EDITORIAL COMMENT

STARR (STudy of Atherosclerosis with Ramipril and Rosiglitazone)

Is the Biggest Big Enough?*

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The relationship between elevated plasma glucose levels and cardiovascular (CV) risk has been confirmed by studies demonstrating that individuals with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) have an increased likelihood of developing major CV events (1).

Metabolic abnormalities such as diabetes, obesity, insulin resistance, and dyslipidemia predispose to atherosclerosis usually via mechanisms involving endothelial activation, inflammation, increased oxidative stress, and thrombogenesis (2). There is a need for effective strategies to reduce CV risk in subjects with early manifestations of these metabolic disorders. In this issue of the *Journal*, Lonn et al. (3) report the results of the STARR (STudy of Atherosclerosis with Ramipril and Rosiglitazone), a challenging substudy of the DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) trial (4), aimed at assessing the effects of the angiotensin-converting enzyme (ACE) inhibitor ramipril and the thiazolidinedione (TZD) rosiglitazone on the progression of carotid intima-media thickness (CIMT), in patients with pre-diabetes but without clinical evidence for CV disease.

Importance of Defining a Therapeutic Regimen in the Pre-Diabetic Population

The rationale for the study is sound in that both ramipril and rosiglitazone have a wide range of properties that could afford vasculoprotection in patients with pre-diabetes. Ramipril has been shown to reduce the incidence of stroke,

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myocardial infarction (MI), and death due to CV disease in high-risk patient groups (5). These beneficial effects are usually attributed to mean arterial pressure reduction. However, studies in humans and experimental animals indicate that ACE inhibitors have additional effects on arterial wall structure contributing to reduced arterial stiffness. Ramipril has been shown to influence the expression and synthesis of matrix components, collagens and elastin, and matrix modulating enzymes (i.e., metalloproteinase-2 and -3). These findings lend support to the argument that the vasculoprotective effects of ACE inhibitors might also be secondary to these molecular changes (6).

The TZDs, peroxisome proliferators-activated receptor activators, are a family of drugs known to influence both glucose and lipid metabolism through transcriptional activation of specific genes. In addition, these agents have a range of cellular effects that are independent of their metabolic effects. The TZDs have anti-inflammatory and anti-atherogenic properties and inhibit smooth muscle cell proliferation, thus providing a mechanism for these drugs to influence medial hyperplasia (7). These observations and recent findings of atheroma reduction in patients with diabetes (8,9) as well as the demonstration of beneficial effects of rosiglitazone on CIMT progression in a nondiabetic population (10) support the idea that the effect might be independent of the metabolic actions of TZDs.

Although both pharmacological agents used in the STARR trial are well known, the clinical use of rosiglitazone has recently come into question after a meta-analysis of 42 trials that showed that, as compared with placebo or other antidiabetic regimens, treatment with rosiglitazone was associated with an increased risk of MI and CV death (11). The worrisome findings in the Nissen and Wolski meta-analysis (11), however, need to be further investigated in prospective studies, because they were of borderline statistical significance and were based both on limited information from trial results obtained from publicly available sources and on a relatively small number of events. The STARR trial, which assessed a population of pre-diabetic patients with a therapeutic need for preventative drug regimens, did not find differences in CV event rates with the use of rosiglitazone during a median follow-up of 3 years. Further to this issue, an interim report of the RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes) study, a well-designed prospective study of 4,447 patients with diabetes, has not shown a significant increase in the incidence of MI or CV death or in the combined primary end point of hospital stay or death from CV causes with rosiglitazone (12). The final evaluation, however, awaits the report of the 3 large prospective trials (RECORD, BARI2D [Bypass Angioplasty Revascularization Investigation 2 Diabetes], and ACCORD [Action to Control Cardiovascular Risk in Diabetes]) to provide a definitive answer.

The STARR Trial: Surrogate Markers, Main Findings, and Clinical Implications

Main findings in the STARR trial (3) were that ramipril reduced blood pressure and had a neutral effect on CIMT progression, whereas rosiglitazone reduced glycemia and had a modest beneficial action on CIMT progression. The absence of a significant effect of ramipril on CIMT contrasts with findings in previous studies showing that ACE inhibitor treatment reduces CIMT progression (13). However, such trials were conducted in high-risk populations with vascular disease, diabetes, or hypertension who are expected to have a more active renin-angiotensin system and rapid vascular disease progression, compared with the subjects entered in the STARR trial. The results for rosiglitazone are not conclusive but suggest a modest beneficial short-term effect on vascular disease progression that could perhaps result in more robust longer-term effects on vascular disease progression.

CIMT, a surrogate end point for the estimation of future risk of CV events, is a validated end point and has been shown to correlate with risk of future CV events (14). The low CIMT progression rates observed in the STARR trial (3) contrast with other reports that showed an increased rate of CV events in subjects with pre-diabetes compared with individuals with normal glucose metabolism. An important difference between the STARR trial and other studies is that patients in the latter group were followed for longer periods of time (13), and this could explain, at least in part, the discrepancies. Moreover, the STARR investigators seem to have overestimated the expected CIMT progression in their study (by approximately 50%), which meant that the STARR participants had a far lower CIMT progression, and thus the ability to observe a 30% inhibitory effect in a population comprising only 1,425 patients might be compromised. The authors suggest that this might account for the unexpected lack of effect of ramipril. Previous trials showing a beneficial effect of ramipril were studies in which the extent of baseline CIMT was greater (13).

The trial is challenging both from the point of view of the size and length of the study and the ability to measure a drug effect on CIMT, a parameter with low baseline values and unlikely to change significantly over a relatively short term in a population where progression of CV disease does not necessarily follow an accelerated course.

The STARR trial (3) is the largest of its kind thus far to examine CIMT progression in individuals with IGT or IFG but without CV disease. In addition, the trial can also claim that it has the longest period of observation, 3.09 (interquartile range 2.86 to 3.50) years, in comparison with other studies evaluating the effects of TZDs on atherosclerosis progression in diabetic patients (8,9). The clinical implications of the study, however, are not extremely clear at present, particularly in view of the neutral effects of ramipril and the modest effects of rosiglitazone on CIMT in pre-diabetic patients found in the trial. Because rosiglitazone in particular is under close scrutiny after the results of the meta-analysis by Nissen and Wolski in 2007 (11) and TZDs in general continue to be monitored in view of reports showing that these drugs can increase the risk for heart failure (15), the possible clinical application of the STARR findings remains uncertain.

Despite the beneficial actions of TZDs in clinical and experimental studies in diabetic and nondiabetic populations—including the modest findings reported in STARR—the true effects of these drugs on ischemic CV events and all-cause mortality and their role in clinical practice regarding CV disease prevention still require further ad hoc investigation. Perhaps the development of new pharmacological agents able to overcome the limitations of TZDs, particularly in relation to their potentially adverse CV effects, and a better understanding of the mechanisms leading to CV events in pre-diabetic individuals might offer better options for patient management in the not so distant future.

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REFERENCES

1. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. Diabetes Care 1999;22:233–40.
2. Grundy SM, Cleeman JI, Daniels SR, et al., American Heart Association, National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112:2735–52.
3. Lonn EM, Gerstein HC, Sheridan P, et al., for the DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) and STARR Investigators. Effect of ramipril and of rosiglitazone on carotid intima-media thickness in people with impaired glucose tolerance or impaired fasting glucose: STARR (STudy of Atherosclerosis with Ramipril and Rosiglitazone). J Am Coll Cardiol 2009;53:2028–35.
4. Gerstein HC, Yusuf S, Bosch J, et al., DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet 2006;368:1096-105.
5. Dagenais GR, Pogue J, Fox K, Simoons ML, Yusuf S. Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. Lancet 2006;368:581–8.
6. Ahimastos AA, Natoli AK, Lawler A, et al., Ramipril reduces large-artery stiffness in peripheral arterial disease and promotes elastogenic remodelling in cell culture. Hypertension 2005;45:1194–9.
7. Marx N, Walcher D. Vascular effects of PPARγ activators—from bench to bedside. Prog Lipid Res 2007;46:283–96.
8. Mazzone T, Meyer PM, Feinstein SB, et al. Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. JAMA 2006;296;2572–81.
9. Nissen SE, Nicholls SJ, Wolski K, et al., for the PERISCOPE Investigators. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. JAMA 2008;299:1561–73.
10. Sidhu JS, Kaposzta Z, Markus HS, Kaski JC. Effect of rosiglitazone on common carotid intima-media thickness progression in coronary artery

disease patients without diabetes mellitus. Arterioscler Thromb Vasc Biol 2004;24;930–4.

11. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;298:1189–95.

12. Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes—an interim analysis. N Engl J Med 2007;357:28–38.

13. Wang JG, Staessen JA, Li Y, et al. Carotid intima-media thickness and antihypertensive treatment: a meta-analysis of randomized controlled trials. Stroke 2006;37:1933–40.

14. Crouse JR. Imaging atherosclerosis: state of the art. J Lipid Res 2006;47:1677–99.

15. Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomized controlled trials. Lancet 2007;370:1129–36.