ARE LDL-C LEVELS AND STATIN-INDUCED DECREASES IN LDL-C LEVELS IMPORTANT DESPITE AHA GUIDELINES: HOW TO TREAT PATIENTS NEEDING LIPID LOWERING WHO APPEAR STATIN INTOLERANT

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WHO NEEDS STATINS?

NEW CHOLESTEROL GUIDELINES
BASED ON HIGH QUALITY EVIDENCE FROM RCTS

Pros

- Limit recommendations to high quality randomized controlled trials
- Utilize Rx that lower CV events
- Simplify
- Minimize LDL measurement
- Eliminate unnecessary CK, LFTs

Cons

- "Lesser" evidence not considered
- Observational, Preclinical, and Angiographic studies
- No LDL-C Targets
- Limited generalizability for understudied (~40, >75 yrs) and subgroups (women, minorities)

Controversy......
WHAT IS THE DATA?

Secondary Prevention:
Heart Protection Study (HPS)

- 20,536 UK adults with coronary disease, other occlusive arterial disease, or diabetes were randomly allocated to receive 40 mg simvastatin daily or matching placebo.
- Conclusions:
  - Adding simvastatin produces substantial additional benefits for a wide range of high-risk patients, irrespective of their initial cholesterol concentrations.
  - Allocation to 40 mg simvastatin daily reduced the rates of myocardial infarction, of stroke, and of revascularization by about one-quarter.

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Primary Prevention with Statins:

Justification for the Use of Statins in Prevention (JUPITER)

- Randomly assigned 17,802 apparently healthy men and women with LDL cholesterol levels of less than 130 mg/dL and high-sensitivity C-reactive protein levels of 2.0 mg per liter or higher to rosuvastatin, 20 mg daily, or placebo.
- Followed for the occurrence of the combined primary end point of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes.
- Conclusions: In this trial of apparently healthy persons without hyperlipidemia but with elevated high-sensitivity C-reactive protein levels, rosuvastatin significantly reduced the incidence of major cardiovascular events.

Ridker PM et al. NEJM 2008;359:2195-2207

Primary Prevention with Statins:

LIPID VARIABILITY IN LDL-C AND NON-HDL-C REDUCTION - A SUB-STUDY FROM THE JUPITER TRIAL

17,802 men (≥50 yrs) and women (≥60) with LDL-C <130 mg/dL and hs-CRP ≥2 mg/L randomized to rosuvastatin (20 mg) or placebo

Ridker PM et al. NEJM 2008;359:2195-2207

Rosuvastatin
Placbo

Statin benefits those with mean age of 66 and elevated hsCRP

Ridker, et al Eur Heart J 2016
Conclusions: In sum, the current data confirm wide variation in the % reduction in cholesterol during high-intensity statin therapy as well as a direct relationship between the magnitude of this per cent reduction and the clinical benefit achieved.

These data provide general support for the concepts of introducing % reduction in LDL-C into broader clinical practice, along with fixed LDL-C targets.

Further consideration of % LDL-C reduction as well as absolute LDL-C reduction while on statin therapy might further provide a partial method to allocate PCSK9 inhibitors should these agents prove effective for cardiovascular event reduction.

Waterfall Plots Showing Variability in LDL-C Response to Simvastatin and Atorvastatin

These results indicate that there is considerable individual variation in the LDL-C reduction at all doses of simvastatin, atorvastatin, and rosuvastatin.

Theoretical Implications for the Allocation of PCSK9 inhibitors

Despite variability in response, levels do matter!

As documented for low- and moderate-intensity regimens, variability in % LDL-C reduction following high-intensity statin therapy is wide yet the magnitude of this % reduction directly relates to efficacy.

These data support guideline approaches that incorporate % reduction targets for statin therapy as well as absolute targets.
Incident Cardiovascular Events according to Achieved Concentrations of LDL-C

Data are adjusted for age, sex, baseline LDL-C and HDL-C, hs CRP, BP, BMI, smoking status and FH of CVD.

Ridker, et al Eur Heart J 2016

META-ANALYSIS

Key Points
- Question: What is the association between lowering low-density lipoprotein cholesterol (LDL-C) and cardiovascular risk reduction across different therapeutic interventions?
- Findings: In a meta-regression analysis of 49 clinical trials with 312,175 participants, each 1-mmol/L (38.7-mg/dL) reduction in LDL-C level was associated with a relative risk (RR) of major vascular events of 0.77 (95% CI, 0.71-0.84; \( P < .001 \)) for statins and 0.75 (95% CI, 0.66-0.86; \( P = .002 \)) for established nonstatin interventions that act primarily via upregulation of LDL receptor expression.
- Meaning: These data suggest statins and nonstatin therapies that act through upregulation of LDL receptor expression are associated with similar cardiovascular risk reduction per decrease in LDL-C.


ASSOCIATION BETWEEN LOWERING LDL-C WITH STATINS AND CARDIOVASCULAR RISK REDUCTION


WEIGHTED BETWEEN-GROUP DIFFERENCE IN ACHIEVED LDL-C LEVEL AND RELATIVE RISK FOR MAJOR VASCULAR EVENTS


IS STATIN INTOLERANCE REAL? GAUSS 3 STUDY

511 patients enrolled at 53 centers with a history of intolerance to multiple statins due to muscle-related adverse effects.

Atorvastatin 20 mg Placebo Placebo Atorvastatin 20 mg

Phase A
10 weeks
Intolerable Muscle Symptoms
On atorvastatin, but not placebo 209 (42.6%)
On placebo, but not atorvastatin 130 (26.5%)
On both placebo and atorvastatin 48 (9.8%)
No symptoms on either treatment 85 (17.3%)

Nissen SE et al. JAMA 2016

IS STATIN INTOLERANCE REAL? GAUSS 3

CONCLUSIONS AND RELEVANCE:
- Among patients with statin intolerance related to muscle-related adverse effects, the use of evolocumab compared with ezetimibe resulted in a significantly greater reduction in LDL-C levels after 24 weeks.
THERAPEUTIC OPTIONS FOR MANAGEMENT OF STATIN “INTOLERANT” PATIENT

- Dietary and health behaviour measures
- Statin based strategies
  - Alternative statin
  - Alternative dosing
- Non-statin alternatives and adjuncts
  - PCSK9 Inhibitors
  - Ezetimibe
  - Bile acid sequestrants
  - Fibrates
  - Niacin

CONCLUSIONS

- Statins reduce cardiovascular events
- There is significant LDL-C variability in response to different Statin Therapies
- The magnitude of LDL-C (and non-HDL-C) variability directly relates to efficacy
- Statin Intolerance is difficult to define and likely is overestimated
- Lipid lowering (even without statins) reduces cardiovascular events
- These data suggest incorporating % reduction targets for lipid lowering therapy

THANK YOU