Advances in the treatment of dyslipidemia

ABSTRACT

Although current guidelines do not set specific targets for lowering levels of low-density lipoprotein cholesterol (LDL-C), several lines of evidence support the concept that “lower is better.” Statin drugs in combination with new agents now make it possible to lower LDL-C to new lows. Determining the risk of cardiovascular disease in apparently healthy adults and how far to extend treatment for primary prevention has critical implications for public health.

KEY POINTS

Patients at high risk of atherosclerotic cardiovascular disease should be treated with high-intensity statin therapy.

To date, no baseline level has been identified beneath which lowering LDL-C does not provide clinical benefit.

The benefits of lower LDL-C are seen with a variety of pharmacologic interventions and in people who have naturally low levels due to genetic variants.

Clinical trial evidence supports that ezetimibe reduces the risk of cardiovascular events.

Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors reduce LDL-C by approximately 60%, and preliminary data show that they reduce the risk of cardiovascular events.

The 2013 joint guidelines of the American College of Cardiology and American Heart Association (ACC/AHA) on the treatment of blood cholesterol to reduce cardiovascular risk recommend high-intensity statin therapy for secondary prevention of cardiovascular events. The question of primary prevention is not so straightforward, and the recommended strategy has come under fire. In addition, the guidelines focus on statins and not on LDL-C levels, and the role of nonstatin lipid-lowering drugs and the value of reducing LDL-C levels to well below levels currently regarded as “normal” remain unclear.

This article comments on the 2013 ACC/AHA guidelines, reviews the data on optimal LDL-C levels, and discusses new nonstatin agents.

ACC/AHA GUIDELINES: A MIXED MESSAGE

The 2013 ACC/AHA cholesterol guidelines can be characterized by the title from the famous Western film “The Good, the Bad, and the Ugly.”

The good: A clear message to treat

The guidelines deliver an unambiguous message to treat patients at high risk with high-intensity statin therapy. This mandate is very helpful as it should reduce the undertreatment of patients.

The seemingly bad

Two common misconceptions regarding the guidelines:

They abandon LDL-C targets. Actually, the guidelines do not argue for or against targets; they simply remain silent, citing that randomized trials have not been conducted with LDL-C targets as specific goals. Technically, this statement is true. However, it seems contrived to argue, for example, that the benefit
Major lipid trials:
LDL-C levels vs rates of coronary events

4S-pbo, Scandinavian Simvastatin Survival Study placebo group; 4S-rx, 4S simvastatin group; A to Z-S20, A to Z trial simvastatin 20 mg group; A to Z-S40-80, A to Z trial simvastatin 40–80 mg group; AFCAPS-pbo, Air Force/Texas Coronary Atherosclerosis Prevention Study placebo group; AFCAPS-rx, AFCAPS lovastatin 20–40 mg group; ALLIANCE-pbo, Aggressive Lipid-Lowering Initiation Abates New Cardiac Events study placebo group; ALLIANCE-rx, ALLIANCE atorvastatin group; ASCOT-pbo, Anglo-Scandinavian Cardiac Outcomes Trial placebo group; ASCOT-rx, ASCOT atorvastatin group; CARDS-pbo, Collaborative Atorvastatin Diabetes Study placebo group; CARDS-Atv10, CARDS atorvastatin 10 mg group; CARE-pbo, Cholesterol and Recurrent Events trial placebo group; CARE-rx, CARE pravastatin group; HPS-pbo, Heart Protection Study placebo group; HPS-rx, HPS simvastatin 40 mg group; IDEAL-Sim20–40, Incremental Decrease in End Points Through Aggressive Lipid Lowering trial simvastatin 20–40 mg group; IDEAL-Atv80, IDEAL atorvastatin 80 mg group; JUPITER-pbo, Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin placebo group; JUPITER-Ros20, JUPITER rosuvastatin 20 mg group; LIPID-pbo, Long-Term Intervention With Pravastatin in Ischaemic Disease placebo group; LIPID-rx, LIPID pravastatin group; MEGA-pbo, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese study placebo group; MEGA-Prv10-20, MEGA pravastatin 10–20 mg group; MIRACL-pbo, Myocardial Ischemia Reduction With Acute Cholesterol Lowering trial placebo group; MIRACL-Atv80, MIRACL trial atorvastatin 80 mg group; POSCH-con, Program on the Surgical Control of the Hyperlipidemias control group; POSCH-surg, POSCH ileal bypass group; PROVE-IT-Prv40, Pravastatin or Atorvastatin Evaluation and Infection Therapy pravastatin 40 mg group; PROVE-IT-Atv80, PROVE-IT atorvastatin 80 mg group; SHARP-pbo, Study of Heart and Renal Protection placebo group; SHARP-S20+ez, SHARP simvastatin 20 mg plus ezetimibe group; TNT-Atv10, Treating to New Targets atorvastatin 10 mg group; TNT-Atv80, TNT atorvastatin 80 mg group; WOSCOPS-pbo, West of Scotland Coronary Prevention Study placebo group; WOSCOPS-rx, WOSCOPS pravastatin group.

**FIGURE 1.** Scatter plot with best-fit lines of major lipid trials (statin and nonstatin trials) for both primary and secondary prevention of coronary heart disease events. Even though the trials were not designed to show differences based on a target LDL-C level, there is a clear relationship of fewer events with lower LDL-C levels.

of atorvastatin 80 mg over 10 mg in the Treat-
ing to New Targets trial could not be reliably
ascribed to the lower LDL-C achieved with
the higher dose, but rather to some undefined
benefit of high-intensity statin therapy, espe-
cially as the guidelines define the intensity of
statins by the degree of LDL-C lowering. In
fact, by correlating the incidence of coronary
heart disease events with the levels of LDL-C
achieved in those trials, conclusions can rea-
sonably be drawn from such data (Figure 1).2

The guidelines do not recommend non-
statin drugs. Actually, the guidelines note
that clinicians are free to consider other ther-
apies, especially those proven to reduce the
risk of cardiovascular events, a central prin-
ciple of medicine. Since the guidelines were
published, data have emerged indicating that
the role of nonstatin drugs also needs consid-
eration.

The ugly: Risk calculator untested

The guidelines promote the use of a risk calcu-
lator developed by the ACC/AHA to estimate
the 10-year risk of an atherosclerotic event
for people whose LDL-C levels are between
70 and 189 mg/dL to help decide whether to
initiate statin therapy for primary prevention
of atherosclerotic cardiovascular disease. Such
an approach is reasonable, although the risk
score was promulgated without evidence to
support its utility.

Media coverage of the risk calculator was
fierce. Some physicians found imperfections
in the risk score (as is true for all risk scores),
resulting in public mistrust of the guidelines
and of the medical community as a whole.
This needless controversy may have compro-
mised the main message—that LDL-C should
be lowered in many people—a message backed
by strong evidence.

Alternative strategies proposed

Ridker et al3 have proposed a hybrid strategy
to guide statin use for apparently healthy peo-
ple that combines the ACC/AHA guideline
approach with entry criteria for randomized
clinical trials that showed statin efficacy for
primary prevention.

Genetic analysis may offer another ap-
proach. Mega et al4 stratified more than 48,000
people by a genetic risk score based on 27 ge-
netic variants and found a significant associa-
tion with risk of coronary events. Targeting
therapy to people found to be at higher risk on
this basis offers greater risk reduction than ex-
pected for the general population. Biomarkers
and imaging tests are other potentially useful
risk determinants.

¶ LDL-C: LOWER IS BETTER

Although no clinical trial has yet targeted spe-
cific LDL-C levels, there is plenty of evidence
that lower LDL-C levels offer greater benefit
(Figure 1).2

In 1994, the Scandinavian Simvastatin
Survival Study5 established the benefit of
statins in patients with known vascular dis-
ease. The mean LDL-C level achieved in
the active treatment group was 120 mg/dL.
More trials followed supporting the benefits of
statins and of reducing LDL-C from average
levels in the 120s down to 100 mg/dL.

In 2004, the Pravastatin or Atorvastatin
Evaluation and Infection Therapy–Throm-
bolysis in Myocardial Infarction 22 trial6 ob-
served an even greater risk reduction in pa-
tients with known risk by treating with statins;
the mean LDL-C level achieved in the group
randomized to an intensive regimen of atorv-
astatin 80 mg per day was 62 mg/dL. The same
year, the Adult Treatment Panel III of the Na-
tional Cholesterol Education Program7 issued
updated guidelines including an optional goal
of LDL-C less than 70 mg/dL for patients at
very high risk.

In 2008, the Justification for the Use of
Statins in Prevention: an Intervention Trial
Evaluating Rosuvastatin (JUPITER)8 found
a significantly lower incidence of major car-
diovascular events in 2 years in apparently
healthy men and women with baseline LDL-
C levels of less than 130 mg/dL after treat-
ment with rosuvastatin 20 mg daily, with an
achieved median LDL-C of 55 mg/dL.

How low should LDL-C go?

Evidence from clinical trials indicates a 20%
to 25% reduction in the risk of cardiovascular
events for every 39-mg/dL decrease in LDL-C.
Extrapolating the data, cardiovascular disease
risk would be reduced to zero if LDL-C were
brought down below 40 mg/dL.

Brown and Goldstein,9 who won the 1985
Nobel Prize in medicine for their work in cho-
DYSLIPIDEMIA

Cholesterol metabolism, estimated that a plasma level of LDL-C of only 25 mg/dL would be sufficient to nourish cells with cholesterol. Cells can synthesize all the cholesterol they need, underscoring that LDL-C is simply the final end-product that the liver removes from circulation.

Other evidence that lower LDL-C does not have adverse effects comes from non-Western populations as well as from other mammals. Total cholesterol levels range in the low 100s mg/dL in Native American and African tribal populations, with LDL-C estimated to be about 50 to 75 mg/dL. Elephants, baboons, and foxes have even lower levels.10

Clinical trial data also support that LDL-C levels below the current “normal” are better. The Cholesterol Treatment Trialists’ Collaboration11 analyzed data from more than 160,000 patients in 26 trials that evaluated either more- vs less-intensive statin regimens or statin treatment vs control. No baseline level below which lowering LDL-C further was not beneficial was found. Patients who started out with an LDL-C level of less than 77 mg/dL had the same risk reduction of major vascular events when the level was dropped to 50 mg/dL as those who started at higher levels and reduced their LDL-C by the same amount. In the JUPITER trial, even those with a baseline LDL-C of less than 60 mg/dL benefitted from statin therapy.12

BEYOND STATINS

Ezetimibe further lowers risk
Ezetimibe is a nonstatin drug that reduces LDL-C by about 15% to 20%. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial13 registered more than 18,000 patients with a baseline LDL-C level of less than 125 mg/dL (or 100 mg/dL if already on lipid-lowering therapy) who had been stabilized shortly after an acute cardiovascular event. They were randomized to receive either simvastatin 40 mg or combined simvastatin 40 mg and ezetimibe 10 mg. The study intended to determine two things: whether ezetimibe could further lower LDL-C when combined with a statin, and whether risk could be reduced further by driving the LDL-C below 70 mg/dL and down to the mid-50s.

After 1 year, the average LDL-C level was 70 mg/dL in the simvastatin group and 53 mg/dL in the combined simvastatin and ezetimibe group. At 7 years, for the primary end point (cardiovascular death, myocardial infarction, unstable angina requiring hospitalization, coronary revascularization, or stroke), there was a 6% reduction of events in the combined drug treatment group, with the number of people needed to treat being 50 to prevent one event. For the narrower end point of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke, there was a 10% risk reduction in the combined drug treatment arm.14

The amount of risk reduction is exactly what was predicted by the Cholesterol Treatment Trialists’ Collaboration’s plot of reduction in events vs reduction in LDL-C based on the analysis of 26 trials, adding further evidence that it is the LDL-C reduction itself, rather than the means by which LDL-C is reduced, that is critical for benefit.

PCSK9 inhibitors: A new approach
Mutations in the gene for proprotein convertase subtilisin kexin type 9 (PCSK9) have become a new focus of interest for reducing LDL-C and cardiovascular risk.15 PCSK9 binds to the LDL-C receptor on the surface of hepatocytes and escorts it to its destruction in the lysosomes, rather than allowing it to return to the cell surface to take more LDL-C out of circulation.

People with a gain-of-function mutation (conferring too much PCSK9, resulting in fewer LDL-C receptors and more LDL-C in circulation) are a more recently recognized subset of those with autosomal-dominant familial hypercholesterolemia. They have total cholesterol levels in the 90th percentile, tendon xanthomas, and a high risk of myocardial infarction and stroke at a young age.

Conversely, those with a nonsense mutation in PCSK9—leading to loss of function—have a 28% reduction in mean LDL-C and 88% reduction in risk of coronary heart disease compared with those without the mutation.16 Two women (ages 32 and 21, fertile) have been found who have inactivating mutations in both PCSK9 alleles, and both are in apparent good health, with LDL-C levels of 14 mg/dL and 15 mg/dL, respectively.17,18
Dramatic reduction in LDL-C
Monoclonal antibodies have been developed that bind PCSK9 and block its action with the goal of developing new LDL-C-lowering treatments. Phase 2 clinical trials of varying doses of evolocumab (Repatha), a drug in this class, combined with standard therapy (a statin with or without ezetimibe), found a 66% reduction of LDL-C at high doses at 12 weeks compared with standard therapy alone, with concomitant reductions in other atherogenic lipoproteins. Patients who could not tolerate statins because of myalgia responded well to evolocumab.

Patients with heterozygous familial hypercholesterolemia also had a substantial reduction in LDL-C (55% at the highest dosage), even though they have fewer LDL-C receptors for the drug to act upon. People with homozygous familial hypercholesterolemia and no LDL-C receptors had a lesser relative reduction in LDL-C that depended on the type of mutations they had. Nonetheless, given how high LDL-C levels are in this population, the absolute decreases in LDL-C level were quite impressive.

Cardiovascular risk reduced
Data at nearly 1 year showed continued reduction of LDL-C by about 60% (absolute reduction: 73 mg/dL), as well as a lower incidence of cardiovascular events starting at just 3 months, much sooner than observed in some statin trials. Benefits were found regardless of subgroup (sex, age, statin use, baseline LDL-C level, or known vascular disease). No difference was found in the safety profile between the evolocumab and control arms. Only 2.4% of participants discontinued evolocumab because of adverse events, and the incidence of adverse effects did not correlate with LDL-C level achieved.

Neurocognitive effects occurred in 0.9% of the evolocumab arm vs 0.3% in the control arm. This difference has not been explained: although there is cholesterol in the central nervous system, it is generated locally, and lipoproteins—and evolocumab—are not thought to cross the blood-brain barrier.

Long-term trials of evolocumab are currently under way for patients with cardiovascular disease, as are trials of two other PCSK9 inhibitors, alirocumab and bococizumab, in addition to standard statin therapy.

On July 24, 2015, the US Food and Drug Administration (FDA) approved the first PCSK9 inhibitor, alirocumab (Praluent) for patients with heterozygous familial hypercholesterolemia or those with clinical atherosclerotic cardiovascular disease who require additional lowering of LDL-C. The starting dosage is 75 mg subcutaneously every 2 weeks, which can be increased up to 150 mg every 2 weeks. Evolocumab was approved by the FDA on August 27, 2015, for the same indications. The dosage is 140 mg subcutaneously every 2 weeks or 420 mg every month.

REFERENCES
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