Leapfrogging Data
No Shortcuts for Safety or Efficacy Information

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Properly designed and conducted randomized controlled clinical trials (RCTs) are the premier tool for both testing mechanistic hypotheses and critically ascertaining the risks and benefits of a therapy or strategy for clinical care. The sample size of a trial is mainly a function of the rates of its primary objectives and the presumed influence of the intervention. Trials focusing on a primary outcome variable that can be readily quantified in each subject, such as blood pressure or plasma cholesterol levels, require substantially fewer participants and shorter durations to determine whether their predefined measurement is altered compared with a morbidity and mortality trial. Trials designed to determine whether clinical prognosis is altered by an intervention depend on the proportion of patients experiencing the predefined adverse clinical event(s) and often require 100s-fold–greater patient-time exposures to test their primary hypothesis and provide even modest information about safety. These resource-intense morbidity and mortality trials are generally only performed when information from observational studies as well as smaller mechanistic and surrogate-outcomes RCTs justify the effort. Despite this understandable stacking of the cards with the best available information, many of the morbidity and mortality trials conducted to test for a potential favorable impact of an intervention conclude by not supporting the prestudy hypothesis-generating data.1 The lessons in humility offered by these neutral or negative outcomes trials underscore the importance of obtaining crucial risk–benefit data before widespread adoption of even an apparently favorable therapy.2

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For rational therapeutic decision making, we would ideally like to have both a framework of reliable mechanistic information and robust clinical outcomes and safety data. Sometimes major clinical outcomes trials are designed with a complement of embedded ancillary trials to generate a more complete picture of mechanistic actions of the therapy within a smaller subset of patients of the overall study population so as not to overburden all participants for the additional measures. In other instances, it is more appropriate to use a disease-related but different population to obtain the mechanistic information without influencing the conduct of the larger outcomes RCT.

Despite the collective advances in risk factor management including reduced prevalence of smoking and an appropriately broader use of antihypertensive agents and statins, atherosclerotic cardiovascular disease has maintained its unfortunate dominant role in global disease burden. The strong epidemiological associations between lower levels of high-density lipoprotein cholesterol (HDL-C) and higher rates of atherosclerotic cardiovascular disease have made the hunt for novel therapies that can raise HDL-C an important investigational focus.3 Early observations that an uncommon mutation in the Japanese population that completely prevents synthesis of cholesterol ester transfer protein (CETP) is associated with very high HDL-C levels prompted the development of pharmaceutical products to inhibit this regulator of the transport of cholesterol esters out of HDL. However, the evidence is conflicting whether this mutation confers protection against coronary heart disease or increases longevity.4 The first candidate CETP inhibitor compound to be clinically evaluated on a large-scale, torcetrapib, produced rather impressive increases in HDL-C with further lowering of low-density lipoprotein cholesterol.5 These changes were so substantial, even on top of high doses of a statin, that they generated the impetus and enthusiasm for further large-scale clinical testing of torcetrapib despite the early-recognized drug-induced increase in arterial pressure. It is important to note that common CETP promoter mutations are associated with only slightly higher HDL-C levels, 4 mg/dL,6 compared to the very large HDL-raising effect of the original Japanese mutation or to the nearly 2-fold increases caused by pharmacological inhibition of CETP. These common mutations are associated with mildly reduced incidence of coronary heart disease in proportion to the increase in HDL-C.6 The complexity of lipoprotein biology, however, raised lingering questions about the functionality of the HDL-C particles increased by CETP inhibition. For example, apolipoprotein E, a multifunctional protein, is enriched in the large-sized HDL that is present in CETP deficiency but not in the large HDL of people who have high HDL-C concentration due to other causes.7 The high apolipoprotein E content of HDL may have clinical relevance because the HDL apolipoprotein E concentration directly predicts cardiovascular disease events, reversing the usual protective direction of concentrations of HDL components like protein A.

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cholsterol or apolipoprotein A-I. This underscores that the apparently favorable alterations in conventional plasma lipid risk factors produced by CETP inhibition, though encouraging, could not be assumed to imply clinical benefits.

Armed with the exciting, indeed unparalleled, capability to raise HDL-C, the torcetrapib developmental program included 3 independent imaging studies to determine the influence of torcetrapib on atherosclerotic burden.\textsuperscript{10–12} Although the imaging studies were designed to provide a mechanistic explanation for how the observed influences on plasma lipoproteins would be translated into measurable improvements in atherosclerotic burden, the hope (but not the promise) also existed that consistent favorable results from imaging trials with a concomitant outcome trial could possibly result in regulatory approval before the completion of a morbidity and mortality RCT.\textsuperscript{13} The clinical outcomes RCT, the linchpin of the torcetrapib development program, Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE), commenced enrollment of its 15,067 men and women with a history of cardiovascular disease or type 2 diabetes mellitus after the imaging trials were well underway.\textsuperscript{14} With its projected 4.5 years of follow-up after randomization to either atorvastatin alone or atorvastatin plus torcetrapib for the outcomes compared with the 2-year duration for the imaging trials, the results of the latter could not be expected to influence the former.

On December 2, 2006, Pfizer, the sponsor of the torcetrapib trials, announced in an unexpected press release that in the interest of patient safety it was stopping all torcetrapib clinical trials.\textsuperscript{15} This abrupt termination of research on torcetrapib was on the advice of the ILLUMINATE Data Safety Monitoring Board to its steering committee based on higher rates of death from all causes in the group randomized to torcetrapib. At this time, 2 of the 3 imaging trials had completed patient follow up. All 3 imaging studies reported their independent results at the 56th Annual Scientific Sessions of the American College of Cardiology in spring of 2007, and the full report from ILLUMINATE was presented at the American Heart Association Scientific Sessions about 6 months later.

The initial reports of the influence of torcetrapib on atherosclerotic vascular disease using quantitative ultrasonographically assessed paired studies (2 years apart) of carotid intima-media thickness in subjects with heterozygous familial hypercholesterolemia (Rating Atherosclerotic Disease Change by Imaging With a New CETP Inhibitor 1 [RADIANCE 1]) and mixed dyslipidemia (Rating Atherosclerotic Disease Change by Imaging With a New CETP Inhibitor 2 [RADIANCE 2]) and coronary intravascular ultrasonography of patients within angiographically documented coronary artery disease in ILLUSTRATE (Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation) were quite consistent.\textsuperscript{10–12} These studies each independently concluded that despite substantial increases in HDL and decreasing low-density lipoprotein cholesterol, no evidence was found of regression of atherosclerosis in their respective vascular territories. Each also reported that the torcetrapib group had a higher systolic blood pressure (2.8, 5.4, and 4.6 mm Hg for RADIANCE 1, RADIANCE 2, and ILLUSTRATE, respectively).

Just months later with the full report from ILLUMINATE, it became evident that the higher mortality with torcetrapib plus atorvastatin was also associated with a 25% increase in the rate of the primary composite outcome of death from coronary heart disease, nonfatal myocardial infarction (excluding procedure-related events after the procedure), stroke, and hospitalization for unstable angina compared with those receiving atorvastatin alone. These statistically significant increases in deaths and atherosclerotic-mediated clinical outcomes occurred despite the impressive (72%) increases in HDL-C (as anticipated from smaller RCTs) and further reductions (25%) in low-density lipoprotein cholesterol.\textsuperscript{14} The investigators offered post hoc analyses for an “off target” action of torcetrapib that resulted in an overall 5.4 mm Hg rise in systolic blood pressure and measurable reductions in potassium, with an increase in serum sodium, bicarbonate, and aldosterone. Cautionary post hoc exploratory analysis raised the possibility of a contribution of torcetrapib-induced increases in aldosterone as a suspect. The possibility that the measured HDL-C increase produced by pharmacological CETP inhibition may be dysfunctional, in addition to producing other yet unknown toxic actions, remained unresolved.

With this clear, indeed definitive, data from ILLUMINATE that torcetrapib should not be used, the quandary was whether treatment inhibiting CETP was inherently dangerous and that the increase in HDL-C produced in this manner was somehow harmful or whether this specific molecule, torcetrapib, had such profound adverse “off target” effects on the renin-angiotensin aldosterone system, in addition to other adverse vascular actions, that it more than offset any potential favorable plasma lipid actions.\textsuperscript{16}

This issue of Circulation features the secondary reports of all of the important independent anatomic studies testing the influence of the CETP inhibitor torcetrapib on atherosclerotic lesions in carotid and coronary arteries.\textsuperscript{17,18} Armed with the knowledge that torcetrapib was harmful, the investigators interrogated their data seeking new information that would generate more insight into this compound that could be applied to any potential development of another CETP inhibitor.

Vergeer and coworkers merged the quantitative results on the influence of adding torcetrapib on the carotid intima-media thickness from RADIANCE 1 of 904 subjects with familial hypercholesterolemia and RADIANCE 2 of 752 subjects with mixed dyslipidemia.\textsuperscript{15} In a highly quantitative fashion, with units of 10\textsuperscript{3} mm/year, they report a slight increase in cIMT progression despite the favorable changes in plasma lipids produced by the addition of torcetrapib. Their new analysis confirms no association between HDL-C levels and changes in cIMT, although the subjects with lower low-density lipoprotein cholesterol had less progression. Moreover, they used this pooled data set to explore the potential adverse link with
blood pressure elevation proposed by the ILLUMINATE investigators and did show that those with the greatest increase in systolic blood pressure had the largest progression in their carotid imaging–based assessment of atherosclerotic burden.17

Also in this issue, Nichols and coworkers amplify their prior report of the influence of torcetrapib on the atherosclerotic burden measured by paired coronary artery intravascular ultrasound studies 2 years apart in 910 patients with coronary artery disease.18 Despite the marked increase in HDL-C and decrease in low-density lipoprotein cholesterol, they reported no decrease in the progression of coronary atherosclerosis.12 In the present contribution, they further explore the relationships between changes in plasma lipids and the IVUS measurement of percent atheroma volume (PAV).18 In the overall context of no change in PAV, they chose to highlight that the quartile treated with this CETP inhibitor with the largest increase in HDL-C appeared to have regression in PAV. The implication from this post-hoc analysis is that the HDL-C increase produced with this CETP inhibitor can be considered functional since there was an association with a favorable anatomic effect. In our view, this admittedly exploratory analysis overinterprets a probability value from a subgroup of a subgroup, the 25% of the patients in the torcetrapib plus atorvastatin that had the greatest increase in HDL-C. Focusing on this cohort seems to negate the remaining 75% treated with torcetrapib who collectively appear on the progression side of the PAV line despite most having quite substantial increases in HDL-C.

The more important and overarching lesson for future drug development is that the initial studies showing improved plasma lipids even combined with imaging studies, by definition, could not provide sufficient exposure to torcetrapib to test for efficacy or generate even rudimentary safety information. Thanks to ILLUMINATE, the danger of torcetrapib was uncovered before widespread use. For the field of CETP inhibition with the fatal problem identified with torcetrapib, the presumption of innocence can no longer be accepted. The smoking gun(s) of blood pressure elevation, alterations in mineralocorticoid activity and/or electrolytes must be actively looked for in any subsequent CETP inhibitor and, if found, would in my opinion be sufficient to stop development. On the other hand, another CETP inhibitor devoid of the identified “off target” effects of torcetrapib that had favorable lipid alterations and appears well tolerated in early development could still hold promise as an agent to improve clinical outcomes.19,20 Mechanistic or surrogate outcome studies are important for generating enthusiasm and selection of dose, but no matter how well conceived and conducted, should not be expected to generate sufficient drug exposure to detect either favorable or harmful impacts on clinical outcomes. The next CETP inhibitors have produced favorable changes in plasma lipids without alterations in blood pressure, electrolytes, and aldosterone.19,20 No matter how much is known prior to a clinical outcome trial, it is an experiment conducted on informed volunteers. Those entrusted with the responsibility of monitoring the safety of the altruistic participants must take into account past experiences with the study drug and all related compounds when evaluating emerging data.

The allure of raising HDL-C as a complementary method for further reducing cardiovascular morbidity and mortality remains high. Our patients with low HDL-C and atherosclerosis despite optimal conventional management need a new supplemental therapy to reduce their risks. The reality is that no leapfrogging of surrogate data can substitute for the human exposure in definitive clinical outcome trials needed to determine whether a novel HDL-C raising agent can be an effective and safe therapy to improve their prognosis.

Disclosures

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References


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