Diabetes and Metabolism

Results of a reevaluation of cardiovascular outcomes in the RECORD trial

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Background The US Food and Drug Administration (FDA) required a reevaluation of cardiovascular (CV) outcomes in the RECORD trial. This provided an opportunity to assess the implications of event adjudication by 2 groups and quantify the differences as well as to use new FDA end point definitions in development.

Methods Original data were used to systematically identify all potential deaths, myocardial infarctions (MIs), and strokes. Site investigators were approached for additional source documents and information about participants lost to follow-up. Suspected events were adjudicated using standard procedures, and the results were compared with the original trial outcomes.

Results Follow-up for mortality was 25,833 person-years, including an additional 328 person-years identified during the reevaluation effort. A total of 184 CV or unknown-cause deaths (88 rosiglitazone, 96 metformin/sulfonylurea), 128 participants with an MI (68 rosiglitazone, 60 metformin/sulfonylurea), and 113 participants with a stroke (50 rosiglitazone, 63 metformin/sulfonylurea) were included. The hazard ratio (HR) for rosiglitazone versus metformin/sulfonylurea for the end point of CV (or unknown cause) death, MI, or stroke was 0.95 (95% CI 0.78-1.17) compared with 0.93 (95% CI 0.74-1.15) for the original RECORD results. Treatment comparisons for MI (HR 1.13, 95% CI 0.80-1.59) and mortality (HR 0.86, 95% CI 0.68-1.08) were also the same compared with the original RECORD results. Sensitivity analyses were also consistent with the original RECORD results. Analyses using the FDA definitions showed similar results.

Conclusions Only a modest number of additional person-years of follow-up were ascertained from this reevaluation of CV end points in RECORD. Observed HRs and CIs from these analyses using the original RECORD or new FDA end point definitions showed similar treatment effects of rosiglitazone compared with the original RECORD results. (Am Heart J 2013;166:240-249.e1.)

The cardiovascular (CV) safety of rosiglitazone therapy has been debated for the past 5 years following the publication of a systematic overview of nonadjudicated data from diverse short-term studies suggesting that rosiglitazone was associated with increased risk of myocardial infarction (MI).[1] Results from the RECORD trial (ClinicalTrials.gov, NCT00379769)[2,3] suggested treatment with rosiglitazone to be noninferior to metformin or a sulfonylurea for the primary composite end point of CV death or CV hospitalization; however, an increased risk of MI with rosiglitazone could not be ruled out.

Review by a US Food and Drug Administration (FDA) Advisory Committee[4] noted concerns with RECORD, including a low event rate potentially related to inadequate ascertainment and processing of events in an open-label trial. The FDA required that the trial sponsor, GlaxoSmithKline, commission a reevaluation of all deaths and specific major CV end points (MIs and strokes). The Duke Clinical Research Institute (DCRI) was contracted to perform the work. All raw participant-level data sources were to be provided to the DCRI team. The FDA requested the original RECORD end point definitions and contemporary definitions under development by the FDA Standardized Data Collection for Cardiovascular Trials Initiative be used.[5]

This reevaluation of the RECORD trial end points provided an opportunity to make a direct comparison between the treatment effects of rosiglitazone determined

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by 2 experienced adjudication groups in a global clinical trial with >25,000 person-years of exposure. It also provided an opportunity to assess the application of the new draft FDA end point definitions.

Methods

Study conduct, event ascertainment, and adjudication

Details of the RECORD study have been published previously.[2,6,7] In the original RECORD clinical events classification (CEC) effort, all deaths and hospitalizations events were to be reported by site investigators using standard paper case report form modules; this was aided by local monitoring visits and screening of serious adverse event reports. Data were collated and quality checked by a commercial research organization (Quintiles, Dublin, Ireland), which also prepared blinded event files and submitted them for independent review by 2 physicians on a Clinical Endpoints Committee. Disagreements between the 2 physician reviews were resolved by consensus of the group.

The detailed procedures used in the reevaluation effort are described separately.[8] In brief, DCRI personnel were to be provided access to the original participant-level data, coordinated efforts to acquire further source documentation from the sites, collaborated with the sponsor and a third-party vendor to obtain vital status on participants previously lost to follow-up, developed the procedures to systematically identify and adjudicate all potential endpoint events, and created processes to redact information about assigned study drug from study documents.

The identification of deaths, suspected MIs, and suspected strokes was accomplished by creating a computer program that scanned the electronic data provided by GlaxoSmithKline to the DCRI. The computer algorithm identified data fields that indicated a potential event may have occurred. The DCRI CEC clinical personnel also performed manual reviews of the case report form, including free text narratives, to identify possible events. All deaths, all suspected MIs, and all suspected stroke events were processed for adjudication. This differed from the original RECORD CEC effort, in which only deaths and hospitalizations that occurred during the CV follow-up were reviewed by physicians. The physicians performing the event adjudication for the original RECORD CEC and the DCRI CEC work were experienced clinical trialists and had cardiology or neurology expertise. The DCRI CEC used a similar review process as the original RECORD CEC with an initial independent review by 2 physicians. If these physicians disagreed, the event was reviewed by a committee of at least 3 physicians, with final determination by consensus.

Each potential event identified by DCRI procedures was adjudicated using the original RECORD end point definitions for cause of death, MI, and stroke, to be consistent with the original RECORD trial. In addition, the draft definitions from the FDA Standardized Data Collection for Cardiovascular Trials Initiative were used to apply a contemporary set of definitions.[5] The DCRI physicians were also asked to assess subjectively whether sufficient or insufficient information was available to adjudicate the event using contemporary standards.

After completion of all adjudications, unblinding of the results, and presentation of the final DCRI-prepared summary of the findings to the sponsor and the FDA, discrepancies in any decision for events reviewed by both the DCRI CEC and the original RECORD CEC were reviewed together by members of the DCRI team and members of the RECORD Steering Committee. The events were evaluated, and reasons for differences were identified. No changes to the event results by the DCRI CEC or the original RECORD CEC groups occurred.

The DCRI Operational Team members, original RECORD CEC and DCRI CEC physicians, and the sponsor partner representatives are listed in the online Appendix.

Statistical analyses

For the current analyses, differences between the rosiglitazone group and the control group were estimated as hazard ratios (HRs) (with 95% CI) based on Cox proportional hazards regression stratified for background medication. The primary composite end point for the analyses in this article was the first occurrence of CV (or unknown cause) death, MI, or stroke occurring on or before December 31, 2008.[7] The DCRI chose this cutoff date because final study visits were to be conducted between August and December 2008. Secondary end points were overall mortality, CV or unknown cause death, MI, and stroke. Analyses presented in this article informally tested the null hypothesis of equality between the rosiglitazone and metformin/sulfonylurea treatment arms by claiming significance if the 95% CI for the HR excluded 1.0. The RECORD trial was originally designed as a noninferiority trial, with a margin of 1.20 for the end point of CV hospitalization or death; however, we analyzed a different primary end point (CV death, MI, or stroke) and did not make conclusions regarding noninferiority.

The original RECORD CEC adjudicated all deaths and CV hospitalizations occurring up to the final study visit or withdrawal of consent. Per protocol, the original CEC did not process and adjudicate any deaths or nonfatal events occurring to a patient after the patient had withdrawn from the CV follow-up phase of the study and was being followed up for vital status only. With the exception of deaths, which were included in the all-cause mortality analysis, events observed in the vital status only follow-up period were neither collected nor reported in the original RECORD analysis.

The DCRI CEC adjudicated all deaths and nonfatal MI and stroke events occurring up to the end of the study (December 31, 2008). Follow-up for participants who did not experience MI, stroke, or CV death was based on the date of the last face-to-face study visit. Therefore, analyses performed by the DCRI group of CV outcomes and their components include identified events that were not included in the original RECORD analyses due to different analytic approaches. To support time-to-event analyses of study end points, DCRI derived follow-up periods for each participant, using all available study documentation.

Analyses were also performed for the components of the CV death, MI, or stroke composite end point and for all-cause mortality. Sensitivity analyses were performed to test the robustness of the results for all-cause mortality; the primary end point; and the components CV death, MI, and stroke. These analyses included on-treatment analyses (censoring at 30 days after last study drug treatment), landmark analyses up to and following the date of a protocol amendment that instituted a tracking substudy to collect data from patients who had withdrawn (February 27, 2006), landmark analyses up to and following the date of the publication of the RECORD interim

Table I. Treatment comparisons using the DCRI CEC results and the original RECORD CEC results using the original RECORD end point definitions

	Rosiglitazone	Metformin/sulfonylurea	HR (95% CI)
DCRI CEC results (original definitions)			
CV (or unknown cause) death, MI, or stroke	181 (8.3%)	188 (8.4%)	0.95 (0.78-1.17)
CV (or unknown cause) death	88 (4.0%)	96 (4.3%)	0.90 (0.68-1.21)
MI	68 (3.1%)	60 (2.7%)	1.13 (0.80-1.59)
Stroke	50 (2.3%)	63 (2.8%)	0.79 (0.54-1.14)
All death	139 (6.3%)	160 (7.2%)	0.86 (0.68-1.08)
Original RECORD CEC results (original definitions)			
CV (or unknown cause) death, MI, or stroke	154 (6.9%)	165 (7.4%)	0.93 (0.74-1.15)
CV (or unknown cause) death	60 (2.7%)	71 (3.2%)	0.84 (0.59-1.18)
MI	64 (2.9%)	56 (2.5%)	1.14 (0.80-1.63)
Stroke	46 (2.1%)	63 (2.8%)	0.72 (0.49-1.06)
All death	136 (6.1%)	157 (7.0%)	0.86 (0.68-1.08)

analysis (June 5, 2007), and analysis to the earliest study completion date (August 24, 2008). An additional sensitivity analysis included only events for which adjudicators reported that there was sufficient information for classification.

Differences in the number of deaths, MIs, or strokes reported by the original RECORD CEC and the DCRI CEC are provided.

Role of the funding source

The sponsor of the study was GlaxoSmithKline (King of Prussia, PA). The role of the sponsor in the conduct of the study has been published previously.[7] Funding for the reevaluation effort was provided to DCRI. The sponsor FDA personnel and members of the RECORD Steering Committee reviewed and commented on the protocol before any work was performed. The DCRI and RECORD Steering Committee representatives made the decision to publish the findings and have written the manuscript jointly. The manuscript and clinical study reports were reviewed by sponsor representatives for accuracy. The sponsor facilitated and enabled access for DCRI personnel to all trial data.

Results

Additional follow-up and events identified

Follow-up for mortality was 25,833 person-years, including an additional 328 person-years identified during the reevaluation effort from participants with incomplete vital status at the end of the original RECORD study. Follow-up for the CV death, MI, or stroke composite was 23,692 person-years because participants without an event were censored on the date of the last face-to-face study visit. Vital status follow-up was complete for 96.0% of the participants (96.7% and 95.4% in the rosiglitazone and metformin/sulfonylurea groups, respectively). For the CV death, MI, or stroke composite end point, follow-up was complete for 83.3% of the participants (84.5% and 82.1% in the rosiglitazone and metformin/sulfonylurea groups, respectively).

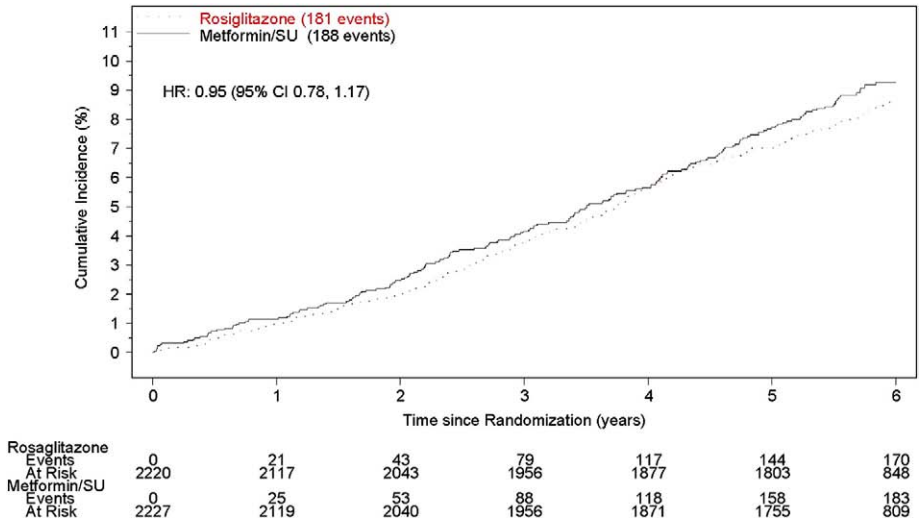
DCRI CEC metrics

Querying of the original RECORD database identified 314 deaths, 2,101 suspected MIs, and 496 suspected strokes. Of these, the computer program screening the database identified 2,052 suspected MIs and 468 suspected strokes, and manual review of documents by DCRI CEC coordinators identified an additional 49 suspected MIs and 28 suspected strokes. Of the 2,911 suspected events identified, 701 nonfatal events were not processed because they were duplicate events or no indication of an event was identified upon further processing. The remaining 314 deaths, 1,474 suspected MIs, and 422 suspected strokes were processed and adjudicated by the DCRI CEC clinicians.

Clinical outcomes

Table I shows the CV death, MI, and stroke outcomes using the DCRI CEC results and the original RECORD CEC results by treatment using the original RECORD end point definitions.[7] Figure 1 shows Kaplan-Meier curves for the primary composite outcome using DCRI CEC results and the original RECORD end point definitions. A total of 184 CV or unknown cause deaths (88 rosiglitazone, 96 metformin/sulfonylurea), 137 MIs in 128 participants (68 rosiglitazone, 60 metformin/sulfonylurea), and 119 strokes in 113 participants (50 rosiglitazone, 63 metformin/sulfonylurea) were identified by the DCRI CEC efforts using the same end point definitions as used in the original RECORD CEC. For the primary end point—time to first occurrence of CV (or unknown cause) death, MI, or stroke—no statistically significant difference was observed between rosiglitazone and metformin/sulfonylurea using the original RECORD end point definitions (HR 0.95, 95% CI 0.78-1.17). These results were comparable with those reported in the original RECORD study (HR 0.93, 95% CI 0.74-1.15). Cardiovascular (or unknown cause) death was similar between rosiglitazone and metformin/sulfonylurea using the original RECORD end point definitions (HR 0.90, 95% CI 0.68-1.21). For time to first fatal and nonfatal MI and for time to first fatal and nonfatal stroke, the comparisons between rosiglitazone and metformin/

Figure 1



Kaplan-Meier curves for the primary composite end point using the DCRI CEC results and the original RECORD end point definitions.

Table II. The DCRI CEC outcomes by randomized treatment comparison using the original RECORD end point definitions and new FDA end point definitions

	Rosiglitazone	Metformin/sulfonylurea	HR (95% CI)
DCRI CEC results—original RECORD end point definitions			
CV (or unknown cause) death, MI, or stroke	181 (8.3%)	188 (8.4%)	0.95 (0.78-1.17)
Death—all cause	139 (6.3%)	160 (7.2%)	0.86 (0.68-1.08)
CV (or unknown cause) death	88 (4.0%)	96 (4.3%)	0.90 (0.68-1.21)
MI	68 (3.1%)	60 (2.7%)	1.13 (0.80-1.59)
Stroke	50 (2.3%)	63 (2.8%)	0.79 (0.54-1.14)
DCRI CEC results—new FDA end point definitions			
CV (or unknown cause) death, MI, or stroke	186 (8.4%)	191 (8.6%)	0.97 (0.79-1.18)
Death—all cause	139 (6.3%)	160 (7.2%)	0.86 (0.68-1.08)
CV (or unknown cause) death	88 (4.0%)	96 (4.3%)	0.90 (0.68-1.21)
MI	72 (3.2%)	62 (2.8%)	1.15 (0.82-1.62)
Stroke	53 (2.4%)	64 (2.9%)	0.82 (0.57-1.18)

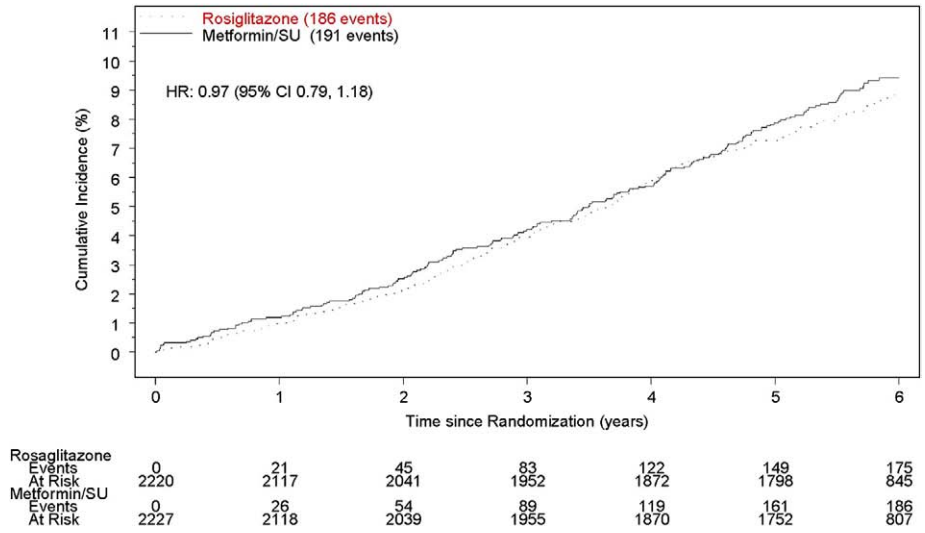
sulfonylurea were HR of 1.13 and 95% CI of 0.80 to 1.59 and HR of 0.79 and 95% CI of 0.54 to 1.14, respectively.

The HR for all-cause mortality was the same using the DCRI CEC and original RECORD CEC results (0.86, 95% CI 0.68-1.08).

Original end point definitions compared with FDA definitions

Table II shows composite CV death, MI, and stroke outcomes and the contribution of each event to the composite from the DCRI CEC results using the original RECORD end point definitions and the new FDA definitions. Figure 2 shows the Kaplan-Meier curves for the CV death, MI, and stroke composite end point using the DCRI CEC results and the new FDA definitions. The event rates and treatment comparisons are similar using the original RECORD end point definitions and the new FDA end point definitions. A comparison at the event level rather than the patient level (as in Table II) of the cause of death adjudications, number of MIs, and number of strokes using the original RECORD end point definitions and the new FDA end point definitions is shown in Table III. The results of cause of death adjudication were the same using both sets of definitions. The use of the new FDA end point definitions resulted in a small number of additional stroke (4) and MI (14) events primarily because the new FDA end point definitions for MI or stroke do not require hospitalization.

Figure 2



Kaplan-Meier curves for the primary composite end point using the DCRI CEC results and the new FDA end point definitions.

Sensitivity analyses

Table IV shows the results of a series of sensitivity analyses using the DCRI CEC results with the new FDA end point definitions. In the on-treatment analyses and landmark analyses attempting to account for potential bias after the interim publication, no evidence of heterogeneity in treatment effect was observed compared with the overall DCRI CEC results. Additional analyses using data acquired before amendment 7 or using an end date of the earliest possible final study visit showed similar results (data not shown).

Of the events adjudicated by the DCRI CEC group using the new FDA definitions, 45.5% of all deaths, 78.1% of MIs, and 94.3% of strokes were determined to have sufficient information by the CEC physicians. Results of the analyses of only those events with sufficient information were consistent with the analyses for the composite of CV death, MI, and stroke and the individual components using the DCRI CEC results.

Comparison of the original RECORD CEC and the DCRI CEC results

Figure 3 details the death reporting of the original RECORD CEC analysis and the DCRI CEC analysis. One participant was reported dead in the original data set, but the DCRI CEC group did not believe that there was enough evidence to confirm that the participant died. In total, the DCRI CEC group identified 20 deaths not reported in the original RECORD report. Of these 20, 8 (5 rosiglitazone and 3 metformin/sulfonylurea) occurred before the DCRI-defined final follow-up of December 31, 2008, and 12 (7 rosiglitazone and 5 metformin/sulfonylurea) occurred after this date. Of the 8 deaths occurring before December 31, 2008, 4 occurred before the end of the original RECORD-defined final follow-up. Seven of the deaths occurred during the additional 328 person-years of follow-up obtained during the reevaluation effort.

Overall, the DCRI CEC effort reported more CV or unknown deaths (184 vs 131), more MI events (128 vs

Table III. Comparison of DCRI CEC results using original RECORD end point definitions and new FDA end point definitions where either definition delivered a confirmed event

	New FDA end point definitions		
Original RECORD end point definitions	**CV death**	**Non-CV death**	**Unknown cause death**
CV death	77	0	0
Non-CV death	0	117	0
Unknown cause death	0	0	120

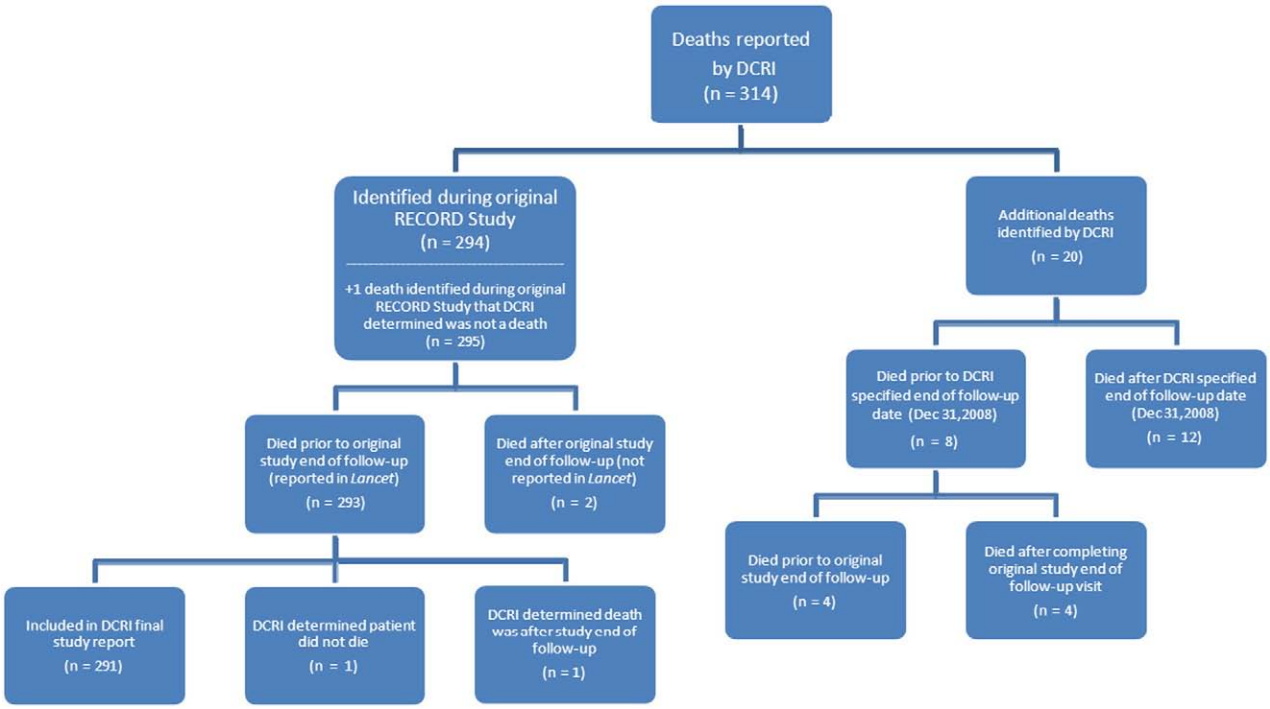
	MI	**No MI**
No MI	14	–
MI	137	0

	Stroke	**No stroke**
No stroke	4	–
Stroke	119	0

Table IV. Treatment comparisons from sensitivity analyses using the DCRI CEC results and the new FDA end point definitions

Subgroup	End point	Rosiglitazone, n = 2220	Metformin/sulfonylurea, n = 2227	HR (95% CI)
On study treatment +30 d				
	CV (or unknown cause) mortality, MI, and stroke	128	129	0.94 (0.73-1.20)
	All-cause mortality	57	70	0.76 (0.54-1.08)
	CV (or unknown cause) death	34	43	0.74 (0.47-1.16)
	MI (fatal and nonfatal)	63	51	1.17 (0.81-1.70)
	Stroke (fatal and nonfatal)	42	52	0.76 (0.51-1.14)
Up to publication of interim report				
	CV (or unknown cause) mortality, MI, and stroke	142	150	0.95 (0.75-1.19)
	All-cause mortality	97	114	0.84 (0.64-1.10)
	CV (or unknown cause) death	55	68	0.80 (0.56-1.14)
	MI (fatal and nonfatal)	59	53	1.11 (0.77-1.61)
	Stroke (fatal and nonfatal)	45	49	0.92 (0.61-1.37)
Only end points with sufficient information for classification				
	CV (or unknown cause) mortality, MI, and stroke	124	122	1.01 (0.79-1.30)
	MI (fatal and nonfatal)	56	51	1.09 (0.75-1.60)
	Stroke (fatal and nonfatal)	52	59	0.87 (0.60-1.27)

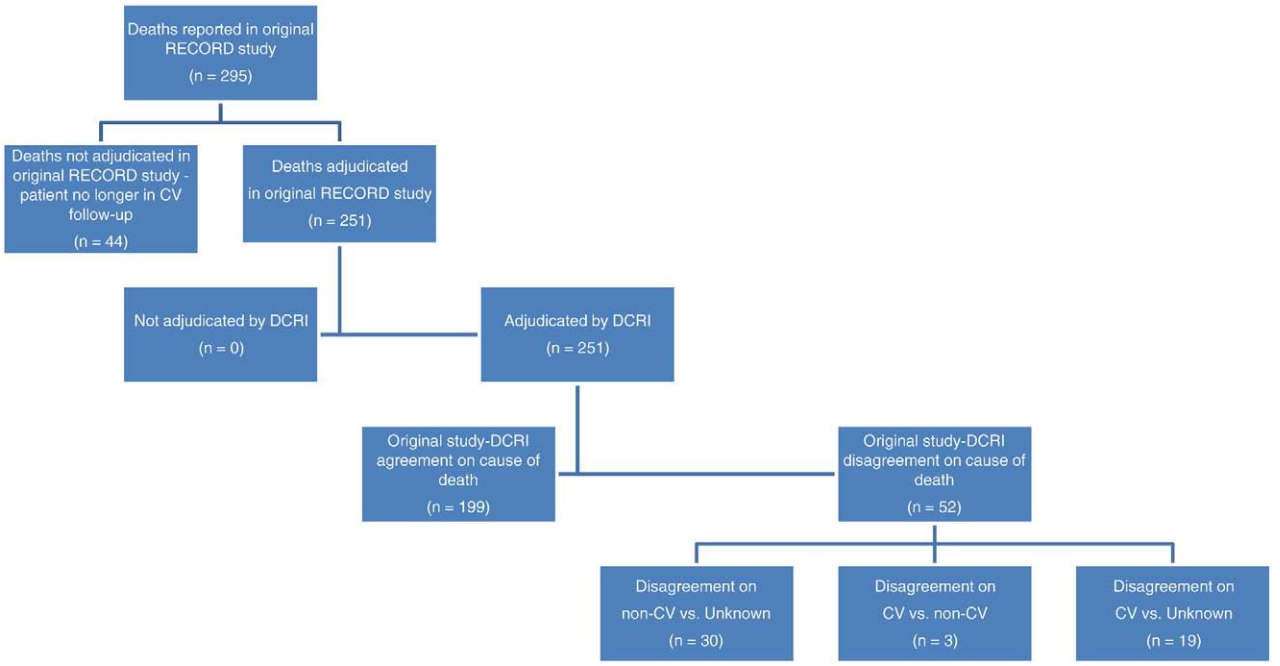
Figure 3



Deaths reported by the DCRI CEC and original RECORD CEC and reasons for differences.

120), and more strokes (113 vs 109) compared with the original RECORD CEC process. Although numbers of all-cause deaths increased modestly with the DCRI CEC effort, the proportion of deaths classified as CV death by the DCRI CEC, which included deaths of unknown cause, was notably higher (see Table I). Most of this was explained by the DCRI CEC group adjudicating deaths with little information or deaths in participants with known cancer but no details about cancer progression available in the months before reported death as unknown cause because patients with cancer may die of many reasons besides cancer; these deaths

Figure 4



Agreements and disagreements in the classification of cause of death between the original RECORD CEC and the DCRI CEC.

were then included in the CV cause of death analyses, as specified in the DCRI and original RECORD analytic plans. Because the original RECORD CEC reported these as non-CV death, they were not included in the CV cause of death analyses.

Figure 4 shows the agreements and disagreements in the classification of cause of death for the 251 events adjudicated by both the original RECORD CEC and the DCRI CEC using the original RECORD cause of death end point definitions. Overall, there was agreement for 199 (79%) and disagreement for 52 (21%).

It was not possible to determine the total number of agreements or disagreements between the 2 CEC groups for MI or stroke because the original RECORD CEC reviewed only hospitalizations to identify MI and stroke events, whereas the DCRI CEC reviewed any suspected MI and stroke events. However, 14 MI events were reported by either the original RECORD CEC or the DCRI CEC but not both. Of these 14 MI events, 11 (5 rosiglitazone and 6 metformin/sulfonylurea) were reported by the DCRI CEC, and 3 (1 rosiglitazone and 2 metformin/sulfonylurea) by the original RECORD CEC. In total, 18 stroke events were reported by either the original RECORD CEC or the DCRI CEC but not both. Of these 18 stroke events, 11 (7 rosiglitazone and 4 metformin/sulfonylurea) were reported by the DCRI CEC, and 7 (3 rosiglitazone and 4 metformin/sulfonylurea) by the original RECORD CEC.

Discussion

A comprehensive reevaluation of all deaths and all suspected MI and stroke events was performed by an academic group (DCRI CEC) using the raw RECORD data. For the primary end point of these analyses—time to first occurrence of a composite of CV or unknown death, MI, or stroke—no meaningful difference between rosiglitazone and metformin/sulfonylurea was observed using the original RECORD end point definitions (HR 0.95, 95% CI 0.78-1.17) or new FDA end point definitions (HR 0.97, 95% CI 0.79-1.18). Furthermore, these results are similar to results from the original RECORD study (HR 0.93, 95% CI 0.74-1.15). The original RECORD study results and the DCRI CEC results were also similar for the individual components of the composite end point. These findings and the additional sensitivity analyses performed support the original RECORD results and suggest that when using essentially the same data, the observations were not affected by different CEC processes, physician adjudicators, or end point definitions.

Two key operational objectives of the DCRI CEC reevaluation effort were to obtain more information in patients lost to follow-up and to identify potentially

missed events in the RECORD trial. Despite a concerted effort to obtain additional information, only a modest amount of additional person-years of follow-up was obtained (328 person-years). Multiple challenges were realized, including many clinical sites with disbanded research groups, inability to obtain institutional review board approval, and regulations in some countries that would not allow access to databases or clinical records. Systematic querying of the original RECORD database and the modest additional follow-up information added only a small number of additional nonfatal events (11 MIs and 11 strokes) and removed a few (3 MIs and 7 strokes).

RECORD was designed as an open-label trial and used a blinded CEC group to adjudicate clinical events. A similar strategy has been used in other large outcome trials. A concern about biased ascertainment of the end point events during the original RECORD trial has been suggested by some individuals, including improper processing of some events that had been reported.[4] The processes used by the DCRI CEC group to identify all possible events and obtain additional follow-up, the statistical analyses including landmark analyses to evaluate potential influence of amendments and publication of interim analyses, and the application of the new FDA end point definitions did not find evidence of systematic bias in processing of events reported by the site investigators. In addition, the overall rate of MI using the DCRI CEC results and the original RECORD end point definition (0.54 per 100 person-years or 2.9%) appears consistent with CV outcomes reported in recent systematic reviews,[9] although the populations, study designs, follow-up, event definitions, and ascertainment varied.[10-27]

A comparison of differences in the classification of cause of death and occurrence of the nonfatal end points between 2 experienced CEC groups showed that the DCRI CEC group identified more CV outcomes using the same end point definitions as the original RECORD CEC. This was primarily because the DCRI CEC attributed more deaths (184 vs 131) to a CV or unknown cause compared with the RECORD CEC. One reason for this was that the RECORD CEC attributed some deaths to cancer, whereas the DCRI CEC classified these same deaths as unknown (n = 17). This discrepancy arose mainly because participants with a diagnosis of cancer who later died were often adjudicated as non-CV deaths by the RECORD CEC, whereas if no follow-up had taken place for a significant period before the participant's death, the DCRI CEC tended to classify the cause as unknown. Although only a modest number of additional MI events (n = 8) and stroke events (n = 4) were identified, they were balanced across treatment groups. These findings, along with the consistent overall results, support lack of obvious systematic concerns in adjudication after review by both CEC groups. Similar findings have been reported previously and highlight that limited data from the study sites and the lack of conventions for the application of standard definitions can make end point adjudication difficult and subject to disagreement.[28-31] There is confidence that all the events reported by the site investigators were identified and processed. The number of events that may not have been reported by the site coordinators or investigators is unknown and is a potential limitation in all clinical trials.

The use of the new FDA end point definitions for cause of death, MI, and stroke provided the first opportunity to apply these definitions in a large CEC effort. The results from the DCRI CEC effort using the original RECORD and the new FDA definitions were similar. The new FDA end point definitions allow classification of MI or stroke based on outpatient evaluations or in patients who died out of hospital. Although controversy exists over specific criteria to use for end point definitions, the comparison of DCRI CEC results using 2 different definitions does not support one definition over another. However, it is clear that standard definitions are needed for consistency in drug development programs and for comparison of event rates between trials.

The HR and 95% CI for MI with rosiglitazone compared with metformin/sulfonylurea were similar using the original RECORD trial data or using the DCRI CEC results with either the original RECORD or the new FDA end point definitions. Potential for a nearly 59% to 63% increase in risk or an 18% to 22% benefit cannot be excluded. However, the RECORD trial was not powered for a comparison on any of the individual components of the primary composite. Systematic reviews have reported a statistically significant increase in MI associated with rosiglitazone, although such analyses have well-known limitations. The definitive approach to understand the potential hazard of MI with rosiglitazone is a large, double-blind, randomized clinical trial. The TIDE trial with rosiglitazone was evaluating CV outcomes but has been put on full clinical hold by the FDA (http://clinicaltrials.gov/ct2/show/NCT00879970).

Limitations

This retrospective reevaluation effort has important limitations. First, it relied heavily on the original RECORD database and source documentation because only a modest amount of additional follow-up was obtained, and most of the additional information obtained was about vital status and not nonfatal MIs or strokes. Second, using contemporary standards, it was determined that 35% of the events reviewed had a subjective assessment of insufficient information to make a confident decision. However, analyses with only events that had sufficient information had similar results. Finally, the entire CEC group was blinded to treatment assignment, but we had no mechanism to overcome other potential biases introduced by the open-label trial design.

Conclusions

The reevaluation of RECORD CV outcomes included a blinded systematic review of the original RECORD database and study documents supplemented by an attempt to contact study investigators for additional participant follow-up information. Because of logistical challenges, only a modest number of additional person-years of information were obtained compared with the initial RECORD data. The results of this reevaluation and analyses provide several key findings. First, results using the DCRI CEC data including extensive sensitivity analyses were consistent with the originally published RECORD results and did not show statistically significant differences between the rosiglitazone and the metformin/sulfonylurea groups for the composite end point of CV death, MI, or stroke and the individual components. Second, a comparison of event adjudication by 2 CEC groups using the same end point definitions showed only a small increase in the number of stroke or MI events reported by the DCRI CEC group compared with the original RECORD CEC group. The DCRI CEC group adjudicated more deaths as CV deaths because physicians were more likely to adjudicate the cause of death as unknown rather than non-CV cause when limited information was available and deaths with unknown cause were included in the CV death analyses per protocol. Third and finally, comparative treatment results were similar using a contemporary set of end point definitions being developed by the FDA compared with the historical definitions.

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