MHIF FEATURED STUDY:
COVID-PACT

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:

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ≥ 18 years old</td>
<td>• Ongoing (&gt;48 hours) or planned full-dose anticoagulation</td>
</tr>
<tr>
<td>• Acute infection with SARS-CoV2</td>
<td>• Ongoing or planned treatment with dual antiplatelet therapy</td>
</tr>
<tr>
<td>• Currently admitted to the ICU or receiving ICU level cares ≤ 96 hours</td>
<td>• Contraindication to antithrombotic therapy or high risk of bleeding</td>
</tr>
<tr>
<td></td>
<td>• History of heparin-induced thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>• Ischemic stroke within the past 2 weeks</td>
</tr>
<tr>
<td></td>
<td>• Pregnancy</td>
</tr>
</tbody>
</table>

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

OPEN AND ENROLLING:
EPIC message: Research MHIF Patient Referral
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

MHIF Cardiovascular Grand Rounds | October 11, 2021
Intense Coaches in NCAA Lacrosse Championship Game
The Ciccarone Center for the Prevention of CV Disease

Focused on the prevention of ASCVD, HF, AFIB, PAD
Ciccarone Team (Cont.)
ABC Approach for Angina (1999)

ACC/AHA/ACP-ASIM
Guidelines for Management of Stable Angina

- Aspirin and anti-anginals
- Beta blocker and blood pressure
- Cholesterol and cigarettes
- Diet and diabetes
- Education and exercise
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$^{2+}$

- **Exertional angina**
  - (+) ETT

- **Revascularization**
  - Anti-anginal Rx

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

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

- **Pharmacologic stabilization**
  - Early identification of high-risk?

Courtesy of PH Stone, MD.
Management of Stable Angina/ASCVD in 2020

Central Illustration: Contemporary Evaluation and Management of Stable Angina

Stable Angina

Initial Medical Treatment

CT Coronary Angiography

- No Atherosclerosis
  - Limited Nonobstructive (<50% stenosis) in 1-2 Vessels
  - Extensive Nonobstructive or Obstructive (≥50%) CAD

- Left Main or 3-Vessel CAD
  - DM or ICM (EF <35%)

- Lifestyle Therapy
  - Risk Factor Modification
  - OMT for functional angina

- Additional Moderate Medical Therapy†
  - PCI/CABG for failed OMT

- Additional Intensive Medical Therapy‡
  - Revascularization

“ABCs” of CVD Prevention & Management

Cholesterol
Cigarette Cessation
Diabetes/Glucose Management
Diet/Weight
Exercise/Education
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
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.
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:

  - Housing instability
  - Food insecurity
  - Transportation difficulties
  - Utility assistance needs
  - Interpersonal safety
Toolbox for Estimating ASCVD Risk

- 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

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>B-NR</td>
<td>4. In adults at intermediate risk (≥7.5% to &lt;20% 10-yr ASCVD risk) or selected adults at borderline risk (5% to &lt;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.</td>
</tr>
<tr>
<td>IIb</td>
<td>B-NR</td>
<td>5. For adults 20-39 y/o and for those 40-59 y/o who have &lt;7.5% 10-yr risk, estimating lifetime or 30-yr risk may be considered.</td>
</tr>
</tbody>
</table>
Lifetime Risk Estimate – ASCVD Risk Estimator Plus

Inputs

- **Sex:** Female
- **Age:** 32
- **Race:** White
- **Total Cholesterol:** 225 mg/dL
- **HDL-Cholesterol:** 48 mg/dL
- **Systolic Blood Pressure:** 136 mm Hg
- **Diabetes:** No
- **Smoker:** Yes
- **Treatment for Hypertension:** No

Recommendation

- **10-Year ASCVD Risk:** 39%
- **Lifetime ASCVD Risk:** 8%

*Not In Statin Benefit Group Due To Age < 40 Years*

From Lloyd-Jones D et al Risk Assessment Nov 2018
A – Assess Risk

Pooled Cohort Equations

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  

“You’re fifty-seven years old. I’d like to get that down a bit.”
A – Assess Risk

Coronary Artery Calcium Score

Background

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

2009: Origin of Power of Zero

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
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

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

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\textsuperscript{1,2}; Vincent A. Pallazola, MD\textsuperscript{2}; Ramzi Dudum, MD, MPH\textsuperscript{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

MHIF Cardiovascular Grand Rounds | October 11, 2021
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**

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>A</td>
<td><strong>1. Low-dose aspirin</strong> (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 <strong>not</strong> at increased bleeding risk.</td>
</tr>
<tr>
<td>III: Harm</td>
<td>B-R</td>
<td><strong>2. Low-dose aspirin</strong> (75-100 mg orally daily) should <strong>not</strong> be administered on <strong>routine</strong> basis for primary prevention among adults &gt;70 y/o.</td>
</tr>
<tr>
<td>III: Harm</td>
<td>C-LD</td>
<td><strong>3. Low-dose aspirin</strong> (75-100 mg orally daily) should <strong>not</strong> be administered for primary prevention among adults <strong>who are at increased risk of bleeding.</strong></td>
</tr>
</tbody>
</table>
A – Antiplatelet Therapy

Aspirin for Primary Prevention

- Aspirin is effective in secondary prevention
- Based on older trials, prior U.S. guidelines had recommended low-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

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

CV Risk Management

- CAC for Aspirin Rx?: General population

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

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)

Primary outcome
- Placebo
- Aspirin

Log-rank p=0.6038
Stratified log-rank p=0.5970

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

A – Antiplatelet Therapy

ASCEND: Primary Outcome

**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

A – Antiplatelet Therapy

Aspirin and CAC (MESA)

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

Among those at low risk of bleeding

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.

# Blood Pressure

## Blood Pressure Categories

<table>
<thead>
<tr>
<th>Blood Pressure Category</th>
<th>Systolic mm Hg (upper number)</th>
<th>Diastolic mm Hg (lower number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>LESS THAN 120</td>
<td>and</td>
</tr>
<tr>
<td>Elevated</td>
<td>120 – 129</td>
<td>and</td>
</tr>
<tr>
<td>High Blood Pressure (Hypertension) Stage 1</td>
<td>130 – 139</td>
<td>or</td>
</tr>
<tr>
<td>High Blood Pressure (Hypertension) Stage 2</td>
<td>140 OR HIGHER</td>
<td>or</td>
</tr>
<tr>
<td>Hypertensive Crisis (consult your doctor immediately)</td>
<td>HIGHER THAN 180</td>
<td>and/or</td>
</tr>
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<td></td>
<td></td>
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</tbody>
</table>

**Note:** Consult your doctor immediately if you fall under the Hypertensive Crisis category.
B – Blood Pressure

10-yr risk <10%
- Heart Healthy lifestyle

10-yr risk ≥10%
- Diabetes
- CKD
- Heart Healthy lifestyle
- Intensive lifestyle modification
- Pharmacotherapy

Goal BP
- 130/80
- 140/90
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

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. 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. 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).
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

Promote a Healthy Lifestyle

Share Decision Making with the Patient

- Measure risk factors
- Evaluate the patient’s risk of ASCVD

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
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
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
Very high event rates in 2º prevention, even in the setting of RCTs and using high-intensity statins.
CENTRAL ILLUSTRATION: TRS 2°P

**TRIS 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 2.2%, NNT 45**

**ARR 6.3%, NNT 16**

C – Cholesterol

Non-Statin Add-On Therapy? PCSK9i

**FOURIER**
Median 2.2yr
LDL-C 92 → 30

**ODYSSEY OUTCOMES**
Median 2.8yr
LDL-C 92 → 30 → 48 → 66

N Engl J Med 2017; 376:1713-1722

2019 ESC/EAS Guidelines

European Treatment goals for LDL-C across categories of total cardiovascular disease risk*

- **Low**
  - SCORE <1%
  - No risk factors

- **Moderate**
  - SCORE 1-5%
  - Young patients (T1DM <35 years; T2DM <50 years without other RF)

- **High**
  - SCORE >5% and <10%
  - Markedly elevated RF (TC>310 (8 mmol/L) or LDL-C >190 (mmol/L))
  - BP > 180/110
  - FH without other major risk factors
  - Moderate CKD (eGFR 30-59 mL/min)
  - DM >10 years or additional RF, w/o target organ damage

- **Very High**
  - SCORE >10%
  - ASCVD (clinical/imaging)
  - FH with ASCVD or with another major RF
  - Severe CKD (eGFR <30 mL/min)
  - DM & target organ damage
  - 2nd Event within 2 years

- **Very High**
  - 2nd Event within 2 years

- **CV RISK**
  - Low
  - Moderate
  - High
  - Very High
  - High with DM

LDL-C goal + > 50% reduction from baseline

- 116 mg/dL (3.0 mmol/L)
- 100 mg/dL (2.6 mmol/L)
- 70 mg/dL (1.8 mmol/L)
- 55 mg/dL (1.4 mmol/L)
- 40 mg/dL (1.0 mmol/L)
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.

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

Hazard ratio, 0.75 (95% CI, 0.68–0.83) P<0.001

Placebo

Icosapent ethyl

B Key Secondary End Point

Hazard ratio, 0.74 (95% CI, 0.65–0.83) P<0.001

Placebo

Icosapent ethyl
C – Cholesterol

Non-Statin Add-On Therapy? 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*

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Icosapent Ethyl</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>705/4089 (17.2)</td>
<td>901/4090 (22.0)</td>
<td>-</td>
<td>0.75 (0.68–0.83)</td>
</tr>
<tr>
<td>Risk stratum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary-prevention cohort</td>
<td>559/2892 (19.3)</td>
<td>738/2893 (25.5)</td>
<td>-</td>
<td>0.73 (0.65–0.81)</td>
</tr>
<tr>
<td>Primary-prevention cohort</td>
<td>146/1197 (12.2)</td>
<td>163/1197 (13.6)</td>
<td>-</td>
<td>0.88 (0.70–1.10)</td>
</tr>
</tbody>
</table>

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

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; Larry 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

(Langsted et al, JACC 2019)
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

<table>
<thead>
<tr>
<th>Nicotine replacement therapy</th>
<th>Patch</th>
<th>If &gt;10 cigarettes/day use 21 mg If &lt;10 cigarettes/day use 14 mg or 7 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gum</td>
<td>2 mg or 4 mg (start with 4 mg if first tobacco is ≤30 min from waking); max is 20 lozenges or 24 pieces of gum per day</td>
</tr>
<tr>
<td></td>
<td>Lozenge</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nasal spray</td>
<td>10 mg/mL</td>
</tr>
<tr>
<td></td>
<td>Oral inhaler</td>
<td>10 10-mg cartridge (max 6-16 cartridges/day)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other pharmacotherapies</th>
<th>Bupropion</th>
<th>150 mg SR daily (up to twice daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Varenicline</td>
<td>0.5 mg daily titrated to 1 mg twice daily</td>
</tr>
</tbody>
</table>
D – Diet

Take Steps in the Right Direction

Make these the majority of your diet

Limit or Eliminate these

Saturated fats
Sodium
Trans fats
Sweet and refined carbs
Red and processed meats

Mediterranean
Vegan/Vegetarian
DASH diet
Eat more of this...

Four core healthy food groups:
- Fruits: Berries, bananas, apples, pears
- Vegetables: Kale, carrots, broccoli, spinach
- Whole grains: Quinoa, barley, oatmeal, whole wheat bread
- Legumes: Lentils, chick peas, black beans, edamame

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
## Diet/Nutrition

### DIET

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-R</td>
<td>1. Emphasize intake of <strong>vegetables, fruits, legumes, nuts, whole grains, &amp; fish to decrease risk factors.</strong></td>
</tr>
<tr>
<td>IIA</td>
<td>B-NR</td>
<td>2. Replacement of saturated fat with dietary monounsaturated &amp; polyunsaturated fats can be beneficial.</td>
</tr>
<tr>
<td>IIA</td>
<td>B-NR</td>
<td>3. Diet containing <strong>reduced amounts of cholesterol &amp; sodium</strong> can be beneficial.</td>
</tr>
</tbody>
</table>
# Diet/Nutrition

## DIET

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>B-NR</td>
<td>4. As part of a healthy diet, it is reasonable to minimize intake of processed meats, refined carbohydrates, &amp; sweetened beverages.</td>
</tr>
<tr>
<td>III- HARM</td>
<td>B-NR</td>
<td>5. As part of a healthy diet, the intake of trans fats should be avoided to reduce risk.</td>
</tr>
</tbody>
</table>
D: Diet

**Central Illustration:** Flow Diagram of the Development of CVD and Possible Prevention by a Healthy Diet

**Primordial Prevention**
- Fruits
- Vegetables
- Whole Grains
- Nuts
- Legumes
- Seafood

**Moderate Alcohol Intake (Optional)**
- Water, Unprocessed Tea and Coffee

**Reduction of Excess Calories**
- Processed Meats
- Refined Grains
- SSBs
- Added Sugar
- Trans Fat
- Sodium
- Saturated Fat

**Drivers of Poor Diet Quality**
- Lack of Knowledge
- Lack of Availability
- Price of Healthy Food
- Time Scarcity
- Social and Cultural Norms
- Marketing and Branding
- Taste and Flavor

**Cardiovascular Disease Risk Factors**

**Primary Prevention**
- Poor Lifestyle
- Tobacco Use
- High Blood Pressure
- High Blood Lipids
- Diabetes

**Diet and Lifestyle**
- Inflammation
- Plaque Formation

**Medication**
- Intervention

**Cardiovascular Disease**

**Secondary Prevention**
- Diet and Lifestyle
- Medication

**Cardiovascular Disease Recurrence and Mortality**

**Actions**
- Cardiovascular Disease as a Global Priority
- Nutritional and Agricultural Policies
- Nutritional Labeling
- Regulation of Marketing
- School and Workplace Interventions
- Standard of Care for Health Care Providers
- Individual Behavior Change

Sodium

• AHA recommended sodium intake: <2300-1500 mg/day

• Leading sources of sodium: processed/packaged foods, restaurant foods
D – Diet

Guidelines

Achieving Healthy Weight

- Comprehensive lifestyle program ≥ 6 months
  - Face-to-face or telephone-delivered weight loss program
- Substantially reduce caloric intake 500+ kcal/day
  - Start by reducing intake > 300 kcal/day
- Increase physical activity to > 150 min of brisk activity weekly
  - 200+ min/week of physical activity for max benefit
- Monitor weight, BMI and WC
  - Measure weight weekly
  - Aim for > 5% of body weight.
<table>
<thead>
<tr>
<th><strong>Diabetes: Non-pharmacologic Recommendations for T2DM</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• <strong>Tailored Comprehensive Nutritional Plan</strong></td>
</tr>
<tr>
<td>• Mediterranean, DASH, vegetarian/vegan</td>
</tr>
<tr>
<td>• Team based approach: registered dietitian-nutritionist or DM education program.</td>
</tr>
<tr>
<td>• <strong>Exercise</strong></td>
</tr>
<tr>
<td>• Combination of aerobic and resistance is better than either alone.</td>
</tr>
<tr>
<td>• <strong>Set A GOAL</strong></td>
</tr>
<tr>
<td>• Better glycemic control + improve weight</td>
</tr>
</tbody>
</table>
### DIABETES

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>B-R</td>
<td>3. For adults with T2DM, it is reasonable to initiate <strong>metformin</strong> as 1st-line Rx along with lifestyle therapies at time of diagnosis to improve glycemic control &amp; reduce risk.</td>
</tr>
</tbody>
</table>
### Diabetes Mellitus – Type 2

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>B-R</td>
<td>4. For adults with T2DM &amp; additional risk factors who require glucose-lowering Rx despite initial lifestyle modifications &amp; 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 &amp; reduce risk.</td>
</tr>
</tbody>
</table>
# D – Diabetes

## Personalized Allocation of Medications

<table>
<thead>
<tr>
<th>CAC 0</th>
<th>1-99</th>
<th>100-399</th>
<th>≥400</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 ASCVD events/1,000 patient-years</td>
<td>10-20 ASCVD events/1,000 patient-years</td>
<td>20-30 ASCVD events/1,000 patient-years</td>
<td>≥30 ASCVD events/1,000 patient-years</td>
</tr>
</tbody>
</table>

- **Lifestyle changes:** healthy diet, physical activity, weight loss, smoking cessation, limit alcohol
- **HbA1C <7%**, metformin as first-line; blood pressure goal <130/80 mmHg; ACE inhibitor or ARBs if albuminuria
- Consider SGLT2i or GLP1-RA given cardiometabolic effects; ASCVD risk reduction likely only at higher CAC scores
- **Moderate-intensity statin**
- **High-intensity statin**
- Intensify adherence to healthy lifestyle and risk factor control
- Icosapent ethyl if fasting triglycerides 150-499 mg/dL

Patient’s CAC burden to guide personalized, progressively aggressive risk management of patients with diabetes.
D – Diabetes

Personalized Allocation of Medications

- **Low-risk patients**
  - The use of CAC=0 to “de-risk” patients with diabetes to forgo statin initiation is not currently recommended.

- **Cardiometabolic agents**
  - SGLT2i and GLP1-RA should be considered in most patients with diabetes given multiple cardiometabolic benefits.
  - CAC may help to identify primary prevention patients most likely to derive benefits in ASCVD risk reduction, particularly for GLP1-RA.

- **High-risk patients: lipid-lowering**
  - CAC can identify a high-risk cohort in primary prevention (e.g., CAC ≥100), which may guide the use of non-statin lipid-lowering agents.

- **High-risk patients: aspirin**
  - Patients with a CAC ≥100 treated with aspirin have a much lower NNT to prevent ASCVD compared to the NNH for major bleeding.

- **CAD screening**
  - CAD screening with CCTA or functional imaging is not indicated in asymptomatic patients with diabetes.
Exercise: “Like Mike”

BASKETBALL

DANCE
E – Exercise

Spectrum of Physical Activity

- Less Sedentary Time/More Physical Activity
  - NO LOWER LIMIT

- 300 min of Moderate-intensity/week
- 150 min of vigorous-intensity/week

- Higher better

- ? Diminished additive benefit
### F – Heart Failure

#### Guidelines – Mortality Benefit

<table>
<thead>
<tr>
<th></th>
<th>Relative Risk</th>
<th>2 Year Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>---</td>
<td>35.0%</td>
</tr>
<tr>
<td>ARNI</td>
<td>↓28%</td>
<td>25.2%</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>↓35%</td>
<td>16.4%</td>
</tr>
<tr>
<td>Aldosterone Antagonist</td>
<td>↓30%</td>
<td>11.5%</td>
</tr>
<tr>
<td>SGLT2 Inhibitor</td>
<td>↓17%</td>
<td>9.5%</td>
</tr>
</tbody>
</table>

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

HR: 0.86 (95.02% CI: 0.74-0.99)
P=0.04 for superiority

Placebo
Empagliflozin

Patients with Event (%)

0 6 30241812 48

0 5 10 15 20

0 6 12 18 24 30 36 42 48

Month
Median follow-up=3.1 yrs

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


ABC’s of CVD Prevention

‘ABCDEF’ of Cardiovascular Disease Management

A
- Antiplatelet therapy (SAP or DAP)
- Anticoagulant therapy (NOAC or warfarin)

B
- Beta-Blocker
- Blood Pressure: goal < 130/80

C
- Cholesterol
- Cigarette Cessation

D
- Diet & Weight Guidance
- Diabetes Prevention/Management (Metformin, SGLT2i, GLP1-RA)

E
- Exercise: >150 min of moderate or > 75 min of vigorous activity per week

F
- Heart Failure
  - ACE-I or ARB
  - ARNI
  - Aldosterone Antagonist
  - Beta blocker
  - SGLT2-i
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

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

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

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 transporter-2-inhibitors
Thank you!

Life’s Simple 7™

Healthy Blood Pressures  Be active  Healthy Blood Cholesterol  Healthy Diet  Maintain normal weight  Don’t smoke  Normal blood sugar