Journal of the American College of Cardiology
© 2009 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 53, No. 22, 2009
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2008.12.072

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)

Eva M. Lonn, MD, MSc,*† Hertzel C. Gerstein, MD, MSc,*† Patrick Sheridan, MSc,† Sandra Smith, RDMS,† Rafael Diaz, MD,‡ Viswanathan Mohan, MD, PhD,§ Jackie Bosch, MSc,† Salim Yusuf, DPhil,*† Gilles R. Dagenais, MD,‖ for the DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) and STARR Investigators

Hamilton, Ontario, Canada; Rosario, Argentina; Chennai, India; and Quebec City, Quebec, Canada

Objectives The aim of this study was to evaluate effects of the angiotensin-converting enzyme (ACE) inhibitor ramipril and the thiazolidinedione (TZD) rosiglitazone on carotid intima-media thickness (CIMT) in people with impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG).

Background People with IGT and/or IFG are at increased long-term risk for cardiovascular disease. Effects of ACE inhibitors and of TZDs on vascular disease in this population are unknown.

Methods One thousand four hundred twenty-five people with IGT and/or IFG but without cardiovascular disease or diabetes were randomized to ramipril 15 mg/day or its placebo and to rosiglitazone 8 mg/day or its placebo with a 2×2 factorial design. The primary study outcome was the annualized change of the aggregate maximum CIMT, computed as the average of the maximum CIMTs across 12 carotid arterial segments. The secondary study outcome was the annualized change of the mean far wall left and right common CIMT. Median follow-up was 3 years and carotid ultrasound examinations were obtained at baseline and yearly thereafter.

Results There were no differences in the primary and secondary outcomes between the ramipril and placebo groups. Compared with placebo, rosiglitazone reduced the primary CIMT outcome, but the difference was not statistically significant (difference = 0.0027 ± 0.0015 mm/year; p = 0.08) and significantly reduced the secondary CIMT outcome (difference = 0.0043 ± 0.0017 mm/year; p = 0.01).

Conclusions In people with IGT and/or IFG without cardiovascular disease and diabetes, treatment with ramipril had a neutral effect on CIMT, whereas rosiglitazone modestly reduced CIMT progression. (The Study of Atherosclerosis With Ramipril and Rosiglitazone; NCT00140647). (J Am Coll Cardiol 2009;53:2028–35) © 2009 by the American College of Cardiology Foundation

People with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) are at increased long-term risk of cardiovascular (CV) events (1). Experimental studies suggest direct atherogenic effects of elevated glucose levels (2). In addition, individuals with IFG and/or IGT frequently have a cluster of metabolic and vascular abnormalities that promote atherosclerosis, including insulin resistance, atherogenic dyslipidemia, hypertension or "pre-hypertension," obesity, increased inflammation, endothelial dysfunction, and altered fibrinolysis (3). Moreover, IGT and IFG, often referred to as "pre-diabetes," identify individuals at

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From the *Department of Medicine and †Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada; ‡Estudios Cardiologicos Latinoamerica, Rosario, Argentina; §Madras Diabetes Research Foundation, Gopalapuram, Chennai, India; and the ‖Quebec Heart Institute/Laval Hospital, Laval University, Quebec City, Quebec, Canada. The STARR trial was funded by the Heart and Stroke Foundation of Canada, Sanofi-Aventis, GlaxoSmithKline, and King Pharmaceuticals. Sanofi-Aventis and King Pharmaceuticals provided ramipril and placebo, and GlaxoSmithKline provided rosiglitazone and placebo. Drs. Lonn and Yusuf have received research funding and consulting and lecture fees from Sanofi-Aventis and GlaxoSmithKline. Dr. Gerstein has received consulting and lecture fees from GlaxoSmithKline. Dr. Dagenais has received consulting and lecture fees from Sanofi-Aventis and GlaxoSmithKline.

Manuscript received August 25, 2008; revised manuscript received December 19, 2008, accepted December 22, 2008.

increased risk of future diabetes, itself a potent risk factor for CV disease (3). Therefore, it is essential to identify vascular protective interventions in this population.

Angiotensin-converting enzyme (ACE) inhibitors lower blood pressure, have additional beneficial actions, and reduce CV events in high-risk patients (4,5). Some but not all previous studies reported reduced carotid intima-media thickness (CIMT) progression in patients with pre-existent vascular disease and/or high-risk diabetes and/or hypertension treated with ACE inhibitors (6,7). These agents were also shown to have favorable effects on glucose homeostasis (8,9).

Thiazolidinediones (TZDs) activate nuclear peroxisome proliferator-activated receptors gamma, which regulate transcription of genes encoding proteins involved in glucose homeostasis and lipid metabolism, with resultant increased hepatic and peripheral insulin sensitivity, improved glycemic status, and generally favorable effects on lipids (10). In addition, TZDs act on vascular and inflammatory signaling pathways, which might reduce atherosclerosis, independent of their metabolic actions (10,11). Treatment with troglitazone and pioglitazone reduced CIMT in several (12–15) but not all (16) small studies, and in a small study in nondiabetic coronary artery disease patients, rosiglitazone reduced CIMT progression (17). More recently, 2 larger studies conducted in patients with diabetes reported that, compared with glimepiride, pioglitazone reduced progression of CIMT (18) and of coronary atherosclerosis measured by intravascular ultrasound (19). However, it remains uncertain whether these agents reduce CV events.

The effects of ACE inhibitors and TZDs on the anatomic progression of vascular disease have not been studied in people with pre-diabetes. Therefore, we evaluated the effects of ramipril and of rosiglitazone on CIMT—a validated marker of vascular disease—in people with IGT and/or IFG but without clinical CV disease or diabetes.

Methods

Study design and participants. The STARR (STudy of Atherosclerosis with Ramipril and Rosiglitazone) trial is a randomized, double-blind, placebo-controlled parallel group study with a 2 × 2 factorial design. It is a substudy of the DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) trial (20,21). As such, all STARR trial participants were part of the parent DREAM trial, and the clinical eligibility criteria, study interventions, and clinical follow-up procedures are those described in detail previously, with the addition of quantitative carotid ultrasound (CUS) examinations. The study was conducted at 32 centers in 9 countries, selected among the DREAM study centers on the basis of availability of high-resolution ultrasound equipment and expert sonographers, and was coordinated by the Population Health Research Institute, McMaster University (Hamilton, Canada).

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
CIMT = carotid intima-media thickness
CUS = carotid ultrasound
CV = cardiovascular
IFG = impaired fasting glucose
IGT = impaired glucose tolerance
TZD = thiazolidinedione

Between July 2001 and August 2003 we enrolled persons 30 years of age or older who had IFG (plasma glucose levels at least 6.1 mmol/l [110 mg/dl] but <7.0 mmol/l [126 mg/dl]) or IGT (plasma glucose levels of at least 7.8 mmol/l [140 mg/dl] but <11.1 mmol/l [200 mg/dl] 2 h after an oral glucose load) and an adequate baseline CUS examination but who did not have CV disease, diabetes, or intolerance to either ACE inhibitors or TZDs. Adequate CUS examinations were defined as those allowing reliable measurements from a minimum of 4 predefined carotid arterial segments.

Eligible participants entered a 17-day, single-blind, double-placebo run-in period. Thereafter, adherent participants were randomly assigned (with a concealed, computerized telephone randomization system, stratified according to center, with a permuted block size of 8) to receive either ramipril (5 mg daily for the first 2 months, with an increase to 10 mg at the 2-month visit and 15 mg after 1 year) or matching placebo and rosiglitazone (4 mg once daily for the first 2 months and then 8 mg thereafter) or matching placebo. Clinical visits were scheduled 2 and 6 months after randomization and then every 6 months until the common termination window between February and April 2006. Blood pressure was measured at each visit; fasting plasma glucose was measured at baseline, yearly thereafter, and at the final visit; and oral glucose tolerance tests were performed at baseline, the 2-year visit, yearly thereafter, and at the final visit. The study was approved by the ethics committees at all participating centers, and all participants provided written informed consent.

Quantitative CUS. Carotid ultrasonography examinations were performed at baseline and yearly thereafter. The ultrasound methods have been reviewed in detail previously (7). Standardized ultrasound training, all quality control procedures, and all CIMT measurements were performed by the Core Laboratory (Population Health Research Institute, Hamilton, Canada). All CUS scans were performed by trained and certified sonographers with high-resolution imaging systems with linear array transducers operating at a fundamental frequency of at least 7.5 MHz. For each subject the same ultrasound imaging system and transducer were used throughout the study. Standardized and validated scanning and measurement protocols were used. At each visit a transverse B-mode scan was recorded, followed by a circumferential longitudinal scan, aimed at recording the maximum CIMT in each of 12 carotid artery segments (1-cm long), which were defined relative to the carotid flow divider as the near and far walls of the internal, bifurcation, and common left and right carotid arteries. Three certified

readers unaware of treatment assignment, performed all measurements with the Image-ProPlus software (Media Cybernetics, Silver Spring, Maryland). For each carotid arterial segment the reader selected a minimum of 3 frames showing the thickest CIMT. The leading edge (far wall) and the trailing edge (near wall) of the boundaries between the lumen and media and the media and adventitia were traced, obtaining measurements of segment maximum and mean CIMT. Within- and between-reader reproducibility was high (intraclass correlation coefficients of 0.90 to 0.96 throughout the study, with no temporal drifts). Completeness of data by carotid arterial segment was: 99% common carotid far wall, 97% common carotid near wall, 93% bifurcation far wall, 89% bifurcation near wall, 82% internal far wall, and 65% internal near wall.

For each patient, the aggregate maximum $CIMT_1$ (defined as the average of the segment maximum CIMTs across the 12 carotid arterial segments) and the common carotid far wall CIMT (defined as the average of the segment mean right and left common carotid far wall CIMTs) were computed, as defined a priori. Due to the observed higher missingness of measurable data for the internal carotid artery segments, an additional computed measurement—the aggregate maximum $CIMT_2$ (the average of the segment maximum CIMTs across 8 carotid arterial segments, the near and far walls of the right and left common carotid and bifurcation)—was defined before unblinding of treatment assignments.

Study outcomes. The primary study outcome was the annualized change in the aggregate maximum $CIMT_1$. The secondary outcome was the annualized change in the common carotid far wall CIMT. An additional outcome (defined before unblinding) was the annualized change in the aggregate maximum $CIMT_2$. The CV events were collected and adjudicated as part of the parent DREAM trial (22).

Statistical analysis. The study was originally designed to randomize 1,000 participants and to allow 80% power to detect a 30% treatment effect at the margins of the factorial, assuming a placebo progression rate of 0.016 mm/year for the primary outcome, a common SD of 0.025, with no significant interaction (subadditivity) between the treatments, and a 5% attrition rate. In August 2002, after review of available baseline CIMT measurements, which were lower than expected, the steering committee for the trial decided to increase the sample size to 1,400, anticipating lower placebo CIMT progression rates than originally hypothesized.

All analyses are by intention-to-treat and were done in SAS version 9.0 (SAS, Cary, North Carolina). Baseline characteristics were compared by *t* tests and chi-square tests as appropriate. The primary analyses compared the primary, secondary, and additional CUS outcomes of ramipril versus ramipril placebo and rosiglitazone versus rosiglitazone placebo, after confirming that there was no significant interaction between the study treatments for the primary or secondary CUS outcomes ($p = 0.36$ and $p = 0.47$, respectively, for interaction terms in the regression models). The pre-specified main efficacy analysis included all participants with at least 2 adequate CUS examinations after the baseline scan, to allow reliable slope estimates. Participants with at least 1 adequate post-baseline CUS examination were included in a sensitivity analysis. Analyses were done with repeated mixed effect linear models with CIMT as the dependent variable, random intercepts and slopes as a function of time, and fixed effects for geographic region, treatment assignment, time, and the interaction between treatment and time. An unstructured covariance matrix was fit for the random intercepts and slope and an AR1 structure for the residual error matrix. All testing was 2-sided and conducted with a 5% type I error rate. Pre-specified subgroup analyses were performed for age (above and below the median [54 years]), sex, history of hypertension, baseline glycemic status (IFG, IGT, or both IFG and IGT), and baseline aggregate maximum $CIMT_1$ (above and below the median).

Results

A total of 1,425 participants met clinical and ultrasound eligibility criteria; 715 were randomly assigned to active ramipril, 710 to ramipril placebo, 709 to active rosiglitazone, and 716 to rosiglitazone placebo. Of these, 7 were lost to follow-up or refused ongoing participation. A total of 1,256 (88.1%) completed at least 2 adequate follow-up CUS examinations and are evaluated in the primary efficacy analysis (637 randomly assigned to ramipril and 619 to its placebo, 621 to rosiglitazone and 635 to its placebo); 1,347 (94.5%) had at least 1 adequate post-baseline CUS examination and are included in the sensitivity analysis (681 randomly assigned to ramipril and 666 to its placebo, 670 to rosiglitazone and 677 to its placebo).

Baseline characteristics are shown in Table 1 and were well-balanced between the treatment groups. Participants' mean age was 54 years; over 54% were women; 41% reported hypertension, 32% hypercholesterolemia, and 11% current smoking; 36% were recruited from North America (Canada, U.S., and Bermuda), 29% from South America (Argentina and Brazil), 23% from India, 10% from Europe (Germany, Hungary, and Slovakia), and 1% from Australia. Mean baseline levels for blood pressure, fasting plasma glucose, and 2-hour glucose level after an oral glucose load were 135/82 ± 19/11 mm Hg, 5.8 ± 0.7 mmol/l, and 8.7 ± 1.4 mmol/l, respectively.

Participants were followed for a median of 3.09 (interquartile range 2.86 to 3.50) years. At 1 year 83.6% of participants in the active ramipril group and 87.2% of those in the ramipril placebo group were adherent (taking >80% of the study medication). The corresponding proportions at 2 years were 77.7% and 82.7%, at 3 years 73.0% and 81.7%, at 4 years 78.1% and 84.6%, and at the final visit 75.4% and 82.5%, respectively. For the rosiglitazone arm of the trial, adherence rates were 88.2% for active rosiglitazone and 91.2% for rosigli-

Table 1 Baseline Characteristics by Treatment Group

	Ramipril		Rosiglitazone	
	Active (n = 715)	Placebo (n = 710)	Active (n = 709)	Placebo (n = 716)
Mean age (yrs)	54.2 ± 10.9	54.5 ± 11.0	53.9 ± 10.8	54.6 ± 10.9
Women	416 (58.2%)	371 (52.3%)*	385 (54.3%)	402 (56.2%)
Isolated IGT	438 (61.3%)	435 (61.2%)	437 (61.6%)	436 (60.9%)
Isolated IFG	99 (13.9%)	93 (13.1%)	94 (13.3%)	98 (13.7%)
Both IGT and IFG	178 (24.9%)	182 (25.6%)	178 (25.1%)	182 (25.4%)
Geographic distribution				
North America	268 (37.5%)	252 (35.5%)	262 (37.0%)	258 (36.0%)
South America	206 (28.8%)	208 (29.3%)	206 (29.1%)	208 (29.1%)
Europe	69 (9.7%)	72 (10.1%)	65 (9.2%)	76 (11.3%)
India	160 (22.4%)	170 (23.9%)	130 (18.3%)	137 (19.1%)
Australia	12 (1.7%)	8 (1.1%)	12 (1.7%)	8 (1.1%)
Medical history				
History of hypertension	279 (39.0%)	299 (42.1%)	290 (40.9%)	288 (40.2%)
History of hypercholesterolemia	227 (31.8%)	227 (32.0%)	216 (30.5%)	238 (33.2%)
Current tobacco use	69 (9.7%)	86 (12.1%)	76 (10.7%)	79 (11.0%)
More than 3 alcoholic drinks/week	154 (21.5%)	141 (19.9%)	153 (21.6%)	142 (19.8%)
Sedentary lifestyle	217 (30.4%)	215 (30.3%)	215 (30.3%)	217 (30.3%)
Drug use				
ASA or antiplatelet agent	83 (11.6%)	70 (9.9%)	82 (11.6%)	71 (9.9%)
Statin	62 (8.7%)	79 (11.1%)	74 (10.4%)	67 (9.4%)
Fibrate	15 (2.1%)	17 (2.4%)	19 (2.7%)	13 (1.8%)
Thiazide diuretic	67 (9.4%)	68 (9.6%)	66 (9.3%)	69 (9.6%)
Other diuretics or aldosterone antagonist	20 (2.8%)	21 (3.0%)	21 (3.0%)	20 (2.8%)
Angiotensin-receptor blocker	40 (5.6%)	44 (6.2%)	45 (6.4%)	39 (5.5%)
Beta-blocker	117 (16.4%)	113 (15.9%)	119 (16.8%)	111 (15.5%)
Calcium-channel blocker	64 (9.0%)	80 (11.3%)	67 (9.4%)	77 (10.6%)
Alpha-blocker	8 (1.1%)	7 (1.0%)	6 (0.9%)	9 (1.3%)
Weight loss drug	2 (0.3%)	2 (0.3%)	2 (0.1%)	3 (0.4%)
Examination				
Weight (kg)	81.6 ± 17.3	83.0 ± 18.3	82.8 ± 17.8	81.7 ± 17.9
Body mass index (kg/m^2)	30.2 ± 5.1	30.3 ± 5.4	30.4 ± 5.4	30.1 ± 5.2
Waist circumference (cm)				
Men	101.2 ± 12.9	101.2 ± 12.3	101.7 ± 12.2	101.6 ± 13.7
Women	94.5 ± 13.0	94.3 ± 12.6	94.2 ± 13.6	93.7 ± 12.5
Waist to hip ratio (men; women)	0.96 ± 0.07; 0.86 ± 0.07	0.96 ± 0.06; 0.86 ± 0.07	0.97 ± 0.06; 0.86 ± 0.07	0.96 ± 0.07; 0.86 ± 0.07
Systolic blood pressure (mm Hg)	134.5 ± 19.1	135.5 ± 19.1	134.7 ± 18.5	135.3 ± 19.7
Diastolic blood pressure (mm Hg)	81.5 ± 11.3	82.1 ± 11.7	81.8 ± 11.3	81.7 ± 11.7
Ankle/brachial index	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2
Investigations				
Mean fasting plasma glucose (mmol/l)	5.75 ± 0.7	5.77 ± 0.7	5.77 ± 0.7	5.75 ± 0.7
Mean 2-h plasma glucose (mmol/l)	8.68 ± 1.4	8.77 ± 1.4	8.72 ± 1.3	8.72 ± 1.4
Left ventricular hypertrophy on ECG	29 (4.1%)	32 (4.5%)	28 (4.0%)	33 (4.6%)
CIMT (mm)				
Aggregate maximum $CIMT_1$	0.75 ± 0.19	0.76 ± 0.19	0.75 ± 0.19	0.76 ± 0.19
Common carotid far wall CIMT	0.66 ± 0.16	0.66 ± 0.16	0.66 ± 0.16	0.67 ± 0.16
Aggregate maximum $CIMT_2$	0.78 ± 0.19	0.79 ± 0.19	0.78 ± 0.19	0.79 ± 0.19

Values presented as frequencies (%) and mean ± SD. Baseline characteristics were similar and well-balanced between treatment groups for the 1,256 STARR (STudy of Atherosclerosis with Ramipril and Rosiglitazone) trial participants included in the primary efficacy outcome and the 1,347 participants included in the sensitivity analysis. *$p < 0.05$ for the active versus placebo groups.

ASA = acetylsalicylic acid; CIMT = carotid intima-media thickness; ECG = electrocardiogram; IFG = impaired fasting glucose; IGT = impaired glucose tolerance.

tazone placebo at 1 year, 83.4% and 87.7% at 2 years, 81.7% and 81.4% at 3 years, 77.8% and 87.1% at 4 years, and 84.0% and 85.3% at study end. More participants in the active ramipril group discontinued the study drug due to cough (7.4%) and fatigue (1.3%), as compared with those in the ramipril placebo group (1.6% and 0.3%, respectively), and more participants in the active rosiglitazone group stopped the study drug due to edema and weight gain, as compared with the rosiglitazone placebo group (1.8% vs. 1.3% and 1.8% vs. 0.9%, respectively).

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Table 2 Blood Pressure and Glucose at Baseline and in Follow-Up

	Baseline	2 Months	6 Months	1 Year	2 Years	3 Years	Study End
Systolic blood pressure (in mm Hg)							
Ramipril active	134.5 ± 19.1	126.4 ± 16.9*	125.6 ± 17.0*	125.7 ± 16.9*	125.7 ± 16.9*	126.0 ± 17.3*	126.1 ± 17.2*
Ramipril placebo	135.5 ± 19.1	131.7 ± 17.5	131.5 ± 16.8	131.5 ± 16.5	130.9 ± 17.2	132.5 ± 17.6	132.4 ± 18.0
Rosiglitazone active	134.7 ± 18.5	128.8 ± 17.3	127.7 ± 16.0†	127.2 ± 16.0†	127.0 ± 16.2‡	128.2 ± 17.6	128.4 ± 17.6
Rosiglitazone placebo	135.3 ± 19.7	129.3 ± 17.5	129.2 ± 17.9	129.7 ± 17.9	129.7 ± 17.9	130.3 ± 17.7	130.1 ± 18.1
Diastolic blood pressure (in mm Hg)							
Ramipril active	81.5 ± 11.3	77.3 ± 10.2*	77.1 ± 10.2*	76.9 ± 10.5*	76.0 ± 10.3*	75.7 ± 10.9*	75.6 ± 10.9*
Ramipril placebo	82.1 ± 11.7	80.2 ± 10.4	79.9 ± 10.3	80.4 ± 9.8	78.8 ± 10.4	79.2 ± 10.4	78.9 ± 11.1
Rosiglitazone active	81.8 ± 11.3	78.5 ± 10.1	77.8 ± 9.9†	77.7 ± 10.1§	76.7 ± 10.6†	76.8 ± 11.1‡	76.7 ± 11.5
Rosiglitazone placebo	81.7 ± 11.7	78.9 ± 10.7	79.1 ± 10.7	79.5 ± 10.4	78.0 ± 10.3	78.0 ± 10.5	77.7 ± 10.7
Fasting plasma glucose (in mmol/l)							
Ramipril active	5.8 ± 0.7	—	—	5.6 ± 1.0	5.6 ± 1.0†	5.7 ± 1.0	5.8 ± 1.0
Ramipril placebo	5.8 ± 0.7	—	—	5.7 ± 1.1	5.7 ± 1.1	5.8 ± 1.0	5.9 ± 1.2
Rosiglitazone active	5.8 ± 0.7	—	—	5.4 ± 0.9*	5.5 ± 1.3*	5.6 ± 0.9*	5.7 ± 1.1*
Rosiglitazone placebo	5.8 ± 0.7	—	—	5.8 ± 1.0	5.8 ± 1.1	6.0 ± 1.1	6.0 ± 1.1
Post-load plasma glucose (in mmol/l)							
Ramipril active	8.7 ± 1.4	—	—	—	7.2 ± 2.5	7.3 ± 2.3	7.4 ± 2.3
Ramipril placebo	8.8 ± 1.4	—	—	—	7.5 ± 2.4	7.4 ± 2.5	7.6 ± 2.7
Rosiglitazone active	8.7 ± 1.3	—	—	—	6.8 ± 2.2*	6.9 ± 2.3*	7.0 ± 2.5*
Rosiglitazone placebo	8.7 ± 1.4	—	—	—	7.9 ± 2.6	7.8 ± 2.4	8.0 ± 2.5

Values presented as mean ± SD. *$p < 0.0001$; †$p < 0.01$; ‡$p < 0.05$; §$p < 0.001$ (refers to comparisons between active ramipril vs. ramipril placebo and active rosiglitazone vs. rosiglitazone placebo).

Changes in blood pressure and glucose. The baseline and subsequent blood pressure, fasting glucose, and 2-h post-challenge glucose levels are summarized in Table 2. Ramipril lowered blood pressure and had a small effect on glucose levels. Rosiglitazone lowered fasting and 2-h post-challenge glucose and had a small blood pressure-lowering effect.

Treatment effects on CIMT. Baseline CIMT did not differ significantly between the treatment groups (Table 1). On average the annualized change in all CIMT measurements was low; in the double placebo cell of the trial the annualized change was 0.0076 mm/year (SE = 0.0015 mm/year) for the aggregate maximum $CIMT_1$, 0.0074 mm/year (SE = 0.0017 mm/year) for the common carotid far wall CIMT, and 0.0068 mm/year (SE = 0.0016 mm/year) for the aggregate maximum $CIMT_2$.

The main study results are summarized in Table 3 and Figure 1. There were no significant differences for the primary, secondary, and the additional CIMT outcomes between the active ramipril and the ramipril placebo groups. For the rosiglitazone arm of the study we observed a nonstatistically significant reduction in CIMT progression for the primary outcome and significant differences, favoring active therapy for the secondary and the additional CIMT outcomes. These findings did not differ significantly in multivariate models adjusting for age, sex, and baseline CIMT, average systolic blood pressure, and average fasting plasma glucose.

We tested the robustness of our findings in the sensitivity analysis, which included all participants with at least 1 post-baseline CUS examination. Findings were similar, with no significant differences between the active and placebo groups in the ramipril arm of the trial, whereas rosiglitazone nonsignificantly reduced the primary CIMT outcome and significantly reduced the secondary and additional CIMT outcomes (Table 4).

Table 3 Main Efficacy Analysis: Primary, Secondary, and Additional CIMT Outcomes

Annualized Change of CIMT (mm/year)	Active	Placebo	Difference (Active–Placebo)	p Value
Ramipril arm of the trial	(n = 637)	(n = 619)		
Primary outcome: aggregate maximum $CIMT_1$	0.0083 ± 0.0011	0.0069 ± 0.0011	0.0014 ± 0.0015	0.37
Secondary outcome: common carotid far wall CIMT	0.0027 ± 0.0012	0.0047 ± 0.0012	−0.0020 ± 0.0017	0.26
Additional outcome: aggregate maximum $CIMT_2$	0.0059 ± 0.0012	0.0054 ± 0.0012	0.0005 ± 0.0016	0.74
Rosiglitazone arm of the trial	(n = 621)	(n = 635)		
Primary outcome: aggregate maximum $CIMT_1$	0.0063 ± 0.0011	0.0090 ± 0.0011	−0.0027 ± 0.0015	0.08
Secondary outcome: common carotid far wall CIMT	0.0015 ± 0.0012	0.0058 ± 0.0012	−0.0043 ± 0.0017	0.01
Additional outcome: aggregate maximum $CIMT_2$	0.0035 ± 0.0012	0.0077 ± 0.0012	−0.0042 ± 0.0016	0.01

Values presented as mean ± SEM. Two multivariate models were evaluated; the first model adjusted for age and sex and the second model for age, sex, average systolic blood pressure, and average plasma glucose. There were no significant differences of the annualized change in carotid intima-media thickness (CIMT) between the ramipril active and the ramipril placebo groups in any of these models; the differences between the rosiglitazone active and rosiglitazone placebo groups were: −0.0027 ± 0.0015 ($p = 0.08$) and −0.0027 ± 0.0015 ($p = 0.08$) for the primary outcome; −0.0042 ± 0.0017 ($p = 0.01$) and −0.0042 ± 0.0017 ($p = 0.01$) for the secondary outcome; and −0.0042 ± 0.0016 ($p = 0.01$) and −0.0041 ± 0.0016 ($p = 0.01$) for the additional CIMT outcome.

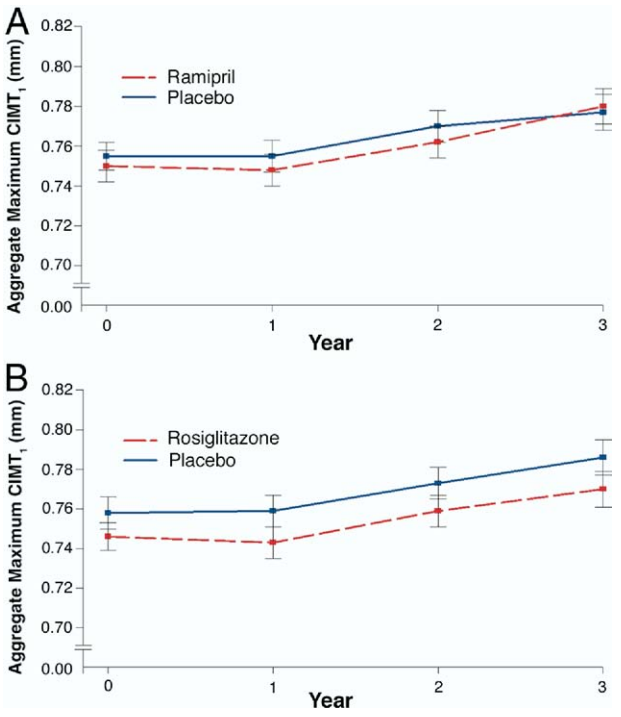

Figure 1 **Aggregate Maximum $CIMT_1$ Over 3 Years of Treatment**

The graph shows the average maximum carotid intima-media thickness (CIMT) derived from 12 carotid segments in study participants in the active ramipril and ramipril placebo groups **(A)** and in the active rosiglitazone and rosiglitazone placebo groups **(B). Bars** represent the SEMs.

For all pre-specified subgroups, no heterogeneity in the differences between study groups for the primary CIMT outcome was observed.

In an explanatory analysis comparing the cells of the factorial design, there were no differences for any of the CIMT outcomes between the active ramipril/ rosiglitazone placebo and double placebo cells; as compared with participants in the double placebo cell, those in the active rosiglitazone/ramipril placebo cell had nonsignificantly lower annualized changes in the primary aggregate $CIMT_1$ (difference = 0.0013; p = 0.56) and the additional aggregate $CIMT_2$ (difference = 0.0030; p = 0.19) and a statistically significantly lower annualized change in the common carotid far wall CIMT (difference = 0.0055; p = 0.02).

CV events. All participants completed at least 6 months of clinical follow-up and are considered in the analysis of clinical outcomes. There were no significant differences in the incidence of major CV events between the active ramipril and the ramipril placebo and between the active rosiglitazone and the rosiglitazone placebo groups (Table 5). Death from any cause occurred in 6 participants in the active ramipril, 7 in the ramipril placebo, 4 in the active rosiglitazone, and 9 in the rosiglitazone placebo groups.

Discussion

The STARR trial is the largest clinical trial of an ACE inhibitor and of a TZD in people with pre-diabetes (IGT and/or IFG). Ramipril reduced blood pressure and had a neutral effect on CIMT progression, whereas rosiglitazone reduced glycemia, had modest blood pressure lowering effects, and modest favorable effects on CIMT progression.

Carotid intima-media thickness is a validated biomarker, shown to independently predict stroke and myocardial infarction in large prospective studies, and has been used extensively in the assessment of the effects of various therapies on vascular disease progression (23). We used an experienced core laboratory and validated and accepted CIMT methodology (24) and implemented stringent quality control measures.

The absence of a significant effect for ramipril is somewhat surprising. Several but not all previous trials suggested that ACE inhibitors reduce CIMT progression (7). However, such trials were conducted in high-risk populations with vascular disease, diabetes, or hypertension and were expected to have more activated renin-angiotensin systems and accelerated vascular disease progression. The STARR study participants had lower-than-expected CIMT progression (approximately one-half of the originally projected progression rate). This is likely related to the exclusion of people with known vascular disease and/or diabetes (mandated by the proven clinical benefits of ACE inhibitors in these patients), the relatively young age of the study partic-

Table 4 **Sensitivity Analysis Conducted in Participants With at Least 1 Adequate Post-Baseline Carotid Ultrasound Scan**

Annualized Change of CIMT (mm/year)	Active	Placebo	Difference (Active–Placebo)	p Value
Ramipril arm of the trial	(n = 681)	(n = 666)		
Primary outcome: aggregate maximum $CIMT_1$	0.0082 ± 0.0011	0.0071 ± 0.0011	0.0011 ± 0.0014	0.47
Secondary outcome: common carotid far wall CIMT	0.0024 ± 0.0012	0.0048 ± 0.0012	−0.0024 ± 0.0017	0.17
Additional outcome: aggregate maximum $CIMT_2$	0.0057 ± 0.0011	0.0056 ± 0.0011	0.0001 ± 0.0016	0.92
Rosiglitazone arm of the trial	(n = 670)	(n = 677)		
Primary outcome: aggregate maximum $CIMT_1$	0.0064 ± 0.0011	0.0088 ± 0.0011	−0.0024 ± 0.0015	0.10
Secondary outcome: common carotid far wall CIMT	0.0017 ± 0.0012	0.0054 ± 0.0012	−0.0037 ± 0.0017	0.03
Additional outcome: aggregate maximum $CIMT_2$	0.0038 ± 0.0011	0.0075 ± 0.0011	−0.0038 ± 0.0016	0.02

Values presented as mean ± SEM.
CIMT = carotid intima-media thickness.

Table 5 Major Cardiovascular Events

Cardiovascular Event	Ramipril			Rosiglitazone		
	Active (n = 715)	Placebo (n = 710)	p Value	Active (n = 709)	Placebo (n = 716)	p Value
Composite cardiovascular outcome*	12 (1.68%)	15 (2.11%)	0.53	16 (2.26%)	11 (1.54%)	0.34
Myocardial infarction†	2	2		3	1	
Stroke†	0	2		1	1	
Cardiovascular death†	1	2		2	1	
New angina†	8	7		9	6	
Revascularizations†	6	13		11	8	
Heart failure†	2	1		1	0	

*The composite cardiovascular outcome represents the first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, new or unstable angina, coronary or peripheral revascularization, or heart failure. †All participants with this outcome are included.

ipants, the relatively short duration of treatment and follow-up, and the fact that participants were not selected on the basis of presence of subclinical atherosclerosis (while some previous trials selected participants on the basis of abnormal baseline CIMT, we used clinical eligibility criteria—probably a more relevant approach, because CIMT is currently not widely used in CV risk assessment and screening). The low baseline CIMT measurements and the low CIMT progression rates are concordant with the low CV event rates observed in STARR and in the parent DREAM trial (22). Whereas people with IGT and IFG have higher CV event rates than people with normal glucose metabolism when followed for extended periods of time, the short-term risk of middle-aged subjects with these metabolic abnormalities, after excluding people with diabetes and CV disease, is relatively low. Moreover, although ramipril effectively lowered blood pressure, on average blood pressure was already adequately controlled at baseline, and any potential benefits of further blood pressure-lowering might require longer periods of observation.

The results for rosiglitazone are not conclusive but suggest a modest beneficial short-term effect on vascular disease progression. This could result in more robust long-term effects on vascular disease progression and possibly on clinical ischemic events, although this hypothesis requires further evaluation. We selected a priori as our primary study outcome the annualized change in the aggregate CIMT measurement, comprising 12 carotid arterial segments, because some previous studies had suggested better correlations with angiographic coronary artery disease and higher sensitivity for the detection of treatment effects for this aggregate outcome (24), and found a nonsignificant trend toward a lower progression rate with rosiglitazone. This result was consistent in the primary efficacy analysis, the sensitivity analysis, in multivariate models, and across subgroups. However, other studies have used the change in the common far wall CIMT, due to higher reproducibility, less data missingness, and better correlations with coronary outcomes (24). Directly relevant, the largest trial of pioglitazone on CIMT in diabetes used common carotid far wall CIMT measurements (18) exclusively. When we analyzed the data with this outcome (our pre-specified secondary outcome), rosiglitazone significantly reduced CIMT progression. Moreover, the analysis of the additional aggregate CIMT outcome, which excluded the internal carotid artery segments (the segments with the highest rate of inadequate visualization), also showed reduced progression in the active rosiglitazone group compared with the rosiglitazone placebo group.

These findings are generally consistent with the vascular protective actions of TZDs observed in experimental settings (10,11), including increased insulin sensitivity, decreased inflammation, and decreased vascular proliferation. They are also consistent with experimental animal studies that show reduced atherosclerosis after rosiglitazone administration (25) and with previous smaller studies that reported reduced CIMT progression in people with diabetes and coronary disease treated with troglitazone (12), pioglitazone (13–15,18), and rosiglitazone (17).

The clinical implications of our findings require further study. At present, TZDs have been shown to increase the risk for heart failure (26), but effects of these drugs on ischemic CV events and all-cause mortality are still unclear. Indeed, 1 large trial of pioglitazone reported a trend favoring reduced CV events (27), whereas meta-analyses of trials not specifically designed and powered for CV outcomes reported increased CV risk with rosiglitazone (28,29). Our findings suggest that, in addition to improving glycemic control, rosiglitazone might retard the progression of vascular disease and support future research aimed at conclusively evaluating its effects on CV outcomes.

Reprint requests and correspondence: Dr. Eva M. Lonn, Hamilton General Hospital, 237 Barton Street East, Hamilton, Ontario L8L 2X2, Canada. E-mail: lonnem@mcmaster.ca.

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Key Words: ACE inhibitors ■ atherosclerosis ■ carotid intima-media thickness ■ pre-diabetes ■ thiazolidinediones.

APPENDIX

For a list of study investigators, please see the online version of this article.