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Waters, David D

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## Review

# Utility of Biomarkers and Imaging in the Development of Drugs for the Treatment of Coronary Atherosclerosis

David D. Waters, MD

*Division of Cardiology, San Francisco General Hospital, and the Department of Medicine, University of California, San Francisco, California, USA*

### ABSTRACT

Biomarkers and imaging trials have often been used as guideposts in the development of drugs for atherosclerosis. This article explores the role of biomarkers and imaging trials in the development of 4 drugs: rimonabant, torcetrapib, ezetimibe, and niacin. Rimonabant, a selective cannabinoid-1 receptor, causes weight loss and exerts favourable effects on lipid biomarkers. An intracoronary ultrasound study showed no effect for the primary but significant benefit for the secondary end point. A large clinical outcomes trial was halted when it became apparent that the drug caused serious psychiatric side effects, including suicide. Torcetrapib, a cholesteryl ester transfer protein inhibitor, lowers low-density lipoprotein (LDL) cholesterol and induces a marked increase in high-density lipoprotein (HDL) cholesterol. However, a large clinical outcomes trial was halted very prematurely due to a 58% increase in all-cause mortality. Neutral imaging studies were reported later. Ezetimibe lowers low density lipoprotein cholesterol but did not reduce carotid intima-media thickness, and there is as yet no clinical trial evidence that it reduces cardiovascular events after a decade on the market. Niacin exerts favourable effects on lipid biomarkers and has shown regression of atherosclerosis in small carotid imaging trials, but did not reduce events in a recent clinical trial that was stopped early due to a lack of efficacy. In summary, favourable effects on lipid biomarkers often do not translate into clinical benefit, and imaging trials, which focus on a narrow measurement of atherosclerosis, are also often not helpful.

### RÉSUMÉ

Les biomarqueurs et les essais en imagerie ont souvent été utilisés comme référence dans le développement de médicaments pour traiter l'athérosclérose. Cet article explore le rôle des biomarqueurs et des essais en imagerie dans le développement de 4 médicaments : le rimonabant, le torcétrapipe, l'ézétimibe et la niacine. Le rimonabant, un récepteur cannabinoïde 1, cause une perte de poids et exerce des effets favorables sur les biomarqueurs lipidiques. Une étude sur les ultrasons intracoronariens n'a montré aucun effet pour le critère d'efficacité primaire, mais un bénéfice significatif pour le critère secondaire. Un vaste essai sur les résultats cliniques a été interrompu lorsque l'on a constaté que le médicament causait des effets secondaires psychiatriques graves, dont le suicide. Le torcétrapipe, un inhibiteur de la protéine de transfert des esters de cholestérol, abaisse le cholestérol à lipoprotéines de faible densité (LDL) et induit une augmentation marquée du cholestérol à lipoprotéines de haute densité (HDL). Cependant, un vaste essai sur les résultats cliniques a été interrompu très prématurément en raison d'une augmentation de 58 % de la mortalité toutes causes confondues. Des études neutres en imagerie ont été rapportées plus tard. L'ézétimibe abaisse le cholestérol à lipoprotéines de basse densité, mais ne réduit pas l'épaisseur de l'intima-média carotidienne, et il n'y a, après une décennie sur le marché, aucune preuve d'essais cliniques qui réduit les événements cardiovasculaires. La niacine exerce des effets favorables sur les biomarqueurs lipidiques et a montré la régression de l'athérosclérose lors de petits essais d'imagerie carotidienne, mais n'a pas réduit les événements au cours d'un essai clinique récent qui a été interrompu prématurément en raison d'un manque d'efficacité. En résumé, les effets favorables sur les biomarqueurs lipidiques ne se traduisent pas souvent en bénéfices cliniques, et les essais en imagerie, qui mettent l'accent sur une mesure précise de l'athérosclérose, sont souvent également inutiles.

The practice of cardiology has flourished over the past few decades as a steady stream of new drugs has emerged from clinical trials to improve patient outcomes. As a consequence,

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Corresponding author: Dr David D. Waters, Division of Cardiology, Room 5G1, San Francisco General Hospital, 1001 Potrero Avenue, San Francisco, California 94965, USA.

E-mail: [dwaters@medsfgh.ucsf.edu](mailto:dwaters@medsfgh.ucsf.edu)

See page 691 for disclosure information.

the costs of the clinical trials needed to document the efficacy of new drugs has increased substantially, because larger sample sizes and longer follow-up periods are required due to the lower event rates seen with modern therapies. In attempts to avoid the large losses caused by failures in late-stage drug development, strategies have been devised to “de-risk” the process. For drugs affecting atherosclerosis, these strategies usually involve imaging trials as the crucial factor in the decision whether or not to proceed with late stage drug development.

Imaging trials offer several appealing features. Each patient contributes to the end point of the study, in contrast to large outcome trials where only a small proportion of the patients suffer a clinical event. Therefore the number of patients required, and the cost, is much lower. The interval between baseline and follow-up imaging is usually 2 years or less, so that the study can at least theoretically be completed in much less time than a larger trial with clinical end points. Additionally, the imaging modality potentially provides information as to the mechanism of action of the drug under study; for example, a reduction in necrotic core in darapladib-treated patients in the **Integrated Biomarkers and Imaging Study-2 (IBIS-2)**<sup>1</sup> suggests that darapladib might reduce plaque rupture, a common cause of coronary events. The imaging study also usually provides practical guidance for the design of the larger clinical event trial to follow.

How successful have imaging trials been in contributing to new drug development? The remainder of this article will attempt to answer this question using recently developed drugs as examples. The list of drugs to be discussed is meant to be illustrative but neither comprehensive or unbiased. Statins will not be discussed because these uniquely potent drugs significantly reduced coronary and cerebrovascular events in almost all adequately designed and executed trials with clinical end points,<sup>2</sup> and also showed benefit in most imaging trials. Furthermore, statin imaging trials were usually predictive of the results of clinical outcomes trials. Statins have made the development of drugs for atherosclerosis look easy. Other drugs have faced more difficulties.

Favourable changes in biomarkers are also commonly used as guideposts in new drug development. Drugs that decrease low-density lipoprotein (LDL) cholesterol, increase high-density lipoprotein (HDL) cholesterol, lower hemoglobin A1C (HbA1c), or reduce blood pressure are expected to produce clinical benefit. Indeed, the first statin drugs were approved for clinical use several years before event trials proved that they reduced cardiovascular events. Regulatory agencies are now unlikely to accept changes in biomarkers as sufficient for drug approval. This shift in policy resulted from the recognition that drugs that favourably influence biomarkers may not only lack clinical benefit, but actually cause harm. For example, rosiglitazone improves fasting blood sugar and HbA1c but may increase the risk of myocardial infarction,<sup>3</sup> and torcetrapib increases HDL cholesterol levels but increases overall mortality.<sup>4</sup>

Let us now look at specific examples of how changes in biomarkers and the results of imaging trials interact to influence the development of drugs for atherosclerosis. These data are summarized in Table 1.

## Rimonabant

Obesity is a major problem in developed countries, contributing to a rising incidence of diabetes and portending a renewed epidemic of cardiovascular disease. Diet and exercise, the preferred treatments for obesity, are ineffective or only temporarily effective for most patients. Current drug treatments for obesity are limited by a lack of efficacy and bothersome side effects.

Rimonabant, a selective cannabinoid-1 receptor, was once a promising drug for the treatment of obesity. In a year-long study of 1036 overweight or obese individuals with dyslipidemia, the 20 mg dose reduced body weight by  $6.7 \pm 0.5$  kg and waist circumference by  $5.8 \pm 0.5$  cm.<sup>5</sup> The 20 mg dose also increased HDL-cholesterol by  $10.0 \pm 1.6\%$  and reduced triglycerides by  $12.4 \pm 3.2\%$ . The main side effects, depression, anxiety, and nausea, were uncommon.

In an intracoronary ultrasound study, 839 patients with obesity and the metabolic syndrome were randomized to placebo or to 20 mg of rimonabant per day.<sup>6</sup> As was expected from earlier studies, rimonabant treatment was associated with weight loss, a decrease in waist circumference, triglycerides, and C-reactive protein levels, and an increase in HDL-cholesterol levels. Intracoronary ultrasound was done at baseline, and after 18 months in the 676 patients who completed the study. Percent atheroma volume, the primary efficacy parameter, increased by less in the rimonabant group, 0.25% vs 0.57%, but this difference was not statistically significant ( $P = 0.22$ ). However, a statistically significant difference was seen for the secondary efficacy parameter, total atheroma volume, with a mean decrease of  $2.2 \text{ mm}^3$  in the rimonabant group and a mean increase of  $0.88 \text{ mm}^3$  in the placebo group ( $P = 0.03$ ). The ambiguous conclusion of this trial was that rimonabant failed to show an effect on the primary end point but showed a favourable effect on the secondary end point, and that “determining whether rimonabant is useful in the management of coronary disease will require additional imaging and outcome trials.”<sup>6</sup>

Rimonabant was approved in Europe for the treatment of obesity in June 2006, but in October 2008, the European Medicines Agency recommended that doctors not prescribe the drug due to serious psychiatric side effects and suicide, and the manufacturer withdrew the drug from the market. Rimonabant was never approved in the United States.

A large randomized clinical trial had been undertaken to compare rimonabant 20 mg with placebo in patients with abdominal obesity and either documented vascular disease or at least 2 major cardiovascular risk factors.<sup>8</sup> The 18,695 patients had been followed for a mean of 13.8 months when the trial

**Table 1. Results of biomarker, imaging, and clinical outcome trials for selected drugs developed to reduce atherosclerosis**

Drug	Biomarker results	IVUS trial	Carotid IMT trial	Large clinical outcome trial
Rimonabant	Benefit <sup>5</sup>	1°: no benefit <sup>6</sup> 2°: benefit	No effect <sup>7</sup>	No effect <sup>8</sup>
Torcetrapib	Benefit <sup>9</sup>	1°: no benefit <sup>10</sup> 2°: benefit	1°: no benefit <sup>11</sup> 2°: harm	Harmful <sup>4</sup>
Ezetimibe	Benefit <sup>12</sup>	—	No effect <sup>13</sup>	Pending <sup>14,15</sup>
Niacin	Benefit <sup>16</sup>	—	Benefit <sup>17,18</sup>	1°: no benefit <sup>19</sup> 2°: benefit; No effect <sup>16</sup>

1°, primary end point; 2°, secondary end point; IMT, intima-media thickness; IVUS, intravascular ultrasound.

was discontinued due to concerns of regulatory agencies about potential side effects. The primary end point, a combination of death, myocardial infarction, and stroke, occurred in 3.9% of rimonabant-treated patients compared with 4.0% in the placebo group (hazard ratio 0.97; 95% confidence interval [CI], 0.84-1.12;  $P = 0.68$ ). Serious psychiatric side effects were reported in 2.5% and 1.3% of patients in the rimonabant and placebo groups respectively.

More recently, the results of the rimonabant carotid imaging trial were published.<sup>7</sup> A total of 661 patients with obesity and the metabolic syndrome were randomized to rimonabant or placebo and were followed for 30 months. Favourable effects on body weight, waist circumference, C-reactive protein, and HDL-cholesterol levels were seen in the rimonabant group compared with the placebo group. Mean carotid intima-medial thickness (IMT) increased by  $0.010 \pm 0.095$  mm in the rimonabant group and by  $0.012 \pm 0.091$  mm in the placebo group ( $P = 0.67$ ).

What are we to make of the rimonabant story? How did the effect of the drug on biomarkers and the 2 imaging trials contribute to our understanding of the drug? The favourable effect of rimonabant on biomarkers was misleading because it did not translate into clinical benefit. The coronary imaging study did not show benefit for the primary end point but did for the secondary end point, and was thus of limited value. The large clinical outcome trial was terminated prematurely but showed no significant reduction in events after a mean follow-up of slightly more than 1 year. The carotid imaging study was completed as the drug was being withdrawn from the market, and thus became a minor postscript to the story. The drug failed because of serious psychiatric side effects, including suicide. Biomarker and imaging studies, due to their relatively small size, are unlikely to detect unexpected, uncommon but serious problems such as this.

## Torcetrapib

The cholesteryl ester transfer protein inhibitor torcetrapib was shown to increase low HDL cholesterol levels by 61% at a dose of 120 mg per day and by 106% at 120 mg twice daily.<sup>9</sup> Additionally, LDL cholesterol decreased by 17%, and both HDL and LDL cholesterol particle sizes were shifted upward. This promising result led to the initiation of an intracoronary ultrasound study, 2 carotid imaging studies, and a large outcomes trial.

In the outcomes trial, 15,067 patients at high cardiovascular risk were treated with an atorvastatin dose to lower LDL cholesterol to less than 100 mg/dL (2.6 mmol/L), and then were randomized to the addition of torcetrapib 60 mg per day or to placebo.<sup>4</sup> The primary end point was a composite of cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina. At 12 months torcetrapib increased HDL cholesterol by 72.1% and lowered LDL cholesterol by 24.9% compared with baseline. After a median follow-up of 550 days, the trial was terminated prematurely on the advice of the data and safety monitoring board. Total mortality (hazard ratio 1.58; 95% CI, 1.14-2.19;  $P = 0.006$ ) and cardiovascular events (hazard ratio 1.25; 95% CI, 1.09-1.44;  $P = 0.001$ ) were both higher in the torcetrapib group. The adverse effects of torcetrapib appeared to be related to stimulation of L-type cal-

cium channels, with increases in blood pressure and serum aldosterone levels.<sup>20</sup>

The results of the torcetrapib imaging trials became available only after the clinical trial had been terminated. In the intracoronary ultrasound trial, 1188 patients were treated with atorvastatin to lower LDL cholesterol below 100 mg/dL (2.6 mmol/L), and then randomized to the addition of torcetrapib 60 mg per day or to placebo, as in the outcomes trial.<sup>10</sup> Intracoronary ultrasound was repeated after 2 years in 910 patients. Percent atheroma volume, the primary efficacy measure, increased by 0.19% in the atorvastatin only group and by 0.12% in the torcetrapib-atorvastatin group ( $P = 0.72$ ). A secondary measure, change in normalized atheroma volume, showed a favourable effect with torcetrapib ( $P = 0.02$ ).

In 1 of the carotid imaging trials (Rating Atherosclerosis Disease Change by Imaging With a New CETP Inhibitor [RADIANCE] 1), 850 patients with heterozygous familial hypercholesterolemia were randomized to atorvastatin or atorvastatin plus torcetrapib for 2 years.<sup>11</sup> The primary measure of efficacy, increase in maximum carotid IMT, was  $0.0053 \pm 0.0028$  mm per year in the atorvastatin only group and  $0.0047 \pm 0.0028$  mm per year in the torcetrapib-atorvastatin group ( $P = 0.87$ ). The secondary efficacy measure, annualized change in mean carotid IMT for common carotid artery, showed a decrease of 0.0014 mm per year in the atorvastatin only group and an increase of 0.0038 mm per year in the torcetrapib-atorvastatin group ( $P = 0.005$ ).

In the other carotid imaging trial (RADIANCE 2), 752 patients with hypertriglyceridemia and an LDL cholesterol level high enough to warrant treatment according to guidelines were randomized to atorvastatin alone or torcetrapib-atorvastatin.<sup>21</sup> After a mean follow-up of 22 months, the change in maximum carotid IMT was  $0.030 \pm 0.005$  mm per year in the atorvastatin alone group and  $0.025 \pm 0.005$  mm per year in the torcetrapib-atorvastatin group ( $P = 0.46$ ). In a pooled analysis of the 2 carotid trials, an increase in blood pressure was associated with more carotid IMT progression, and a decrease in LDL cholesterol with less progression.<sup>22</sup> Changes in HDL cholesterol had no effect on carotid IMT.

The sequence of events in the development of torcetrapib was very unusual in that the large clinical outcomes trial was stopped because of harm before the imaging trials were completed. One can speculate that if the results of the imaging trials had been known beforehand, the large clinical outcomes trial could have been avoided. However, this is not certain, or perhaps even not likely, given the high level of enthusiasm that existed at the time for any HDL cholesterol-raising therapy.

The 58% increase in total mortality seen in slightly more than 1 year of follow-up in the clinical outcome trial was shocking and surprising. No cardiology trial in recent history has had such a bad result so quickly. Imaging trials, with their narrow focus on the measurement of atherosclerosis, would not be expected to detect such a problem. Imaging trials did not fail with torcetrapib, but the torcetrapib story reminds us of their limitations.

## Ezetimibe

Ezetimibe at a dose of 10 mg per day reduces LDL cholesterol by a mean of 18.5% in short-term studies, with small improvements in HDL cholesterol and triglyceride levels.<sup>12</sup>

Ezetimibe was approved in the United States in October, 2002, based upon its LDL cholesterol-lowering properties and benign safety profile. A decade later, evidence that ezetimibe reduces coronary events is still lacking. The combination of simvastatin plus ezetimibe has been shown to reduce coronary events in patients with aortic stenosis<sup>23</sup> or chronic kidney disease,<sup>24</sup> but benefit has not been shown for ezetimibe alone.

In a carotid imaging study (**Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression [ENHANCE]**), 720 patients with familial hypercholesterolemia were all treated with simvastatin 80 mg per day and randomized to ezetimibe 10 mg per day or to placebo.<sup>13</sup> At the end of the 2-year follow-up period, mean LDL cholesterol was 16.5% lower and C-reactive protein levels were 25.7% lower in the ezetimibe group. Mean carotid IMT increased by  $0.0058 \pm 0.0037$  mm in the simvastatin only group and by  $0.0111 \pm 0.0038$  mm in the ezetimibe-simvastatin group ( $P = 0.29$ ).

The results of this trial ignited a major controversy. Apologists for ezetimibe brought forward several potential explanations for the failure of ezetimibe to demonstrate benefit. The American College of Cardiology Expert Panel comments on the trial emphasized that it was not possible to know at this point whether ezetimibe was beneficial, harmful, or without a clinically important effect.<sup>25</sup> Recognizing that a low LDL cholesterol was a strong predictor of outcomes, and that ezetimibe lowered LDL cholesterol, they emphasized that the clinical effect of a drug cannot be inferred based solely on its effect on a biomarker.

The results of another carotid imaging trial, **Stop Atherosclerosis in Native Diabetics Study (SANDS)**, have suggested that ezetimibe may have a beneficial effect on carotid IMT.<sup>26</sup> In that study, 499 American Indians with type 2 diabetes were randomized to more aggressive vs standard LDL cholesterol goals; specifically  $\leq 70$  mg/dL (1.8 mmol/L) or  $\leq 100$  mg/dL (2.6 mmol/L). Regression of carotid IMT was seen over the 3 years of treatment in the group with the aggressive goal compared with progression in the group with the standard target. Approximately 1/3 of the aggressively treated patients required ezetimibe in addition to a statin to reach their LDL cholesterol target. Regression was similar in patients with ezetimibe and with a statin alone, and in a logistic regression model, higher baseline carotid IMT and changes in LDL cholesterol, but not ezetimibe use, were predictors of regression. These findings, derived from a post hoc analysis based on postrandomization treatment decisions made in an open-label study, suggest that ezetimibe may have a beneficial effect on carotid IMT, but do not carry the weight of the ENHANCE findings.

An ongoing clinical trial, **Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT)**, is enrolling up to 18,000 patients stabilized after an acute coronary syndrome and randomizing them to either simvastatin 40 mg per day or this dose of simvastatin plus ezetimibe 10 mg per day.<sup>14</sup> The primary end point is a composite of cardiovascular death, myocardial infarction, rehospitalization for unstable angina, coronary revascularization, or stroke. Patients will be followed for a minimum of 2.5 years and until at least 5250 patients experience a primary end point. The number of end points to be accrued has increased from 2995 to 5250 since the trial began, with a corresponding increase in sample size from 10,000 to approximately 18,000 patients. The trial will have a 90% power to detect a treatment effect of  $<10\%$ , and is ex-

pected to be completed in June, 2013.<sup>15</sup> The results of this trial will validate either the biomarker, LDL cholesterol, or the carotid imaging trial.

## Niacin

Whether niacin reduces coronary events has been controversial for 40 years. The Coronary Drug Project, conducted between 1966 and 1975, randomized 8341 men aged 30-64 years with previous myocardial infarction to placebo, clofibrate, dextrothyroxine, niacin 3 gm per day, or 1 of 2 estrogen doses.<sup>19</sup> (These were considered to be the best cholesterol-lowering therapies of that era.) The dextrothyroxine and estrogen arms of the trial were discontinued early due to harm. After a mean follow-up of 6.2 years, clofibrate showed no benefit, and for the primary endpoint, total mortality, there was a trend toward benefit with niacin, 24.8% vs 25.9%. These extremely high mortality rates were typical for that time, when even aspirin was not used for secondary prevention. The rate of recurrent myocardial infarction, a secondary end point, was significantly reduced in the niacin group compared with the placebo group (10.4% vs 14.9%).

In 1980, the Coronary Drug Project Research Group recontacted the original patients in the trial.<sup>19</sup> The purpose of this extended follow-up was to determine whether any further adverse effects had occurred as a result of treatment, given the excess cancer risk seen with estrogen and the excess mortality seen with clofibrate in another study. Instead, after a mean follow-up of 15 years, nearly 9 years after the end of the trial, all-cause mortality was reduced in the niacin group compared with placebo, 52.0% vs 58.2% ( $P = 0.0004$ ). The lower myocardial infarction rate during the trial was not thought to be sufficient to explain this difference.

Niacin has consistently shown benefit in imaging studies. The combination of simvastatin plus niacin induced average regression of coronary lesions during a 3-year trial, while placebo and antioxidant vitamins were associated with progression.<sup>27</sup>

In a carotid imaging trial, 167 patients with known coronary disease and low HDL cholesterol levels were randomized to placebo or niacin 1 gm per day added to background statin therapy and followed for 1 year.<sup>17</sup> Among the 149 patients who completed the trial, carotid IMT progressed compared with baseline in the placebo group ( $P < 0.001$ ) but was unchanged in the niacin group. The intergroup difference did not quite attain statistical significance ( $P = 0.08$ ) overall but did in patients without insulin resistance ( $P = 0.026$ ).

In a later study by the same group, niacin 2 gm per day or ezetimibe 10 mg per day were added to statin therapy in 363 patients with an LDL cholesterol  $<100$  mg/dL (2.6 mmol/L).<sup>18</sup> Patients were to be followed for 14 months; however, the study was stopped after 208 patients had undergone end-of-study imaging because of a significant difference in the primary end point, mean carotid IMT ( $P = 0.003$ ). Despite LDL cholesterol lowering, no change in carotid IMT occurred in the ezetimibe group, but regression of carotid IMT occurred in the niacin group ( $P = 0.001$ ). In addition, major cardiovascular events were documented in 9 ezetimibe vs 2 niacin patients, (5% vs 1%;  $P = 0.04$ ). The results of this study could be interpreted as showing harm for ezetimibe or benefit for niacin.

Based upon the favourable effect of niacin on lipid biomarkers, the results of the carotid imaging trials, and the long-term outcomes of patients treated with niacin in the Coronary Drug Project, it seemed reasonable to assume that niacin would show benefit in modern clinical outcome trials. However, the **Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH)** trial was stopped in 2011 due to a lack of efficacy.<sup>16</sup> This trial enrolled 3414 patients with coronary, cerebrovascular, or peripheral vascular disease, low HDL cholesterol, and high triglyceride levels, and an LDL-cholesterol level of 40-80 mg/dL (1.03-2.07 mmol/L) on treatment with simvastatin. Patients were randomized to either niacin 1.5-2.0 gm per day or to placebo. The trial was stopped after a mean follow-up of 3 years. The primary end point was a composite of coronary death, myocardial infarction, ischemic stroke, hospitalization for acute coronary syndrome, or symptom-driven coronary or cerebral revascularization. The primary end point occurred in 282 patients in the niacin group and 274 patients in the placebo group (16.4% vs 16.2%, hazard ratio, 1.02; 95% CI, 0.87-1.21;  $P = 0.79$ ). This lack of benefit was coincident with favourable changes in lipid biomarkers: the HDL cholesterol level increased by 25.0% to 42 mg/dL (1.09 mmol/L) in the niacin group, whereas it had increased by 9.8% to 38 mg/dL (0.98 mmol/L) in the placebo group ( $P < 0.001$ ). Triglyceride levels decreased by 28.6% in the niacin group and by 8.1% in the placebo group and the LDL cholesterol level decreased by 12.0% in the niacin group and by 5.5% in the placebo group.

What are we to make of the conflicting results with niacin? It is possible that the clinical trial was underpowered, and that a larger sample size or longer follow-up would have revealed the benefits of niacin. If this is the case, an ongoing study comparing niacin with placebo in more than 25,000 patients, the **Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE)** (NCT00461630) will provide a positive result when it is complete in early 2013.<sup>28</sup> However, the positive carotid imaging results with niacin were detected in a small sample size with a short follow-up. Is it possible that the carotid imaging changes are unrelated to the clinical benefit of niacin, assuming that there is clinical benefit?

## Conclusions

For at least 2 of the drugs discussed here, rimonabant and torcetrapib, but possibly also for ezetimibe and niacin, favourable effects on established lipid biomarkers did not translate into a clinical reduction in events. For torcetrapib, off-target effects of the drug that increased mortality caused this failure. For rimonabant, noncardiac adverse events led to withdrawal of the drug from the market, so that even if clinical benefit were present, it would not be relevant. For ezetimibe and niacin, it is possible that ongoing trials will validate the favourable effects of these drugs on lipids.

The imaging trials for these drugs produced results that were not particularly helpful. The intracoronary ultrasound trials for rimonabant and torcetrapib were negative for the primary end point but positive for the secondary end point, engendering a sense of uncertainty. The carotid imaging trial for ezetimibe, ENHANCE,<sup>13</sup> may turn out to have correctly pre-

dicted the lack of effect of this drug, but the results of ENHANCE are contradicted by the secondary analysis from SANDS.<sup>26</sup> The results of the carotid imaging trials with niacin are flatly contradicted by the negative results from the much larger clinical trial, AIM-HIGH.<sup>16</sup> By focusing on 1 narrow end point, change in a measure of atherosclerosis, imaging trials may miss crucial features of a drug. Furthermore, the imaging end point may not correlate with important clinical outcomes.

## Disclosures

David D. Waters has received remuneration for participating in trial committees or for consulting for the following companies developing drugs for atherosclerosis: Anthera, Aegerion, Genentech, Merck Schering-Plough, Pfizer, Roche, and Sanofi Aventis, and has received honoraria for lectures from Bristol-Myers Squibb and Pfizer.

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