SCIENCE ADVISORY

Thiazolidinedione Drugs and Cardiovascular Risks

A Science Advisory From the American Heart Association and American College of Cardiology Foundation

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The purpose of this science advisory is to summarize the currently available data concerning thiazolidinediones and cardiovascular risk, with a focus on ischemic heart disease (IHD) events, and to provide practical recommendations to healthcare workers seeking to minimize the burden of cardiovascular disease (CVD) and other complications in their patients with type 2 diabetes mellitus. On May 21, 2007, the US Food and Drug Administration (FDA) released a safety alert concerning a possible increased risk of ischemic cardiovascular events in patients prescribed the thiazolidinedione rosiglitazone. This safety alert was prompted by the results of a large meta-analysis that reported that treatment with rosiglitazone resulted in a 43% increase in risk for myocardial infarction (MI) and a possible increase in risk for cardiovascular death (1). These data were particularly alarming because the metabolic effects of thiazolidinediones were widely presumed, although not proven, to reduce the risk for IHD. Subsequently, a number of additional reports using alternative meta-analytic techniques (2,3), new meta-analyses (4–10), recently published results of new clinical trials (11–15), and observational studies of both rosiglitazone and pioglitazone (16–24) have provided variable evidence regarding an adverse cardiovascular effect of these agents. On November 14, 2007, after a specially convened FDA Advisory Panel meeting on July 30, 2007, the FDA decided not to withdraw rosiglitazone from the market. They issued new prescribing information that included a new boxed warning regarding the potential risk for myocardial ischemia, particularly in patients with heart disease taking nitrates, and in patients for whom rosiglitazone was added to established insulin therapy (25).

Diabetes mellitus is increasing in prevalence in the United States and worldwide. An estimated 23.6 million people in the United States, 7.8% of the population, had diabetes in 2007, with more than 90% of cases being type 2 diabetes mellitus. Diabetes increases the risk of CVD events by 2- to 4-fold, and CVD accounts for nearly two thirds of deaths among diabetic patients (26). Among people who experience CVD events, diabetes is highly prevalent: 45% of those hospitalized for acute MI have known or previously undiagnosed diabetes (27). Diabetes is also an independent predictor of secondary adverse events, such as reinfarction, heart failure, and death (28,29). Similar trends have been observed in the global incidence of diabetes and its consequences. Improving care for diabetic patients has therefore become a global health priority (30,31).

The pathophysiology of type 2 diabetes mellitus involves both insulin resistance and progressive loss of the insulin-secretory capacity of pancreatic beta cells. Prior to the late 1990s, pharmacological therapy for type 2 diabetes mellitus was directed at stimulating or replacing endogenous insulin secretion. Insulin resistance precedes the clinical manifestation of diabetes and has been shown to be associated with other cardiovascular risk factors and with increased cardiovascular risk (32). The thiazolidinedione class of drugs, ligands of the peroxisome-proliferator–activated receptor-γ, which is intricately involved in insulin signaling, were the first drugs developed that directly targeted insulin resistance (33). By improving hepatic and peripheral tissue utilization of glucose, thiazolidinediones reduce plasma glucose and insulin levels and may be associated with improvements in plasma lipoproteins and certain inflammatory cytokines.

Two thiazolidinediones are currently available in the United States, rosiglitazone (Avandia) and pioglitazone (Actos). A third thiazolidinedione, troglitazone (Rezulin), was withdrawn from the market in 2000 because of drug-induced liver injury, including rare cases of hepatic failure and death.

Rosiglitazone and IHD Risk

To date, there has been only 1 randomized clinical trial prospectively designed to assess the effect of rosiglitazone on cardiovascular outcomes, the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial (12,13). The majority of evidence regarding the cardiovascular effects of rosiglitazone is derived from meta-analyses of randomized clinical trials that evaluated the effects of rosiglitazone on glycemic control (1–10). Supplementary evidence is also available from observational studies (16–24) and analyses of nonrandomized use of rosiglitazone in clinical trials that focused on glycemic targets rather than specified pharmacological interventions (11,14,15).

Table 1 summarizes the characteristics and results of these studies (see also Figure 1). There are important differences in trial design, eligibility, follow-up, sample size, analytical methods, and outcomes among the studies.

In the RECORD trial, 4447 patients with type 2 diabetes mellitus that was controlled inadequately with metformin or sulfonylurea were randomized to receive either open-label add-on rosiglitazone or add-on metformin or sulfonylurea (12,13). The primary objective was to determine whether rosiglitazone (plus metformin or sulfonylurea) was noninferior to metformin plus sulfonylurea in reducing the combined end point of hospitalization or cardiovascular death. An interim analysis after 3.7 years of follow-up yielded inconclusive results (12). Recently published results of the completed trial showed that after 5.5 years of follow-up, there were 321 events in the rosiglitazone group and 323 in the control group, which yielded an intention-to-treat hazard ratio (HR) of 0.99 (95% confidence interval [CI] 0.85 to 1.16) for the primary end point, which met the prespecified criterion for noninferiority (HR less than 1.20) (13). The HR was 1.14 (95% CI 0.80 to 1.63) for MI and 0.84 (95% CI 0.59 to 1.18) for cardiovascular death. Consistent with previous trials, rosiglitazone caused an increase in heart failure (HR of 2.10, 95% CI 1.35 to 3.27) and fractures (HR of 1.57, 95% CI 1.12 to 2.19) (13). In a prespecified subgroup analysis, the HR for the primary end point was 1.26 (95% CI 0.95 to 1.68) among patients with previous IHD (interaction p=0.06, unadjusted for multiple comparisons). Unfortunately, the RECORD study was limited by a lower-than-anticipated event rate, which resulted in low power for analysis of the primary end point, the suboptimal study medication adherence and/or high crossover rate, and imbalance in disease-modifying therapies such as statins and thiazides that favored the rosiglitazone-treated group (both presumably attributable to the open-label study design). As such, the results of RECORD are inconclusive with respect to the effects of the drug on cardiovascular risk. The data are compatible with as much as a 15% improvement or as much as a 16% worsening in overall cardiovascular risk and as much as a 20% improvement or as

much as a 63% worsening in risk of MI with rosiglitazone compared with metformin plus sulfonylurea.

In the absence of data from adequately powered randomized trials, meta-analyses of smaller trials provide the next best approach to evaluate a relationship between rosiglitazone and cardiovascular events. In the first large meta-analysis of clinical trials of the effects of rosiglitazone on glycemic control, Nissen and Wolski (1) examined data from 42 trials that included 27 847 patients. Their analysis indicated that treatment with rosiglitazone was associated with an increase in the odds of MI (odds ratio 1.43, 95% CI 1.03 to 1.98, p=0.03) and a nonsignificant increase in the odds of cardiovascular death (odds ratio 1.64, 95% CI 0.98 to 2.74, p=0.06) compared with a control group (active comparator or placebo) (1). However, this report excluded 4 trials from the MI analysis and 19 trials from the cardiovascular death analysis in which no events occurred in either trial arm (2,3). Diamond et al. (2) reanalyzed the same clinical trials in the report by Nissen and Wolski (1) using methods that allowed the inclusion of zero-event trials that were excluded in the earlier analysis. Although the resultant odds ratios remained elevated (which suggests a "signal" for increased risk), the CIs were wide and overlapped unity, which indicates greater uncertainty than was reported originally (2). A different meta-analysis by Psaty and Furberg (6), in which the unplanned interim results of RECORD were combined with the meta-analysis by Nissen and Wolski (1) using the variance-weighted fixed-effects model, suggested that rosiglitazone was associated with increased odds for MI (odds ratio 1.33, 95% CI 1.02 to 1.72).

The integrated clinical trial analyses conducted by the maker of rosiglitazone, GlaxoSmithKline (4), and the meta-analysis conducted by the FDA (5) were based on 42 randomized trials (only 28 of which overlapped with the meta-analysis by Nissen and Wolski (1)). The number of patients included in the GlaxoSmithKline and FDA analyses was smaller because of the inclusion of only diabetic patients and double-blind trials; however, patient-level data were available, which allowed more detailed analyses. Both the GlaxoSmithKline and FDA meta-analyses, which used slightly different modeling techniques, concluded that rosiglitazone was associated with an increase in any IHD event, including unadjudicated chest pain, but no statistically significant increase in the composite of cardiovascular death, MI, or stroke. The subgroup analyses in the FDA review identified a potentially higher risk of adverse events with rosiglitazone in patients who were older, had preexistent heart failure, or took nitrates, angiotensin-converting enzyme inhibitors, or insulin (which presumably reflected high-risk patients with CVD) (5).

Additional meta-analyses have reported inconsistent results. A Cochrane review did not reveal a statistically significant increase in the risk of MI (7). In contrast, the meta-analysis by Singh et al. (8) reported a 42% increase in MI; however, there was no significant increase in cardiovascular mortality (0.90, 95% CI 0.63 to 1.26) or all-cause mortality (0.90, 95% CI 0.71 to 1.15). In the meta-analysis by Lago et al. (9), despite a nearly 2-fold increase in the risk of congestive heart failure (CHF), rosiglitazone was not associ-

ated with an increase in risk of cardiovascular death (risk ratio 0.91, 95% CI 0.63 to 1.32). Shuster et al. (10) observed a significant increase in the risk of cardiovascular death (risk ratio 2.37, 95% CI 1.38 to 4.07), but there was uncertainty with regard to the risk of MI (risk ratio 1.51, 95% CI 0.91 to 2.48). These discordant results may be related to inconsistencies in trial design and number, analytical methodology, and end-point criteria.

Five large observational studies also have examined the IHD risk associated with rosiglitazone, 1 commissioned by GlaxoSmithKline that used the Ingenix Database and was known as the Balanced Cohort Study (16) and others conducted independently by Tricare for the Department of Defense (17), by WellPoint (18), by the Institute for Clinical Evaluative Sciences (Ontario, Canada) (19), and by the Institute of Health and Welfare Policy/Center for Health and Welfare Policy Research (Taipei, Taiwan) (20). Studies varied in their design and ability to overcome residual confounding and biases. In 3 of the 5 studies, rosiglitazone was not associated with an increased IHD risk compared with other antidiabetic agents (16–18). However, the Ontario study suggested an increase in the risk of CHF, death, or MI in elderly patients with type 2 diabetes mellitus (19). Similarly, the Taiwanese study reported a higher risk of any cardiovascular event and MI for patients prescribed rosiglitazone monotherapy than for patients prescribed metformin or sulfonylurea alone (20). Caution must be observed in drawing definitive conclusions from observational studies because of the possibility of bias and confounding, which may lead to erroneous conclusions.

Finally, limited data are available from 3 clinical trials of intensive versus standard glycemic control in patients with diabetes. The intensive blood sugar–lowering treatment arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (11), a study of more than 10 251 patients with diabetes and high cardiovascular risk, reported a 20% increase in the annual risk of death (from 1.1% to 1.4%) in the intensive-treatment compared with the standard-treatment group; however, preliminary post hoc exploratory analyses do not suggest a link between differences in the use of drugs (including rosiglitazone) and the increased deaths in the intensive-treatment group (11). Similarly, the results from the VA Diabetes Trial of 1791 patients randomized to standard or intensive glucose control do not suggest increased cardiovascular risk with the use of rosiglitazone (HR 0.88, 95% CI 0.74 to 1.05, p=0.14) (14). However, the extensive and nonrandomized use of rosiglitazone in both arms of the ACCORD study (92% in the intensive-treatment group versus 58% in the standard-treatment group) and the VA Diabetes Trial (72% in the intensive-treatment group versus 62% in the standard-treatment group) reduces the likelihood of detecting a safety signal associated with rosiglitazone. The results of the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) trial, a study of 2368 patients with stable coronary artery disease funded by the National Institutes of Health, suggest that insulin-sensitization agents (metformin or thiazolidinedione; 89% of the thiazolidinedione users received rosiglitazone) are not harmful compared with insulin-provision treatment (insulin or sulfonylurea) and

may in fact provide a benefit, especially in patients undergoing surgical coronary revascularization (15). At 5 years, neither the rate of survival (88.2% versus 87.9%, difference 0.3%, 95% CI −2.2% to 2.9%, p=0.89) nor the rate of freedom from major cardiovascular events (77.7% versus 75.4%, difference 2.4%, 95% CI −1.2 to 6.0, p=0.13) differed significantly between the insulin-sensitization group and the insulin-provision group. Patients randomized to both coronary artery bypass graft surgery and insulin-sensitization therapy had a significantly lower rate of major cardiovascular events than any of the other treatment-combination groups (15). Because of the design of the BARI 2D trial, it is not possible to determine whether the findings with the insulin-sensitization agents apply to metformin monotherapy, thiazolidinedione monotherapy, or their combination.

In summary, an association between rosiglitazone and IHD outcomes has not yet been firmly established. Additional prospective clinical trials designed for the specific purpose of establishing the cardiovascular benefit or risk of rosiglitazone would be the best way to resolve the uncertainties regarding the safety of rosiglitazone. However, sufficient evidence has emerged to raise concerns about a potential adverse effect. These uncertainties were reflected in the vote of the FDA Advisory Panel, who on July 30, 2007, voted 20 to 3 in favor of an increased risk for ischemic cardiac events with rosiglitazone but voted 22 to 1 against removing rosiglitazone from the market (34). On October 18, 2007, the European Medicines Agency issued a statement that concluded that "the benefits of both rosiglitazone and pioglitazone in the treatment of type 2 diabetes continue to outweigh their risks." (35) The FDA's decision on November 14, 2007, to allow rosiglitazone to remain on the market with an additional boxed warning about the risk of IHD events further reflects these uncertainties (25). The FDA stated that additional studies "have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive." Given this clinical equipoise, we call on academic researchers, industry, and government agencies to collaborate on definitive randomized trials to answer these important clinical questions.

Pioglitazone and IHD Risk

Table 2 summarizes the characteristics and results of studies regarding IHD risk of pioglitazone (see also the Figure). A large clinical trial designed to assess the effect of pioglitazone on ischemic cardiovascular outcomes, the PROactive trial (PROspective pioglitAzone Clinical Trial In macroVascular Events), showed no statistically significant effect of pioglitazone on the primary composite outcome (HR 0.90, 95% CI 0.80 to 1.02) (36). However, pioglitazone treatment significantly reduced a secondary composite outcome of all-cause mortality, nonfatal MI, and stroke (HR 0.84, 95% CI 0.72 to 0.98). Nevertheless, this finding awaits confirmation in an additional prospective clinical trial.

A meta-analysis of 19 trials (in which nearly 80% of pooled events were contributed by the PROactive trial) reported a significant reduction in the composite end point of

Table 1. Studies of Rosiglitazone and IHD Risk

Study	Design (Treatment)	Follow-Up	No. of Trials (Sample Size)	Analytical Method	Outcomes of Interest	Results	Interpretation
RSG randomized trial							
RECORD (13)	RCT of diabetics, open-label (RSG+MET/SU vs MET+SU)	5.5 y	1 (4447)	Noninferiority analysis (HR)	**CV death/CV hospitalization** **MI** **CV death**	**0.99 (0.85–1.16)** **1.14 (0.80–1.63)** **0.84 (0.59–1.18)**	Limitations in trial design and conduct preclude reliable interpretation of the results
RSG meta-analyses							
Nissen and Wolski (1)	RCTs of diabetics, prediabetics, nondiabetics; double-blind and open-label (RSG vs placebo/active Rx)	>24 wk	42 (27 847)	Peto fixed-effects model (OR)	**MI** **CV death**	**1.43 (1.03–1.98)** **1.64 (0.98–2.74)**	Significant increase in the risk of MI and borderline increase in risk of CV death
Diamond et al. (2)	As Nissen and Wolski[1]	>24 wk	42 (27 847)	Mantel-Haenszel fixed-effects model with continuity correction (OR)	**MI** **CV death**	**1.26 (0.93–1.69)** **1.17 (0.77–1.77)**	Uncertainty in the risk of MI and CV death
Psaty and Furberg (6)	As Nissen and Wolski[1] plus RECORD (open-label) (RSG vs placebo/active Rx)	>24 wk	43 (32 294)	Variance-weighted fixed-effects model (OR)	**MI**	1.33 (1.02–1.72)	Significant increase in risk of MI
ICT (GSK) (4)	RCTs of diabetics; double-blind only (RSG vs placebo/active Rx)	Average 6 mo	42 (14 237)	Multivariable Cox proportional hazards model (HR)	**IHD** **CV death/MI/stroke**	**1.31 (1.01–1.70)** **1.16 (0.80–1.70)**	Increased risk of IHD, uncertain CV death/MI/stroke risk
FDA (5)	As ICT[4]	Average 6 mo	42 (14 237)	(1) Exact test (OR); (2) Mantel-Haenszel fixed-effects model with continuity correction (OR)	**IHD** **CV death/MI/stroke**	**1.39 (1.1–1.8)** **1.15 (0.8–1.6)**	Increased risk of IHD, uncertain CV death/MI/stroke risk
Cochrane review (7)	RCTs of diabetics; double-blind and open-label (RSG vs placebo/active Rx)	>24 wk	18 (3888)	Fixed-effects model (OR)	**MI**	0.91 (0.75–1.71)	No significant increase in risk of MI
Singh et al. (8)	RCTs of diabetics, prediabetics (RSG vs placebo/active Rx)	>1 y	4 (14 291)	Fixed-effects model (RR)	**MI** **CV death**	**1.42 (1.06–1.91)** **0.90 (0.63–1.26)**	Significantly increased risk of MI, no significant increase in risk of CV death
Lago et al. (9)	RCTs of diabetics, prediabetics; double-blind (RSG vs placebo/active Rx)	Average 29.7 mo	5 (14 491)	Random-effects model (RR)	CV death	0.91 (0.63–1.32)	No significant increase in risk of CV death
Shuster et al. (10)	As Nissen and Wolski[1] plus 6 trials excluded by Nissen and Wolski	>24 wk	48 (NA)	Random-effects model (RR)	**MI** **CV death**	**1.51 (0.91–2.48)** **2.37 (1.38–4.07)**	Uncertainty in risk of MI, significant increase in risk of CV death
RSG observational data							
Ingenix study (16)	Retrospective cohort study of diabetics (RSG vs non-RSG active Rx)	1.2 y	1 (33 363)	Propensity-matched Cox proportional hazard model (HR)	**MI/CR** **MI**	**0.93 (0.80–1.10)** **0.92 (0.73–1.16)**	No significant increase in risk of MI and/or revascularization

(Continued)

Table 1. Continued

Study	Design (Treatment)	Follow-Up	No. of Trials (Sample Size)	Analytical Method	Outcomes of Interest	Results	Interpretation
WellPoint study (18)	Observational study of diabetics (RSG vs non-RSG active Rx)	NA	1 (142 821)	Cox proportional hazard (HR)	MI	1.03 (0.89–1.19)	No significant increase in risk of MI
Ontario study (19)	Retrospective case-control study of elderly diabetics (RSG vs non-RSG active Rx)	3.8 y	1 (159 026)	Logistic regression (RR)	**MI** **Death**	**1.76 (1.27–2.44)** **1.47 (1.12–1.93)**	Increased risk of MI and death
Taiwan study (20)	Retrospective cohort study of diabetics (RSG* vs non-RSG active Rx)	NA	1 (473 000)	Multivariate Cox proportional hazard model (HR)	**Any CV event (vs SU)** **Ay CV event (vs MET)** **MI (vs SU)** **MI (vs MET)**	**1.54 (1.29–1.85)** **1.89 (1.57–2.28)** **1.49 (0.99–2.24)** **2.09 (1.36–3.24)**	Increased risk of any CV event and MI, especially compared with MET

ACM indicates all-cause mortality; CR, coronary revascularization; CV, cardiovascular; GSK, GlaxoSmithKline; HR, hazard ratio; ICT, integrated clinical trials; MET, metformin; NA, not available; OR, odds ratio; RCT, randomized, controlled trial; RR, risk ratio; RSG, rosiglitazone; Rx, treatment; and SU, sulfonylurea.

*Only 2093 patients (0.44) received RSG alone; any CV event includes the composite outcome of any of the 5 events of MI, CHF, stroke, transient ischemic attack, or angina pectoris.

all-cause death, MI, or stroke with pioglitazone compared with control (HR 0.82, 95% CI 0.72 to 0.94) (37). Observational studies suggest no increased IHD risk with pioglitazone compared with other oral hypoglycemic agents (18–20).

In summary, the majority of published studies do not suggest an increased hazard for IHD events in pioglitazone-treated patients. Accordingly, there is no boxed warning on the risk of IHD for pioglitazone.

Pioglitazone Versus Rosiglitazone and IHD Risk

There are currently no prospective randomized, controlled trials that have examined the risk of IHD events associated with pioglitazone compared with rosiglitazone. Observational studies have reached different conclusions regarding the relative safety of pioglitazone compared with rosigli-
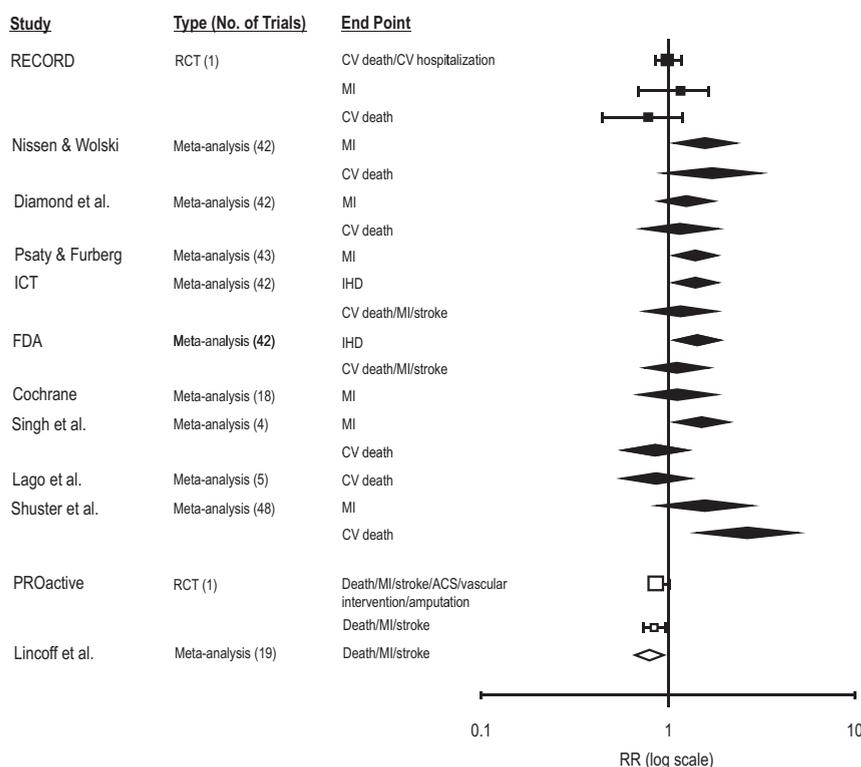
Figure 1. Thiazolidinediones and IHD risk based on randomized controlled trials (closed and open squares) and their meta-analyses (closed and open diamonds). Data for rosiglitazone are shown as closed squares and diamonds, whereas data for pioglitazone are shown as open squares and diamonds. There is overlap among the individual studies included in the different meta-analyses. RCT indicates randomized, controlled trial; CV, cardiovascular; ICT, integrated clinical trial; and ACS, acute coronary syndrome.

Table 2. Studies of Pioglitazone and IHD Risk

Study	Design (Treatment)	Follow-Up	No. of Trials (Sample Size)	Analytical Method	Outcomes of Interest	Results	Interpretation
PIO randomized trial							
PROactive Study (36)	RCT of diabetics (PIO vs placebo)	34.5 mo	1 (5238)	Cox proportional hazard (HR)	Death/MI/ stroke/ACS/ vascular intervention/ amputation	0.90 (0.80–1.02)	Nonsignificant reduction in composite ischemic events
PIO meta-analysis							
Lincoff et al. (37)	RCT of diabetics (PIO vs non-PIO active Rx)	4 mo to 3.5 y	19 (16 390)	Fixed-effects model (HR)	Death/MI/stroke	0.82 (0.72–0.94)	Significant reduction in risk of ischemic vascular events
PIO observational data							
WellPoint study (18)	Observational study of diabetics (PIO vs non-PIO active Rx)	NA	1 (144 531)	Cox proportional hazard (HR)	MI	1.04 (0.91–1.21)	No significant increase in risk of MI
Ontario study (19)	Retrospective case-control study of elderly diabetics (PIO vs non-PIO active Rx)	3.8 y	1 (159 026)	Logistic regression (RR)	**MI** **Death**	**0.73 (0.40–1.36)** **0.94 (0.61–1.45)**	No increased risk of MI and death with PIO
Taiwan study (20)	Retrospective cohort study of diabetics (PIO* vs non-PIO active Rx)	NA	1 (473 000)	Multivariate Cox proportional hazard model (HR)	**Any CV event (vs SU)** **Any CV event (vs MET)** **MI (vs SU)** **MI (vs MET)**	**1.03 (0.65–1.65)** **1.29 (0.81–2.07)** **0.72 (0.19–2.77)** **1.00 (0.26–3.89)**	No increased risk of any CV event or MI, but wide CIs due to small sample size
PIO vs RSG observational data							
Taiwan study (20)	Retrospective cohort study of diabetics (add-on PIO vs add-on RSG with SU and MET-based Rx)	NA	1 (473 000)	Multivariate Cox proportional hazard model (HR)	**MI (SU-based Rx)** **MI (MET-based Rx)** **MI (SU+MET-based Rx)**	**0.69 (0.30–1.55)** **6.34 (1.80–22.31)** **1.04 (0.73–1.47)**	Increased risk of MI with addition of PIO to MET, but wide CIs indicate limited statistical power
Ingenix study (21)	Retrospective cohort study of diabetics (PIO vs RSG)	1.3 y PIO 1.2 y RSG	1 (29 911)	Multivariate Cox proportional hazard model (HR)	**MI/CR** **MI**	**0.85 (0.63–0.96)** **0.78 (0.75–0.98)**	22 Lower risk of MI and/or revascularization with PIO
Winkelmayer et al. (22)	Retrospective cohort study of elderly diabetics (PIO vs RSG)	1.0 y PIO 1.0 y RSG	1 (28 361)	Multivariate Cox proportional hazard model (IRR)	**Death** **MI**	**0.87 (0.79–0.95)** **0.93 (0.80–1.08)**	13 Lower risk of death, but not MI, with PIO
Juurlink et al. (23)	Retrospective cohort study of elderly diabetics (PIO vs RSG)	72 mo	1 (39 736)	Multivariate Cox proportional hazard model (HR)	**Death/MI/ CHF** **Death** **MI**	**0.83 (0.76–0.90)** **0.86 (0.75–0.98)** **0.95 (0.81–1.11)**	Significant reduction in composite events and death, but not MI, with PIO
Dormuth et al. (24)	Nested case-control study of diabetics taking MET (RSG vs PIO or SU)	47 mo	1 (158 578)	Conditional logistic regression model (OR)	**MI (vs PIO)** **MI (vs SU)**	**1.00 (0.67–1.49)** **0.90 (0.69–1.17)**	No increased risk of MI with addition of RSG vs PIO or SU in prior MET users

ACS indicates acute coronary syndromes; CR, coronary revascularization; CV, cardiovascular; HR, hazard ratio; IRR, incident rate ratio; MET, metformin; NA, not available; OR, odds ratio; PIO, pioglitazone; RCT, randomized, controlled trial; RR, risk ratio; RSG, rosiglitazone; Rx, treatment; and SU, sulfonylurea.

*Only 495 patients (0.10) received PIO alone; any CV event includes the composite outcome of any of the 5 events of MI, CHF, stroke, transient ischemic attack, or angina pectoris.

tazone (Table 2). One large study that used Taiwan's National Health Insurance database suggested a nonsignificant association toward a more favorable overall cardiovascular effect in those individuals prescribed add-on pioglitazone compared with add-on rosiglitazone (20). However, an increased risk of MI was observed with the addition of pioglitazone compared with rosiglitazone to metformin-based therapy, although the wide CI indicates

limited statistical power for this observation (20). Another study suggested a 22% lower risk of MI with pioglitazone compared with rosiglitazone (21). Two additional studies that used insurance claims databases for elderly patients with diabetes in New Jersey and Pennsylvania (22) and in the province of Ontario (23) found that pioglitazone was associated with a reduced risk of overall mortality and CHF but not MI compared with rosiglitazone. Finally, in a nested case-control study in British Columbia, in a cohort of prior metformin users, the addition of rosiglitazone was not associated with an increased risk of MI compared with the addition of a sulfonylurea or the addition of pioglitazone (24).

Taken together, these observations add further uncertainty with regard to the cardiovascular risk associated with thiazolidinediones. Substantial differences between the pioglitazone and rosiglitazone meta-analyses exist, e.g., placebo-controlled versus active-controlled trials, patient demographics, and treatment duration. Each of these factors potentially can have a material impact on outcomes. This type of indirect comparison is potentially misleading, may result in conflicting results depending on the end points compared, and generally should be avoided. Healthcare databases used in observational studies are limited by bias and confounding, and therefore, they are not particularly well suited for drawing definitive conclusions to impact policy or clinical practice recommendations. There are some differences among the thiazolidinediones with respect to changes in lipid profile; pioglitazone has more favorable effects on serum lipids than does rosiglitazone (38). Although these metabolic differences are expected to result in lower rates of IHD events with pioglitazone, only direct head-to-head comparisons of outcomes data in prospective randomized trials can provide convincing conclusions about the comparability of these 2 agents.

Thiazolidinediones and Heart Failure Risk

The effects of thiazolidinediones in exacerbating CHF have been detailed in a previously published American Heart Association/American Diabetes Association scientific statement (39). A meta-analysis by Lago et al. (9) demonstrated a 1.7-fold increase in risk of CHF with thiazolidinediones, with a slightly greater increase in risk with rosiglitazone (2.2-fold) than with pioglitazone (1.3-fold), although the between-treatment differences were not statistically significant. Despite the increase in risk of CHF, no increase in risk of cardiovascular death was observed with either thiazolidinedione, which leads one to question whether the volume retention/weight gain associated with thiazolidinediones is prognostically benign or harmful. Lincoff et al. (37) also reported an increase in the risk of CHF (1.4-fold) but not ischemic cardiovascular outcomes with pioglitazone. This, together with the observation that rosiglitazone did not adversely affect left ventricular systolic or diastolic function in patients with type 2 diabetes mellitus and New York Heart Association functional class I or II CHF despite edema and weight gain (40), raises question about the link between thiazolidinediones and CHF exacerbation. Furthermore, these find-

ings reinforce the message for establishing the clinical diagnosis of heart failure on the basis of associated symptoms (such as orthopnea, paroxysmal nocturnal dyspnea, unexplained cough or fatigue, or pedal edema) and signs (such as jugular venous distention, an S_3 gallop, and pulmonary rales) in patients with volume retention or weight gain while taking thiazolidinediones (39). Nonetheless, as summarized in the product label for both drugs, caution is urged for the use of rosiglitazone or pioglitazone in all patients with signs and symptoms suggestive of CHF. Initiation of either agent is contraindicated in patients with class III or IV CHF (41).

Recommendations to Reduce Vascular Disease in Patients With Type 2 Diabetes Mellitus

Diabetes is considered a coronary heart disease equivalent in adults older than 40 years. There is substantial clinical trial and other evidence that the standard secondary prevention strategies also affect the risk for coronary heart disease events in patients with type 2 diabetes mellitus. Thus, the cornerstone for prevention of IHD events in patients with type 2 diabetes mellitus includes tobacco avoidance, maintenance of optimal body weight, diet, physical activity, control of blood pressure and lipids (with statins as first-line therapy), and use of aspirin. The American Heart Association and the American College of Cardiology have published guidelines for CVD prevention that extend to patients with diabetes (42). The American Diabetes Association and European Association for the Study of Diabetes have issued a consensus statement with a related algorithm on the medical management of hyperglycemia (43). That statement indicates that a hemoglobin A_{1c} level greater than or equal to 7% should serve as a call to action to initiate or change therapy, with the goal of achieving a hemoglobin A_{1c} level less than 7%. Recent statements have been published in an attempt to harmonize the recommendations of the American Heart Association, American College of Cardiology, and American Diabetes Association (44).

In addition to conventional secondary prevention strategies, the current guidelines for patients with type 2 diabetes mellitus recommend that if lifestyle modifications including high-quality diet, physical activity, and weight reduction are insufficient to achieve the glycemic targets, antidiabetic agents should be considered. There are 10 classes of antidiabetic agents currently available (43): Biguanides (metformin), glinides (repaglinide, nateglinide), sulfonylureas, alpha-glucosidase inhibitors, thiazolidinediones, incretin mimetics (glucagon-like peptide-1 mimetics), dipeptidyl peptidase-IV inhibitors, amylin analogs (pramlintide), bile acid sequestrants (colesevelam), and insulin. However, it is important to recognize that the recommendation for glycemic control is based principally on evidence for reduced microvascular risk in patients with type 2 diabetes mellitus, which is available for some but not all glucose-lowering pharmacological therapies. Despite the favorable effects these therapies have on cardiometabolic risk profile (glucose control, insulin resistance, and dyslipidemia), there is a paucity of evidence that any glucose-lowering agent reduces macrovascular risk,

and as reviewed above, there are questions about whether rosiglitazone or even intensive glycemic control may have adverse effects on risk for IHD. Of the available agents, metformin in obese patients with type 2 diabetes mellitus has provided the strongest evidence of CVD benefit (45), including long-term benefits that persisted up to 10 years after completion of the United Kingdom Prospective Diabetes Study (UKPDS; vide infra) (46).

Where should glucose-lowering agents, including thiazolidinediones, be placed in the list of therapeutic options to prevent vascular disease in patients with type 2 diabetes mellitus? A prospective randomized study of obese patients enrolled in the UKPDS demonstrated significant reductions in diabetes-related deaths (42% risk reduction, p=0.017), any diabetes-related end point (32% risk reduction, p=0.0023), and MI (39% risk reduction, p=0.01) in patients treated with metformin (45). In a smaller subgroup in the UKPDS study in which metformin was added early to sulfonylurea-treated patients, there was an increase in diabetes-related deaths (45). Nevertheless, on the basis of the UKPDS data, the absence of evidence of any adverse cardiovascular effects, the existence of few other adverse side effects, and its low cost, metformin is generally recommended as first-line therapy to be initiated along with lifestyle modification, especially in obese diabetic patients. There is no consensus concerning which of the remaining classes of agents should be used next to achieve the recommended glycemic targets to reduce microvascular complications, nor is it well established what effect these agents may have on risk for macrovascular disease.

On the basis of all available evidence, thiazolidinediones should not be used with an expectation of benefit with respect to IHD events. Thiazolidinediones should be used with the understanding that they might increase the risk of heart failure. Of the 2 currently available thiazolidinediones, meta-analyses have raised important concerns about a potential adverse effect of rosiglitazone on IHD, a concern that has not been raised by the available data for pioglitazone. However, there remains an inadequate foundation of randomized clinical trials to properly judge the safety or efficacy of either agent with respect to IHD events. Thus, patients who have successfully achieved recommended glycemic control with a thiazolidinedione might consider remaining on their medication; however, if either the treating physician or the patient is uncomfortable continuing with a thiazolidinedione, another medication could be substituted, with the recognition that the fund of knowledge about the effect of other glucose-lowering agents on IHD risk is similarly sparse.

Recommendations to the Clinical Community, Pharmaceutical Industry, and Regulatory Agencies Concerning Treatments for Type 2 Diabetes Mellitus

The controversy over the unexpected findings from the meta-analyses of rosiglitazone glycemic control trials coupled with the similarly unexpected findings from the ACCORD trial has unmasked major deficiencies in our understanding of the role of glycemia in the pathogenesis and prevention of IHD in type 2 diabetes mellitus. Given the large and continually increasing

number of people with type 2 diabetes mellitus and the magnitude of the attendant burden of IHD in these patients, it is incumbent on the medical community to identify optimal strategies to prevent both the microvascular and macrovascular complications of the disease. Unfortunately, as the rosiglitazone case illustrates, clinical trials focused purely on glycemic control as the primary outcome do not provide the quality of evidence required to make informed decisions regarding the clinical efficacy and safety of glucose-lowering regimens with respect to both microvascular and macrovascular disease. The clinical community must insist on having adequate data to make decisions about optimal treatment for their patients with type 2 diabetes mellitus, including properly designed randomized trials with subclinical and clinical cardiovascular outcomes as the primary or important secondary outcomes. The pharmaceutical industry should immediately initiate appropriately designed clinical trials of currently approved glucose-lowering agents to determine their effect on clinical cardiovascular events. Finally, the FDA and other regulatory agencies should require that such trials be included as part of the initial or ongoing evaluation of new glucose-lowering agents and explore novel strategies such as phased approval and other measures to permit clinical efficacy and safety data to be generated without causing undue delays in or significant barriers to the development of urgently needed therapies to prevent all forms of vascular disease in patients with type 2 diabetes mellitus.

Summary

Minimization of the risk of microvascular and macrovascular disease is a critical clinical goal in the management of patients with diabetes. Control of hyperglycemia is recommended to reduce microvascular complications; achievement of a hemoglobin A_{1c} less than 7% without causing hypoglycemia may be particularly important, if accomplished early in the disease and maintained successfully. Attainment of this glycemic goal when lifestyle modification is not enough will require a choice of 1 or more glucose-lowering agents.

Conventional risk-reduction measures, such as lifestyle modification, the use of aspirin (especially in patients with preexisting CVD), and appropriate blood pressure– and lipid-lowering drugs, are of proven benefit in reducing macrovascular disease and saving lives; however, the evidence concerning the effects of specific glucose-lowering agents on macrovascular disease is limited and inconclusive. There is evidence that suggests a macrovascular benefit with metformin, especially for obese diabetic patients, and some inconclusive evidence of potential harm from rosiglitazone but not pioglitazone. For most of the other glucose-lowering agents, there are few or no data to support either harm or benefit with regard to macrovascular disease.

More data are urgently needed to clarify the effects of all existing and future glucose-lowering agents, including thiazolidinediones, on IHD events. In the meantime, patients and clinicians will need to weigh the accepted benefits of improved glycemic control on risk for microvascular disease from glucose-lowering agents against the worrisome, inconclusive, or completely absent information about the effects of these agents on macrovascular disease.

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*Modest.

†Significant.

Keys to Patient Management

The following are keys to patient management:

- Identification and treatment of correctable risk factors
  - Smoking cessation
  - High-quality diet
  - Weight control
  - Exercise

- Use of established secondary prevention strategies
  - Aspirin (or clopidogrel in patients intolerant of aspirin)
  - Lipid lowering, with statins as the first-line therapy
  - Blood pressure lowering

- Early and consistent attention to controlling hyperglycemia while avoiding hypoglycemia
  - Metformin is generally first-line therapy, particularly in obese patients
  - Thiazolidinediones should not be used with an expectation of benefit with respect to IHD events
    - Insufficient data exist to support the choice of pioglitazone over rosiglitazone
    - Thiazolidinediones increase the risk of heart failure and should not be initiated in patients with class III/IV CHF

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