A multicentre, randomized, double-blind placebo-controlled trial evaluating rosiglitazone for the prevention of atherosclerosis progression after coronary artery bypass graft surgery in patients with type 2 diabetes. Design and rationale of the VeIn-Coronary aTherOsclerosis and Rosiglitazone after bypass surgery (VICTORY) trial

Olivier F Bertrand MD PhD¹, Paul Poirier MD PhD¹, Josep Rodés-Cabau MD¹, Stéphane Rinfret MD SM², Lawrence Title MD³, Vladimir Dzavik MD⁴, Madhu Natarajan MD⁵, Juan Angel MD⁶, Nuria Batalla MD⁶, Natalie Alméras PhD¹, Olivier Costerousse PhD¹, Robert De Larochellière MD¹, Louis Roy MD¹, Jean-Pierre Després PhD¹; for the VICTORY trial investigators

OF Bertrand, P Poirier, J Rodés-Cabau, et al; for the VICTORY trial investigators. A multicentre, randomized, double-blind placebo-controlled trial evaluating rosiglitazone for the prevention of atherosclerosis progression after coronary artery bypass graft surgery in patients with type 2 diabetes. Design and rationale of the VeIn-Coronary aTherOsclerosis and Rosiglitazone after bypass surgery (VICTORY) trial. *Can J Cardiol* 2009;25(9):509-515.

BACKGROUND: The number of patients with coronary artery disease and type 2 diabetes will increase dramatically over the next decade. Diabetes has been related to accelerated atherosclerosis and many patients with diabetes will require coronary artery bypass graft (CABG) surgery utilizing saphenous vein grafts. After CABG, accelerated atherosclerosis in saphenous vein grafts leads to graft failure in approximately 50% of cases over a 10-year period. Rosiglitazone, a peroxisome proliferator-activated receptor-gamma agonist, has been shown to improve multiple metabolic parameters in patients with type 2 diabetes. However, its role in the prevention of atherosclerosis progression is uncertain.

STUDY DESIGN: VeIn-Coronary aTherOsclerosis and Rosiglitazone after bypass surgery (VICTORY) is a cardiometabolic trial in which patients with type 2 diabetes, one to 10 years after CABG, will be randomly assigned to receive rosiglitazone (up to 8 mg/day) or a placebo after qualifying angiography and intravascular ultrasound of a segment of one vein graft with or without a native anastomosed coronary artery. A comprehensive set of athero-thrombo-inflammatory markers will be serially assessed during the 12-month follow-up period. Body fat distribution and body composition will be assessed by computed tomography and dual energy x-ray absorptiometry, respectively, at baseline, six months and 12 months follow-up. For atherosclerosis progression evaluation, repeat angiography and intravascular ultrasound will be performed after 12 months follow-up. The primary end point of the study will be the change in atherosclerotic plaque volume in a 40 mm or longer segment of one vein graft.

CONCLUSIONS: The VICTORY trial is the first cardiometabolic study to evaluate the antiatherosclerotic and metabolic effects of rosiglitazone in post-CABG patients with type 2 diabetes.

Key Words: Atherosclerosis; Cardiovascular risk factors; Catheterization; Coronary artery disease; Diabetes mellitus; Graft patency; Intravascular ultrasound; Metabolic syndrome

Étude clinique multicentrique, randomisée, à double insu, comparant la rosiglitazone au placebo sur la prévention de la progression de l'athérosclérose après une chirurgie pour pontage aorto-coronarien chez les patients diabétiques de type 2. Objectifs et principes de l'étude VICTORY (athérosclérose veino-coronarienne et rosiglitazone après chirurgie de pontage)

HISTORIQUE: Le nombre de patients coronariens diabétiques de type 2 augmentera significativement au cours de la prochaine décennie. Le diabète est associé à une athérosclérose accélérée et de nombreux patients coronariens diabétiques nécessiteront une chirurgie de pontage avec utilisation de greffes veineuses saphènes. L'athérosclérose accélérée au sein des pontages veineux amène à leur occlusion dans environ 50% des cas dans les 10 ans suivant la chirurgie. La rosiglitazone, un agoniste du récepteur gamma activé de prolifération des peroxyosomes, présente de nombreux effets métaboliques chez le patient diabétique, cependant la possibilité d'une action limitant la progression de l'athérosclérose n'est pas démontrée.

MÉTHODE: VICTORY est une étude cardiométabolique dans laquelle les patients diabétiques de type 2 ayant eu une opération de pontage aorto-coronarien, un à 10 ans au préalable seront randomisés à la rosiglitazone (jusqu'à 8 mg) ou au placebo après angiographie et échographie intravasculaire d'un greffon veineux ± artère native anastomosée. Une évaluation complète et sériée des marqueurs de l'athérosclérose, de la thrombose et de l'inflammation sera réalisée. La distribution du tissu adipeux et la composition corporelle seront évaluées par tomographie axiale et par absorptiométrie au début de l'étude, après 6 mois et 12 mois de suivi. Pour l'évaluation de la progression de l'athérosclérose, l'angiographie et l'échographie intravasculaire seront répétées après un suivi de 12 mois. L'objectif primaire sera le changement du volume de plaque athérosclérotique dans un segment du greffon veineux ≥ 40 mm.

CONCLUSIONS: L'essai VICTORY est la première étude cardiométabolique qui évaluera les effets de la rosiglitazone sur l'athérosclérose et le métabolisme chez des patients diabétiques après chirurgie de pontage aorto-coronarien.

¹Hôpital Laval, Québec Heart and Lung Institute, Québec; ²Hôpital Notre-Dame, Centre Hospitalier de l'Université de Montréal, Montréal, Québec;

³Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia; ⁴Toronto General Hospital, Toronto; ⁵Hamilton Civic Hospital, McMaster University, Hamilton, Ontario; ⁶Hospital Vall d'Hebron, Barcelona, Spain

Correspondence: Dr Olivier F Bertrand, Interventional Cardiology Laboratories, Hôpital Laval, Institut universitaire de cardiologie et de pneumologie, affilié à l'Université Laval, 2725 chemin Sainte-Foy, Québec, Québec. Telephone 418-656-8711 ext 5947, fax 418-656-4904, e-mail olivier.bertrand@crhl.ulaval.ca

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ATHEROSCLEROSIS, DIABETES AND CORONARY ARTERY BYPASS GRAFT SURGERY

In the coming decade, the burden of cardiovascular diseases related to diabetes will increase dramatically (1). Most patients with diabetes die of cardiovascular disease, and atherosclerosis accounts for approximately 80% of all diabetic mortalities (2). Although strict control of hyperglycemia has been consistently linked to a reduction in the incidence of microvascular complications of diabetes in large clinical trials, less evidence has been provided on the reduction in macrovascular complications. The United States Food and Drug Administration has recently stated that there is no conclusive evidence of macrovascular risk reduction with any current oral antidiabetic drug.

Although arterial grafts have shown superior early and long-term patency, saphenous vein grafts (SVGs) are still commonly used for coronary artery bypass graft surgeries (CABGs). In the United States alone, more than 300,000 CABGs are performed yearly (3). Whereas early vein graft failure is usually related to thrombosis, late graft stenosis and occlusion are related to intimal changes similar to classic atherosclerotic changes (4). Numerous pathological studies have demonstrated that accelerated atherosclerosis develops during the first decade after the operation (5). Angiographic studies in the 1980s showed that 10 years after CABG, approximately 50% of SVGs are severely narrowed or occluded (6,7). More recent studies have reported that current patient populations referred for CABG have more diffuse and severe distal coronary artery disease, leading to a significant decrease in the patency rate of SVGs early after CABG (3,8).

There has been recent enthusiasm related to the use of intravascular ultrasound (IVUS) to evaluate atherosclerotic changes and the effects of new pharmacological compounds in native coronary vessels (9). Recent IVUS studies have shown relatively modest or no change in atherosclerotic plaque volume as assessed by three-dimensional IVUS reconstruction after up to 18 months follow-up (10-12). Despite improved control of plasma lipid levels, we have shown that angiographic lesions still progress rapidly in SVGs (13). Because atherosclerosis remains an accelerated process in SVGs compared with native vessels, IVUS in an SVG model could serve to assess significant vessel changes in a limited period of time.

Despite its invasive nature, IVUS has already been proven to be remarkably safe in atherosclerotic coronary arteries and saphenous vein grafts (9,14,15). As demonstrated in coronary and peripheral arteries, IVUS allows researchers to assess atherosclerotic changes in saphenous vein grafts (16-19). In accordance with pathological findings, these atherosclerotic changes are better identified at least 12 months after surgery. The advantages and limitations of IVUS in vein grafts and native coronary arteries are presented in Table 1.

VISCERAL ADIPOSITY AS AN EMERGING CARDIOVASCULAR RISK FACTOR

There is considerable evidence supporting the notion that the health hazards of obesity are more closely related to the localization of excess body fat rather than to an elevated body weight per se (20-22). Using magnetic resonance imaging and computed tomography scan techniques, it has been shown that the presence of abdominal obesity accompanied by an excess of visceral adipose tissue is associated with an atherothrombotic, inflammatory profile leading to a substantial increase in the risk of cardiovascular disease (23,24).

Studies conducted in our laboratory have indicated that the features of the metabolic syndrome are mostly the consequence of an excessive accumulation of abdominal fat, especially when accompanied by a high accumulation of visceral adipose tissue (25). Abdominal obesity has also been related to alterations in indexes of plasma glucose-insulin homeostasis (26-28). Recently, it was suggested that the insulin-resistant/dyslipidemic profile of abdominally obese individuals is also accompanied by a prothrombotic, inflammatory state. Because visceral obesity is highly prevalent in patients with type 2 diabetes, targeting visceral adiposity and limiting expansion of the visceral fat compartment could have a beneficial impact on the progression of atherosclerosis in those patients.

TABLE 1
Intravascular ultrasound in saphenous vein grafts (SVGs) and native coronary arteries

	SVG	Native	Comments
Length	+++	++	Length available in SVGs > native coronary arteries
Branches	+++	–	No branches in SVGs. Distal and proximal anastomoses are used as fiducial marks in SVGs
Calcium	+ / ++	+ / – / +	Usually less calcium in SVGs than in coronary arteries
Size	+++	++	Size of SVGs > coronary arteries
Lumen tracing	+++	+++	Lumen tracing is easy in both vessels
Vessel tracing	+ / ++	++ / +++	EEM can be lacking in SVGs

– Unfavourable; + / – Suboptimal; + Adequate; ++ Good; +++ Optimal imaging; EEM External elastic lamina

THIAZOLIDINEDIONES

Thiazolidinediones (TZDs) are widely used in patients with type 2 diabetes. Their mechanism of action depends on agonist effects on the peroxisome proliferator-activated receptor-gamma (1). Peroxisome proliferator-activated receptor-gamma receptors are members of the nuclear receptor superfamily of ligand-activated transcription factors. They are expressed in numerous organs including atherosclerotic plaque (29,30). Agonists of these receptors have an insulin-sensitizing action but may also inhibit transcription of proinflammatory genes within atherosclerotic plaques and have antithrombotic effects (31,32). TZDs have numerous and complex impacts on the cardiovascular system. Evidence strongly suggests that TZDs can affect atherosclerosis progression in animals and humans (33).

TZDs also generally induce body weight gain. However, part of this effect can be related to a 'remodelling' of adipose tissue. Indeed, TZDs have been shown to promote fat accumulation in the subcutaneous fat compartment in patients with type 2 diabetes with no associated change or a small decrease in visceral adipose tissue (34-36). On the basis of the previous associations between indexes of plasma glucose-insulin homeostasis and the presence of an excess visceral fat accumulation, the shift in energy accumulation from the visceral fat depot to subcutaneous adipose tissue may represent an important 'remodelling' mechanism by which TZD therapy may improve insulin resistance and the related atherothrombotic inflammatory features of the visceraally obese patient with the metabolic syndrome or type 2 diabetes. However, no clinical trial has tested whether TZDs create a 'metabolic sink' that shifts lipid accumulation to subcutaneous fat, thereby protecting other tissues and organs from the complications of ectopic fat deposition.

Rosiglitazone (Avandia; GlaxoSmithKline Inc, Canada) and pioglitazone (Actos; Takeda Pharmaceuticals North America Inc and Eli-Lilly Canada Inc) are currently approved for clinical use worldwide. Despite many favourable effects on glycemic, metabolic and cardiovascular parameters, questions have recently been raised regarding their safety profile (37). In patients with long-standing cardiovascular disease and those who are at risk for heart failure, fluid retention associated with both glitazones has been a concern and some guidance has been issued. More recently, unexpected higher rates of bone fracture have been observed with glitazones in large clinical trials (38,39).

There is currently much controversy and intense debate regarding whether the cardiovascular profile of rosiglitazone is different from other oral antidiabetic agents. Therefore, additional information using surrogate cardiovascular and metabolic end points, and the safety of the use of rosiglitazone in high-risk patient populations, such as post-CABG patients with type 2 diabetes, is of interest.

OBJECTIVES

The primary objective of the present study is to assess the efficacy and safety of rosiglitazone to reduce atherosclerosis progression in vein

Figure 1) The Veln-Coronary aTherOsclerosis and Rosiglitazone after Bypass SurgerY (VICTORY) trial design. CT Computed tomography; DEXA Dual energy x-ray absorptiometry; HbA1c Glycosylated hemoglobin

grafts and adjacent native coronary arteries in post-CABG patients with type 2 diabetes by using IVUS after a 12-month follow-up period. The secondary objectives are to assess cardiometabolic changes induced by rosiglitazone therapy using IVUS, quantitative angiography (QCA), metabolic risk factors, body composition and clinical outcomes data.

METHODS

Study population

Patients with Canadian Cardiovascular Society class I and II angina with stable diabetes treated with oral hypoglycemic medications (no change in the dose of oral hypoglycemic medication for at least three months), with a glycosylated hemoglobin level of 9.0% or lower, and previous CABG (between one year and 10 years previously) with at least one SVG are eligible for the study. Percutaneous catheter-based interventions must not have been used on the target segments post-CABG. Subjects will be enrolled in centres located in Canada and Spain.

Study design

The present study is a prospective, multicentre, randomized, placebo-controlled double-blind trial assessing the efficacy and safety of rosiglitazone in the prevention of atherosclerosis progression in vein grafts and native coronary arteries of patients with type 2 diabetes. The study design is summarized in Figure 1, and the inclusion and exclusion criteria are outlined in Tables 2 and 3, respectively. Stable patients with a previous CABG (between one year and 10 years previously) will be screened. After baseline evaluation, all eligible patients will undergo a

TABLE 2
Inclusion criteria

At screening

- 1) Men or women* between 40 and 75 years of age
- 2) Type 2 diabetes mellitus as defined by the criteria of the Canadian Diabetes Association (41,42)
- 3) No new medication for hyperglycemia and no change in the dose of oral hypoglycemic medication within the three months before the screening
- 4) Patients with type 2 diabetes with ischemic heart disease and previous CABG with at least one SVG (between one year and 10 years previously)
- 5) Signed informed consent

At intravascular ultrasound (IVUS) and angiography procedure visit

- 1) At least one patent SVG
- 2) Segment length of at least 40 mm in an SVG suitable for IVUS analysis
- 3) Reference of the target (SVG) diameter ≥ 2.5 mm as assessed by visual estimation
- 4) If the anastomosed native coronary artery (scenarios A and B in Figure 2) or nongrafted coronary artery (scenario C in Figure 2) can be evaluated, the following criteria must be met:
 - a) Reference of the target anastomosed native coronary artery or nongrafted coronary artery diameter ≥ 2.5 mm as assessed by visual estimation
 - b) Segment length of at least 20 mm in the anastomosed native coronary artery corresponding to the SVG chosen or, in case of the impossibility of performing IVUS in the anastomosed coronary artery, a nongrafted coronary artery (≥ 30 mm length segment) might be used for reference. Four scenarios are possible (Figure 2)

*In menopause, sterile or with adequate contraceptive measures. CABG Coronary artery bypass graft; SVG Saphenous vein graft

TABLE 3
Exclusion criteria

At screening

- 1) Type 1 diabetes or known history of diabetic ketoacidosis
- 2) Recent myocardial infarction (≤ 90 days)
- 3) Last left ventricular ejection fraction $\leq 35\%$
- 4) Unstable or Canadian Cardiovascular Society class III and IV angina, acute heart failure or congestive heart failure (NYHA class III and IV)
- 5) History of hepatocellular reaction or severe edema, or other potentially fluid-related adverse events associated with the use of any thiazolidinedione or peroxisome proliferator-activated receptor-gamma agonist
- 6) Clinically significant hepatic disease
- 7) Significant renal dysfunction (creatinine >200 $\mu\text{mol/L}$)
- 8) Hemoglobin concentration <11.0 g/dL (110 g/L) for men or <10.0 g/dL (100 g/L) for women
- 9) Treatment involving thiazolidinediones within three months before screening
- 10) Subjects who have required ≥ 6 months use of insulin for glycemic control
- 11) Current use of anorectic agents or use within three months of screening

At intravascular ultrasound (IVUS) and angiography procedure

- 1) PCI performed on the target segment(s) after the CABG
- 2) Target SVG and/or target native coronary artery show $\geq 50\%$ angiographic lesions by visual estimate precluding the IVUS examination
- 3) Thrombus in the target vessels
- 4) Surgical endarterectomy (ie, right coronary artery)

CABG Coronary artery bypass graft; NYHA New York Heart Association; PCI Percutaneous coronary intervention; SVG Saphenous vein graft

baseline coronary angiogram. No clinical indication for angiography is required before inclusion. IVUS will be performed in a segment length of at least 40 mm in an SVG suitable for IVUS analysis and in a segment

Figure 2) Intravascular ultrasound scenarios. SVG Saphenous vein graft

length of at least 20 mm in the anastomosed native coronary artery corresponding to the SVG chosen. If the anastomosed coronary artery cannot be imaged by IVUS, a nongrafted coronary segment can be used (Scenarios A, B, C and D in Figure 2)

Following the IVUS procedure, patients will be randomly assigned to receive rosiglitazone treatment or a placebo in addition to their standard drug regimen. The study drug will be titrated over an eight-week period up to a dose of 8 mg/day (or to the maximum tolerated dose). Patients will receive the study drug or placebo for 50 to 54 weeks in a double-blind protocol. At the beginning and at two, four, six, eight, 10 and 12 months of treatment, patients will be subjected to serial morphological, physiological and metabolic evaluations. At the final visit (at 12 months), patients will also undergo control IVUS and angiography.

Study end points

The primary end point of the study will be the change (12-month IVUS minus baseline IVUS) in plaque volume in a 40 mm or longer segment in one SVG.

IVUS: The secondary end point will be the change (12-month IVUS minus baseline IVUS) in plaque volume in an adjacent segment of coronary artery of at least 20 mm as measured by IVUS. Calcification will also be assessed. The proportion of patients showing atherosclerosis changes (progression or regression) will be determined (more than 10% change from baseline). Computer-assisted measurements (CMS; Medis, The Netherlands) will include the tracings of lumen area, plaque area and vessel area (area within the external elastic lamina) at baseline and at 12 months (Figure 3). Images will be acquired using 40 MHz IVUS catheters (Ultracross; Boston Scientific Scimed Inc, USA) and stored on Super-VHS videotapes during automatic pullback at a constant speed of 0.5 mm/s. All IVUS images will be analyzed blindly by the same two experienced technicians and reviewed by one cardiologist (RD). For the analysis, every 30th image will be used, generating a series of cross-sections spaced exactly 0.5 mm apart. No interpolated measurements will be performed. For the vein segment and three-dimensional reconstruction, a total of 80 images (40 mm) will be analyzed and for the native segment, 40 images (20 mm for scenario A) or 60 images (30 mm

Figure 3) Representative results of intravascular ultrasound (IVUS), a computed tomography scan and dual energy x-ray absorptiometry (DEXA) at baseline. A Lumen saphenous vein graft tracings are shown in red, vessel contours in green. B Visceral fat is shown in red, subcutaneous fat in green. C DEXA measurements include total body fat and trunk/leg fat ratio. AT Adipose tissue

for scenarios B and C) will be used. For scenarios A and B, the distal SVG anastomosis will be used as the fiduciary site; for scenarios C and D, the proximal SVG anastomosis will be used. To ensure optimal accuracy, the exact same segment length (ie, number of images) will be used for comparison between follow-up and baseline assessments. Using data from 25 subjects, the variability ($\pm$ SD) in the IVUS core laboratory in repeated SVG plaque volume measurements has been calculated to be $3.4\pm2.8\%$.

Angiographic: Using QCA measurements (CMS; Medis), changes in lumen diameter will be assessed at baseline and at follow-up over the entire length of the target SVG. The percentage of patent SVGs that had significant progression at the site of the most severe lesion at baseline and at follow-up will be evaluated. The proportion of patients showing new occlusions will also be assessed. All angiograms will be analyzed blindly by the same experienced technician and reviewed by one cardiologist (LR). Using data from 20 subjects, the variability in the QCA core laboratory in repeated SVG mean and minimum lumen diameters has been calculated to be $1.5\pm1.9\%$ and $2.0\pm2.0\%$, respectively. For segment length, the variability has been calculated to be $1.4\pm1.6\%$ in the QCA core laboratory.

Metabolic risk factors: Changes from baseline to six months (early) and 12 months (late) will be assessed for plasma glucose and insulin, various lipid fractions and lipoproteins, adipokines and a comprehensive list of markers of thrombosis and inflammation.

Body composition and distribution: Changes in body composition will be assessed by dual energy x-ray absorptiometry from baseline (Figure 3) to six months (early) and 12 months (late). Fluid retention will be assessed every two months by bioelectrical impedance analysis. Simple measures such as body weight, waist circumference and body mass index will also be serially recorded. The changes in abdominal areas and volumes of adipose tissue as well as midthigh areas of adipose tissue and muscle attenuations will be assessed by computed tomography from baseline to six months (early) and 12 months (late) (Figure 3). Using data from 90 subjects, the coefficient of variation in the imaging core laboratory has been calculated to be $0.04\pm0.08\%$ and $0.1\pm0.2\%$ for total and visceral adipose tissue, respectively.

Clinical outcomes: Apart from safety parameters, clinical outcomes defined by the occurrence of any of the following clinical events will

be recorded: death from any cause, Q or non-Q wave myocardial infarction, transient ischemic attack, stroke, hospitalization and ischemia-driven revascularization (percutaneous coronary intervention/CABG) between the baseline procedure and repeat angiography at 12 months $\pm$ 14 days.

Trial organization

The present trial is investigator initiated and is supported by an unrestricted grant provided by GlaxoSmithKline (Canada). The study was registered on www.clinicaltrials.gov and has been given the following reference number: NCT001698323. The study is coordinated by the Laval Hospital Research Centre (LHRC) in Laval, Quebec, where all core laboratories are located. Study and site monitoring have been given by contract to a third party (CATO Research, USA). The protocol was designed by LHRC investigators and the database remains the property of the LHRC project office. All image analyses will be performed in core laboratories located at the LHRC. A Data and Safety Monitoring Board (DSMB) has been instituted before study initiation. The DSMB (chairman, H Gerstein MD; members, M Bourassa MD, JM Brophy MD and MC Guertin PhD [biostatistician]) will meet regularly and recommendations on study conduct will be transferred to the steering committee after each meeting.

SAMPLE SIZE AND DATA ANALYSIS

The sample size was calculated according to the initial amount of atherosclerosis in typical SVG segments. At the time of study design, only one IVUS report was available and it showed an increase in SVG plaque area from $0.90 \pm 0.80 \text{ mm}^2$ one month post-CABG to $5.26 \pm 1.38 \text{ mm}^2$ 12 months post-CABG (16). The sample size is based on a two-sided *t* test at the 0.05 level of significance. The SD of SVG plaque area from a report by Hozumi et al (16) was used as a reference (1.38 mm^2) (16). To take into account an assumed 20% dropout rate, a sample size of approximately 280 patients was calculated to provide 80% power to detect a 10% change in plaque area of SVGs between baseline and follow-up.

All analyses will be performed among patients in the intent-to-treat population and as per protocols. The primary end point will be analyzed using a one-way ANOVA model. A two-way repeated ANOVA model with treatment, visit and treatment $\times$ visit interaction variables will be performed for continuous secondary end points. All categorical secondary end points will be analyzed using the χ^2 test. The results will be considered significant at $P \leq 0.05$. All analyses will be conducted using the statistical SAS package 9.1 (SAS Institute Inc, USA).

BASELINE CHARACTERISTICS AND SUMMARY RESULTS

The first patient was recruited in October 2003. Until May 2007, the DSMB met regularly and recommended pursuing enrollment as initially planned. However, due to decreasing enrollment and finite funding, the steering committee recommended interruption after 36 months of recruitment. At the present time, 193 patients have been randomized. Angiographic and IVUS follow-up of the final patient was completed by August 2007. Overall, 93% of patients were recruited in Canada and 7% in Spain. In Quebec, there are two university hospitals – Hôpital Laval in Quebec City (primary investigator [PI]: OF Bertrand, $n=125$) and Hôpital Notre-Dame in Montréal (PI: S Rinfret, $n=22$) – and one satellite site in Bonaventure (PI: R Audet, $n=7$). In Ontario, there are two university hospitals – Toronto General Hospital in Toronto (PI: V Dzavik, $n=7$) and Hamilton Civic Hospital in Hamilton (PI: M Natarajan, $n=3$). In Nova Scotia, there is one university hospital – Queen Elizabeth II Health Sciences Centre in Halifax (PI: L Tittle, $n=15$).

A number of observations can be drawn from the baseline characteristics of the study population (Table 4). The mean age of the population was 65 years and the vast majority were moderately obese men (92%). The mean duration between CABG and study entry was less than five years, whereas the mean duration of diabetes was eight years.

TABLE 4
Demographic and clinical characteristics of the patients (n=193)

Characteristic	Values
Age, years, mean $\pm$ SD	65 $\pm$ 7
Men, n (%)	177 (92)
Previous myocardial infarction, n (%)	111 (58)
Percutaneous coronary intervention, n (%)	31 (16)
Previous stroke, n (%)	13 (7)
Hypertension, n (%)	162 (84)
Dyslipidemia requiring medication, n (%)	188 (97)
Family history of heart disease, n (%)	107 (55)
Current smoker, n (%)	20 (10)
Diabetes treated with diet only, n (%)	25 (13)
Diabetes treated with oral medication, n (%)	168 (87)
Diabetes duration, years, mean $\pm$ SD	8 $\pm$ 7
Time since CABG, years, mean $\pm$ SD	4 $\pm$ 2
Medication use, n (%)	
Antiplatelet agents	193 (100)
Beta-blockers	127 (66)
Calcium channel blockers	140 (73)
ACEI/ARA	162 (84)
Diuretics	43 (22)
Statins	183 (95)
Fibrates	35 (18)
Metformin	144 (75)
Sulfonylureas	99 (51)
Alpha-glucosidase inhibitor	6 (3)
Anthropometric measures and vital signs, mean $\pm$ SD	
Weight, kg	85 $\pm$ 15
Body mass index, kg/m ²	29.8 $\pm$ 4.4
Waist circumference, cm	105 $\pm$ 11
Resting heart rate, beats/min	67 $\pm$ 12
Resting systolic blood pressure, mmHg	129 $\pm$ 14
Resting diastolic blood pressure, mmHg	72 $\pm$ 9
Blood values, mean $\pm$ SD	
Fasting glucose, mmol/L	7.6 $\pm$ 1.8
Fasting insulin, pmol/L	115 $\pm$ 66
Glycosylated hemoglobin, %	6.9 $\pm$ 1.0
Total cholesterol, mmol/L	3.94 $\pm$ 0.77
Low-density lipoprotein cholesterol, mmol/L	2.27 $\pm$ 0.64
High-density lipoprotein cholesterol, mmol/L	1.07 $\pm$ 0.23
Triglycerides, mmol/L	1.72 $\pm$ 0.88
C-reactive protein*, mg/L	2.17 $\pm$ 1.90

*Median value was 1.53 mg/L (interquartile range 0.84 mg/L to 2.93 mg/L)
ACEI Angiotensin I-converting enzyme inhibitor; ARA Angiotensin-II receptor antagonist; CABG Coronary artery bypass graft

Of note, all patients received antiplatelet therapy, 95% received a statin and 84% received angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. For diabetes control, 75% of patients were on metformin and 51% were on sulfonylureas. In accordance with guidelines, diabetes and blood pressure were well controlled with a baseline glycosylated hemoglobin of less than 7% and a blood pressure lower than 130/75 mmHg. Lipid parameters were also optimally managed.

Despite several preclinical and clinical studies demonstrating significant benefit in atherosclerosis control, and positive effects on inflammatory markers and adipose tissue biology, the role of TZD therapy in preventing atherosclerosis progression and macrovascular complications in type 2 diabetes is currently highly debated. In contrast to rosiglitazone, clinical studies with pioglitazone have had

positive outcomes (40). It is still premature to conclude whether there is a class effect related to currently used glitazones. Although the present study is underpowered for clinical outcomes, data from the VICTORY trial will provide important safety information on rosiglitazone in high-risk cardiovascular patients with type 2 diabetes. The study will also validate the use of IVUS in SVG and hence, validate the use of this model of accelerated atherosclerosis in evaluating and comparing new pharmacological compounds that aim to prevent atherosclerosis progression.

CONCLUSION

VICTORY will be the first cardiometabolic trial to evaluate the anti-atherosclerotic effects of rosiglitazone in post-CABG patients with

type 2 diabetes. The comprehensive markers of metabolism, and the measurements of body composition and adipose tissue distribution will provide further insight into the early and late impact of TZDs in this human model of accelerated atherosclerosis.

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