Cholesterol Treatment Targets and Clinical Outcomes
A JUPITER Trial Update

Percent Reduction in LDL Cholesterol Following
High Intensity Statin Therapy:
Potential Implications for Guidelines
and for the Prescription of PCSK9 Inhibitors

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**LDL Cholesterol Treatment Targets Following Statin Therapy**

### ESC - 2012
- **Low Risk**
  - LDL < 3 mmol/L (115 mg/dL)
- **High Risk**
  - LDL < 2.5 mmol/L (100 mg/dL)
- **Very High Risk**
  - LDL < 1.8 mmol/L (70 mg/dL) or a >50% LDL reduction when the target level cannot be reached

### CCS - 2012
- **Low Risk**
  - > 50% reduction in LDLC
- **Int/High Risk**
  - LDL < 2.0 mmol/L (80 mg/dL) or a >50% LDL reduction when the target level cannot be reached

### ACC/AHA 2013
- **Lower Risk**
  - Moderate-Intensity Statin (30-50% LDL reduction)
- **Higher Risk**
  - High-Intensity Statin (≥ 50% LDL reduction)
How variable is the percent reduction in LDLC on high-intensity statin therapy?

Might greater awareness of this variation be useful for clinical care and have potential relevance as PCSK9 inhibitors are emerging as a major new class of lipid lowering drugs?
Percent Reduction in LDLC Following Hi-Intensity Statins: Methods

We sought to address the variability in percent reduction in LDLC in the contemporary multinational, randomized, double-blind, placebo-controlled JUPITER trial inclusive of 17,802 initially healthy men and women who were allocated to rosuvastatin 20 mg daily and followed for up to 5 years.

(a) waterfall plots to assess the inter-individual variability in LDLC;

(b) evaluate the impact of reaching the ACC/AHA target of a >50 percent reduction in LDLC on rates of first ever cardiovascular events (myocardial infarction, stroke, hospitalization for unstable angina requiring coronary intervention, or cardiovascular death);
On an a priori basis, multivariable adjusted hazard ratios and 95% confidence intervals were computed after adjusting for those variables found on regression analysis to have a significant impact on on-treatment LDLC levels (baseline lipid level, gender, smoking status, age, HTN, BMI, family history of CAD).

All analyses were repeated separately for non-HDLC and apolipoprotein B.

Sensitivity analyses: tertiles of percent lipid reduction rather than the ACC/AHA specified > 50 % threshold.
JUPITER
Multi-National Randomized Double Blind Placebo Controlled Trial of Rosuvastatin in the Prevention of Cardiovascular Events Among Individuals With Low LDL and Elevated hsCRP

No Prior CVD or DM
Men >50, Women >60
LDL <130 mg/dL
hsCRP >2 mg/L

4-week run-in

Rosuvastatin 20 mg (N=8901)

Placebo (N=8901)

MI
Stroke
Unstable Angina
CVD Death
CABG/PTCA

Argentina, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Costa Rica, Denmark, El Salvador, Estonia, Germany, Israel, Mexico, Netherlands, Norway, Panama, Poland, Romania, Russia, South Africa, Switzerland, United Kingdom, Uruguay, United States, Venezuela

Mean LDLC 104 mg/dL, Mean HDLC 50 mg/dL, hsCRP 4 mg/L

NEJM 2008;359:2195-2207
JUPITER
Primary Trial Endpoint: MI, Stroke, UA/Revascularization, CV Death

HR 0.56, 95% CI 0.46-0.69
P < 0.00001

Number Needed to Treat (NNT<sub>5</sub>) = 25

Placebo 251 / 8901
Rosuvastatin 142 / 8901

- 44%
Percent Change in LDL C

Event Rate / 1000 person years

Individual Observations (N = 7,856)

Placebo

No Reduction

< 50% Reduction

≥ 50% Reduction

LDL Cholesterol
(median reduction 50%)
The graph represents the percent change in LDL cholesterol with median reduction of 50%. The data includes individual observations with a total of 7,856 participants. The y-axis shows the percent change in LDL cholesterol, and the x-axis represents individual observations. The graph is categorized into four groups based on the reduction in LDL cholesterol:

- **Placebo**: No Reduction
- **No Reduction**
- **< 50% Reduction**
- **≥ 50% Reduction**

Event rates per 1,000 person years are shown for each category:

- Placebo: 1.0
- No Reduction: 9.2
- < 50% Reduction: 0.61
- ≥ 50% Reduction: 0.41

The P-trend is less than 0.00001, indicating a statistically significant difference in event rates across the reduction categories.
Percent Change in Non-HDL Cholesterol (median reduction 44%)
Apo B Cholesterol (median reduction 40%)

Individual Observations (N = 7,827)

Percent Change in Apo B Cholesterol

Event Rate / 1000 person years

- Placebo
- No Reduction
- < 50% Reduction
- ≥ 50% Reduction

P-trend < 0.00001
Percent Reduction in LDL Response to High-Intensity Statin Therapy: Potential Implications for PCSK9 Prescription

Percent Change in LDL (High Intensity Statin)

- No reduction in LDL (N = 2,734 (34.8%))
- < 40% reduction in LDL (N = 3,549 (45.2%))
- 40-60% reduction in LDL (N = 1,573 (20.0%))
- > 60% reduction in LDL

Individual Observations (N = 7,856)
In a contemporary placebo-controlled trial of high-intensity statin therapy, we found exceptionally wide variability in percent reduction of LDLC, non-HDLC, and apo B, yet that the magnitude of percent cholesterol reduction directly related to the magnitude of risk reduction observed.

These effects were robust to multivariable adjustment for characteristics associated with greater lipid response to statin therapy, and were minimally impacted when tertile reductions in on-treatment lipid levels were used instead of the pre-specified $\geq 50$ percent threshold.
Confirm Meta-Analyses Inclusive of Several Lower Intensity Statin Regimens

Boekholdt et al; JACC 2014;64:485-94.
These data provide general support for the concepts of introducing percent reduction in LDLC into broader clinical practice, an approach consistent with that being advocated by current European, Canadian, and U.S. guidelines.

Further consideration of percent LDLC reduction while on statin therapy might also provide a method to thoughtfully allocate PCSK9 inhibitors should these agents prove effective for cardiovascular event reduction. This process will be assisted if ongoing trials of PCSK9 inhibitors report results stratified by the percent reduction in LDLC achieved by background statin therapy.