Microvascular Angina: Where are We?

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What is your background in medicine?

A. Cardiologist
B. Internal medicine
C. Other primary care
D. Other subspecialty
E. Research only
Microvascular disease

• New classification
• Diagnostics
  • Invasive
  • Non-invasive (established)
  • Non-invasive (novel)
• Therapeutics
  • Existing
  • Future needs
Ischemic Heart Disease: Remains the global leading cause of death

• Angina
  • Most common presentation
  • Problem of supply:demand mismatch, typically provoked by exercise or stress
  • Invasive coronary angiography is the reference test
• In U.S. and Europe, up to 4 million angiograms are performed
  • Only half have evidence of obstructive CAD
Taxonomy

Ischaemic Heart Disease

Stable Coronary Syndrome
- Obstructive CAD
- INOCA

Acute Coronary Syndrome
- MINOCA
- UA / NSTEMI
- STEMI

CAD=coronary artery disease
INOCA=ischemia and no obstructive coronary disease
MINOCA=myocardial infarction and no obstructive coronary disease
UA=unstable angina
NSTEMI=non ST elevation myocardial infarction
STEMI=ST elevation myocardial infarction

Ford TJ et al. Heart 2018;104:284-292
**Ischaemic Heart Disease**

**Stable Coronary Syndrome**
- Obstructive CAD
- INOCA
- MINOCA

**Acute Coronary Syndrome**
- UA / NSTEMI
- STEMI

**Definitions**
- CAD = coronary artery disease
- INOCA = ischemia and no obstructive coronary disease
- MINOCA = myocardial infarction and no obstructive coronary disease
- UA = unstable angina
- NSTEMI = non ST elevation myocardial infarction
- STEMI = ST elevation myocardial infarction

Ford TJ et al. Heart 2018;104:284-292
Traditional paradigm of IHD focuses on obstructive CAD, but overlooks other factors.

- **Systemic factors**
  - Myocardial supply: demand ratio (SEVR or Buckberg index)
  - Pulse rate
  - Blood pressure
  - Heightened sympathetic activation

- **Coronary factors**
  - Microvascular dysfunction
  - Endothelial impairment
  - Occult diffuse epicardial CAD
  - Coronary artery spasm
  - Myocardial bridging

- **Cardiac factors**
  - Impaired diastolic relaxation
  - Left ventricular hypertrophy
  - Diastolic dysfunction
  - Valvular heart disease
  - Left ventricular outflow tract obstruction

Ford TJ et al. Interv Cardiol. 2019 May 21;14(2):76-82
Structural and functional disorders of the coronary circulation

Ford TJ et al. Heart 2018;104:284-292
### Table 1: Classification of coronary microvascular dysfunction (CMD)

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Primary CMD in the absence of underlying myocardial disease or obstructive epicardial CAD</td>
</tr>
<tr>
<td>Type 2</td>
<td>CMD in the presence of myocardial disease (e.g., hypertrophic cardiomyopathy, hypertensive heart disease)</td>
</tr>
<tr>
<td>Type 3</td>
<td>CMD in the presence of obstructive CAD (either stable CAD or acute coronary syndrome)</td>
</tr>
<tr>
<td>Type 4</td>
<td>Iatrogenic CMD secondary to myocardial revascularisation</td>
</tr>
<tr>
<td>Type 5</td>
<td>CMD following cardiac transplantation</td>
</tr>
</tbody>
</table>

Ford TJ et al. Heart 2018;104:284 292
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Ford TJ et al. Heart 2018;104:284-292
Invasive diagnostic testing

Invasive coronary angiography

No obstructive CAD

No substrate for angina: (FFR 0.84, CFR 5.3, IMR 9)

Diagnostic guidewire (adenosine)

Microvascular dysfunction (FFR 0.95, CFR 1.3, IMR 33)

Vasoreactivity (acetylcholine)

ACh GTN

Vasospasm with ACh (resolves with nitrate)

Endothelial dysfunction without vasospasm to ACh

Vasospastic Angina
- Calcium channel blocker
- Long-acting nitrate
- Avoid betablockers
- Smoking cessation
- Lifestyle factors and cardiac rehabilitation

Microvascular Angina
- Beta-blocker
- Consider an ACEI or statin
- Smoking cessation
- Weight loss, cardiac rehabilitation
- Avoid long-acting nitrates

Diagnosis and management

Diagnostic criteria

Flow-limiting epicardial stenosis:
- FFR ≤0.80
- Contrast FFR ≤0.83
- iFR ≤0.89

Impaired epicardial and microvascular vasodilatation:
- CFR <2.0

Increased microvascular resistance:
- IMR ≥25
- HMR >2.4

Endothelial dysfunction:
- >20% angiographic reduction in coronary luminal diameter during acetylcholine infusion

Epicardial vasospasm:
- chest pain
- ischaemic ECG changes
- >90% vasoconstriction

Microvascular vasospasm:
- chest pain
- ischaemic ECG changes
- ≤90% vasoconstriction

CFR=coronary flow reserve
iFR=instantaneous flow reserve
HMR=hyperemic microvascular resistance

Ford TJ et al. Interv Cardiol. 2019 May 21;14(2):76 82

ACEI = angiotensin-converting enzyme inhibitor; ACh = acetylcholine; CAD = coronary artery disease; FFR = fractional flow reserve; GTN = glyceryl trinitrate; IMR = index of microcirculatory resistance.
Cardiac Stress Testing Algorithm

Exclude obstructive epicardial CAD

**Exercise**
- Without imaging (EKG only, $)
- Echo ($$
- SPECT
- Nuclear ($$$$$)
- Magnetic resonance imaging (MRI, $$$)

**Pharmacologic**
- Echo (~$487)*
- SPECT or PET ($1203-1377)* nuclear
- Magnetic resonance imaging (MRI, $681)*

*2018 CMS rates. American Association of Nuclear Cardiology.
Cardiac Stress Testing Algorithm

Evaluate for microvascular disease

Pharmacologic

- Contrast-enhanced echo (not widely available, $487)
- PET
  - Nuclear (limited, $1377)
- Magnetic resonance imaging (MRI, $681)
Non-invasive diagnostic testing

**Figure 1. Microvascular Disease Without Epicardial Coronary Stenosis**

Quantitative perfusion cardiac PET

- **A**
  - Anterior Mean 84%
  - Perfusion
  - Cine function

- **B**
  - Anterior Mean 87%
  - Perfusion
  - T1 for fibrosis

- **C**
  - Anterior Mean 1.27
  - Perfusion
  - T1 for fibrosis (LGE)

- **D**
  - Anterior Mean 1.41
  - Perfusion
  - Cine function

Ford TJ et al. Heart 2018;104:284 292

Gould et al. JACC Cardiovascular imaging 2016;9:465 82
Spectrum of ischemic heart disease

Mild stenosis

- MVR = microvascular resistance
- FFR = fractional flow reserve
- MBV = myocardial blood volume

Diffuse atherosclerosis

Severe stenosis

CMVD

- MVR = microvascular resistance
- FFR = fractional flow reserve
- MBV = myocardial blood volume

Circ Cardiovasc Imaging. 2017;10:e006427
VA-MERIT Project: Ferumoxytol-enhanced MRI Mapping of the Intramyocardial Vascular Compartment

- At baseline, 8% of LV mass constitutes blood in the microcirculation
- 90% is in the capillaries, and reflects the myocardial blood volume (MBV), which represents “myocardial reserve”

Ischemia = imbalance between metabolic demand & blood supply

Blood supply = myocardial blood flow (MBF) and myocardial blood volume (MBV)
T1 myocardial mapping

- T1 mapping = a color-encoded map of the myocardium whereby each pixel represents the T1 value in a voxel (rather than arbitrary signal intensity units)
- T1 values reflect normal physiology or in some cases pathophysiology

FE-MRI T1 reactivity as a surrogate for MBV

Extravascular

Intravascular

Ferumoxytol

Cells

Interstitium

Blood vessel

Ferumoxytol

Physics & Biology in Medicine Graduate Program
**HYPOTHESIS:** The percent change in FE myocardial T1 relaxation time at rest and peak stress, which we refer to as the FE T1 reactivity, reflects a dynamic change in the fractional myocardial blood volume (MBV)
**HYPOTHESIS:** The percent change in FE myocardial T1 relaxation time at rest and peak stress, which we refer to as the FE T1 reactivity, reflects a dynamic change in the fractional myocardial blood volume (MBV).

Using a vasodilator (such as adenosine), we may be able to:

- map the dynamic nature of epicardial coronary stenoses and myocardial capillary network = ischemic burden
- quantify the fractional MBV
VA-MERIT funded project

Inclusion
- Women (>18 years)
- Angina
- Positive stress cardiac PET or gadolinium enhanced stress cardiac MRI
- Agree to allow banking of blood specimen and enrollment in study registry

Exclusion
- Contraindications to MRI
- Arrhythmias
- History of intravenous iron intolerance or history of iron overload

Proposed FE MRI steady state cardiac stress testing

Reference standard

Ford TJ et al. Heart 2018;104:284 292
FE T1 reactivity as surrogate for MBV in stress testing

Multicenter, prospective, randomized, blinded outcome evaluation (PROBE design) evaluating IMT vs. Usual Care in 4,422 symptomatic women with ischemia but no obstructive CAD

HYPOTHESIS: IMT (intensive medical therapy) will reduce MACE 20% vs UC.

- primary outcomes: occurrence of death, MI, Stroke/TIA, Hospitalization for chest pain or heart failure
- secondary outcomes: QOL, health resource consumption, angina, CV death and primary outcome components
- Follow-up will be 3-years using 50 sites: primarily VA, Active Duty Military Hospitals/Clinics, PCORnet practice sites, and interested practice groups in the state of Florida.
Rationale and design of the Coronary Microvascular Angina Cardiac Magnetic Resonance Imaging (CorCMR) diagnostic study: the CorMicA CMR sub-study

Figure 2  CorCMR multiparametric imaging protocol. CorCMR, Coronary Microvascular Angina Cardiac MRI.
CAD=coronary artery disease
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MINOCA

• 5-10% of all patients with acute MI
• Younger, female
• Mechanisms
  • Plaque disruption
  • Spasm
  • Thromboembolism
  • Dissection
  • Microvascular dysfunction
  • Myocarditis or Takotsubo cardiomyopathy
388 consecutive patients with MINOCA

Underwent CMR ➔ prognosis (all cause mortality within 3.5 years)

Using STE on presentation, ECG and CMR diagnosis of CM as risk factors, the presence of 0, 1, and 2 factors were associated with a mortality risk rate of 2%, 11%, and 21%

*Prior work showed CMR in MINOCA led to a change in diagnosis of 54% and change in management in 41% of patients.

MINOCA patients from **SWEDEHEART** (Swedish Web-based system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapy)

- 199162 patients with MI ➔ **9466** with MINOCA (LHC <50% stenoses, 7/2003-6/2013, followed until 12/2013 for MACE – all cause mortality, hospitalization for MI/ischemic stroke/heart failure)
- Stratified propensity analysis to match treated vs untreated
- Cox proportional hazards models for association between treatment and outcomes
- **Exposures were:** treatment with statins, ACEI/ARB, b-blockers, dual antiplatelet

Medical Therapy for Secondary Prevention and Long-Term Outcome in Patients With Myocardial Infarction With Nonobstructive Coronary Artery Disease

Treatment options

**CORMiCA Study:** sponsored by British Heart Foundation
- N=391 with probable angina
- No obstructive CAD in 185 patients

Ford TJ et al. J Am Coll Cardiol 2018;72:2841 55
Ford TJ et al. Interv Cardiol. 2019 May 21;14(2):76 82
### Treatment options

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Investigation</th>
<th>Pathophysiology</th>
<th>Treatment</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microvascular angina ↓ vasoconstriction</td>
<td>↓ CFR and/or ↑ microvascular resistance</td>
<td>Anatomical remodelling, vascular rarefaction, disturbed coronary regulation</td>
<td>Beta-blockers (e.g. nebivolol 2.5–10mg)</td>
<td>↓ myocardial oxygen consumption</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ACE inhibitors (e.g. ramipril 2.5 mg)</td>
<td>Improve CFR, ↓ workload, may improve small vessel remodelling</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ranolazine (e.g. 375 mg twice daily)</td>
<td>Improves microvascular perfusion reserve index in patients with MVA and reduced CFR</td>
</tr>
<tr>
<td>Microvascular angina ↑ vasoconstriction</td>
<td>Hyper-reactivity to stimuli (e.g. acetylcholine, exercise, stress)</td>
<td>Endothelial dysfunction, inappropriate pre-arteriolar vasoconstriction</td>
<td>Calcium antagonists (e.g. amlodipine 10 mg)</td>
<td>Vascular smooth muscle relaxation, ↓ myocardial oxygen consumption</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ACE inhibitors (e.g. ramipril 2.5 mg)</td>
<td>Improves endothelial vasomotor dysfunction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nicorandil (e.g. 5–10mg twice daily)</td>
<td>Potassium-channel activator with coronary microvascular dilatory effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Statins (e.g. rosuvastatin 10–20 mg)</td>
<td>Improve coronary endothelial function, pleiotropic effects including reduced vascular inflammation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hormone replacement therapy</td>
<td>Oestrogen therapy improves symptoms but not proven to improve ischaemia or endothelial function</td>
</tr>
</tbody>
</table>

CORMiCA Study: sponsored by British Heart Foundation
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## Treatment options

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<th>Treatment</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microvascular angina</td>
<td>↑ nociception</td>
<td>Dysfunctional cortical pain processing</td>
<td>Tricyclic antidepressants (e.g. imipramine up to 25 mg)</td>
<td>Improved symptom burden potentially through ↓ visceral pain</td>
</tr>
<tr>
<td>Abnormal pain processing</td>
<td></td>
<td></td>
<td>Xanthine derivatives (e.g. aminophylline 225 mg twice daily)</td>
<td>Anti-algogenic effect (due to the direct involvement of adenosine in cardiac pain generation)</td>
</tr>
<tr>
<td>Vasospastic angina</td>
<td>Propensity to coronary vasospasm</td>
<td>Vascular smooth muscle hyper-reactivity</td>
<td>Calcium channel blockers (e.g. amlodipine 10 mg or verapamil 240 mg SR)</td>
<td>↓ spontaneous and inducible coronary spasm via vascular smooth muscle relaxation and ↓ oxygen demand</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nitrates (e.g. isosorbide mononitrate XL 30 mg)</td>
<td>↓ spontaneous and inducible coronary spasm via large epicardial vasodilation, ↓ oxygen demand, lack of efficacy in microvascular angina with potential deleterious effect</td>
</tr>
<tr>
<td>Adjunctive non-pharmacological interventions</td>
<td>May be useful in all endotypes</td>
<td>Metabolic syndrome, endothelial dysfunction, cardiovascular risk factors, anxiety/depression</td>
<td>Smoking cessation, exercise, cardiac rehabilitation, Mediterranean diet, cognitive behavioural therapy*</td>
<td></td>
</tr>
</tbody>
</table>

*ACE = angiotensin converting enzyme; CFR = coronary flow reserve; MVA = microvascular angina; SR = sustained-release preparation.
Future Directions & Take Away Points

• Development of non-diagnostic testing
  • Non-ionizing radiation
  • CMR is most promising with high spatial resolution

• New therapeutics to tailored to the specific mechanism
  • Medications
  • Exercise
  • Cognitive behavioral therapy and stress management
Acknowledgements

Our work is supported by

- UCLA Radiological Sciences Exploratory Research Program
- UCLA Department of Medicine Pilot Funding
- American Heart Association Transformational Award 18TPA34170049
- NIH (NHLBI) R01HL127153
- VA MERIT 1I01CX001901

Many thanks to the giants in my life...

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- Jesse W Currier, MD
- Tzung K. Hsiai, MD/PhD
- Andrew E. Arai, MD (NHLBI)
- UCLA DLAM and TRIC Lab
- UCLA 3D Lab
- VA GLA Women’s CV Health Group (Bevanne B. Upperman, MD/MHS)

QUESTIONS? Please email
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Primary Prevention of Cardiovascular Disease

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STAFF CARDIOLOGIST/ASSISTANT PROFESSOR
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VA GREATER LOS ANGELES HEALTHCARE SYSTEM
DAVID GEFFEN SCHOOL OF MEDICINE AT UCLA

<table>
<thead>
<tr>
<th>Rank</th>
<th>Cause of Death</th>
<th>Age-adjusted Death Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>Diseases of the heart</strong></td>
<td>181.2</td>
</tr>
<tr>
<td>2</td>
<td>Malignant neoplasms</td>
<td>171.8</td>
</tr>
<tr>
<td>3</td>
<td>Chronic lower respiratory diseases</td>
<td>51.5</td>
</tr>
<tr>
<td>4</td>
<td><strong>Cerebrovascular disease</strong></td>
<td>38.4</td>
</tr>
<tr>
<td>5</td>
<td>Accidents (unintentional)</td>
<td>36.4</td>
</tr>
<tr>
<td>6</td>
<td>Alzheimer’s</td>
<td>50.9</td>
</tr>
<tr>
<td>7</td>
<td>Diabetes mellitus</td>
<td>22.5</td>
</tr>
<tr>
<td>8</td>
<td>Influenza and pneumonia</td>
<td>17.6</td>
</tr>
<tr>
<td>9</td>
<td>Nephritis, nephrotic syndrome, and nephrosis</td>
<td>15.1</td>
</tr>
<tr>
<td>10</td>
<td>Septicemia</td>
<td>12.9</td>
</tr>
<tr>
<td>11</td>
<td><strong>Essential hypertension and hypertensive renal disease</strong></td>
<td>11.8</td>
</tr>
</tbody>
</table>
Figure 3. Death rates, by age and sex: United States, 1955–2017

Figure 5. Age-adjusted death rates for selected leading causes of death: United States, 1958–2017


*Rates are based on population estimates which differ from infant mortality rates (based on live births); see Figure 7 in this report for further discussion of the differences. SOURCE: NCHS, National Vital Statistics System, Mortality.
2019 Primary Prevention Writing Committee

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Joseph Yeboah, MD, MS, FACC, FAHA*
Boback Ziaeian, MD, PhD, FACC, FAHA§

*ACC/AHA Representative, †Lay Representative, § Task Force Performance Measures Representative
### Class (Strength) of Recommendation

<table>
<thead>
<tr>
<th>Class</th>
<th>Benefit vs. Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I (Strong)</td>
<td>Benefit &gt;&gt; Risk</td>
</tr>
<tr>
<td>Class IIa (Moderate)</td>
<td>Benefit &gt;&gt; Risk</td>
</tr>
<tr>
<td>Class IIb (Weak)</td>
<td>Benefit &gt; Risk</td>
</tr>
<tr>
<td>Class III: No Benefit (Moderate) (Generally, LOE A or B only)</td>
<td>Benefit = Risk</td>
</tr>
<tr>
<td>Class III: Harm (Strong)</td>
<td>Risk &gt; Benefit</td>
</tr>
</tbody>
</table>

#### Suggested Phrases for Writing Recommendations:
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

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### Level (Quality) of Evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Evidence Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level A</td>
<td>High-quality evidence from more than 1 RCT</td>
</tr>
<tr>
<td></td>
<td>Meta-analyses of high-quality RCTs</td>
</tr>
<tr>
<td>Level B-R</td>
<td>Moderate-quality evidence from 1 or more RCTs</td>
</tr>
<tr>
<td></td>
<td>Meta-analyses of moderate-quality RCTs</td>
</tr>
<tr>
<td>Level B-NR</td>
<td>Moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies</td>
</tr>
<tr>
<td></td>
<td>Meta-analyses of such studies</td>
</tr>
<tr>
<td>Level C-LD</td>
<td>Randomized or nonrandomized observational or registry studies with limitations of design or execution</td>
</tr>
<tr>
<td></td>
<td>Meta-analyses of such studies</td>
</tr>
<tr>
<td></td>
<td>Physiological or mechanistic studies in human subjects</td>
</tr>
<tr>
<td>Level C-EO</td>
<td>Consensus of expert opinion based on clinical experience</td>
</tr>
</tbody>
</table>

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**COR and LOE are determined independently (any COR may be paired with any LOE).**

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR I and IIa, LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

† The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.
Assessment of risk
Nutrition and diet
Exercise and physical activity
Overweight and obesity
Type 2 diabetes
High blood cholesterol
High blood pressure and hypertension
Tobacco use
Aspirin use
1. Prevention by promoting a healthy lifestyle is the key to reducing the burden of atherosclerotic vascular disease, heart failure, and atrial fibrillation.
Top 10 Take Home Messages

2. Team-based care is an effective strategy for delivering evidence-based care and management.

1. A team-based care approach is recommended for the control of risk factors associated with ASCVD.
Top 10 Take Home Messages

3. Adults who are 40-75 years of age and are being evaluated for cardiovascular disease prevention should undergo 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimation. Shared-decision making before starting pharmacological therapy.

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1</td>
<td>B-NR</td>
</tr>
</tbody>
</table>

1. For adults 40 to 75 years of age, clinicians should routinely assess traditional cardiovascular risk factors and calculate 10-year risk of ASCVD by using the pooled cohort equations (PCE).
In adults at borderline risk (5% to <7.5% 10-year ASCVD risk) or intermediate risk (≥7.5% to <20% 10-year ASCVD risk), it is reasonable to use additional risk-enhancing factors to guide decisions about preventive interventions (e.g., statin therapy).

Not all factors are included in PCE:

<table>
<thead>
<tr>
<th>Factor</th>
<th>Aspirin therapy</th>
<th>Elevated triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Family history</td>
<td>hsCRP</td>
</tr>
<tr>
<td>Sex</td>
<td>Obesity</td>
<td>Lp(a)</td>
</tr>
<tr>
<td>Race</td>
<td>Physical inactivity</td>
<td>ApoB level</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Socioeconomic factors</td>
<td>Ankle-brachial index</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>Pregnancy related CVD</td>
<td>Coronary artery calcium</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>Inflammatory conditions</td>
<td>Lp(a)</td>
</tr>
<tr>
<td>Smoking</td>
<td>Mental stress/ depression</td>
<td>hsCRP</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Chronic kidney disease</td>
<td>Lp(a)</td>
</tr>
<tr>
<td>Statin therapy</td>
<td>Metabolic syndrome</td>
<td>Coronary artery calcium</td>
</tr>
<tr>
<td></td>
<td>South Asian ethnicity</td>
<td></td>
</tr>
</tbody>
</table>
PCE may underestimate risk

HIV patients
(Group 1:<5%, Group 2: 5%–7.5%, Group 3: >7.5%)

Rheumatoid Arthritis patients
(Black: observed events, Gray: predicted events)


Risk-Enhancing Factors

- **Whom to use in?**
  - **Borderline** (5% to <7.5%) or
  - **Intermediate** (≥7.5% to <20%) 10-year ASCVD risk

- **When to use?**
  - If patient would value information in making treatment recommendation.

- **What to do if risk still uncertain?**
  - CAC strong factor, but probably not an effective population strategy.

---

### Table 1. ASCVD risk enhancers

- Family history of premature ASCVD
- Primary hypercholesterolemia
- 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
4. A healthy diet emphasizes vegetables, fruits, legumes, nuts, whole grains, and fish. Minimize intake of trans fats, red meat and processed meats, refined carbohydrates, and sweetened beverages. For overweight and obese adults, recommend and caloric restriction and physical activity for achieving and maintaining weight loss.
Assuming the meta-analyzed evidence from cohort studies represents life-span–long causal associations, for a baseline life expectancy of 80 years, nonexperts presented with only relative risks may falsely infer that eating 12 hazelnuts daily (1 oz) would prolong life by 12 years (i.e., 1 year per hazelnut), drinking 3 cups of coffee daily would achieve a similar gain of 12 extra years, and eating a single mandarin orange daily (80 g) would add 5 years of life.
The harm of Trans fat

REGARDS

Recommendations for Nutrition and Diet
Referenced studies that support recommendations are summarized in Online Data Supplements 4 and 5.

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>III: Harm</td>
<td>B-NR</td>
<td>5. As a part of a healthy diet, the intake of <em>trans</em> fats should be avoided to reduce ASCVD risk (S3.1-12, S3.1-17, S3.1-25–S3.1-27).</td>
</tr>
</tbody>
</table>

83,349 women from the Nurses’ Health Study


Wang et al., JAMA Intern Med. 2016;176:1134-45
Top 10 Take Home Messages

5. Adults should engage in **at least 150 minutes per week of accumulated moderate-intensity** physical activity or **75 minutes per week of vigorous-intensity** physical activity.

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>1.</td>
<td>B-R</td>
<td>Adults should be routinely counseled in healthcare visits to optimize a physically active lifestyle.</td>
</tr>
<tr>
<td>2.</td>
<td>B-NR</td>
<td>Adults should engage in at least 150 minutes per week of accumulated moderate-intensity or 75 minutes per week of vigorous-intensity aerobic physical activity (or an equivalent combination of moderate and vigorous activity) to reduce ASCVD risk.</td>
</tr>
</tbody>
</table>
22.9% of Americans met minimum physical activity recommendations 2010-2015

Met recommended duration for both aerobic and muscle-strengthening activities

- Met goal
- Did not...

National Health Statistics Reports  ■  Number 112  ■  June 28, 2018
The spectrum of physical activity

150 min of Mod-int/week
75 min of vigor-int/week

The higher the better
NO LOWER LIMIT

300 min of Mod-int/week
150 min of vigor-int/week

Higher better

No more benefit
Top 10 Take Home Messages

6. For adults with DMII, lifestyle changes (diet and exercise) are initial recommendations. If Rx are indicated, metformin is 1st-line therapy (IIa, B-R), followed by consideration of a sodium-glucose cotransporter 2 inhibitor (SGLT2i) or a glucagon-like peptide-1 (GLP-1) receptor agonist (IIb,B-R).

<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>1. For all adults with T2DM, a tailored nutrition plan focusing on a heart-healthy dietary pattern is recommended to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors (S4.2-1, S4.2-2).</td>
</tr>
<tr>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>2. Adults with T2DM should perform at least 150 minutes per week of moderate-intensity physical activity or 75 minutes of vigorous-intensity physical activity to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors (S4.2-3, S4.2-4).</td>
</tr>
</tbody>
</table>
# Recommendations for Adults With Type 2 Diabetes Mellitus

Referenced studies that support recommendations are summarized in [Online Data Supplement 10](#).

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>I</td>
<td>A</td>
<td>1. For all adults with T2DM, a tailored nutrition plan focusing on a heart-healthy dietary pattern is recommended to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors (S4.2-1, S4.2-2).</td>
</tr>
<tr>
<td>I</td>
<td>A</td>
<td>2. Adults with T2DM should perform at least 150 minutes per week of moderate-intensity physical activity or 75 minutes of vigorous-intensity physical activity to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors (S4.2-3, S4.2-4).</td>
</tr>
<tr>
<td>IIa</td>
<td>B-R</td>
<td>3. For adults with T2DM, it is reasonable to initiate metformin as first-line therapy along with lifestyle therapies at the time of diagnosis to improve glycemic control and reduce ASCVD risk (S4.2-5–S4.2-8).</td>
</tr>
<tr>
<td>IIb</td>
<td>B-R</td>
<td>4. For adults with T2DM and additional ASCVD risk factors who require glucose-lowering therapy despite initial lifestyle modifications and 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 and reduce CVD risk (S4.2-9–S4.2-14).</td>
</tr>
</tbody>
</table>
Type 2 Diabetes: SGLT-2 inhibitors

<table>
<thead>
<tr>
<th>EMPA-REG OUTCOME</th>
<th>CANVAS</th>
<th>DECLARE–TIMI 58</th>
</tr>
</thead>
<tbody>
<tr>
<td>7028 patients with type 2 DM</td>
<td>10,142 patient with type 2 diabetes and high</td>
<td>17160 T2DM who had or were at risk (10,186) for ASCVD</td>
</tr>
<tr>
<td>Empagliflozin vs. placebo</td>
<td>Canagliflozin or placebo</td>
<td>Dapagliflozin vs placebo</td>
</tr>
<tr>
<td><strong>14% reduction</strong> in death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Reduction in HF</td>
<td><strong>14% reduction</strong> in death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Reduction in HF</td>
<td>Did not reduce MACE. <strong>17% reduction in CVD death or HF hospitalization.</strong> Reduced CKD progression.</td>
</tr>
</tbody>
</table>

NEJM. 2017;377:644-57  
Type 2 Diabetes: GLP1 agonists

### LEADER

- 9340 patients with T3DM and high CVD risk
- Liraglutide vs. placebo
- **13% reduction in first** occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke

### Harmony Outcomes

- 9463 patients with T2DM and CVD
- Albiglutide vs. placebo
- **22% reduction** in occurrence of cardiovascular death, myocardial infarction, or stroke

### SUSTAIN-6

- 3297 patients with T2DM
- Semaglutide vs. placebo
- **26% reduction** in first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke

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Lancet. 2018 Oct 27;392(10157):1519-1529  
NEJM. 2016 Nov 10;375(19):1834-1844
7. All adults should be assessed at every healthcare visit for tobacco use. Those who use tobacco should be assisted and strongly advised to quit.
Top 10 Take Home Messages

8. Aspirin should be used infrequently in the routine primary prevention of ASCVD because of lack of net benefit.
## Recommendations for Aspirin Use

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>A</td>
<td>1. Low-dose aspirin (75-100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk.</td>
</tr>
<tr>
<td>III: Harm</td>
<td>B-R</td>
<td>2. Low-dose aspirin (75-100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults &gt;70 years of age.</td>
</tr>
<tr>
<td>III: Harm</td>
<td>C-LD</td>
<td>3. Low-dose aspirin (75-100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding.</td>
</tr>
</tbody>
</table>
Trials of aspirin for primary prevention

<table>
<thead>
<tr>
<th>ASCEND</th>
<th>ARRIVE</th>
<th>ASPREE, 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>15,480 with diabetes and no evident CVD.</td>
<td>12,546 with Moderate CVD risk w/o DM or high risk of GI bleeding</td>
<td>19,114 adults &gt; 70 yr with no cardiovascular disease.</td>
</tr>
<tr>
<td>100 mg of aspirin vs. placebo</td>
<td>100 mg aspirin vs. placebo</td>
<td>100 mg aspirin vs. placebo</td>
</tr>
<tr>
<td>Reduction in vascular events was counterbalanced by bleeding</td>
<td>No difference in a composite of CV death, MI, UA, CVA, or TIA. With increased risk of bleeding</td>
<td>Aspirin did not prolong disability free survival but increased major hemorrhage</td>
</tr>
</tbody>
</table>

Lancet. 2018;392:1036-46  
Prescribing based on totality of evidence

- Elevated PCE + CAC + risk enhancing factors
- Inability to achieve lipid or BP targets

Low dose ASA (Class IIb)

Patient-clinician preference
Shared-decision making

Avoid ASA (Class III)
Focus on other risk factors

Previous GIB or PUD
Bleeding from other sites
Age >70 years
Thrombocytopenia
Coagulopathy
CKD
Use of NSAIDs, steroids, DOAC, and warfarin
Top 10 Take Home Messages

9. Statin therapy is 1\textsuperscript{st}-line treatment for primary prevention of ASCVD in patients with elevated low-density lipoprotein cholesterol levels (≥190 mg/dL), those with diabetes mellitus, who are 40 to 75 years of age, and at sufficient ASCVD risk (PCE) after a clinician–patient risk discussion.
Top 10 Take Home Messages

10. Nonpharmacological interventions are recommended for all adults with elevated blood pressure or hypertension. For those requiring pharmacological therapy, the target blood pressure should generally be <130/80 mm Hg.
Figure 4. BP Thresholds and Recommendations for Treatment

BP indicates blood pressure; and CVD, cardiovascular disease.
Figure 1. ABCDE of Primary Prevention: Lifestyle Changes and Team-Based Care

A: Assess risk
- Aspirin
  - Low-dose aspirin in primary prevention now reserved for select high-risk patients

B: Blood pressure
- Maintain < 130/80 mm Hg

C: Cholesterol
- Assess ASCVD risk, personalize with risk enhancers, reclassify with CAC as needed

D: Diabetes
- Control through diet and exercise. Metformin (primary), SGLT-2 inhibitor or GLP-1 receptor agonist (secondary)

E: Exercise
- Perform >150 min/week or moderate or >75 min/week of vigorous physical activity

Shared decision-making, preventive care, economic, social, and behavioral factors

Diet / weight
- Emphasis on intake of vegetables, fruits, nuts, legumes, fish and whole grains

Cigarettes
- Pharmacotherapy + behavior interventions recommended to maximize quit rates

Prevention of CVD