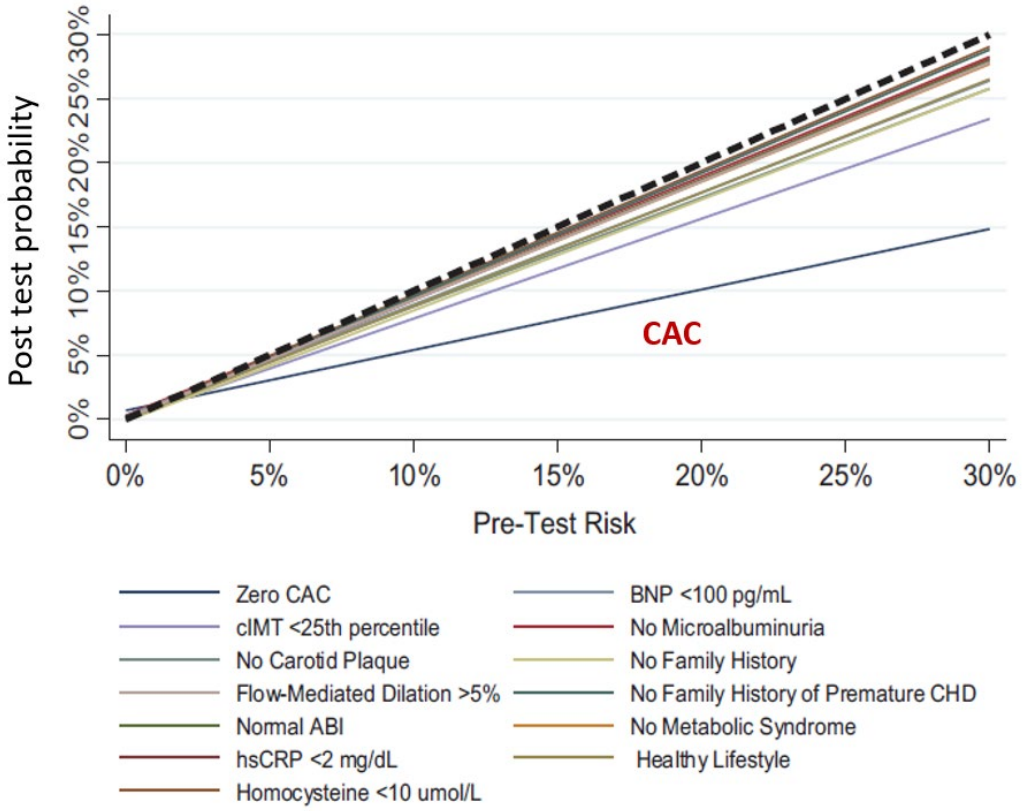
- If statin decision uncertain in intermediate risk patients, measure **CAC** to refine predicted statin benefit potential
- Consider CAC Subgroup?
    1. "Intermediate" Risk Patient (i.e. ASCVD 5-20%)
    2. Statin Reluctant Patient
    3. Statin Intolerant Patient
    4. Decisions for Non-Statin Rx
    5. Decisions For Aspirin Rx
    6. Low Risk Chest Pain Syndrome
    7. MOTIVATION!

A – Assess Risk

Coronary Artery Calcium Score

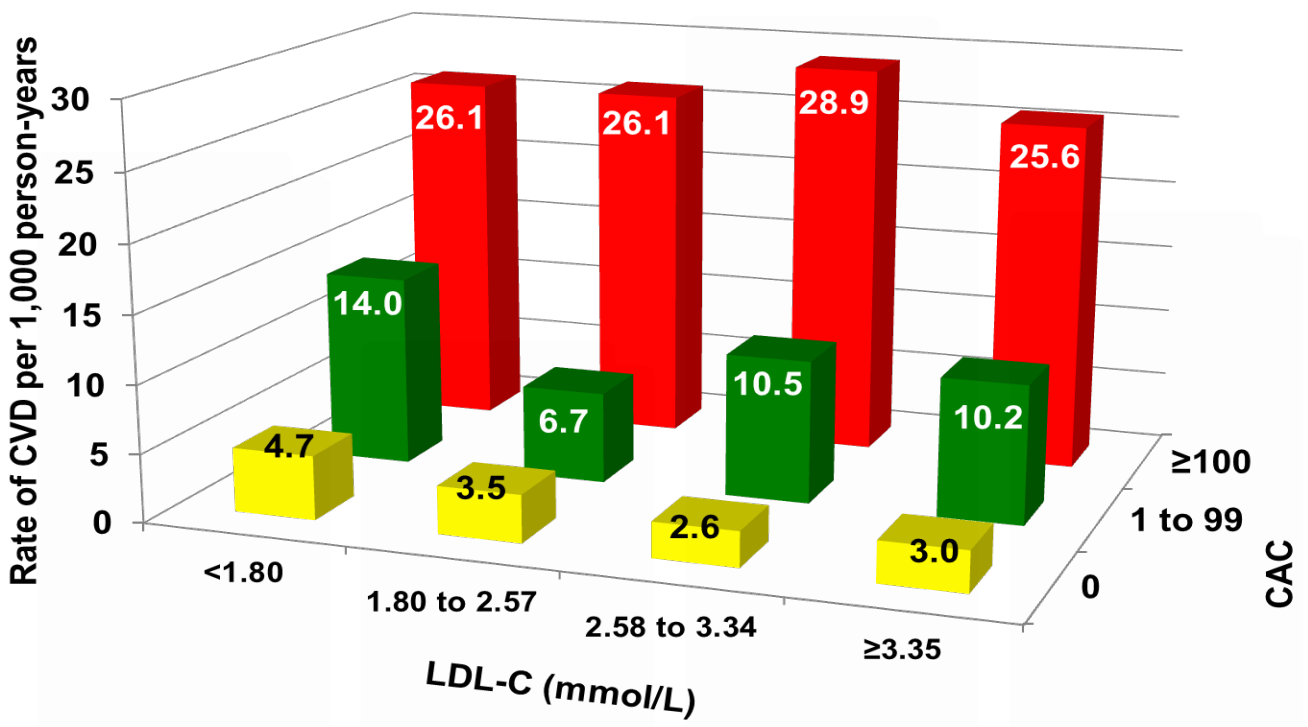
CAC for "De-Risking"

Negative Risk Markers for CVD



Blaha et al. Circulation 2016; 33:849-858

CAC and LDL-C



Martin SS, et al. *Circulation.* 2013 Oct 20.

A – Assess Risk

Pooled Cohort Equations

- Assessment of Risk - Can We Improve Communication?

Current Risk Assessment

- ASCVD
  - Fatal or nonfatal MI or stroke

Future Comprehensive Risk Assessment ??

- Global composite CVD
  - MI, stroke
  - Heart Failure, Afib
  - Revascularization

A – Assess Risk

Risk Enhancing Factors

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Assessment of Coronary Artery Calcium Scoring to Guide Statin Therapy Allocation According to Risk-Enhancing Factors

The Multi-Ethnic Study of Atherosclerosis

Jaideep Patel, MD[1,2]; Vincent A. Pallazola, MD[2]; Ramzi Dudum, MD, MPH[2]; et al

» Author Affiliations

JAMA Cardiol. Published online July 14, 2021. doi:10.1001/jamacardio.2021.2321

A – Assess Risk

Risk Enhancing Factors

Figure 1. Distribution of Coronary Artery Calcium Scores at Baseline by Risk-Enhancing Factor Group

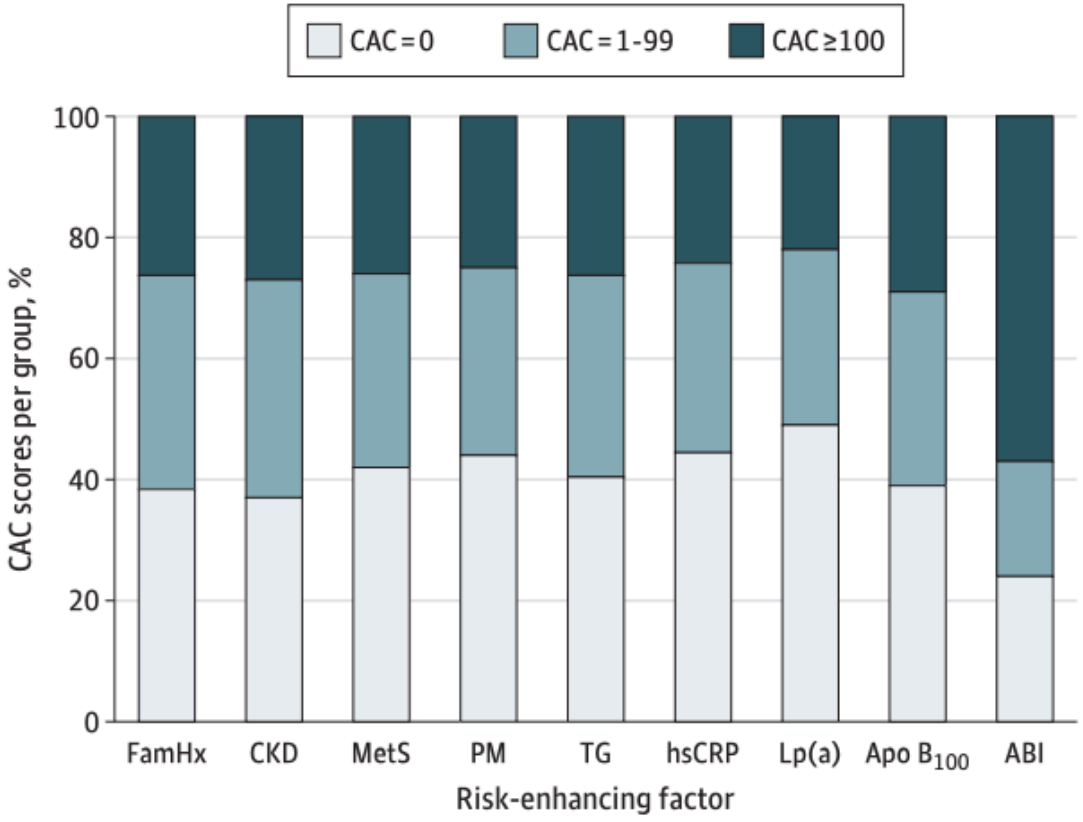
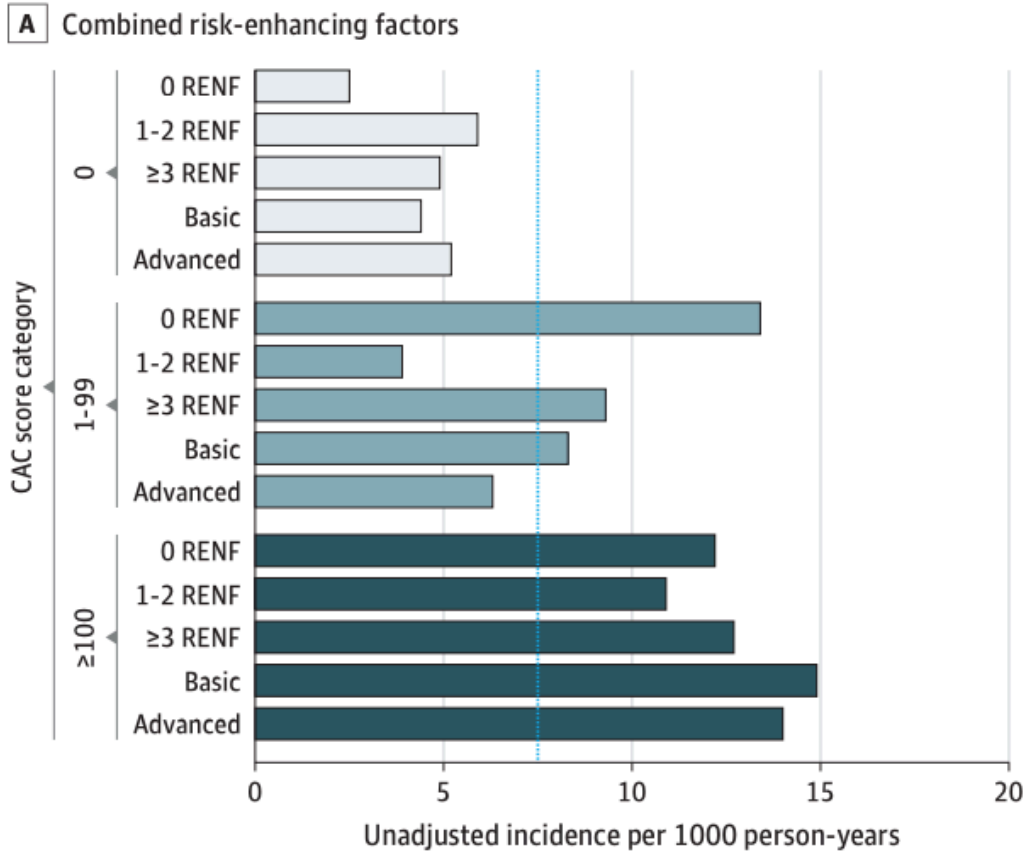
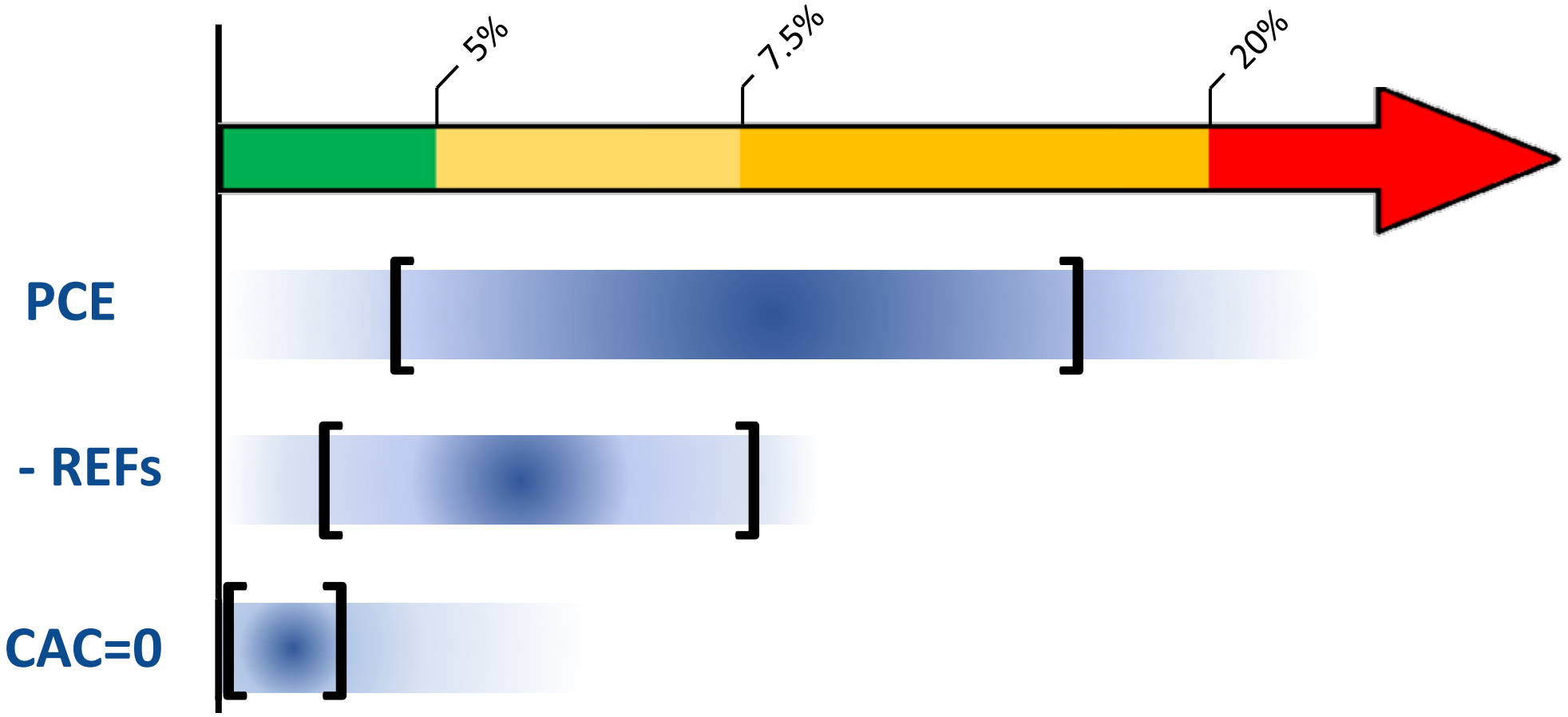


Figure 3. Unadjusted Incidence Rates for Risk-Enhancing Factors Across Coronary Artery Calcium Categories



A – Assess Risk

Risk Reclassification for Primary Prevention



#ThePowerofZero

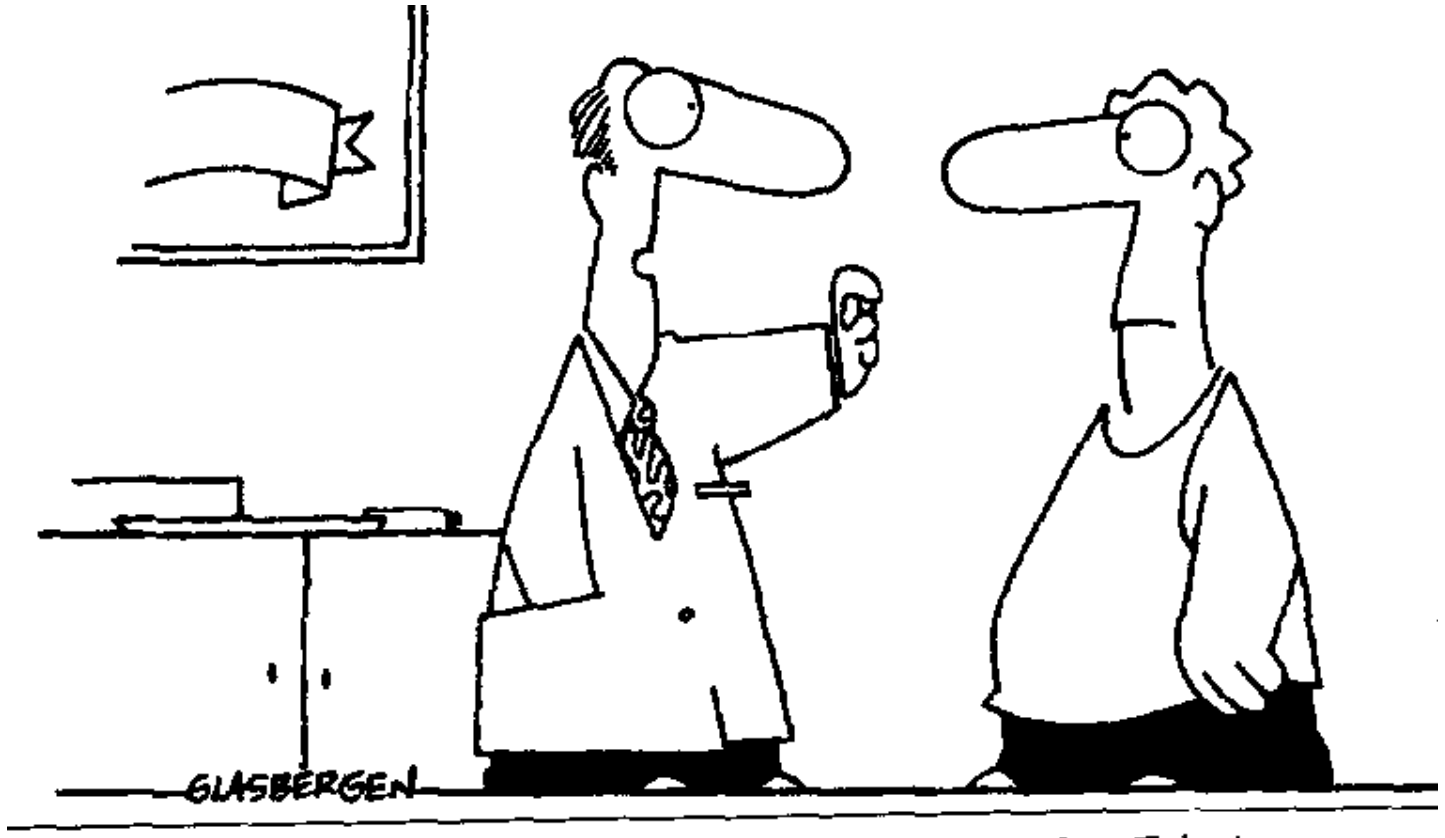
A – Assess Risk

Personalized Allocation of Medications

- **Healthy lifestyles (-):** Good for all
- **Statin Rx (+/-):**
  - ✓ Limited side-effects
  - ✓ Generic, low cost
  - ✓ Consistent benefit in most groups
- **Other therapies (+):**
  - ✓ More potential for **side effects** in some (aspirin)
  - ✓ **High cost** (Icosapent ethyl, PCSK9i, GLP-1RAs, SGLT2i)
  - ✓ Allocating interventions to those most likely to benefit has implications for sustainability of health systems, safety, out-of-pocket costs

A – Antiplatelet Therapy

Aspirin



"To prevent a heart attack, take one aspirin a day. Take it out for a jog, then take it to the gym, then take it for a bike ride…"

A – Antiplatelet Therapy

Aspirin

ASPIRIN		
COR	**LOE**	**Recommendations**
IIb	A	1. Low-dose aspirin (75-100 mg orally daily) might be considered for primary prevention of ASCVD among select adults 40-70 y/o who are at higher ASCVD risk but not at increased bleeding risk.
III: Harm	B-R	2. Low-dose aspirin (75-100 mg orally daily) should not be administered on routine basis for primary prevention among adults >70 y/o.
III: Harm	C-LD	3. Low-dose aspirin (75-100 mg orally daily) should not be administered for primary prevention among adults who are at increased risk of bleeding.

A – Antiplatelet Therapy

Aspirin for Primary Prevention

- Aspirin is effective in secondary prevention
- Based on older trials, prior U.S. guidelines had recommended lose dose aspirin for primary ASCVD prevention only in the setting of elevated 10-year CVD risk

Prior AHA/ACC Aspirin Recommendations ('97 and '02)

Primary Prevention

Aspirin (75-162 mg daily) should be used in adults at intermediate risk (10-year risk of CHD ≥10%)

A – Antiplatelet Therapy

Aspirin for Primary Prevention

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2014 Meta-analysis

- **ASCVD Events – 10% ↓**
  - **RR 0.90 (95% CI 0.85, 0.95)**

- **Major Bleeding – 55% ↑**
  - **RR 1.55 (1.35, 1.78)**

- NNT to prevent 1 major ASCVD event over mean f/u of 7 years = 284
- NNH to cause 1 major bleed = 299

Xie M et al. PLoS ONE 2014; 9(10): e90286

CV Risk Management

- **CAC for Aspirin Rx?: General population**

Original Article

Use of Coronary Artery Calcium Testing to Guide Aspirin Utilization for Primary Prevention: Estimates From the Multi-Ethnic Study of Atherosclerosis

Michael D. Miedema, MD, MPH; Daniel A. Duprez, MD, PhD; Jeffrey R. Misialek, MPH; Michael J. Blaha, MD, MPH; Khurram Nasir, MD, MPH; Michael G. Silverman, MD; Ron Blankstein, MD; Matthew J. Budoff, MD; Philip Greenland, MD; Aaron R. Folsom, MD, MPH

Background—Aspirin for the primary prevention of coronary heart disease (CHD) is only recommended for individuals at high risk for CHD although the majority of CHD events occur in individuals who are at low to intermediate risk.

Methods and Results—To estimate the potential of coronary artery calcium (CAC) scoring to guide aspirin use for primary prevention of CHD, we studied 4229 participants from the Multi-Ethnic Study of Atherosclerosis who were not on aspirin at baseline and were free of diabetes mellitus. Using data from median 7.6-year follow-up, 5-year number-needed-to-treat estimations were calculated by applying an 18% relative CHD reduction to the observed event rates. This was contrasted to 5-year number-needed-to-harm estimations based on the risk of major bleeding reported in an aspirin meta-analysis. Results were stratified by a 10% 10-year CHD Framingham Risk Score (FRS).

Miedema MD et al. Circ Cardiovasc Qual Outcomes. 2014;7:453-460

CAC for Aspirin Rx in CV Risk Management

Table 3. Estimated Number Needed to Treat and Number Needed to Harm With Use of Aspirin in MESA Participants Stratified by 10-Year CHD Risk and Baseline CAC Assuming an 18% Reduction in CHD in Both Sexes

CHD Risk	No. of Participants	5-Year CHD Event Rate (%)	Estimated 5-Year NNT	5-Year Estimated Absolute Increase in Bleeding Rate (%)	Estimated 5-Year NNH
<10%					
CAC=0	1907	0.27	2036	0.23	442
CAC=1–99	633	0.97	571		
CAC≥100	289	3.22	173		
≥10%					
CAC=0	454	0.69	808	0.23	442
CAC=1–99	460	3.82	146		
CAC≥100	486	6.07	92		

CAC indicates coronary artery calcification; CHD, coronary heart disease; MESA, Multi-Ethnic Study of Atherosclerosis; NNH, number needed to harm; and NNT, number needed to treat.

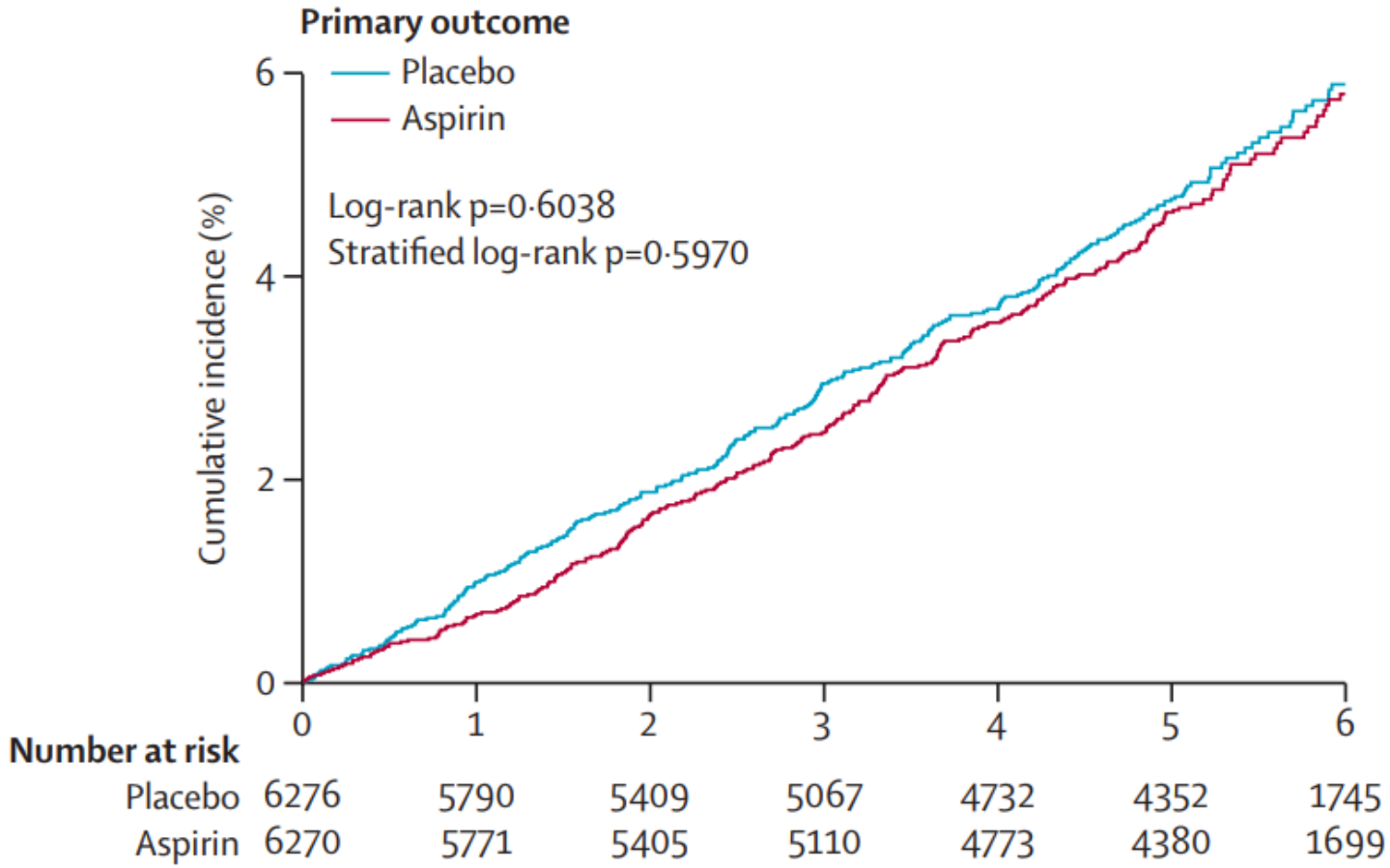
In general population, CAC may be useful guiding a more personalized, safer allocation of aspirin

Miedema MD et al. Circ Cardiovasc Qual Outcomes. 2014;7:453-460

A – Antiplatelet Therapy

ARRIVE: Primary Outcome Intention to Treat

Time to First Occurrence of CV Death, MI, UA, Stroke or TIA (Intent-to-Treat population)



HR (95% CI)*
0.96 (0.81;1.13)

p-Value*
0.6038

*Comparison: Aspirin vs Placebo

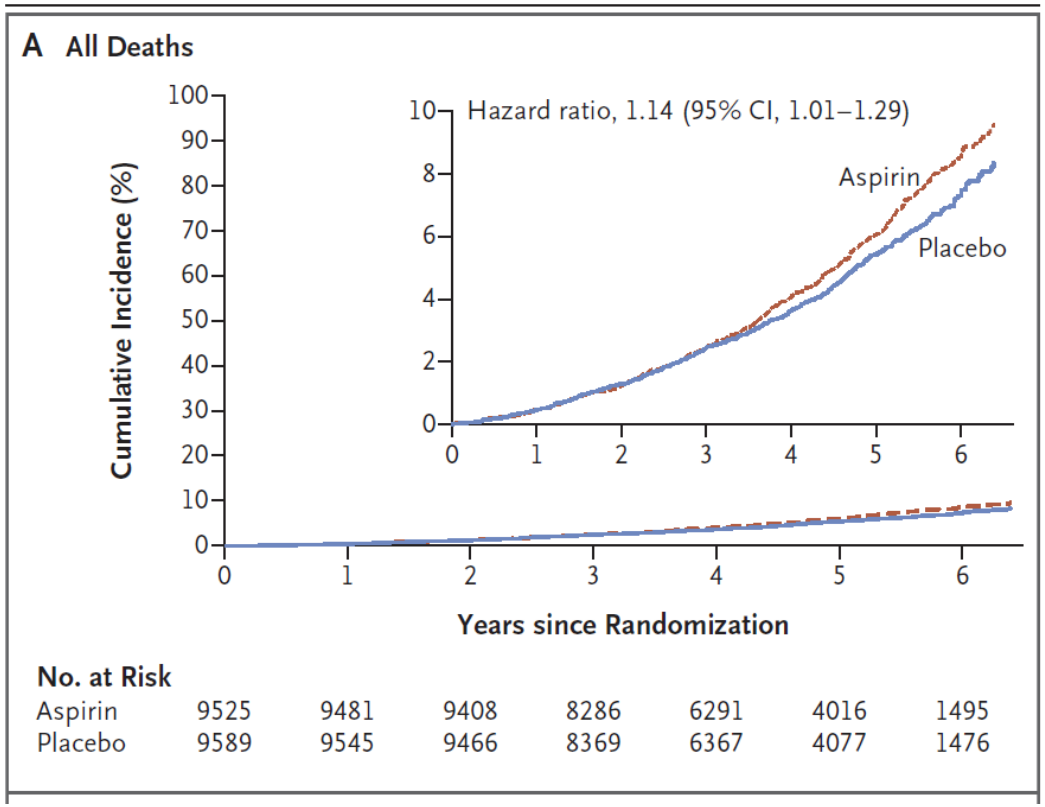
Gaziano JM et al. The Lancet. 2018; 392

A – Antiplatelet Therapy

ASPREE: Death, Dementia, Disability

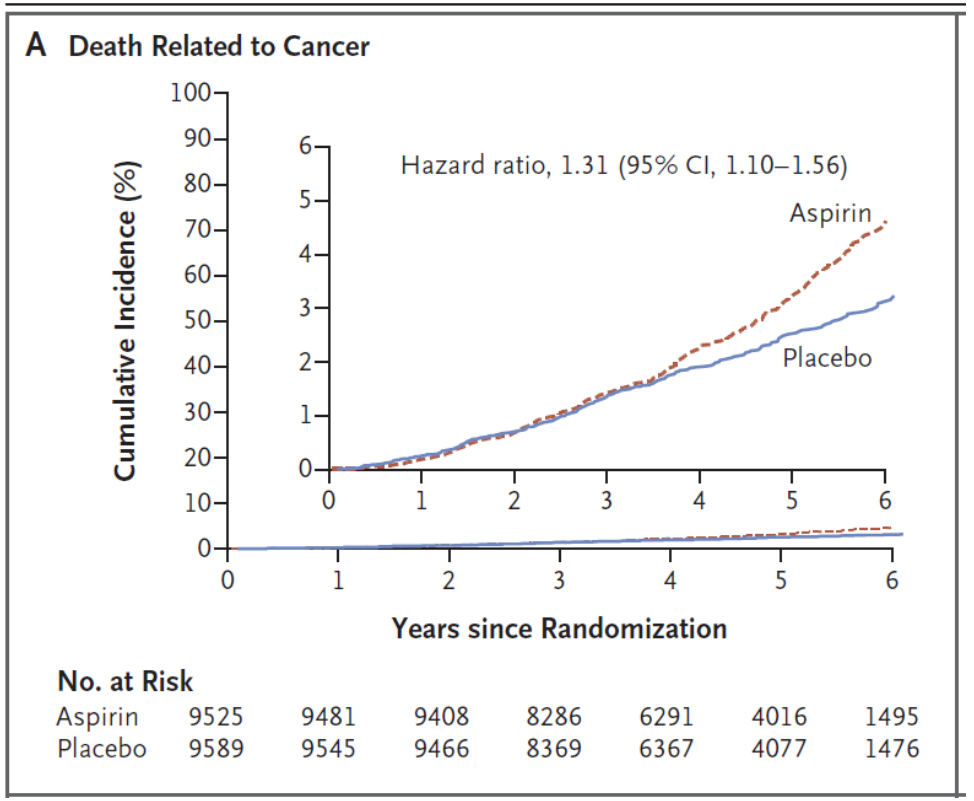
All Deaths

HR 1.14 (1.01-1.29)



Cancer Deaths

HR 1.31 (1.1-1.56)

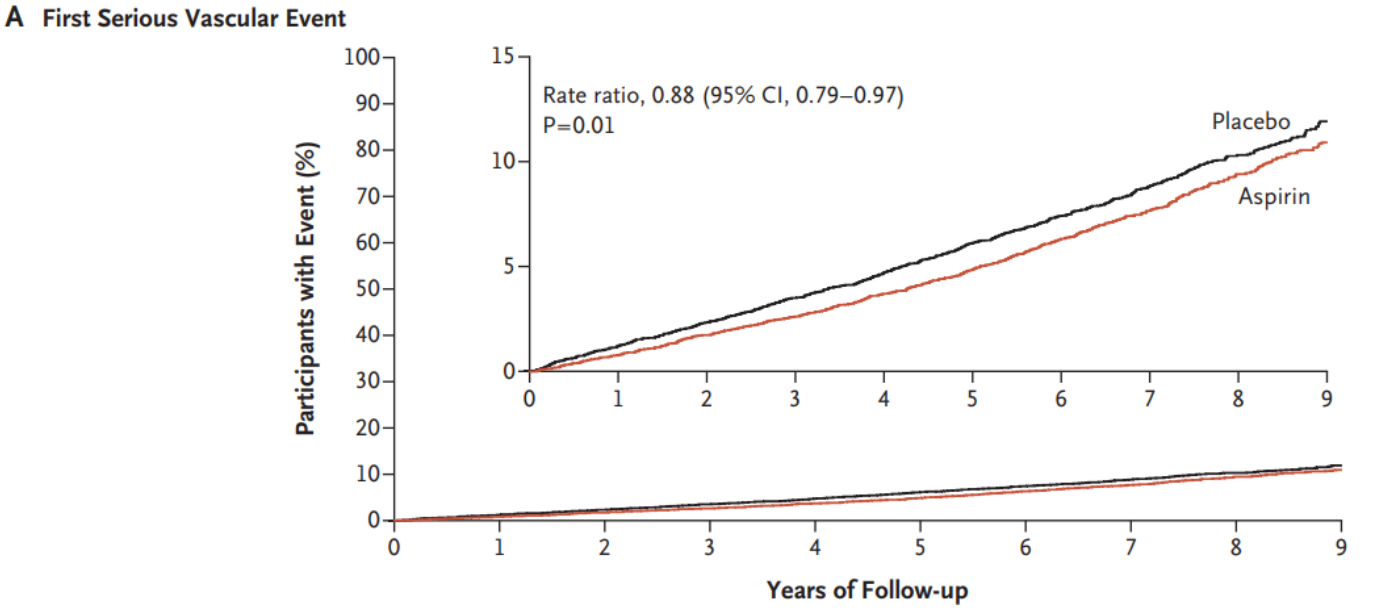


No Benefit on Dementia or Persistent Physical Disability

McNeil JJ et al. N Engl J Med 2018;379

A – Antiplatelet Therapy

ASCEND: Primary Outcome



No. at Risk										
Placebo	7740	7618	7486	7342	7188	7001	5771	3890	2200	1430
Aspirin	7740	7655	7536	7404	7252	7096	5825	3966	2222	1428
Cumulative benefit per 1000 participants in aspirin group		4±2	6±2	9±3	10±3	13±4	11±4	12±5	9±6	10±7

BENEFIT: Vascular Events

- Aspirin [8.5%] vs. Placebo [9.6%]

HR 0.88 (0.79 - 0.97)

12% RRR

HARM: Bleeding Events

- Aspirin [4.1%] vs. Placebo [3.2%]

HR 1.29 (1.09 – 1.52)

29% RRR

Bowman L et al. ASCEND Collaborative Group. N Engl J Med 2018;379:1529-39

A – Antiplatelet Therapy

Aspirin and CAC (MESA)

JOHNS HOPKINS MEDICINE

Coronary Artery Calcium for Personalized Allocation of Aspirin in Primary Prevention of Cardiovascular Disease in 2019

The MESA Study (Multi-Ethnic Study of Atherosclerosis)

Miguel Cainzos-Achirica ✉, Michael D. Miedema, John W. McEvoy, Mahmoud Al Rifai, Philip Greenland, Zeina Dardari, Matthew Budoff, Roger S. Blumenthal, Joseph Yeboah, Daniel A. Duprez, Martin Bødtker Mortensen, Omar Dzaye, Jonathan Hong, Khurram Nasir, Michael J. Blaha

Originally published 1 Apr 2020 | https://doi.org/10.1161/CIRCULATIONAHA.119.045010 | Circulation. 2020;141:1541–1553

A – Antiplatelet Therapy

Aspirin and CAC

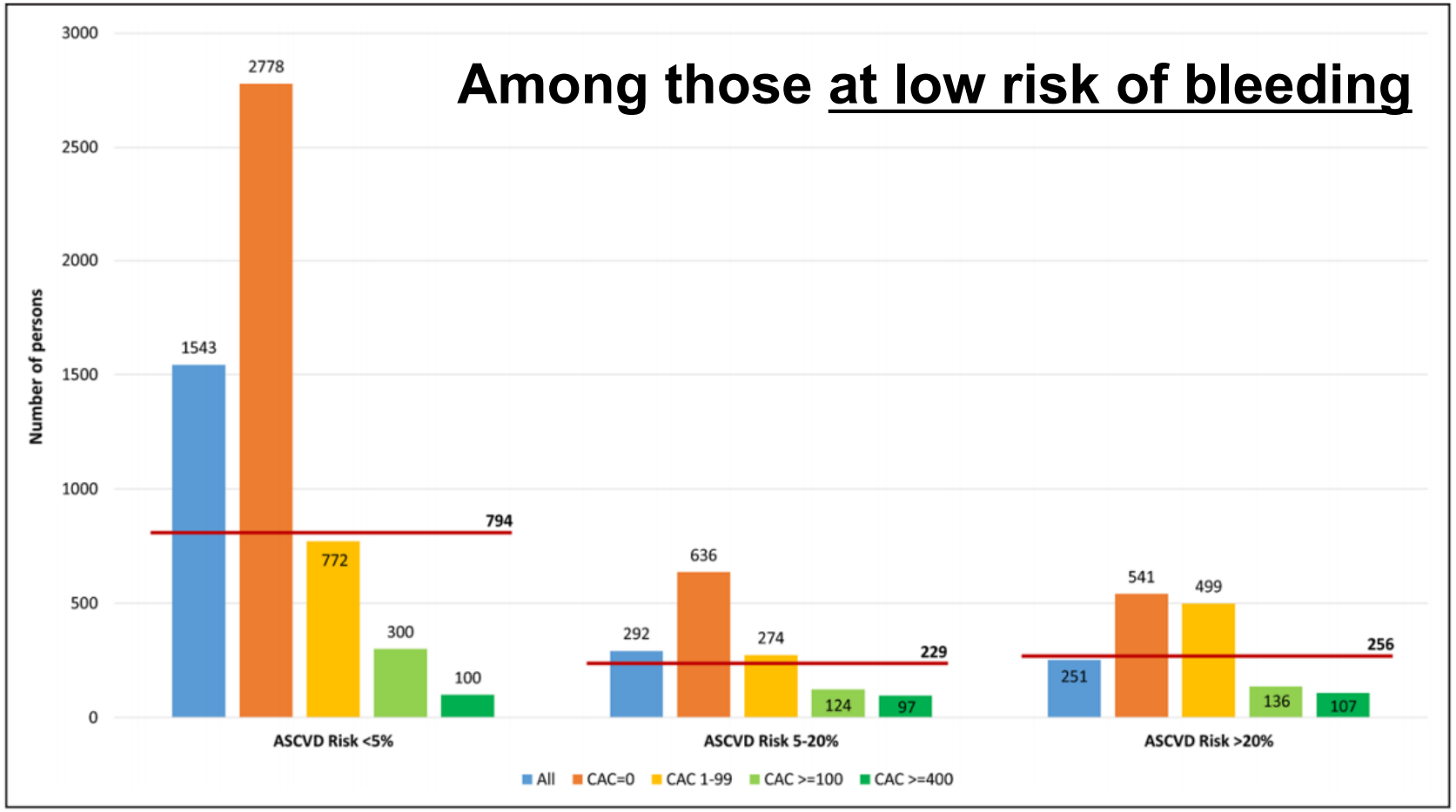
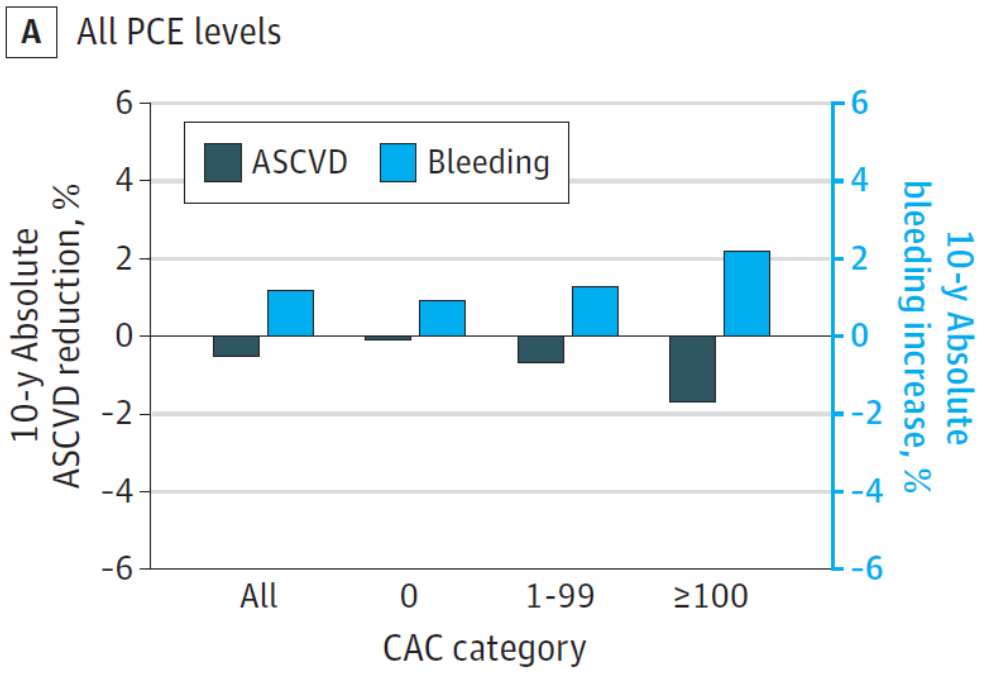
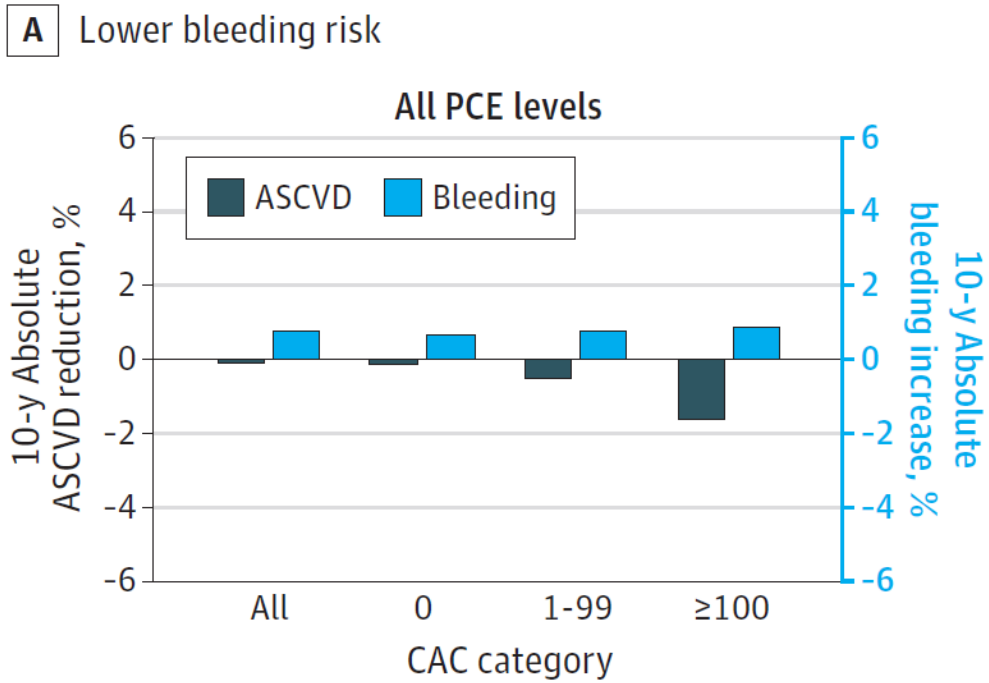


Figure 4. Number needed to treat with aspirin during 5 years to prevent 1 CVD event and number needed to cause a major bleeding event, by estimated ASCVD risk and CAC.

A – Antiplatelet Therapy

Aspirin & CAC





CONCLUSIONS AND RELEVANCE Higher CAC is associated with both ASCVD and bleeding events, with a stronger association with ASCVD. A high CAC score identifies individuals estimated to derive net benefit from primary prevention aspirin therapy from those who would not, but only in the setting of lower bleeding risk and estimated ASCVD risk that is not low.

Ajufo E et al. JAMA Cardiol. 2021;6(2):179-187.

B – Blood Pressure

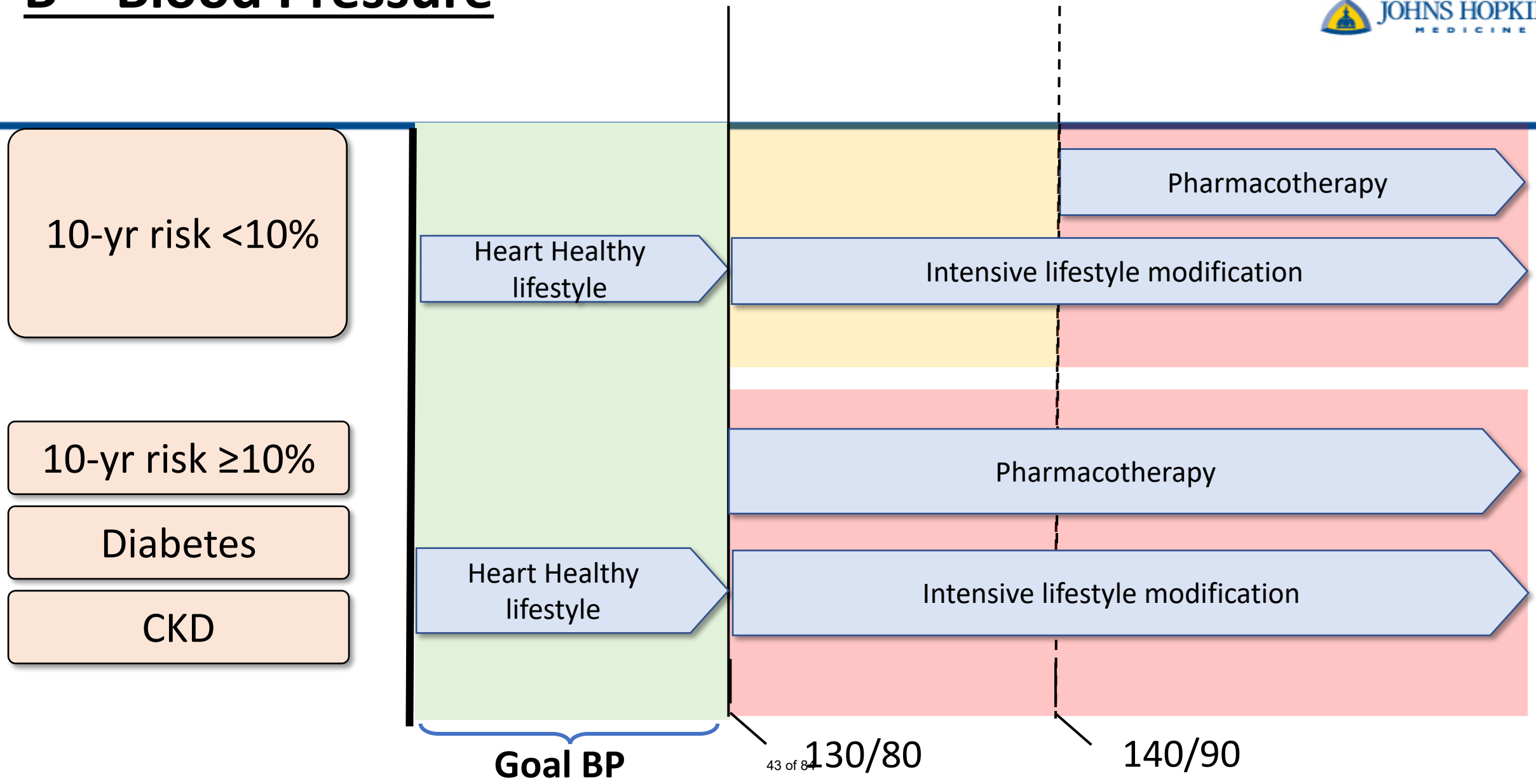
JOHNS HOPKINS MEDICINE

Blood Pressure Categories

American Heart Association | American Stroke Association

BLOOD PRESSURE CATEGORY	SYSTOLIC mm Hg (upper number)		DIASTOLIC mm Hg (lower number)
NORMAL	LESS THAN 120	and	LESS THAN 80
ELEVATED	120 – 129	and	LESS THAN 80
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 1	130 – 139	or	80 – 89
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 2	140 OR HIGHER	or	90 OR HIGHER
HYPERTENSIVE CRISIS (consult your doctor immediately)	HIGHER THAN 180	and/or	HIGHER THAN 120

B – Blood Pressure



B – Blood Pressure

BLOOD PRESSURE		
COR	**LOE**	**Recommendations**
I	A	1. In adults with elevated blood pressure (BP) including those requiring antihypertensive medications nonpharmacological interventions are recommended: • weight loss • heart-healthy dietary pattern • sodium reduction • dietary potassium supplementation • increased physical activity with a structured exercise program • limited alcohol

B – Blood Pressure

Avoid Unnecessary Stressors

i.e. Standing in front 100 mph lacrosse shots

i.e. Arguing with referee calls

Cholesterol

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Lipid Management for the Prevention of Atherosclerotic Cardiovascular Disease

Erin D. Michos, M.D., M.H.S., John W. McEvoy, M.B., B.Ch., M.H.S., and Roger S. Blumenthal, M.D.

IN 1961, THE INVESTIGATORS INVOLVED IN THE FRAMINGHAM HEART STUDY identified serum cholesterol as one of the "factors of risk" for coronary heart disease.[1] Since then, numerous epidemiologic studies and randomized clinical trials have established that an elevated level of low-density lipoprotein (LDL) cholesterol is a major contributor to atherosclerotic cardiovascular disease.[2,3] As a consequence, the management of serum cholesterol levels has become a central objective in the effort to prevent cardiovascular events. The currently used therapies with demonstrated efficacy (see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org) predominantly target the apolipoprotein B–associated lipoproteins reflected in levels of LDL cholesterol, non–high-density lipoprotein cholesterol (non-HDL cholesterol), and triglycerides (Fig. 1).

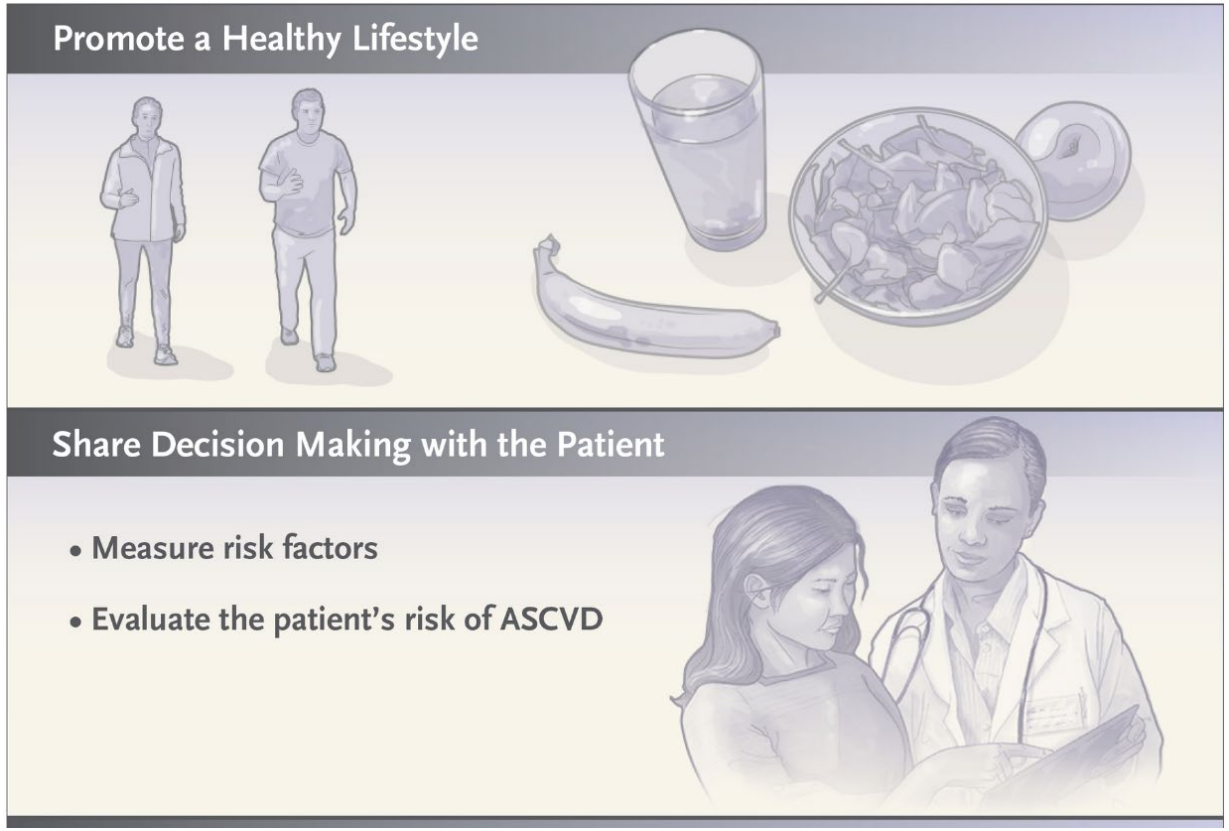
From the Ciccarone Center for the Prevention of Cardiovascular Disease, Johns Hopkins University School of Medicine, Baltimore (E.D.M., R.S.B), and the National Institute for Prevention and Cardiovascular Health, National University of Ireland, Galway (J.W.M.). Address reprint requests to Dr. Michos at the Division of Cardiology, Johns Hopkins School of Medicine, Blalock 524-B, 600 N. Wolfe St., Baltimore, MD 21287, or at edonnell@jhmi.edu.

N Engl J Med 2019;381:1557-67.
DOI: 10.1056/NEJMra1806939

N Engl J Med Volume 381(16):1557-1567 October 17, 2019

Lipid Management for Prevention of ASCVD

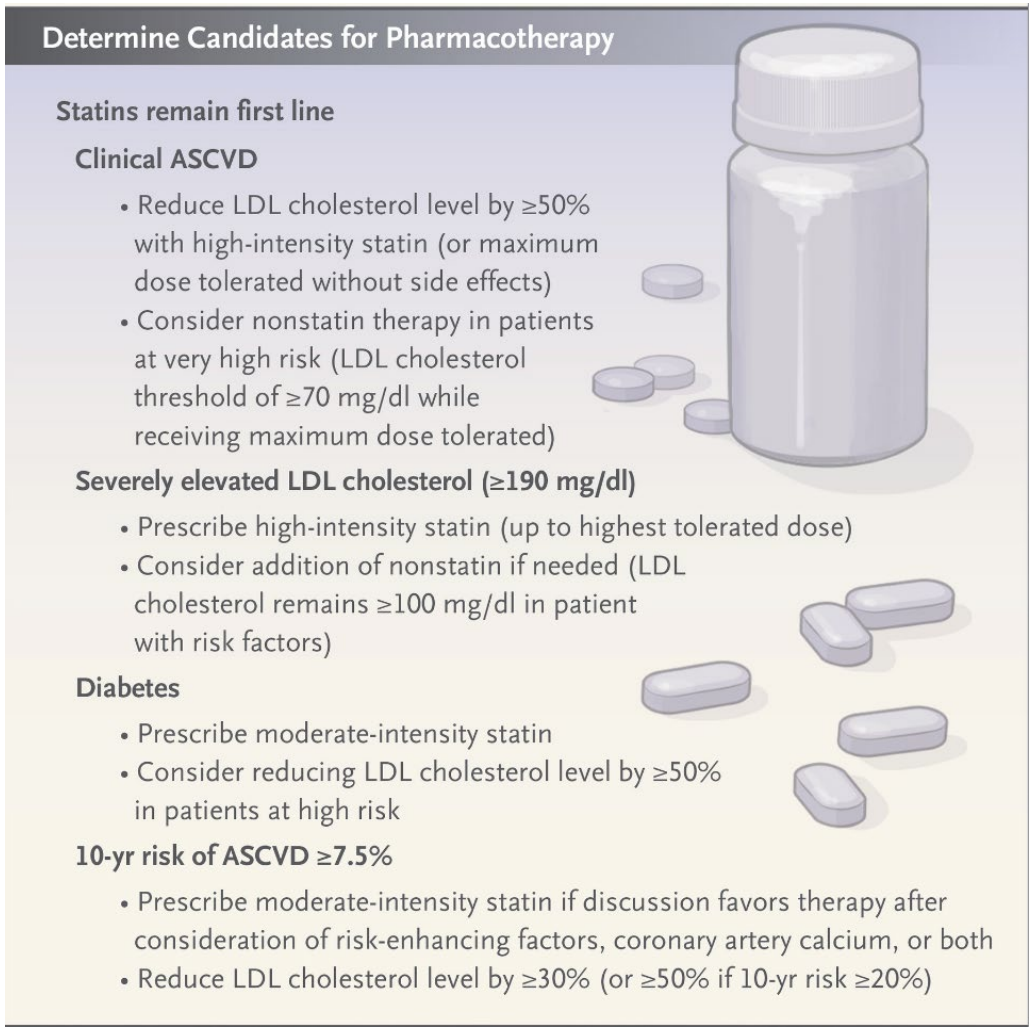
Current guidelines recommend calculation of ASCVD risk, with treatment decisions based on these data and clinician–patient discussion of risk



STEP 1

STEP 2

Lipid Management for the Prevention of ASCVD



Management of serum cholesterol level is a central objective in preventing events

- **Statins remain 1st line**

STEP 3

Numbers Matter: (Thresholds/Targets)

- Lower LDL-C is better with proven therapies
- High intensity statin: >50% LDL-C drop
- Threshold of 70 mg/dL for non-statins: Consider Ezetimibe 1st, PCSK9i 2nd
- FH: LDL-C threshold of 100 mg/dL
- Friedewald method limitations → Martin/Hopkins method

Aggressive LDL-C Rx & Threshold of 70

Very high-risk ASCVD: use LDL-C threshold of 70 mg/dL to consider nonstatin

- Very high-risk: multiple major events or 1 major event + high-risk conditions
- Reasonable to add ezetimibe to max. tolerated statin if LDL-C remains ≥70
- If LDL-C ≥70 on max. statin + ezetimibe → adding PCSK9i is reasonable but cost-effectiveness less certain

C – Cholesterol

Non-Statin Add-On Therapy? Ezetimibe

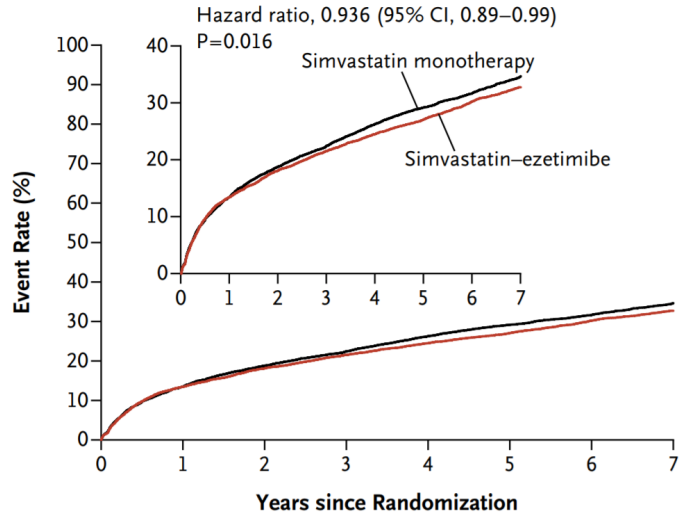
JOHNS HOPKINS MEDICINE

Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes

Christopher P. Cannon, M.D., Michael A. Blazing, M.D., Robert P. Giugliano, M.D., Amy McCagg, B.S., Jennifer A. White, M.S., Pierre Theroux, M.D., Harald Darius, M.D., Basil S. Lewis, M.D., Ton Oude Ophuis, M.D., Ph.D., J. Wouter Jukema, M.D., Ph.D., Gaetano M. De Ferrari, M.D., Witold Ruzyllo, M.D., Paul De Lucca, Ph.D., KyungAh Im, Ph.D., Erin A. Bohula, M.D., D.Phil., Craig Reist, Ph.D., Stephen D. Wiviott, M.D., Andrew M. Tershakovec, M.D., M.P.H., Thomas A. Musliner, M.D., Eugene Braunwald, M.D., and Robert M. Califf, M.D., for the IMPROVE-IT Investigators*

Table 2. Primary, Secondary, and Individual End Points.*

Outcome	Simvastatin Monotherapy (N=9077)	Simvastatin–Ezetimibe (N=9067)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
Primary end point: death from cardiovascular causes, major coronary event, or nonfatal stroke	2742 (34.7)	2572 (32.7)	0.936 (0.89–0.99)	0.016
Secondary end points				
Death from any cause, major coronary event, or nonfatal stroke	3246 (40.3)	3089 (38.7)	0.95 (0.90–1.0)	0.03
Death from coronary heart disease, nonfatal MI, urgent coronary revascularization ≥30 days	1448 (18.9)	1322 (17.5)	0.91 (0.85–0.98)	0.02
Death from cardiovascular causes, nonfatal MI, hospitalization for unstable angina, all revascularization ≥30 days, nonfatal stroke	2869 (36.2)	2716 (34.5)	0.95 (0.90–1.0)	0.04

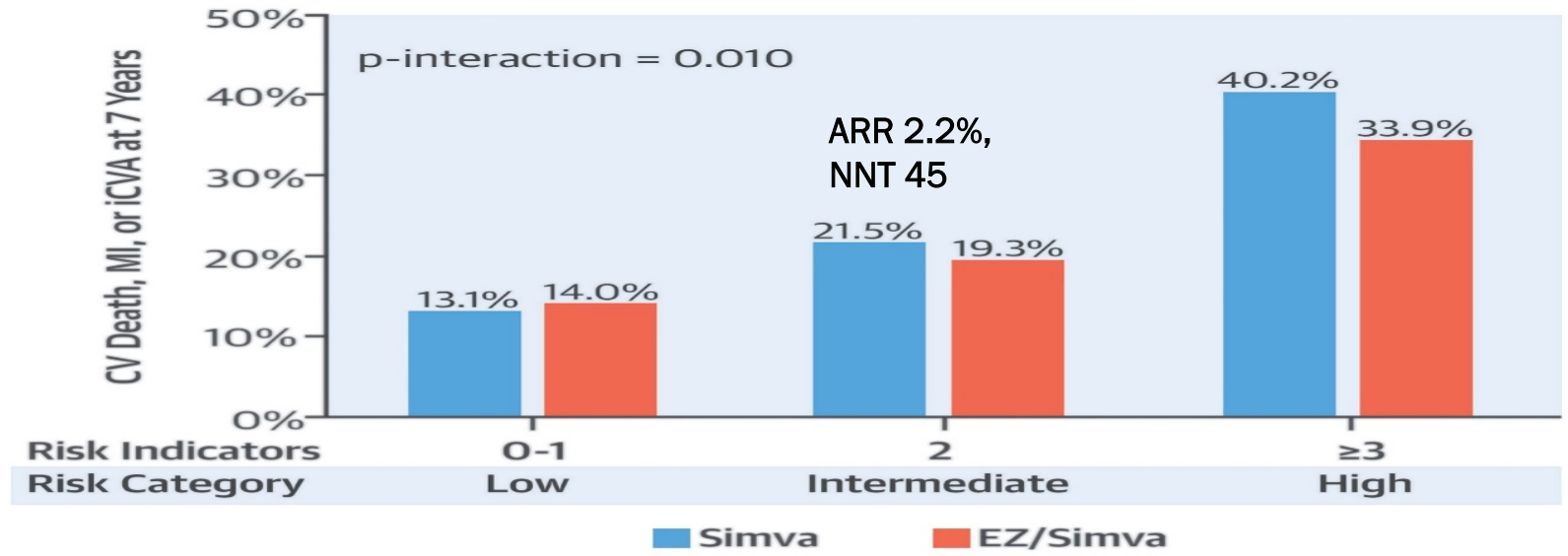


Very high event rates in 2º prevention, even in the setting of RCTs and using high-intensity statins

CENTRAL ILLUSTRATION: TRS 2°P

TRS 2°P Risk Indicators	Points
CHF	1
HTN	1
Age ≥75	1
DM	1
Prior Stroke	1
Prior CABG	1
PAD	1
eGFR <60	1
Smoking	1
Maximum Possible	9

ARR 6.3%,
NNT 16



Bohula, E.A. et al. J Am Coll Cardiol. 2017;69(8):911–21.

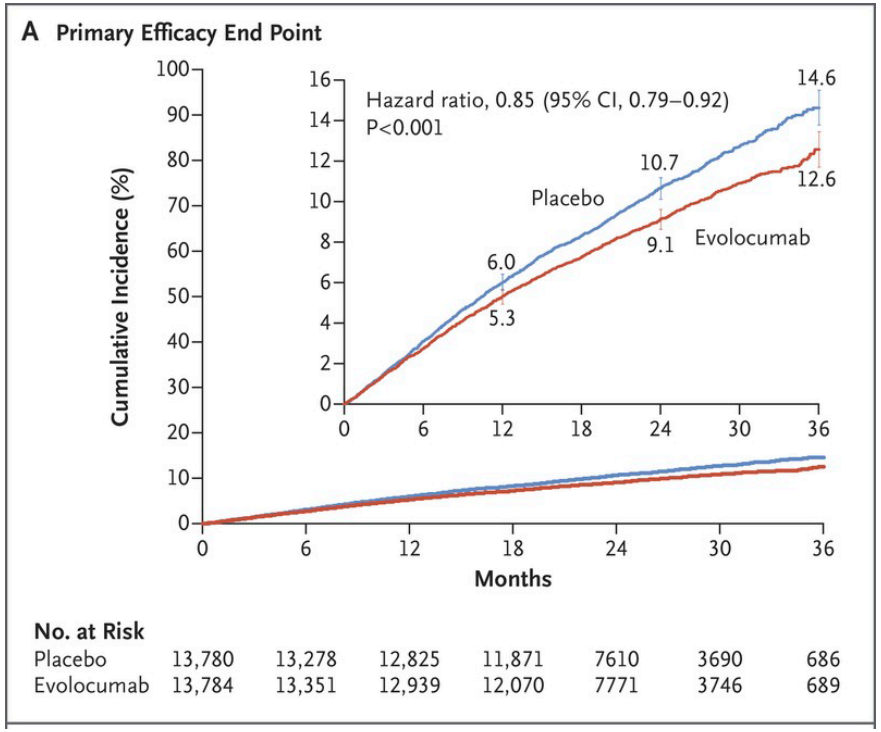
C – Cholesterol

Non-Statin Add-On Therapy? PCSK9i

FOURIER

Median 2.2yr

LDL-C 92 → 30

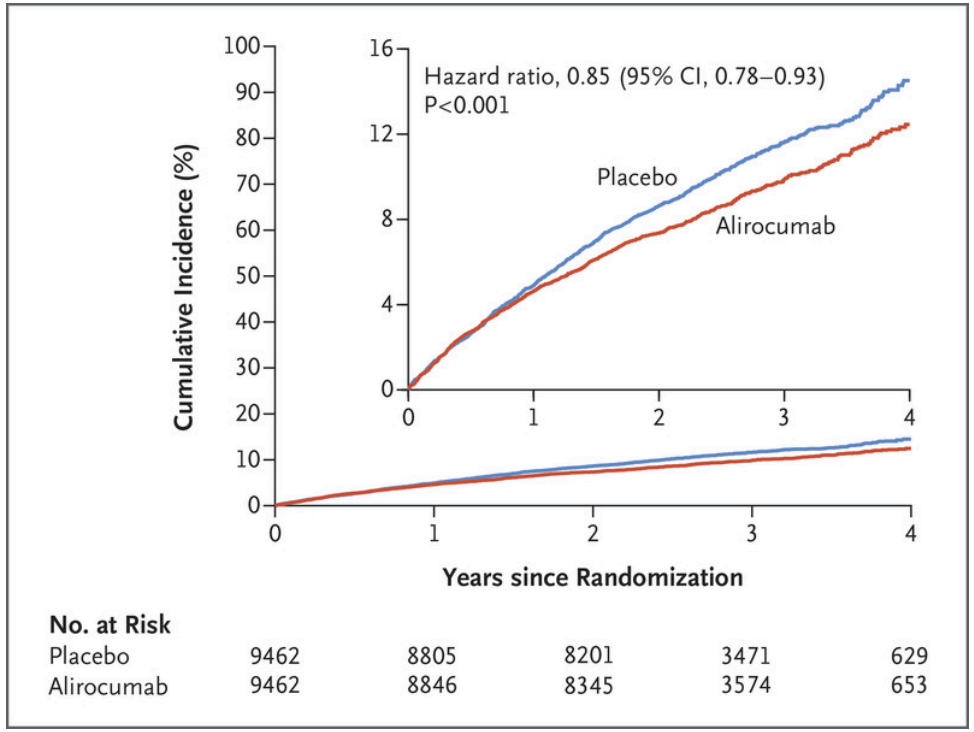


N Engl J Med 2017; 376:1713-1722

ODYSSEY OUTCOMES

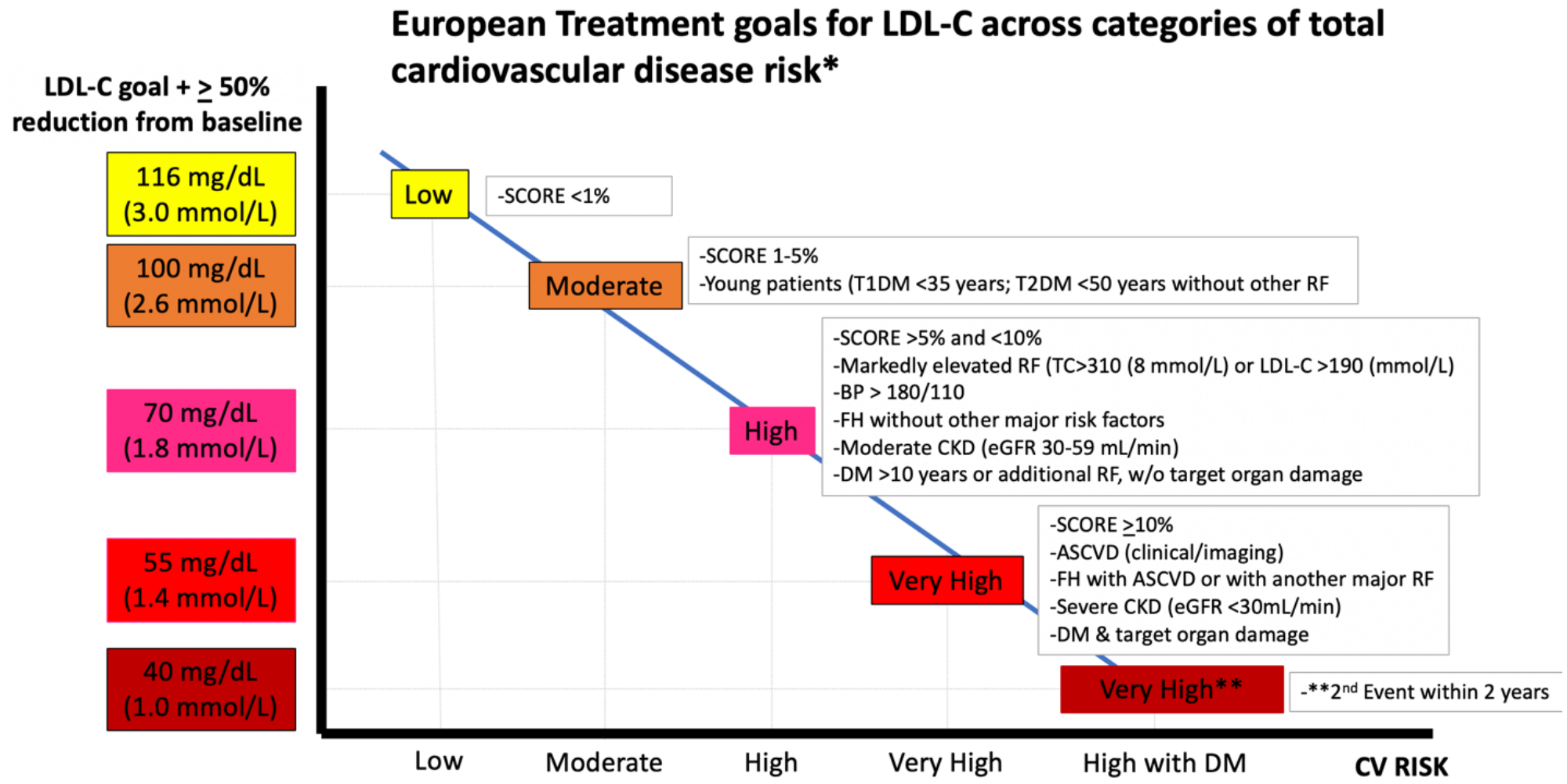
Median 2.8yr

LDL-C 92 → 30 → 48 → 66

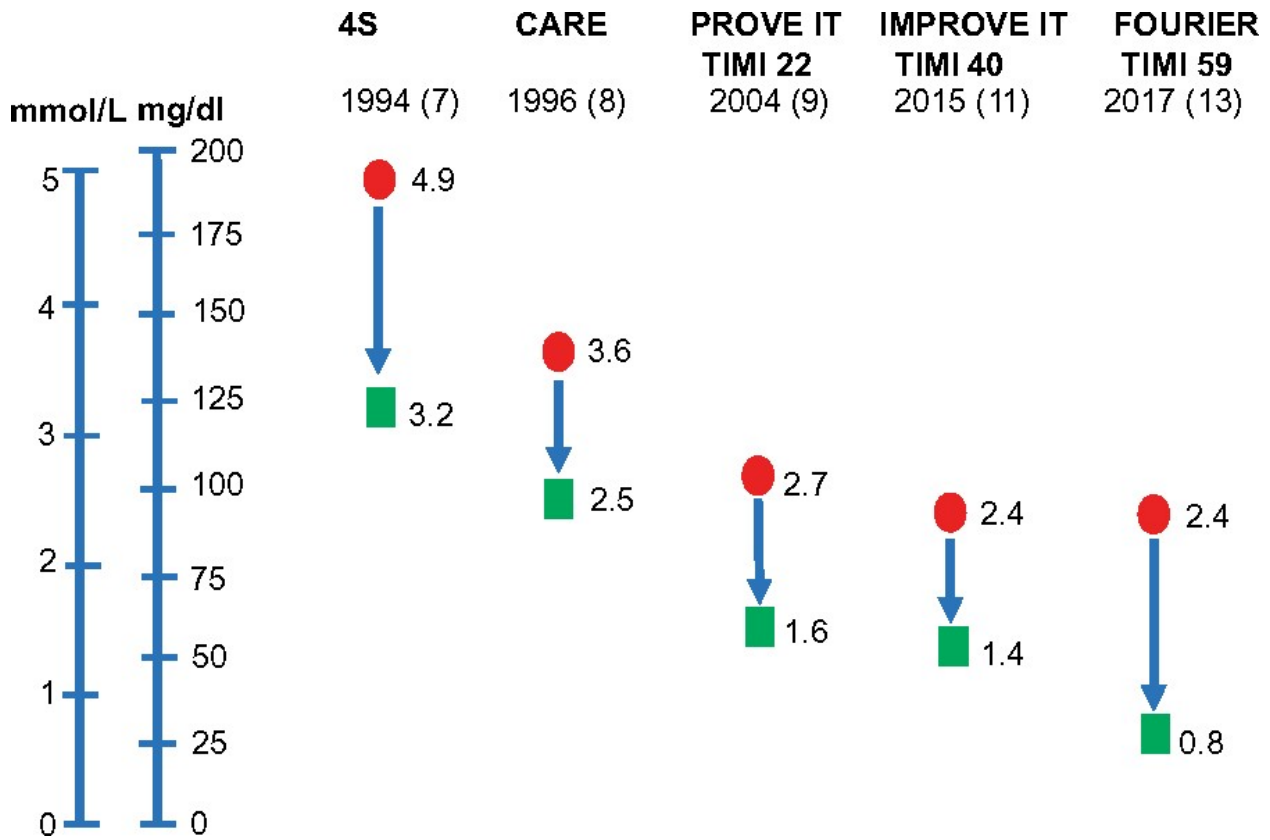


N Engl J Med 2018; 379:2097-2107

2019 ESC/EAS Guidelines



https://www.acc.org/latest-in-cardiology/articles/2019/09/09/13/08/key-takeaways-comparing-lipid-guidelines-across-the-pond



Eur Heart J, ehab446, https://doi.org/10.1093/eurheartj/ehab446

Key Inclusion Criteria – REDUCE-IT

1. Age ≥45 years with established CVD (Secondary Prevention Cohort) *or* ≥50 years with DM with ≥1 additional risk factor for CVD (Primary Prevention Cohort)
2. Fasting TG levels ≥150 mg/dL & <500 mg/dL*
3. LDL-C >40 & ≤100 mg/dL & on stable statin Rx (± ezetimibe) for ≥4 weeks prior to qualifying measurements for randomization

*Due to the variability of triglycerides, a 10% allowance existing in the initial protocol, which permitted patients to be enrolled with qualifying triglycerides ≥135 mg/dL. protocol amendment 1 (May 2013) changed the lower limit of acceptable triglycerides from 150 mg/dL to 200 mg/dL, with no variability allowance.

Adapted with permission‡ from: Bhatt DL, Steg PG, Brinton EA, et al; on behalf of the REDUCE-IT Investigators. Rationale and design of REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial. *Clin Cardiol*. 2017;40:138-148. [‡https://creativecommons.org/licenses/by-nc/4.0/]

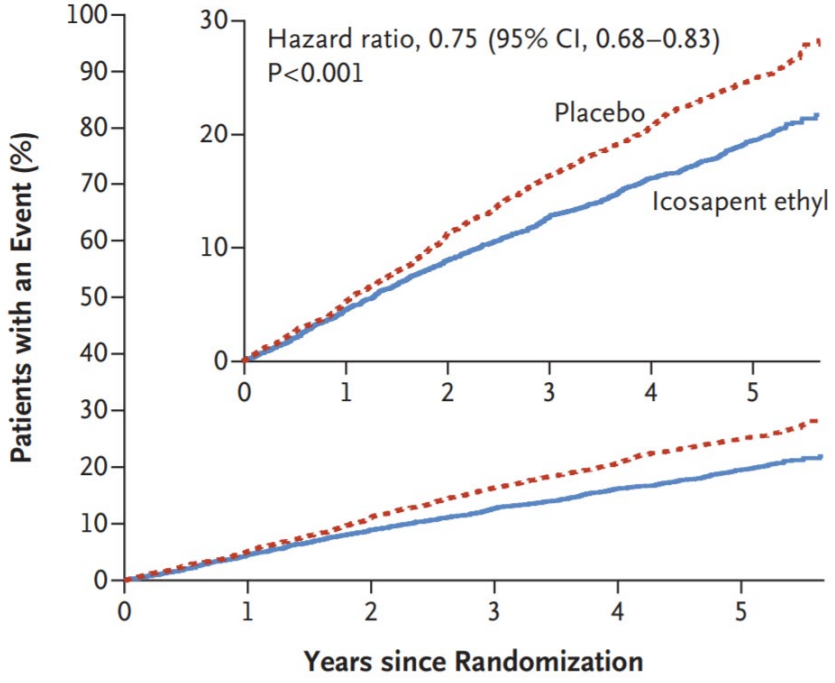
C – Cholesterol

Non-Statin Add-On Rx? Icosapent Ethyl

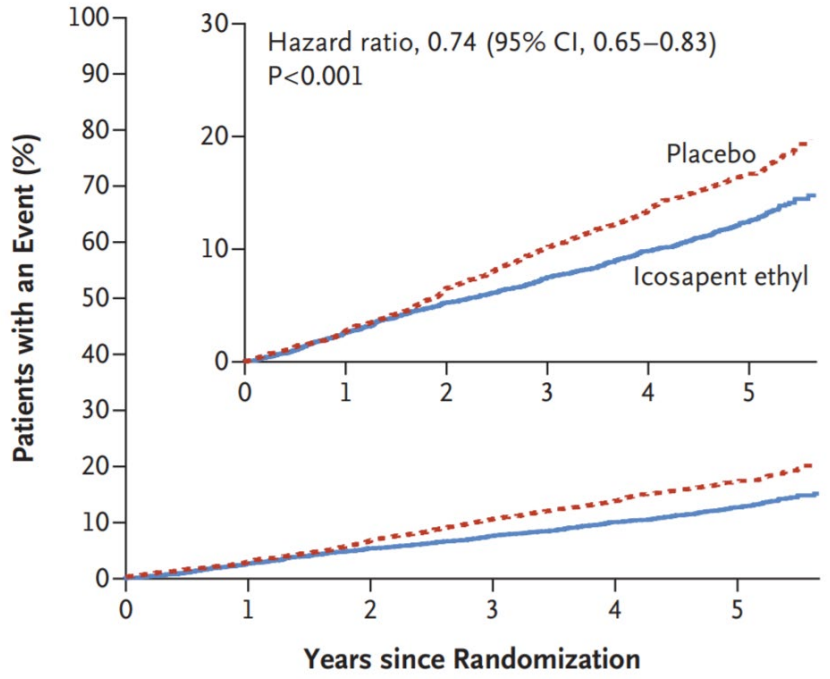
Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D., Terry A. Jacobson, M.D., Steven B. Ketchum, Ph.D., Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D., Lixia Jiao, Ph.D., Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and Christie M. Ballantyne, M.D., for the REDUCE-IT Investigators*

A Primary End Point



B Key Secondary End Point



C – Cholesterol

Non-Statin Add-On Therapy? Icosapent Ethyl

JOHNS HOPKINS MEDICINE

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D., Terry A. Jacobson, M.D., Steven B. Ketchum, Ph.D., Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D., Lixia Jiao, Ph.D., Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and Christie M. Ballantyne, M.D., for the REDUCE-IT Investigators*

Subgroup	Icosapent Ethyl	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients with event/total no. of patients (%)			
All patients	705/4089 (17.2)	901/4090 (22.0)	0.75 (0.68–0.83)	
Risk stratum				0.14
Secondary-prevention cohort	559/2892 (19.3)	738/2893 (25.5)	0.73 (0.65–0.81)	
Primary-prevention cohort	146/1197 (12.2)	163/1197 (13.6)	0.88 (0.70–1.10)	

Event rates in the REDUCE-IT primary prevention (using statins + high TGs + DM + another RF) arm were **almost half** those in the secondary prevention arm

C – Cholesterol

Non-Statin Add-On Therapy? Omega-3

JOHNS HOPKINS MEDICINE

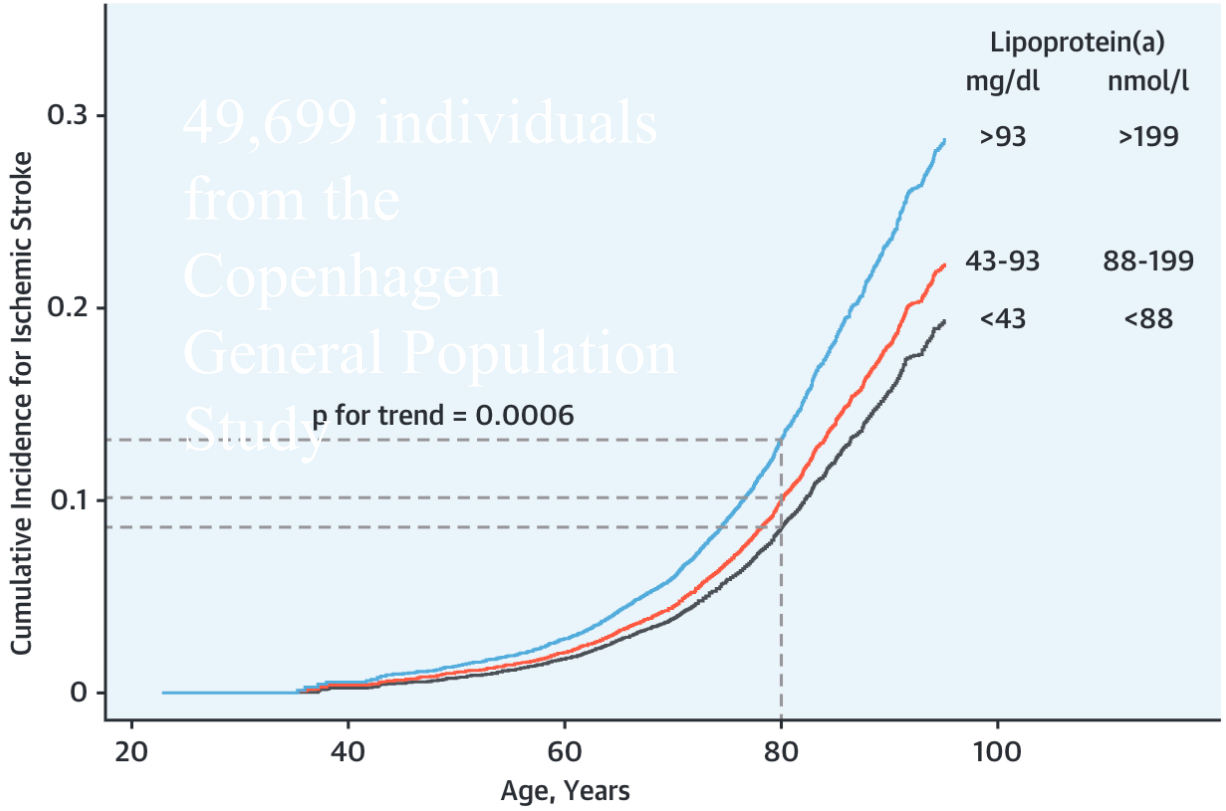
JAMA | Original Investigation

Effect of High-Dose Omega-3 Fatty Acids vs Corn Oil on Major Adverse Cardiovascular Events in Patients at High Cardiovascular Risk
The STRENGTH Randomized Clinical Trial

Stephen J. Nicholls, MBBS, PhD; A. Michael Lincoff, MD; Michelle Garcia, RN, BSN, CCRC; Dianna Bash, BSN; Christie M. Ballantyne, MD; Philip J. Barter, MBBS, PhD; Michael H. Davidson, MD; John J. P. Kastelein, MD, PhD; Wolfgang Koenig, MD; Darren K. McGuire, MD, MHSc; Dariush Mozaffarian, MD, DrPH; Paul M Ridker, MD; Kausik K. Ray, MBChB, MD, MPhil; Brian G. Katona, PharmD; Anders Himmelmann, MD, PhD; Larrye E. Loss, PharmD, MBA; Martin Rensfeldt; Torbjörn Lundström, MD, PhD; Rahul Agrawal, MD; Venu Menon, MD; Kathy Wolski, MPH; Steven E. Nissen, MD

Lp(a) –↑risk of CVA, aortic stenosis, PAD, DVT, PE

FIGURE 2 Cumulative Incidences of Ischemic Stroke in Categories of Lipoprotein(a) Levels

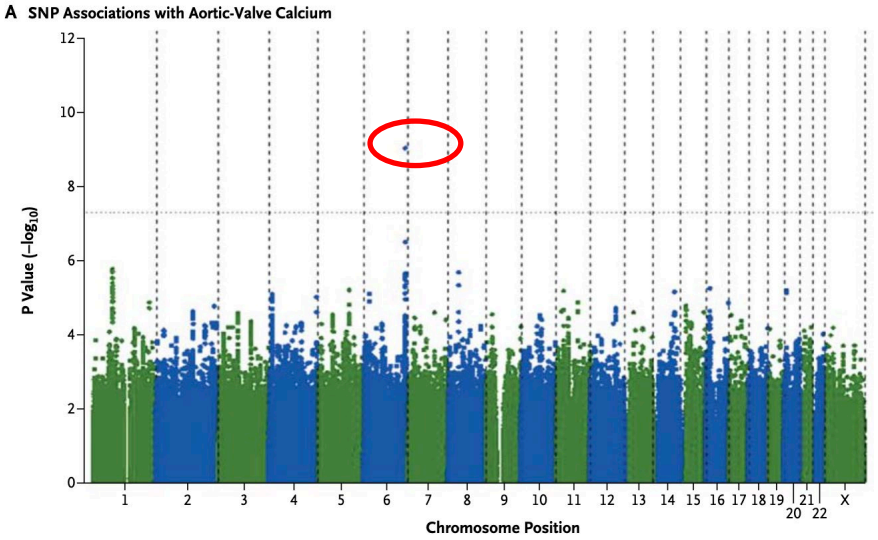


(Langsted et al, JACC 2019)

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 FEBRUARY 7, 2013 VOL. 368 NO. 6

Genetic Associations with Valvular Calcification and Aortic Stenosis

George Thanassoulis, M.D., Catherine Y. Campbell, M.D., David S. Owens, M.D., J. Gustav Smith, M.D., Ph.D., Albert V. Smith, Ph.D., Gina M. Peloso, Ph.D., Kathleen F. Kerr, Ph.D., Sonali Pechlivanis, Ph.D., Matthew J. Budoff, M.D., Tamara B. Harris, M.D., Rajeev Malhotra, M.D., Kevin D. O'Brien, M.D., Pia R. Kamstrup, M.D., Ph.D., Børge G. Nordestgaard, M.D., D.M.Sc., Anne Tybjaerg-Hansen, M.D., D.M.Sc., Matthew A. Allison, M.D., M.P.H., Thor Aspelund, Ph.D., Michael H. Criqui, M.D., M.P.H., Susan R. Heckbert, M.D., Ph.D., Shih-Jen Hwang, Ph.D., Yongmei Liu, Ph.D., Marketa Sjogren, Ph.D., Jesper van der Pals, M.D., Ph.D., Hagen Kälsch, M.D., Thomas W. Mühleisen, Ph.D., Markus M. Nöthen, M.D., L. Adrienne Cupples, Ph.D., Muriel Caslake, Ph.D., Emanuele Di Angelantonio, M.D., Ph.D., John Danesh, F.R.C.P., Jerome I. Rotter, M.D., Sigurdur Sigurdsson, M.Sc., Quenna Wong, M.S., Raimund Erbel, M.D., Sekar Kathiresan, M.D., Olle Melander, M.D., Ph.D., Vilmundur Gudnason, M.D., Ph.D., Christopher J. O'Donnell, M.D., M.P.H., and Wendy S. Post, M.D., for the CHARGE Extracoronary Calcium Working Group



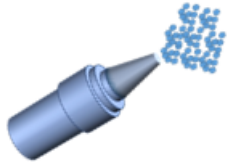
(NEJM 2013)

Lp(a) – making a comeback in Preventive Cardiology
(Prof. Ron Blankstein)

- ✓Lp(a) is a causal factor in development of CVD; also associated with calcific AoSt
- ✓Elevated in ~ 20% of the population
- ✓Atherogenic, pro-inflammatory, pro-thrombotic
- ✓Current Rx: LDL lowering; antiplatelet Rx
- ✓Future therapies anticipated; several new agents under investigation

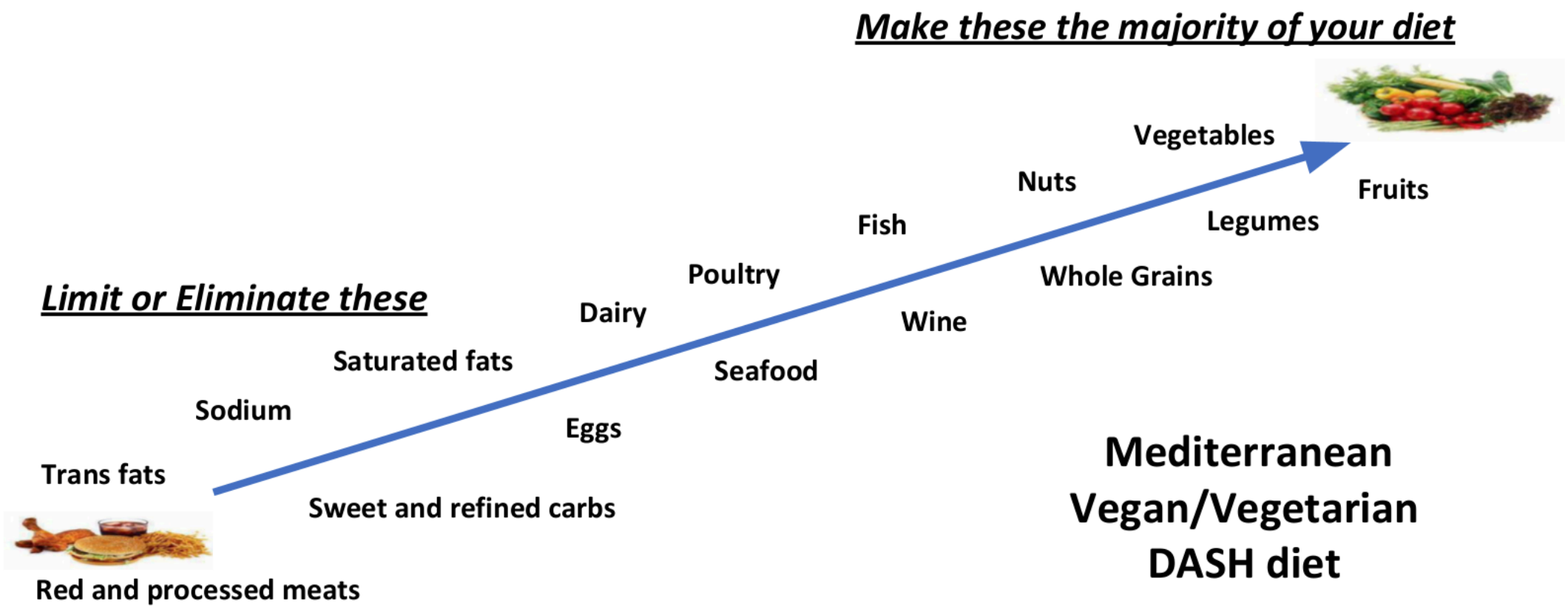
C – Cigarette Cessation

Cigarette Cessation Pharmacotherapy

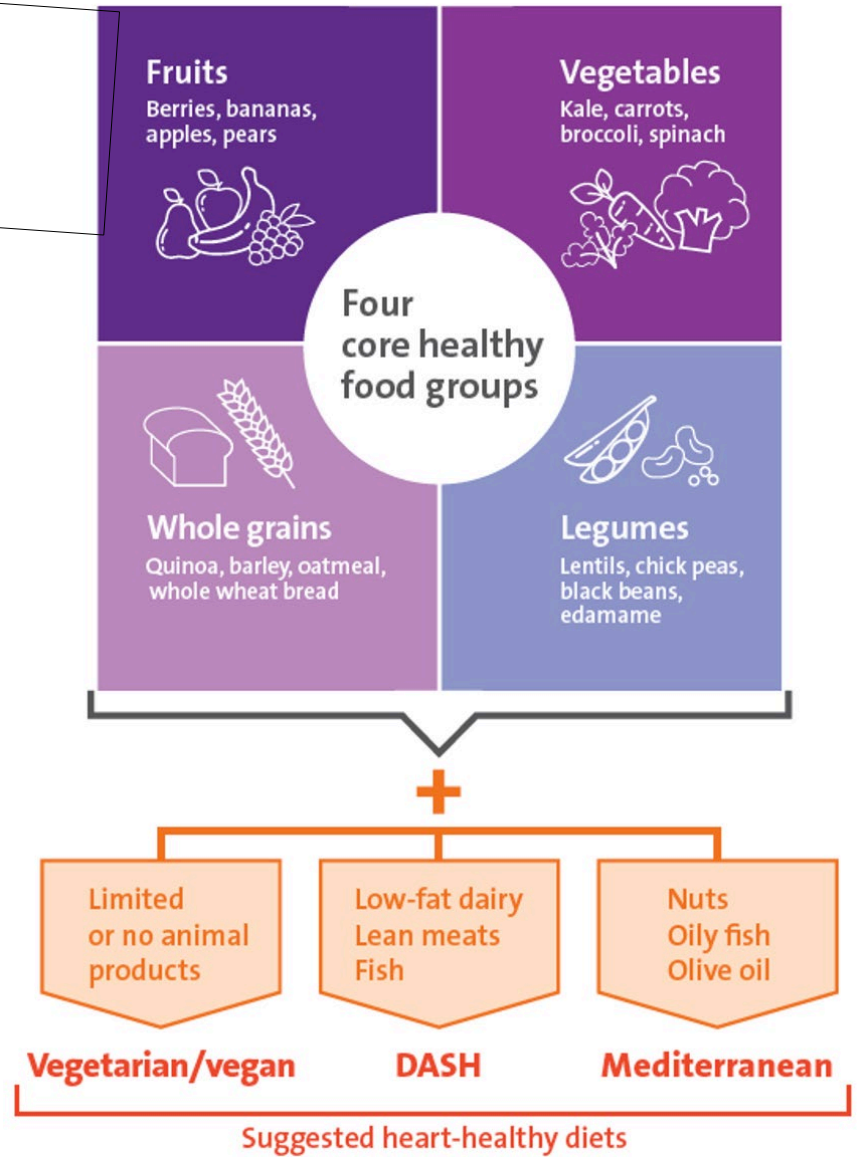
Nicotine replacement therapy		Patch	**If >10 cigarettes/day use 21 mg If <10 cigarettes/day use 14 mg or 7 mg**
		Gum	**2 mg or 4 mg (start with 4mg if first tobacco is ≤30 min from waking); max is 20 lozenges or 24 pieces of gum per day**
		Lozenge	
		Nasal spray	**10 mg/mL**
		Oral inhaler	**10 10-mg cartridge (max 6-16 cartridges/day)**
Other pharmacotherapies		Bupropion	**150 mg SR daily (up to twice daily)**
		Varenicline	**0.5 mg daily titrated to 1 mg twice daily**

D – Diet

Take Steps in the Right Direction



Eat more of this…



and less of this

Limit or eliminate the following:

Red and processed meats

Sausages, cold cuts, bacon, beef, lamb

Saturated fats

Red meats, ice cream, cheese, butter

Trans fats

Hydrogenated fat,
partially hydrogenated fat, trans fat

Sweet and refined carbs

Sugar, juices, corn syrup, candy

Sodium

Frozen meals, canned foods, pickles, chips

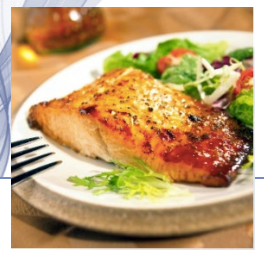
Northwell Health educational hand-out- courtesy of Dr. Eugenia Gianos

Diet/Nutrition

DIET		
COR	LOE	Recommendations
I	B-R	1. Emphasize intake of vegetables, fruits, legumes, nuts, whole grains, & fish to decrease risk factors.
IIa	B-NR	2. Replacement of saturated fat with dietary monounsaturated & polyunsaturated fats can be beneficial.
IIa	B-NR	3. Diet containing reduced amounts of cholesterol & sodium can be beneficial.

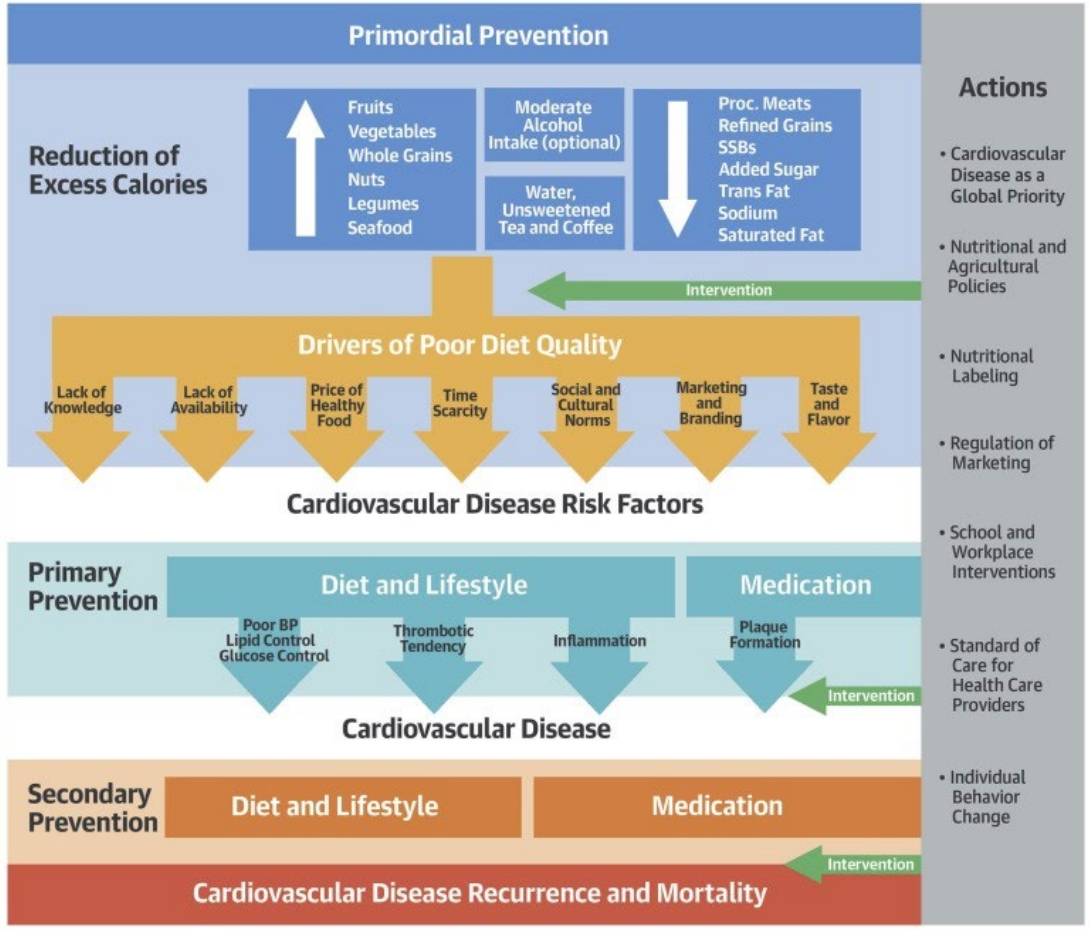
Diet/Nutrition

DIET		
COR	**LOE**	**Recommendations**
IIa	**B-NR**	**4. As part of a healthy diet, it is reasonable to minimize intake of processed meats, refined carbohydrates, & sweetened beverages.**
III-Harm	**B-NR**	**5. As part of a healthy diet, the intake of *trans* fats should be avoided to reduce risk.**

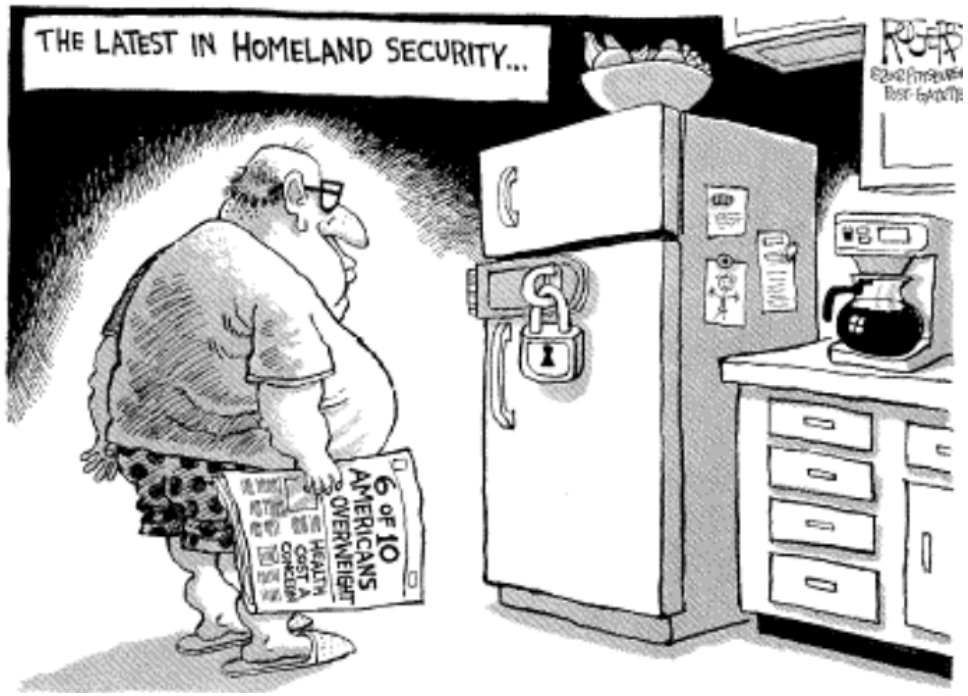


D: Diet

CENTRAL ILLUSTRATION: Flow Diagram of the Development of CVD and Possible Prevention by a Healthy Diet



Yu, E. et al. J Am Coll Cardiol. 2018;72(8):914-26.



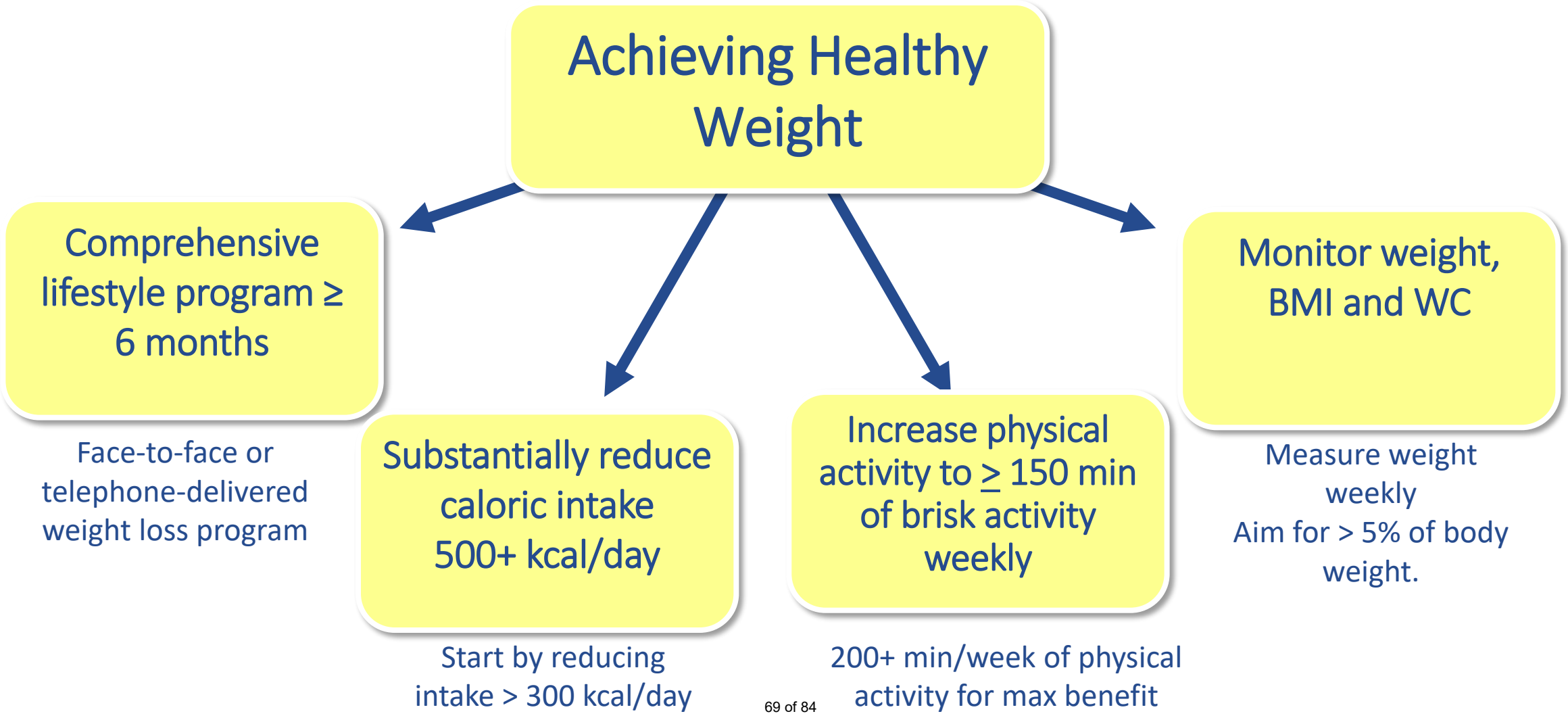
Sodium

- AHA recommended sodium intake: <2300-1500 mg/day
- Leading sources of sodium: processed/packaged foods, restaurant foods

Appel, L. J., Moore, T. J., Obarzanek, E., Vollmer, W. M., Svetkey, L. P., Sacks, F. M., ... & Harsha, D. W. (1997). A clinical trial of the effects of dietary patterns on blood pressure. *New England journal of medicine*, *336*(16), 1117-1124.
https://www.heart.org/en/healthy-living/healthy-eating/eat-smart/sodium/salty-six-infographic

D – Diet

Guidelines



Diabetes: Non-pharmacologic Recommendations for T2DM

- **Tailored Comprehensive Nutritional Plan**
  - Mediterranean, DASH, vegetarian/vegan
  - Team based approach: registered dietitian-nutritionist or DM education program.

- **Exercise**
  - Combination of aerobic and resistance is better than either alone.

- **Set A GOAL**
- Better glycemic control + improve weight

Diabetes Mellitus – Type 2

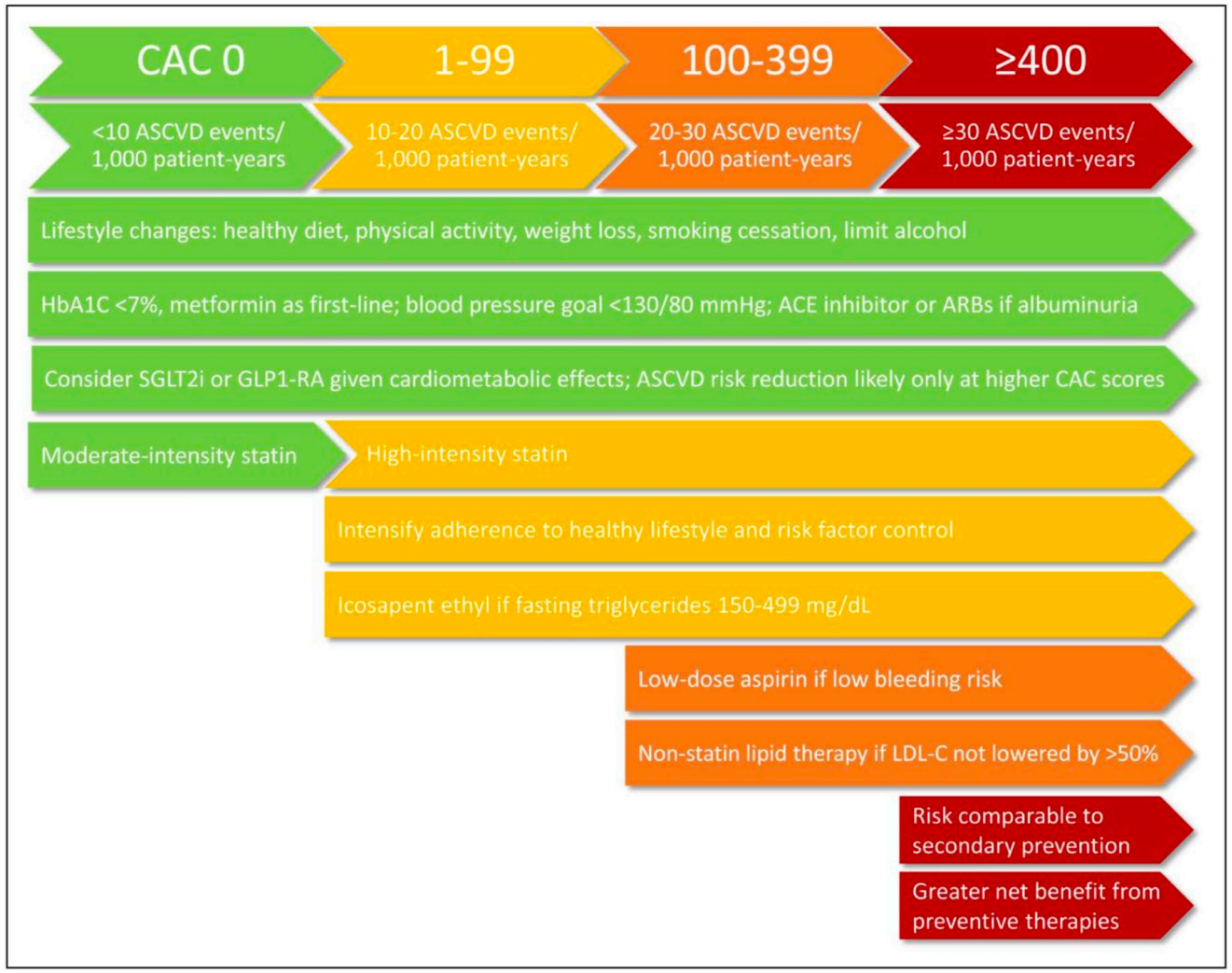
DIABETES		
COR	**LOE**	**Recommendations**
IIa	**B-R**	**3. For adults with T2DM, it is reasonable to initiate metformin as 1st-line Rx along with lifestyle therapies at time of diagnosis to improve glycemic control & reduce risk.**

Diabetes Mellitus – Type 2

DIABETES		
COR	**LOE**	**Recommendations**
IIb	**B-R**	**4. For adults with T2DM & additional risk factors who require glucose-lowering Rx despite initial lifestyle modifications & metformin, it may be reasonable to initiate a sodium-glucose cotransporter 2 (SGLT-2) inhibitor or a glucagon-like peptide-1 receptor (GLP-1R) agonist to improve glycemic control & reduce risk.**

D – Diabetes

Personalized Allocation of Medications

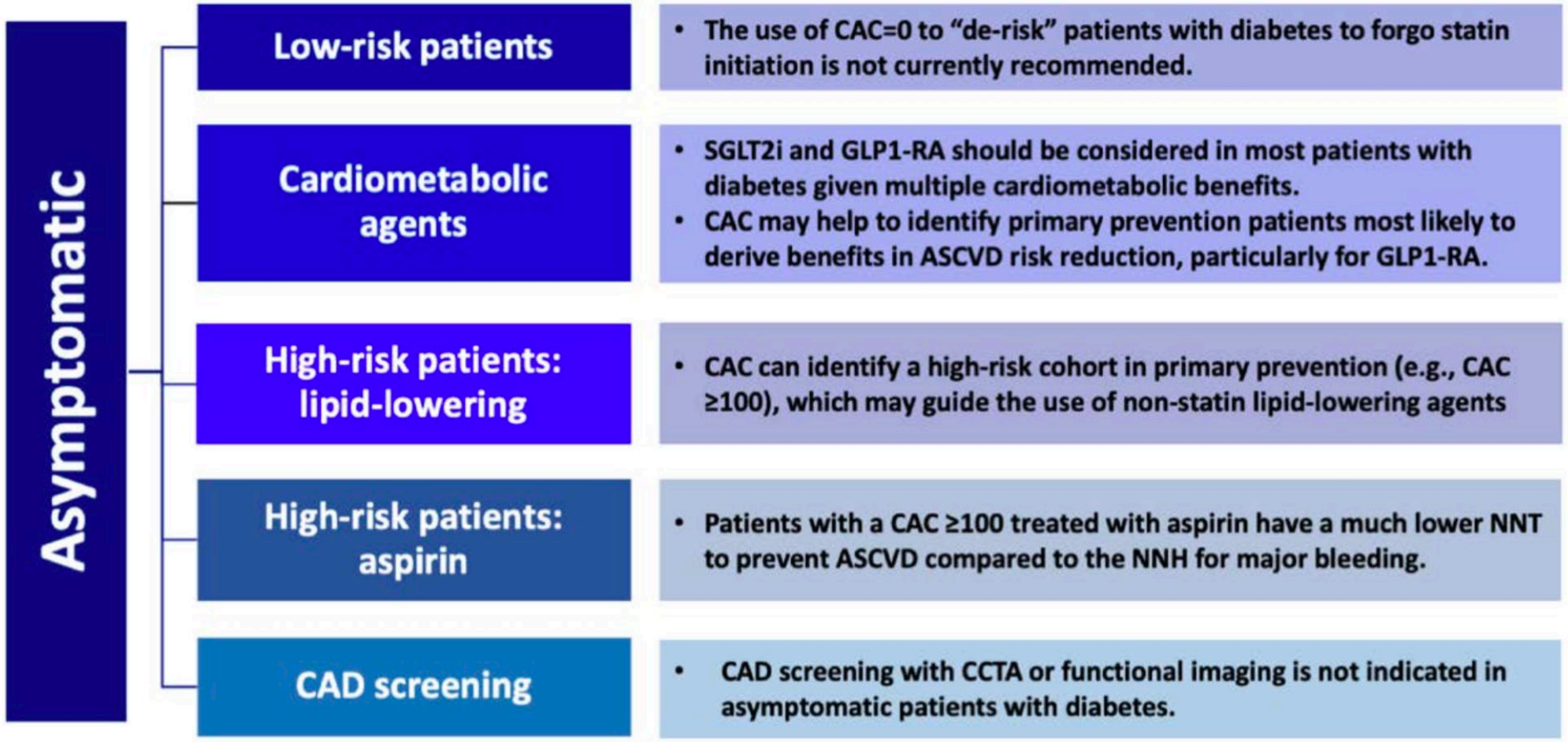


Patient's CAC burden to guide personalized, progressively aggressive risk management of patients with diabetes

Cardoso et al. Circulation: CV Imaging 2020

D – Diabetes

Personalized Allocation of Medications



Cardoso et al. Circulation: CV Imaging 2020

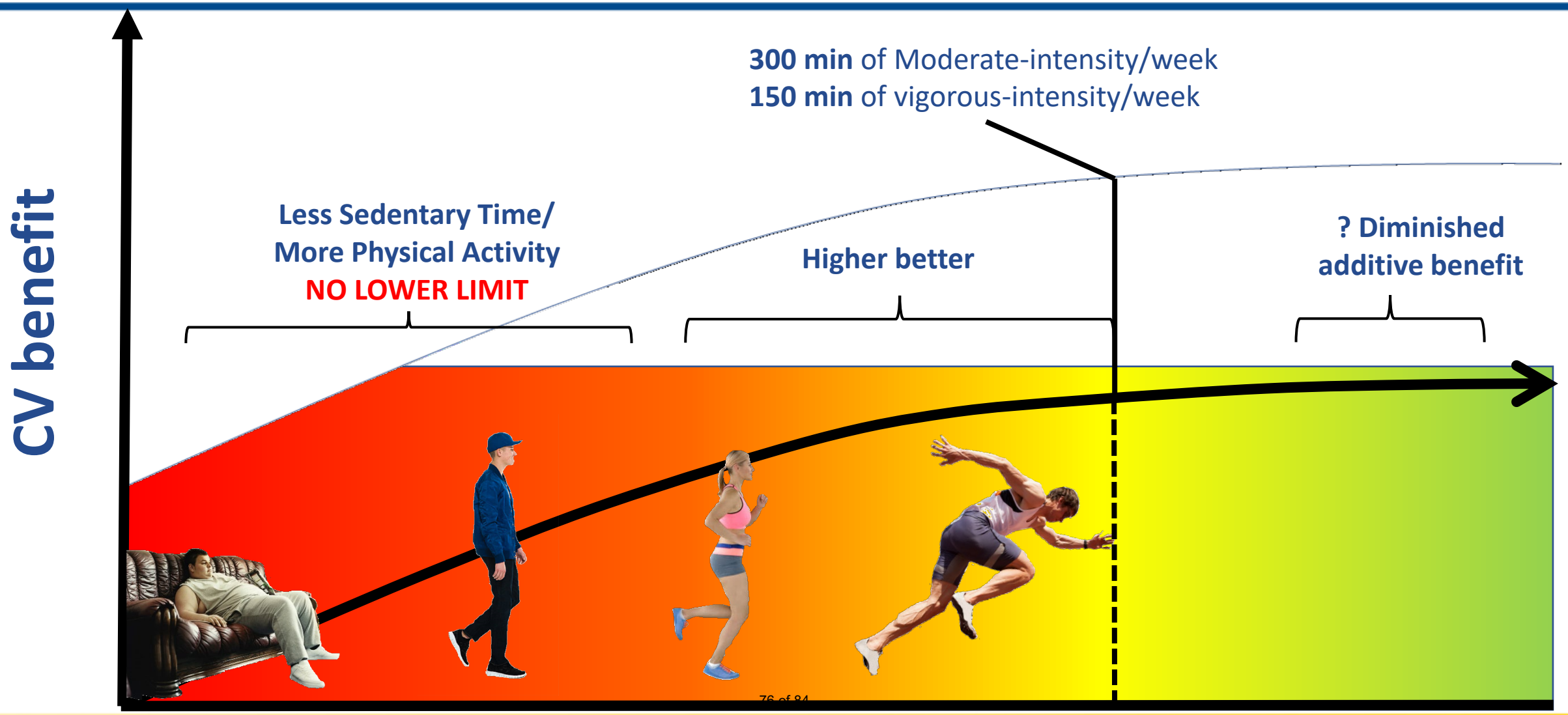
*E*xercise: “Like Mike”

BASKETBALL

DANCE

E – Exercise

Spectrum of Physical Activity



F – Heart Failure

Guidelines – Mortality Benefit

	Relative Risk	2 Year Mortality
None	---	35.0%
ARNI	↓28%	25.2%
Beta Blocker	↓35%	16.4%
Aldosterone Antagonist	↓30%	11.5%
SGLT2 Inhibitor	↓17%	9.5%

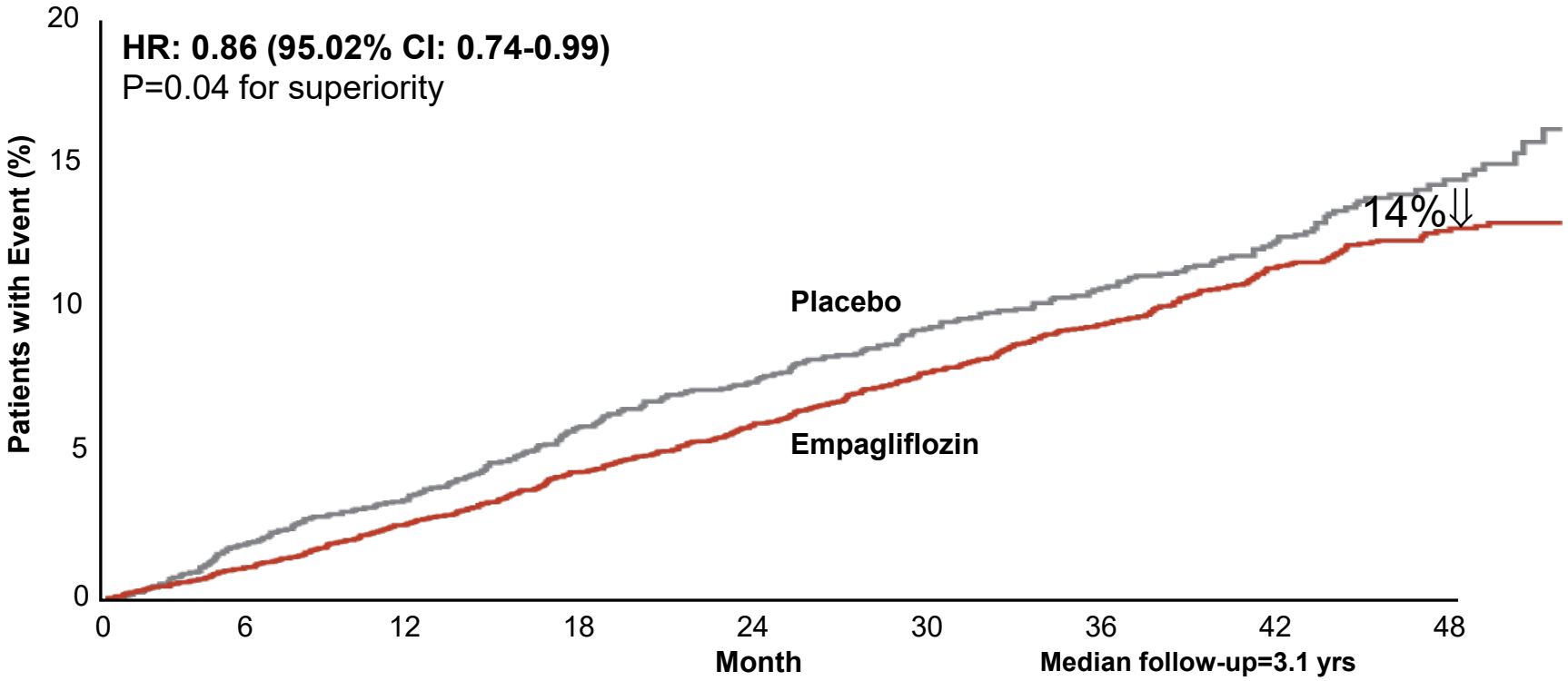
Updated from Fonarow Gc et al. Am Heart J. 2011;161(6):1024-30 & Fonarow GC. Lancet. 2008;372(9645):1195-6.

Cumulative risk reduction in mortality if all evidence-based medical therapies are used: **Relative risk reduction** 72.9%, **Absolute risk reduction:** 25.5%, **NNT =** 3.9

SGLT2i: Empagliflozin (EMPA-REG)

Primary Endpoint: CV Event Rate

Death from CV Disease: P<0.001
Fatal or Nonfatal MI: P=0.22
Fatal or Nonfatal Stroke: P=0.26

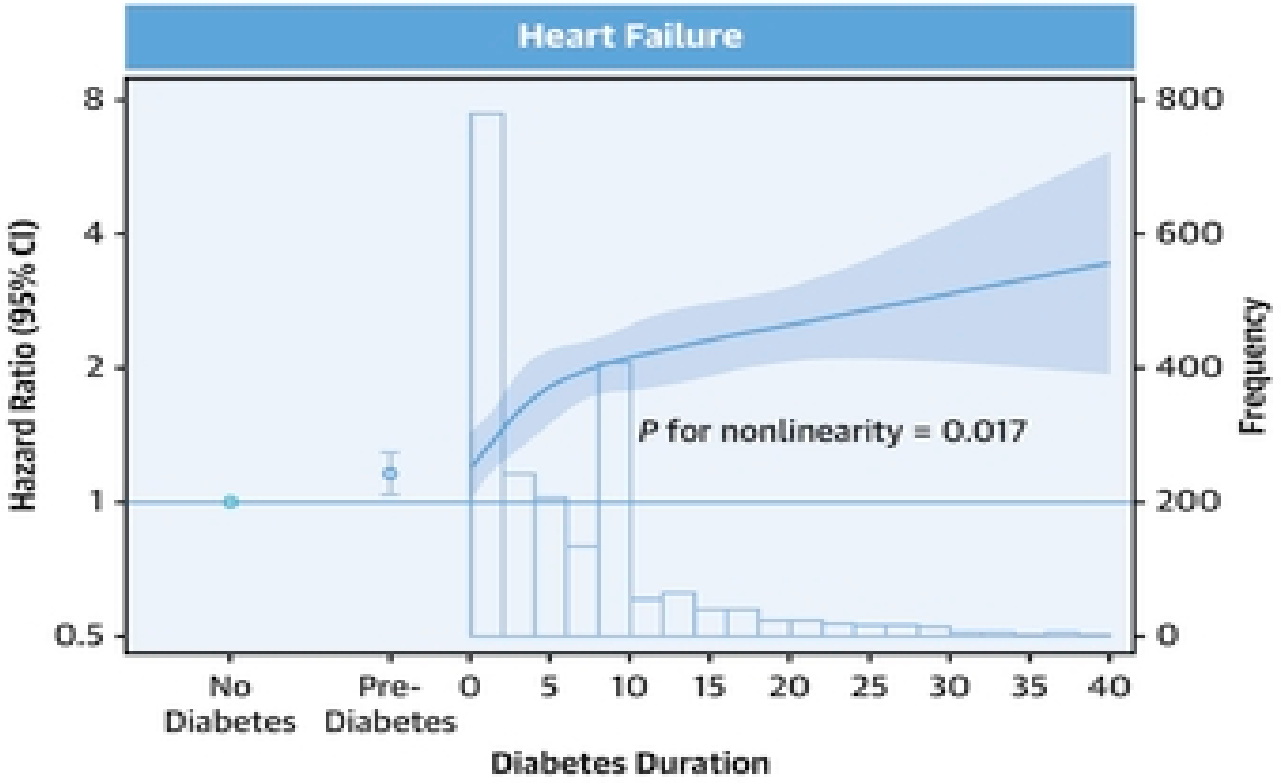


Zinman B, et al. *N Engl J Med.* 2015;373:2117-28; Neal B, et al. *N Engl J Med*. 2017;377(7)644-657.

Key Takeaways of T2DM Rx (Dr. Seth Baum)

- When managing patients with CVD, CKD, &/or DM – treating 1 affects others
- Prior to EMPA-REG, management of T2DM hinged on glucose control
- SGLT2i & GLP1 RA Trials have demonstrated CV Risk Reduction & changed our focus in management of T2DM
- SGLT-2i: most robust & consistent benefits are reduction in HF hospitalizations & progression of CKD;
- ADA /ACC: clinicians must address CV Risk in patients with T2DM and Established ASCVD by prescribing DM drugs proven to reduce CV Risk

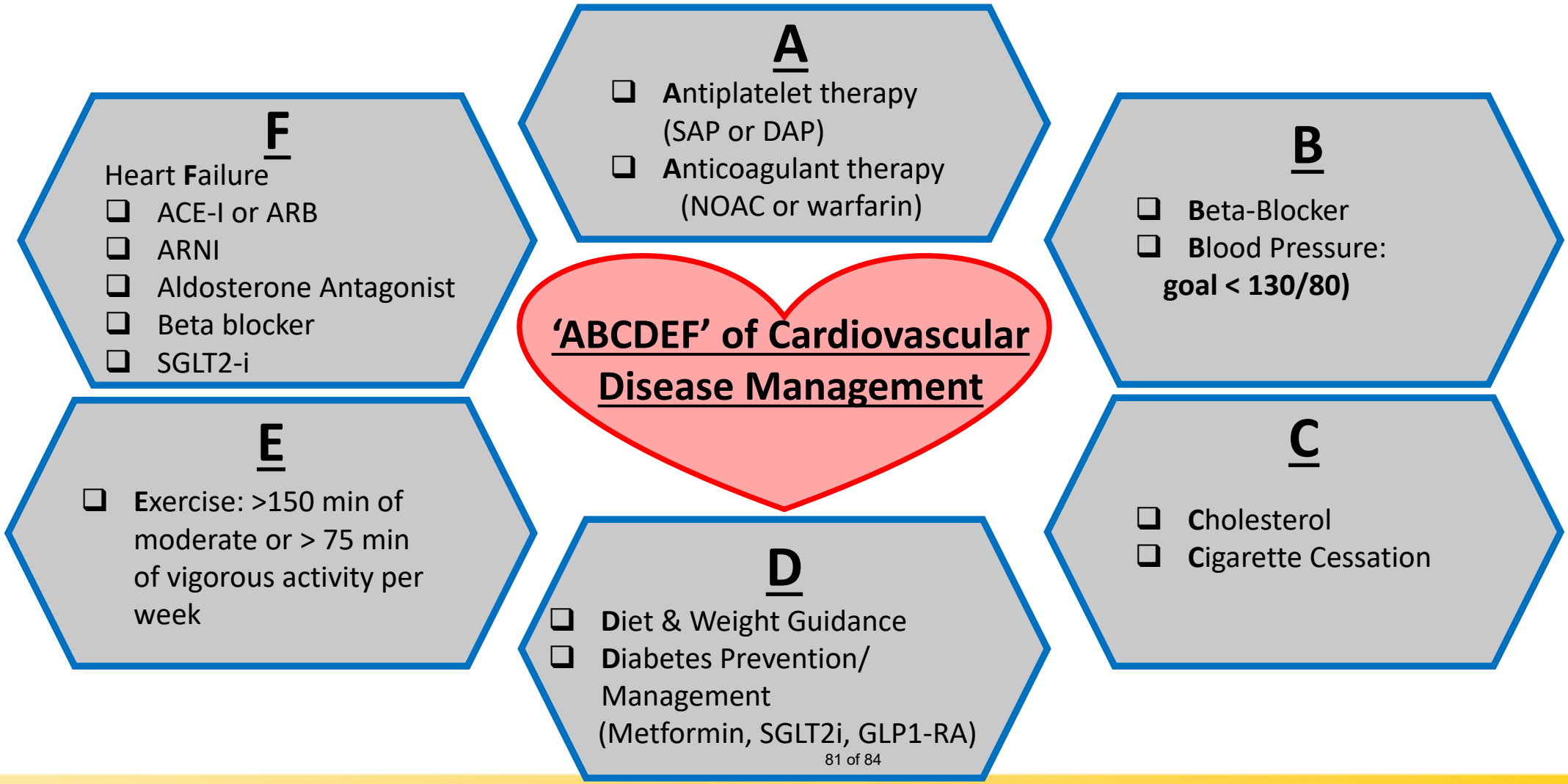
CENTRAL ILLUSTRATION: Restricted Cubic Splines of the Diabetes Duration Association With Heart Failure Among Individuals With Diabetes



Echouffo-Tcheugui, J.B. et al. J Am Coll Cardiol HF. 2021;9(8):594-603.

Justin B. Echouffo-Tcheugui ,Chiadi E. Ndumele et al. *J Am Coll Cardiol HF* 2021; 9:594-603.

ABC's of CVD Prevention



ASSESS THE RISK & AC

- Use the pooled cohort equation to assess 10-year risk
- Consider risk enhancing factors
- Consider CAC score to further classify risk
- Consider statin and/or aspirin
- Consider anticoagulation for atrial fibrillation or flutter

DREAM, DIET, DM

- Good quality sleep
- Recommend Mediterranean or heart healthy diet
- Consider GLP-1RA, SGLT2-i
- Target HbA1c <7%

BMI & BP

- Target BP < 130/80 mm Hg in most patients
- Target BMI < 25 kg/m2
- Encourage weight loss and/or maintenance

EXERCISE

- 150 mins/week of moderate intensity or
- 75 mins/week of vigorous exercise
- Monitor exercise with digital devices

CIGARETTES & CHOLESTEROL

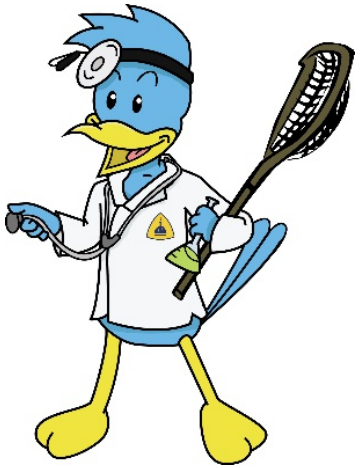
- Quit Smoking and Vaping through behavioral/pharmacological intervention
- Recommend statins for patients aged 40-75 years with DM ,LDL>190 mg/dL and 10-year risk ≥ 7.5% after risk discussion
- Use risk enhancers and CAC score (in select patients) to advise statin decision

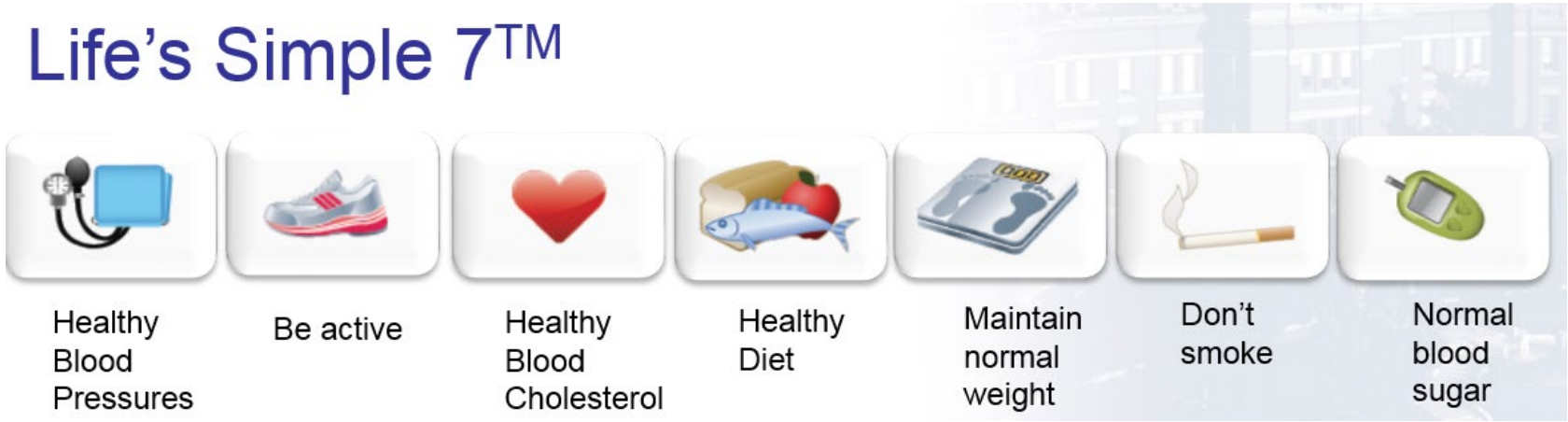
FAILURE (REDUCED EF)

- ARNI or ACEi/ARB if unable to tolerate/afford ARNI
- Aldosterone antagonist
- Beta blockers
- Sodium glucose tranporter-2-inhibitors

The Ciccarone Center for the Prevention of Cardiovascular Disease at Johns Hopkins

Thank you!





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