Diabetes mellitus affects 28.5 million people in the United States with another 79 million people having prediabetes at high risk for developing diabetes mellitus, despite current preventive efforts using lifestyle or antidiabetic agents such as metformin. Because cardiovascular disease (CVD) is the major cause of death and disability in diabetes mellitus, and its impact on health remains considerable despite intensified diabetes mellitus management, early identification of diabetes mellitus and those at risk for it offers the optimal opportunity for effective prevention of vascular complications. The demonstration that low-density lipoprotein (LDL)–lowering with statin therapy is beneficial in preventing CVD and its progression in these patients has led to their increasingly widespread application. As a consequence, the recently released American College of Cardiology/American Heart Association Blood Cholesterol Task Force now recommends >50% LDL-cholesterol (LDL-C)–lowering in those with diabetes mellitus who are 40 to 75 years old with LDL-C levels >70 mg/dL. This expands the requirement for high-intensity statin treatment, as well as the need for add-on therapy with second-line LDL-lowering drugs. Another recommendation by the Task Force is for the use of moderate- to high-intensity statin therapy in nondiabetic subjects and in those who have a 10-year CVD risk of >7.5%, many of whom have prediabetes or metabolic syndrome. Although statin therapy has yielded significant benefit in CVD prevention, many subjects are unable to tolerate statins because of myalgia, particularly at higher doses. Furthermore, it is now recognized that statin therapy increases risk for diabetes mellitus especially in those with diabetes mellitus risk factors and receiving intensive statin therapy, raising questions about its net benefit in primary prevention.

Targeting Low-Density Lipoprotein AND Dysmetabolism in Type 2 Diabetes Mellitus

Ronald Goldberg

Diabetes mellitus is for the use of moderate- to high-intensity LDL-lowering drugs. Another recommendation by the Task Force is for the use of moderate- to high-intensity statin therapy in nondiabetic subjects and in those who have a 10-year CVD risk of >7.5%, many of whom have prediabetes or metabolic syndrome. Although statin therapy has yielded significant benefit in CVD prevention, many subjects are unable to tolerate statins because of myalgia, particularly at higher doses. Furthermore, it is now recognized that statin therapy increases risk for diabetes mellitus especially in those with diabetes mellitus risk factors and receiving intensive statin therapy, raising questions about its net benefit in primary prevention.

See accompanying article on page 676

In this issue of the journal, Gutierrez et al report the results of a proof-of-concept, 4-week, in-house, randomized, placebo-controlled clinical trial of a new investigational LDL-lowering agent, ETC-1002, in 60 subjects with type 2 diabetes mellitus mostly receiving metformin monotherapy. ETC-1002 is a dicarboxylic acid derivative with a novel, dual mode of action. In the free acid form, it activates adenosine monophosphate–activated protein kinase (AMPK) and, in addition, it is rapidly acetylated in the liver to form a thioester, which inhibits adenosine triphosphate–citrate lyase (ACL). These 2 enzymes, ACL and AMPK, have important effects on fatty acid and cholesterol metabolism. ACL generates cytoplasmic acetyl coenzyme A required for fatty acid and cholesterol synthesis, and its inhibition reduces the activities of these pathways, increasing fatty acid oxidation. AMPK inhibits both hydroxymethylglutaryl coenzyme A reductase, the rate-limiting enzyme in cholesterol synthesis, as well as acetyl coenzyme A carboxylase, which initiates fatty acid synthesis, and as a consequence fatty acid oxidation is also increased.

Gutierrez et al demonstrate several findings worthy of comment. First, they show after withdrawal of previous lipid-lowering and antihyperglycemia medications ≥4 weeks before dosing with 120 mg of ETC-1002 daily that LDL-C fell by 43% without any change in triglyceride or high-density lipoprotein cholesterol. This degree of LDL-C reduction is impressive, approaching the effect of high intensity statin therapy. It may reflect the dual actions of the agent on ACL and AMPK to impair cholesterol synthesis, enhancing LDL-receptor activity in a similar fashion to statins, although this remains to be proven. In this regard, it is of interest that metformin, widely used in the treatment of diabetes mellitus through its action to increase AMPK activity and inhibit gluconeogenesis, has rather modest effects on LDL-C. This may mean that the dominant effect of ETC-1002 on LDL-C operates through inhibition of ACL or through synergism of ACL inhibition and AMPK activation. Of further interest, in a recently published 12-week dose-ranging study of ECT-1002 in 177 nondiabetic subjects, was the demonstration that the 120-mg dose led to a smaller 27% reduction in LDL-C. The reason for the greater LDL-C reduction in this study is unclear and obviously needs further investigation. If confirmed, it would point to a heightened responsivity associated with diabetes mellitus as it relates to the action of this agent on LDL-C and not seen with statin therapy, such as for example the presence of reduced AMPK activity in diabetes mellitus. Although myalgia was not noted in this small, short-term study, 4% to 7% of subjects in the larger 12-week study did report muscle aches. This is relevant because statin-associated myalgia may be related to deficiency of isoprenoids resulting from the reduced flux of intermediates along the cholesterol synthetic pathway. Because ETC-1002 also operates on this pathway, its value in subjects intolerant to statin therapy could be limited. A related consideration would be whether combining this agent with a statin would have an additive effect or not.

A second noteworthy finding is that ETC-1002 reduced high sensitivity C reactive protein (hsCRP) values by 40.5%. This too differed from findings in the earlier dose-ranging study in which no significant reduction was noted, except in...
those with baseline hsCRP levels >2.0 mg/l in which there was a 43% to 65% reduction. These observations suggest that like statins, ETC-1002 has anti-inflammatory properties that may be associated with CVD benefit beyond LDL reduction particularly in those with heightened subclinical inflammation. However, unlike with statins, the anti-inflammatory effect of ECT-1002 may be more closely tied to improvements in the dysmetabolism of type 2 diabetes mellitus. The principal metabolic role of AMPK is as master cellular fuel gauge, switching metabolism in ATP-depleted states, for example, exercise, from ATP-consuming activities, such as hepatic glucose production and lipid synthesis, to ATP-producing activities, such as fatty acid oxidation. Recently, activation of AMPK by ETC-1002 complemented by ACL inhibition in rodent models of obesity has been shown to produce broad anti-inflammatory effects such as suppression of leukocyte homing and reduced adipose inflammation, as well as lower hepatic lipids, and glucose and insulin levels. Thus, by activating AMPK and inhibiting ACL, ETC-1002 may help to ameliorate steatosis, inflammation, and insulin resistance as has been shown with pioglitazone and metformin therapies.

Although there were downward trends, Gutierrez et al did not find significant lowering of fasting, postprandial, and hourly plasma glucose levels or during continuous glucose monitoring, nor of fasting insulin after 4 weeks of ETC-1002 therapy. Daily peak and postprandial glucose levels in the obese subgroup were significantly lower, and there was more frequent reporting of hyperglycemia as an adverse event in the placebo versus ETC-1002 groups. The fact that glucose levels did not rise in the placebo group despite discontinuation of metformin therapy suggests that lifestyle changes during the in-house dosing period contributed to improved glycemic control making it difficult to interpret these results. The effects of ETC-1002 on insulin sensitivity and hepatic glucose production measured directly and under steady-state conditions are clearly needed. Thus, although these preliminary findings do not allow us to conclude that ETC-1002 has a clinically useful antihyperglycemic effect in diabetic subjects, together with previously published data they provide a basis for anticipating that this agent, in contrast to statins, does not aggravate glucose intolerance and, like metformin, may reduce hepatic glucose production and improve insulin sensitivity.

In summary, ETC-1002 seems to provide a novel therapeutic approach to the prevention of vascular complications in type 2 diabetes mellitus in that it combines significant LDL lowering with improvements in the cross-linkages between subclinical inflammation and dysmetabolism in this disease. These properties may therefore also have application to the larger population with prediabetes and metabolic syndrome. Ultimately, as in the development of any new drug that influences central metabolic pathways, documenting long-term safety will be crucial. It is, however, somewhat reassuring that lengthy clinical experience with an agent known to increase AMPK activity, namely metformin, has proven positive.

Disclosures
None.

References

Key Words: Editorials ■ LDL-cholesterol ■ type 2 diabetes
Targeting Low-Density Lipoprotein AND Dysmetabolism in Type 2 Diabetes Mellitus

Ronald Goldberg

doi: 10.1161/ATVBAHA.114.303171
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/34/3/477

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org/subscriptions/