If one could design a metabolic intervention to prevent incident or recurrent cardiovascular events, it might look a lot like torcetrapib. Torcetrapib is the first cholesteryl ester transfer protein (CETP) inhibitor extensively studied in humans. Torcetrapib, in addition to statin therapy, raised high-density lipoprotein (HDL) by $\geq 70\%$, lowered low-density lipoprotein by 25%, and lowered triglycerides by $\approx 10\%$. This is an impressive profile for a pharmaceutical agent. What if someone told you that this therapy also improves glycemic control?

That is precisely what Barter et al. tell us in the current issue of *Circulation*. In a post hoc analysis of the Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events (ILLUMINATE) trial, the authors report the results of multiple glycemic measures among atorvastatin-treated patients randomly assigned to torcetrapib versus placebo. Torcetrapib/atorvastatin-treated patients had modest, but consistently lower, levels of plasma glucose and glycosylated hemoglobin than patients taking atorvastatin alone. These differences were observed in the setting of lower levels of plasma insulin, suggesting that torcetrapib was associated with better insulin sensitivity and less insulin resistance. These changes were more prominent in subjects with diabetes mellitus, but also seemed to be present in subjects without diabetes mellitus. These findings emerged early, within 1 month, and increased progressively during follow-up (12 months). The glycemic results in ILLUMINATE are subject to the play of chance, 1 significant observation among many possible observations across multiple parameters tested. In addition, the relatively small effects on glycemic parameters could be seen as a variation across measurements. However the consistency of the findings across multiple subgroups, measures (glucose, glycosylated hemoglobin, diabetes mellitus, even hypoglycemia), and time points suggests that these findings may indeed be real.

With these important reductions of key surrogate markers of the risk of cardiovascular disease, including low-density lipoprotein, HDL, triglycerides, and glycerina, this seems like a drug that should be widely prescribed to those at risk for cardiovascular disease. Of course, it is not now, and will never be prescribed to our patients for these indications. The reason for this is that, despite the observed benefits on these key surrogates, patients treated with torcetrapib in ILLUMINATE had 25% more cardiovascular events, including 58% more total deaths than those treated with placebo.1

Much has been discussed and written about the surprising failure of torcetrapib in ILLUMINATE. Some have opined that the mechanism of action of the drug (CETP inhibition) is a physiologically ineffective way of raising HDL, creating higher levels of HDL that do not modify atherosclerosis.2 Others, including the authors of the present article, suggest that the off-target effects of torcetrapib, including hyperaldosteronism and hypertension, are responsible for the worse outcomes observed with torcetrapib in ILLUMINATE, and that CETP inhibition may still be a reasonable therapeutic target.3 Regardless, torcetrapib is not a clinically viable drug.

So, why is this new information about the glycemic results of ILLUMINATE interesting and potentially important? First, this analysis may provide additional insight into the relationships between 2 key risk factors for cardiovascular disease, lipids (in particular, HDL) and glycemia. It has recently been recognized that statins afford a modest but real increase in glycemic parameters and slightly increase the rate of incident diabetes mellitus.4 In the case of statins, the reduction in cardiovascular events is substantial and out-weighs this risk.5 Indeed, when comparing pretrial and on-therapy analyses, much of the improvement of glycemic parameters in ILLUMINATE appears to be a counterbalancing effect of torcetrapib on the increase in glucose from statin therapy.5 For instance, the glycosylated hemoglobin values in the atorvastatin group increased from 7.06% to 7.36% during the trial, and these values also increased in the torcetrapib/atorvastatin group, but to a lesser extent, from 7.07% to 7.16%, thereby, a relative decrease (0.2%, $P<0.0001$).

The mechanism of the torcetrapib effects on glycemia cannot be definitively determined from this analysis, but is a key question. Are these findings a downstream effect of raising HDL, an effect of inhibiting CETP, or another off-target effect unique to torcetrapib? Clearly, drugs that raise HDL do not uniformly improve glycemic status. Niacin is known to have detrimental effects on glycemic parameters. A systematic review of niacin studies indicates that niacin is associated with an increase of 4% to 5% on blood glucose and an $\approx 0.3\%$ absolute increase in glycosylated hemoglobin, effects similar in magnitude, but opposite in direction to those observed with torcetrapib in the present analysis. Whether this is a CETP effect remains to be seen. There are clean CETP inhibitors: dalcetrapib,7 which raises HDL by $\approx 33\%$, and anacetrapib,8 which raises HDL by $\approx 140\%$. Dalcetrapib and anacetrapib do not seem to share the hyperaldosteron-ism/hypertension off-target effects of torcetrapib. Both drugs...
are being studied currently in phase III clinical outcomes trials. Dalcetrapib is being evaluated in the dal-OUTCOMES trial (NCT00658515), a 15 600-patient trial in patients with acute coronary syndromes; this trial has completed the enrollment phase. Anacetrapib is to be evaluated in the HPS 3–REVEAL–TIMI 55 trial (NCT01252953), which includes 30 000 stable patients with a history of atherosclerotic vascular disease (myocardial infarction, stroke, or peripheral vascular disease) or diabetes mellitus and asymptomatic coronary artery disease. These trials will determine whether CETP inhibition is a successful means of preventing recurrent cardiovascular events. On the basis of the results of the analysis by Barter et al, it will be of substantial interest to determine from dalcetrapib and anacetrapib whether the glycemic effects of torcetrapib are a class effect of CETP inhibitors, or unique to this agent.

Second, this is another example of the complex interplay between cardiovascular disease and diabetes mellitus. As the epidemic of diabetes mellitus rages, we as clinicians and scientists must be cognizant of the 2-way interplay of cardiovascular and diabetic therapies. Two examples, the abovementioned (statins and niacin) agents for the management of lipids and, in the case of statins, cardiovascular event prevention, have been provided of therapeutics that clinicians should recognize that may worsen diabetic control. The well-publicized saga of rosiglitazone, an antidiabetic agent that improves glycemic control, but increases cardiovascular risk, has led in part to changes in the ways regulators evaluate diabetes mellitus medications, with a requirement for a cardiovascular outcomes trial to demonstrate safety.

In another recent publication in Circulation, renal denervation for refractory hypertension also improved glycemic control and insulin sensitivity. Indeed, another recent report demonstrated that ranolazine, an antiangiinal agent, improved diabetic control in patients with acute coronary syndromes. As with torcetrapib, the mechanism of the potential glycemic effects these agents or interventions is not certain. As we move forward, we must continue to be cognizant of the effects of our therapies on multiple risk factors, including glycemia. Whereas the longstanding belief that we can improve cardiovascular outcomes by aggressively modulating glycemia has proven elusive, perhaps in the future management of diabetes mellitus may be modestly improved by agents that have beneficial cardiovascular effects, and also favorably modulate glycemia.

Finally, and perhaps most importantly, this study serves as a further reminder of the key and ongoing role of large-scale clinical outcomes trials. No matter how well a drug performs with several major surrogate end points, until a clinical outcomes trial is complete, one cannot say with certainty how the interaction of chemical entity with complex human physiology will turn out. In addition, this study should serve as a reminder of the absolute necessity of the use of the clinical trials machinery to facilitate the collection and subsequent analysis of biological samples within these pivotal clinical trials to advance our understanding of human health and disease. Although torcetrapib will not be used to improve the outcomes in patients with diabetes mellitus or coronary disease, perhaps information from the study of this agent can contribute to this goal.

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