REVIEW OF THE QUALITY OF OBSERVATIONAL STUDIES OF THE ASSOCIATION BETWEEN ROSIGLITAZONE AND ACUTE MYOCARDIAL INFARCTION

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ABSTRACT

Background
Following the publication of a meta-analysis reporting a risk of acute myocardial infarction (AMI) with rosiglitazone that led to severe restrictions being placed on its use, several observational studies of the association were reported. The lifting of restrictions in the United States in 2013 makes a review of these studies pertinent.

Objective
To evaluate the quality of population-based observational studies of the rosiglitazone-AMI association.

Methods
PubMed and Embase literature databases were searched for observational studies evaluating the association that were published between 2006 and 2010. Publications satisfying the inclusion criteria were reviewed using the Checklist for Retrospective Database Studies.

Results
Nineteen studies satisfied the inclusion criteria. Reasons for the research design and data source were absent or unclear in 18 (95%) and 16 (84%), respectively. Administrative data were used exclusively in 14 (74%). Baseline periods for prior diagnoses and medications varied widely. Reimbursement constraints on rosiglitazone use were reported in only seven studies (37%), although all were likely to have been impacted by them. What was being tested in half of the rosiglitazone treatment comparisons lacked specificity and clarity. All relied on risk ratios and, for 90% of the comparisons, the ratios were between 0.5 and two – a level at which residual confounding can lead to spurious significance.

Conclusion
Important deficiencies existed in the rosiglitazone studies suggesting that standards for methods and reporting of observational safety analyses need improvement. In particular, detailed clinical data should be included when the risk of confounding by indication is likely to be high.

Key Words: *Pharmacoepidemiology research; administrative data; confounding by indication; rosiglitazone; acute myocardial infarction*

Concerns about cardiovascular adverse events occurred soon after rosiglitazone was first marketed when an association with heart failure was reported in the early 2000s.[1,2] However, a watershed was reached with the publication in May 2007 of a meta-analysis of acute myocardial infarction (AMI) events reported in 42 randomized clinical trials that found a marginally significant odds ratio for AMI in rosiglitazone patients.[3] Although it received significant criticism,[4-10] the meta-analysis led to the discontinuation of rosiglitazone in Europe and severe restrictions on its use in the United States and Canada. Several population-based observational studies of the association between rosiglitazone and AMI were subsequently performed.

Increasing attention is being focused on "real-world" drug safety and effectiveness with initiatives in North America and Europe.[11-13] However, confounding is frequently a significant and uncontrolled problem in observational studies. The confounding factor is commonly the indication being treated because physicians prescribe drugs that they consider will be most effective for their patient's disease profile,[14-16] resulting in confounding by indication being intrinsic in observational studies of effectiveness. Similarly, confounding by indication is highly likely in safety studies where a potential adverse outcome is analogous to a lack of effectiveness. An example of this is a type 2 diabetic patient who has had the condition for several years and has poor glycemic control, which increases the risk of cardiovascular complications such as AMI.[17] The patient's condition requires second- or third-line therapy to try to achieve glycemic control. If the patient experiences an AMI, is it a result of the new drug or a part of the diabetes disease progression?

With the removal of restrictions on the use of rosiglitazone in the United States in November 2013,[18] a review of the population-based observational studies of the rosiglitazone-AMI association is appropriate. The objective of this work was to evaluate the quality of these studies, especially the suitability of the data, the comparisons investigated and the potential confounding variables included, which are key factors for a successful pharmacoepidemiology study[19] and important topics to be addressed in its reporting.[20-22]

METHODS

Systematic searches of the PubMed and Embase literature databases were performed, using the terms "rosiglitazone" and "myocardial infarction" or "coronary heart disease" or "coronary artery disease," for articles published in English between January 2006 and December 2010 (all the studies were known to have been published within this time frame). Each identified record was reviewed and selected if it appeared to be a population-based cohort or case-control observational study that assessed the rosiglitazone-AMI association. Full texts of the selected publications were obtained and their bibliographies scanned for additional reports that satisfied the inclusion criteria.

The Checklist for Retrospective Database Studies[23] developed by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) was used to evaluate the studies. The Checklist was chosen because it was available in 2003 before concerns were raised about an association between rosiglitazone and AMI and because it is straightforward to use, being written in the form of 27 questions that can be utilized by researchers to develop a study protocol and by decision makers to consider the appropriateness of the study methods and the use of the database. The questions encompass a wide range of issues including relevance, reliability and validity, eligibility determination, research design, treatment effects, sample selection, variable definitions, statistical analysis, generalizability and interpretation.

The Checklist questions were distilled into 15 items in five groups considered critical to examine:

1. *Data source*: (a) rationale for using the data source; (b) relevant reliability and validity assessments of the data source; (c) patient eligibility for drug coverage and prescribing or reimbursement limitations.
2. *Research design*: (a) rationale for and potential limitations of the research design; (b) appropriateness of treatment comparison groups, i.e. were patients in the study comparisons similar in the characteristics that would have caused them to receive the treatment?[24,25]
3. *Study population*: (a) study inclusion and exclusion criteria for treatment exposure and outcome, including baseline history and outcome periods; (b) operational definition of the outcome; (c) relevant sensitivity analyses.
4. *Statistical method*: (a) rationale for the analytical method; (b) inclusion of all relevant variables hypothesized to influence the study outcome, especially potential confounders; (c) assessment of the validity of the statistical assumptions; (d) adjustment for multiple statistical tests.
5. *Review of findings*: (a) assessment of possible alternative explanations for the findings; (b) statistical versus clinical significance including sample size; (c) generalizability of the results.

Information was abstracted from each publication and any online appendix on the 15 items and evaluated using a qualitative scale of "adequate," "unclear" or "absent" ("unclear" and "absent" were considered inadequate), except for items 3a, 3b, 3c, 4d, 5a and 5b which were assessed as "present" or "absent."

RESULTS

The literature searches identified 176 articles published between 2006 and 2010 which were screened for eligibility. The inclusion criteria were not satisfied for 148 articles (84%), which consisted of 115 reviews, editorials, commentaries, letters, news items or meta-analyses, 16 randomized trial reports, 15 laboratory or animal comparative studies, and 2 other publications. The review of the full texts of the remaining 28 studies identified 9 that were inappropriate because the outcome was not AMI (4), AMI was not analyzed as a separate diagnosis (3), or the study design was cross-sectional (2). Thus, 19 studies were included in the review (the final publication year of one study was 2011).[26-44] The bibliography scan found no additional studies that met the inclusion criteria. Five studies were sponsored or performed by staff of the manufacturers of rosiglitazone[26,30,31,40] and pioglitazone.[27]

Data Source

In 13 studies (68%), the design was a retrospective cohort, while the other 6 (32%) were nested case-control analyses (Table 1). In 14 studies (74%), the data source was exclusively administrative healthcare utilization data (AHUD): 9 used claims from US insurance schemes, 4 used claims from Canadian provincial health plans, and 1 used claims from the Taiwan National Health Insurance system. In the other 5 studies, four used electronic medical record systems from the United Kingdom, the United States and Israel, while the fifth used linked administrative and laboratory data that may have been part of an electronic medical record system but was not specified as such.

The rationale for the use of the data source was absent or unclear in 16 reports (84%). The other three gave an adequate reason beyond the fact that the data were accessible, such as the ability to include information in addition to AHUD, total population prescription coverage, or comprehensiveness of the system.[29,35,38] Although diagnostic reliability was considered in 15 reports (79%), the validity of the AMI diagnosis was examined by reviewing a sample of charts in only one.[42] In four others, a relevant article on AMI in the same database was cited.[29,39-41] The remaining 10 reports (53%) relied on the original data coder's recording accuracy, with seven citing articles that examined AMI in other databases[27,32,33,35,37,43] or an unrelated diagnosis[26] and three making unsupported claims.[28,30,31] Thus, in 74% of the studies, the consideration of diagnostic validity was assessed as inadequate.

Research Design

The rationale for and potential limitations of the research design were only touched upon in one study.[28] In general, the authors did not appear to consider this aspect to be of importance. The reason for the choice of a nested case-control design was not specified in any of the studies using this method, although all six were among the nine studies with the smallest numbers of rosiglitazone patients (Table 1). In addition, the choice of patient age criteria, which varied widely from only seniors through seniors and the middle-aged to all adults (no limit was reported in five studies), was only explained in the studies of seniors by the fact that drug coverage was limited to this group.

The type of patients included in the 19 studies varied considerably (Table 2). One study comprised newly diagnosed diabetics, two included new recipients of rosiglitazone and other oral anti-diabetic drugs and seven focused on a comparison of new use of rosiglitazone and pioglitazone in addition to existing therapy, while the patients in the other nine studies were current anti-diabetic drug recipients. Prior use of metformin, sulfonylureas and insulin by rosiglitazone patients was not reported in seven (37%), seven (37%) and four (21%) studies, respectively, and where use was reported, the proportion of rosiglitazone patients also receiving these drugs varied between 0% and 85% for metformin, 0% and 91% for sulfonylureas and 0% and 43% for insulin.

TABLE 1 Selected characteristics of the 19 rosiglitazone studies

Year	Study design	Exposure period	Country	Data resource	Data type	Age restriction	Rosiglitazone patients: Number	Rosiglitazone patients: Average age	Statistical analysis
McAfee et al[26]	RC	7/00-12/04	USA	i3 Innovus	A	≥18	12874	52	PSM/CPH
Gerrits et al[27]	RC	1/03-12/06	USA	i3 Innovus	A	≥45	15104	58	CPH
Lipscombe et al[28]	NCC	4/02-3/05	Canada	Province of Ontario	A	≥66	1886	73	CLR
Margolis et al[29]	RC	1/02-12/06	UK	THIN	EMR	≥40	7282	64	CPH
Walker et al[30]	RC	7/00-3/07	USA	PharMetrics	A	≥18	57381	52	PSM/CPH
Koro et al[31]	NCC	1/99-12/06	USA	IHCIS	A	Not reported	3839	56	CLR
Winkelmayer et al[32]	RC	1/99-12/05	USA	Medicare	A	≥66	14101	76	CPH
Stockl et al[33]	NCC	1/02-6/06	USA	Prescription Solutions	A	18-84	1039	73	CLR
Vanasse et al[34]	NCC	1/01-12/02	Canada	Province of Quebec	A	≥65	10911	75	CLR
Dormuth et al[35]	NCC	5/03-3/07	Canada	Province of British Columbia	A	Not reported	462	70	CLR
Habib et al[36]	RC	1/00-12/06	USA	Henry Ford Health System	A+L	>18	1363	58	PSM/CPH
Dore et al[37]	NCC	1/01-12/02	USA	Medicaid	A	Not reported	1636	65	CLR
Hsaio et al[38]	RC	3/01-12/05	Taiwan	National Health Insurance	A	Not reported	49624	55	CPH
Juurlink et al[39]	RC	4/02-3/08	Canada	Province of Ontario	A	≥66	16951	73	CPH
Ziyadeh et al[40]	RC	7/00-3/07	USA	i3 Innovus	A	≥18	47501	51	PSM/CPH
Tzoulaki et al[41]	RC	1/90-12/05	UK	GPRD	EMR	35-90	18082	65	CPH
Brownstein et al[42]	RC	1/00-12/06	USA	Partners Healthcare	EMR	>18	1879	64	GLM
Graham et al[43]	RC	7/06-6/09	USA	Medicare	A	≥65	67593	75	CPH
Loebstein et al[44]	RC	1/00-6/07	Israel	Maccabi Health Services	EMR	Not reported	3498	59	CPH

A: Administrative claims; CLR: Conditional logistic regression; CPH: Cox proportional hazard; EMR: Electronic medical record; GLM: Generalized linear modeling; GPRD: General Practice Research Database; IHCIS: Integrated Health Care Information Services; L: Laboratory data; NCC: Nested case-control; PSM: Propensity score matching; RC: Retrospective cohort; THIN: The Health Information Network

TABLE 2 Type of patients, drug coverage eligibility and reimbursement constraint reporting, and baseline use of metformin, sulfonylureas and insulin in the rosiglitazone patients in the 19 studies

Study	Type of patients	Drug coverage eligibility	Reimbursement constraint	Metformin (%)	Sulfonylureas (%)	Insulin (%)
McAfee et al[26]	New recipients of R, M, S, R+M, R+S, R+I or OAD+I	Adequate	*	0	0	0
Gerrits et al[27]	New recipients of R or P in current users of OADs[a]	Adequate	*	55	31	9
Lipscombe et al[28]	Current recipients of OADs	Adequate	Reported	*[b]	*[b]	*
Margolis et al[29]	Current recipients of OADs[a]	†	*	*[c]	*[c]	*[c]
Walker et al[30]	New recipients of R, P, M, S, R+M, R+S, P+M, P+S, M+S, R+I, P+I, M+I, S+I or OAD+I	†	*	0	0	0
Koro et al[31]	Current recipients of OADs	†	*	*	*	*
Winkelmayer et al[32]	New recipients of R or P in current users of OADs[a]	Adequate	Reported	33	56	17
Stockl et al[33]	Current recipients of OADs[a]	†	*	*	*	6
Vanasse et al[34]	Current recipients of OADs[a]	Adequate	*	*[d]	*[d]	*[d]
Dormuth et al[35]	New recipients of R, P or S in current users of M	Adequate	Reported	78	58	0
Habib et al[36]	New recipients of R or P in current users of OADs[a]	Adequate	Reported	76	77	43
Dore et al[37]	Current P or R use with M+S[a]	Adequate	Reported	*[d]	*[d]	*[d]
Hsaio et al[38]	Newly diagnosed diabetics receiving R, P, R+M, R+S, P+M, P+S, R+M+S or P+M+S	Adequate	Reported	85	91	0
Juurlink et al[39]	New recipients of R or P in current users of OADs	Adequate	*	81	69	0
Ziyadeh et al[40]	New recipients of R or P in current users of OADs[a]	†	*	56	34	1
Tzoulaki et al[41]	Current recipients of OADs	†	*	42	34	0
Brownstein et al[42]	Current recipients of OADs[a]	†	*	*	*	24
Graham et al[43]	New recipients of R or P in current users of OADs[a]	Adequate	*	49	48	14
Loebstein et al[44]	Current recipients of OADs[a]	†	Reported	79	90	7

I: Insulin; M: Metformin; OAD: Oral anti-diabetic; P: Pioglitazone; R: Rosiglitazone; S: Sulfonylurea
* Not reported; † Not reported or unclear
a: May also have received insulin; b: Only reported for all glitazone patients; c: Only reported for all study patients; d: Only reported for patients with acute myocardial infarction

Patient eligibility for drug coverage was considered to be reported adequately in 11 studies (58%), but this aspect was omitted or unclear in the others (Table 2). Only seven studies (37%) reported a formulary or reimbursement constraint on the treatment positioning of rosiglitazone.

Numerous treatment comparisons were tested in the 19 studies. However, only those that involved rosiglitazone were included in this analysis. Moreover, where a study provided the results of several models,[41] only the one with the highest level of adjustment was included. In addition, the results of sub-analyses by duration of exposure[29,31,33,35,37] or limited to new onset patients[29] were excluded. Forty-eight treatment comparisons involving rosiglitazone were tested in the studies, which were of two basic types: (a) rosiglitazone use compared with other oral anti-diabetic use and (b) rosiglitazone use compared with pioglitazone use. Half of the comparisons were specific (Table 3), while the other half were imprecise (Table 4) since "rosiglitazone patients" could also be recipients of unspecified other oral anti-diabetics and, in some cases, insulin. Furthermore, the comparison group was commonly undefined "other oral anti-diabetic use." Only six studies (32%) provided the 24 specific comparisons.[26,30,37,38,41,42] Statistical significance was achieved in five of these comparisons, which came from two studies with relatively small numbers of rosiglitazone patients,[38,42] one of which used an unusual statistical method that may have produced outcomes inconsistent with the other studies.[42] Both studies demonstrated an increased risk of AMI for rosiglitazone compared with metformin and one found an increased risk for rosiglitazone compared with sulfonylurea. In comparisons of rosiglitazone and pioglitazone, the same studies demonstrated an increased AMI risk for rosiglitazone and metformin compared with pioglitazone and metformin[38] and a decreased risk for rosiglitazone compared with pioglitazone.[42] Tables 3 and 4 also show that several comparisons had small numbers of patients (implying low statistical power) and a potential for differences between the drugs being due to comparing patients at varying stages in the progression of diabetes.

Comparing outcomes in patients exposed to rosiglitazone or pioglitazone is more appropriate since both were used as second- or third-line therapy. Table 5 shows the proportion of pioglitazone and rosiglitazone patients with baseline use of diabetes drugs and statins and with a prior history of relevant cardiovascular conditions from seven of the nine cohort studies in which a comparison was made between the two drugs (the information was not reported in the other two studies). While the characteristics were reasonably consistent within each study, there was wide variation between the studies that was not explained by the type of patients in the study (Table 1), their mean age, or the varying baseline periods for prior drug use or disease history (Table 6).

Study Population

The inclusion and exclusion criteria for AMI were considered to be reported adequately in 18 studies, with the diagnostic codes being reported in 13 (68%). However, the event that defined the outcome varied across hospitalization with AMI as the primary diagnosis, hospitalization with AMI as any diagnosis, hospitalization or emergency room attendance with a diagnosis of AMI, or any mention of AMI in the patient's record (Table 6).

The baseline period for prior diagnoses and medications was not explicitly defined in four studies (Table 6). In the other 15, the diagnosis baseline period varied between 3 and 60 months (most were 6 or 12 months), while the period for drug use ranged from 3 to 12 months (almost half the studies used a 6 month timeframe). The average or median follow-up period was reported in 9 studies and varied widely between 5 and 85 months.

TABLE 3 24 specific treatment comparisons of rosiglitazone with other anti-diabetic drugs, by mean age group from the 19 studies

Mean age	Comparison	Test statistic (95% CI)	Number of patients		Comment
			Group 1	Group 2	
≤60 years	R *v.* M	HR: 1.19 (0.84, 1.68)[26]	8977	8977	2nd/3rd *v.* 1st line therapy
	R *v.* M	HR: 1.05 (0.67, 1.66)[30]	12440	131075	2nd/3rd *v.* 1st line therapy
	R *v.* M	HR: 2.09 (1.36, 3.24)[38]	2093	46444	2nd/3rd *v.* 1st line therapy
	R *v.* S	HR: 0.79 (0.58, 1.07)[26]	8977	8977	2nd/3rd *v.* 1st line therapy
	R *v.* S	HR: 0.70 (0.46, 1.07)[30]	12440	48376	2nd/3rd *v.* 1st line therapy
	R *v.* S	HR: 1.49 (0.99, 2.24)[38]	2093	267754	2nd/3rd *v.* 1st line therapy
	R+M *v.* M+S	HR: 0.41 (0.16, 1.04)[26]	1362	1362	1st + 2nd/3rd *v.* 1st + 2nd line therapy. Small numbers of patients
	R+M *v.* M+S	HR: 0.91 (0.67, 1.22)[30]	26885	79004	1st + 2nd/3rd *v.* 1st + 2nd line therapy
	R+S *v.* M+S	HR: 1.45 (0.76, 2.75)[26]	1362	1362	1st + 2nd/3rd *v.* 1st + 2nd line therapy. Small numbers of patients
	R+S *v.* M+S	HR: 1.28 (0.88, 1.87)[30]	10021	79004	1st + 2nd/3rd *v.* 1st + 2nd line therapy
	R+I *v.* M+I	HR: 1.39 (0.96, 2.02)[30]	8035	21841	
	R+I *v.* S+I	HR: 1.01 (0.70, 1.46)[30]	8035	12147	
	R *v.* P	HR: 0.82 (0.49, 1.37)[30]	12440	16302	
	R+M *v.* P+M	HR: 1.38 (0.83, 2.29)[30]	26885	17282	
	P+M *v.* R+M	HR: 6.34 (1.80, 22.31)[38]	774	2408	Small numbers of patients may have led to significant result
	R+S *v.* P+S	HR: 1.05 (0.64, 1.70)[30]	10021	10133	
	P+S *v.* R+S	HR: 0.69 (0.30, 1.55)[38]	1231	5141	Small numbers of patients
	R+I *v.* P+I	HR: 1.41 (0.88, 2.27)[30]	8035	7924	
	P+M+S *v.* R+M+S	HR: 1.04 (0.73, 1.47)[38]	9510	39982	
>60 years	R *v.* M	HR: 0.79 (0.41, 1.53)[41]	8442	68181	2nd/3rd *v.* 1st line therapy
	R *v.* M	RR: 2.2 (1.6, 3.1)[42]	1879	12490	2nd/3rd *v.* 1st line therapy. Unusual analytical method may have led to significant result
	R *v.* S	RR: 1.3 (1.1, 1.6)[42]	1879	11200	2nd/3rd *v.* 1st line therapy. Unusual analytical method may have led to significant result
	R+M+S*v.* M+S	OR: 1.00 (0.72, 1.39)[37]	1636	NR	3rd *v.* 2nd line therapy
	R *v.* P	RR: 2.2 (1.5, 3.4)[42]	1879	806	Small numbers of patients. Unusual analytical method may have led to significant result

CI: Confidence interval; HR: Hazard ratio; M: Metformin; I: Insulin; NR: Not reported; OR: Odds ratio; P: Pioglitazone; R: Rosiglitazone; RR: Relative risk; S: Sulfonylurea

TABLE 4 24 non-specific treatment comparisons of rosiglitazone with other anti-diabetic drugs, by mean age group from the 19 studies

Mean age	Comparison	Test statistic (95% CI)	Number of patients		Comment
			Group 1	Group 2	
≤60 years	R[a] *v.* M[a]	HR: 1.13 (0.60, 2.12)[44]	745	11938	2nd/3rd *v.* 1st line therapy. Small number of R patients
	R[a] *v.* OOADs[b]	OR: 1.03 (0.93, 1.12)[31]	3839	19346	
	R[a] *v.* OOADs[b]	HR: 1.06 (0.66, 1.70)[36]	1056	14591	Small number of R patients
	R+M[a] *v.* M[a]	HR: 0.95 (0.51, 1.41)[44]	2753	11938	1st + 2nd/3rd *v.* 1st line therapy
	R+I *v.* OOADs+I	HR: 0.79 (0.46, 1.36)[26]	1173	1173	Small numbers of patients
	R+I *v.* OOADs+I	HR: 2.69 (0.64, 11.21)[30]	8035	1380	Small number of OOAD+I patients
	P[a] *v.* R[a]	HR: 0.78 (0.63, 0.96)[27]	14807	15104	
	R[b] *v.* P[b]	HR: 1.41 (1.13, 1.75)[40]	47510	47501	
>60 years	R[c] *v.* M[c]	RR: 2.4 (1.0, 4.2)[42]	1879	12490	2nd/3rd *v.* 1st line therapy. Small number of R patients
	R[c] *v.* S[c]	RR: 1.4 (1.0, 1.9)[42]	1879	11200	2nd/3rd *v.* 1st line therapy. Small number of R patients
	R+M[c] *v.* S+M[c]	OR: 0.90 (0.69, 1.17)[35]	4162	1612	1st + 2nd/3rd *v.* 2nd line therapy. Small number of S+M patients
	R[b] *v.* OOADs[b]	OR: 1.76 (1.27, 2.44)[28]	200	22046	Very small number of R patients. Large numbers of patients in one group does not compensate for low numbers in the other
	R[a] *v.* OOADs[b]	HR: 0.6 (0.5, 0.6)[29]	7282	NR	Difficult to assess reason for statistically significant protective effect result
	R[a] *v.* OOADs[b]	OR: 0.93 (0.72, 1.21)[33]	1039	7001	Small number of R patients
	R[a] *v.* OOADs[b]	HR: 1.41 (1.21, 1.65)[34]	3235	5190	
	R+OOADs *v.* M	HR: 0.82 (0.56, 1.20)[41]	9640	68181	Combination *v.* 1st line therapy
	R+OOADs[b] *v.* OOADs[b]	OR: 1.00 (0.87, 1.16)[28]	1686	22046	Small number of R+OOAD patients
	R[b] *v.* P[b]	HR: 1.14 (~0.6, >2.0[d])[41]	9640	3816	
	R[a] *v.* P[a]	IRR: 1.08 (0.93, 1.25)[32]	14101	14260	
	R[a] *v.* P[a]	HR: 1.06 (0.96, 1.18)[43]	67593	159978	
	P[b] *v.* R[b]	HR: 0.95 (0.81, 1.11)[39]	16951	22785	
	P[b] *v.* R[b]	RR: 2.0 (1.0, 4.2)[42]	808	1879	Small numbers of patients. Unusual analytical method
	P[a] *v.* R[a]	HR: 1.0 (0.8, 1.3)[29]	2244	7282	Small number of P patients
	R+M[b] *v.* P+M[b]	OR: 1.00 (0.67, 1.49)[35]	462	235	Very small numbers of patients

CI: Confidence interval; HR: Hazard ratio; IRR: Incidence rate ratio; M: Metformin; I: Insulin; OOAD: Other oral anti-diabetic; OR: Odds ratio; R: Rosiglitazone; RR: Relative risk; S: Sulfonylurea

a: May also have received other oral anti-diabetics and/or insulin; b: May also have received insulin; c: May also have received other oral anti-diabetics; d: Estimated

TABLE 5 History of use of selected drugs and cardiovascular conditions in seven studies comparing rosiglitazone and pioglitazone

Study	Gerrits et al[27]		Walker et al[30]		Winkelmayer et al[32]		Hsaio et al[38]		Juurlink et al[39]		Ziyadeh et al[40]		Graham et al[43]	
	R	P	R	P	R	P	R	P	R	P	R	P	R	P
	%	%	%	%	%	%	%	%	%	%	%	%	%	%
History of receipt of														
Metformin	55	42	47	34	33	33	85	86	81	81	56	55	49	52
Sulfonylureas	31	29	18	20	56	56	91	89	69	69	34	34	48	50
Other oral anti-diabetics	3	3	5	6	5	6	*	*	6	7	3	3	6	8
Insulin	9	9	14	15	17	18	*	*	0	0	1	1	14	14
Statins	35	40	38	42	9	10	12	13	72	72	38	38	57	59
History of														
Acute myocardial infarction	4	4	1	2	2	2	1	1	4	4	2	2	1	1
Heart failure	6	5	3	3	22	21	<1	<1	2	2	2	3	7	6
Hypertension	70	72	49	50	57	56	35	35	*	*	53	53	*	*
Hyperlipidemia	69	74	*	*	*	*	12	13	*	*	64	64	*	*

P: Pioglitazone; R: Rosiglitazone; * Not reported

TABLE 6 Definition of acute myocardial infarction in the rosiglitazone patients

Definition	Study	Baseline period (months) for: Prior diagnoses	Prior drug use	Average follow-up (months)
Primary diagnosis in a hospital record	Walker et al[30]	6	6	8
	Stockl et al[33]	12	12	Undefined
	Dormuth et al[35]	60	12	Undefined
	Dore et al[37]	6	6	Undefined
	Ziyadeh et al[40]	6	6	8
Any diagnosis in a hospital record	McAfee et al[26]	6	6	14
	Gerrits et al[27]	6	6	15
	Koro et al[31]	3	3	25
	Vanasse et al[34]	Undefined	Undefined	Undefined
	Habib et al[36]	12	6	Undefined
	Hsaio et al[38]	12	12	30
	Brownstein et al[42]	Undefined	Undefined	Undefined
	Graham et al[43]	12	6	5
Any diagnosis in a hospital or ER record	Lipscombe et al[28]	60	12	Undefined
	Juurlink et al[39]	60	12	10*
Any mention in a patient's record	Margolis et al[29]	Undefined	Undefined	Undefined
	Winkelmayer et al[32]	6	6	Undefined
	Tzoulaki et al[41]	Undefined	Undefined	85
	Loebstein et al[44]	6	6	Undefined

ER: Emergency room; * Median follow-up

TABLE 7 Principal baseline variables in the 19 studies available for confounding adjustment

Variable type	Measure	Reference 26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	Total (%)
Demographics/ health status	Age	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	19 (100.0)
	Gender	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	19 (100.0)
	Race							√				√	√					√	√		5 (26.3)
	Income*			√							√	√			√				√		5 (26.3)
	Obesity measure	√	√		√	√		√					√			√	√				8 (42.1)
	Smoking history	√	√		√	√							√			√	√				7 (36.8)
	Comorbidity index			√					√		√	√	√		√			√	√		8 (42.1)
	Other	√		√				√	√		√	√	√		√	√		√	√		11 (57.9)
Diabetes	Duration/diagnosis			√	√						√				√		√			√	6 (31.6)
	Complication/ emergency				√			√									√		√		4 (21.1)
Clinical measures	HbA1c				√							√					√	√		√	5 (26.3)
	Blood pressure				√												√				2 (10.5)
	Cholesterol											√					√			√	3 (15.8)
	Other				√							√					√	√			4 (21.1)
History of CV & other diseases	Angina	√	√	√	√	√			√		√	√	√	√	√	√		√			13 (68.4)
	Heart failure	√	√	√		√		√	√	√	√	√	√	√	√	√	√	√	√	√	17 (89.5)
	Other cardiac	√	√			√		√	√			√	√			√	√		√	√	11 (57.9)
	Stroke/TIA		√					√	√			√	√	√				√	√		8 (42.1)
	Hypertension	√	√			√	√	√	√				√	√		√		√		√	11 (57.9)
	Dyslipidemia	√	√			√	√						√	√		√		√			8 (42.1)
	Other CV							√	√	√		√					√		√		6 (31.6)
	Cardiac procedures	√	√	√	√	√		√			√	√	√	√	√	√	√	√	√		15 (78.9)
	Renal			√	√			√		√	√	√		√	√			√			9 (47.4)
	Other diseases			√	√			√	√	√	√	√	√	√	√			√			11 (57.9)
History of receipt of CV & other drugs	ACEI/ARB	√	√	√		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	18 (94.7)
	Beta-blocker	√	√	√		√	√	√	√		√	√	√	√	√	√		√	√		15 (78.9)
	CCB	√	√	√		√			√		√	√	√	√	√	√	√	√	√		15 (78.9)
	Diuretic	√	√	√		√	√		√		√	√	√	√	√	√	√	√	√		15 (78.9)
	Anti-cholesterol	√	√	√		√	√	√	√	√	√	√	√	√	√	√	√	√	√		17 (89.5)
	Nitrate	√	√			√	√	√	√				√		√	√	√		√		11 (57.9)
	Anti-platelet	√	√			√		√	√		√		√		√	√			√	√	11 (57.9)
	Other CV		√	√					√		√		√	√	√	√		√	√		10 (52.6)
	Other drugs		√	√					√	√	√		√	√	√		√				9 (47.4)

ACEI: Angiotensin converting-enzyme inhibitor; ARB: Angiotensin receptor blocker; CCB: Calcium channel blocker; CV: Cardiovascular; TIA: Transient ischemia attack; * Neighbourhood income

Statistical Method

Conditional logistic regression was used in the six nested case-control studies, while a Cox proportional hazard model was utilized in 12 of the 13 retrospective cohort analyses, four of which also employed propensity score matching (Table 1). The remaining cohort study employed an unusual approach using generalized linear modeling for the statistical analysis.[42] The rationale for the analytical method was addressed in only two studies.[28,42] Relevant sensitivity analyses performed to evaluate the validity of the model assumptions were reported in seven studies[28,32,36,37,39,41,43] and the authors of a further study confirmed their estimates using a different model.[29] Although multiple statistical tests were performed in some studies,[26,30,38,42] the potential need for significance level adjustment was considered only superficially in one.[36]

The principal variables reported as being available at baseline for matching or adjusting in the analysis as potential confounders are shown in Table 7. Because the majority of the studies used AHUD exclusively, few were able to include crucial measures such as diabetes severity, glycemic control, or blood pressure, which was considered to be inadequate. Three studies using AHUD included an assessment of diabetes duration which is not usually available in such data.[45] However, in two of these,[28,39] duration was measured in an extremely limited manner because it could only be categorized as <2, 2-5 and >5 years and, since 70-80% of the patients were in the latter group, the variable provided little differentiation.

Review of Study Findings

All the studies included some discussion of the limitations of their findings. In addition to diagnostic code validity, the main limitations considered were the possibility of residual confounding (15 studies; 79%) and the potential impact of the lack of clinical or laboratory data (nine of 14 studies without such data; 64%). The fact that prescribing and dispensing data are surrogates for patient drug use was mentioned in eight studies (42%) and just two drew attention to disease severity differences between the rosiglitazone patients and the other treatment groups, despite such differences occurring in at least nine studies.

Statistical versus clinical significance was not considered in any study report and statistical power was only assessed in three studies,[35-37] although, wide confidence intervals suggested that the power was low in several treatment comparisons. The authors of eight studies commented on the generalizability of their findings,[26,28,29,34,37,38,40,43] but only in the latter two was this considered to have been done adequately. Two reports[26,40] stated that the research complied with the Guidelines for Good Pharmaco-epidemiology Practices[46] and one study[36] indicated that it was reported in accordance with the Strengthening The Reporting of Observational Studies in Epidemiology principles.[21,22]

DISCUSSION

This analysis of 19 population-based observational studies of AMI in rosiglitazone patients was designed to examine their quality. The results reveal some critical deficiencies concerning the choice of data source, validity of the data, research design rationale, appropriateness of treatment comparisons, justification for baseline history and outcome time periods, evaluation of the statistical assumptions, consideration of statistical versus clinical significance, and assessment of possible alternative explanations for the findings.

Three-quarters of the studies used only AHUD. The use of AHUD in pharmaco-epidemiology research has increased dramatically over the past 25 years[47] such that they have been said to be the "state-of-the-art" in drug safety studies.[48] However, the lack of a rationale for the choice of the data source in the majority of the studies suggests that the use of AHUD was based on ease of access, which should not be the primary criterion for the use of a data source.[49] AHUD have numerous well-known limitations.[19,50-62] The validity of diagnostic information in these databases is always a concern and in many systems is variable or unknown.[43,55,57,63-66] Data from US health insurance claims appear to be especially prone to increased risks of false-positive "rule out" coding

and "up-coding" to increase reimbursement.[1,2,53,56,67,68] Only one study retrieved medical charts to evaluate diagnostic validity, in spite of such action being repeatedly recommended as necessary.[53-59,62,65,66] The rest relied on the accuracy of the coding of the diagnostic information in the original medical record, which is a risky assumption because there are several points between physician-patient interaction and computerized record where errors and inaccuracies can occur.[52,56,57,69] Some authors cited validation reports but, while relevant references may provide confidence in a study's results,[70] citing work using different data or unrelated diagnoses does not. It cannot be assumed that a diagnosis reliably recorded in one data system will be similarly recorded elsewhere or that all diagnostic codes in a system are reliable because a limited number have been demonstrated to be valid.

AHUD also have some significant pitfalls that are not always apparent. In particular, pharmaceutical insurance schemes in which drugs have restricted access based on clinical guidelines or reimbursement rules can lead to incomplete dispensing histories in AHUD due to patients obtaining drugs outside the plan.[36] This is especially of concern for the glitazones. For example, between 2000 and 2005 in Ontario, which had highly restrictive regulations for glitazone use,[71,72] 15-20% of seniors filled a prescription paid by a private insurer that was not recorded in the provincial drug plan database.[50] Other access issues can also prejudice the completeness and usefulness of AHUD for research, e.g. higher socioeconomic status patients who likely have better overall health are able to buy drugs that are not covered by their insurance but lower status patients with poorer health cannot afford to do so.[72-74]

The motivation for the study design was unspecified or unclear in every study. However, most likely because a new user design is a recommended method in observational research,[24,75] half of the studies focused on "new recipients" of rosiglitazone and pioglitazone, who were most frequently defined as patients with no prescription in a baseline period of six months. This time frame may be too short for drugs like rosiglitazone that is commonly a second- or third-line treatment so that the patients may not be true new recipients of the drug. Moreover, when a drug is positioned by clinical practice guidelines, formulary requirements[28,35,72-74] or higher copayments or deductibles[76] as a therapy for use later in the progression of a disease, the various clinical and bureaucratic pathways by which patients arrive at its use can introduce a significant degree of heterogeneity. Public and private health insurance schemes in North America have a plethora of limitations that affect patient access.[77-79] However, contrary to the ISPOR Checklist,[23] only seven studies (37%) reported a constraint on the use of rosiglitazone, although all were likely to have some restriction, and none addressed the potential implications of such limitations on their findings.[49,70]

In half of the rosiglitazone treatment comparisons, what was actually being tested lacked precision, which raises the question "were apples and oranges being compared?" A standard epidemiological principle is that comparisons should be made between patients who were similar in the characteristics that would have caused them to receive the treatment and in their likelihood of benefiting from the treatment.[24,25,70] However, this is not adhered to when patients who were exposed to rosiglitazone (many of whom may also have received other multiple specified and unspecified other oral anti-diabetics or insulin at varying rates of use) are compared with recipients of other oral anti-diabetics (often undefined and at differing rates of use) and possibly insulin. While this situation is representative of the real-world setting, it means that the results of such studies may be misleading and incomplete because use of other drugs for the condition varies widely between comparison groups and may be markers of underlying unmeasured diseases that differ between the groups, which are not adjusted for in the analyses.

This concern is further heightened by the fact that, despite being acknowledged in only a few studies, almost half had baseline data that suggested health differences between the comparison groups. For example, the rates of prior heart failure and renal disease in the rosiglitazone patients exceeded those in the

"control" patients in five and three studies, respectively.[28,32-35,37] This was particularly true in the case-control studies which had less control over patient group comparability. Adjustments for confounding should be included in the analysis,[80] but they are dependent upon all relevant variables being available, since none can be made for undetermined measures. When the risk of confounding by indication is high, it is crucial that as many relevant potential confounding variables as possible are adjusted for in observational studies.[15,16,20-22,81] Nevertheless, despite earlier reports of an increased risk of heart failure in rosiglitazone users[1,2] and the fact that half of the 19 studies evaluated heart failure in addition to AMI, none included an assessment of left ventricular ejection fraction or the New York Heart Association cardiac functional status as potential confounders.

The sole use of AHUD in three-quarters of the studies means that vital confounding variables, especially clinical information on the severity and duration of diabetes and relevant pre-existing cardiovascular conditions, were not available. The use of easily available surrogate measures from AHUD, particularly those using International Classification of Diseases codes,[82] does not compensate for a lack of appropriate clinical variables.[83]

The majority of the 19 studies used traditional statistical methods and, although six included relevant sensitivity analyses as recommended by experts[84,85] and best practice guidelines,[70,86,87] only one reported assessing the validity of the model assumptions (another recommended procedure[81]) by repeating the analysis using a different model. None employed a more innovative analytical method[14,88-90] of the sort that may be appropriate in settings where use of a therapy is influenced by prior drug use[91] or a design that can incorporate important external data into the model.[92,93] Moreover, only four (31%) of the 13 retrospective cohort studies employing Cox proportional hazards modeling used propensity score matching in the primary analysis which, for many, has become an accepted standard.[94]

The emphasis of the analyses of all the studies was on statistical, not clinical, significance. Statistical significance with tight confidence limits is not difficult to achieve with large patient numbers.[62,70] However, when a risk ratio is relatively close to one, whether statistically significant or not, it may have little clinical importance,[95] especially where the absolute risk is low. Attributable risk should be reported in addition to the risk ratio[96] but only one study did (the estimated excess risk of AMI attributable to rosiglitazone was 1.5 per 1,000 years).[43] Even with large numbers of patients, selection and information biases and residual confounding can lead to spurious significant results when an estimated risk ratio is between 0.5 and two.[97,98] Almost 90% of the estimates in Tables 3 and 4 fall into this category and some had relatively small numbers of patients. This issue was not addressed in any study.

Discussions around the limitations of the methods and findings were generally limited, e.g. in two-thirds of the studies using only AHUD, the authors simply noted that there may be residual confounding due to the lack of clinical data without attempting to assess the potential impact. This brevity may be due to space limitations enforced by the journals. High impact medical journals frequently impose word length restrictions, especially in the discussion section, which seems counter-intuitive as they should require authors to provide full details of the limitations and nuances of their work rather than constrain them.

The present analysis is not without limitations. It was performed by only one reviewer, albeit one with extensive experience in the use of AHUD in Canada and the United States.[47,52,57,61,77] It was not possible to engage a group of reviewers. In addition, some readers may have already made up their minds about the safety of rosiglitazone so that a review of this type may seem irrelevant.

The controversial meta-analysis, subsequent observational studies and ensuing regulatory restrictions placed on the use of rosiglitazone in North America had a major impact on patients. Rosiglitazone use declined dramatically,[99-101] which in some cases led to a reduction in glycemic control due to switching to less effective treatment or even discontinuation of

therapy.[102,103] The observational studies and other trials have provided limited support for the rosiglitazone-AMI association and, although rosiglitazone has other adverse effects,[104] it is now considered to be "relatively safe" from a cardiovascular perspective.[105]

Although based on only one drug-event association, this review has wider implications concerning how pharmacoepidemiology research is conducted, especially when the risk of confounding by indication is high. The rosiglitazone studies appear to be performed much the same as studies were in the previous decade, especially in those from North America. Guidelines[20-25,46,49,70,81,86,87,95] developed by regulatory organizations and scientific associations for the design, analysis and reporting of observational studies, many of which were available when the rosiglitazone studies were reported, appear to have had limited impact. One may argue that the researchers were doing the best they could with the resources and expertise available to them and that perfection is impossible. However, there was a rush of population-based observational studies evaluating the rosiglitazone-AMI association in some form in the 24 months after the publication of the meta-analysis in mid-2007 (almost 60% of the 19 studies were published in this period of which half were more rapidly performed nested case-control studies, more than 80% used only AHUD and, compared with studies published subsequently, several included relatively few covariates).

It is crucial that we do not settle for the status quo in population-based pharmaco-epidemiology research. Researchers should decide what data resources and analytical methods are required to answer their research question in a manner consistent with peer-developed scientific guidelines and not compromise on data or method to provide a rapid publication. In particular, AHUD should not be regarded as the universal resource for pharmacoepidemiology research regardless of their ability to answer the research question,[49] especially in situations where strong confounding by indication is highly likely and detailed clinical data are essential for adequate adjustment.

Disclaimer

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