Canadian Journal of Cardiology 32 (2016) 275–277

Editorial

Tribulations of Recent Cardiology Trials, the Audacity of Hope, and HOPE-3

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See article by Lonn et al., pages 311-318 of this issue.

Hope is an optimistic attitude of mind based on an expectation of positive outcomes. For most recently completed large trials of drugs to reduce cardiovascular (CV) events, the hoped-for positive outcome did not materialize. Examining not just why these trials failed, but the basis for the hope that they would be successful, might lead to wiser decisions for future trials.

Drugs That Increase High-Density Lipoprotein Cholesterol

A low high-density lipoprotein cholesterol (HDL-C) level is such a strong, independent predictor of CV events that it seemed obvious that a drug that increased the level of HDL-C would reduce events. The calculation from epidemiologic data, that a 1 mg/dL increase in HDL-C is associated with a 2% decrease in coronary disease risk in men and a 3% decrease in women,[1] added precision to this relationship and made it seem more real.

The failure of torcetrapib to reduce CV events in the first large outcome trial of a cholesteryl ester transfer protein (CETP) inhibitor, despite a 72% increase in HDL-C, was rightly attributed to off-target toxicity.[2] The failure of the CETP inhibitor dalcetrapib to reduce CV events is more difficult to explain.[3] Anacetrapib and evacetrapib, CETP inhibitors that decrease low-density lipoprotein cholesterol (LDL-C) levels in addition to increasing levels of HDL-C, are currently being tested in large phase III clinical trials, and might well fulfil hopeful expectations.[4]

An intracoronary ultrasound study of apolipoprotein $A1_{Milano}$ infusions for 5 weeks in patients with acute coronary syndromes raised high hopes because the infusions were associated with a significant improvement in the primary end point, a change in percentage of atheroma volume.[5] Although the trial was billed as "placebo-controlled," changes in the placebo group were not compared with changes in the active treatment groups. Two subsequent trials of HDL-C infusion therapies with intracoronary ultrasound end points did not show a beneficial treatment effect.[6,7] A more recent, much larger intracoronary ultrasound trial of intravenous infusions of the HDL-C mimetic agent CER-001 also showed no benefit.[8]

Why have therapies to increase levels of HDL-C mainly failed, at least so far? Does not HDL-C promote cholesterol efflux from macrophages, and participate in a variety of other atheroprotective mechanisms? As recently summarized by Rader and Hovingh,[9] the genetic disorders associated with lifelong extremely low levels of HDL-C are not associated with premature coronary disease. HDL-C is still a useful marker of risk in populations, and is used in most CV risk calculators; however, how well HDL-C particles function and not their absolute number is more closely linked to atherogenesis. Treatments that increase HDL-C levels do not necessarily increase HDL-C function.

Other Markers of CV Risk That Have Failed as Drug Targets

Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) is a circulating enzyme secreted by inflammatory cells, bound mainly to apolipoprotein B-containing lipoproteins, and is expressed in the necrotic core of atherosclerotic lesions.[10] Lp-PLA_2 activity has been linked to increased coronary risk in several studies, but genetic variants with modest effects on Lp-PLA_2 activity were found not to be associated with increased coronary risk.[11]

Darapladib, an Lp-PLA_2 inhibitor, prevented necrotic core expansion compared with placebo in an intracoronary ultrasound study with virtual histology.[12] However, neither the primary end points of the trial, nor any of the other secondary end points, showed a positive effect of darapladib. On the basis of this evidence, 2 large clinical trials were performed, and in both of them darapladib did not reduce CV events.[13,14]

Analogously, varespladib, an inhibitor of secretory phospholipase A_2, a biomarker implicated in atherosclerosis, failed to reduce CV events in a clinical trial of patients who had an acute coronary syndrome; in fact, the drug was actually associated with an increase in myocardial infarction.[15]

Received for publication August 19, 2015. Accepted August 19, 2015.

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See page 277 for disclosure information.

http://dx.doi.org/10.1016/j.cjca.2015.08.020

The Audacity of Hope

The trials described represent a limited sample from one area of cardiology. Many similar examples of heart failure or antiarrhythmic drug trials could be cited. But the pattern is the same: an expensive, time-consuming trial is launched on the basis of some level of evidence, seasoned with hope.

Can more be done to reduce the number of failed trials? Or would more caution invariably lead to fewer successful new therapies? One aspect of this problem is that CV trials have become much more expensive, and recommendations to streamline procedures and cut costs have been proposed.[16] Implementation of these recommendations would surely help, but it might be that human biology is just extremely complex, and our understanding of it incomplete. Failed trials are inevitable.

The value of failed trials might not be fully appreciated. Although the previously mentioned trials of therapies to increase levels of HDL-C were unsuccessful, they certainly have led to a better understanding of the relationship between HDL-C and atherosclerosis and pointed subsequent research in a more fruitful direction.[9]

Statin Trials

As ably summarized by the Cholesterol Treatment Trialists' Collaboration,[17] 26 large, randomized trials involving 170,000 subjects have clearly shown that statins reduce CV events in a broad spectrum of patients with atherosclerosis or with CV risk factors. The reduction averages 22% (95% confidence interval [CI], 20%-24%) for each mmol/L reduction in LDL-C.[17] Statins do not reduce events in patients with severe chronic kidney disease who undergo dialysis,[18] and have only a small effect on CV events in patients with chronic heart failure,[19] probably because the high rates of CV events unrelated to atherosclerosis in these 2 conditions swamp any benefit of statin treatment.

Armed with the knowledge gleaned from completed statin trials, one can ensure that a new trial will yield a positive result. The study population must have enough atherosclerotic CV events, which depend on baseline risk and duration of follow-up, and the average LDL-C differential between the treatment groups must be wide enough. Hope has given way to knowledge.

HOPE-3, the Rosuvastatin Arm

As described by Lonn et al. in this issue of the *Canadian Journal of Cardiology*, Heart Outcome Prevention Evaluation-3 (HOPE-3) has randomized, to placebo or rosuvastatin 10 mg/d, 12,705 intermediate risk subjects without a clear indication or contraindication to a statin.[20] Mean follow-up will average 5.8 years when the trial ends in October 2015, ensuring an accrual of at least 500 coprimary end points.

Given the aforementioned 26 major statin trials involving 170,000 subjects, why do we need HOPE-3? As noted by the authors, most of the data we have that document the benefit of statins in low- and intermediate-risk subjects comes from specific populations: Scotsmen with high LDL-C, Texans with low HDL-C, patients with diabetes, hypertensive patients with multiple risk factors, and subjects with high C-reactive protein levels without diabetes or known vascular disease. Showing benefit in a broad spectrum of intermediate-risk subjects will strengthen the already strong case for primary prevention.

Only 27% (46,675 of 174,149) of participants in 27 randomized statin trials analyzed by the Cholesterol Treatment Trialists' Collaboration were women.[21] The effectiveness of statins in preventing major CV events was similar in women and men at equivalent risk, but in subjects without known vascular disease, women appeared to have a smaller treatment benefit (relative risk per 1 mmol/L reduction in LDL-C was 0.85; 95% CI, 0.72-1.00 for women, and 0.72, 95% CI, 0.66-0.80 for men; adjusted P value for heterogeneity $= 0.02$).

Women comprise 46.2% of participants in HOPE-3. All were at least 65 years old at the time of enrollment according to study entry criteria, and average follow-up will be 5.8 years.[20] The outcome of these participants should remove any lingering doubt as to the utility of statins in this group.

One barrier to statin treatment in much of Asia is the notion that because nearly all of the randomized statin trials were performed predominantly in Caucasian populations, statins might be less effective and have more adverse effects in Asian individuals. Almost 50% of the subjects in HOPE-3 were enrolled in China (28.9%), India (14.4%), and other Asian countries (5.9%). The outcome in these participants is crucially important because in the future, most CV events will occur in Asia.

Atorvastatin, simvastatin, and pravastatin have each been shown to reduce CV events in at least 3 large randomized trials, but rosuvastatin has only 1. In the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), 17,802 men and women without known vascular disease, with LDL-C levels < 130 mg/dL and C-reactive protein levels of ≥ 2.0 mg/L were randomized to rosuvastatin 20 mg/d or placebo.[22] The trial was stopped after a median follow-up of only 1.9 years because of a highly statistically significant 44% reduction in the primary end point. Physician-reported new-onset diabetes was more common in the rosuvastatin compared with the placebo group.

As noted by the HOPE-3 authors,[20] the JUPITER participants were highly selected and not representative of most primary prevention patients who might be eligible for statin treatment. We would predict that HOPE-3 will demonstrate that rosuvastatin reduces CV events in a broader population, and with longer follow-up, 5.8 vs 1.9 years.

HOPE-3, the Candesartan/Hydrochlorthiazide Arm

In the HOPE-3 trial the effects of rosuvastatin on intermediate-risk patients are being investigated, and participants are also being randomized to candesartan/hydrochlorothiazide 16/12.5 mg/d or to placebo. As in the statin arm, in which the inclusion criteria are broader and study participants' risk profiles are more moderate than in previous trials, there are no strict blood pressure (BP) entry thresholds. In fact, the average systolic and diastolic pressure of participants at baseline was 136.6 and 81.6 mm Hg, respectively.[20]

Most of the large trials on the effects of BP reduction on CV events used a BP threshold to compare CV risk and events.[23] Hence, the 2014 Joint National Committee 8 (JNC8)

guidelines for BP management recommends a target BP of < 140/90 or 150/90 mm Hg depending on age and comorbidities.[24] Despite the use of these thresholds, BP reduction reduces CV events, whether targets are met or not. A meta-analysis of 61 studies involving 1 million patients, on BP reduction across age groups, found a negative linear relationship in all age groups between BP and CV events down to a systolic BP of at least 115 mm Hg.[25] Yet another large meta-analysis of 29 BP trials found that a decrease of systolic BP by 5 mm Hg for 5 years reduced the risk of CV events by approximately 25%.[26]

On the basis of these findings, we predict that the HOPE-3 trial, even with an average baseline BP that is already at goal according to the 2014 JNC8 guidelines, will show a reduction in CV events in the candesartan/hydrochlorothiazide arm. Because female and Asian populations have not been well represented in previous BP trials, the results in these groups will be of particular interest.

In conclusion, in contrast to several recent trials with new compounds, the results of HOPE-3 seem to be quite predictable. Hopefully, the knowledge gained from HOPE-3 will be rapidly applied to a broad spectrum of patients at risk, with a corresponding reduction in CV events.

Disclosures

Dr Waters has received remuneration for participating in clinical trial committees from Cerenis, CSL Ltd, Medimmune, Merck Schering-Plough, Pfizer, Resverlogix, Sanofi, and honoraria for lectures from Pfizer and Zydus Medica. Dr Chau has no conflicts of interest to declare.

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