Treating dyslipidemia: Re-evaluating the data using evidence-based medicine

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Evidence-based medicine and decision-support tools have been cited as key components for ensuring quality and safety in the patient-centered medical home (PCMH). These two elements of the PCMH demand attention in the treatment of dyslipidemia, where recent data warrant evaluation in the context of these interventions.

While the relationship between low-density lipoprotein cholesterol (LDL-C) lowering and coronary heart disease (CHD) risk reduction has been recognized for several years and demonstrated in several studies, a number of other risk markers have emerged. These risk markers require attention from clinicians who seek to improve outcomes via the PCMH approach.

The impact of this emerging data on treatment practices is evident when looking at the ever-evolving guidelines for lipid management. Furthermore, questions have arisen as to which lipid-lowering strategy is the most effective for each different subset of patients with dyslipidemia in light of the available clinical evidence.

Aside from the universally accepted dyslipidemia disease marker of LDL-C, several other emerging markers have been identified that can enhance global risk assessment to guide the intensity of conventional (ie, LDL-focused) treatment. It should be noted that while the following markers demonstrate significant potential in the characterization and treatment of dyslipidemia, they do not serve as a substitute for global risk assessment.

**Emerging markers**
- High-sensitivity C-reactive protein (hs-CRP)
- Coronary Calcium Score (EBCT)
- Small, dense LDL
- HDL subspecies
- Homocysteine
- Fibrinogen
- Apolipoproteins (A1 and B)
- Microalbuminuria
- Metabolic Syndrome
- Lp(a)
- Lipoprotein-Associated Phospholipase A2 (Lp-PLA2/PLAC) Test
- Carotid Intimal Medial Thickness (CIMT)
- Coronary CT Angiogram

The review that follows presents the evidence associated with some of these emerging markers in dyslipidemia, along with considerations on updated lipid-lowering guidelines and evidence of current treatment regimens.

Robert S. Rosenson, MD, the director of lipoprotein disorders and clinical atherosclerosis research at the University of Michigan in Ann Arbor, re-examined correlates of plaque progression (decreases in minimum lumen diameter) with LDL subclass cholesterol content and found that the single best predictor of progression was elevated small LDL-C (>30 mg/dL, which was the median). The odds ratio (OR) for progression was 9.1 times with this measure versus only 1.4 times with LDL particle concentration. In the combined pravastatin treatment and placebo groups, the statistically significant correlates with progression were small LDL-C, LDL average size, and LDL particle number, with small LDL-C demonstrating a far better predictive value for angiographic progression than LDL particle number. Currently, the Vertical Auto Profile (VAP) Test is available to measure small/dense LDL cholesterol directly (as LDL4-C plus LDL3-C). Nuclear magnetic resonance (NMR) imaging can also be used to calculate small LDL; while this isn’t a direct assessment of the marker, it is likely still a valid method.

Raggi et al recently reported on the prognostic utility of coronary artery calcium (CAC) in the elderly by assessing all-cause mortality in 35,388 patients (3,570 were ≥70 years old at screening and 50% were women) after a mean follow-up of 5.8±3 years. The researchers found that, in older patients, risk factors and CAC were more prevalent. Overall survival was 97.9% at the end of follow-up. Mortality increased with each age decile, with a relative HR of 1.09 (95% CI, 1.08-1.10; P <0.0001), and rates were greater for men than women (HR, 1.53; 95% CI, 1.32-1.77, P <0.0001).

Increasing CAC scores were associated with decreasing survival across all age deciles (P <0.0001). Survival for a man aged <40 years and a man aged ≥80 years with CAC scores ≥400 was 88% and 19% (95% and 44% for a woman, P <0.0001), respectively. Among the 20,562 patients with no CAC, annual mortality rates ranged between 0.3% and 2.2% for patients aged 40 to 49 years and ≥70 years, respectively (P <0.0001).

The use of CAC allowed the researchers to reclassify >40% of the patients aged ≥70 years more often by...
excluding risk (ie, CAC < 400) in those with >3 risk factors. The benefits of utilizing this emerging marker in clinical practice are evident from the results of this study. Despite the limited life expectancy of elderly patients, the use of CAC discriminates mortality risk in this subset of patients with dyslipidemia. Furthermore, the use of CAC allows physicians to reclassify risk in the elderly.

Contrary to popular belief at the time of its release, data from the Framingham Heart Study indicate that low high-density lipoprotein cholesterol (HDL-C) is an independent risk factor of CHD despite low LDL-C levels. Even in individuals whose low-density lipoprotein cholesterol (LDL-C) levels were approximately 100 mg/dL, HDL-C remained a very strong risk factor, and individuals with low HDL-C were still at considerably elevated risk for CHD. In the years since the Framingham data were published in 1977, HDL-C has joined LDL-C as a marker to be regularly considered in the assessment of patients with dyslipidemia.

Evolution of guidelines for lipid management

The National Cholesterol Education Program’s (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel [ATP]) guidelines have been revised twice (ie, ATP II and III) since being initially published in 1988, and an additional NCEP report was issued in 2004 suggesting further changes. This latter report was released as an update to ATP III and in anticipation of a third revision, ATP IV, which is expected to be published in the summer of 2010.

The successive versions of the guidelines have become increasingly more aggressive toward LDL-C during the course of their evolution, and each subsequent revision has included additional disease markers and therapeutic classes of drugs (ie, statins, fibrates) for consideration in the first-line treatment of dyslipidemia (Figure 1). Furthermore, the ATP III included increased emphasis on the use of combination therapy for managing dyslipidemia. The 2006 update of the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines for patients with CHD echo the most recent (and most aggressive) LDL-C goals published in the ATP III update.

In ATP III, the NCEP included a decision-support tool for stratifying risk in patients with dyslipidemia in order to determine the appropriate lipid goals and the course of therapy indicated. This risk-stratification tool can essentially be simplified into three questions, with next steps dictated by each subsequent answer:

1. Does patient have established atherosclerotic cardiovascular disease (CVD) or diabetes mellitus?
   - If yes: high or very high risk
   - If no: go to question #2
2. What is patient’s number of traditional risk factors?
   - If 0-1: low risk
   - If ≥2: go to question #3
3. What is the Framingham Risk Score?
   - If <10%: moderate risk
   - If 10% to 20%: moderately high risk
   - If >20%: high risk

Despite the consideration of additional markers in subsequent ATP guidelines, the 2004 update to ATP III recommends targeting LDL-C first in the treatment of dyslipidemia.

According to the most recent NCEP
recommendations, lipid-lowering therapy should be initiated in patients who do not meet LDL-C goals with therapeutic lifestyle changes (TLC) alone.\(^\text{12}\) In addition to these guidelines, and in accordance with the aforementioned risk-stratification tool, the American Diabetes Association (ADA) recommended that statin therapy be added to TLC regardless of baseline lipid levels in diabetic patients with overt CVD or in those without CVD aged \(\geq 40\) years with \(\geq 1\) CVD risk factors.\(^\text{14}\)

If after six weeks the LDL-C goal is still not met, the NCEP recommends intensifying the lipid-lowering therapy and reassessing again in another six weeks, followed by further intensification of lipid-lowering therapy or referral to a lipid specialist if goals are not met.\(^\text{12}\) Combination therapy using statins and other lipid-lowering agents may be considered to intensify lipid-lowering therapy and achieve LDL-C targets.\(^\text{12}\) Once LDL-C goals are met, the ATP III update recommends monitoring response and adherence to therapy every four to six months.\(^\text{15}\)

**Selected evidence of current treatment regimens**

Statins have gained increasing favor in the treatment of dyslipidemia as data supporting their efficacy have emerged. Whereas the NCEP ATP I guidelines featured strong support for resins and niacin as first-line therapy, statins were not included as “major drugs” and fibrates were not recommended for mixed hyperlipidemia until the release of ATP II in 1993.\(^\text{11}\) Now, robust data support the use of these agents and combination regimens in the treatment of dyslipidemia, warranting a brief review.

In the Heart Protection Study (HPS), the risk of major vascular events with simvastatin 40 mg/d was significantly lower than that with placebo.\(^\text{15}\) Compared with patients taking simvastatin, the larger percentage of patients in the placebo group who had a major vascular event (including nonfatal myocardial infarction [MI], coronary death, revascularization, or stroke) was evident by year one, and the differences continued to grow as the study progressed.\(^\text{15}\) The cumulative difference per 1,000 patients who benefited from simvastatin and avoided a major vascular event increased each year, reaching 60±18 patients by year six.\(^\text{15}\) The relative risk (RR) of any major vascular events with simvastatin...
was 24% (P <0.0001) in this analysis.\textsuperscript{15}

JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) enrolled 17,802 patients with no history of coronary artery disease (CAD) (men aged \( \geq 50 \) y; women aged \( \geq 60 \) y; LDL-C \( < 130 \) mg/dL; hs-CRP levels \( \geq 2.0 \) mg/L; baseline LDL-C = 108 mg/dL, HDL-C = 49 mg/dL) randomized to either rosuvastatin or placebo.\textsuperscript{16} Treatment with rosuvastatin resulted in a significantly lower (P \( < 0.05 \)) rate of any stroke; any MI; stroke, MI, or death; and any death per 100 patient-years than that for placebo.\textsuperscript{16} These findings led the researchers to conclude that the statin reduces mortality in primary prevention, with patients at highest risk experiencing the greatest benefit from rosuvastatin therapy.\textsuperscript{16}

Four statin monotherapy trials—West of Scotland (WOSCOPS primary prevention), Scandinavian Simvastatin Survival Study (4S), CARE, and the HPS—demonstrated that pravastatin (WOSCOPS and CARE) or simvastatin (4S and the HPS) alone only reduced cardiovascular events by 25% to 35%.\textsuperscript{17} This is typical of statin monotherapy trials, which primarily demonstrate reduced LDL-R-C and LDL-C particle number with treatment. The previously discussed HPS was heralded for showing that clinicians can achieve a 25% risk reduction with simvastatin monotherapy if a patient’s baseline LDL-C is 90 to 100 mg/dL. However, it also seems that even if simvastatin reduced a patient’s LDL-C to 60 to 70 mg/dL in the HPS, statin monotherapy cannot achieve the order of risk reduction demonstrated in combination therapy trials. In fact, the combination therapy trials FATS (1986-1990 niacin + colestipol and niacin + lovastatin), FATS Ten Year (1990-2000 niacin 2.5 g/d, colestipol 20 g/d, lovastatin 40 mg/d), and HATS (simvastatin + niacin) demonstrated that combination therapy with niacin and a statin resulted in event reductions of 80% to 95%.\textsuperscript{17}

Similarly, Grundy et al conducted a US-based multicenter, randomized, double-blind, active-controlled, 18-week study to determine if combination therapy with simvastatin plus fenofibrate was more effective than simvastatin alone in reducing elevated triglyceride (TG) levels, thus improving the lipoprotein pattern in patients with combined hyperlipidemia compared with simvastatin monotherapy.\textsuperscript{18}

From baseline to week 12, median TG levels decreased 43% in the combination therapy group and 20.1% in the simvastatin monotherapy group (treatment difference, -23.6%; P \( < 0.001 \)).\textsuperscript{18} Mean LDL-C levels decreased by 31.2% and 25.8% (treatment difference, -5.4%; P \( < 0.001 \)) and mean HDL-C levels increased by 18.6% and 9.7% (treatment difference, 8.8%; P \( < 0.001 \)) in the combination therapy and monotherapy groups, respectively.\textsuperscript{18}

The researchers concluded that combination therapy with simvastatin 20 mg and fenofibrate 160 mg in patients with combined hyperlipidemia resulted in additional improvement in all lipoprotein parameters measured compared with simvastatin 20 mg monotherapy, proving this combination therapy to be beneficial in managing combined hyperlipidemia.\textsuperscript{18}

The combination of simvastatin and the cholesterol absorption-inhibitor ezetimibe likewise has demonstrated improvements in lipid parameters over statin monotherapy.\textsuperscript{19,20} Davidson et al reported that patients who received combination therapy with 10 mg eze-

\begin{figure}
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\caption{Incremental LDL-C reduction achieved by titrating statin monotherapy versus statin-ezetimibe combination therapy.\textsuperscript{18}}
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timibe and 10 mg simvastatin had the same improvement in lipid parameters as patients who received eight times the dose of simvastatin alone (80 mg).\(^{19}\)

Because the magnitude of incremental LDL-C reduction with a combination of ezetimibe and a starting dose of a statin is similar to that seen with three-step statin titration, and because statin titration is associated with increased incidence of adverse events, the combination of ezetimibe and a statin represents a useful option for achieving targeted LDL-C levels in a greater proportion of individuals (Figure 2).\(^{20}\) Ezetimibe does not alter the pharmacokinetics and bioavailability of statins, and the safety and tolerability profile of the combination of ezetimibe and a statin is comparable to that of statin alone.\(^{20}\)

The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6: HDL and LDL Treatment Strategies in Atherosclerosis (ARBITER 6-HALTS) study also evaluated the addition of ezetimibe to statin monotherapy, this time compared with extended-release niacin plus a statin.\(^{21}\)

However, in this case, the trial was stopped prematurely due to a precisely defined prespecified interim analysis showing niacin to be superior to ezetimibe.\(^{21}\)

Specifically, as compared with ezetimibe, niacin had greater efficacy regarding a change in mean carotid intima-media thickness by a margin of 0.014 mm (IMT) over 14 months (\(P=0.003\)), leading to significant reduction of both mean (\(P=0.001\)) and maximal carotid IMT (\(P=0.001\) for all comparisons).\(^{21}\) Although these results demonstrate superior efficacy of extended-release niacin over ezetimibe in preventing the progression of carotid atherosclerosis, they give little guidance regarding ezetimibe’s effectiveness, given that no placebo arm was included in the study. Furthermore, some clinicians advise taking caution when interpreting the findings of ARBITER 6-HALTS since it was a small, short-duration, surrogate-end-point study that was prematurely stopped (40% of patients did not undergo the final IMT measurement at 14 months).\(^{21}\)

In an editorial accompanying the ARBITER 6-HALTS data, Blumen-thal and Michos cite the existence of substantial evidence supporting the use of adjunctive therapy with a fibrate, niacin, a bile-acid sequestrant, n-3 fatty-acid supplements or ezetimibe if lipid goals cannot be met with a statin alone; however, these recent data suggest niacin should be the first-line choice after statin monotherapy.\(^{23}\) Still, some clinicians question the validity of a surrogate end-point (IMT) in determining the true clinical benefit of therapy and state that the magnitude of difference between extended-release niacin and ezetimibe may have been exaggerated because the trial was stopped early.\(^{22,23}\)

**Final notes**

Although a clear relationship exists between LDL-C lowering and cardiovascular risk reduction, emerging dyslipidemia disease markers and clinical trial data supporting new treatment regimens have led to numerous revisions of treatment guidelines. In treating dyslipidemia according to the PCMH approach, evidence-based medicine and clinical decision-support tools dictate the evaluation of these emerging data, including clinical trial evidence supporting the use of TLC in all patients and early initiation of medication for higher risk patients. Since the use of two or more lipid-modifying agents—each with a different mechanism of action—may be necessary to achieve guideline-recommended targets for LDL-C, HDL-C, and TG, the PCMH approach necessitates that physicians also consider combination regimens for improving outcomes in dyslipidemia where indicated.
References


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