Residual cardiovascular risk: What is the best approach?

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Disclosure Statement
Dr. Firnhaber has nothing to disclose

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ESC/EAS guidelines

- All current guidelines on the prevention of CVD in clinical practice recommend the assessment of total CAD or CV risk because, in most people, atherosclerotic CVD is the product of a number of risk factors.

ESC/EAS guidelines

- Many risk assessment systems are available and have been comprehensively reviewed, including Framingham, SCORE (Systemic Coronary Risk Evaluation), ASSIGN (CV risk estimation model from the Scottish Intercollegiate Guidelines Network), Q- Risk, PROCAM (Prospective Cardiovascular Munster study), and the WHO (World Health Organization).

- Most guidelines use risk estimation systems based on either the Framingham or the SCORE projects.

Statin therapy offers predictable cardiovascular risk reduction

- The evidence report accompanying the 2016 USPSTF guidelines on Statins for Prevention of Cardiovascular Disease demonstrated that use of low-or moderate-dose statin therapy is associated with:
  - an approximate 30% relative risk reduction in cardiovascular events and in cardiovascular deaths
  - 10% to 15% relative risk reduction in all-cause mortality

Statin therapy offers predictable cardiovascular risk reduction

- While the 2016 USPSTF guidelines addressed the use of statins for primary prevention of CVD,

the same relative risk reduction is seen with statin use in those with existing cardiovascular disease.

- Thus, those with greater baseline CVD risk will have greater absolute risk reduction than those at low baseline risk.

Residual risk

- Again, low-or moderate-dose statin therapy provides an approximate 30% relative risk reduction in cardiovascular events and in cardiovascular deaths. The “leftover” is termed residual risk.

Statin therapy is an *imperfect tool* for the reduction of cardiovascular risk.

Residual risk

Statin therapy is an *imperfect tool* for the reduction of cardiovascular risk.

- What should the clinician do to address residual risk?
- Which is the most cost-effective approach?
- Which approach is the most appropriate for a population?

Disappointing statin statistics

Despite nearly overwhelming evidence that statins effectively lower LDL cholesterol and predictably reduce cardiovascular events,

fewer than half of patients with clinical coronary heart disease (CHD) receive high-intensity statin therapy

leaving this population at increased risk for future events.

Non-statin lipid-lowering therapy: Niacin

Niacin in Patients with Low HDL Cholesterol Levels Receiving Intensive Statin Therapy – AIM-HIGH

- Evaluated the incremental benefit of extended-release niacin (1500-2000 mg/d) on patients already receiving simvastatin 40-80 mg/d (+/- ezetimibe 10 mg/d) to achieve LDL cholesterol 40-80 mg/dL

- Primary end point: the first event of the composite of death from coronary heart disease, nonfatal MI, ischemic stroke, hospitalization for ACS, or symptom-driven coronary or cerebral revascularization.

N Engl J Med. 2011;365:2255-67.

Niacin in Patients with Low HDL Cholesterol Levels Receiving Intensive Statin Therapy – AIM-HIGH

- After 2 years of niacin therapy:
  - HDL increased from 35 to 42 mg/dL
  - Triglycerides decreased from 164 to 122 mg/dL
  - LDL decreased from 74 to 62 mg/dL

- *The trial was stopped after a mean follow-up period of 3 years owing to a lack of efficacy.*

Niacin in Patients with Low HDL Cholesterol Levels Receiving Intensive Statin Therapy – AIM-HIGH

- The primary end point occurred in:
  - 282 patients in the niacin group (16.4%)
  - 274 patients in the placebo group (16.2%) (HR, 1.02; 95% CI, 0.87 to 1.21; P=0.79)

Niacin in Patients with Low HDL Cholesterol Levels Receiving Intensive Statin Therapy – AIM-HIGH

Conclusion:

Among patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of less than 70 mg/dL, *there was no incremental clinical benefit from the addition of niacin to statin therapy* during a 36-month follow-up period, despite significant improvements in HDL cholesterol and triglyceride levels.

HPS2-THRIVE

- 25,673 adults age 50-80 years with vascular disease, treated at baseline with simvastatin 40mg; if total cholesterol remained > 135 mg/dL after 4 weeks, ezetimibe 10mg was added.

- Randomized to ER niacin 1g plus 20mg laropiprant 20mg daily; titrated to 2g/40mg after 4 weeks

N Engl J Med. 2014;371:203-12.

HPS2-THRIVE

- During median follow-up of 3.9 years, niacin/laropoprant group, compared to placebo, had:
  - LDL 10mg/dL lower
  - HDL 6 mg/dL higher
- However, there was *no significant difference in major vascular events*, and:
  - Absolute increase in disturbances in diabetes control 3.7%
  - Absolute increase in diabetes diagnosis of 1.3%

Non-statin lipid-lowering therapy: Omega-3 fatty acids

Omega-3 fatty acids and sudden death

- Omega-3 fatty acids contribute to production of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA):
  - Inhibit inflammatory immune response
  - Inhibit platelet aggregation
  - Mild vasodilators
  - Possible antiarrhythmic properties

Omega-3 fatty acids and sudden death

- (Prior) AHA guidelines suggested omega-3 supplements for patients with:
  - Preexisting disease
  - High risk of disease
  - High triglycerides
- GISSI-P (1997) found 850mg of EPA and DHA daily decreased:
  - Mortality
  - Nonfatal MI
  - Stroke
  - Rate of sudden death

Omega-3 fatty acids in primary and secondary prevention

- RCTs subsequent to GISSI-P, particularly those in the “treatment guideline era”, have (largely) failed to replicate that study’s findings
- Multiple meta-analyses published over the past several years have concluded that the addition of omega-3 fatty acid supplements to the current standard of cardiovascular care (statin, ACEI/ARB, beta-blocker, antiplatelet agent) offers no statistically significant benefit

Non-statin lipid-lowering therapy: Fibrates

ACCORD Lipid

- 5518 of the 10,251 high-risk type 2 diabetics randomized to simvastatin + fenofibrate or simvastatin + placebo

- At mean follow-up of 4.7 years, *no difference* was seen in major CV events (HR 0.92 for fenofibrate; 95% CI 0.79-1.08, p=0.32)

N Engl J Med. 2010;362:1563-1574

ACCORD Lipid

- Mean triglyceride at start = 162 mg/dL
- In subgroup with dyslipidemia (mean triglycerides 204, HDL 29.5 mg/dL) rate of primary outcome was 12.4% with fenofibrate vs. 17.3% with placebo – still nonsignificant

ACCORDION

- An additional 5 years of observation-only follow-up were completed for 4644 surviving ACCORD-Lipid trial participants.
- Only 4.3% of study participants continued treatment with fenofibrate following completion of ACCORD.
- ACCORDION looked for a “legacy effect” of fenofibrate treatment during ACCORD.

JAMA Cardiol. doi:10.1001/jamacardio.2016.4828 Published online December 28, 2016.

ACCORDION

- During the combined trial plus post-trial period, the primary outcome in study participants with dyslipidemia who were randomized to fenofibrate was 27% lower than those randomized to placebo,
- but only 1% lower in nondyslipidemic study participants.
- (HR, 0.73 [95% CI, 0.56-0.95; P = 0.25] vs HR, 0.99 [95% CI, 0.86-1.13; P = .05] for dyslipidemic vs non-dyslipidemic, respectively)

ACCORDION

- An additional 5 years of follow-up of surviving ACCORD-Lipid study cohort members:
  - extended the original overall neutral outcome of ACCORD,
  - provided additional support for possible benefit of fenofibrate therapy in patients with type 2 diabetes in whom triglycerides remain elevated and HDL-C levels remain low despite statin therapy.

Non-statin lipid-lowering therapy: Ezetimibe

IMPROVE-IT

- Background: ENHANCE published in 2008, showed no reduction in CIMT in patients with familial hypercholesterolemia when ezetimibe was added to statin therapy.

- *9 years* after study launch, IMPROVE-IT data presented at AHA 2014 Scientific Sessions (during the late-breaking clinical trials session).

N Engl J Med. 2015;372: 2387-2397.

IMPROVE-IT

- >18,000 patients from 39 countries who were stable following ACS (≤10 days)
- Simvastatin 40mg vs. simvastatin 40mg + ezetimibe 10mg
- Primary endpoint: composite of CV death, MI, unstable angina requiring rehospitalization, coronary revascularization, or stroke
- Over 7 years, RRR 6.4%; ARR 2.0%; NNT 50

At $225 per month of treatment = $945K per event saved

HIJ-PROPER

- Trial Design: n= 1734; open-label, blinded, multi-center Japanese study; 3 year f/u; randomized to:
  - intensive LDL-C lowering (LDL-C target <70 mg/dL; pitavastatin + ezetimibe) or
  - standard LDL-C lowering (LDL-C target 90–100 mg/dL; pitavastatin alone).
- Primary Endpoint: Adverse event composite (total all-cause death, non-fatal MI and stroke, unstable angina, revascularization)
- Results: % reduction in adverse events:
  - Pitavastatin + ezetimibe: 32.8%
  - Pitavastatin alone: 36.9%

Presented at the European Society of Cardiology Congress, Rome, Italy. August 2016.

Non-statin lipid-lowering therapy: PCSK9 inhibitors

PCSK9 inhibitors

- Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a natural protein that binds and destroys LDL receptors in the liver, preventing them from removing LDL-C.

- Injectable monoclonal antibodies bind to PCSK9 allowing the receptors to continue clearing LDL-C.
  - Evolocumab (Repatha)
  - Alirocumab (Praluent)

PCSK9 inhibitors: cautions

- Little is known about non-LDL lowering effects of PCSK9 inhibitors.
- No guarantee that the benefit of LDL-C lowering with PCSK9 inhibitors will be linear, as seen with statin therapy.
- Multiple other non-statin therapies have failed to demonstrate benefit when added to a statin.
- Expensive ($14,000 per year)

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

- 27,564 patients with ASCVD and LDL cholesterol ≥70 mg/dL or higher who were receiving statin therapy
- Randomly assigned to evolocumab (140 mg q2 weeks or 420 mg monthly) or matching placebo as subcutaneous injections
- Primary efficacy end point: composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization
- Median duration of follow-up: 2.2 years.
- Industry-funded; FOURIER study.

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

- At 48 weeks, mean reduction in LDL with evolocumab, as compared with placebo, was 59%, from a median baseline value of 92 mg/dL
- Evolocumab reduced the risk of the primary end point:

(9.8% vs. 11.3%; HR, 0.85; 95% CI, 0.79 to 0.92; P<0.001)

Evolocumab had no observed effect on cardiovascular mortality.

Note: absolute risk reduction of 1.5% = NNT 67; at $14,000 per year x 2.2 years, this translates to $2.06M per event prevented.

New Engl J Medicine. 2017;376:1713–1722.

Impact of treating to current guidelines

- In 2012, approximately 66.3 million US patients – 20.3% of the US population – were taking lipid-lowering therapy.
- If the 2013 ACC/AHA Cholesterol Treatment Guidelines were fully implemented, an estimated additional 24.3% of the US population would be treated with statins.
- Full implementation of the more-conservative USPSTF guidelines would result in an incremental 15.8% of the US population initiating statin therapy, in addition to the 20.3% 2012 use estimate.

One cost-effectiveness analysis estimated that initiating statins in these high-risk populations not currently using statins would

save $12 billion over five years.

Statin therapy: risks in perspective

- Treatment of 10,000 patients for five years would *cause*:
  - 1 case of rhabdomyolysis
  - 5 cases of myopathy
  - 7 hemorrhagic strokes
  - 75 new cases of diabetes
- The same treatment would *avert*:
  - approximately 1000 CVD events among those *with preexisting disease*
  - approximately 500 CVD events among those *with elevated risk but without preexisting disease*

2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

J Am Coll Cardiol. 2016;68(1):92–125.

2016 ACC Expert Consensus Decision Pathway

Factors to consider:

- Percentage LDL-C reduction achieved with evidence-based statin therapy (if <50% and not on maximally tolerated statin, should increase statin first and reinforce lifestyle modifications).
- For patients with ASCVD, patient's baseline ASCVD risk on evidence-based statin therapy (with or without comorbidities).
- For patients without ASCVD or baseline LDL-C ≥190 mg/dL, patient's baseline predicted 10-year ASCVD risk pre-statin and presence of high-risk markers.

2016 ACC Expert Consensus Decision Pathway

Factors to consider:

- For patients without ASCVD or baseline LDL-C ≥190 mg/dL, patient's baseline predicted 10-year ASCVD risk pre-statin and presence of high-risk markers.
- Available scientific evidence of ASCVD risk reduction (and magnitude of benefit) when non-statin therapy is added to evidence-based statin therapy.
- Additional desired % LDL-C lowering beyond that achieved on evidence-based statin therapy.
- Mean percentage LDL-C lowering expected with proposed non-statin therapy when added to evidence-based statin therapy.

2016 ACC Expert Consensus Decision Pathway

Factors to consider:

- Cost of proposed additional therapy.
- Potential for side effects with proposed additional therapy.

After consideration of factors, verification of adherence to statin therapy, and estimation of residual risk:

- Consider ezetimibe.
- (Consider bile acid sequestrant).
- Consider PCSK9 inhibitor.

Non-statin lipid lowering therapy

1. Niacin: no incremental benefit when added to statin.
2. Omega-3 fatty acids: better than nothing but no incremental benefit when added to statin.
3. Fibrates: no incremental benefit when added to statin, except (perhaps) in the most dyslipidemic patients.
4. Ezetimibe: (very) modest benefit in high-risk patients.
5. PCSK9 inhibitors: robust LDL lowering; limited early data demonstrating incremental benefit.

Residual risk: summary

- Residual risk is real and is important.
- Currently, no therapy adds robust incremental improvement in cardiovascular risk above the improvement offered by statin therapy.

The most cost-effective approach to decreasing the risk of atherosclerotic cardiovascular outcomes appears to be maximizing statin therapy for patients in whom treatment is indicated but not yet prescribed.

Additional references

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