DEBATE: Lowering LDL-C Levels With Statins And PCSK9 inhibitors in Vascular And At Risk Patients Prevents Cardiovascular Events And Deaths, Is Reasonably SAFE and Helps Patients To Have Longer and Better Life

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Disclosure Statement of Financial Interest
Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

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PCSK9 Inhibitors: Monoclonal AB that bind PCSK9, increase number of free LDL receptors so lower LDL

For illustration purposes only

Trial Design
27,564 high-risk, stable patients with established CV disease (prior MI, prior stroke, or symptomatic PAD)

Screening, Lipid Stabilization, and Placebo Run-in
High or moderate intensity statin therapy (+ ezetimibe)

LDL-C ≥70 mg/dL (1.8 mmol/L) or non-HDL-C ≥100 mg/dL (2.6 mmol/L)

Follow-up Q 12 weeks
Median f/up 2.2 yrs

Evolocumab SC
140 mg Q2W or 420 mg QM

Placebo SC
Q2W or QM

LDL-C ≥70 mg/dL (1.8 mmol/L) or non-HDL-C ≥100 mg/dL (2.6 mmol/L)

RANDOMIZED DOUBLE BLIND

Sabatine MS et al.
Am Heart J
2016;173:94-101

Evolocumab (median 30 mg/dl, IQR 19-46 mg/dl)

Placebo

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

Summary of Effects of PCSK9i Evolocumab
• ↓ LDL-C by 59% to a median of 30 mg/dl.
• ↓ CV outcomes in patients on statin
• Safe and well-tolerated

HR 0.65 (0.79-0.92)
P<0.0001

HR 0.80 (0.73-0.88)
P<0.0001
Summary for Evolocumab

• ↓LDL-C by 59%
  - Consistent throughout duration of trial
  - Median achieved LDL-C of 30 mg/dl (IQR 19-46 mg/dl)

• ↓CV outcomes in patients already on statin therapy
  - 15% ↓ broad primary endpoint, 20% ↓ CV death, MI, or stroke
  - Consistent benefit, incl. in those on high-intensity statin, low LDL-C
  - 25% reduction in CV death, MI, or stroke after 1st year
  - Long-term benefits consistent w/ statins per mmol/L ↓ LDL-C

• Safe and well-tolerated
  - Similar rates of AEs, incl DM & neurocog events w/ EvoMab & pbo
  - Rates of EvoMab discontinuation low and no greater than pbo
  - No neutralizing antibodies developed

Primary Endpoint

Hazard ratio 0.85
(95% CI, 0.79-0.92)
P<0.0001

Key Secondary Endpoint

Hazard ratio 0.80
(95% CI, 0.73-0.88)
P=0.00001

Landmark Analysis

16% RRR
HR 0.84 (95% CI 0.74-0.96)
P=0.003

25% RRR
HR 0.75 (95% CI 0.66-0.85)
P<0.00001

Fatal or Nonfatal MI or Stroke

19% RRR
HR 0.81 (95% CI 0.70-0.93)
P=0.003

33% RRR
HR 0.67 (95% CI 0.59-0.77)
P=0.00001

Glacov Study
What about Carotid Arteries?

ABSTRACT
European Society Cardiology Congress
August 26-30, 2017 Barcelona, Spain

Rapid Carotid Plaques Reversal of PCSK9 Inhibitors When Added to Statins and Eicosapentaenoic acid (EPA) in High Risk Cardiovascular Patients

- Average LDL-C was 75, TG 102 in the Control group, and LDL-C 22, TG 92 in the Trio Combo group (EPA, atorvastatin)
- 3 months after therapy. 20% to 65% plaque reversal occurred after 6 months of evolocumab therapy in 37 patients (65%), P = 0.0006, -28% (progression) to 0% reversals in 10 patients
- The added cost of evolocumab as part of Trio Combo therapy in high risk patients could more than offset the lesser occurrence of CVE and its associated economic cost to healthcare.
LDL-C Lower is Better
A Quarter of a Century of Treating LDL-C

Summary and Conclusions
- LDL-C can now be reduced to unprecedented low levels with statin + PCSK9i (<< 1 mM)
- LDL-C reduction associated with coronary and carotid plaque regression.
- A strong progressive relationship of achieved LDL-C and CV events seen, down to LDL <0.26 mM (<10 mg/dL)
- No excess in safety events with very low achieved LDLC <0.5 mM (<20 mg/dL) at 2.2 years
- Benefits extend to PAD with an ARR for MACE or MALE of 6.3% (NNT 16) at 2.5 years

These data suggest that we should target considerably lower LDL-C than is currently recommended for our patients with atherosclerotic CV disease