Updating insights into rosiglitazone and cardiovascular risk through shared data: individual patient and summary level meta-analyses

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ABSTRACT

OBJECTIVES

To conduct a systematic review and meta-analysis of the effects of rosiglitazone treatment on cardiovascular risk and mortality using multiple data sources and varying analytical approaches with three aims in mind: to clarify uncertainties about the cardiovascular risk of rosiglitazone; to determine whether different analytical approaches are likely to alter the conclusions of adverse event meta-analyses; and to inform efforts to promote clinical trial transparency and data sharing.

DESIGN

Systematic review and meta-analysis of randomized controlled trials.

DATA SOURCES

GlaxoSmithKline's (GSK's) ClinicalStudyDataRequest.com for individual patient level data (IPD) and GSK's Study Register platforms, MEDLINE, PubMed, Embase, Web of Science, Cochrane Central Registry of Controlled Trials, Scopus, and ClinicalTrials.gov from inception to January 2019 for summary level data.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES

Randomized, controlled, phase II-IV clinical trials that compared rosiglitazone with any control for at least 24 weeks in adults.

DATA EXTRACTION AND SYNTHESIS

For analyses of trials for which IPD were available, a composite outcome of acute myocardial infarction, heart failure, cardiovascular related death, and non-cardiovascular related death was examined. These four events were examined independently as secondary analyses. For analyses including trials for which IPD were not available, myocardial infarction and cardiovascular related death were examined, which were determined from summary level data. Multiple meta-analyses were conducted that accounted for trials with zero events in one or both arms with two different continuity corrections (0.5 constant and treatment arm) to calculate odds ratios and risk ratios with 95% confidence intervals.

RESULTS

33 eligible trials were identified from ClinicalStudyDataRequest.com for which IPD were available (21 156 patients). Additionally, 103 trials for which IPD were not available were included in the meta-analyses for myocardial infarction (23 683 patients), and 103 trials for which IPD were not available contributed to the meta-analyses for cardiovascular related death (22 772 patients). Among 29 trials for which IPD were available and that were included in previous meta-analyses using GSK's summary level data, more myocardial infarction events were identified by using IPD instead of summary level data for 26 trials, and fewer cardiovascular related deaths for five trials. When analyses were limited to trials for which IPD were available, and a constant continuity correction of 0.5 and a random effects model were used to account for trials with zero events in only one arm, patients treated with rosiglitazone had a 33% increased risk of a composite event compared with controls (odds ratio 1.33, 95% confidence interval 1.09 to 1.61; rosiglitazone population: 274 events among 11 837 patients; control population: 219 events among 9319 patients). The odds ratios for myocardial infarction, heart failure, cardiovascular related death, and non-cardiovascular related death were 1.17 (0.92 to 1.51), 1.54 (1.14 to 2.09), 1.15 (0.55 to 2.41), and 1.18 (0.60 to 2.30), respectively. For analyses including trials for which IPD were not available, odds ratios for myocardial infarction and cardiovascular related death were attenuated (1.09, 0.88 to 1.35, and 1.12, 0.72 to 1.74, respectively). Results were broadly consistent when analyses were repeated using trials with zero events across both arms and either of the two continuity corrections was used.

CONCLUSIONS

The results suggest that rosiglitazone is associated with an increased cardiovascular risk, especially for heart failure events. Although increased risk of myocardial infarction was observed across analyses, the strength of the evidence varied and effect

WHAT IS ALREADY KNOWN ON THIS TOPIC

Since 2007, several meta-analyses have been conducted that have used various analytic approaches and reported conflicting findings about the cardiovascular risk of rosiglitazone

Previous meta-analyses did not have access to individual patient level data (IPD) from clinical trials and mostly relied on summary level data

Little consensus exists on which method should be used to account for sparse adverse event data in meta-analyses

WHAT THIS STUDY ADDS

Among trials for which IPD were available, rosiglitazone use was consistently associated with an increased cardiovascular risk, especially for heart failure events

Increased myocardial infarction risk was observed across analyses, but the magnitudes of risk varied and were attenuated when summary level data were used in addition to IPD

Among trials for which IPD were available, more myocardial infarctions and fewer cardiovascular deaths were reported in IPD compared with summary level data

estimates were attenuated when summary level data were used in addition to IPD. Because more myocardial infarctions and fewer cardiovascular related deaths were reported in the IPD than in the summary level data, sharing IPD might be necessary when performing meta-analyses focused on safety.

SYSTEMATIC REVIEW REGISTRATION
OSF Home https://osf.io/4yvp2/.

Introduction

Rosiglitazone is manufactured by GlaxoSmithKline (GSK) under the brand name Avandia. In 1999, the Food and Drug Administration (FDA) in the United States first approved this drug to treat type 2 diabetes mellitus.[1 2] Although the European Medicines Agency initially rejected the drug in 1999, market authorization was granted in Europe in 2000.[3] Despite regulatory warnings for heart failure,[3] use of rosiglitazone grew rapidly and annual sales peaked at approximately $3.3bn (£2.5bn; €2.9bn) in 2006.[4] However, in May 2007 a meta-analysis of 42 GSK trials suggested a 43% increased risk of myocardial infarction.[5] The ensuing discussion in the media and the peer reviewed literature resulted in widespread awareness of the cardiovascular safety concerns about rosiglitazone. These findings, which led to questions about why the European Medicines Agency approved rosiglitazone[3] and whether GSK and the FDA should have released similar information earlier, resulted in congressional hearings and an FDA safety alert.[6-8] In 2007 the European Medicines Evaluation Agency recommended new warnings for patients with ischemic heart disease, and by 2010 rosiglitazone was suspended from European markets owing to cardiovascular risks.[3]

Between 2010 and 2011, the FDA updated rosiglitazone's product label to include information on cardiovascular risks and limited the availability of the drug as part of a Risk Evaluation Mitigation Strategy (REMS) programme, where patients could only receive rosiglitazone from specialty mail order pharmacies.[2 9] The restrictions were withdrawn in 2013 after an analysis of the RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes) study found that rosiglitazone's cardiovascular safety profile did not differ from that of other drugs used for diabetes management (eg, sulfonylurea).[10] However, the design and conduct of the RECORD study were widely criticized, and apprehension seems to remain among patients and physicians about use of the drug.[11 12] Although rosiglitazone has been removed from the market in most countries,[3] and use in the US has rapidly dropped since boxed warnings were issued in 2007,[13 14] the drug is still available in the US.

Since 2007, several meta-analyses have been conducted that have used various analytic approaches and reported conflicting findings about rosiglitazone's cardiovascular risk. According to UpToDate, an online clinical decision support resource, the use of rosiglitazone is currently not recommended because of concerns "about its atherogenic lipid profiles and a potential increased risk for cardiovascular events."[15] However, UpToDate also notes that "the effect of rosiglitazone on the risk of MI [myocardial infarction] is uncertain."[15] Some of this uncertainty about rosiglitazone's cardiovascular risk might be caused by limitations in previous meta-analyses and in the original trial designs.[16-21]

Firstly, previous systematic reviews and meta-analyses relied on GSK summary level data and publication level data.[5 21] Since the approval of rosiglitazone and the original meta-analyses were published, dozens of additional trials have been published. Moreover, the meta-analyses did not have access to individual patient level data (IPD), which are raw data from clinical trial participants (table 1). Unlike publicly available summary level data sources, which often report only composite study outcomes and rarely summarize safety events,[22 23] IPD can be used to more consistently identify events,[24-26] classify and evaluate individual or composite adverse events, and determine potentially missing or poorly reported outcomes. These characteristics might help minimize the impact of selective adverse event reporting in publications.[24]

Secondly, many reviews used meta-analytic approaches that excluded trials with zero events in the treatment and control groups,[5 21] even though these studies suggest that, at least in a clinical trial population, certain outcomes occur infrequently. While trials with zero events do not provide information about the direction or magnitude of relative treatment effects, arguments have been made that the inclusion of these trials in meta-analyses can lead to more precise effect estimates.[17 18 27-30]

Initiatives to promote open science and data sharing,[25 31 32] including recent efforts by GSK to make IPD available to external investigators for research that can help advance medical science or improve patient care,[33] present a unique opportunity to better address the concerns about rosiglitazone's cardiovascular risk. Our objective was to determine the effects of rosiglitazone treatment on cardiovascular risk and mortality. We conducted a comprehensive systematic

Table 1 | Examples of data sources for meta-analyses

Summary or aggregate level data			Individual patient level data
Published literature	**Registries**	**Clinical study reports**	
Publications, available through publication databases, provide aggregate results, including effect estimates, measures of precision, or adverse event counts observed in treatment arms and comparator arms	Registries are online databases that report information about timing, design, and results of clinical trials (eg, ClinicalTrials.gov). Results reported on registries often include summary effect estimates or adverse event counts	Clinical study reports are detailed documents that describe design and results of clinical trials. Full reports include efficacy and safety data, but do provide patient specific information	Raw data from individual participants in clinical trials

review and meta-analysis of all trials for which IPD were available from GSK's rosiglitazone clinical trial programme, and we used supplemental summary level data when IPD data were not available. We intended to advance knowledge in three main areas. Firstly, to clarify uncertainties about the cardiovascular risk of rosiglitazone among clinicians, patients, and policy makers. We combined trials identified through different data sources and considered several analytical methods to better estimate the effects of rosiglitazone on cardiovascular risk and mortality. We also examined the risk of a composite outcome of four events: heart failure, acute myocardial infarction, cardiovascular related deaths, and non-cardiovascular related deaths. This composite outcome was informed by previous meta-analyses and black box warnings.[5 21] We also examined these four events independently as secondary analyses.

Secondly, we aimed to determine whether different analytical approaches are likely to alter the conclusions of adverse event meta-analyses. Meta-analyses of adverse event data involve analytical complexities, such as estimating effects from trials with zero events in one or both treatment arms. Our work could elucidate whether common analytical approaches that have been proposed to account for sparse data could alter conclusions about rosiglitazone, potentially guiding future safety focused meta-analyses.

Finally, our analysis could help to promote clinical trial transparency and trial data sharing initiatives, including the role of IPD in meta-analyses of drug safety. Overall, the findings from this study could inform how diabetes drugs are approved and how data sources and methods should be considered when monitoring the safety of drugs in the postmarket setting.[34]

Methods

This systematic review and meta-analysis is reported according to the preferred reporting items for systematic reviews and meta-analyses IPD (PRISMA-IPD) statement.[35 36] The original proposal for the IPD portion of the study and study protocol is available online: https://osf.io/4yvp2/.

Search strategy and data sources

Clinical trial data on the effects of rosiglitazone treatment on cardiovascular risk and mortality might be reported in multiple public and non-public sources.[37] We first identified and requested all phase II, III, and IV clinical trials of rosiglitazone with IPD made available by GSK through ClinicalStudyDataRequest.com (CSDR). CSDR was developed by GSK as a system for providing access to patient level data from clinical trials.[33] CSDR allows independent researchers to request clinical trial IPD from over 1500 studies. We then reviewed the references included in three previous meta-analyses that focused on rosiglitazone and identified 220 candidate trials for inclusion.[5 21 38] On 3 May 2017, we searched "rosiglitazone" in the "interventional/treatment" field of ClinicalTrials.gov, a registry of clinical trials run by the US National Library of Medicine, and identified 220 entries. We then performed a full text search for "rosiglitazone," limited to phase II-IV trials, on GSK Study Register (gsk-clinicalstudyregister.com). The GSK Study Register is a repository of data and information about GSK studies, which includes protocol summaries, scientific results summaries, protocols, and clinical study reports. The final search retrieved a total of 150 entries with scientific result summaries.

Database searches

We performed a systematic literature search in accordance with the PRISMA statement to identify all published phase II, III, and IV clinical trials for which IPD or clinical study reports were not available. An experienced medical librarian (HKGN) consulted on methods and ran a medical subject heading analysis of known key articles provided by the research team (mesh.med.yale.edu).[39] In each database, we ran scoping searches and used an iterative process to translate and refine the searches. The formal search used minimal controlled vocabulary terms and synonymous free text words plus the CAS registry number to maximize sensitivity and to capture the concepts of "rosiglitazone" and "Avandia." We combined this set with the concept of clinical trials using the Cochrane Highly Sensitive Search Strategies for identifying randomized trials in MEDLINE.

On 13 December 2017, the librarian performed a comprehensive search of multiple databases: MEDLINE (Ovid ALL, from 1946 to December week 1 2017), PubMed for in-process and unindexed material, Embase (Ovid, from 1974 to 13 December 2017), Web of Science, Science Citation Index Expanded (Thompson Reuters, all years), Cochrane Central Registry of Controlled Trials (Wiley, issue 12 of 12, December 2017), and Scopus (Elsevier, all years). English and foreign language articles were eligible for inclusion. No date limit was applied. The search retrieved a total of 5629 references, which we pooled in EndNote and deduplicated (https://www.endnote.com/).[40] We uploaded this set to Covidence (https://www.covidence.org/),[41] which identified additional duplicates, leaving 4774 for screening. On 31 January 2019, all searches were updated and an additional 162 records were added to Covidence and screened. In all, we retrieved 6049 studies across all databases and dates, and screened 4604 studies. Supplementary appendix box 1 summarizes all the search strategies, and figure 1 and figure 2 present PRISMA flowcharts.

Finally, for all published articles with unclear adverse events reported, we sent individual emails that referenced the specific population of interest, outlined the number of relevant adverse events reported in the publication, and asked the authors to verify whether the abstracted values were correct. Because public sources such as journals and trial registrations are more likely to be incomplete,[37 42] we prioritized the information reported in IPD and clinical study reports. However, we only requested IPD for studies made available through CSDR.

Eligibility criteria

We included all randomized controlled trials that compared the effect of rosiglitazone with any control

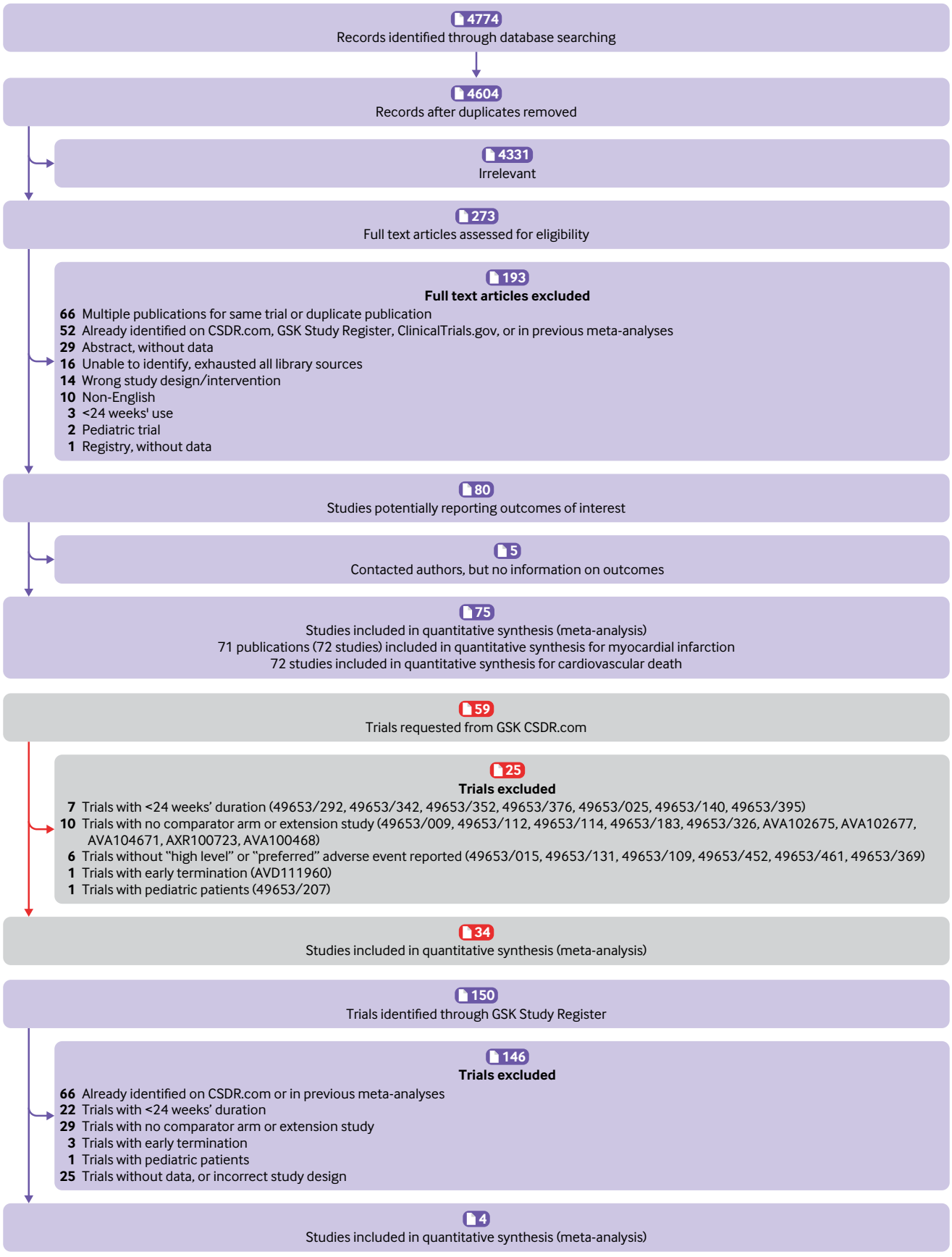

Fig 1 | Modified PRISMA (preferred reporting items for systematic reviews and meta-analyses) flowchart of search showing trials identified through literature search, trials requested from GSK CSDR.com, and those identified through GSK Study Register. CSDR.com=ClinicalStudyDataRequest.com; GSK=GlaxoSmithKline

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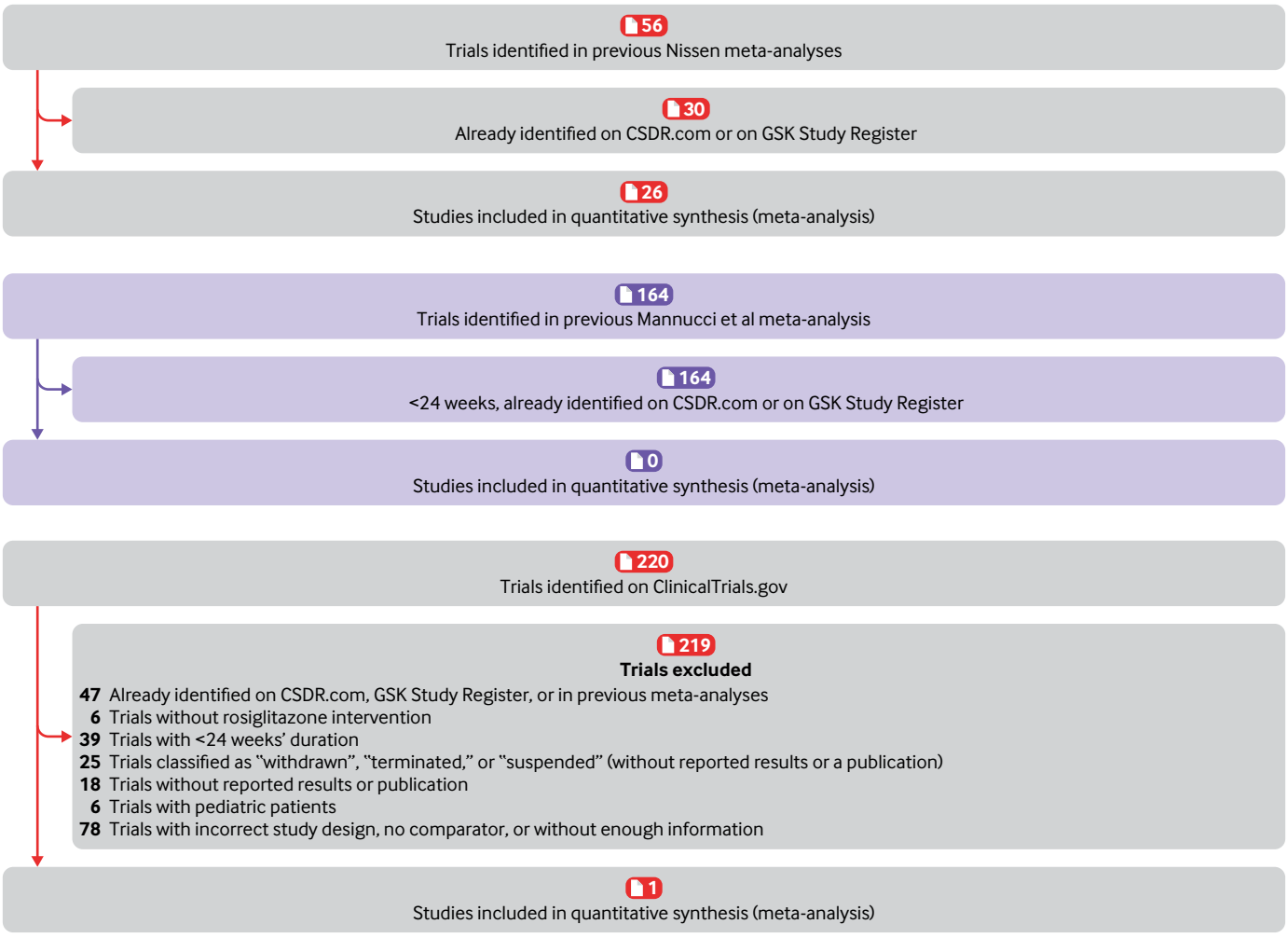

Fig 2 | Modified PRISMA (preferred reporting items for systematic reviews and meta-analyses) flowchart of search showing trials identified in previous meta-analyses and on ClinicalTrials.gov. CSDR.com=ClinicalStudyDataRequest.com; GSK=GlaxoSmithKline

group. We excluded studies that had less than 24 weeks of drug use (previous meta-analyses have used similar criteria[5 21]); studies that had no comparator arms; studies that focused on pediatric patient populations; those that were terminated early, unless they were stopped after 24 weeks or longer, or they were stopped for cardiovascular related safety reasons; extension studies when it was unclear whether patients switched treatment groups; studies that had non-clinical study designs (eg, animal studies or trials with healthy participants); and those that were presentations or abstracts without adverse events.

Study selection

Three reviewers (JDW, DC, JSR) screened all of the records identified on CSDR and one independent reviewer (JDW) screened all other records at the title and abstract level. Potentially eligible studies were assessed in full text by two reviewers (JDW, ADZ), with arbitration by a third reviewer (JSR). When multiple publications of one study were retrieved, we used data from the report with the longest duration of follow-up. For each potentially eligible trial identified, we determined overlapping ClinicalTrials.gov registrations, publications, clinical study reports, and IPD. When sponsor or funder trial identifiers, or ClinicalTrials.gov national clinical trial identifiers were provided, we used those to match trials reported across multiple sources. When publications had corresponding ClinicalTrials.gov registrations with reported results, we abstracted data from the source with the greatest number of events. However, if a publication or registration had IPD or a corresponding GSK Clinical Study ID on gsk-clinicalstudyregister.com, we prioritized the IPD and then the clinical study report or scientific result summary data.

Data collection and analysis

For all included studies, we either used the demographic and study design characteristics provided in publications, or when available, data provided by GSK or on ClinicalTrials.gov registries. We recorded the intention to treat population, average age, proportion male, and proportion white race for each treatment arm. We also recorded the treatment regimen, treatment dosage, treatment duration, and relevant adverse events. Groups of patients who received any dosage of rosiglitazone were pooled together to make

up the treatment group. The control group was defined as patients who received any drug regimen other than rosiglitazone, including placebo.

Individual patient level data

The outcomes selected for this meta-analysis were informed by the previous meta-analyses and black box warnings.[5 21] The primary outcome for the trials for which IPD were available was the composite of four cardiovascular risk and mortality outcomes: acute myocardial infarction events, heart failure events, cardiovascular related deaths, and non-cardiovascular related deaths. We examined these four events independently as secondary analyses. All clinical trials conducted by GSK used the Medical Dictionary for Regulatory Activities (MedDRA) terms to report trial adverse events (supplementary appendix box 2). MedDRA is the international medical terminology developed under the guidance of the International Conference of Technical Requirements for Registration of Pharmaceuticals for Human Use.[43] Four authors (JDW, DC, KW, JSR) reviewed all adverse event listings and abstracted data from the adverse event tabulations to identify acute myocardial infarctions, heart failures, deaths from cardiovascular related cause, and deaths from non-cardiovascular related cause. Trials made available by GSK through CSDR were excluded if they did not report "high level" or "preferred" adverse event terms because our outcomes of interest could only be derived from their use.

Summary data

For trials for which IPD were not available, we focused on myocardial infarction and cardiovascular related deaths (determined by any cardiac cause, cerebrovascular disease, sudden death, cardiac arrest of unspecific origin, or peripheral artery disease) because of reporting limitations in publications and clinical study reports. We excluded articles that failed to mention a specific adverse event of interest and also those that did not disclose that serious adverse events were not observed. These exclusions applied unless additional information was provided by the corresponding authors, even though failure to mention a particular outcome does not necessarily imply that there were no such events in the study.

Assessment of risk of bias in included studies and validation

Two reviewers (JDW, ADZ) assessed the risk of bias based on the Cochrane Collaboration risk of bias assessment tool (supplementary appendix box 3). For validation, supplementary appendix tables 1 and 2 note the specific outcome classification for a subset of trials for which IPD were available that were also included in previously conducted meta-analyses.

Statistical analysis

We prespecified a series of two stage meta-analyses that account for different data sources and various analytical approaches because we combined results from trials with and without IPD (table 2). In the first stage, we calculated trial specific odds ratios or relative risks and their corresponding 95% confidence intervals. In the second stage, effect estimates from each individual trial were combined by fixed or random effects meta-analysis models. We also used Peto's method to pool odds ratios because this was the method reported in the original rosiglitazone meta-analysis.[5] Peto's method is often the standard method for meta-analyses with rare events and small intervention effects.[16 44] While this method does not require correction for trials in which one arm has no events (single zero event trials), the method performs best when event rates are low (<1%) and the treatment arm allocations are balanced.[45] Previous studies have noted that substantial imbalance exists in the number of patients in many of the rosiglitazone trials.[44] We then combined the results from each individual trial using conventional fixed (Mantel-Haenszel) or random (Dersimonian and Laird) effects methods (table 2). We repeated all analyses by including single zero event trials and trials with zero events in both arms (total zero event trials), and we applied two different continuity corrections: a constant continuity correction, which adds 0.5 to each cell in a 2×2 contingency table for the trials with at least one zero event; and a treatment arm continuity correction, when values proportionate to the reciprocal of the size of the opposite treatment group are added to each cell.

We considered four different combinations of data sources: IPD only; IPD and the RECORD study; IPD and the summary level data (clinical study reports, data from previous meta-analyses, and publications or ClinicalTrials.gov registrations); and IPD, the summary level data, and the RECORD study. Although the RECORD study included observational follow-up of a clinical trial, which fails to meet our prespecified inclusion criteria, RECORD data were used to inform the easing of restrictions of the rosiglitazone REMS and are therefore an important source of evidence.[11 21 46 47] Previous studies have noted that the Peto odds ratio is not recommended when there is substantial imbalance in the number of patients and inverse variance methods perform poorly when data are sparse.[16 44] Therefore, we focused our reporting on odds ratios by using a constant continuity correction of 0.5 and random effects weighting procedures. We assessed heterogeneity between trials by using the I^2 statistic.

Sensitivity analyses

A large number of approaches have been proposed to analyze sparse data in meta-analyses. We selected and prioritized the approaches that are most likely to be included in meta-analytical software and therefore used in future evaluations.[17 30 44 45 48 49] However, as suggested during peer review, we also evaluated whether one stage generalized fixed and random study specific models (the Simmonds and Higgins model with random study specific effects using the lme4 package in R) produced effect estimates and 95% confidence intervals that were consistent with the two

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Table 2 | Primary analytical methods, continuity corrections, assumptions, and outcomes

Method, measure, effect type, and data sources	Single zero event trials	Zero total event trials	Continuity correction	Assumptions to satisfy or difficulties to consider	Outcomes
Peto, odds ratio, fixed effect					
IPD only, IPD+RECORD, IPD+summary, IPD+summary+RECORD	Included	Excluded	None	Event rates <1%, balanced groups (treatment arms), small/moderate treatment effects	Analyses with IPD only: composite outcome, heart failure, myocardial infarction, cardiovascular related deaths, non-cardiovascular related deaths Analyses including summary data: myocardial infarction, cardiovascular related deaths
Mantel-Haenszel or Dersimonian and Laird (inverse variance), odds ratio or relative risk, fixed or random effects					
IPD only, IPD+RECORD, IPD+summary, IPD+summary+RECORD	Included	Excluded or Included	Constant continuity correction of 0.5 or treatment arm continuity correction	Sample must be "large" overall (crude totals across all studies need to be ≥5),[44] might perform comparably or better than Peto's method at even rates of 5-10%[44]	Analyses with IPD only: composite outcome, heart failure, myocardial infarction, cardiovascular related death, non-cardiovascular related deaths Analyses including summary data: myocardial infarction, cardiovascular related deaths

IPD=individual patient level data; RECORD=Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes study.

stage models.[50] One stage approaches have certain advantages, for example they do not require continuity corrections. However, simulations and evaluations suggest that one stage and two stage approaches can give similar results, and differences are often influenced by modeling assumptions.[51]

We also conducted four post hoc subgroup analyses (constant continuity correction of 0.5 and random effects weighting procedures), which included and excluded total zero event trials: indication (type 2 diabetes mellitus *v* other) for all outcomes; trial duration (<26 weeks, 26-48 weeks, >48 weeks); data source (IPD, clinical study reports, or previous meta-analyses *v* published articles or ClinicalTrials.gov registrations) for myocardial infarction and cardiovascular related deaths; and comparator (placebo, metformin, sulfonylureas *v* other) for all outcomes. Because of the large number of proposed analyses and our focus on evaluating the impact of using different data sources, regardless of trial size, and various statistical techniques, additional sensitivity analyses that excluded trials based on their risk of bias were outside the scope of this evaluation. As suggested during peer review, we investigated whether Hartung-Knapp confidence interval corrections would alter the conclusions of the primary meta-analyses for the composite outcome with constant continuity corrections. We assessed potential publication bias by generating funnel plots and using Egger's test for the analyses using odds ratios with constant continuity corrections.[52] All statistical analyses were performed by one reviewer (JDW) using the "meta" package in R (version 3.3) and verified by a second statistician (KW).

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results.

Results

Description of included studies

Of the 59 trials identified and requested from the GSK clinical trial registry database, 33 met the inclusion criteria and had IPD (n=34, including the RECORD study which contained observational follow-up data). We identified an additional 31 eligible trials included in previous meta-analyses (n=26),[5 21 38] on the GSK Study Register (n=4), and on ClinicalTrials.gov (n=1). Among the 4774 titles and abstracts identified through the literature search, 170 were excluded as duplicates, leaving 4604 for initial screening. We excluded 4331 during the initial screening based on the title and abstract. Among the remaining 273 records screened at the full text level, 193 were excluded, mostly because they represented multiple publications from the same trial, publications from trials for which we already had IPD or clinical study reports, or abstracts without data. We were left with 80 trials that met the initial inclusion criteria, potentially reported outcomes of interest, and which were not available on the GSK database (fig 1 and fig 2). Of these trials, we were able to obtain either myocardial infarction or cardiovascular related death event data for a total of 75 additional included trials.

Among the 33 trials for which IPD were available, there were a total of 21156 patients, over half of whom (11837, 56.0%) received rosiglitazone (dosages ranging from 2 to 8 mg each day). Although most trials enrolled patients with type 2 diabetes mellitus (25 of 33, 75.8%), eight (24.2%) focused on other non-FDA approved (off label) indications (two psoriasis, one rheumatoid arthritis, one atherosclerosis, and four Alzheimer's disease; supplementary appendix table 1). Among 11837 patients allocated to rosiglitazone treatment, there were 274 composite events (2.3%) and 147 myocardial infarctions (1.24%), 122 heart failures (1.03%), 15 cardiovascular related deaths (0.13%), and 22 non-cardiovascular related deaths (0.19%). Among 9319 patients allocated to comparator treatments, there were 219 composite events (2.4%) and 133 myocardial infarctions (1.4%), 80 heart failures (0.86%), 10 cardiovascular related deaths (0.11%), and 13 non-cardiovascular related deaths (0.14%; supplementary appendix table 2). Median trial duration was 24 weeks (interquartile range 24-52 weeks).

Among the 103 trials for which IPD were not available included in the meta-analyses for myocardial infarction, there were a total of 23683 patients, of which 12630 (53.3%) were randomized to rosiglitazone and 11053 (46.7%) to comparator arms. Approximately two thirds of the trials included adult patients with type 2 diabetes mellitus (69, 67.0%). Among the rosiglitazone and

comparator arms, there were 43 (0.34%) and 40 (0.36%) myocardial infarctions, respectively. Median duration was 26 weeks (interquartile range 26-52 weeks). Coincidentally, the same number of trials without IPD contributed to the meta-analyses for cardiovascular death. These trials included 22 772 patients, of which 12 183 (53.5%) were randomized to rosiglitazone and 10 589 (46.5%) to comparator arms. Most trials (71, 68.9%) enrolled patients with type 2 diabetes mellitus. Among the rosiglitazone and comparator arms, there were 26 (0.21%) and 20 (0.19%) cardiovascular related deaths, respectively (supplementary appendix table 2). Median trial duration was 26 weeks (interquartile range 26-52 weeks).

Comparing IPD and summary level data

We identified 29 trials for which IPD were available and that were included in previous meta-analyses using GSK's summary level data. Among these, three trials had the same number of myocardial infarction events reported in both sources and 23 trials had the same number of cardiovascular related deaths (supplementary appendix table 2). However, we identified more myocardial infarction events using IPD instead of summary level data for 26 trials, and more cardiovascular related deaths for one trial. The IPD contained fewer myocardial infarctions than reported through GSK's summary level data for only one trial, however fewer cardiovascular related deaths were reported for five trials. Finally, the IPD for the RECORD study contained more myocardial infarctions and fewer cardiovascular related deaths than reported in GSK's summary level data.

Meta-analyses

IPD trials

We found a 33% increased odds of a composite event (that is, myocardial infarction events, heart failure events, cardiovascular related deaths, and non-cardiovascular related deaths) among rosiglitazone arms compared with comparator arms (odds ratio 1.33, 95% confidence interval 1.09 to 1.61, P=0.005, I^2=0; 31 single zero event trials; random effects and continuity correction 0.5; table 3). The effect estimate and 95% confidence interval did not change when total zero event trials were included (1.33, 1.09 to 1.61, P=0.005, I^2=0; 33 total zero event trials; random effects and continuity correction 0.5; table 3). When each of the four outcomes was examined independently, the odds ratios were 1.17 (0.92 to 1.51, I^2=0; 30 single zero event trials; random effects and continuity correction 0.5; table 4) for myocardial infarction; 1.54 (1.14 to 2.09, P=0.005, I^2=0; 26 single zero event trials; random effects and continuity correction 0.5; table 5) for heart failure; 1.15 (0.55 to 2.41, I^2=0; 16 single zero event trials; random effects and continuity correction 0.5; table 6) for cardiovascular related death; and 1.18 (0.60 to 2.30, I^2=0; 16 single zero event trials; random effects and continuity correction 0.5; table 7) for non-cardiovascular related death. Although all effect estimates were attenuated towards the null when we included the RECORD trial and total zero event trials with 0.5 continuity corrections, effect estimates were consistently larger when we applied treatment arm continuity corrections.

Meta-analysis using all trials

Across all data sources, rosiglitazone was associated with a 9% increased odds of myocardial infarction (odds ratio 1.09, 95% confidence interval 0.88 to 1.35, I^2=0; 60 single zero event trials; random effects and continuity correction 0.5; table 4). When we considered all 136 trials (33 from IPD and 103 from clinical summary reports or previous meta-analyses, and publications or ClinicalTrials.gov registrations), including single zero event and total zero event trials, the odds ratio was 1.08 (0.89 to 1.31, I^2=0; 136 single zero event and zero total event trials; random effects and continuity correction 0.5; table 4). Rosiglitazone was associated with a 12% increased odds of cardiovascular related deaths (1.12, 0.72 to 1.74, I^2=0; 33 single zero event trials; random effects and continuity correction 0.5; table 6). Across all 136 single zero event and total zero event trials, we found no association between rosiglitazone and death from cardiovascular related causes (1.00, 0.74 to 1.33, I^2=0; 136 single zero event and zero total event trials; random effects and continuity correction 0.5; table 6). Similar to the analyses limited to IPD, effect estimates were larger (more harmful) when we applied treatment arm continuity corrections. Forest plots for the primary analyses are available online at https://osf.io/4yvp2/. All I^2 and τ^2 values were 0.0.

Sensitivity analyses

The effect estimates and 95% confidence intervals from one stage analyses were consistent with those from two stage analyses (table 8). We found no statistically significant differences in the post hoc subgroup analyses for indication (type 2 diabetes mellitus *v* other); trial duration (≤26 weeks, 26-48 weeks, >48 weeks); data source (IPD *v* other); or comparator (placebo, sulfonylureas, metformin *v* other; data available online at https://osf.io/4yvp2). Among the trials for which IPD and summary level data were available, effect estimates and 95% confidence intervals were broadly consistent, regardless of whether we used the IPD or summary level data, or which statistical approach was used (supplementary appendix tables 3 and 4).

When we limited our analyses to only include trials with IPD, we found visual and statistical evidence of asymmetry. However, when we considered all data sources, no visual asymmetry or statistical indication of publication bias was identified (funnel plots are available online at https://osf.io/4yvp2). Hartung-Knapp confidence interval corrections did not alter the conclusions of the primary meta-analyses for the composite outcome (supplementary appendix table 5).

Quality assessment

Among the 34 trials for which IPD were available (including the RECORD study), most had a low risk of

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Table 3 | Rosiglitazone meta-analyses for composite outcome

Method (fixed or random effects), and data sources	Single zero event trials	Zero total event trials	Continuity correction	Effect estimate (95% CI)	P value	No of trials
Peto (fixed)						
IPD only	Included	Excluded	None	OR 1.40 (1.16 to 1.69)	0.000	31
IPD+RECORD	Included	Excluded		OR 1.20 (1.06 to 1.36)	0.004	32
Mantel-Haenszel (fixed)						
IPD only	Included	Excluded	Constant continuity correction of 0.5	OR 1.39 (1.15 to 1.68)	0.001	31
				RR 1.37 (1.14 to 1.64)	0.001	31
IPD+RECORD	Included	Excluded		OR 1.20 (1.06 to 1.36)	0.005	32
				RR 1.17 (1.05 to 1.31)	0.005	32
IPD only	Included	Included		OR 1.39 (1.15 to 1.68)	0.001	33
				RR 1.36 (1.14 to 1.63)	0.001	33
IPD+RECORD	Included	Included		OR 1.20 (1.06 to 1.36)	0.005	34
				RR 1.17 (1.05 to 1.31)	0.005	34
Dersimonian and Laird (random)						
IPD only	Included	Excluded	Constant continuity correction of 0.5	OR 1.33 (1.09 to 1.61)	0.005	31
				RR 1.30 (1.08 to 1.56)	0.005	31
IPD+RECORD	Included	Excluded		OR 1.17 (1.03 to 1.33)	0.02	32
				RR 1.14 (1.02 to 1.28)	0.02	32
IPD only	Included	Included		OR 1.33 (1.09 to 1.61)	0.005	33
				RR 1.30 (1.08 to 1.56)	0.005	33
IPD+RECORD	Included	Included		OR 1.17 (1.03 to 1.33)	0.02	34
				RR 1.14 (1.02 to 1.28)	0.02	34
Mantel-Haenszel (fixed)						
IPD only	Included	Excluded	Treatment arm correction	OR 1.41 (1.16 to 1.70)	0.001	31
				RR 1.38 (1.15 to 1.65)	0.001	31
IPD+RECORD	Included	Excluded		OR 1.20 (1.06 to 1.36)	0.004	32
				RR 1.18 (1.05 to 1.32)	0.004	32
IPD only	Included	Included		OR 1.40 (1.16 to 1.70)	0.001	33
				RR 1.38 (1.15 to 1.65)	0.001	33
IPD+RECORD	Included	Included		OR 1.20 (1.06 to 1.36)	0.004	34
				RR 1.18 (1.05 to 1.32)	0.004	34
Dersimonian and Laird (random)						
IPD only	Included	Excluded	Treatment arm correction	OR 1.33 (1.09 to 1.61)	0.005	31
				RR 1.30 (1.08 to 1.56)	0.005	31
IPD+RECORD	Included	Excluded		OR 1.17 (1.03 to 1.33)	0.02	32
				RR 1.14 (1.02 to 1.28)	0.20	32
IPD only	Included	Included		OR 1.33 (1.09 to 1.61)	0.005	33
				RR 1.30 (1.08 to 1.56)	0.005	33
IPD+RECORD	Included	Included		OR 1.17 (1.03 to 1.33)	0.02	34
				RR 1.14 (1.02 to 1.28)	0.02	34

IPD=individual patient level data; OR=odds ratio; RECORD=Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes study; RR=relative risk.
For all analyses, numbers of composite events observed among the total population of patients were as follows: IPD only, rosiglitazone population: 274 events among 11 837 patients; IPD only, control population: 219 events among 9319 patients; RECORD, rosiglitazone population: 333 events among 2226 patients; RECORD, control population: 316 events among 2232 patients.

bias for sequence generation (33, 97.1%); allocation concealment (33, 97.1%); blinding of participants and personnel (30, 88.2%); blinding of outcome assessment (25, 73.5%); and reporting bias (33, 97.1%; supplementary appendix table 6). However, 30 (88.2%) had high or unclear risk of bias for incomplete outcome data. Among the 31 trials that had GSK summary level data, a ClinicalTrials.gov registration, or were included in previous meta-analyses, most had an unclear risk of bias for sequence generation (23, 74.2%); allocation concealment (24, 77.4%); blinding of participants and personnel (15, 48.4%); and blinding of outcome assessment (29, 93.5%). Eighteen (58.1%) had a high risk of bias for incomplete outcome data and 30 (96.7%) had a low risk of bias for reporting bias.

Finally, among the 75 articles (reporting on 76 trials) we identified through the literature search and for which summary data were available, 42 (56.0%), 50 (66.7%), 28 (37.3), 59 (78.7%), 22 (29.3%), and 62 (82.7%) had an unclear risk of bias for sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and reporting bias, respectively.

Discussion

We used multiple clinical trial data sources and different analytical methods in this comprehensive meta-analysis to evaluate the effect of rosiglitazone on cardiovascular risk and mortality. Among 33 trials for which IPD were available, we observed a 33% increased odds of a composite outcome (that is, myocardial infarction, heart failure, cardiovascular related deaths, and non-cardiovascular related deaths) among patients who received rosiglitazone compared with controls. However, this association was probably partly because of an increased risk of heart failure associated with rosiglitazone. Furthermore, the interpretation of rosiglitazone's cardiovascular

risk was complicated by different magnitudes of myocardial infarction risk, which were attenuated by combining summary level data with IPD.

Clarifying uncertainties about the cardiovascular risk of rosiglitazone

Although we observed that rosiglitazone use was associated with an increased cardiovascular risk of approximately 30% among trials for which IPD were available, this could partly be explained by a large increase in the number of heart failure events. This finding is consistent with a previous meta-analysis, which reported an increased risk of heart failure of nearly 70% among those who received rosiglitazone,[38] and is consistent with FDA warnings issued in 2001 and 2006.[3] However, since 2007, the controversy

Table 4 | Rosiglitazone meta-analyses for myocardial infarction

Method (fixed or random effects), and data sources	Single zero event trials	Zero total event trials	Continuity correction	Effect estimate (95% CI)	No of trials
Peto (fixed)					
IPD only	Included	Excluded	None	OR 1.30 (1.02 to 1.67)*	30
IPD+RECORD	Included	Excluded		OR 1.17 (0.99 to 1.38)	31
IPD+summary	Included	Excluded		OR 1.19 (0.96 to 1.48)	60
IPD+summary+RECORD	Included	Excluded		OR 1.13 (0.97 to 1.32)	61
Mantel-Haenszel (fixed)					
IPD only	Included	Excluded	Constant continuity correction of 0.5	OR 1.25 (0.99 to 1.60)	30
				RR 1.25 (0.99 to 1.58)	30
IPD+RECORD	Included	Excluded		OR 1.15 (0.98 to 1.36)	31
				RR 1.14 (0.98 to 1.33)	31
IPD+summary	Included	Excluded		OR 1.13 (0.92 to 1.39)	60
				RR 1.13 (0.92 to 1.38)	60
IPD+summary+RECORD	Included	Excluded		OR 1.10 (0.95 to 1.28)	61
				RR 1.10 (0.95 to 1.27)	61
IPD only	Included	Included		OR 1.25 (0.98 to 1.59)	33
				RR 1.24 (0.98 to 1.57)	33
IPD+RECORD	Included	Included		OR 1.15 (0.97 to 1.35)	34
				RR 1.14 (0.98 to 1.33)	34
IPD+summary	Included	Included		OR 1.11 (0.92 to 1.34)	136
				RR 1.11 (0.93 to 1.33)	136
IPD+summary+RECORD	Included	Included		OR 1.09 (0.95 to 1.26)	137
				RR 1.09 (0.95 to 1.25)	137
Dersimonian and Laird (random)					
IPD only	Included	Excluded	Constant continuity correction of 0.5	OR 1.17 (0.92 to 1.51)	30
				RR 1.16 (0.91 to 1.49)	30
IPD+RECORD	Included	Excluded		OR 1.11 (0.94 to 1.32)	31
				RR 1.10 (0.94 to 1.29)	31
IPD+summary	Included	Excluded		OR 1.09 (0.88 to 1.35)	60
				RR 1.09 (0.88 to 1.34)	60
IPD+summary+RECORD	Included	Excluded		OR 1.08 (0.92 to 1.26)	61
				RR 1.07 (0.92 to 1.24)	61
IPD only	Included	Included		OR 1.17 (0.91 to 1.51)	33
				RR 1.16 (0.91 to 1.48)	33
IPD+RECORD	Included	Included		OR 1.11 (0.94 to 1.31)	34
				RR 1.10 (0.94 to 1.29)	34
IPD+summary	Included	Included		OR 1.08 (0.89 to 1.31)	136
				RR 1.07 (0.89 to 1.30)	136
IPD+summary+RECORD	Included	Included		OR 1.07 (0.93 to 1.24)	137
				RR 1.07 (0.92 to 1.23)	137
Mantel-Haenszel (fixed)					
IPD only	Included	Excluded	Treatment arm correction	OR 1.29 (1.01 to 1.64)	30
				RR 1.28 (1.01 to 1.63)	30
IPD+RECORD	Included	Excluded		OR 1.16 (0.99 to 1.37)	31
				RR 1.15 (0.99 to 1.35)	31
IPD+summary	Included	Excluded		OR 1.17 (0.96 to 1.44)	60
				RR 1.17 (0.96 to 1.43)	60
IPD+summary+RECORD	Included	Excluded		OR 1.12 (0.97 to 1.31)	61
				RR 1.12 (0.97 to 1.29)	61
IPD only	Included	Included		OR 1.29 (1.01 to 1.64)	33
				RR 1.28 (1.01 to 1.62)	33
IPD+RECORD	Included	Included		OR 1.16 (0.99 to 1.37)	34
				RR 1.15 (0.99 to 1.35)	34
IPD+summary	Included	Included		OR 1.14 (0.95 to 1.38)	136
				RR 1.14 (0.95 to 1.37)	136
IPD+summary+RECORD	Included	Included		OR 1.11 (0.96 to 1.28)	137
				RR 1.11 (0.96 to 1.27)	137

Continued

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Table 4 | Continued

Method (fixed or random effects), and data sources	Single zero event trials	Zero total event trials	Continuity correction	Effect estimate (95% CI)	No of trials
Dersimonian and Laird (random)					
IPD only	Included	Excluded	Treatment arm correction	OR 1.18 (0.92 to 1.53)	30
				RR 1.17 (0.92 to 1.50)	30
IPD+RECORD	Included	Excluded		OR 1.12 (0.94 to 1.32)	31
				RR 1.11 (0.94 to 1.30)	31
IPD+summary	Included	Excluded		OR 1.10 (0.89 to 1.37)	60
				RR 1.10 (0.89 to 1.36)	60
IPD+summary+RECORD	Included	Excluded		OR 1.09 (0.92 to 1.27)	61
				RR 1.08 (0.93 to 1.25)	61
IPD only	Included	Included		OR 1.18 (0.92 to 1.52)	33
				RR 1.17 (0.91 to 1.50)	33
IPD+RECORD	Included	Included		OR 1.12 (0.94 to 1.32)	34
				RR 1.11 (0.94 to 1.30)	34
IPD+summary	Included	Included		OR 1.08 (0.89 to 1.32)	136
				RR 1.08 (0.89 to 1.31)	136
IPD+summary+RECORD	Included	Included		OR 1.08 (0.93 to 1.25)	137
				RR 1.07 (0.93 to 1.23)	137

IPD=individual patient level data; OR=odds ratio; RECORD=Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes study; RR=relative risk.
For all analyses, numbers of myocardial infarction events observed among total population of patients was as follows: IPD only, rosiglitazone population: 147 events among 11 837 patients; IPD only, control population: 133 events among 9319 patients; RECORD, rosiglitazone population: 167 events among 2226 patients; RECORD, control population: 158 events among 2232 patients; summary, rosiglitazone population: 43 events among 12 630 patients; summary, control population: 40 events among 11 053 patients.
*P=0.04; this was the only significant P value.

surrounding rosiglitazone has focused primarily on the possible increased risk of myocardial infarction. For instance, Nissen and colleagues reported 43% and 28% increased odds for myocardial infarction in their 2007 and 2010 meta-analyses, respectively.[5 21] Our analysis also suggests an increased risk of myocardial infarction, albeit with less certainty because the 95% confidence interval just crosses 1.0 in most of the analyses. Furthermore, across different analytic approaches, odds ratios ranged from 1.07 to 1.30, with the most attenuated estimates occurring by combining summary level data with IPD.

Clinical and regulatory implications

Given the large number of patients treated for diabetes, drugs with even modest cardiovascular risks can have major public health implications.[53] Almost 20 years after rosiglitazone was approved, uncertainties still exist among patients, clinicians, and policy makers about the effect of the drug on the risk of myocardial infarction. Consistent with previous studies,[5 21 38] our meta-analyses suggest modest increases in myocardial infarction risk. Rosiglitazone, which along with pioglitazone is one of two currently marketed thiazolidendiones in the US, has been suspended by the European Medicines Agency and is no longer recommended for use in the US.[15] In the US, pioglitazone, which has also been associated with an increased risk of heart failure, is the preferred treatment option.[15] According to the PROACTIVE (PROspective pioglitAzone Clinical Trial In macroVascular Events) trial, pioglitazone does not have the same cardiovascular risks as rosiglitazone.[54 55] Additionally, a recent meta-analysis of 16 observational studies found that rosiglitazone was associated with higher risk of congestive heart failure, myocardial infarction, and death compared with pioglitazone.[56]

Our study highlights the need for independent evidence assessment to promote transparency and ensure confidence in approved therapeutics, and postmarket surveillance that tracks known and unknown risks and benefits. As a result of the rosiglitazone controversy, the FDA issued guidance for industry in 2008 that outlined requirements for demonstrating the cardiovascular safety for new drugs developed for glycemic management in patients with type 2 diabetes.[34] In particular, the document states that new diabetes drugs should rule out cardiovascular risk by demonstrating an upper bound of the two sided 95% confidence interval for the risk ratio less than 1.8 before approval for the composite end point of major adverse cardiovascular events. For upper bounds between 1.3 and 1.8, FDA might require additional postapproval trials.[34] Across multiple cardiovascular outcomes, we found that most of the upper bounds observed in the meta-analyses were above 1.3.

However, restrictions for rosiglitazone have actually been eased since 2013. The FDA determined that REMS were no longer necessary and that the benefits of rosiglitazone outweighed the risk.[10] While evidence suggests that the 2008 FDA guidance has increased the amount of cardiovascular evidence generated, uncertainties remain about the design and timing of postapproval studies, and whether the information generated will be available to the public.[57] Furthermore, in 2018, a Endocrinologic and Metabolic Drugs Advisory Committee meeting discussed the value of FDA's 2008 guidance, including the upper bounds of the two sided 95% confidence interval for the estimated risk ratio before approval.[58] Whether any changes will be made as a result of the recommendations from the committee members is currently unclear.

Table 5 | Rosiglitazone meta-analyses for heart failure

Method (fixed or random effects), and data sources	Single zero event trials	Zero total event trials	Continuity correction	Effect estimate (95% CI)	P value	No of trials
Peto (fixed)						
IPD only	Included	Excluded	None	OR 1.66 (1.24 to 2.22)	0.001	26
IPD+RECORD	Included	Excluded		OR 1.80 (1.46 to 2.22)	0.000	27
Mantel-Haenszel (fixed)						
IPD only	Included	Excluded	Constant continuity correction of 0.5	OR 1.60 (1.20 to 2.14)	0.002	26
				RR 1.57 (1.18 to 2.08)	0.002	27
IPD+RECORD	Included	Excluded		OR 1.78 (1.44 to 2.20)	0.000	27
				RR 1.74 (1.42 to 2.14)	0.000	27
IPD only	Included	Included		OR 1.56 (1.17 to 2.07)	0.002	33
				RR 1.53 (1.16 to 2.02)	0.003	33
IPD+RECORD	Included	Included		OR 1.75 (1.42 to 2.16)	0.000	34
				RR 1.71 (1.40 to 2.10)	0.000	34
Dersimonian and Laird (random)						
IPD only	Included	Excluded	Constant continuity correction of 0.5	OR 1.54 (1.14 to 2.09)	0.005	26
				RR 1.52 (1.14 to 2.03)	0.004	26
IPD+RECORD	Included	Excluded		OR 1.75 (1.41 to 2.18)	0.000	27
				RR 1.72 (1.39 to 2.11)	0.000	27
IPD only	Included	Included		OR 1.50 (1.12 to 2.01)	0.007	33
				RR 1.48 (1.12 to 1.97)	0.006	33
IPD+RECORD	Included	Included		OR 1.72 (1.39 to 2.13)	0.000	34
				RR 1.69 (1.37 to 2.08)	0.000	34
Mantel-Haenszel (fixed)						
IPD only	Included	Excluded	Treatment arm correction	OR 1.65 (1.23 to 2.20)	0.001	26
				RR 1.61 (1.21 to 2.14)	0.001	26
IPD+RECORD	Included	Excluded		OR 1.81 (1.46 to 2.24)	0.000	27
				RR 1.77 (1.44 to 2.17)	0.000	27
IPD only	Included	Included		OR 1.62 (1.21 to 2.15)	0.001	33
				RR 1.59 (1.20 to 2.10)	0.001	33
IPD+RECORD	Included	Included		OR 1.79 (1.45 to 2.21)	0.000	34
				RR 1.75 (1.42 to 2.15)	0.000	34
Dersimonian and Laird (random)						
IPD only	Included	Excluded	Treatment arm correction	OR 1.58 (1.17 to 2.13)	0.003	26
				RR 1.55 (1.16 to 2.08)	0.003	26
IPD+RECORD	Included	Excluded		OR 1.77 (1.42 to 2.20)	0.000	27
				RR 1.73 (1.41 to 2.14)	0.000	27
IPD only	Included	Included		OR 1.55 (1.15 to 2.09)	0.004	33
				RR 1.53 (1.15 to 2.03)	0.004	33
IPD+RECORD	Included	Included		OR 1.75 (1.41 to 2.17)	0.000	34
				RR 1.72 (1.40 to 2.11)	0.000	34

IPD=individual patient level data; OR=odds ratio; RECORD=Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes study; RR=relative risk.
For all analyses, numbers of heart failure events observed among total population of patients was as follows: IPD only, rosiglitazone population: 122 events among 11 837 patients; IPD only, control population: 80 events among 9319 patients; RECORD, rosiglitazone population: 119 events among 2226 patients; RECORD, control population: 61 events among 2232 patients.

Promoting clinical trial transparency, data sharing initiatives, and role of IPD in meta-analyses of drug safety

Rosiglitazone provides an ideal case to assess the impact of using IPD for safety related meta-analyses that examine relatively rare adverse events. Previous studies have consistently observed incomplete safety reporting in randomized trials, with some estimates suggesting that less than 50% of randomized trials adequately report clinical adverse effects.[59] Furthermore, concerns have been raised about discrepancies in the reporting of outcomes across different sources of data,[37 42] with registries (eg, ClinicalTrials.gov) having poorer reporting quality than clinical summary reports.[60] Clinical summary reports provide detailed information on study design and outcomes, and are often believed to be sufficient for systematic reviews.[61] However, we identified more myocardial infarctions and fewer cardiovascular deaths in the IPD compared with the numbers previously reported based on clinical summary reports. Among 29 trials for which IPD were available and which were included in previous meta-analyses using GSK's summary level data, 26 had more identifiable myocardial infarctions and five had fewer cardiovascular related deaths in the IPD compared with the GSK summary level data. Before CSDR was introduced, IPD from rosiglitazone trials conducted by GSK were not available to researchers, and only certain stakeholders had access to the data. Therefore, previous meta-analyses of rosiglitazone safety might not have included the data necessary to accurately classify all adverse events. Our study suggests that when evaluating drug safety and performing meta-analyses focused on safety, IPD might be necessary to accurately classify all adverse events. By including these data in research, patients, clinicians, and researchers would be able to make more informed decisions about the safety of interventions.[25 62]

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Numerous initiatives to promote open science and foster clinical trial data sharing have been developed over the last few years.[25 31 32 63-67] In 2013, GSK launched CSDR, which contains over 1500 trials from more than a dozen major pharmaceutical companies, including Bayer, Novartis, and Roche.[33] Similarly, Supporting Open Access to Research, a partnership between Bristol-Myer Squibb and Duke Clinical Research Institute, provides access to Bristol-Myer Squibb trial data.[68] University based platforms also exist, including the Yale Open Data Access project, which has partnered with Johnson & Johnson, Medtronic, and SI-BONE.[32 69 70] These platforms ensure that all shared data are deidentified, and they also require requestors to prespecify their research questions and methods. Furthermore, they employ a

Table 6 | Rosiglitazone meta-analyses for cardiovascular related deaths

Method (fixed or random effects), and data sources	Single zero event trials	Zero total event trials	Continuity correction	Effect estimate (95% CI)	No of trials
Peto (fixed)					
IPD only	Included	Excluded	None	OR 1.34 (0.60 to 2.98)	15
IPD+RECORD	Included	Excluded		OR 1.11 (0.76 to 1.62)	16
IPD+summary	Included	Excluded		OR 1.23 (0.77 to 1.98)	33
IPD+summary+RECORD	Included	Excluded		OR 1.13 (0.82 to 1.55)	34
Mantel-Haenszel (fixed)					
IPD only	Included	Excluded	Constant continuity correction of 0.5	OR 1.13 (0.58 to 2.21)	15
				RR 1.13 (0.58 to 2.20)	15
IPD+RECORD	Included	Excluded		OR 1.07 (0.75 to 1.54)	16
				RR 1.07 (0.75 to 1.53)	16
IPD+summary	Included	Excluded		OR 1.10 (0.73 to 1.65)	33
				RR 1.09 (0.73 to 1.64)	33
IPD+summary+RECORD	Included	Excluded		OR 1.08 (0.80 to 1.44)	34
				RR 1.07 (0.80 to 1.44)	34
IPD only	Included	Included		OR 0.97 (0.56 to 1.66)	33
				RR 0.97 (0.57 to 1.65)	33
IPD+RECORD	Included	Included		OR 1.02 (0.73 to 1.42)	34
				RR 1.02 (0.73 to 1.41)	34
IPD+summary	Included	Included		OR 1.00 (0.75 to 1.32)	136
				RR 1.00 (0.76 to 1.32)	136
IPD+summary+RECORD	Included	Included		OR 1.01 (0.80 to 1.28)	137
				RR 1.01 (0.80 to 1.27)	137
Dersimonian and Laird (random)					
IPD only	Included	Excluded	Constant continuity correction of 0.5	OR 1.15 (0.55 to 2.41)	15
				RR 1.15 (0.55 to 2.39)	15
IPD+RECORD	Included	Excluded		OR 1.08 (0.64 to 1.56)	16
				RR 1.08 (0.75 to 1.55)	16
IPD+summary	Included	Excluded		OR 1.12 (0.72 to 1.74)	33
				RR 1.12 (0.72 to 1.73)	33
IPD+summary+RECORD	Included	Excluded		OR 1.08 (0.80 to 1.47)	34
				RR 1.08 (0.80 to 1.46)	34
IPD only	Included	Included		OR 0.95 (0.53 to 1.69)	33
				RR 0.95 (0.54 to 1.68)	33
IPD+RECORD	Included	Included		OR 1.01 (0.72 to 1.43)	34
				RR 1.01 (0.72 to 1.42)	34
IPD+summary	Included	Included		OR 1.00 (0.74 to 1.33)	136
				RR 1.00 (0.74 to 1.32)	136
IPD+summary+RECORD	Included	Included		OR 1.01 (0.79 to 1.29)	137
				RR 1.01 (0.80 to 1.28)	137
Mantel-Haenszel (fixed)					
IPD only	Included	Excluded	Treatment arm correction	OR 1.23 (0.62 to 2.42)	15
				RR 1.22 (0.62 to 2.42)	15
IPD+RECORD	Included	Excluded		OR 1.10 (0.77 to 1.58)	16
				RR 1.10 (0.77 to 1.57)	16
IPD+summary	Included	Excluded		OR 1.17 (0.77 to 1.77)	33
				RR 1.17 (0.77 to 1.77)	33
IPD+summary+RECORD	Included	Excluded		OR 1.11 (0.83 to 1.50)	34
				RR 1.11 (0.83 to 1.49)	34
IPD only	Included	Included		OR 1.15 (0.66 to 1.99)	33
				RR 1.14 (0.66 to 1.99)	33
IPD+RECORD	Included	Included		OR 1.09 (0.77 to 1.52)	34
				RR 1.08 (0.78 to 1.52)	34
IPD+summary	Included	Included		OR 1.08 (0.81 to 1.44)	136
				RR 1.08 (0.81 to 1.43)	136
IPD+summary+RECORD	Included	Included		OR 1.07 (0.84 to 1.36)	137
				RR 1.07 (0.85 to 1.35)	137

Continued

Table 6 | Continued

Method (fixed or random effects), and data sources	Single zero event trials	Zero total event trials	Continuity correction	Effect estimate (95% CI)	No of trials
Dersimonian and Laird (random)					
IPD only	Included	Excluded	Treatment arm correction	OR 1.26 (0.58 to 2.72)	15
				RR 1.26 (0.59 to 2.70)	15
IPD+RECORD	Included	Excluded		OR 1.10 (0.76 to 1.59)	16
				RR 1.10 (0.76 to 1.58)	16
IPD+summary	Included	Excluded		OR 1.19 (0.75 to 1.88)	33
				RR 1.18 (0.75 to 1.86)	33
IPD+summary+RECORD	Included	Excluded		OR 1.11 (0.82 to 1.52)	34
				RR 1.11 (0.82 to 1.51)	34
IPD only	Included	Included		OR 1.15 (0.63 to 2.10)	33
				RR 1.15 (0.63 to 2.09)	33
IPD+RECORD	Included	Included		OR 1.08 (0.77 to 1.54)	34
				RR 1.08 (0.77 to 1.53)	34
IPD+summary	Included	Included		OR 1.08 (0.80 to 1.45)	136
				RR 1.08 (0.80 to 1.45)	136
IPD+summary+RECORD	Included	Included		OR 1.07 (0.84 to 1.37)	137
				RR 1.07 (0.84 to 1.36)	137

IPD=individual patient level data; OR=odds ratio; RECORD=Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes study; RR=relative risk.
For all analyses, numbers of cardiovascular related deaths observed among total population of patients was as follows: IPD only, rosiglitazone population: 15 events among 11 837 patients; IPD only, control population: 10 events among 9319 patients; RECORD, rosiglitazone population: 44 events among 2226 patients; RECORD, control population: 42 events among 2232 patients; summary, rosiglitazone population: 26 events among 12 183 patients; summary, control population: 20 events among 10 589 patients.

"trusted intermediary" approach, with independent review committees screening detailed proposals and making data sharing decisions. While there has already been a rapid shift towards a data sharing and transparency culture, further opportunities exist for industry, funders, and researchers to facilitate clinical trial data sharing.

Determining whether analytical approaches alter conclusions of adverse event meta-analyses

In addition to the implications of using IPD compared with summary level data, our study suggests that various statistical methods used to account for sparse adverse event data in meta-analyses might not drastically alter interpretations about rosiglitazone's risk. Across all outcomes, when trials with zero events in both arms were included after adding 0.5, risk estimates were attenuated towards the null. When a treatment arm continuity correction was used, the risk estimates increased. However, all 95% confidence intervals were broadly consistent and crossed the null odds ratio value of 1.0. Currently, no consensus exists on whether zero total event trials should be included in meta-analyses. For instance, the Cochrane handbook states that "the standard practice in meta-analyses of odds ratios and risk ratios is to exclude studies from the meta-analysis when there are no events in both arms,"[71] because they do not contribute to the magnitude of effect.[72] However, some methodologists argue that zero event total trials should be included in meta-analyses of sparse data because they use all potential data, lead to more precise estimates, and can avoid overestimating treatment effects.[73]

While multiple methods and continuity correction factors can be included as sensitivity analyses, it is unclear which methods should be used across different situtations.[45] In our study, we prioritized odds ratio approximations including single zero event trials with a 0.5 constant continuity correction because this is the standard approach used in meta-analytical software. Meanwhile, Sweeting and colleagues recommend using a treatment arm continuity correction, which adds a factor of the reciprocal of the opposite treatment arm to the zero event cells instead of a constant continuity correction, especially when treatment groups are unbalanced.[45] Future meta-analyses that need to account for sparse data could benefit from performing multiple sensitivity analyses that compare the results across a number of commonly proposed methods. While these analyses might not always alter perceptions of safety, they could provide insight on the consistency of effect estimates.

For myocardial infarction and cardiovascular related deaths, effect estimates were attenuated towards the null when we included summary level data from publications, ClinicalTrials.gov, and clinical summary reports. Numerous study design characteristics exist that can potentially explain these results. Firstly, the meta-analysis by Nissen and colleagues in 2007, which resulted in an increased awareness of the risk of rosiglitazone, could have altered the types of patients who were recruited into subsequent trials, thereby minimizing potential cardiovascular adverse events.[5]

Secondly, different study design considerations in more recent trials, including treatment comparators, concurrent treatments, and patient populations, could have reduced the risk of adverse cardiovascular outcomes or minimized differences across the treatment arms. For instance, trials might have preferentially enrolled patients into rosiglitazone trials who were at lower cardiovascular risk. However, our post hoc subgroup analyses based on comparator type did not reveal any statistically significant interactions.

Thirdly, the studies for which IPD were not available were generally small, with high or unclear risk of

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Table 7 | Rosiglitazone meta-analyses for non-cardiovascular related deaths

Method (fixed or random effects), and data sources	Single zero event trials	Zero total event trials	Continuity correction	Effect estimate (95% CI)	No of trials
Peto (fixed)					
IPD only	Included	Excluded	None	OR 1.42 (0.72 to 2.81)	16
IPD+RECORD	Included	Excluded	None	OR 0.85 (0.66 to 1.10)	17
Mantel-Haenszel (fixed)					
IPD only	Included	Excluded	Constant continuity correction of 0.5	OR 1.18 (0.64 to 2.17)	16
				RR 1.18 (0.65 to 2.15)	16
IPD+RECORD	Included	Excluded		OR 0.84 (0.65 to 1.08)	17
				RR 0.84 (0.66 to 1.08)	17
IPD only	Included	Included		OR 1.04 (0.62 to 1.73)	33
				RR 1.04 (0.63 to 1.71)	33
IPD+RECORD	Included	Included		OR 0.83 (0.65 to 1.06)	34
				RR 0.84 (0.66 to 1.06)	34
Dersimonian and Laird (random)					
IPD only	Included	Excluded	Constant continuity correction of 0.5	OR 1.18 (0.60 to 2.30)	16
				RR 1.18 (0.61 to 2.28)	16
IPD+RECORD	Included	Excluded		OR 0.83 (0.64 to 1.07)	17
				RR 0.83 (0.65 to 1.07)	17
IPD only	Included	Included		OR 1.01 (0.58 to 1.74)	33
				RR 1.01 (0.59 to 1.74)	33
IPD+RECORD	Included	Included		OR 0.82 (0.64 to 1.05)	34
				RR 0.83 (0.65 to 1.05)	34
Mantel-Haenszel (fixed)					
IPD only	Included	Excluded	Treatment arm correction	OR 1.32 (0.71 to 2.45)	16
				RR 1.32 (0.71 to 2.44)	16
IPD+RECORD	Included	Excluded		OR 0.85 (0.66 to 1.10)	17
				RR 0.86 (0.67 to 1.10)	17
IPD only	Included	Included		OR 1.22 (0.73 to 2.06)	33
				RR 1.22 (0.73 to 2.05)	33
IPD+RECORD	Included	Included		OR 0.86 (0.67 to 1.10)	34
				RR 0.87 (0.68 to 1.10)	34
Dersimonian and Laird (random)					
IPD only	Included	Excluded	Treatment arm correction	OR 1.25 (0.63 to 2.50)	16
				RR 1.25 (0.63 to 2.48)	16
IPD+RECORD	Included	Excluded		OR 0.83 (0.64 to 1.08)	17
				RR 0.84 (0.65 to 1.07)	17
IPD only	Included	Included		OR 1.16 (0.66 to 2.04)	33
				RR 1.16 (0.66 to 2.03)	33
IPD+RECORD	Included	Included		OR 0.84 (0.65 to 1.08)	34
				RR 0.85 (0.66 to 1.08)	34

IPD=individual patient level data; OR=odds ratio; RECORD=Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes study; RR=relative risk.
For all analyses, numbers of non-cardiovascular related deaths observed among total population of patients was as follows: IPD only, rosiglitazone population: 22 events among 11 837 patients; IPD only, control population: 13 events among 9319 patients; RECORD, rosiglitazone population: 91 events among 2226 patients; RECORD, control population: 116 events among 2232 patients.

bias, which could have biased the results. Although FDA draft guidance for industry on performing meta-analysis of randomized trials to evaluate drug safety emphasized the importance of prioritizing trial quality over quantity,[74] it might not always be clear which, if any, study characteristics actually influence the results of a meta-analysis. Considering that we observed different results when including various data sources, our findings highlight the importance of presenting and discussing potential differences across all possible data sources.

Limitations

Analytical limitations

Firstly, we conducted a large number of prespecified analyses, and certain analyses had a relatively low number of events, which could have reduced the statistical power. Furthermore, the low number of events suggests that trials might have preferentially enrolled lower risk patients, the findings from which could be less generalizable to high risk patients treated in real world practice. Because multiple testing and lower power in meta-analyses can be problematic, we did not focus on statistical significance and presented the results from all analyses to minimize the risk of selective reporting. Secondly, and relatedly, our meta-analyses might also be limited by the designs of the trials. In particular, eligible trials were generally designed to evaluate short term efficacy, and not long term cardiovascular safety, and seemingly preferentially enrolled lower risk patients. Cardiovascular risk might not be evident with short term use, and our sample might not represent the true long term benefit-risk profile of rosiglitazone.

Thirdly, we selected only two commonly used continuity corrections to account for sparse data.

Table 8 | Rosiglitazone one stage meta-analyses

Outcome and data sources	Events/total population	Effect estimate (95% CI)	
		Fixed effect	Random study specific effects*
Composite outcome			
IPD	RSG: 274/11 837; control: 219/9319	1.39 (1.15 to 1.68)	1.39 (1.15 to 1.83)
Myocardial infarction			
IPD	RSG: 147/11 837; control: 133/9319	1.27 (1.00 to 1.64)	1.27 (1.00 to 1.92)
IPD+summary	RSG: 190/24 467; control: 173/20 372	1.20 (0.97 to 1.49)	1.20 (0.96 to 1.51)
Heart failure			
IPD	RSG: 122/11 837; control: 80/9319	1.64 (1.22 to 2.21)	1.64 (1.22 to 2.24)
Cardiovascular related deaths			
IPD	RSG: 15/11 837; control: 10/9319	1.25 (0.56 to 2.92)	1.25 (0.46 to 2.92)
IPD+summary	RSG: 41/24 020; control: 30/19 908	1.22 (0.76 to 1.98)	1.22 (0.74 to 1.98)
Non-cardiovascular related deaths			
IPD	RSG: 22/11 837; control: 13/9319	1.36 (0.69 to 2.84)	1.36 (0.61 to 2.83)

IPD=individual patient level data; RSG=rosiglitazone.
*Simmonds and Higgin's model with random study specific effects.

Although many other methods have been proposed, currently no consensus exists on whether or how meta-analysis should include information from trials with zero events in either one or all study arms.[44] Future evaluations could explore the impact of performing more advanced analyses that account for sparse data, such as Poisson or zero inflated negative binomial models.[17 49]

Fourthly, we abstracted and classified the adverse events across treatment arms and focused on comparing the results from different two stage meta-analytical approaches. Although we conducted a series of one stage sensitivity analyses, we did not conduct time to event analyses. There were a number of reasons for not conducting time to event analyses, which we discussed before conducting the study. Although IPD can be used to conduct time to event analyses, we would not have been able to synthesize the data from studies with and without IPD. Because the rosiglitazone trials were not specifically designed to evaluate long term safety, we did not believe that hazard ratios would be particularly informative. It is possible that analyses of hazard ratios could alter some of the observed estimates. However, summary odds ratios do not have an actual timepoint that they relate to, and when we conducted a series of post hoc subgroup analyses, we found no statistical difference between odds ratios across clinical trials categorized by treatment duration. Future evaluations could consider additional one stage and time to event analyses, with different model assumptions and adjustments for prognostic factors.

Finally, we did not analyze whether certain characteristics, including age, sex, and race, influenced study heterogeneity because these variables are difficult to adjust for when combining summary level and IPD data. With only five studies classified as having a low risk of bias, we were also unable to conduct additional sensitivity analyses that evaluated the impact of risk of bias.

Data source limitations

We only included published articles that mentioned specific adverse events of interest or disclosed that serious adverse events were not observed. Additionally, we did not request IPD from investigators of trials for which we had access to summary level data. IPD are commonly not made available for small, investigator initiated trials more than a decade old that are probably in older formats.[75] Although we contacted corresponding authors to clarify potential uncertainties, failure to mention a particular outcome does not necessarily imply that there were no such events in the study.[37] Furthermore, we could have missed certain adverse events, including those unreported by patients, clinicians, and trial authors, which increases the potential for publication and data availability biases. Trials for which IPD were available used different terminologies with different levels of specificity. Although multiple reviewers evaluated the lists of trial adverse events, it is possible that certain outcomes could have been misclassified or missed altogether. Finally, as noted earlier, our study could be limited by the quality of the individual studies, most of which did not have IPD available, had small sample sizes, and were classified as having a high risk of bias. Nevertheless, our results were consistent across many analyses that make use of different combinations of data sources.

Conclusion

When we limited our analysis to trials for which IPD were available, rosiglitazone use was associated with an increased cardiovascular risk, probably owing to heart failure events. However, clinical uncertainties about interpreting the cardiovascular risk of rosiglitazone might not be fully resolved because of different magnitudes of myocardial infarction risk that were attenuated when summary level data were used in addition to IPD. Different analytical approaches to account for sparse data did not alter the conclusions across analyses, however multiple sensitivity analyses provided insight into the consistency of effect estimates. Finally, among trials for which IPD were available, more myocardial infarctions and fewer cardiovascular deaths were reported in IPD compared with summary level data reported in publications, clinical summary reports,

and on ClinicalTrials.gov. This finding suggests that IPD might be necessary to accurately classify all adverse events when performing meta-analyses focused on safety.

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Data sharing: The summary level dataset will be made available through a publicly accessible repository on publication: https://osf.io/4yvp2/. Individual patient level data must be requested from GlaxoSmithKline through ClinicalStudyDataRequest.com

The lead authors (JDW and JSR) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant registered) have been explained.

Dissemination to participants and related patient and public communities: We will promote the dissemination of these results to the relevant patient communities; since no patients were recruited for this study, there are no plans to disseminate the results of the research to study participants.

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Web appendix: Supplementary appendix