

# Cardiovascular Outcomes in Trials of Oral Diabetes Medications

## A Systematic Review

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**Background:** A wide variety of oral diabetes medications are currently available for the treatment of type 2 diabetes mellitus, but it is unclear how these agents compare with respect to long-term cardiovascular risk. Our objective was to systematically examine the peer-reviewed literature on the cardiovascular risk associated with oral agents (second-generation sulfonylureas, biguanides, thiazolidinediones, and meglitinides) for treating adults with type 2 diabetes.

**Methods:** We searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials, from inception through January 19, 2006. Forty publications of controlled trials that reported information on cardiovascular events (primarily myocardial infarction and stroke) met our inclusion criteria. Using standardized protocols, 2 reviewers serially abstracted data from each article. Trials were first described qualitatively. For comparisons with 4 or more independent trials, results were pooled quantitatively using the Mantel-Haenszel method. Results are presented as odds ratios (ORs) and corresponding 95% confidence intervals (CIs).

**Results:** Treatment with metformin hydrochloride was associated with a decreased risk of cardiovascular mortality (pooled OR, 0.74; 95% CI, 0.62-0.89) compared with any other oral diabetes agent or placebo; the results for cardiovascular morbidity and all-cause mortality were similar but not statistically significant. No other significant associations of oral diabetes agents with fatal or nonfatal cardiovascular disease or all-cause mortality were observed. When compared with any other agent or placebo, rosiglitazone was the only diabetes agent associated with an increased risk of cardiovascular morbidity or mortality, but this result was not statistically significant (OR, 1.68; 95% CI, 0.92-3.06).

**Conclusions:** Meta-analysis suggested that, compared with other oral diabetes agents and placebo, metformin was moderately protective and rosiglitazone possibly harmful, but lack of power prohibited firmer conclusions. Larger, long-term studies taken to hard end points and better reporting of cardiovascular events in short-term studies will be required to draw firm conclusions about major clinical benefits and risks related to oral diabetes agents.

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**A** WIDE VARIETY OF ORAL diabetes medications are currently available for the treatment of type 2 diabetes mellitus. With the addition of newer oral therapies to the market in the late 1990s (eg, thiazolidinediones

and meglitinides), it is critical to evaluate how these agents compare with older medications. This is particularly important in light of the expense of many of the newer therapies. Clinical trials examining the efficacy of these different therapies have largely focused on intermediate clinical outcomes such as changes in levels of hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) or se-

*For editorial comment  
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rum lipids and in blood pressure. Improvements in control of glucose levels per se have been shown to reduce the incidence of microvascular disease,<sup>1</sup> and there is accumulating evidence of potential macrovascular benefits.<sup>2-5</sup> Nonetheless, the specific effects of oral diabetes agents on cardiovascular risks remain unclear.

An important clinical question is whether the different oral medications for type 2 diabetes variously affect hard clinical outcomes, including cardiovascular morbidity and mortality and all-cause mortality. These outcomes have unequivocal clinical relevance. There has been recent controversy regarding possible cardiovas-

cular risk associated with rosiglitazone.<sup>6-9</sup> The debate surrounding rosiglitazone highlights the need for a comprehensive examination of all oral diabetes medications, alone and in combination. The objective of this study was to conduct a systematic review of all published peer-reviewed, randomized clinical trials of oral diabetes agents (second-generation sulfonylureas, biguanides, thiazolidinediones, and meglitinides) to evaluate the risk of fatal and nonfatal cardiovascular disease and all-cause mortality. We hypothesized that the newer medications (thiazolidinediones and meglitinides) would be similar to the older medications (metformin hydrochloride and second-generation sulfonylureas) with respect to cardiovascular risk, given that these medications had similar effects on HbA<sub>1c</sub> levels in a previous systematic review.<sup>10</sup>

## METHODS

### DATA SOURCES AND SEARCHES

We searched MEDLINE (1966 to January 19, 2006), EMBASE (1974 to January 19, 2006), and the Cochrane Central Register of Controlled Trials (1966 to issue 4, 2005) databases for original articles. Details regarding our search strategy have been previously published.<sup>10</sup> We selected studies from the peer-reviewed literature that assessed the benefits or the harms of the US Food and Drug Administration–approved oral diabetes agents available in the United States as of January 1, 2006. Studies must have reported original data in adults with type 2 diabetes. We included studies of combinations of therapies that are commonly used, such as metformin, second-generation sulfonylureas, and thiazolidinediones. We excluded studies that evaluated combinations of any 3 oral diabetes agents and studies of first-generation sulfonylureas because few clinicians prescribe these medications. We also excluded the  $\alpha$ -glucosidase inhibitors because they have been reviewed previously<sup>11</sup> and are not commonly used in clinical practice in the United States. In addition, we excluded studies that did not report all-cause mortality or cardiovascular morbidity or mortality anywhere in the article and studies that were less than 3 months in duration or where the total sample size was less than 40. We focus herein on the peer-reviewed

literature because it provides the strongest levels of evidence.

This study was conducted by the Johns Hopkins Evidence-Based Practice Center as part of a larger project commissioned by the Agency for Healthcare Research and Quality. The full technical report provides a detailed description of the study methods.<sup>12</sup>

### DATA EXTRACTION AND QUALITY ASSESSMENT

Two investigators (E.S. and S.B.) used standardized data abstraction forms to independently abstract all data. Disagreements were resolved by consensus. The scale created by Jadad et al<sup>13</sup> was used to assess study quality. If cardiovascular disease was not a primary end point of the study, we separately rated the quality of the adverse event reporting for cardiovascular outcomes in each trial using a 4-point scale based on the US Food and Drug Administration and the Consolidated Standards of Reporting Trials guidelines for adverse event reporting (available from the authors on request).<sup>14-16</sup> For data abstraction, we relied on definitions of cardiovascular morbidity and mortality as defined in the respective studies (available from the authors on request). We excluded cases of congestive heart failure when possible, but there were instances where studies reported combined end points in which heart failure cases could not be separated. We assumed that events and deaths were reported for all arms if they were reported for one. Events were recorded as not reported for those studies that did not indicate the occurrence (or lack thereof) of events or deaths for that particular outcome. We used outcome definitions that were inclusive (for instance, in one study,<sup>17</sup> chest pain was included with cardiovascular events because no other information was provided).

### DATA SYNTHESIS AND ANALYSIS

We first summarized the trials qualitatively. In the quantitative synthesis, all analyses were conducted following the principle of intention to treat. Trials with no cardiovascular events in any treatment arm were excluded from the quantitative analysis. We conducted meta-analyses of comparisons for which there were at least 4 relatively homogeneous trials. We combined the comparator arms to create an any-other comparator group (drug or placebo). The comparisons of interest were metformin vs any comparator (oral agent or placebo/diet), metformin vs any sulfonylurea combined with metformin, any sulfonylurea vs any com-

parator, any sulfonylurea vs any sulfonylurea combined with metformin, rosiglitazone vs any comparator, rosiglitazone plus metformin vs metformin alone, pioglitazone hydrochloride vs any comparator, and either of the meglitinides vs any comparator.

For trials with more than 1 dosing arm, we combined the dosing arms as long as the doses were consistent with current clinical practice. For trials with more than 1 comparison group, we combined groups when appropriate. Odds ratios (ORs) were calculated and pooled using a Mantel-Haenszel fixed-effects model (with a 0.5 continuity correction)<sup>18,19</sup> and the Peto method.<sup>20</sup> Statistical heterogeneity was assessed with the I<sup>2</sup> statistic.<sup>21</sup> Sensitivity analyses were conducted to examine the effect of inclusion/exclusion of influential studies (eg, the United Kingdom Prospective Diabetes Study [UKPDS] and the Prospective Pioglitazone Clinical Trial in Macrovascular Events [PROactive]) and different dosing and control group arms. All analyses were conducted using Stata/SE statistical software, version 10.0 (StataCorp, College Station, Texas).

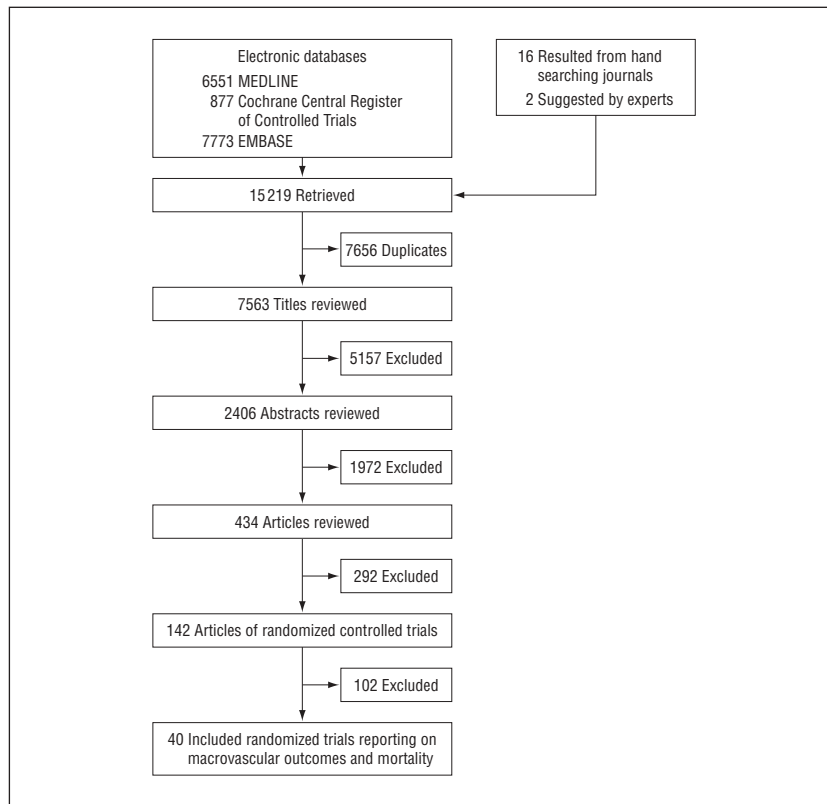
## RESULTS

### SEARCH RESULTS

**Figure 1** details the search and selection process; more details are found in the full technical report.<sup>12</sup> Briefly, of the 7563 unique citations retrieved, 434 were determined to be relevant to our study questions and were identified for full-text article review. One hundred forty-two of these publications were of randomized controlled trials and only 40 reported data on cardiovascular events and/or mortality. The main findings from the UKPDS were reported in 2 separate publications.<sup>1,22</sup> For the purposes of our study, the UKPDS 33 and 34 are considered separate trials and the UKPDS 34 is further divided into 2 separate comparisons so that the sulfonylurea, metformin, and early addition of metformin to the sulfonylurea arms are analyzed separately as in the originally published reports. Forty articles made up our final study population.

### QUALITATIVE SUMMARY

Characteristics of the 40 included clinical trials are summarized in **Table 1**. Most of the trials were con-



**Figure 1.** Summary of the literature search. Numbers indicate the number of articles.

ducted in the United States or the United Kingdom. The mean age of the participants ranged from 52 to 69 years; mean HbA<sub>1c</sub> level at baseline ranged from 6.2% in the UKPDS<sup>1</sup> to 10.2% in 2 small, short-term studies.<sup>23,38</sup> Twenty-seven of the trials (68%) were less than 1 year in duration. Twenty-eight studies (more than half) reported receiving support from the pharmaceutical industry (information available from the authors on request).

In most studies, cardiovascular outcomes were recorded as adverse events and were not a primary or secondary outcome of the trial, with the exception of the PROactive Study<sup>31</sup> and UKPDS.<sup>1,22</sup> With approximately 4000 participants and a mean of 10.7 years of follow-up, the UKPDS is the longest trial of oral diabetes medications in the published literature. The UKPDS 33 compared the effects of intensive glucose control with sulfonylurea or insulin therapy and conventional treatment on the risk for microvascular and macrovascular complications.<sup>1</sup> A median difference in HbA<sub>1c</sub> level of 0.9% was achieved between the 2 arms, and intensive control

with a sulfonylurea or insulin was shown to substantially decrease the risk of microvascular outcomes compared with conventional treatment. The results for macrovascular outcomes were more equivocal, with no significant differences observed for stroke or a combined end point of amputation or death due to peripheral vascular disease but a borderline significant 16% reduction in myocardial infarctions ( $P = .052$ ). When the intensive therapy group was further subdivided into glyburide (glibenclamide) vs conventional treatment, the observed effect was similar; specifically, a borderline 22% reduction in myocardial infarctions was seen with glyburide therapy compared with conventional treatment ( $P = .06$ ).

In the UKPDS 34, metformin, chlorpropamide, glyburide, and insulin were compared in one analysis, and a second supplementary analysis compared the sulfonylurea arm with the early addition of metformin to sulfonylurea therapy.<sup>22</sup> The main findings of the UKPDS 34 suggested no difference in cardiovascular outcomes when the different therapies were compared indirectly.

Only metformin therapy compared with conventional treatment in overweight individuals showed a significant 36% and 39% reduction in all-cause mortality and myocardial infarction, respectively. In addition, the early addition of metformin to sulfonylurea therapy unexpectedly showed a 60% significantly increased risk of all-cause mortality compared with the sulfonylurea arm, where metformin or insulin was added only if the participant was markedly hyperglycemic. The UKPDS was conducted before the emergence of thiazolidinediones.

The PROactive Study of more than 5000 participants followed up for an average of just less than 3 years (34.5 months) was designed to investigate whether treatment with the thiazolidinedione pioglitazone would be associated with a reduced risk of cardiovascular end points compared with treatment with placebo (taken in addition to existing diabetes medications).<sup>31</sup> The PROactive Study showed a nonsignificant reduction in the primary composite end point (10% reduction in relative risk [RR];  $P = .10$ ) and a significant reduction in the main secondary end point of all-cause mortality, nonfatal myocardial infarction, and stroke (16% reduction in RR;  $P = .03$ ). The median decrease in HbA<sub>1c</sub> level in the pioglitazone arm was 0.8% compared with 0.3% in the control arm.

Most of the trials included in the present study were not designed (or powered) to examine cardiovascular events. A history of cardiovascular disease was an exclusion criterion for most studies, but 4 studies specifically examined the effects of oral agents in populations with a history of cardiovascular disease.<sup>28,46,47,54</sup> Choi et al,<sup>28</sup> Nishio et al,<sup>46</sup> and Takagi et al<sup>54</sup> each assessed restenosis rates in small, 6-month trials of oral diabetes therapy in persons with type 2 diabetes. Because it is unclear whether those 3 studies are generalizable to the population of all persons with type 2 diabetes, they were excluded from our quantitative analysis. A study by Rachmani et al<sup>47</sup> was unusual in that it aimed to examine the safety of metformin in patients with contraindications. Because that study was not typical in

**Table 1. Characteristics of Included Randomized Clinical Trials of Oral Diabetes Medications**

Source	Duration of Follow-up, mo	Intervention Arms	Dosage (esc), mg	Baseline Characteristics				Outcome, No. of Cases		
				Sample Size, No.	Mean Age, y	Male, %	Mean HbA <sub>1c</sub> Level, %	CVD Morbidity	CVD Mortality	All-Cause Mortality
Aronoff et al, <sup>23</sup> 2000	6.5	Pioglitazone hydrochloride	Range, 7.5-45	329	54 <sup>a</sup>	58 <sup>a</sup>	10.2	12	NR	NR
Bailey et al, <sup>24</sup> 2005	6	Placebo	NA	79	54 <sup>a</sup>	58 <sup>a</sup>	10.4	5	NR	NR
		Metformin hydrochloride	2500 (esc 3000)	280	58	57	7.5	NR	0	0
Baksi et al, <sup>25</sup> 2004	6.5	Rosiglitazone + metformin	4 (esc 8) 2000 (fixed)	288	58	58	7.4	NR	1	1
		Glyburide (gliclazide)	160 (esc to 320)	241	62	63	8.6	NR	0	0
Barnett et al, <sup>26</sup> 2003	6.5	Glyburide + rosiglitazone	4 (fixed) + 160	225	61	57	8.5	NR	1	1
		Rosiglitazone + existing unspecified SU	4 BID (fixed) NR (NR)	84	54	80	9.2	5	NR	NR
Carlson et al, <sup>27</sup> 1993	3	Placebo + existing unspecified SU	NR (NR)	87	54	75	9.1	0	NR	NR
		Glyburide (reformulated)	3 (fixed)	104	59	59	7.6	Unclear	1	1
Choi et al, <sup>28</sup> 2004	6	Glyburide (original)	5 (fixed)	102	60	61	7.6	Unclear	0	0
		Rosiglitazone + existing medications	8 (decreased to 4)	38	61	63	7.8	4 Revasc; 9 restenosis	0	0
Cryer et al, <sup>29</sup> 2005 (COSMIC trial)	12	Uptitration of existing diabetes medications	NR (esc)	45	60	76	7.7	9 Revasc; 21 restenosis	0	0
		Metformin <sup>b</sup>	500 (esc 2500)	7227	58	49	NR	237	506	80
DeFronzo and Goodman; Multicenter Metformin Study Group, <sup>30</sup> 1995 (protocol 2)	7.25	Usual care <sup>b</sup>	NA	1505	59	50	NR	49	136	20
		Metformin	500 (esc 2500)	210	55	46	8.9	NR	1	1
		Glyburide	10 (esc 20)	209	56	49	8.5	NR	0	0
Dormandy et al; PROactive investigators, <sup>31</sup> 2005	48	Metformin + glyburide	500 (esc 2500) + 10 (esc 20)	213	55	46	8.8	NR	0	0
		Thiazolidinedione (pioglitazone) <sup>b</sup>	15 (esc 45)	2605	62	67	7.8 (median)	514 <sup>c</sup>	127	177
Draeger et al, <sup>32</sup> 1996	12	Placebo <sup>b</sup>	NR	2633	62	66	7.9 (median)	572 <sup>c</sup>	136	186
		Glimepiride	1 (esc 8)	524	60	62	8.1	NR	5	11
Fonseca et al, <sup>33</sup> 2000	6.5	Glyburide (glibenclamide)	2.5 (esc 20)	520	61	65	8.1	NR	3	5
		Metformin + placebo	2500 (fixed)	113	59	74	8.6	NR	0	0
		Metformin + rosiglitazone	2500 (fixed) + 4 (fixed)	116	58	62	8.9	NR	1	1
Fujioka et al, <sup>34</sup> 2003	6	Metformin + rosiglitazone	2500 (fixed) + 8 (fixed)	110	58	68	8.9	NR	0	0
		Metformin IR	1000 (500 BID) (fixed)	71	54	44	7.1	0	0	0
		Metformin ER	1000 (QD) (fixed)	75	54	45	7.0	Unclear (0-4?)	0	0
Garber et al, <sup>35</sup> 2003	4	Metformin ER	1500 (QD) (fixed)	71	55	39	7.0	Unclear (0-4?)	0	1
		Metformin	500 (esc 2000)	164	55	43	8.5	NR	NR	0
		Glyburide	2.5 (esc 10)	151	55	44	8.7	NR	NR	0
Goldberg et al, <sup>36</sup> 1998	4.5	Glyburide + metformin	1.25 + 250 (esc 5 + 1000)	171	56	44	8.8	NR	NR	2
		Placebo	NA	33	56	76	8.1	0	0	0
Goldstein et al, <sup>37</sup> 2003	4.5	Repaglinide	0.25 (esc to 8.0)	67	59	74	8.3	1	0	0
		Glipizide	30	84	57	64	8.9	NR	0	0
Gómez-Perez et al, <sup>38</sup> 2002	6.5	Metformin	500 (esc 2000)	76	57	62	8.7	NR	0	0
		Glipizide + metformin	5 (esc 20) + 500 (esc 2000)	87	55	59	8.7	NR	0	0
		Metformin + placebo	2500 (fixed)	34	53	29	9.8 <sup>d</sup>	1	0	NR
		Rosiglitazone + metformin	2 BID (fixed) + 2500 (fixed)	35	52	29	10.2 <sup>d</sup>	1	0	NR
		Rosiglitazone + metformin	4 BID (fixed) + 2500 (fixed)	36	54	19	9.7 <sup>d</sup>	2	0	NR

(continued)

**Table 1. Characteristics of Included Randomized Clinical Trials of Oral Diabetes Medications (cont)**

Source	Duration of Follow-up, mo	Intervention Arms	Dosage (esc), mg	Baseline Characteristics				Outcome, No. of Cases		
				Sample Size, No.	Mean Age, y	Male, %	Mean HbA <sub>1c</sub> Level, %	CVD Morbidity	CVD Mortality	All-Cause Mortality
Hanefeld et al, <sup>39</sup> 2004	12	Pioglitazone <sup>b</sup>	15 (esc 45)	319	60	54	8.8	10	NR	1
		Metformin <sup>b</sup>	850 (esc 2550)	320	60	55	8.8	13	NR	2
Hanefeld et al, <sup>40</sup> 2000	3	Placebo	NA	60	57	60	8.5	NR	0	0
		Nateglinide	30	51	58	71	8.4	NR	1	1
		Nateglinide	60	58	56	71	8.3	NR	0	0
		Nateglinide	120	63	54	70	8.3	NR	0	0
		Nateglinide	180	57	57	63	8.5	NR	0	0
Hermann et al, <sup>41</sup> 1994	6	Metformin + diet <sup>e</sup>	1000 (esc 3000)	38	60 <sup>a</sup>	63 <sup>a</sup>	7.3	2	NR	NR
		Glyburide + diet <sup>e</sup>	3.5 (esc 10.5)	34	60 <sup>a</sup>	63 <sup>a</sup>	7.1	3	NR	NR
		Metformin + glyburide	500 (esc 1500) 1.75 (esc 5.25)	72	60 <sup>a</sup>	63 <sup>a</sup>	7.2	10	NR	NR
Horton et al, <sup>42</sup> 2000	6	Nateglinide	360 (fixed)	179	59	62	8.3	NR	0	0
		Metformin	1500 (fixed)	178	57	68	8.4	NR	1	1
		Placebo	NA	172	60	61	8.3	NR	0	0
Jovanovic et al, <sup>17</sup> 2000	6	Repaglinide	1 TID (fixed)	140	58	69	8.9	1 MI; 4 chest pain	NR	NR
		Repaglinide	4 TID (fixed)	146	58	60	8.7	1 MI; 4 chest pain	NR	NR
		Placebo	NA	75	59	65	8.6	0 MI; 1 chest pain	NR	NR
Kipnes et al, <sup>43</sup> 2001	4	Pioglitazone + existing unspecified SU	15 (fixed) + NR	184	57	59	10.0	22 for both pioglitazone groups combined	NR	NR
		Pioglitazone + existing unspecified SU	30 (fixed) + NR	189	57	60	9.9		NR	NR
		Placebo + existing unspecified SU	NR (fixed)	187	57	58	9.9	10	NR	NR
Lawrence et al, <sup>44</sup> 2004	6	Pioglitazone	30 (esc 45)	21 <sup>f</sup>	60	70	7.4	0	0	0
		Metformin	500 (esc 1500)	21 <sup>f</sup>	60	60	8.0	0	1	1
		Gliclazide	80 (esc 160) BID	22 <sup>f</sup>	64	65	7.9	1	0	0
Marbury et al, <sup>45</sup> 1999	12	Repaglinide	0.5 (esc 12)	362	58	67	8.7	19	2	3
		Glyburide	2.5 (esc 15)	182	59	66	8.9	4	1	1
Nishio et al, <sup>46</sup> 2006	6	Control	NA	28	68	71	6.9	17 (primary end point); 1 MI	0	0
		Pioglitazone	30 (fixed)	26	66	73	7.7	2 (primary end point); 0 MI	0	0
Rachmani et al, <sup>47</sup> 2002	48	Stopped metformin therapy <sup>b</sup>	NR	198	64	52	8.6	53	52	64
		Continued metformin therapy <sup>b</sup>	NR	195	65	53	8.6	51	50	62
Rosenstock et al, <sup>48</sup> 1996	3.5	Placebo	NA	79	61	67	8.0	NR	0	0
		Glimepiride	8 (QD)	88	62	74	8.1	NR	0	0
		Glimepiride	4 (BID)	81	59	70	8.1	NR	1	1
		Glimepiride	16 (QD)	83	60	66	8	NR	0	0
		Glimepiride	8 (BID)	85	62	72	8.3	NR	0	0
Rosenstock et al, <sup>49</sup> 2006	24	Placebo + uptitration of glipizide <sup>g</sup>	10 (esc to 20)	111	69	72	7.7	NR	2	2
		Glipizide + rosiglitazone <sup>g</sup>	4 + 10 (esc to 20)	116	68	74	7.7	NR	0	0
Schernthaner et al, <sup>50</sup> 2004	12	Pioglitazone + placebo + diet	30 (esc 45)	597	57	53	8.7	12	NR	3
		Metformin + placebo + diet	850 (esc 2550)	597	56	58	8.7	13	NR	2
Simonson et al, <sup>51</sup> 1997	4	Placebo	NA	69	60	77	8.3	NR	NR	0
		Glipizide (all dosing arms combined)	5-60 (fixed)	278	58	65	8.6	NR	NR	1
Sonnenberg et al, <sup>52</sup> 1997	3.75	Glimepiride	3 (fixed)	48	NR	NR	NR	Unclear	0	0
		Glimepiride	6 (fixed)	46	NR	NR	NR	Unclear	0	0
St John Sutton et al, <sup>53</sup> 2002	12	Rosiglitazone	4 BID (fixed)	104	55	72	9.1	16	NR	NR
		SU (glyburide)	NR (esc 20)	99	56	72	9.5	12	NR	NR

(continued)

**Table 1. Characteristics of Included Randomized Clinical Trials of Oral Diabetes Medications (cont)**

Source	Duration of Follow-up, mo	Intervention Arms	Dosage (esc), mg	Baseline Characteristics				Outcome, No. of Cases		
				Sample Size, No.	Mean Age, y	Male, %	Mean HbA <sub>1c</sub> Level, %	CVD Morbidity	CVD Mortality	All-Cause Mortality
Takagi et al, <sup>54</sup> 2003	6	Pioglitazone + existing medications	30 (fixed)	23	64	87	6.8	5	NR	NR
		Control	NR (esc to target)	21	65	67	6.7	11	NR	NR
UKPDS Group, <sup>1</sup> 1998 (UKPDS 33) <sup>h</sup>	133	Glyburide (glibenclamide) + diet	2.5 (esc 20)	615	54	62	6.3	90 MI; 45 stroke	73 <sup>i</sup>	121
		Diet	NR	896	54	62	6.2	162 MI; 47 stroke	113 <sup>i</sup>	190
UKPDS Group, <sup>22</sup> 1998 (UKPDS 34) <sup>h</sup>	128	Metformin + diet	850 (esc 2550)	342	53	46	7.3	39 MI; 12 stroke	28 <sup>i</sup>	50
		Diet	NA	411	53	47	7.1	73 MI; 23 stroke	55 <sup>i</sup>	89
UKPDS Group, <sup>22</sup> 1998 (UKPDS 34) <sup>h</sup>	128	Unspecified SU + diet	NA	269	58	61	7.6	31 MI; 13 stroke	14	31
		Unspecified SU + metformin + diet	NA + 850 (esc 2550)	268	59	59	7.5	33 MI; 15 stroke	26 <sup>i</sup>	47
Virtanen et al, <sup>55</sup> 2003 <sup>l</sup>	6.5	Rosiglitazone + diet	2 BID (esc 4 BID)	15	58	71	6.8	0	NR	NR
Hällsten et al, <sup>56</sup> 2002 <sup>l</sup>		Metformin + diet	500 BID (esc 1000 BID)	15	58	61	6.9	1	NR	NR
Weissman et al, <sup>57</sup> 2005	6	Placebo	NA	14	58	71	6.3	0	NR	NR
		Existing metformin therapy + rosiglitazone	1000 + 4 (esc 8)	382	56	NR	8.1	7	0	1
Wolffenbuttel and Landgraf; Dutch and German Repaglinide Study Group, <sup>58</sup> 1999	12	Uptitration of existing metformin therapy	1000 (esc 2000)	384	56	NR	8.0	4	0	0
		Repaglinide	1.5 (esc 12)	286	61	62	7.1	NR	NR	NR <sup>k</sup>
Zhu et al, <sup>59</sup> 2003	6	Placebo (+ existing SU)	NA	112	59	46	9.8	0	0	0
		Rosiglitazone (+ existing SU)	2 BID (fixed)	221	59	41	9.8	0	0	0
		Rosiglitazone (+ existing SU)	4 BID (fixed)	221	59	48	9.9	0	1	1

Abbreviations: BID, twice daily; CVD, cardiovascular disease; ER, extended release; esc, escalated to; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; IR, immediate release; MI, myocardial infarction; NA, not available; NR, not reported; QD, every day; revasc, revascularization; SU, sulfonylurea; TID, 3 times daily.

SI units: To convert HbA<sub>1c</sub> to a proportion of total hemoglobin, multiply by 0.01.

<sup>a</sup>Not reported separately for the study arms; overall estimates are recorded herein.

<sup>b</sup>Medication was added to existing therapy.

<sup>c</sup>The composite primary end point of the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROActive) trial included death, nonfatal MI, silent MI, stroke, major leg amputation, acute coronary syndrome; coronary revascularization, and leg revascularization.

<sup>d</sup>Baseline HbA<sub>1c</sub> levels were derived from the figure.

<sup>e</sup>Metformin or glyburide therapy was added if the glycemic target was not reached.

<sup>f</sup>Baseline sample size is unclear because 3 subjects withdrew at 6 weeks owing to hyperglycemia, but the respective treatment arms were not identified.

<sup>g</sup>Both groups were receiving glipizide (10 mg BID) before enrollment.

<sup>h</sup>The UKPDS 33 and 34 are considered separate trials and the UKPDS 34 is further divided into 2 separate comparisons.

<sup>i</sup>Includes any diabetes-related death (death due to MI, stroke, peripheral vascular disease, renal disease, hyperglycemia, hypoglycemia, or sudden death).

<sup>l</sup>Virtanen et al<sup>55</sup> and Hällsten et al<sup>56</sup> report the same trial.

<sup>k</sup>The authors state that "cardiac events were reported at similar frequencies in both treatment groups."

its design and included participants with contraindications, it was excluded from our analysis.

The bulk of other studies identified by our search were more typical randomized clinical trials comparing the efficacy or effectiveness of various oral medications on intermediate clinical measures (eg, change in levels of

HbA<sub>1c</sub> or lipids or in blood pressure) and also reported collecting data on adverse events, including cardiovascular events. A meta-analysis of the effects of oral diabetes drugs on intermediate measures has been previously published by our research group.<sup>10</sup> Our search identified 2 dose-response studies,<sup>34,52</sup> one study comparing 2 differ-

ent formulations of glyburide,<sup>27</sup> and the other study comparing 2 different sulfonylurea therapies.<sup>32</sup> These 4 trials were included in Table 1 but were excluded from our quantitative analyses because they did not contribute to our comparisons of interest.

Across all trials, the average Jadad quality score was 3 (maximum

**Table 2. Pooled ORs for Comparisons of Interest**

End Point	No. of Studies	Total No. of Participants	Pooled ORs (95% CI)	P Value for Heterogeneity
<b>Cardiovascular morbidity</b>				
Metformin hydrochloride vs any comparator	7	11 986	0.85 (0.69-1.05)	.22
Metformin vs any sulfonylurea + metformin	2	831	<sup>a</sup>	<sup>a</sup>
Any sulfonylurea vs any comparator	5	2795	0.89 (0.71-1.11)	.40
Any sulfonylurea vs any sulfonylurea + metformin	1	577	<sup>a</sup>	<sup>a</sup>
Rosiglitazone vs any comparator	5	1338	1.68 (0.92-3.06)	.64
Rosiglitazone + metformin vs metformin alone	2	886	<sup>a</sup>	<sup>a</sup>
Pioglitazone hydrochloride vs any comparator	6	9287	0.88 (0.78-1.00)	.88
Meglitinide (neteglide or repaglinide) vs any comparator	3	1049	<sup>a</sup>	<sup>a</sup>
<b>Cardiovascular mortality</b>				
Metformin vs any comparator	6	11 385	0.74 (0.62-0.89)	.27
Metformin vs any sulfonylurea + metformin	2	1251	<sup>a</sup>	<sup>a</sup>
Any sulfonylurea vs any comparator	5	3466	0.92 (0.68-1.26)	.97
Any sulfonylurea vs any sulfonylurea + metformin	2	748	<sup>a</sup>	<sup>a</sup>
Rosiglitazone vs any comparator	5	3202	1.03 (0.30-3.53)	.70
Rosiglitazone + metformin vs metformin alone	3	909	<sup>a</sup>	<sup>a</sup>
Pioglitazone vs any comparator	2	5566	<sup>a</sup>	<sup>a</sup>
Meglitinide (neteglide or repaglinide) vs any comparator	2	1256	<sup>a</sup>	<sup>a</sup>
<b>All-cause mortality</b>				
Metformin vs any comparator	9	13 046	0.81 (0.60-1.08)	.58
Metformin vs any sulfonylurea + metformin	3	1631	<sup>a</sup>	<sup>a</sup>
Any sulfonylurea vs any comparator	6	4255	0.90 (0.70-1.15)	.99
Any sulfonylurea vs any sulfonylurea + metformin	2	939	<sup>a</sup>	<sup>a</sup>
Rosiglitazone vs any comparator	6	2927	1.21 (0.39-3.77)	.78
Rosiglitazone + metformin vs metformin alone	4	1676	2.52 (0.51-12.52)	.99
Pioglitazone vs any comparator	4	7507	0.96 (0.78-1.18)	.90
Meglitinide (neteglide or repaglinide) vs any comparator	2	1257	<sup>a</sup>	<sup>a</sup>

Abbreviations: CI, confidence interval; OR, odds ratio.

<sup>a</sup>Data were pooled only for those comparisons with 4 or more trials.

possible score, 5). More detailed information regarding the quality of these trials is presented in the complete report.<sup>12</sup> Of the relevant 142 randomized trials initially identified in our search, only 40 indicated collection of data on serious adverse events, including mortality or cardiovascular events. Of the 40 trials reviewed herein, 8 included cardiovascular events in the primary or secondary end point. The quality of serious adverse event reporting among the 32 trials where cardiovascular events were not included in the primary or secondary outcome was fair, with an average

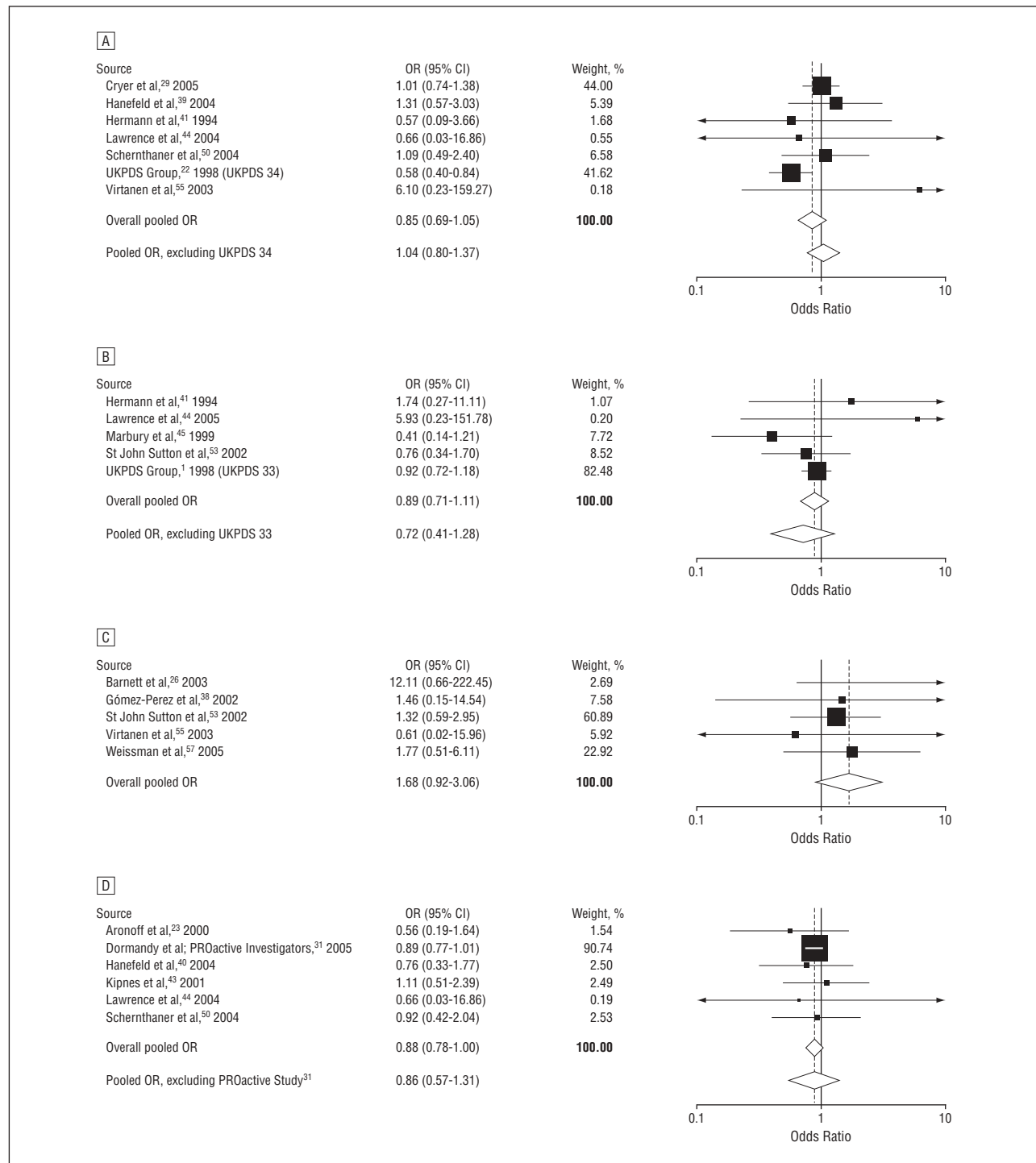
quality score of 3 (maximum possible score, 4). Only 12 trials scored a perfect 4, indicating that all serious adverse events, withdrawals, and dropouts were reported and that clear definitions of serious adverse events were provided in the manuscript. Serious adverse events, such as fatal and nonfatal cardiovascular events, may be underreported in this literature; however, we were unable to directly evaluate this phenomenon.

#### QUANTITATIVE SUMMARY

Pooled results for all comparisons of interest are presented in **Table 2**.

Pooled analyses using the Peto and Mantel-Haenszel methods did not differ appreciably, and thus only the Mantel-Haenszel results are presented herein. There were insufficient numbers of trials (<4 studies) for many of the comparisons, and we were thus unable to pool these data (Table 2). **Figure 2** presents graphical displays (Forrest plots) of the pooled and individual ORs for cardiovascular morbidity for the following comparisons: metformin vs any comparator, any sulfonylurea vs any comparator, rosiglitazone vs any comparator, and pioglitazone vs any comparator. Our comparisons for metformin vs any comparator (other oral agent or placebo/diet) were the most robust, with 7 trials that included 11 986 total participants who contributed to the pooled estimate for cardiovascular morbidity (OR, 0.85; 95% confidence interval [CI], 0.69-1.05), 6 trials that included 11 385 individuals who contributed to the pooled estimate for cardiovascular mortality (0.74; 0.62-0.89), and 9 trials that included 13 046 individuals contributing to the pooled estimate for all-cause mortality (0.81; 0.60-1.08). No other significant associations were observed for any oral agent with cardiovascular morbidity, mortality, or all-cause mortality. In the analysis of the sulfonylureas, the UKPDS was highly influential (accounting for >500 participants and most of the events). When the UKPDS was excluded from these comparisons, the results remained nonsignificant, but the CIs were substantially wider, reflecting the imprecision of the remaining studies (Figure 2). Similarly, the PROactive trial was highly influential in our analyses of pioglitazone and, when this trial was excluded, the results remained nonsignificant but far less precise (Figure 2).

Rosiglitazone was the only oral agent that was associated with an increased risk of cardiovascular morbidity and mortality and all-cause mortality (all ORs, >1.0); however, none of these estimates was statistically significant, possibly owing to the small sample sizes and limited number of included studies. Many small studies reported only 1 or 2 cardiovascular events or



**Figure 2.** Forrest plots of odds ratios (ORs) of cardiovascular morbidity for major comparisons of interest. A, Metformin hydrochloride vs placebo or other oral agent. B, Any sulfonylurea vs placebo or other oral agent. C, Rosiglitazone vs placebo or other oral agent. D, Pioglitazone hydrochloride vs placebo or oral agent. The ORs (boxes) and 95% confidence intervals (CIs) (horizontal bars) are estimated from each study. The size of the box is proportional to the weight of the study in the pooled analysis. The pooled Mantel-Haenszel ORs are represented by the diamonds; the width of the diamond represents the pooled 95% CI. The vertical line at 1.0 indicates no effect. Because of rounding, the weight percentages may not total 100.

deaths in any arm; these studies provided imprecise estimates of cardiovascular risk and did not contribute substantially to our comparisons. For those comparisons with larger populations and longer studies (and corresponding higher numbers of

events), the pooled estimates were most reliable, such as those for metformin. No significant quantitative heterogeneity was observed, although our formal tests for statistical heterogeneity were likely underpowered.

#### COMMENT

Few rigorous systematic reviews of hard clinical outcomes have compared oral diabetes agents. Recent meta-analyses have focused on pos-

sible cardiovascular effects of single drugs, particularly the newer thiazolidinediones, rosiglitazone and pioglitazone.<sup>6,7,60,61</sup> We included the most common oral diabetes medications currently in use in the United States to provide a comprehensive picture of possible cardiovascular risk. When compared with any other treatment or placebo, we found that metformin was associated with a statistically significant decrease in cardiovascular mortality (OR, 0.74; 95% CI, 0.62-0.89). The point estimates for metformin with cardiovascular morbidity and all-cause mortality were similar but not statistically significant. When compared with any other diabetes agent or placebo, rosiglitazone was the only therapy that was associated with a possible increase in the risk of cardiovascular morbidity or mortality, but these results were not statistically significant. No other differences in cardiovascular risk between other commonly used oral diabetes medications were evident in this literature. Nonetheless, the poor quality and inconsistent reporting of adverse events and the profound lack of long-term studies make it difficult to draw firm conclusions.

The UKPDS was designed principally to examine the effect of absolute reductions in glucose levels on long-term outcomes. In the UKPDS, the lack of a difference in cardiovascular risk reduction when indirect comparisons were made across treatments and the significant reduction observed when intensive control was compared with the conventional treatment group suggest that it is glycemic control per se that may be partially driving cardiovascular risk reduction. This is consistent with several other large epidemiologic studies.<sup>2-4</sup> Furthermore, in the PROactive Study, the pioglitazone group had a 0.8 absolute percentage point decrease in the HbA<sub>1c</sub> level compared with a 0.3 absolute percentage point decrease in the control arm; this trial showed a corresponding moderate reduction in the secondary end points (all-cause mortality, nonfatal myocardial infarction, and stroke) in the pioglitazone-treated group compared with the control group.

Questions have recently been raised regarding the possible cardio-

toxic effects of rosiglitazone, a newer thiazolidinedione. The Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication (DREAM) study,<sup>62</sup> a large study in individuals with prediabetes published in 2006, showed that rosiglitazone was associated with a reduced risk of the composite outcome of incident diabetes (based on glucose levels) and death. The interpretation of this trial has been controversial because of a borderline statistically significant increase in cardiovascular events (RR, 1.37; *P* = .08) and a statistically significant increase in congestive heart failure cases in the treatment arm (RR, 7.03; *P* = .01).<sup>63</sup> A second study in persons with type 2 diabetes, A Diabetes Outcome Prevention Trial (ADOPT),<sup>64</sup> was published after the completion of our literature search and was not included in our analyses. The ADOPT results showed a nonsignificant increase in fatal and nonfatal myocardial infarction in the rosiglitazone group compared with the metformin group or the glyburide group. A recent meta-analysis by Nissen and Wolski<sup>6</sup> suggested a statistically significant excess of cardiovascular morbidity due to treatment with rosiglitazone in a pooled analysis that included a diverse population of published and unpublished studies of individuals with and without type 2 diabetes (including the ADOPT and the DREAM study). An interim analysis of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial showed no statistically significant elevation in cardiovascular risk (besides congestive heart failure) related to rosiglitazone treatment compared with metformin and the sulfonylureas.<sup>65</sup> Some data relevant to the question of cardiovascular risk among persons taking oral diabetes medications exist outside the peer-reviewed literature and have been included in previous reviews, including that by Nissen and Wolski.<sup>6</sup> A sensitivity analysis in which data from the ADOPT, the RECORD trial, and eligible unpublished trials analyzed by Nissen and Wolski<sup>6</sup> were pooled with our included studies resulted in pooled ORs of 1.28 (95% CI, 0.95-1.76) for cardiovascular morbidity and 1.24 (0.87-1.79) for

cardiovascular mortality when rosiglitazone was examined against any other comparator. Our main results, based exclusively on published data in persons with type 2 diabetes, are not inconsistent with an increase in cardiovascular risk with rosiglitazone treatment, but we had an insufficient number of studies to draw firm conclusions. The interpretation of the data on rosiglitazone remains controversial.

The limitations of this meta-analysis largely reflect the limitations of the published literature on oral diabetes medications. A major weakness is that few trials have examined the comparative effectiveness of oral diabetes medications on cardiovascular outcomes. Indeed, only 2 studies included in our quantitative analyses had participant follow-up for longer than 2 years. Despite combining multiple comparator groups, the total number of events in each of our comparisons of interest was small, and we included only studies that had at least 1 cardiovascular event in 1 arm. Studies that did not report collecting information on cardiovascular events were excluded from the review. Furthermore, although we attempted to exclude cases of congestive heart failure from all analyses, we relied on the definitions in the individual studies, and there were instances in which the reporting of cardiovascular events was ambiguous.

The current evidence based on comparison of specific oral diabetes medications for the risk of cardiovascular morbidity and mortality is inconclusive. Our study demonstrates that there have been few trials of oral diabetes therapies that have lasted longer than 6 months and that reporting of adverse events for cardiovascular disease is poor. Because most medications have similar short-term efficacy,<sup>10</sup> the selection of appropriate oral therapy is largely based on patient and provider preferences, a medication's profile of adverse effects, and cost. There is a critical need for studies of oral diabetes medications with long-term outcomes. The relatively modest differences in blood pressure, cholesterol levels, and weight observed after treatment with oral diabetes medications in short-term trials may not translate to

changes in long-term cardiovascular risk. Only long-term trials can provide definitive conclusions regarding the comparative efficacy of oral diabetes medications and long-term risks. Because individuals with diabetes are at a dramatically elevated risk of cardiovascular disease, trials of even 1 to 2 years' duration with rigorous and standardized reporting of adverse events can provide important information, especially when the results of separate studies can be pooled. One clear conclusion from the literature is that all clinical trials comparing oral diabetes medications, regardless of duration, should endeavor to collect and report adverse events rigorously, including cardiovascular and all-cause mortality. Clear protocols for reporting adverse events and determining reasons for withdrawal of study participants should also be included. The development of the Consolidated Standards of Reporting Trials statement<sup>14,66,67</sup>—which requires reporting of “all important adverse events or side effects in each intervention group”—should help ameliorate this problem, but such standards need to be rigorously and consistently applied.

In conclusion, our meta-analysis suggested that, compared with other oral diabetes agents and placebo, metformin appeared moderately protective against cardiovascular effects and that rosiglitazone was possibly harmful, but a lack of power prohibited firmer conclusions. Larger, long-term studies taken to hard end points and better reporting of cardiovascular events in short-term studies will be required to draw firm conclusions about major clinical benefits and risks related to oral diabetes agents.

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