Novel Strategies for Reducing Cardiovascular Disease: From New Cholesterol Guidelines and Therapies to Fish Oil and Influenza and Atherosclerosis Vaccinations

Nathan D. Wong, PhD, FACC, FAHA, FNLA, FASPC
Professor and Director
Heart Disease Prevention Program
Division of Cardiology, University of California, Irvine
Past President, Pacific Lipid Association (Chapter of NLA)
Past President, American Society for Preventive Cardiology

UC Irvine Health
<table>
<thead>
<tr>
<th>Company</th>
<th>Role/Support</th>
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<tbody>
<tr>
<td>Amarin</td>
<td>Grant/Research Support</td>
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<tr>
<td>Amgen</td>
<td>Consultant</td>
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<tr>
<td>Novartis</td>
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<td>Astra Zeneca</td>
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<td>Sanofi</td>
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UC Irvine Health
Agenda

- New guidelines for cardiovascular risk assessment
- Latest lifestyle management guidelines
- 2018 Multisociety Cholesterol Management guideline and evidence for newer therapies
- Cardiometabolology and newer evidence-based therapies
- Influenza and atherosclerosis vaccinations?
Burden of Cardiovascular Disease in the US

- Cardiovascular disease accounts for nearly 801,000 deaths in the US. That’s about 1 of every 3 deaths in the US.
- About 2,200 Americans die of cardiovascular disease each day, an average of 1 death every 40 seconds.
- About 92.1 million American adults are living with some form of CVD or the after-effects of stroke.
- Costs of CVD/stroke are estimated to total more than $316 billion in health expenditures and lost productivity.
Current Medical Practice vs. Need for Prevention

“We are too busy mopping the floor to turn off the faucet.”
Major Risk Factors for Atherosclerosis

- ↑LDL-C or Lp(a)
- ↓HDL-C
- Hypertension
- Diabetes
- Smoking
- Age
- Gender
- Family History of CVD

Six of the top 10 causes of death are lifestyle-related risk factors for cardiovascular disease!
Patient-Centered Approaches

### Recommendations for Patient-Centered Approaches to Comprehensive ASCVD Prevention

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A</td>
<td>1. A team-based care approach is recommended for the control of risk factors associated with ASCVD.</td>
</tr>
<tr>
<td>I</td>
<td>B-R</td>
<td>2. Shared decision-making should guide discussions about the best strategies to reduce ASCVD risk.</td>
</tr>
<tr>
<td>I</td>
<td>B-NR</td>
<td>3. Social determinants of health should inform optimal implementation of treatment recommendations for the prevention of ASCVD.</td>
</tr>
</tbody>
</table>
Concept of Cardiovascular Risk Factors

Age, sex, hypertension, hyperlipidemia, smoking, diabetes, (family history), (obesity)

Framingham director Dr. William Kannel had noted risk functions provide an “economic and efficient method of identifying persons at high cardiovascular risk who need preventive treatment,” (AJC 1976)
ASCVD Risk Estimator Plus

- Estimates 10-year hard ASCVD (nonfatal MI, CHD death, stroke) for ages 40-79 and lifetime risk for ages 20-59
- Intended to promote patient-provider risk discussion and best ways to reduce risk
- Used as a starting point in risk assessment, consider risk enhancing factors to refine risk

Estimates risk reduction from therapy or smoking cessation

tools.acc.org/ascvd-risk-estimator-plus
Refining Risk Estimates for Individual Patients

- Estimate Absolute 10-year ASCVD Risk
  - Low Risk: 0 - <5%
  - Borderline Risk: 5% - <7.5%
  - Intermediate Risk: 7.5% - <20%
  - High Risk: ≥20%

- Clinician-patient discussion considering risk-enhancing factors and net benefit of therapy

- Lifestyle modification
- Lifestyle and drug therapy
Refining Risk Estimates for Individual Patients

### Risk-Enhancing Factors for Clinician–Patient Risk Discussion

- **Family history of premature ASCVD**: (males, age <55 y; females, age <65 y)
- **Primary hypercholesterolemia** (LDL-C, 160-189 mg/dL [4.1- 4.8 mmol/L]; non-HDL-C 190-219 mg/dL [4.9-5.6 mmol/L])
- **Metabolic syndrome** (increased waist circumference, elevated triglycerides [>175 mg/dL], elevated blood pressure, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 in women mg/dL] are factors; tally of 3 makes the diagnosis)
- **Chronic kidney disease** (eGFR 15-59 mL/min/1.73 m² with or without albuminuria, not treated with dialysis or kidney transplantation)
- **Chronic inflammatory conditions** such as psoriasis, RA, or HIV/AIDS
- **History of premature menopause (before age 40 y)** and history of pregnancy-associated conditions that increase later ASCVD risk such as pre-eclampsia
- **High-risk race/ethnicities** (e.g. South Asian ancestry)
- **Lipid/biomarkers**: Associated with increased ASCVD risk
  - Persistently* elevated, primary hypertriglyceridemia (≥175 mg/dL);
  - If measured:
    - **Elevated high-sensitivity C-reactive protein** (≥2.0 mg/L)
    - **Elevated Lp(a)** A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥ 50 mg/dL or ≥125 nmol/L constitutes a risk enhancing factor especially at higher levels of Lp(a)
    - **Elevated apoB** ≥130 mg/dL - A relative indication for its measurement would be triglyceride ≥ 200 mg/dL. A level ≥ 130 mg/dL corresponds to an LDL-C >160 mg/dL and constitutes a risk enhancing factor
    - **ABI (ABI)** <0.9
Refining Risk Estimates for Individual Patients

Estimate Absolute 10-year ASCVD Risk

Low Risk
0 - <5%

Borderline Risk
5% - <7.5%

Intermediate Risk
7.5% - <20%

High Risk
≥20%

Clinician-patient discussion considering risk-enhancing factors and net benefit of therapy

If uncertainty remains, consider CAC score and revise decision based on results

Lifestyle modification

Lifestyle and drug therapy
Refining Risk Estimates for Individual Patients

10-year risk
5% - <7.5% or 7.5% - <20%

Engage patient in discussion regarding net benefit of statin therapy

Consider risk-enhancing factors

Decision

Patient Undecided or Clinical Uncertainty Regarding Net Benefit of Statin Therapy

Consider CAC measurement if performed:

CAC = 0

Below Threshold for Statin Benefit
Consider avoiding or postponing drug therapy.*

CAC 1 – 99 and <75th %ile for age/sex/race

Subclinical atherosclerosis present; risk estimate similar. Repeat clinician-patient discussion with new information. Consider statin therapy now or postpone statin and consider repeat CAC in 5 years

CAC ≥ 100 or ≥75th %ile for age/sex/race

Above Threshold for Statin Benefit
Recommend statin therapy.

Decision for No Drug Therapy

Decision for Drug Therapy

See ACC/AHA 2018 Guideline for Cholesterol Management

*Clinicians and patients may not wish to postpone therapy in patients with a CAC score of 0 and diabetes mellitus, heavy current cigarette smoking, or strong family history of premature ASCVD.

Refining Risk Estimates for Individual Patients
Refining risk estimates for individual patients

A

Dotted line represent reference line for 10-year ASCVD risk estimate of 7.5%

Nasir et al., JACC. 2015;66(15):1657-68
Risk of Total Cardiovascular Events by Calcium Quartile (n=881)
(compared to those with no calcium; age and risk-factor adjusted)
Wong ND et al., Am J Cardiol 2000; 86: 295-8

![Bar graph showing relative risk (RR) by total calcium score.](image-url)
Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD) events: the multi-ethnic study of atherosclerosis (MESA) (Budoff et al., Eur Heart J 2018)

- At 10 years of follow-up, all participants with CAC > 100 were estimated to have >7.5% risk regardless of demographic subset.
- Ten-year ASCVD event rates increased steadily across CAC categories regardless of age, sex, or race/ethnicity.
- For each doubling of CAC, there was a 14% increment in ASCVD risk
Lifestyle Factors Affecting Cardiovascular Risk
Evidence-Based Cardioprotective Dietary Patterns

DASH and Mediterranean-style dietary patterns

High intake of
- Plant-based foods: vegetables, fruits, and whole grain foods; legumes, nuts, and seeds
- Fish or seafood, lean meats, and non-fat or low-fat (1%) dairy products
- Plant-based oils (non-tropical) in place of animal fats

Limit intake of
- High-fat red meat and high-fat dairy products
- Sweets, sugar-sweetened beverages

## Exercise and Physical Activity

### Recommendations for Exercise and Physical Activity

<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. Adults should be routinely counseled in healthcare visits to optimize a physically active lifestyle.</td>
</tr>
<tr>
<td>I</td>
<td>B-NR</td>
<td>2. 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>
Table 4. Definitions and Examples of Different Intensities of Physical Activity

<table>
<thead>
<tr>
<th>Intensity</th>
<th>METs</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedentary behavior*</td>
<td>1–1.5</td>
<td>Sitting, reclining, or lying; watching television</td>
</tr>
<tr>
<td>Light</td>
<td>1.6–2.9</td>
<td>Walking slowly, cooking, light housework</td>
</tr>
<tr>
<td>Moderate</td>
<td>3.0–5.9</td>
<td>Brisk walking (2.4–4 mph), biking (5–9 mph), ballroom dancing, active yoga, recreational swimming</td>
</tr>
<tr>
<td>Vigorous</td>
<td>≥6</td>
<td>Jogging/running, biking (≥10 mph), singles tennis, swimming laps</td>
</tr>
</tbody>
</table>

*Sedentary behavior is defined as any waking behavior characterized by an energy expenditure ≤1.5 METs while in a sitting, reclining, or lying posture. Standing is a sedentary activity in that it involves ≤1.5 METs, but it is not considered a component of sedentary behavior. MET indicates metabolic equivalent; mph, miles per hour.
Primary Prevention: Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle

- Age 0-19 y
  - Lifestyle to prevent or reduce ASCVD risk
  - Diagnosis of Familial Hypercholesterolemia → statin

- Age 20-39 y
  - Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk
  - Consider statin if family history premature ASCVD and LDL-C ≥160 mg/dL (≥4.1 mmol/L)

- Age 40-75 y and LDL-C ≥70-<190 mg/dL (≥1.8-<4.9 mmol/L) without diabetes mellitus
  - 10-year ASCVD risk percent begins risk discussion

- LDL-C ≥190 mg/dL (≥4.9 mmol/L)
  - No risk assessment; High-intensity statin (Class I)

- Diabetes mellitus and age 40-75 y
  - Moderate-intensity statin (Class I)

- Diabetes mellitus and age 40-75 y
  - Risk assessment to consider high-intensity statin (Class IIa)

- Age >75 y
  - Clinical assessment, Risk discussion

ASCVD Risk Enhancers:
- Family history of premature ASCVD
- Persistently elevated LDL-C ≥160 mg/dL (≥4.1 mmol/L)
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (e.g., preeclampsia, premature menopause)
- Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity (e.g., South Asian ancestry)

Lipid/Biomarkers:
- Persistently elevated triglycerides (≥175 mg/dL, ≥2.0 mmol/L)

In selected individuals if measured:
- hs-CRP ≥2.0 mg/L
- Lp(a) levels >50 mg/dL or >125 nmol/L
- apoB ≥130 mg/dL
- Ankle-brachial index (ABI) <0.9

Risk discussion:
- If risk enhancers present then risk discussion regarding moderate-intensity statin therapy (Class IIb)

Risk discussion:
- If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% - 49% (Class I)

Risk discussion:
- Initiate statin to reduce LDL-C ≥50% (Class I)

If risk decision is uncertain:
- Consider measuring CAC in selected adults:
  - CAC = zero (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
  - CAC = 1-99 favors statin (especially after age 55)
  - CAC = 100+ and/or ≥75th percentile, initiate statin therapy
Intensity of Statin Therapy

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL-C on average, by approximately ≥50%</td>
<td>Daily dose lowers LDL-C on average, by approximately 30% to &lt;50%</td>
<td>Daily dose lowers LDL-C on average, by &lt;30%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Atorvastatin (40†)-80 mg</th>
<th>Rosuvastatin 20 (40) mg</th>
<th>Simvastatin 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rosuvastatin (5) 10 mg</td>
<td>Pravastatin 10-20 mg</td>
</tr>
<tr>
<td></td>
<td>Simvastatin 20-40 mg‡</td>
<td>Lovastatin 20 mg</td>
</tr>
<tr>
<td></td>
<td>Pravastatin 40 (80) mg</td>
<td>Fluvastatin 20-40 mg</td>
</tr>
<tr>
<td></td>
<td>Lovastatin 40 mg</td>
<td>Pitavastatin 1 mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin XL 80 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluvastatin 40 mg bid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pitavastatin 2-4 mg</td>
<td></td>
</tr>
</tbody>
</table>

*Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biologic basis for a less-than-average response.

†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL (Pedersen et al).

‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.
**Diabetes Mellitus in Adults**

**Recommendations for Patients With Diabetes Mellitus**

<table>
<thead>
<tr>
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<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>B-R</td>
<td>In adults with diabetes mellitus who have multiple ASCVD risk factors, it is reasonable to prescribe high-intensity statin therapy with the aim to reduce LDL-C levels by 50% or more.</td>
</tr>
<tr>
<td>IIa</td>
<td>B-NR</td>
<td>In adults older than 75 years of age with diabetes mellitus and who are already on statin therapy, it is reasonable to continue statin therapy.</td>
</tr>
<tr>
<td>IIb</td>
<td>C-LD</td>
<td>In adults with diabetes mellitus and 10-year ASCVD risk of 20% or higher, it may be reasonable to add ezetimibe to maximally tolerated statin therapy to reduce LDL-C levels by 50% or more.</td>
</tr>
</tbody>
</table>
## Diabetes Mellitus in Adults

### Recommendations for Patients With Diabetes Mellitus

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<tr>
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<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>C-LD</td>
<td>In adults older than 75 years with diabetes mellitus, it may be reasonable to initiate statin therapy after a clinician–patient discussion of potential benefits and risks.</td>
</tr>
<tr>
<td>IIb</td>
<td>C-LD</td>
<td>In adults 20 to 39 years of age with diabetes mellitus that is either of long duration (≥10 years of type 2 diabetes mellitus, ≥20 years of type 1 diabetes mellitus), albuminuria (≥30 mcg of albumin/mg creatinine), estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m², retinopathy, neuropathy, or ankle-brachial index (ABI; &lt;0.9), it may be reasonable to initiate statin therapy.</td>
</tr>
</tbody>
</table>
Secondary Prevention

Clinical ASCVD

Healthy Lifestyle

ASCVD not at very high-risk*

Age ≤75 y

High-intensity statin (Goal: ↓ LDL-C ≥50%) (Class I)

If high-intensity statin not tolerated, use moderate-intensity statin (Class I)

If on maximal statin therapy and LDL-C ≥70 mg/dL (≥1.8 mmol/L), adding ezetimibe may be reasonable (Class IIb)

Age >75 y

Initiation of moderate- or high-intensity statin is reasonable (Class IIa)

Continuation of high-intensity statin is reasonable (Class IIa)

Very high-risk* ASCVD

High-intensity or maximal statin (Class I)

If on maximal statin and LDL-C ≥70 mg/dL (≥1.8 mmol/L), adding ezetimibe is reasonable (Class IIa)

If PCSK9-I is considered, add ezetimibe to maximal statin before adding PCSK9-I (Class I)

If on maximal statin and LDL-C ≥70 mg/dL (≥1.8 mmol/L), or non-HDL-C ≥100 mg/dL (≥2.6 mmol/L), adding PCSK9-I is reasonable (Class IIa)

Dashed arrow indicates RCT-supported efficacy, but is less cost effective
Table 4. Very High-Risk* of Future ASCVD Events

<table>
<thead>
<tr>
<th>Major ASCVD Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent ACS (within the past 12 mo)</td>
</tr>
<tr>
<td>History of MI (other than recent ACS event listed above)</td>
</tr>
<tr>
<td>History of ischemic stroke</td>
</tr>
<tr>
<td>Symptomatic peripheral arterial disease (history of claudication with ABI &lt;0.85, or previous revascularization or amputation)</td>
</tr>
</tbody>
</table>

* Very High-Risk is defined as multiple major ASCVD events or one major ASCVD event and multiple high risk conditions (next slide)
### Table 4 continued

<table>
<thead>
<tr>
<th>High-Risk Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65 y</td>
</tr>
<tr>
<td>Heterozygous familial hypercholesterolemia</td>
</tr>
<tr>
<td>History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>CKD (eGFR 15-59 mL/min/1.73 m²)</td>
</tr>
<tr>
<td>Current smoking</td>
</tr>
<tr>
<td>Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe</td>
</tr>
<tr>
<td>History of congestive HF</td>
</tr>
</tbody>
</table>
Identifying the Very-High-Risk Atherosclerotic Cardiovascular Disease Patient
Does It Really Matter?*

Nathan D. Wong, PhD

More than 20 years ago, the 27th Bethesda Conference (1) noted that the intensity of treatment should match the patient risk of future cardiovascular events. The Third Adult Treatment Panel of the National Cholesterol Education Program in 2001 (2) first used risk scoring to stratify the intensity of treatment. The strictest goal intensity statin therapy (with the removal of specific LDL-C goals) was given for all persons with atherosclerotic cardiovascular disease (ASCVD), thus creating and treating all ASCVD patients as “equal” (4).

The American Association of Clinical Endocrinologists (AACE) in 2017 (5) actually was the first to clearly
Impact of an PCSK9 mAb on LDL Receptor Expression
**LDL Cholesterol**

**Placebo**

- 59% mean reduction (95% CI 58-60), P < 0.00001
- Absolute reduction: 56 mg/dl (95% CI 55-57)

**Evolocumab**

- Median 30 mg/dl, IQR 19-46 mg/dl
Event rates of 11.3% placebo and 9.8% evolocumab at 2.2 years for absolute risk reduction of 1.5% (NNT 67).

NNT 50 at 3 years.
Exploratory Analysis Pts with LDL-C <0.26 mM (<10 mg/dL) at 4 wks

N=504: Median [IQR] LDL-C 0.18 [0.13-0.23] mM = 7 [5-9] mg/dL

**Cardiovascular Efficacy**

- CVD, MI, Stroke, UA, Cor Revasc
  - Adj HR 0.69 (0.49-0.97) P=0.03
  - 11.9
  - 7.3

- CVD, MI, Stroke
  - Adj HR 0.59 (0.37-0.92) P=0.02
  - 7.8
  - 4.4

**Safety**

- ≥2.6 mM
  - Adj HR 0.94 (0.74-1.20) P=0.61
  - 23.3
  - 22.8

- <0.26 mM
  - Adj HR 1.08 (0.63-1.85) P=0.78
  - 3.4
  - 3.4

Giugliano RP, ESC Congress 2017, Barcelona 8/28/2017
Benefit of EvoMab Based on # of Prior MIs

≥2 Prior MIs

21% RRR

HR 0.79
(95% CI 0.67-0.94)
P=0.006

15.0% RRR

Δ 2.6%

NNT 38

1 Prior MI

16% RRR

HR 0.84
(95% CI 0.74-0.96)
P=0.008

8.2%

Δ 1.7%

NNT 60

P_{interaction}=0.57

Sabatine MS et al, LBCT Update, AHA 2017, Anaheim, CA
Benefit of EvoMab Based on Multivessel Disease

**Multivessel Disease**

- 30% RRR
- HR 0.70 (95% CI 0.58-0.84)
- P<0.001
- NNT 29

**Placebo**

- 9.2%

**Evolocumab**

- 12.6%
- Δ 3.4%

**No Multivessel Disease**

- 11% RRR
- HR 0.89 (95% CI 0.79-1.00)
- P=0.055

**Placebo**

- 8.9%

**Evolocumab**

- 7.6%
- Δ 1.3%
- NNT 78

P_{interaction}=0.03

Sabatine MS et al, LBCT Update, AHA 2017, Anaheim, CA
Primary Efficacy Endpoint: MACE

MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

Number at Risk
- Placebo: 9462
- Alirocumab: 9462

Years Since Randomization
- 0: 8805
- 1: 8846
- 2: 8201
- 3: 3471
- 4: 629

ARR* 1.6%
HR 0.85
(95% CI 0.78, 0.93)
P=0.0003

*Based on cumulative incidence
Odyssey Outcomes Subgroups with Greatest Benefit

- Greater AARs in the subgroup with polyvascular disease: ARR’s of 1.4%, 1.9%, and 16.2% in those with monovascular, 2-bed vascular, or 3 bed vascular disease) (Jukema et al., JACC 2019)

- Those with prior CABG had a 6.4% ARR (Goodman et al., JACC 2019)

- Those defined to be at very high risk (ARR 2.1%) according to the Multisociety Cholesterol Guideline criteria (Roe et al., Circulation 2019)
## Hypertriglyceridermia

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-NR</td>
<td>In adults 20 years of age or older with moderate hypertriglyceridermia (fasting or nonfasting triglycerides 175 to 499 mg/dL [1.9 to 5.6 mmol/L]), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes mellitus, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that increase triglycerides.</td>
</tr>
<tr>
<td>IIA</td>
<td>B-R</td>
<td>In adults 40 to 75 years of age with moderate or severe hypertriglyceridermia and ASCVD risk of 7.5% or higher, it is reasonable to reevaluate ASCVD risk after lifestyle and secondary factors are addressed and to consider a persistently elevated triglyceride level as a factor favoring initiation or intensification of statin therapy (see Section 4.4.2.).</td>
</tr>
</tbody>
</table>
**Negative* Fenofibrate CVOTs (As Statin Adjunct)**

<table>
<thead>
<tr>
<th>Study</th>
<th>CV Risk Profile</th>
<th>Statin Use</th>
<th>Daily Intervention</th>
<th>Median Baseline TG Level</th>
<th>Effect on TG Level</th>
<th>Primary Outcome</th>
<th>Primary Outcome Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACCORD</strong></td>
<td>• T2DM • 40-79 yrs w/CVD or • 55-79 yrs w/ ≥2 CV risk factors</td>
<td>All pts: Open-label simvastatin (mean dose: 22 mg/d)</td>
<td>Fenofibrate</td>
<td>162 mg/dL</td>
<td>−26%</td>
<td>• Nonfatal MI or Stroke or CV death</td>
<td>• HR=0.92* (95% CI, 0.79-1.08) • P=0.32</td>
</tr>
<tr>
<td>(N=5518)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Mean f/u: 4.7 yrs)</td>
<td></td>
</tr>
<tr>
<td><strong>FIELD</strong></td>
<td>• T2DM • 50-75 yrs</td>
<td>Added during study in 2547 pts (26%)</td>
<td>Fenofibrate</td>
<td>154 mg/dL</td>
<td>−30% (at 1 yr)</td>
<td>• Nonfatal MI or CHD death</td>
<td>• HR=0.89* (95% CI, 0.75-1.05) • P=0.16</td>
</tr>
<tr>
<td>(N=9795)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median f/u: 5 yrs</td>
<td></td>
</tr>
</tbody>
</table>

*Note that *post hoc* analysis for both studies found statistically significant benefit in the subgroup of patients with TG≥204 mg/dL & HDL-C ≤34 md/dL (Sacks FM et al. *N Engl J Med.* 2010;363:692-4).

Negative Niacin Outcome Studies (Added to Statin Therapy)

AIM-HIGH (~29% TG)

- Cumulative % with Primary Outcome
- Time (years)
- Monotherapy: HR 1.02, 95% CI 0.87–1.21, Log-rank P=0.79
- Combination Therapy: 16.4%, Monotherapy: 16.2%
- N at risk:
  - Monotherapy: 1696, 1581, 1381, 910, 436
  - Combination Therapy: 1718, 1606, 1366, 903, 428

HPS2-THRIVE (~26% TG)

- Effect of ERN / LRPT on Major Vascular Events
- Risk ratio 0.96 (95% CI 0.90–1.03), Log-rank P=0.29
- Patients Suffering Events (%)
- Years of Follow-up
- Placebo: 14.5%, ERN / LRPT: 15.0%


Fish Oil Dietary Supplements Are Widely Used

- Estimated global market for omega-3 products was $31 billion in 2015
- In a large UK prospective study, 31% of adults reported taking fish oils
- Estimates suggest 7.8% of US population (19 million people) take fish oil supplements
- Benefits claimed on the heart, brain, weight, vision, inflammation, skin, pregnancy and early life, liver fat, depression, childhood behavior, mental decline, allergies, bones…
Fatty Acid Content of Leading U.S. Fish Oil Supplement

Mason RP, Sherratt SCR. Biochem Biophys Res Commun. 2017;483:425-429
Supplement Total Oxidation (TOTOX) Values Exceed International Thresholds

Dietary Sample (DS) Contains Oxidized Lipids


Adapted from: Mason RP, Sherratt SCR. Biochem Biophys Res Commun. 2017;483:425-429
**Dietary Supplement Fish Oil:**

*Not Useful for ASCVD Prevention*

1. FDA Product Classification
   - Food
2. Clinical Trials/FDA Pre-Approval
   - Not Required
3. Often difficult to achieve high doses likely needed for efficacy
4. Often have high saturated fat content
5. Omega-3 content often overstated
6. Tend to contain relatively high amounts of oxidized lipids which may increase CV risk
7. Can contain PCBs and dioxins at harmful levels
8. Ability to reduce ASCVD
   - Not demonstrated
9. Use for Treatment of Disease
   - Not Recommended

References:

Key Inclusion Criteria

1. Age ≥45 years with established CVD (Secondary Prevention Cohort) or ≥50 years with diabetes with ≥1 additional risk factor for CVD (Primary Prevention Cohort)

2. Fasting TG levels ≥150 mg/dL and <500 mg/dL*

3. LDL-C >40 mg/dL and ≤100 mg/dL and on stable statin therapy (± 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 et al. *Clin Cardiol.* 2017;40:138-48. [*https://creativecommons.org/licenses/by-nc/4.0/]
Primary Endpoint:
CV Death, MI, Stroke, Coronary Revasc, Unstable Angina

<table>
<thead>
<tr>
<th>Years since Randomization</th>
<th>Placebo</th>
<th>Icosapent Ethyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>23.0%</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>28.3%</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td></td>
</tr>
</tbody>
</table>

Hazard Ratio 0.75
(95% CI 0.68–0.83)
RRR=24.8%
ARR=4.8%
NNT=21 (95% CI 15–33)
P=0.00000001

### Prespecified Hierarchical Testing

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Hazard Ratio (95% CI)</th>
<th>Icosapent Ethyl</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
<th>RRR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Composite (ITT)</td>
<td></td>
<td>705/4089 (17.2%)</td>
<td>901/4090 (22.0%)</td>
<td>0.75 (0.68–0.83)</td>
<td>25%▼</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Key Secondary Composite (ITT)</td>
<td></td>
<td>459/4089 (11.2%)</td>
<td>606/4090 (14.8%)</td>
<td>0.74 (0.65–0.83)</td>
<td>26%▼</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular Death or Nonfatal Myocardial Infarction</td>
<td></td>
<td>392/4089 (9.6%)</td>
<td>507/4090 (12.4%)</td>
<td>0.75 (0.66–0.86)</td>
<td>25%▼</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fatal or Nonfatal Myocardial Infarction</td>
<td></td>
<td>250/4089 (6.1%)</td>
<td>355/4090 (8.7%)</td>
<td>0.69 (0.58–0.81)</td>
<td>31%▼</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urgent or Emergency Revascularization</td>
<td></td>
<td>216/4089 (5.3%)</td>
<td>321/4090 (7.8%)</td>
<td>0.65 (0.55–0.78)</td>
<td>35%▼</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular Death</td>
<td></td>
<td>174/4089 (4.3%)</td>
<td>213/4090 (5.2%)</td>
<td>0.80 (0.66–0.98)</td>
<td>20%▼</td>
<td>0.03</td>
</tr>
<tr>
<td>Hospitalization for Unstable Angina</td>
<td></td>
<td>108/4089 (2.6%)</td>
<td>157/4090 (3.8%)</td>
<td>0.68 (0.53–0.87)</td>
<td>32%▼</td>
<td>0.002</td>
</tr>
<tr>
<td>Fatal or Nonfatal Stroke</td>
<td></td>
<td>98/4089 (2.4%)</td>
<td>134/4090 (3.3%)</td>
<td>0.72 (0.55–0.93)</td>
<td>28%▼</td>
<td>0.01</td>
</tr>
<tr>
<td>Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke</td>
<td></td>
<td>549/4089 (13.4%)</td>
<td>690/4090 (16.9%)</td>
<td>0.77 (0.69–0.86)</td>
<td>23%▼</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total Mortality</td>
<td></td>
<td>274/4089 (6.7%)</td>
<td>310/4090 (7.6%)</td>
<td>0.87 (0.74–1.02)</td>
<td>13%▼</td>
<td>0.09</td>
</tr>
</tbody>
</table>

**RRR** = relative risk reduction

Treatment of Other Lipoprotein Fractions or Targets:

In patients with ASCVD or other cardiac risk factors on a statin with controlled LDL-C, but elevated triglycerides (135-499), the addition of icosapent ethyl should be considered to reduce cardiovascular risk. A

“It should be noted that data are lacking with other omega-3 fatty acids, and results of the REDUCE-IT trial should not be extrapolated to other products.”

https://hyp.is/JHhz_ICrEembFJ9L1VBZlw
Icosapent ethyl (Vascepa) is the first and only drug approved by the FDA “as an adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated triglyceride (TG) levels (≥150 mg/dL) and established cardiovascular disease or diabetes mellitus and two or more additional risk factors for cardiovascular disease.”
A New Paradigm for ASCVD Residual Risk Reduction?

RCT-proven Non-statin Additive Therapies for ASCVD Risk Reduction in High-risk Patients

Maximally Tolerated Statin

- **Ezetimibe**: Acute coronary syndrome within 10 days
- **Eicosapentaenoic Acid**: Stable ASCVD; or Diabetes + ≥1 additional risk factor
- **PCSK9 Inhibitor**: Stable ASCVD + additional risk factors; or ACS within 1-12 months

ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; PCSK = proprotein convertase subtilisin kexin; RCT = randomized controlled trial.

Orringer C. AHA 2018, Chicago.
FDA Approval for LDL-C Lowering February 21, 2020 monotherapy and February 28, 2020 for the Bempedoic Acid – Ezetimibe combination

Indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or established atherosclerotic cardiovascular disease (ASCVD) who require additional lowering of LDL-C. The effect of on cardiovascular morbidity and mortality has not been determined. First oral, once-daily, non-statin LDL-C lowering medicine approved since 2002 for indicated patients.
CLEAR HARMONY trial reported at ESC showed in 2000+ pts on maximally tolerated statin therapy placebo corrected LDL-C reduction of 16.8% in treated group.

Both trials showed no safety concerns.
Bempedoic Acid / Ezetimibe Combination

- Patients randomized to 12 wks to the bempedoic acid/ezetimibe combination (n = 81), bempedoic acid alone (n = 88), ezetimibe alone (n = 86), or placebo (n = 41).
- 61.6% of patients had existing ASCVD/FH and 38.4% were secondary-prevention patients with multiple RF. Mean LDL cholesterol approx. 150.0 mg/dL.
- One-third of patients were taking high-intensity statins and more than 35% were taking no statin at all.
- The absolute reduction in LDL cholesterol levels with bempedoic acid/ezetimibe was approximately 58.0 mg/dL (36.2%). Treatment with bempedoic acid alone and ezetimibe alone lowered LDL cholesterol by 17.2% and 23.2%, respectively (27.1 mg/dL and 38.67 mg/dL).
Causes of Mortality in Patients With Diabetes

- Heart Disease: 55%
- Cerebrovascular Disease: 10%
- Malignant Neoplasms: 13%
- Diabetes: 13%
- Pneumonia/Influenza: 4%
- Other: 5%

Coronary Heart Disease

Annual CHD Event Rates (in %) by Calcium Score Events by CAC Categories in Subjects with DM, MetS, or Neither Disease (Malik and Wong et al., Diabetes Care 2011)

Coronary Artery Calcium Score

ACCF/AHA 2010 Guideline: CAC Scoring for CV risk assessment in asymptomatic adults aged 40 and over with diabetes (Class IIa-B)
CVD Risk Factor Control in DM Remains Poor and We Can do Better!

Analysis of 74,393 US adults with diabetes from the Diabetes Collaborative Registry

- 74% HbA1C <7% (<8% if with ASCVD)
- 69% BP <140/90 mmHg (40% if <130/80 mmHg)
- 49% LDL-C <100 mg/dL (<70 mg/dL if with ASVD)
- 85% nonsmoking

Only 25% at goal for HbA1c, BP, LDL-C (15% if BP <130/80 mmHg)

Only 22% at goal for all 4 measures (13% if BP <130/80 mmHg)

These data underscore the need for greater efforts for composite risk factor control!

Fan W and Wong ND, et al. *Diab Obes Metab* 2019
CVD and CHD Event Rates by Number of Risk Factors Controlled: Pooling of ARIC, JACKSON, and MESA Study DM Subjects

Multivariable adjusted risks of CVD events 62% lower and CHD events 60% lower with all 3 risk factors controlled (versus none at control)

STENO II Trial

CV events (%)

Conventional Therapy
Intensive Therapy

53% Risk Reduction

Treatment Goals:
Intensive TLC
HgbA1c <6.5%
Cholesterol <175
Triglycerides <150
BP <130/80

Gaede, P. et al, NEJM 2003;348:390-393
New Approaches to Reducing Blood Glucose

**GLP1 agonists** – liraglutide, semaglutide
- ↓ SBP 2-4 mmHg
- ↓ TC, LDL ~5%
- ↓ Weight
- ↓ CRP, BNP

**SGLT2 Inhibitors** – empagliflozin, canagliflozin, dapagliflozin
- ↓ BP
- ↓ TC, LDL ~5%
- ↓ Weight
- ↓ albuminuria
2018 ACC Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes and Atherosclerotic Cardiovascular Disease

A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways

**Patient has T2D* and established clinical ASCVD.**

**Address concurrently.**

**Guideline-directed medical therapy (lifestyle, antiplatelet, blood pressure, lipids) and glucose-lowering therapy (metformin).**

**Consider addition of an SGLT2 inhibitor or GLP-1RA with demonstrated CV outcome benefit.**

**Initiate clinician-patient discussion.**

- No additional action taken at this time
- SGLT2 inhibitor selected
- GLP-1RA selected
<table>
<thead>
<tr>
<th>Consider Using an SGLT2 Inhibitor First When Patient and Clinician Priorities Include:</th>
<th>Consider Using a GLP-1RA First When Patient and Clinician Priorities Include:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reducing MACE and CV death</td>
<td>Reducing MACE and CV death</td>
</tr>
<tr>
<td>Preventing heart failure hospitalization</td>
<td>Substantial weight loss</td>
</tr>
<tr>
<td>Reducing blood pressure</td>
<td>Once weekly (subcutaneous) dosing</td>
</tr>
<tr>
<td>Orally administered therapies</td>
<td>Therapy when eGFR consistently &lt;45 ml/min/1.73 m²*</td>
</tr>
</tbody>
</table>

Consider alternative agents if:
- Significant CKD*
- History of prior amputation, severe peripheral arterial disease, neuropathy, or diabetic foot ulcers (avoid canagliflozin)
- History of recurrent genital candidiasis
- History of diabetic ketoacidosis
- History of osteoporosis (avoid canagliflozin)

Consider alternative agents if:
- Persistent nausea, even at low doses
- History of pancreatitis
- History of gastroparesis
- History of MEN2 or medullary thyroid cancer
- History of proliferative retinopathy (semaglutide)

*eGFR <45 ml/min/1.73 m² is currently a caution due to a decrease in glycemic efficacy (not due to safety), but SGLT2 inhibitors are currently being investigated for nephroprotection in these patients.

CKD = chronic kidney disease; CV = cardiovascular; DPP4 = dipeptidyl-peptidase 4; eGFR = estimated glomerular filtration rate; GLP-RAs = glucagon-like peptide-1 receptor agonists; MACE = major adverse cardiovascular event; MEN2 = multiple endocrine neoplasia type 2; SGLT2 = sodium-glucose cotransporter-2.
### Recommendations for Adults With Type 2 Diabetes Mellitus

<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 metformin as first-line therapy along with lifestyle therapies at the time of diagnosis to improve glycemic control and reduce ASCVD risk.</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.</td>
</tr>
</tbody>
</table>

AHA Primary Prevention Guideline 2019
Cardiovascular benefits of SGLT2i or GLP-1 RA are not dependent upon A1C lowering, so initiation can be considered in people with T2DM and CVD independent of the current A1C or A1C goal.

- If already on dual therapy or multiple glucose-lowering therapies and not on an SGLT2i or GLP-1 RA, consider switching to one of these agents with proven cardiovascular benefit.

- Introduce SGLT2i or GLP-1 RA in patients with CVD at A1C goal for cardiovascular benefit.
Eligibility Criteria¹:
- T2DM with HbA1c 7.0%-10.0%a
- Age ≥18 years
- BMI ≤45 kg/m²
- GFR ≥30 mL/min/1.73 m²
- Had established CV disease

Empagliflozin (10 mg or 25 mg QD) + Standard Care
N=4687b

Placebo + Standard Care
N=2333

Primary Outcome:
- Composite of CV death, nonfatal MI, or nonfatal stroke

Key Secondary Outcome
- Composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for UA

Study design: Multicenter, randomized, double-blind, placebo-controlled study

Primary objective: To assess the effects of empagliflozin vs. placebo on CV morbidity and mortality in patients with T2DM who were at high risk for CV events and were receiving standard care


¹HbA1c 7.0%-9.0% in patients who did not receive any glucose lowering agents ≥12 weeks prior to randomization
²Pooled empagliflozin group
EMPA-REG: Cardiovascular Outcomes and Death from Any Cause

Empagliflozin:

**A** Primary Outcome
- reduced risk for by 14%
  - 3-point MACE
  - Hazard ratio, 0.86 (95.02% CI, 0.74–0.99)
  - P=0.04 for superiority
  - Patients with Event (%) vs. Month
  - No. at Risk:
    - Empagliflozin: 4687, 4580, 4455, 4328, 3851, 2821, 2359, 1534, 370
    - Placebo: 2333, 2256, 2194, 2112, 1875, 1380, 1161, 741, 166

**B** Death from Cardiovascular Causes
- reduced CV death by 38%
  - Hazard ratio, 0.62 (95% CI, 0.49–0.77)
  - P<0.001
  - Patients with Event (%) vs. Month
  - No. at Risk:
    - Empagliflozin: 4687, 4651, 4608, 4556, 4128, 3079, 2617, 1722, 414
    - Placebo: 2333, 2303, 2280, 2243, 2012, 1503, 1281, 825, 177

**C** Death from Any Cause
- improved survival by reducing all-cause mortality by 32%
  - Hazard ratio, 0.68 (95% CI, 0.57–0.82)
  - P<0.001
  - Patients with Event (%) vs. Month
  - No. at Risk:
    - Empagliflozin: 4687, 4651, 4608, 4556, 4128, 3079, 2617, 1722, 414
    - Placebo: 2333, 2303, 2280, 2243, 2012, 1503, 1281, 825, 177

**D** Hospitalization for Heart Failure
- reduced hospitalization for heart failure by 35%
  - Hazard ratio, 0.65 (95% CI, 0.50–0.85)
  - P=0.002
  - Patients with Event (%) vs. Month
  - No. at Risk:
    - Empagliflozin: 4687, 4614, 4523, 4427, 3988, 2950, 2487, 1634, 395
    - Placebo: 2333, 2271, 2226, 2173, 1932, 1424, 1202, 775, 168

* 3-Point MACE = CV Death, Non-Fatal MI, Non-Fatal Stroke

[DOI: 10.1056/NEJMoa1504720]
CANVAS: Study Design and Objectives

Eligibility Criteria:
- T2DM with HbA1c 7.0%-10.5%
- Elevated risk for CV disease

R 1:1:1

Canagliflozin (100 mg) N=1445
Canagliflozin (300 mg) N=1441
Placebo N=1441

Primary Outcome:
- Composite of CV death, nonfatal MI, or nonfatal stroke

Key Secondary Outcome
- Composite of CV death, nonfatal MI, nonfatal stroke, hospitalization for UA

Study design: Multicenter, randomized, double-blind, placebo-controlled, parallel group study
Primary objective: To determine the effects of canagliflozin compared to placebo (against a background of standard care) on the risk of CV disease and to provide data on safety and tolerability
Study start - expected completion: December 2009 - February 2017
Primary MACE Outcome
CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke

Hazard ratio 0.86 (95% CI, 0.75-0.97)
p < 0.0001 for noninferiority
p = 0.0158 for superiority

No. of patients
Placebo 4347 4153 2942 1240 1187 1120 789
Canagliflozin 5795 5566 4343 2555 2460 2363 1661
## Summary

<table>
<thead>
<tr>
<th>Primary cardiovascular outcome</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death</td>
<td>0.87 (0.72-1.06)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>0.85 (0.69-1.05)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>0.90 (0.71-1.15)</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>0.67 (0.52-0.87)</td>
</tr>
<tr>
<td>CV death or hospitalization for heart failure</td>
<td>0.78 (0.67-0.91)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.87 (0.74-1.01)</td>
</tr>
</tbody>
</table>

Favors Canagliflozin: 0.5 to 1.0
Favors Placebo: 1.0 to 2.0
**CREDENDE: Canagliflozin Cuts Risk of Renal Failure, Death 30% in Patients With Type 2 Diabetes, CKD**

- Randomized 4401 patients with an average follow-up of 2.62 years.
- Mean age of 63 years (± 9.2 years) and had lived with T2D for an average of 15.8 years (± 8.6 years).
- eGFR of 30 to <90 ml/min/1.73m2
- All treated with standard of care RAS blockade

---

**Summary**

<table>
<thead>
<tr>
<th>Primary</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. ESKD, doubling of serum creatinine, or renal or CV death</td>
<td>0.70 (0.59–0.82)</td>
<td>0.00001</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. CV death or hospitalization for heart failure</td>
<td>0.69 (0.57–0.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3. CV death, MI, or stroke</td>
<td>0.80 (0.67–0.95)</td>
<td>0.01</td>
</tr>
<tr>
<td>4. Hospitalization for heart failure</td>
<td>0.61 (0.47–0.80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5. ESKD, doubling of serum creatinine, or renal death</td>
<td>0.66 (0.53–0.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6. CV death</td>
<td>0.76 (0.61–1.00)</td>
<td>0.0502</td>
</tr>
<tr>
<td>7. All-cause mortality</td>
<td>0.83 (0.68–1.02)</td>
<td>–</td>
</tr>
<tr>
<td>8. CV death, MI, stroke, hospitalization for heart failure, or</td>
<td>0.74 (0.63–0.86)</td>
<td>–</td>
</tr>
<tr>
<td>hospitalization for unstable angina</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NEJM 2019
DAPA-HF: First trial specifically in HF pts with reduced EF to examine effect of SGLT-2 (dapagliflozin) on incident CVD death and HF

HR=0.74 (0.65-0.85), p=0.00001, NNT=21 for Primary Outcome of CHD Death / HF Hospitalization / Urgent HF Visit

**Trial Description:** Patients with heart failure with reduced ejection fraction (irrespective of diabetes status) were randomized to dapagliflozin 10 mg daily vs. placebo.

**RESULTS**
- Primary efficacy endpoint: cardiovascular death, hospitalization for heart failure, or urgent heart failure visit occurred in 16.3% of the dapagliflozin group compared with 21.2% of the placebo group (p < 0.001)
- Cardiovascular death: 9.6% with dapagliflozin vs. 11.5% with placebo
- Hospitalization for heart failure: 9.7% with dapagliflozin vs. 13.4% with placebo

**CONCLUSIONS**
- Among patients with symptomatic heart failure due to reduced left ventricular ejection fraction, dapagliflozin was beneficial
- Dapagliflozin vs. placebo was associated with a reduction in cardiovascular deaths and heart failure events

Study design: International, randomized, placebo-controlled study

Primary objective: To evaluate the effect of liraglutide compared to placebo on the incidence of CV events in adults with type 2 diabetes

Eligibility Criteria:
- T2DM with HbA1c ≥7.0%
- Age ≥50 years with ≥1 coexisting CV condition\(^a\) or
- Age ≥60 years with ≥1 CV risk factor\(^b\)

Liraglutide (0.6-1.8 mg)\(^c\) + Standard Care
N=4668

Placebo + Standard Care
N=4672

Primary Outcomes:
- Composite of CV death, nonfatal MI, or nonfatal stroke

Key Secondary Outcome
- Composite of CV death, nonfatal MI, nonfatal stroke, revascularization, hospitalization for UA, or heart failure

\(^a\)Coronary heart disease, cerebrovascular disease, peripheral vascular disease, CKD stage ≥3, chronic heart failure NYHA class II/III

\(^b\)Microalbuminuria or proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, or an ankle-brachial index (the ratio of the systolic BP at the ankle to the systolic BP in the arm) of <0.9

\(^c\)Liraglutide was administered at 0.6 mg daily for 1 week, 1.2 mg/day for an additional week, and a potential maximum dosage of 1.8 mg/day thereafter

The primary composite outcome in the time-to-event analysis was the first occurrence of CV death, nonfatal MI, or nonfatal stroke. The cumulative incidences were estimated with the use of the Kaplan-Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses were truncated at 54 months, because <10% of the patients had an observation time beyond 54 months.

SUSTAIN 6: Study Design and Objectives

1. Study design: Multicenter, randomized, placebo-controlled, double-blind study

2. Primary objective: To evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes

Eligibility Criteria:
- T2DM with HbA1c ≥7.0%
- Age ≥50 years with evidence of CVD or ≥60 years with subclinical evidence of CVD
- Drug naïve or treated with 1-2 OADs or insulin

Semaglutide (0.5 mg or 1.0 mg once a week) + Standard Care
Placebo + Standard Care

Primary Outcome:
- Composite of CV death, nonfatal MI, or nonfatal stroke

Key secondary Outcome
- Expanded composite CV outcome

https://clinicaltrials.gov/ct2/show/NCT01720446
SUSTAIN-6: Semaglutide Reduces Cardiovascular Outcomes in DM2

CV safety trial showed 24% reduction in primary composite outcome and 39% reduction in stroke.
Influenza Vaccination

Patients with cardiovascular disease should have influenza vaccination
# Influenza Vaccination Evidence

## Effectiveness of Influenza Vaccination during the Influenza Seasons

<table>
<thead>
<tr>
<th>Hospitalization</th>
<th>Vaccinated Subjects (N=77,738)</th>
<th>Unvaccinated Subjects (N=62,317)</th>
<th>Adjusted Odds Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia or influenza</td>
<td>495 (0.6)</td>
<td>581 (0.9)</td>
<td>0.68 (0.60–0.78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>888 (1.1)</td>
<td>1026 (1.6)</td>
<td>0.81 (0.73–0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>457 (0.6)</td>
<td>535 (0.9)</td>
<td>0.80 (0.70–0.91)</td>
<td>0.001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>466 (0.6)</td>
<td>538 (0.9)</td>
<td>0.81 (0.70–0.92)</td>
<td>0.002</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>398 (0.5)</td>
<td>427 (0.7)</td>
<td>0.84 (0.72–0.97)</td>
<td>0.018</td>
</tr>
<tr>
<td>Death</td>
<td>943 (1.2)</td>
<td>1361 (2.2)</td>
<td>0.52 (0.47–0.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospitalization or death</td>
<td>2387 (3.1)</td>
<td>2910 (4.7)</td>
<td>0.65 (0.62–0.70)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Association Between Influenza Vaccination and Cardiovascular Outcomes in High-Risk Patients: A Meta-Analysis (Udell JAMA 2013)

- Six randomized clinical trials of 6735 patients (mean age, 67 years; 51.3% women; 36.2% with a cardiac history; mean follow-up time, 7.9 months) were included.
- Influenza vaccine was associated with a lower risk of composite cardiovascular events (2.9% vs 4.7%; RR, 0.64 [95% CI, 0.48-0.86], P = .003) in published trials.
- A treatment interaction was detected between patients with (RR, 0.45 [95% CI, 0.32-0.63]) and without (RR, 0.94 [95% CI, 0.55-1.61]) recent ACS (P for interaction = .02).
 Harnessing the natural process of RNAi

- Nucleotides modified for durability and low immunogenicity
- Distributed to liver due to GalNAc conjugation
- Inhibits production of PCSK9 specifically, durably and potently

Small interfering double-stranded RNA
ORION-11: Efficacy
Durable, potent and consistent effect over 18 months

- Percent change in LDL-C over time – observed values ITT patients

P-value for placebo – inclisiran comparison at each time point <0.00001
Summary

1. The new cholesterol guidelines retain the same statin eligible groups as the prior 2013 guidelines: ASCVD, LDL-C >=190, diabetes, and high risk primary prevention.
2. Risk enhancing factors are to be used in the clinician-patient discussion regarding treatment of those at 5-<20% 10-year ASCVD risk.
3. Persons with ASCVD are categorized into those at versus not at very high risk for consideration of ezetimibe and/or PCSK9 mAb therapy.
4. Emerging non-statin therapies (inclisiran, bempedoic acid) may have an important future role in LDL-C lowering.
Being healthy is better than being sick or dead. This is the sole argument for prevention. It is sufficient.

Professor Geoffrey Rose
Thank You!

www.aspconline.org

Preventive Cardiology Program
Take control of your health

Life-threatening cardiac events often can be prevented through early diagnosis, risk assessment, treatment and lifestyle changes.

The UC Irvine Health Preventive Cardiology Program uses the latest evidence-based guidelines for cardiovascular disease prevention. Services include:

- Initial evaluation by cardiologist, plus follow-up to track progress
- Comprehensive laboratory measures for cardiac risk factors and biomarkers, plus further evaluation with optional imaging tests
- Computerized cardiovascular risk profiles and risk scoring
- Comprehensive dietitian consultation with a specific focus on cardiovascular risk factor management
- Physical activity prescriptions and consultations with an exercise specialist
- A full report sent to the patient’s referring physician when the program is finished

Our preventive cardiology program’s multidisciplinary team includes:

- Cardiologists
- Registered dietitian
- Exercise physiologist
- Prevention researchers/specialists

Our program can help you if you have been diagnosed with at least one risk factor for cardiovascular disease, including:

- Hypertension
- Hypercholesterolemia/dyslipidemia
- Metabolic syndrome
- Diabetes
- Cigarette smoking

Patients with pre-existing cardiovascular disease who need more guidance with risk factor modification to prevent disease progression or recurrence are also ideal candidates.

To learn more, call 714-456-6699.

UC Irvine Health
101 The City Drive South
Orange, CA 92866
ucvinhealth.org/heart