Determinants of evolving metabolic and cardiovascular benefit/risk profiles of rosiglitazone therapy during the natural history of diabetes: molecular mechanisms in the context of integrated pathophysiology

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Submitted 23 January 2012; accepted in final form 23 February 2012

Sgarra L, Addabbo F, Potenza MA, Montagnani M. Determinants of evolving metabolic and cardiovascular benefit/risk profiles of rosiglitazone therapy during the natural history of diabetes: molecular mechanisms in the context of integrated pathophysiology. Am J Physiol Endocrinol Metab 302: E1171–E1182, 2012. First published February 28, 2012; doi:10.1152/ajpendo.00038.2012.—Rosiglitazone is a thiazolidinedione, a synthetic PPARγ receptor agonist with insulin-sensitizing properties that is used as an antidiabetic drug. In addition to improving glycemic control through actions in metabolic target tissues, rosiglitazone has numerous biological actions that impact on cardiovascular homeostasis. Some of these actions are helpful (e.g., improving endothelial function), whereas others are potentially harmful (e.g., promoting fluid retention). Since cardiovascular morbidity and mortality are major endpoints for diabetes, it is essential to understand how the natural history of diabetes alters the net benefits and risks of rosiglitazone therapy. This complex issue is an important determinant of optimal use of rosiglitazone and is critical for understanding cardiovascular safety issues. We give special attention to the effects of rosiglitazone in diabetic patients with stable coronary artery disease and the impact of rosiglitazone on atherosclerosis and plaque instability. This provides a rational conceptual framework for predicting evolving benefit/risk profiles that inform optimal use of rosiglitazone in the clinical setting and help explain the results of recent large clinical intervention trials where rosiglitazone had disappointing cardiovascular outcomes. Thus, in this perspective, we describe what is known about the molecular mechanisms of action of rosiglitazone on cardiovascular targets in the context of the evolving pathophysiology of diabetes over its natural history.

atherosclerosis; coronary artery disease; type 2 diabetes

Thiazolidinediones: From Rise to Fall

Thiazolidinediones (TZDs) include ciglitazone, troglitazone, pioglitazone, and rosiglitazone. Despite their striking chemical similarity, these compounds have different effectiveness and safety profiles. Ciglitazone (57) never reached the market, and troglitazone became clinically available in 1997. Approximately 1 year after its market release, the Food and Drug Administration (FDA) had already received 560 reports of troglitazone-associated hepatotoxicity, which eventually resulted in troglitazone’s withdrawal (93). Rosiglitazone and pioglitazone, which do not induce liver failure (140), were authorized as second-line treatment for type 2 diabetes (T2DM) when other drugs were unsuitable or unsuccessful. During the last 10 years, rosiglitazone has been prescribed increasingly for the treatment of metabolic abnormalities in patients with T2DM because of its ability to increase insulin sensitivity without causing hypoglycemia. The risk/benefit profile of rosiglitazone was questioned when in 2007 the first meta-analysis by Nissen and Wolski (117) reported a 43% increase of myocardial infarction (MI) and a 64% increase in cardiovascular-related death (CVD) in T2DM patients treated with rosiglitazone. The existence of several limitation observed in Nissen and Wolski’s (117) meta-analysis prompted a number of other investigators to evaluate the cardiovascular safety of rosiglitazone. However, the results were often confusing and rather contradictory (130). For example, using alternative meta-analytic approaches that use continuity corrections, Diamond et al. (44) concluded that the risk for MI and CVD for diabetic patients taking rosiglitazone was uncertain, with neither increased nor decreased risk established.

The only randomized clinical trial prospectively designed to assess the effect of rosiglitazone on cardiovascular outcomes was the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial (73, 74). Analysis of data from the RECORD trial after a 3.75-yr followup did not highlight a significant risk for CVD in T2DM patients treated with rosiglitazone with respect to patients treated with either sulfonylureas or metformin, although risk for congestive heart failure was doubled in rosiglitazone-treated patients (74). Concomitantly, another meta-analysis of four randomized controlled trials found that rosiglitazone use for ≥12 mo was associated with a significantly increased risk of MI and heart failure, but not an increased risk of CVD, among patients with impaired glucose tolerance or T2DM (147). An extensive revision of previously published data was promoted by the Drug Safety and Risk Management Advisory Committee of the FDA in conjunction with the Endocrinologic and Metabolic Drug Advisory Committee (48). Despite growing concerns for cardiovascular effects of rosiglitazone, data were still controversial, and the FDA decided to keep rosiglitazone on the market, adding a black box to its label warning about the risk of MI (51). When the final RECORD report was published 2 years later in 2009 (73), conclusions were similar to those obtained during the interim analysis; with respect to metformin plus sulfonylurea, rosiglitazone treatment did not seem to significantly increase the risk for total CVD in type 2 diabetic patients. On the contrary, data on MI were not considered conclusive. However, although apparently reassuring, these conclusions were biased by the sponsor participation in the study and by concerns on data integrity and quality.

In a systematic and updated revision of their prior meta-analysis, Nissen and Wolski (118) examined the results of 56 trials containing more than 35,000 patients and concluded that
rosiglitazone-treated patients were at increased risk for MI but not for CVD. Similar recent retrospective analysis comparing the effects of rosiglitazone and pioglitazone established that rosiglitazone was associated with an increased risk of stroke, heart failure, and CVD in diabetic patients aged 65 yr and older (66). In addition to clinical trials, observational data from seven case-control and 14 cohort studies provide further support for the higher CVD risk in patients exposed to rosiglitazone with respect to pioglitazone (reviewed in Ref. 86).

In 2010, the unresolved question on cardiovascular risk associated with rosiglitazone prompted the European Medicine Agency to recommend the withdrawal of all licensed rosiglita zone-containing drugs from the European market. Conversely, the FDA decision was to further limit prescription of rosiglitazone and restrict its use in the US (133, 134). Thus, to date the FDA has not removed the drug from the market. Interestingly, after initial worry and despite the black box warning on the increased risk of MI (52), rosiglitazone prescription in the US remains relatively stable (133).

The desire to balance patient protection with the availability of the broadest possible range of therapies for diabetes almost certainly explains the FDA’s course of action with respect to rosiglitazone. Therefore, prior to a definitive decision being reached, it would be important to recognize whether peculiar pharmacological properties of rosiglitazone may provide any potential advantage for its use under specific circumstances. In this respect, it is important to underline that, with the exception of the RECORD trial, the majority of evidence regarding the cardiovascular effects of rosiglitazone is derived from observational studies or meta-analyses of randomized clinical trials that have focused on glycemic targets rather than specified pharmacological interventions (see Ref. 86 for review). In addition, rosiglitazone is taken mostly by patients whose blood glucose levels are not adequately controlled by other available treatments. The long history of diabetes in this population is sufficient to set a higher cardiovascular risk that is related mostly to complex changes in vascular and coronary districts associated with the development of diabetic atherosclerosis. In the future, the restricted access to the drug will limit the possibility to design clinical prospective studies to assess the potential advantage of rosiglitazone in specific populations. Alternative possibilities may consider focused in-depth analysis of retrospective studies integrated with results from translational research.

Natural History of Diabetes

Type 2 diabetes is a progressive metabolic disorder characterized by variable degrees of insulin resistance and pancreatic β-cell dysfunction (reviewed in Ref. 39). The interaction of key genes with environmental factors such as physical inactivity, quality and quantity of nutrients, puberty, and aging concurs to promote adiposity, impair β-cell function, and impair insulin action (5, 37, 68). When pancreatic insulin secretion is no longer sufficient to compensate for insulin resistance, glucose intolerance progresses to chronic hyperglycemia and overt diabetes (10, 42). Insulin resistance usually precedes by many years the onset of T2DM (38, 84). On a molecular basis, insulin resistance is related to impaired signaling through the insulin receptor substrate-1 (IRS-1)/phosphatidylinositol 3-kinase (PI3K) pathway (see Refs. 145 and 163 for review). In metabolic target tissues of insulin action such as liver, skeletal muscles, and adipose tissue, impaired insulin-dependent activation of PI3K signaling results in decreased translocation of glucose carrier glucose transporter 4 with subsequent reduced glucose uptake, increased hepatic glucose production, increased lipolysis, and increased release of nonesterified fatty acids (121). Early in the natural history of this disease, before the emergence of marked hyperglycemia, increased insulin secretion partially compensates for insulin resistance (49). Compensatory hyperinsulinemia, which overdrives unaffected molecular signaling such as the extracellular-regulated kinase (ERK) MAPK pathways, enhances de novo lipogenesis and augments hepatic very-low-density lipoprotein synthesis (94). In adipose tissues, insulin resistance and hyperinsulinemia alter the balance of metabolic hormones such as leptin and adiponectin and trigger the activation of inflammatory pathways, resulting in increased production of cytokines, including tumour necrosis factor-α (TNFα) and interleukin-6 (IL-6). Over time, chronic exposure to hyperglycemia and dyslipidemia further impair metabolic function via glycoxicity, lipotoxicity, oxidative stress, and sustained inflammation (reviewed in Refs. 4, 18, and 36).

T2DM is an independent risk factor for CVD. Indeed, cardiovascular complications, including coronary artery disease (CAD), peripheral arterial disease, and stroke, are leading causes of morbidity and mortality in patients with T2DM (6, 58, 81). Pathologically, atherosclerosis represents most of the macrovascular disease found in T2DM (8). In diabetic patients, atherosclerosis is more rapid and more severe than in control population, resulting in a pervasive process that affects the arterial wall in the peripheral, carotid, and cerebrovascular arterial beds (16). At the coronary level, accelerated atherosclerotic plaque rupture explains >75% of all fatal coronary thrombi and represents a critical step in clinically overt ischemic events. Atherosclerosis is a chronic inflammatory process whose progression involves many risk factors and complex changes of the vascular components (reviewed in Ref. 50). These include perturbation/injury of the endothelium, adhesion and transmigration of monocytes/macrophages into the intima, foam cell formation, and migration and proliferation of medial vascular smooth muscle cells (VSMC) with concomitant intima hyperplasia. These changes, together with the enhanced coagulability and impaired fibrinolysis, concur to increase the risk of vascular occlusion and cardiovascular events in patients with T2DM (67, 111).

Multiple mechanisms contribute to arterial remodeling and vascular tissue damage during T2DM (reviewed in Refs. 36 and 106). Hyperglycemia fosters the nonenzymatic formation of advanced glycosylated end products (AGEs) and promotes activation of key mediators regulating proinflammatory and proatherosclerotic target genes in endothelial cells, vascular smooth muscle cells, and macrophages (18, 21). Hyperglycemia may also activate matrix-degrading metalloproteinases, enzymes implicated in plaque rupture, and arterial remodeling, inducing similar responses in vascular smooth muscle cells. Even before hyperglycemia develops, insulin resistance may play a pivotal role in the development of vascular impairment (89). In endothelial cells, insulin resistance decreases production of nitric oxide (NO) via the impaired IRS-1/PI3K pathway, whereas compensatory hyperinsulinemia promotes mitogenic effects via unaffected MAPK signaling pathways (124).
In arterial smooth muscle cells, hyperinsulinemia under insulin resistance conditions increases LDL cholesterol transport, collagen synthesis, and cell proliferation and activates multiple genes involved in inflammation and atherosclerosis. In platelets, hyperglycemia and hyperinsulinemia concur to impair NO generation, increase free radical formation, alter calcium regulation, and elevate levels of plasminogen activator inhibitor-1 with resulting increased platelet aggregation and impaired fibrinolysis.

**Molecular and Cellular Properties of Rosiglitazone**

Like the other TZDs, rosiglitazone acts as the exogenous ligand of peroxisome proliferator-activated receptor-γ (PPARγ), a transcription factor belonging to the nuclear receptor family (169). The high expression of PPARγ receptors in adipose tissue and their role in adipogenesis, glucose homeostasis, and lipid metabolism easily explain the effectiveness of TZDs as insulin-sensitizing and antidiabetic agents.

In insulin metabolic target tissues, PPARγ-dependent effects include decrease in insulin resistance (57), induction of adipocyte differentiation (92), modulation in levels of leptin (32) and adiponectin (167), and decrease in levels of proinflammatory cytokines, including TNFα and IL-6 (146). PPARγ signaling also upregulates the expression of genes involved in fatty acid uptake, β-oxidation, electron transport, and oxidative phosphorylation (13), which may reduce plasma levels of lipids and help to protect vessels from lipotoxicity.

In vascular tissues, PPARγ is known to regulate production of endothelial mediators, including NO (23), and to modulate expression of genes involved in cell adhesion (26), inflammation (104), oxidative stress (78), and vasoconstriction (43, 137). In macrophages, PPARγ anti-inflammatory effects play a protective role in atherosclerosis (131).

Treatment with exogenous PPARγ agonists is expected to enhance vascular protection in T2DM patients for at least three reasons: 1) reduced metabolic insulin resistance, with subsequent decreased glucotoxicity-and lipotoxicity-mediated vascular damage; 2) improved vascular insulin sensitivity, with amelioration of endothelial function and hemodynamics; and 3) activation of anti-inflammatory signaling on endothelial cells, vascular smooth muscle cells, and macrophages, with potential inhibition on atherogenic evolution. Indeed, a number of experimental studies in vitro and in animal models have shown that TZDs, including rosiglitazone, possess a broad spectrum of antiatherogenic effects (75, 80, 151, 161) that may be expected to delay the development of atherosclerosis and protect against plaque progression. Despite promising preclinical data, human studies, including the VICTORY trial, have failed to observe significant antiatherosclerotic effects of rosiglitazone (11, 12, 54, 153, 168), although a tendency to reduce plaque progression has been observed in some subgroups of diabetic patients (60). Nevertheless, an increased risk of coronary heart disease has been observed in patients treated with rosiglitazone (117), whereas the majority of published studies do not suggest a similar increased risk of cardiovascular events in pioglitazone-treated patients (86).

Presently, the discrepancy between preclinical and clinical data as well as the precise mechanism by which rosiglitazone may increase the incidence of cardiovascular events in humans is still uncertain. Although experimental studies in vitro and in animals are essential to provide basic information on molecular mechanisms of rosiglitazone with specific phenotypes, controlled conditions may eliminate factors such as ethnicity, economic and geographic variables, drug interactions, sex and age differences, diet, and clinical heterogeneity (128). This may be one reason to help explain why promising results from preclinical observations have failed to predict rosiglitazone effects in the complex and evolving pathophysiology of the human disease. Another possibility is that rosiglitazone, which is metabolized differently from pioglitazone and exhibits distinct pharmacological profile with respect to other TZDs, may selectively affect PPARγ-dependent gene expression in different cell types. Moreover, the still insufficient knowledge of the cardiovascular biology of PPARγ-mediated signaling may contribute to explain the unfavorable effects of a full agonist such as rosiglitazone in the cardiovascular setting of patients with diabetes. Alternatively, it is possible that part of rosiglitazone-mediated effects may be independent on PPARγ signaling, as reported for some TZDs from studies with PPARγ pharmacological antagonists or in PPARγ-null cells. For example, certain TZDs inhibit the production of inflammatory mediators in both wild-type and PPARγ-deficient macrophages (25) and inhibit pancreatic cell invasiveness via mechanisms that involve matrix metalloproteases and plasminogen activator inhibitor-1 (59). Interestingly, PPARγ-independent effects of TZDs have been shown to regulate cell proliferation and survival by multiple mechanisms, including phosphorylation of MAPK family members (99, 112, 132). The signaling pathways mediated by the Bcl-2 family of proteins are central in regulation of cell fate and can either promote cell survival (Bcl-2, Bcl-xL, Bcl-W, and others) or advance cell death (Bax, Bak, Bcl-xS, Bad, and others) (1a). By inhibiting Bcl-xL and Bcl-2 antiapoptotic activity, TZDs have been shown to shift the balance from cell survival toward programmed cell death in precancerous cells (76, 142).

Recently, rosiglitazone has been identified as a modulator of transient receptor potential (TRP) channels (102) that is involved in Ca2+ and Na+ entry on cells (156). Upregulated expression of TRP channels such as TRPC5 is a characteristic of the metabolic syndrome and coronary atherosclerosis (47, 165), and TRPC channels have been implicated in hypertension (27), vascular remodeling (166), and hyperglycemia-induced endothelial injury (115). PPARγ-independent effects of rosiglitazone also include acute inhibition of VSMC contraction induced by α1-adrenoceptor stimulation (136) and production of endothelial NO via LKB1/AMPK-dependent signaling (15).

Thus, rosiglitazone possesses a multiplicity of vascular effects that are both PPARγ-dependent and independent (Fig. 1). Some of these effects, which may be beneficial at the early stage of diabetes, may contribute to disrupt pathophysiologic compensatory mechanisms and precipitate acute cardiovascular events in a more advanced stage of the disease.

**Rrosiglitazone and endothelial activation.** Endothelial activation is involved in the onset and progression of atherosclerosis and is characterized by impaired bioavailability of NO and enhanced secretion of proadhesive molecules (see Refs. 34 and 35 for review). These early changes contribute to impaired regulation of vascular tone, activation of proinflammatory signaling, and induced expression of adhesion molecules, including intercellular adhesion molecule-1 (ICAM-1), vascular
cell adhesion molecule-1 (VCAM-1), E-selectin, and monocyte chemoattractant protein-1 (MCP-1). In T2DM patients, both hyperglycemia and insulin resistance contribute independently to endothelial dysfunction, increased vascular stiffness, and atherosclerotic progression (33, 103, 159). Arterial stiffness refers to vascular properties such as distensibility, compliance, and elasticity that are different between elastic and muscular arteries. A number of factors are believed to be responsible for arterial stiffness, including decreased elastin and increased collagen content in the arterial wall, abnormal endothelial regulation of arterial smooth muscle tone, and the accumulation of AGEs leading to protein cross-linking. Increased arterial stiffness has been observed in both elastic and muscular arteries of patients with T2DM (70, 87) and in subjects with insulin resistance and prediabetes (148).

Since insulin physiologically increases NO production by stimulation of endothelial PI3K/Akt signaling (109, 149, 171), insulin resistance with impaired PI3K activation results in decreased production of NO (89, 110). Concomitantly, compensatory hyperinsulinemia overdrives unaffected Ras/MAPK signaling (30), resulting in unbalanced secretion of proatherosclerotic mediators such as endothelin-1 (20, 126) and increased expression of VCAM-1 and E-selectin (110). These effects sum up with hyperglycemia-mediated activation of proinflammatory NF-κB signaling and apoptotic cascades (7, 72), resulting in profound changes of vascular functionality and morphology.

Rosiglitazone-mediated amelioration of PI3K/Akt signaling in endothelium stimulates phosphorylation of eNOS at Ser1177 (123), improves insulin-dependent NO production (127), and contributes to amelioration of function and migration of endothelial progenitor cells (101). Besides improving insulin-mediated NO production, rosiglitazone rapidly stimulates NO synthesis in an AMPK-dependent manner (15) and contributes to maintain NO bioavailability by reducing reactive oxygen species in the aortas of diabetic and insulin-resistant animals (22, 125) and in human leukocytes (105) with a mechanism involving PKC inhibition (24). Moreover, treatment with rosiglitazone inhibits the expression of several adhesion molecules, such as VCAM-1, ICAM-1, MCP-1, and P-selectin (152), with subsequent decreased leukocyte adhesion and macrophage infiltration (100).

Under rosiglitazone therapy, amelioration of arterial stiffness with concomitantly reduced serum levels of C-reactive protein, matrix metalloprotease 9, and MCP-1 has been observed in patients with prediabetes (90), overt diabetes (91), and diabetes associated with CAD (170).

Rosiglitazone and intimal hyperplasia. In response to endothelial injury, VSMCs can switch from a contractile (or quiescent) phenotype to a synthetic (or activated) phenotype. In this process, VSMCs regain their proliferative and migratory capacities and downregulate smooth muscle contractile proteins such as α-smooth muscle actin, smooth muscle 22α, smooth muscle myosin heavy chain, and calponin (reviewed in Ref. 119). This phenotypic switch of VSMC triggered by endothelial insults is undoubtedly required for vascular repair. Nevertheless, persistent and inappropriate modulation of these processes may aggravate vascular injury and facilitate progression of intimal hyperplasia and atherosclerotic lesions. In the long term, VSMC migration to intima and deposition of extracellular matrix components contribute to create a mature fibro-fatty atheroma.
Besides its effects on vascular tone and permeability, endothelial NO is considered the limiting factor for conferring a "protective steady state" to the medium smooth muscle layer (61). This effect is dependent on regulation of several cell cycle proteins (150) that are involved directly in inhibition of a "synthetic" phenotypic switch in VSMC. The importance of NO to ensure the correct function of VSMC and avert the onset of atherosclerosis is proven by a number of experimental studies in vitro and in vivo. In a cellular model of atherosclerosis, insulin-stimulated NO production limits VSMC migration (82) and prevents intima hyperplasia (155). Interestingly, increased expression of endothelial NO synthase at plaque level has been demonstrated in patients with acute coronary syndrome rather than in patients with stable angina (135), further suggesting that NO production may have a pivotal role in plaque progression. Insulin is also able to promote the expression of inducible NO synthase (iNOS) in VSMC (98), and NO produced by iNOS is required for insulin-dependent inhibition of VSMC migration (83). Conversely, chronic high insulin and high glucose markedly reduce iNOS expression in VSMC (9).

Multiple signal transduction pathways involved in VSMC migration and proliferation include PKC, MAPKs, and NF-κB signaling pathways (46, 107, 143, 164). Of particular importance in this process is the role played by the PI3K/Akt transduction pathways. Activation of PI3K/Akt signaling in VSMC stimulates cell adhesion and spreading, thus favouring VSMC migration and proliferation (160). Absence of Akt impairs VSMC proliferation and migration (53), and PPARγ activation can inhibit Akt phosphorylation in response to growth factors in endothelial cells (62) and negatively regulate phenotypic modulation of VSMC (172). One target of activated Akt is ribosomal p70S6 kinase (S6K) associated with the mammalian target of rapamycin (mTOR) mitogenic signal transduction cascade (3). In turn, overactivation of mTOR/S6K signaling as a result of deregulated activation of MAPK signaling has been implied in impaired insulin-mediated activation of Akt via elevated serine phosphorylation of IRS-1 in muscles of insulin-resistant animal models (88, 174).

Rosiglitazone and other non-TZD ligands of PPARγ inhibit VSMC proliferation at the G1/S phase transition by suppressing mitogen-induced phosphorylation of proteins that are essential regulators of the DNA replication (19, 157). This inhibition of VSMC proliferation correlates with a potent suppression of neointima formation after balloon injury in rat models of insulin resistance as well as in animals with normal insulin sensitivity in vivo (2, 77, 96, 144). The most recent findings suggest that rosiglitazone improves the impaired expression of α-smooth muscle actin and smooth muscle 22α in aortic vessels (172) and inhibits proliferation of isolated VSMCs by suppressing NF-κB activity and reducing matrix metalloprotease-9 expression via GSK-3β activation (97). Rosiglitazone’s ability to attenuate neointimal hyperplasia after vascular injury seems to involve suppression of inflammatory processes mediated by Toll-like receptor 4 (173) and by ERK/MAPK pathways (63). The regulatory effect of rosiglitazone on MAPK and protein phosphatase 2A-dependent signaling (28) may also have been involved in decreased activation of mTOR-p70S6K with subsequent inhibition of insulin-stimulated VSMC proliferation and reduced intima hyperplasia in obese and diabetic animals (Fig. 2) (120).

**Rosiglitazone and plaque effects.** The natural course of the vessel remodeling in response to the initial atherosclerotic lesion strongly influences the composition of the individual plaque and its clinical presentation (95, 154). Rupture and fissuring of advanced arteriosclerotic lesions with subsequent formation of an occluding thrombus are major causes of acute coronary syndromes. These advanced plaques are character-
ized by the presence of a large necrotic lipid core and a covering thin fibrous cap, which separates the circulating blood from the plaque underneath. In addition, numerous monocytes/macrophages in the shoulder region of the plaque contribute to plaque instability through the expression of inflammatory mediators. In this evolving process, the significance of VSMC proliferation and migration from media to intima and the relative proportion of VSMC in the plaque structure is one major determinant for clinical symptoms; for example, unstable plaques (that are prone to rupture) contain a higher proportion of inflammatory cells and lipid and a lower proportion of VSMC than stable lesions (31). Thus, in an advanced phase of plaque formation, a fibrous cap relatively rich in VSMC is considered “protective” against plaque rupture. The loss of VSMC components in the atherosclerotic plaque is dependent mainly on apoptotic processes; in turn, VSMC apoptosis with subsequent release of IL-1 and -8 and upregulation of MCP-1 favors infiltration of macrophages (138, 139) and promotes thrombin generation and vascular calcification (55, 129). Thus, VSMC apoptosis alone is sufficient to induce features of plaque vulnerability in atherosclerosis (29). The impaired activation of PI3K/Akt signaling under insulin resistance conditions is involved directly in VSMC apoptotic processes and may be related to the high plaque instability and vulnerability (53) (Fig. 3).

The powerful ability of rosiglitazone to influence cellular activity of each vascular component during initiation and progression of atherosclerotic lesions may partially explain its contrasting effects on cardiovascular protection. At the onset of the atherosclerotic process, mechanisms activated by rosiglitazone may help to preserve endothelial function and inhibit VSMC proliferation, and therefore, they contribute to stabilize the vulnerable atherosclerotic plaques in an animal model of atherosclerosis (175) as well as in carotid arteries from non-diabetic patients (108). However, in an advanced phase of plaque formation these same effects may turn dangerous and shift the balance toward increased VSMC apoptosis by favoring activation of the ERK1/2-independent pathway (65) or by direct caspase-mediated expression of DNA damage-inducible gene 45 (19). Thus, at different stages of plaque progression, rosiglitazone may contribute to disrupt a compensatory equilibrium, profoundly influence plaque reshaping, and turn a stable lesion into a vulnerable one.

Altogether, several factors may contribute to determine the cardiovascular risk/benefit profile of rosiglitazone in patients with a long history of diabetes, e.g., the high pharmacological potency of rosiglitazone as a full PPARγ agonist. The triggering of PPARγ signaling pathways connected with gene programming, cell survival, proliferation, and phenotype switching may have protective effects at the early step of vascular injury, but the cardiovascular biology of these nuclear receptors is still incompletely understood. Thus, unfavorable effects of rosiglitazone during advanced diabetes may depend on inadequate activation of the PPARγ signaling in the context of diabetic pathophysiology. In addition, rosiglitazone possesses a broad spectrum of PPARγ-independent molecular activities. Some of these effects may generate conflicting consequences in different cell types as well as unpredictable outcomes in the same cell type under different pathophysiological conditions. Therefore, it is possible that the strong and multifaceted ability of rosiglitazone to promote functional and morphological changes in cardiovascular components may be one of the reasons for its undesirable effects resulting from disruption of adaptive rearrangements taking place during the evolution of diabetes pathophysiology in cardiovascular and coronary districts. Prescription of rosiglitazone as a first-line drug in the initial therapy of diabetes is not advisable in light of the strong concerns about its cardiovascular safety. However, rosiglitazone’s powerful ability to increase metabolic and vascular insulin sensitivity, together with its unquestionable direct effects on the cardiovascular system, may still be worthy of consideration in patients with early diabetes and very low macrovascular risk (particularly at the coronary district), especially when intensive glycemic control is not achieved with other conventional treatments.

Rationale for rosiglitazone therapy in diabetic patients with stable CAD. Prevention of cardiovascular events acquires paramount importance in diabetic patients with stable CAD.
Nevertheless, the best therapeutic strategy to reduce cardiovascular risk in these patients is still uncertain. There are two approaches currently available. One choice is optimal medical therapy (OMT), which consists of an adequate change in lifestyle, a severe glycemic control, and an aggressive secondary prevention, and the alternative option is prompt surgery therapy. In this respect, the first Bypass Angioplasty Revascularization Investigation (BARI) study, released in 1996, found that 5-yr survival was significantly higher in diabetic patients undergoing coronary artery bypass grafting (CABG) compared with patients subjected to percutaneous coronary intervention (PCI) (1). The second BARI-2D study, a 6-yr multicenter trial, was designed to evaluate survival and freedom from major cardiovascular events in T2DM subjects with angiographically documented CHD (21a). The study compared patients randomized to undergo coronary revascularization (PCI or CABG) or maintain OMT. This last group was treated with insulin sensitizers (metformin, TZDs) or insulin provision therapies (insulin, sulfonylureas) to obtain HbA1c levels <7%. Data obtained at 5-yr followup suggested that patients treated with CABG had the best and most rapid recovery, although initial performance tended to level down during the next 4 yr. Surprisingly, both survival and freedom from major cardiovascular events were completely comparable between patients in OMT with respect to patients treated with PCI revascularization (56). Moreover, patients with extensive coronary disease who were treated with a TZD had a lower rate of death/MI in the revascularization arm compared with the medical treatment arm (21 vs. 29.2%, respectively) (56).

Further analysis enlightened the fact that in the OMT group patients treated with insulin-sensitizing therapy had higher HDL cholesterol levels, less weight gain, less frequent severe hyperglycemia, and lower HbA1c levels compared with patients treated with insulin provisional therapy (64). Moreover, data analysis by other investigators found equal effectiveness of OMT or PCI revascularization strategy in physical and psychological recovery of T2DM patients (17). More recently, subanalysis of the BARI-2D findings reported that rosiglitazone therapy, compared with no TZD therapy, was not associated with an excess risk of MI or stroke in the trial (114). Conclusions of the BARI-2D study substantially overlapped those of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation trial (14), which was designed to evaluate whether association of PCI to OMT is superior to OMT alone in reducing the risk of cardiovascular events in diabetic patients with stable CAD. There were no significant differences between the PCI group and the OMT group in the composite of death, MI, stroke, or hospitalization for acute coronary syndrome or MI. In a subsequent analysis it was found out that an initial strategy of OMT alone did not result in increased death or MI or worse angina in the high-risk diabetic subcohort of patients (14). A previous meta-analysis evaluating the risk of MI in patients with chronic CAD found that PCI does not confer any clear benefit in terms of long-term hard clinical outcomes compared with the conservative OMT approach (85). Taken together, these results support the hypothesis that OMT therapy is as effective as PCI revascularization strategy in diabetic patients with stable CAD. Although rosiglitazone did not reduce progression of coronary artery plaque more than glipizide, no significant additional cardiovascular risk was measured in T2DM patients with CAD, and a trend toward antiatherogenic protection was observed in a subcohort of patients (60). Thus, the contradiction between potential prevention or precipitation of cardiovascular events by rosiglitazone may be due partially to the different stage of diabetes and the individual responsiveness of diabetic patients to the effects of rosiglitazone.

Consistent with this, in the first report on rosiglitazone-related cardiovascular risk (117), it was observed that the majority of MI events were experienced in the short term from the beginning of rosiglitazone therapy. It is likely that the most “sensitive” subjects to rosiglitazone cardiovascular risk would have been patients with underlying unstable coronaryopathy and vulnerable plaques in which rosiglitazone administration may trigger plaque rupture and precipitation of cardiovascular events. Additional support for this view comes from an in-depth analysis of individual trials by Nissen and Wolski (118) in their updated meta-analysis. Among 202 trials gathered from the GSK trial registry, the FDA registry, and independent studies on MEDLINE, those with the higher incidence of MI included diabetic patients with a long history of uncontrolled diabetes, severe impairment of ventricular function, or a previous history of coronaryography or PCI (60).

If the higher risk of cardiovascular events by rosiglitazone is observed in diabetic patients with jeopardized cardiovascular physiology, it could be suggested that administration of rosiglitazone may obtain the most beneficial effects in patients with initial glucose impairment (40), when rosiglitazone-dependent activity on metabolic and cardiovascular homeostasis may successfully prevent or delay the most deleterious consequences of diabetes. In line with this, rosiglitazone enhances flow-mediated endothelium-dependent vasodilation with a parallel reduction of serum of C-reactive protein and soluble adhesion molecules in healthy nondiabetic subjects (71, 158) or insulin-resistant patients (162) and ameliorates endothelial function and arterial stiffness and elasticity in prediabetic (90) or early diabetic subjects (122, 141). Such results suggest that rosiglitazone, like pioglitazone (41), may provide some protection against the development of atherosclerotic cardiovascular disease, which is consistent with reports of reductions in the volume of coronary plaque (116) and in mortality, nonfatal MI, and strokes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events) (45).

Conclusions

Cellular and molecular studies suggest that rosiglitazone’s ability to increase endothelial NO production and limit VSMC proliferation may substantially delay intima hyperplasia at the early- to middle-stage progression of atherosclerosis. Nevertheless, the very same capacity of rosiglitazone to oppose VSMC migration and enhance VSMC apoptosis may turn deleterious in end-stage atherosclerotic progression and contribute to plaque instability and rupture. Large, randomized clinical trials suggest that treatment with rosiglitazone does not seem to increase the risk of cardiovascular accidents in T2DM patients with stable CAD. Conversely, an increased risk of CVD or MI by rosiglitazone has been reported in trials recruiting mainly T2DM patients with a long history of diabetes and important cardiovascular risk features.

Thus, one possibility for the apparent controversy of rosiglitazone-dependent effects may be inherent to incomplete

AJP-Endocrinol Metab • doi:10.1152/ajpendo.00038.2012 • www.ajpendo.org
knowledge of PPARγ-mediated activity in the cardiovascular system, with subsequent insufficient evaluation of rosiglitazone risk/benefit ratio and inappropriate recruitment of T2DM patients.

Considering the restricted possibility of designing clinical prospective studies to assess the potential advantage of rosiglitazone in specific populations and the limited potential of translational research, additional randomized retrospective trials evaluating the clinical features of T2DM patients will be important to clarify whether rosiglitazone may still retain potential pharmacological advantages in specific subgroups of T2DM patients.

GRANTS
This work was supported in part by the Juvenile Diabetes Research Foundation (CDA 2-2006-32).

DISCLOSURES
The authors declare no conflicts of interest, financial or otherwise.

AUTHOR CONTRIBUTIONS
L.S. did the conception and design of the research; L.S., F.A., M.A.P., and M.M. prepared the figures; L.S., F.A., and M.A.P. drafted the manuscript; L.S., F.A., M.A.P., and M.M. approved the final version of the manuscript; M.M. edited and revised the manuscript.

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