CLINICAL RESEARCH STUDY

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2013 Cholesterol Guidelines Revisited: Percent LDL Cholesterol Reduction or Attained LDL Cholesterol Level or Both for Prognosis?

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ABSTRACT

BACKGROUND: The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guideline on the treatment of blood cholesterol recommends moderate- to high-intensity statins for patients with atherosclerotic cardiovascular disease but departs from the traditional treat-to-target approach. Whether percent low-density lipoprotein cholesterol (LDL-C) reduction or attained LDL-C levels add incremental prognostic value to statin dose is not known.

METHODS: Patients in the Treating to New Targets (TNT), Incremental Decrease in Endpoints through Aggressive Lipid Lowering (IDEAL), and Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trials (patient-level data) randomized to a statin arm (atorvastatin 80 mg/10 mg or simvastatin 20 mg) were chosen. Patients were divided into groups based on attained LDL-C levels ($\leq$70 vs >70 mg/dL) and percent LDL-C reduction ($\geq$50% vs <50%). Primary outcome was major cardiovascular event defined as death due to coronary heart disease, nonfatal myocardial infarction, resuscitated cardiac arrest, or stroke. Incremental prognostic value was assessed by using a forward conditional Cox proportional hazards model. Two models were tested: Model 1: Step 1 statin dose; Step 2 add attained LDL-C levels (continuous variable); Step 3 add percent LDL-C reduction (continuous variable). Model 2: Steps 2 and 3 were reversed.

RESULTS: Among 13,937 patients included in this study, percent LDL-C reduction added incremental prognostic value over both statin dose and attained LDL-C levels (global chi-square increased from 3.64 to 26.1 to 47.5; P <.0001). However, attained LDL-C level did not provide incremental prognostic value over statin dose and percent LDL-C reduction (global chi-square increased from 3.64 to 47.5 to 47.5; P <.0001 and .94, respectively). Among patients with attained LDL-C $\leq$70 mg/dL, those with percent LDL-C reduction of <50% had a significantly higher risk of primary outcome (hazard ratio [HR], 1.51; 95% confidence interval [CI], 1.16-1.97; P = .002) and stroke (HR, 2.07; 95% CI, 1.46-2.93; P <.0001) and a numerically higher risk of death (HR, 1.37; 95% CI, 0.98-1.90; P = .06) when compared with the group with percent LDL-C reduction of $\geq$50%.

CONCLUSIONS: In patients with atherosclerotic cardiovascular disease, percent LDL-C reduction provides incremental prognostic value over statin dose and attained LDL-C levels. However, the attained LDL-C level does not provide additional prognostic value over statin dose and percent LDL-C reduction.

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KEYWORDS: LDL-C targets; Percent reduction; Statins

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The 2013 American College of Cardiology/American Heart Association (ACC/AHA) guideline on the treatment of blood cholesterol recommends moderate- to high-intensity statins for patients with atherosclerotic cardiovascular disease but departs from the traditional treat-to-target approach.[1] The guideline states "There is no evidence to support continued use of specific low-density lipoprotein cholesterol (LDL-C) and/or non-high-density lipoprotein cholesterol (HDL-C) treatment targets. The appropriate intensity of statin therapy should be used to reduce risk in those most likely to benefit".[1] High intensity of statin is defined as a dose that reduces LDL-C by at least 50%, and moderate intensity of statin is defined as a dose that reduces LDL-C by 30% to 50%. The guideline recommendations are in contrast to the previous third report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) and the European Society of Cardiology/European Atherosclerotic Society guidelines for the management of dyslipidemia, which were principally based on a treat-to-target approach.[2] On the other hand, the 2014 National Institute for Health and Care Excellence (NICE) guidelines recommend atorvastatin 80 mg for secondary prevention but recommend measuring cholesterol levels at 3 months of treatment to aim for a greater than 40% reduction in non-HDL cholesterol.[3]

The rationale for doing away with the treat-to-target approach in the 2013 ACC/AHA guidelines is because no randomized trial has specifically evaluated treatment targets. In the absence of randomized trials, we aimed to evaluate whether percent LDL-C reduction or attained LDL-C level or both provide incremental prognostic value over statin dose in patients with atherosclerotic cardiovascular disease using pooled patient-level data from the Treating to New Targets (TNT), Incremental Decrease in Endpoints through Aggressive Lipid Lowering (IDEAL), and Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trials.

CLINICAL SIGNIFICANCE

- In the cohort of 13,937 patients, among those with attained low-density lipoprotein cholesterol (LDL-C) $\leq$70 mg/dL, patients with percent LDL-C reduction $<$50% had a higher risk of primary outcome and stroke and a numerically higher risk of death when compared with the group with percent LDL-C reduction $\geq$50%.
- Percent LDL-C reduction added incremental prognostic value over statin dose and attained LDL-C levels. However, attained LDL-C level did not provide incremental value over statin dose and percent LDL-C reduction.

MATERIALS AND METHODS

Patient Population

This is a pooled individual patient-level analysis from the TNT, IDEAL, and SPARCL trials. The design and main results of the trials have been described in detail.[4-7] The inclusion criteria of the present study were as follows: (1) patients randomized to a statin (atorvastatin 80 mg/10 mg or simvastatin 20 mg) and (2) statin-naïve patients (subset from the IDEAL trial) or non-naive patients but who underwent a statin washout phase (TNT and SPARCL trials) (to assess true percent LDL-C reduction from baseline). The exclusion criteria were as follows: (1) patients randomized to placebo and (2) patients with a major cardiovascular event (composite of death from coronary heart disease, nonfatal nonprocedure-related myocardial infarction, resuscitation after cardiac arrest, or fatal or nonfatal stroke) before month 3 LDL-C measurement. Informed consent was obtained from each patient, and the institutional review board at each enrolling center approved the respective trials.

Statin Treatment

Patients in the TNT trial randomized to atorvastatin 80 mg versus 10 mg, statin-naive patients in the IDEAL trial randomized to atorvastatin 80 mg versus simvastatin 20 mg, and patients in the SPARCL trial randomized to atorvastatin 80 mg were chosen for this study.

Follow-up

Patients were followed up at week 12 and periodically thereafter up to 5 years. At each visit, vital signs, clinical endpoints, adverse events, and concurrent medication information were collected. In addition, physical examinations and electrocardiograms were performed and laboratory specimens were collected annually.

Percent Low-density Lipoprotein Cholesterol Reduction and Attained Low-density Lipoprotein Cholesterol Levels

For each patient included in this study, percent LDL-C reduction and attained LDL-C levels were determined at the month 3 cholesterol measurement. For trials that had a run-in phase (eg, the TNT trial), the percent LDL-C reduction was calculated using LDL-C values before the run-in phase compared with the LDL-C values at the month 3 visit.

Study Outcomes

The primary outcome for this analysis was the occurrence of a major cardiovascular event, defined as death due to coronary heart disease, nonfatal nonprocedure-related myocardial infarction, resuscitation after cardiac arrest, or