MHIF FEATURED STUDY: ATTR CM

DESCRIPTION: A Phase 3 Global, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ION-682884 in Patients with Transthyretin-Mediated Amyloid Cardiomyopathy

ION-682884 vs. placebo administered by subcutaneous injection once every 4 weeks in patients with ATTR-CM receiving available background therapy. ION-682884 is a ligand-conjugated antisense drug designed to reduce the production of transthyretin to treat all types of TTR amyloidosis.

CRITERIA LIST/QUALIFICATIONS:

Inclusion
- Amyloid deposits in cardiac or non-cardiac tissue
- Medical history of HF secondary to hereditary or wild-type ATTR-CM

Exclusion
- Cardiomyopathy not primarily caused by ATTR-CM
- Significant co-morbidities
- Current treatment with inotersen, patisiran, diflunisal, doxycycline, non-dihydropyridine calcium-channel blocker

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PI: Mosi Bennett, MD

CONDITION: Transthyretin-Mediated Amyloid Cardiomyopathy

SPONSOR: Ionis Pharmaceuticals

OPEN and ENROLLING: EPIC message to Research MHIF Patient Referral
Food As Medicine

Courtney Jordan Baechler, MD, MS
Medical Director
Emerging Science Centers

Disclosures...
Food as medicine (FAM) is old news

Ask any doctor how to avoid or mitigate the effects of the leading killers of Americans and you’ll hear that eating healthier plays a big role.

Creating a World without Heart and Vascular Disease...

- According to NHANES (National Health and Nutrition Examination Survey; 2015–2016), <10% adults met the guidelines for whole grains (≥3 servings per day), whole fruits (≥2 cups per day), and nonstarchy vegetables (≥2.5 cups per day).

- According to the AHA primary diet score, 47.8% of US adults had poor diet quality in 2015 to 2016. On the basis of the secondary score, 36.4% of US adults had poor diet quality in 2015 to 2016.

- In a large primary prevention trial among patients with CVD risk factors, patients randomized to unrestricted-calorie Mediterranean-style diets supplemented with extra-virgin olive oil or mixed nuts had a ≈30% reduction in the risk of stroke, myocardial infarction, and death attributable to cardiovascular causes, without changes in body weight.

Heart Disease and Stroke, 2021 Statistics
45% of deaths in one year from heart disease, stroke and DMII were linked to poor diet.
What Foods Are Best?

**Benefit**
- Fruits, Nuts, Fish
- Vegetables, Vegetable Oils
- Whole Grains, Beans, Yogurt
- Cheese
- Eggs, Poultry, Milk
- Butter
- Unprocessed Red Meats
- Refined Grains, Starches, Sugars
- Processed Meats, High Sodium Foods
- Industrial Trans Fat

**Harm**

$50.4 Billion Dollars Annually

<table>
<thead>
<tr>
<th>Food Category</th>
<th>Ideal Daily Consumption</th>
<th>Annual Cardiometabolic Costs* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fruits</td>
<td>300 g/day</td>
<td>9.552 (8.904–10.248)</td>
</tr>
<tr>
<td>Vegetables</td>
<td>400 g/day</td>
<td>10.055 (9.408–10.922)</td>
</tr>
<tr>
<td>Nuts/seeds</td>
<td>20 g/day</td>
<td>13.574 (12.432–14.448)</td>
</tr>
<tr>
<td>Whole grains</td>
<td>125 g/day</td>
<td>7.541 (7.056–8.064)</td>
</tr>
<tr>
<td>Red meat</td>
<td>14.3 g/day</td>
<td>0.503 (0.4704–0.538)</td>
</tr>
<tr>
<td>Sugar-sweetened beverages</td>
<td>0 oz/day</td>
<td>10.223 (9.890–11.088)</td>
</tr>
<tr>
<td>Processed meat</td>
<td>0 g/day</td>
<td>9.72 (9.072–10.248)</td>
</tr>
<tr>
<td>Polysaturated fatty acids</td>
<td>11% Energy/day</td>
<td>3.352 (3.192–3.696)</td>
</tr>
<tr>
<td>Seafood omega-3</td>
<td>250 mg/day</td>
<td>12.736 (11.76–13.944)</td>
</tr>
<tr>
<td>Sodium</td>
<td>2000 mg/day</td>
<td>3.854 (3.696–4.2)</td>
</tr>
</tbody>
</table>

*Values given in 2018 US billions of dollars. Total cost does not reflect sum of individual components based on the assumption that the benefits of the 10 food groups are not independent.

https://doi.org/10.1371/journal.pmed.1002981.1004

Medically Tailored Meals (MTM)

What is the Medi-Cal MTM Program?

The Medi-Cal MTM Pilot Program is a medical nutrition intervention for high utilizing Medi-Cal beneficiaries with a diagnosis of congestive heart failure (CHF). The intervention is 12 weeks in duration.

- **Who:** Discharged Medi-Cal patients who were admitted due to CHF and have a history of being a high utilizer of health care services and/or likely at risk for readmission within 30 days.

- **Intervention Goal:** Reduce hospital and emergency department 30-day and 90-day readmissions.

- **Cost:** No cost to patient. Must be on Medi-Cal.
What is the Intervention?

MTM Intervention

Medically Tailored Meals  Medical Nutrition Therapy  Information & Referral Services

Goal: Reduce hospital readmissions and ED visits!

Ant-Inflammatory Food Pyramid
Functionalizing FAM...

MHIF Research Project with NUMC & Hy-Vee & Benovate
Patient Criteria

• Using measurements documented within 6 months of study start date:
  • Adults diagnosed with hypertension (≥140/90 mm Hg)
  • Adults diagnosed with pre-diabetes (A1c between 5.7 to 6.4)
  • Adults diagnosed with diabetes (A1c 6.5 and above)

Success Measures

Clinical
• Improvement in blood pressure
• Improvement in hemoglobin A1c
• Improvement in fasting blood sugar

App Adoption
• Engagement (percentage of population using the app)
• Stickiness (frequency of use)
• Activation (behavior change)

Retail
• Units (volume of category of items sold)
• Margins (corresponding profit impact of unit change)
Fish Oil for Cardiovascular Prevention

Michael D Miedema, MD MPH
Director of Cardiovascular Prevention
Minneapolis Heart Institute

April 5, 2021

Low incidence of CHD in Greenland Inuit
"Oily Fish"

- Salmon
- Herring
- Trout
- Anchovy
- Sardines
- Mackerel
- Tuna

A serving of salmon ~ 1,000mg of Omega-3 Fatty Acids
OTC vs Prescription Fish Oil

Over the Counter Options
- Numerous
- Variable dosing
  - Variable ratios

Prescription Fish Oil
- Epanova
- Lovaza
- Omtryg
  - All combinations of EPA/DHA
  - ↓ Triglycerides
  - ↑ LDL-C
- Icosapent Ethyl (Vascepa)
  - Purified EPA

Physician’s Health Study

Figure 1.—Multivariate adjusted relative hazard of sudden death across increasing levels of fish intake expressed as servings of fish per week. The solid line represents the maximum partial likelihood estimate of the smooth relative hazard function, using a restricted cubic spline model with 4 knots. The dotted lines represent pointwise 95% confidence intervals for the relative hazard function.

Albert CM at el. PHS, JAMA, 1998
**Pooled Analysis of Studies of Cardiac Death**

Meta-analysis of 16 prospective cohort studies (total n=326,572) and 4 randomized controlled trials (total n=35,115) from the U.S., Europe, and Asia.

Relative Risk of Cardiac Death

EPA+DHA Intake (mg/d)

Total risk reduction = 36%
(95% CI= 20 to 50%; p<0.001)

250 mg/day
(~ 2 g/week)

Mozaffarian & Rimm. JAMA 2006

**Fish Oil for Cardiovascular Prevention**

**ORIGIN Trial**

>12k individuals with prior CVD or DM

**R&P Study Group**

>12k individuals with CVD risk factors or ASCVD

ORIGIN Trial, NEJM, 2012

N-3 Fatty Acids, R&P Study Group, NEJM, 2013
Fish Oil for Cardiovascular Prevention

**ASCEND Trial**
- >15k individuals with T2DM

**OMEMI**
- >1k elderly individuals with recent MI

ASCEND Trial, NEJM, 2018

OMEMI, Circulation, 2021

- 25,871 Individuals (men > 50 years or women > 55 years without CVD)
  - Including 5,105 black participants
  - 1 Gram of Fish Oil (840mg of EPA/DHA)
  - Followed up for 5.3 years
  - Primary Outcome of MI, Stroke, or CVD death

Manson et al, VITAL, NEJM, 2018
A Major Cardiovascular Events

No. at Risk
Placebo 12,938 12,862 12,745 12,592 12,281 9,825 775
n-3 Fatty acids 12,933 12,842 12,725 12,594 12,322 9,878 765

Hazard ratio, 0.92 (95% CI, 0.80–1.06)
P = 0.24

Years since Randomization

B Invasive Cancer of Any Type

No. at Risk
Placebo 12,938 12,747 12,544 12,330 11,981 9,543 756
n-3 Fatty acids 12,933 12,756 12,566 12,356 11,996 9,557 734

Hazard ratio, 1.03 (95% CI, 0.93–1.13)
P = 0.56
### Table 2. Hazard Ratios and 95% Confidence Intervals for the Primary, Secondary, and Other End Points, According to Randomized Assignment to n−3 Fatty Acids or Placebo, in Intention-to-Treat Analyses.

<table>
<thead>
<tr>
<th>End Point</th>
<th>n−3 Group (N = 12,933)</th>
<th>Placebo Group (N = 12,938)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary end point: major cardiovascular event†</td>
<td>386</td>
<td>419</td>
<td>0.92 (0.80–1.06)</td>
</tr>
<tr>
<td>Cardiovascular event in expanded composite end point‡</td>
<td>527</td>
<td>567</td>
<td>0.93 (0.82–1.04)</td>
</tr>
<tr>
<td>Total myocardial infarction</td>
<td>145</td>
<td>200</td>
<td>0.72 (0.59–0.90)</td>
</tr>
<tr>
<td>Total stroke</td>
<td>148</td>
<td>142</td>
<td>1.04 (0.83–1.31)</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>142</td>
<td>148</td>
<td>0.96 (0.76–1.21)</td>
</tr>
</tbody>
</table>

Manson et al, VITAL, NEJM, 2018

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**Figure 3.** Hazard Ratios and 95% Confidence Intervals for Major Cardiovascular Events According to Subgroup, Comparing the n−3 Group with the Placebo Group.

- Fish consumption
  - Median of 1.5 servings/wk: Hazard Ratio 0.81 (0.67–0.98)
  - >Median of 1.5 servings/wk: Hazard Ratio 1.08 (0.88–1.32)

Manson et al, VITAL, NEJM, 2018
• 13,078 individuals with elevated CVD risk, high trig’s, and low HDL-C
• 4 grams/day of Fish Oil vs Placebo (corn oil)
• Primary outcome of MI, stroke, USA, PCI/CABG, or CVD death

Study stopped early at ~3.5 years for futility
• 18,645 individuals (~70% women) aged 45-75 with hyperlipidemia
  • Primary and Secondary Prevention
  • In Japan (high background fish intake)
  • Statin + 1,800mg of EPA vs Statin only
  • Mean follow-up of 4.6 years
  • Primary outcome – major coronary event
Figure 4: Percentage changes from baseline in serum lipid profile. TC = total cholesterol. LDL-C = low-density lipoprotein cholesterol. HDL-C = high-density lipoprotein cholesterol.
• 8,179 patients with either established CVD or diabetes + 2 CVD risk factors
  • Triglycerides 135-499mg/dl and LDL 41-100mg/dl
  • Randomized to 2 grams of EPA bid vs placebo (mineral oil)
  • Follow-up for median 4.9 years
  • Primary end-point of MI, CVA, CVD death, or USA
REduceaspers-

- Slight increase in LDL in the placebo group
  - Unlikely to impact trial results
- Slight increase in atrial fibrillation/flutter
  - 5.3% vs 3.9%, p-value 0.004
- Comparison with STRENGTH
  - >250% increase in EPA levels in both studies
    - Inverse relation with CVD events in REDUCE-it but not STRENGHT
    - 20% reduction in Trig’s vs 20% reduction in Trig’s

Bhatt et al, REDUCE-IT, NEJM, 2019

-80 patients with non-obstructive coronary atherosclerosis, on statin therapy, with elevated triglycerides
- Treated with 4 gram of IPE vs placebo
- CT coronary angiography performed after 18 months of therapy to determine the impact of IPE on plaque progression

Budoff et al, EVAPORATE, EHJ, 2020
Final Conclusions

- Seafood, especially fish high in omega-3 fatty acids, is an important part of a heart-healthy diet
- Routine fish oil supplementation is not supported by large randomized trials
  - Eat the real thing!!
  - An opportunity to reduce medication burden
  - Individuals with low fish intake may be an exception
- Consider icosapent ethyl (Vascepa) for patients at very high CVD risk
  - Vascepa is not the same as OTC fish oil
  - $$$
Thank You
SGLT2 Inhibitors & Cardiovascular Risk Reduction

Elizabeth Tuohy, MD
Cardiologist, United Heart & Vascular Clinic, MHI/Allina Health Heart Institute
Medical Director, Heart Disease Prevention Clinic
MHI Grand Rounds 4/2/2021

10-minute rapid overview of SGLT2 Inhibitors

• No disclosures
• Objectives:
  1) Understand the mechanism of action of SGLT2 Inhibitors
  2) Appreciate the cardiovascular risk reduction with SGLT2 Inhibitors
  3) Review utilization in clinical practice
Why should cardiologists know about a diabetes medication?

- ~12% of Americans have physician diagnosed diabetes (noting heterogeneity across demographics)
- ~2-5% have undiagnosed diabetes
- ~34% have prediabetes

NHANES 2013-2015

Why should cardiologists know about a diabetes medication?

- At least 68% of people >65 years of age with diabetes die of some form of heart disease; 16% die of stroke
- Heart disease death rates among adults with diabetes are 2 to 4 times higher than the rates for adults without diabetes

AHA Stats 2019
2019 ACC/AHA Guidelines for Primary Prevention of Cardiovascular Disease

- For adults with type 2 diabetes mellitus, lifestyle changes, such as improving dietary habits and achieving exercise recommendations, are crucial.
- If medication is indicated, metformin is first-line therapy, followed by consideration of a sodium-glucose cotransporter 2 inhibitor (SGLT2i) or a glucagon-like peptide-1 (GLP-1) receptor agonist.

SGLT2-Inhibitor Glucose Effect

- Inhibitors of sodium glucose cotransporter-2 act in the proximal renal tubule to increase urinary excretion of glucose, leading to a reduction in rates of hyperglycemia in patients with type 2 diabetes (A1c reduction of ~0.5-1%)
SGLT2-Inhibitor Glucose Effect

- Inhibitors of sodium glucose cotransporter-2 act in the proximal renal tubule to increase urinary excretion of glucose, leading to a reduction in rates of hyperglycemia in patients with type 2 diabetes (A1c reduction of ~0.5-1%)

Paola Fioretto et al. Dia Care 2016;39:S165-S171

Additional Potential SGLT2-Inhibitor Effects

- **Kidney**: decreased blood glucose (glycosuria), increased natriuresis/diuresis, decreased hyperuricemia, improved energy metabolism

- **Heart**: Improved energy metabolism, decreased inflammation, improved remodeling, decreased ischemia, decreased oxidative stress, decreased epicardial fat

- **Vasculature**: decreased inflammation, decreased BP, increased pro-vascular progenitor cells, improved vascular function

- **Whole body**: weight loss, inhibited sympathetic nervous system, increased erythropoietin

JACC Basic Transl Sci. 2020 Jun; 5 (6): 632-644
Available SGLT2 Inhibitors

- empagliflozin (Jardiance)
- canagliflozin (Invokana)
- dapagliflozin (Farxiga)
- ertugliflozin (Steglatro)

**EMPA-REG OUTCOME** trial examined the effects of empagliflozin on cardiovascular morbidity and mortality in patients with DM2 and established ASCVD

- Mean A1c decreased from 8.2% to 7.8%

Zinman, NEJM, 2015. 373: 2117-28
• CANVAS Program: 10,142 participants, 4330 in CANVAS and 5812 in CANVAS-R
• ≥ 30 years old with ASCVD
• ≥ 50 years old with 2 risk factors (DM for ≥ 10 years, SBP >140 mmHg while on at least one antihypertensive, current smoking, albuminuria, HDL < 38.7 mg/dl)

Neal B, NEJM 2017. 377: 644-57
Death from CV cause, Nonfatal MI, or Nonfatal stroke

* Non-significant difference between individual endpoints of death from CV cause, nonfatal MI or nonfatal stroke

Neal B, NEJM 2017. 377: 644-57

Hospitalization for Heart Failure

Neal B, NEJM 2017. 377: 644-57
• DECLARE-TIMI 58 Trial: 17,160 patients
• Established ASCVD or multiple risk factors
• followed for a median of 4.2 years

Wiviott SD, NEJM 2019 380:347-57

Major Adverse CV Events – no significant difference

8.8% in the dapagliflozin group and 9.4% in the placebo group; hazard ratio, 0.93; 95% CI, 0.84 to 1.03; P=0.17 for superiority

Wiviott SD, NEJM 2019 380:347-57
CV Death or Hospitalization for Heart Failure

4.9% vs. 5.8%; hazard ratio, 0.83; 95% CI, 0.73 to 0.95; P=0.005

HF hospitalization 6.2% vs 8.5%; HR 0.73; 95% CI, 0.61 to 0.88

No between-group difference in cardiovascular death.
HR 0.98; 95% CI, 0.82 to 1.17

Wiviott SD, NEJM 2019 380:347-57

• VERTIS CV
• 8246 patients with DM2 and ASCVD, followed for a mean of 3.5 years
• Non-significant difference in MACE
• Significant reduction in heart failure hospitalization (2.5% vs 3.6%, HR 0.7, 95% CI 0.54-0.90)

SGLT2 Inhibitor Adverse Events

- Urinary tract infections, yeast infections
  - Incidence of infections are 15-20% higher vs. placebo
  - Women >>>>> Men
- Urethritis and vaginal irritation
- Hypovolemia / orthostatic hypotension
- Slight increase risk DKA
- Canagliflozin – increase in amputations (6.3% vs 3.4%, P <0.001). Caution in patients with neuropathy, hx foot ulceration, foot deformity

Contraindications/Precautions

- Type 1 diabetes
- Prior DKA
- Caution in CKD:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>empagliflozin</td>
<td>10mg, 25mg</td>
<td>Discontinue if GFR &lt; 45</td>
</tr>
<tr>
<td>dapagliflozin</td>
<td>5mg, 10mg</td>
<td>Discontinue if GFR &lt; 45</td>
</tr>
<tr>
<td>canagliflozin</td>
<td>100mg, 300mg</td>
<td>100mg if GFR &lt; 60, Ok to cont until dialysis</td>
</tr>
<tr>
<td>ertugliflozin</td>
<td></td>
<td>Discontinue if GFR &lt; 60</td>
</tr>
</tbody>
</table>
Available SGLT2 Inhibitors and Cost/Month

- empagliflozin (Jardiance) $529
- canagliflozin (Invokana) $570
- dapagliflozin (Farxiga) $504
- ertugliflozin (Steglatro) $316
Thank you
Update in Lipid Management

Thomas Knickelbine, MD
Objectives

Review Updated Cholesterol Treatment Guidelines

Lipid Lowering Therapies Beyond Statins
64 yo male with recent ACS, h/o DM, HTN and CKD. Current therapy rosuvastatin 40 mg with 53% reduction from baseline. Current LDL of 74 mg/dl and normal triglycerides.

What is the next best option according to the 2018 AHA/ACC multisociety guidelines?

1. Add Icosapent ethyl (Vascepa)
2. No further rx, Pt has achieved goal of > 50% LDL reduction.
3. Add ezetimibe 10 mg
4. Add PCSK9i
LDL is primary target in lipid RX guidelines

A Direct Correlation
LDL-C and CVD Risk

Slope steepens over time:
Causal and cumulative effect of LDL-C on CVD risk

2018 AHA/ACC Multisociety Guideline on the Management of Blood Cholesterol

Nov 10, 2018 | Melvyn Rubenfire, MD, FACC

Authors: Grundy SM, Stone NJ, Bailey AL, et al.


Related Content:
- Guideline Hub | Blood Cholesterol
- Use of Risk Assessment Tools to Support Decision-Making in ASCVD Prevention
- New AHA/ACC Cholesterol Guidelines Call for More Personalized Care; New Treatment Options
- Further Cardiovascular Outcomes With PCSK9 Inhibition in Subjects With Elevated Risk
- IMPROVED Reduction of Outcome Events Efficacy International Trial
- ODYSSEY ESCAPE
- ODYSSEY-COMBO-I
- ODYSSEY-COMBO-II
- ODYSSEY-HIGH-FH
- ODYSSEY-LONG-TERM
"Very High Risk" in ASCVD Patients
2018 AHA/ACC Guidelines

Major ASCVD Events

- ACS within 12 months
- Prior MI
- Prior ischemic stroke
- Symptomatic PAD

"Very High Risk" in ASCVD Patients
2018 AHA/ACC Guidelines (cont)

Major ASCVD Events
• ACS within 12 months
• Prior MI
• Prior ischemic stroke
• Symptomatic PAD

High Risk Conditions
• Age ≥ 65 years
• Heterozygous FH
• Prior CABG or PCI
• Diabetes
• Hypertension
• CKD
• Current smoking
• LDL-C ≥ 100 mg/dL on maximally tolerated statin
• History of heart failure

"Very High Risk" in ASCVD Patients
2018 AHA/ACC Guidelines (cont)

**Major ASCVD Events**
- ACS within 12 months
- Prior MI
- Prior ischemic stroke
- Symptomatic PAD

**Definition: Very High Risk**
- Multiple major ASCVD events or
- 1 major ASCVD event and multiple high risk conditions

**High Risk Conditions**
- Age ≥ 65 years
- Heterozygous FH
- Prior CABG or PCI
- Diabetes
- Hypertension
- CKD
- Current smoking
- LDL-C ≥ 100 mg/dL on maximally tolerated statin
- History of heart failure

AHA/ACC Clinical ASCVD Algorithm

Clinical ASCVD Algorithm (cont)

Not Very High Risk
- Age ≤ 75: high-intensity statin first, with potential add-on therapy with ezetimibe if on maximal statin therapy and LDL-C is ≥ 70 mg/dL (class IIb)
- Age > 75: either moderate- or high-intensity statin (class IIa)

Clinical ASCVD Algorithm

Very High Risk ASCVD

- Step 1: high-intensity or maximally tolerated statin
- Step 2: If inadequate response or LDL-C is ≥ 70 mg/dL, ezetimibe and PCSK9 inhibitor are considered. Guideline recommends an "ezetimibe first" approach due to cost concerns.

# Getting to Goal Is Possible

**Expected Benefit of Lipid-Lowering Therapies**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Average LDL-C Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate-intensity statin</td>
<td>≈ 30%</td>
</tr>
<tr>
<td>High-intensity statin</td>
<td>≈ 50%</td>
</tr>
<tr>
<td>High-intensity statin + ezetimibe</td>
<td>≈ 65%</td>
</tr>
<tr>
<td>PCSK9 inhibitor</td>
<td>≈ 60%</td>
</tr>
<tr>
<td>PCSK9 inhibitor + high-intensity statin</td>
<td>≈ 75%</td>
</tr>
<tr>
<td>PCSK9 inhibitor + high-intensity statin + ezetimibe</td>
<td>≈ 85%</td>
</tr>
</tbody>
</table>

Relationship Between Achieved LDL-C and Change in Percent Atheroma Volume

Plaque regression begins < 80 mg/dl; Consistent < 60 mg/dl

Change in Percent Atheroma Volume, %

Evolocumab + Statin vs Statin

LDL-C (mg/dl) 37 93

On-Treatment LDL-C, mg/dL (76 wks)

Nicholls et al JAMA Nov 2016

CI=95% Confidence Interval
Lower LDL-C Is Better for CV Outcomes

*Data From FOURIER*

**Primary efficacy endpoint:**
composite of CV death, MI, stroke, coronary revascularization, or hospital admission for unstable angina

**Key secondary efficacy endpoint:**
composite of CV death, MI, or stroke

"Very High Risk" in ASCVD Patients
2019 ESC/EAS Guidelines

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very high risk:</strong> &lt; 1.8 mmol/L (&lt; 70 mg/dL) or ≥ 50% ↓ if LDL-C 1.8 to 3.5 mmol/L (70-135 mg/dL)</td>
<td><strong>Very high risk:</strong> &lt; 1.4 mmol/L (&lt; 55 mg/dL) and ≥ 50% ↓</td>
</tr>
<tr>
<td><strong>High risk:</strong> &lt; 2.6 mmol/L (&lt; 100 mg/dL) or ≥ 50% ↓ if LDL-C 2.6 to 5.2 mmol/L (100-200 mg/dL)</td>
<td><strong>High risk:</strong> &lt; 1.8 mmol/L (&lt; 70 mg/dL) and ≥ 50% ↓</td>
</tr>
<tr>
<td><strong>Moderate risk:</strong> &lt; 3 mmol/L (&lt; 115 mg/dL)</td>
<td><strong>Moderate risk:</strong> &lt; 2.6 mmol/L (100 mg/dL)</td>
</tr>
<tr>
<td><strong>Low risk:</strong> &lt; 3 mmol/L (&lt; 115 mg/dL)</td>
<td><strong>Low risk:</strong> <em>no change from 2016</em> &lt; 3 mmol/L (&lt; 116 mg/dL)</td>
</tr>
</tbody>
</table>

64 yo male with recent ACS, h/o DM, HTN and CKD. Current therapy rosuvastatin 40 mg with 53% reduction from baseline. Current LDL of 77 mg/dl and normal triglycerides.

What is the next best option according to the 2018 AHA/ACC multi-society guidelines?

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2. No further rx, Pt has achieved goal of > 50% LDL reduction.
3. Add ezetimibe 10 mg
4. Add PCSK9i
Emerging Therapies
Therapeutic Approaches to Reducing LDL-C

- Antibodies: Extracellularly located
- Anti-PCSK9 mAbs: Transiently block PCSK9 binding to LDLR extracellularly
- Small molecule: Intracellularly and extracellularly located
- Statins: Intracellular cholesterol depletion increases LDLR synthesis via transcription
- Gene silencing: Intracellularly located
- PCSK9 synthesis inhibitors: Long-term inhibition of PCSK9 synthesis and all intracellular and extracellular PCSK9 functions

siRNA to PCSK9

ORION-10 and ORION-11: Efficacy of Inclisiran

Percentage Change in LDL-C, ORION-10 Trial

Percentage Change in LDL-C, ORION-11 Trial

CV Risk Reduction and LDL-C Reduction Based on Adherence and Treatment Intensity

**CV Risk**

- Untreated ≥1 y HR, 1.0
- Moderate intensity, nonadherent HR, 0.93 (0.87-0.99)
- High intensity, nonadherent HR, 0.90 (0.86-0.95)

**LDL-C Reduction**

- Untreated ≥1 y % change -0.1 (-0.1 to -0.1)
- Low intensity, nonadherent % change, -4.2 (-4.4 to -4.1)
- High intensity, nonadherent % change, -8.8 (-9.1 to -8.5)

siRNA Targets Beyond PCSK9 and LDL-C

Target mRNA degradation by siRNA

- **INCLISERAN** (Novartis)
  - ↓ LDL cholesterol
  - ↓ Lipoprotein(a)

- **VOLANESORSEN** (Ackcea)
  - ↓ Triglyceride-rich lipoproteins

- **HORIZON TRIAL - MHIF**
  - ↓ Lipoprotein(a)

- **Evinacumab** (Regeneron)
  - ↓ Triglyceride-rich lipoproteins
  - ↓ LDL cholesterol

Reduces LDL 50% on top of max statin AND PCSK9i

Bempedoic Acid: Esperion Pharmaceuticals
Bemedoic acid 180 mg+/--exetibibe 10 mg

![Diagram of cholesterol biosynthesis pathway involving ETC-1002 and statins.](image-url)
<table>
<thead>
<tr>
<th>CLEAR Harmony</th>
<th>CLEAR Wisdom</th>
<th>CLEAR Serenity</th>
<th>CLEAR Tranquility</th>
<th>Bempedoic Acid/Ezetimibe Combination Tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1002-040)</td>
<td>(1002-047)</td>
<td>(1002-046)</td>
<td>(1002-048)</td>
<td>(1002FDC-053)</td>
</tr>
<tr>
<td>(N=2,230)</td>
<td>(N=779)</td>
<td>(N=345)</td>
<td>(N=269)</td>
<td>(N=382)</td>
</tr>
<tr>
<td>(placebo: n=742)</td>
<td>(placebo: n=257)</td>
<td>(placebo: n=111)</td>
<td>(placebo: n=88)</td>
<td>(EZE: n=109)</td>
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<tr>
<td><strong>LDL-C Reduction</strong></td>
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<tr>
<td></td>
<td><strong>-18.1% (P&lt;0.001)</strong></td>
<td><strong>-17.4% (P&lt;0.001)</strong></td>
<td><strong>-21.4% (P&lt;0.001)</strong></td>
<td><strong>-28.5% (P&lt;0.001)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>BA: -16.5%</strong></td>
<td><strong>BA: -15.1%</strong></td>
<td><strong>BA: -22.6%</strong></td>
<td><strong>BA: -23.5%</strong></td>
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<tr>
<td></td>
<td><strong>Placebo: +1.6%</strong></td>
<td><strong>Placebo: +2.4%</strong></td>
<td><strong>Placebo: -1.2%</strong></td>
<td><strong>Placebo: +5.0%</strong></td>
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<tr>
<td></td>
<td><strong>-29.0% (P&lt;0.001)</strong></td>
<td></td>
<td></td>
<td><strong>BA/EZE: -31.5%</strong></td>
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<td><strong>BA: -17.7%</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Ezetimibe: -21.0%</strong></td>
</tr>
</tbody>
</table>
• Long term nature of new therapies
• Improved adherence
• Simple dosing with lasting effects
• Can target various protein modulators
Apo(a) antisense technology

RCT, double-blind, placebo-controlled, phase 1, UK

**Study Type**: Interventional (Clinical Trial)

**Estimated Enrollment**: 7,680 participants

**Allocation**: Randomized

**Intervention Model**: Parallel Assignment

**Masking**: Double (Participant, Investigator)

**Primary Purpose**: Treatment

**Official Title**: A Randomized Double-blind, Placebo-controlled, Multicenter Trial Assessing the Impact of Lipoprotein (a) Lowering With TQJ230 on Major Cardiovascular Events in Patients With Established Cardiovascular Disease

**Actual Study Start Date**: December 12, 2019

**Estimated Primary Completion Date**: March 1, 2024

**Estimated Study Completion Date**: March 1, 2024

**TQJ230**: 80 mg injected monthly administered subcutaneously

**Key Inclusion Criteria**

- Lp(a) ≥ 70 mg/dL at the screening visit, measured at the Central laboratory
- Myocardial infarction: ≥ 3 months from screening and randomization to ≤ 10 years prior to the screening visit
- Ischemic stroke: ≥ 3 months from screening and randomization to ≤ 10 years prior to the screening visit
- Clinically significant symptomatic peripheral arterial disease

**AKCEA-APO(a)-LRx, from Akcea Therapeutics, an affiliate of Ionis Pharmaceuticals, for targeted cardiovascular therapy**
GalNAc-siRNA Conjugate Facilitates Hepatic Uptake

Asialoglycoprotein receptor (ASGPR)
- Highly expressed in hepatocytes only
- High rate of uptake

Inclisiran*
- siRNA conjugated to N-acetylglactosamine (GalNAc)
- Subcutaneous administration
- Targeted delivery to hepatocytes

*Inclisiran is pending FDA and EMA approval for adults with atherosclerotic cardiovascular disease or heterozygous familial hypercholesterolemia who have elevated LDL-C while on statin therapy (as of October 6, 2020)
There is a Linear Correlation Between LDL-C Lowering and Risk of CV Events

*Secondary prevention trials.
2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway: Nonstatin Therapies for ASCVD

≥ 21 years old, clinical ASCVD + comorbidities, on statin

≥ 50% LDL-C reduction (or LDL-C < 70, non-HDL-C < 100 mg/dL) on MTD statin

NO

YES

≥ 50% LDL-C reduction (or LDL-C < 70, non-HDL-C < 100 mg/dL) on MTD statin

NO

Address factors related to adherence, lifestyle, and statin tolerance

YES

Clinicin-patient discussion on treatment factors, and patient preferences

Decision for no additional medication

Optional non-statin therapy

Consider ezetimibe or PCSK9 inhibitor; add other second agent if needed

When to Choose Ezetimibe?

- Patients requiring < 25% additional LDL-C lowering
- Recent ACS < 3 months
- Cost considerations
- Preference of oral agent
- Patient preference
- Other risk factors

When to Choose PCSK9 Inhibitor?

- Patients requiring > 25% additional LDL-C lowering
- Cost-benefit considerations should be discussed
- Administration, dosing schedule, and storage should be discussed

≥ 50% LDL-C reduction on treatment

NO

YES

Continue to monitor adherence and LDL-C response to therapy

Residual Cardiovascular Risk in Placebo-Controlled Statin Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Placebo</th>
<th>Statin</th>
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<tbody>
<tr>
<td>4S</td>
<td>28.0</td>
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<tr>
<td>LIPID</td>
<td>15.9</td>
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<tr>
<td>CARE</td>
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<td>10.2</td>
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<tr>
<td>HPS</td>
<td>11.8</td>
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<td>WOSCOPS</td>
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<tr>
<td>AFCAPS/TexCAPS</td>
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</table>

<table>
<thead>
<tr>
<th>N</th>
<th>Δ LDL</th>
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</thead>
<tbody>
<tr>
<td>4S</td>
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