SAFEGUARD

Cardiovascular Risk With Glitazones and Metformin:

Results From a Systematic Review of Observational Studies

Cristina Varas-Lorenzo,[1] Nuria Riera-Guardia,[1] Brian Calingaert,[2] Andrea V Margulis,[1] Manel Pladevall,[1] Miguel Gil,[3] Silvana Romio,[4,5] Miriam Sturkenboom,[5] Susana Perez-Gutthann[1]

[1]RTI Health Solutions, Barcelona, Spain; [2]RTI Health Solutions, Research Triangle Park, NC, United States; [3]Spanish Agency for Drugs and Medical Devices, Madrid, Spain; [4]University Milano-Bicocca, Milan, Italy; [5]Erasmus University Medical Center, Rotterdam, Netherlands

CONFLICT OF INTEREST STATEMENT

- The research leading to these results received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement number 282521—the SAFEGUARD project.
- RTI Health Solutions employees work on projects funded by pharmaceutical companies, including manufacturers of treatments for patients with diabetes. As employees of RTI Health Solutions, Manel Pladevall, Susana Perez-Gutthann, and Cristina Varas-Lorenzo also participate in advisory boards funded by pharmaceutical companies.

BACKGROUND

- The goal of the Safety Evaluation of Adverse Reactions in Diabetes (SAFEGUARD) project is to evaluate the cardiovascular (CV) and pancreatic safety of noninsulin glucose-lowering drugs in patients with type 2 diabetes mellitus (T2DM).
- Within the context of this project, one of the first steps was to systematically evaluate the available published scientific evidence on the CV safety of noninsulin glucose-lowering drugs in T2DM.

OBJECTIVE

- To systematically review published observational studies on the risk of acute myocardial infarction (AMI), stroke, heart failure (HF), and CV mortality in T2DM users of rosiglitazone or pioglitazone versus users of metformin.

METHODS

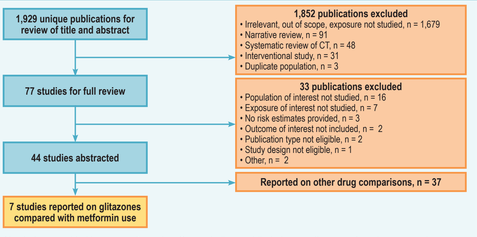
Eligible Studies for Meta-Analysis

- Types of studies: observational prospective, retrospective cohort, or case-control studies of noninsulin glucose-lowering drugs in patients with T2DM
- Period of publication: up to November 31, 2011
- Types of comparisons: risk of AMI, stroke, HF, or CV mortality in current users of rosiglitazone or pioglitazone compared with current users of metformin
- Adjusted for age and sex at a minimum

Literature Search and the Screening Process to Identify Studies for Meta-Analysis

- We searched Medline, Embase, and the Cochrane Library.
- Of 1,929 publications identified, 44 studies on CV events were selected and abstracted.
- Out of 44 studies, 7 reported on the risk of AMI or HF in users of rosiglitazone or pioglitazone compared with risk in users of metformin.[1-7] One study reported on the risk of stroke,[4] and no studies reported on CV mortality.
- Two investigators independently assessed the quality of each study using the RTI Item Bank,[8] and the discordances were solved by consensus. Quality also was assessed by applying the Newcastle-Ottawa Scale,[9] as recommended by the Cochrane Non-Randomised Studies Methods Working Group.

Figure 1. Flow Chart of Included Studies



No study was added by cross-referencing. Some studies contribute to more than one drug-drug comparison.

Meta-Analysis Methods

- Pooled estimates across studies of the comparison between "current use" of rosiglitazone or pioglitazone, as monotherapy or as an add-on or combined regimen, as defined in each study, and current use of metformin.
  - At least three available independent point estimates were required.
  - The following ad-hoc analyses were performed, as available in each study: pooled analyses for incident and prevalent cases combined (main analysis), incident cases only, prevalent and new users or new users only.
- Data were insufficient to estimate the pooled effects of the exposures of interest according to dose and duration.
- Relative risks (RR) across studies were estimated by random effect models using Review Manager (RevMan).[10]
- Heterogeneity between studies was assessed by graphical inspections of the forest plots, Cochran's χ^2 test of homogeneity, Tau^2 for random effect models, and I^2.
- Publication bias was examined by visual inspection of funnel plots.

RESULTS

Description of Eligible Studies for Pooled Analysis

- Seven studies were eligible for meta-analysis.[1-7]
- Two studies[1,2] reported some effect measures that could not be used because of incongruent estimates and 95% confidence intervals (CIs).
- All studies used a cohort design, with one performing a nested case-control analysis.[1] Only one study was restricted to first-ever events (Table 1).[7]
- Overall, the studies contributing to this comparison were of acceptable quality. However, the quality assessment indicated that three studies presented methodological issues that might have introduced bias in their results.[2-4]

Table 1. Main Characteristics of Published Studies on the Risk of AMI and/or HF Associated With Current Use of Glitazones Compared With Current Use of Metformin Use

First Author, Year	Source Population, Study Period	N, Age	Study Design and Endpoints	Case Validation	Exposure Assessment	Exposure Recency
Dormuth, 2009[1]	British Columbia Health Databases, Canada 1997-2007	11,147 Not reported	Nested case-control • Hospitalizations for fatal and nonfatal AMI	No	New users Dispensed prescriptions	Current, use in last 90 days
Loebstein, 2011[2]	Maccabi Healthcare Services, Israel 2000-2007	15,436 Mean = 59.1 years; SD = ± 11.4 years	Cohort • Fatal and nonfatal AMI • Fatal and nonfatal acute coronary syndrome • Fatal and nonfatal hospitalization for HF • All-cause mortality	No	Prevalent and new users Dispensed prescriptions	Current, use in last month
Brownstein, 2010[3]	Partners Healthcare System: Research Patient Data Registry, US 2000-2006	26,375 ≥ 18 years	Cohort • Hospitalization for fatal and nonfatal AMI	Yes	Prevalent and new users Prescriptions issued and dispensed	Current, use in last 6 months
Hsiao, 2009[4]	Taiwan Health Insurance Database 2001-2005	473,483 Not reported	Cohort • Fatal and nonfatal hospitalization for stroke • Fatal and nonfatal hospitalization for HF • Fatal and nonfatal hospitalization for AMI	No	New users Dispensed prescriptions	Use during study
Walker, 2008[5]	PharMetrics Integrated Outcomes Database, US 2000-2007	≈543,000 ≥ 18 years	Cohort • Hospitalization for fatal and nonfatal AMI	No	New users Dispensed prescriptions	Current, use at index date
McAfee, 2007[6]	Ingenix Research Database, US 2000-2004	33,363 ≥ 18 years	Cohort • Hospitalization for fatal and nonfatal AMI • Composite endpoint including AMI and coronary revascularization	External	New users Dispensed prescriptions	Current, use at index date
Tzoulaki, 2009[7]	GPRD, UK 1990-2005	91,521 35-90 years	Cohort, first ever • Fatal and nonfatal AMI • Fatal and nonfatal HF • All-cause mortality	External: AMI and congestive HF confirmed in 83%-90%	Prevalent and new users Prescriptions issued	Current, use at index date

GPRD = General Practice Research Database; SD = standard deviation; UK = United Kingdom; US = United States.

Meta-Analysis Results by Outcome

Acute Myocardial Infarction

Rosiglitazone Compared With Metformin (Figure 2 and Figure 3)

- The overall summary estimate (Figure 2) based on seven studies was 1.34 (95% CI, 1.01-1.77). There was an indication of strong heterogeneity when combining the seven studies.
  - Based on data from six studies, the summary RR of AMI for rosiglitazone monotherapy compared with metformin was 1.43 (95% CI, 0.98-2.08). Heterogeneity was present across the studies in this group (I^2 = 82%).
  - If rosiglitazone was added to a metformin-based regimen or combined with other T2DM drugs, the summary estimate was 1.12 (95% CI, 0.95-1.32), but this analysis included only two of the three studies that reported this subgroup analysis.
- In the analysis restricted to studies reporting the risk among new users (n = 4), the summary RR of AMI (Figure 3) was 1.29 (95% CI, 0.99-1.67). Heterogeneity, although present, was not strong. (I^2 = 55%).

Figure 2. Forest Plots of the RR of AMI in Users of Rosiglitazone Compared With the Risk in Users of Metformin, Results From Published Studies and Pooled Estimates by Random Effects

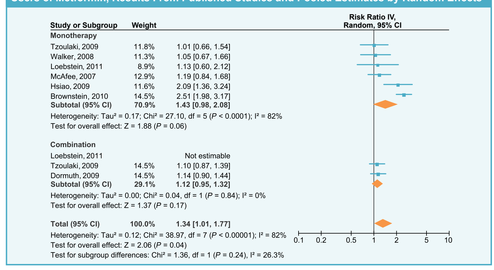


Figure 3. Forest Plots of the RR of AMI in New Users of Rosiglitazone Compared With the Risk in New Users of Metformin, Results From Published Studies and Pooled Estimates by Random Effects

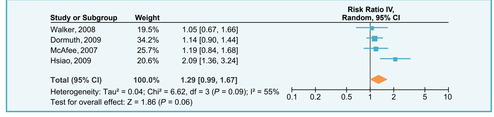
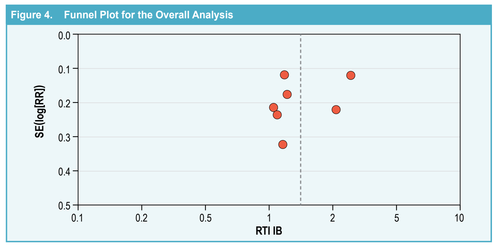


Figure 4 displays the funnel plot for the overall analysis. The RR of AMI for rosiglitazone versus metformin from each study is plotted on the horizontal axis, and an estimate of its precision, SE(log [RR]), on the vertical axis. The apex in the funnel plot for AMI is pointing up around an RR of 1.5, and the plot does not suggest publication bias.

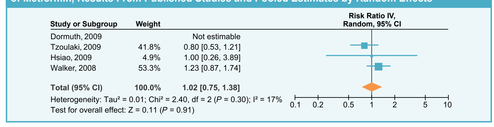
Figure 4. Funnel Plot for the Overall Analysis



Pioglitazone Compared With Metformin (Figure 5)

- Figure 5 displays the forest plot for the overall analysis without further stratification by type of regimen, based on the three studies (RR, 1.02; 95% CI, 0.75-1.38).
- For pioglitazone monotherapy compared with metformin, the summary RR was 1.21 (95% CI, 0.87-1.70), based on only two studies including new users (data not shown).

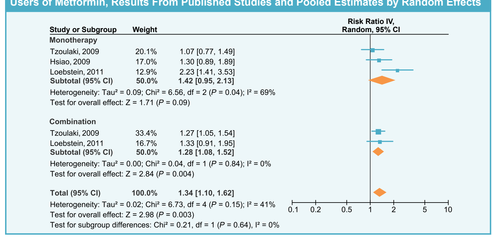
Figure 5. Forest Plots of the RR of AMI in Users of Pioglitazone Compared With the Risk in Users of Metformin, Results From Published Studies and Pooled Estimates by Random Effects



Heart Failure

- In the three identified studies, the summary RR (95% CI) for rosiglitazone, monotherapy or in combination with other noninsulin blood glucose-lowering agents, versus metformin was 1.34 (1.10-1.62) (Figure 6).
- Based on only two studies, the RR (95% CI) for pioglitazone versus metformin was 1.14 (0.86-1.50) (data not shown).

Figure 6. Forest Plots of the RR of HF in Users of Rosiglitazone Compared With the Risk in Users of Metformin, Results From Published Studies and Pooled Estimates by Random Effects



CONCLUSIONS

- Observational studies reporting on the risk of CV events associated with individual glitazones compared with metformin are scarce and heterogeneous. However, the evidence is compatible with an approximated 30% increase of either AMI or HF in rosiglitazone users as compared with metformin users. The evidence was most limited for pioglitazone users for both endpoints.
- Results of the large ongoing SAFEGUARD project will help elucidate the CV safety of these medications.

References & Related Abstracts Presented in This Conference

Please see handout for complete list.

CONTACT INFORMATION

Cristina Varas-Lorenzo, PhD, MD
Director, Epidemiology

RTI Health Solutions
Trav. Gracia 56 Ático 1
08006 Barcelona, Spain

Phone: +34 93 241 7761
Fax: +34 93 414 2610
E-mail: cvaras@rti.org

Presented at:
29th International Conference on Pharmacoepidemiology and Therapeutic Risk Management
August 25-28, 2013
Montreal, Canada

Project website: www.safeguard-diabetes.org

The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement nº 282521 - the SAFEGUARD project.