THE RISE AND FALL OF THE THIAZOLIDINEDIONES: IMPACT OF CLINICAL EVIDENCE PUBLICATION AND FORMULARY CHANGE ON THE PRESCRIPTION INCIDENCE OF THIAZOLIDINEDIONES

Salman Hashim[1], Tara Gomes[2,3], David Juurlink[2,4,5], Chelsea Hellings[2], Muhammad Mamdani[3,6,7]

[1]The Royal College of Surgeons Ireland; Toronto, Ontario, Canada; [2]The Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada; [3]Leslie Dan Faculty of Pharmacy, University of Toronto; [4]Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; [5]Medical Toxicologist for Ontario Poison Centre; [6]Applied Health Research Centre, St. Michael's Hospital, Toronto, Ontario, Canada; [7]Department of Health Policy, Management, and Evaluation, University of Toronto, Toronto, Ontario, Canada

Corresponding Author: ***mamdanim@smh.ca***

ABSTRACT

Background
Numerous factors affect drug utilization including clinical trials, promotional activity, drug safety signals and funding practices. We sought to investigate the impact of cardiovascular safety concerns and public drug formulary restrictions on the use of the thiazolidinediones (TZDs): rosiglitazone and pioglitazone.

Methods
We conducted a population-based cross-sectional time series analysis among more than 1.6 million older residents of Ontario, Canada using administrative healthcare claims databases from January 2000 to September 2010 to examine the impact of two events on the rate of initiation of TZDs among those aged 66 years and older: 1) the publication of a prominent meta-analysis suggesting cardiovascular harm for rosiglitazone, and 2) the introduction of prescribing restrictions for TZDs on the public formulary.

Results
Incident rosiglitazone prescribing decreased significantly from 5.32 to 0.44 prescriptions per 1,000 patients in the quarter following the publication of a meta-analysis, suggesting safety concerns for rosiglitazone ($p<0.01$). Similarly, incident pioglitazone prescribing continued to decline from 1.89 just prior to the publication of the meta-analysis to 0.53 prescriptions per 1,000 patients just prior to the policy implementation ($p<0.01$). Following the implementation of formulary restrictions for TZDs in Q2 of 2009, the rate of incident prescriptions for rosiglitazone fell further, from 0.20 prescriptions per 1,000 patients in the preceding quarter to 0.03 prescriptions per 1,000 patients in the subsequent quarter (Q3 of 2009; $p<0.01$). The rate of prescriptions dispensed for pioglitazone also decreased from 0.53 in Q1of 2009 to 0.11 prescriptions per 1,000 patients in Q3 of 2009 ($p <0.01$).

Conclusion
Both the publication of clinical evidence and drug policy changes can significantly influence the utilization of the TZDs.

Key Words: *Diabetes, drug utilization, drug policy, pharmacoepidemiology*

Drug prescribing is driven by a number of factors including clinical research supporting their efficacy and safety, cost, drug policy, and marketing.[1-3] Fueled by clinical trials demonstrating significant reductions in hemoglobin A1c (HbA1c)[4,5], thiazolidinedione drugs became popular for the treatment of type 2 diabetes. Subsequently, safety concerns[6] led to significant policy changes related to their use in some jurisdictions.[7] In a meta-analysis, Nissen and

Wolski[8] suggested an increased risk of myocardial infarction with rosiglitazone relative to placebo. This led to warnings and eventually restrictions on the use of rosiglitazone in the United States by the Food and Drug Administration.[9] Further, the European Medicines Agency has suspended use of this TZD in the European Union.[10] Conversely, pioglitazone is currently still available for the management of diabetes for the general public in both the US and the EU, although some payers limit reimbursement of these drugs on public formularies.[11] In Ontario, Canada, both rosiglitazone and pioglitazone were removed as unrestricted drug benefits on the public drug formulary in June 2009, and are currently only reimbursed on an 'as requested' basis among a select group of patients at low risk of adverse events.[12] While several studies have examined the impact of the safety warnings on the use of TZDs[13-19], none have examined the impact of both warnings and formulary changes on utilization.

The objective of this study was to determine the impact of safety signals and public drug formulary listing changes arising from academic publications on the incidence of thiazolidinedione treatment in Ontario, Canada.

DESIGN and METHODS

We conducted a population-based cross-sectional time series analysis using administrative healthcare databases covering more than 1.6 million adults aged 66 and older in Ontario, Canada. This population has universal access to hospital care, physicians' services, and prescription drugs on the public drug formulary. We divided the study period into quarterly intervals from January 1, 2000 to September 30, 2010. All TZD prescriptions dispensed over this period were identified using the Ontario Drug Benefit (ODB) database, which is an anonymized database containing all prescriptions dispensed to ODB eligible residents of Ontario in the community and long-term care settings and has an overall error rate of <1%.[20] Pioglitazone and rosiglitazone were approved for unrestricted use in October 2006 and January 2007, respectively, on the Ontario public formulary. Within each quarter, we identified new prescriptions for rosiglitazone and pioglitazone, defined as the first prescription for the drug over the study period, with no prescription in the 365 days prior. For each quarter we determined the incident prescribing rate by dividing the number of individuals newly dispensed either TZD (rosiglitazone or pioglitazone) by the total number of individuals alive and aged 66 or older at the beginning of the interval, using population census estimates.[21] Linear interpolation was used to generate quarterly denominators using annual population estimates.

We sought to determine the impact of two subsequent events on incident TZD use: 1) the publication of the Nissen study (June 14, 2007)[8], and 2) the restriction of TZDs to the OPDP's exceptional access program (June 1, 2009).[9] We applied interventional autoregressive integrated moving average (ARIMA) models to assess the impact of the above interventions on incident TZD utilization using SAS 9.2 (SAS, Cary, NC).[22] This study was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre, Toronto, Ontario.

RESULTS

Safety Warnings Published

Incident rosiglitazone prescriptions decreased significantly from 5.32 prescriptions per 1,000 patients to 0.44 prescriptions per 1,000 patients in the quarter following publication ($p<0.01$). Similarly, pioglitazone initiation continued to decline from 1.89 just prior to the publication of the Nissen study to 0.53 prescriptions per 1,000 patients just prior to the policy implementation ($p<0.01$).

Formulary Restrictions

As expected, incident pioglitazone and rosiglitazone prescriptions decreased substantially following the change in funding status of pioglitazone and rosiglitazone on the public formulary in the second quarter of 2009. Incident prescriptions of pioglitazone decreased nearly five-fold from 0.53 in the first quarter of 2009 to 0.11 prescriptions per 1,000 in the third quarter of 2009 just following its removal ($p <0.01$). The rate of incident prescriptions for rosiglitazone

decreased nearly 10-fold from 0.20 in the first quarter of 2009 to 0.03 prescriptions per 1,000 patients in the third quarter of 2009 just after its removal ($p<0.01$).

CONCLUSION

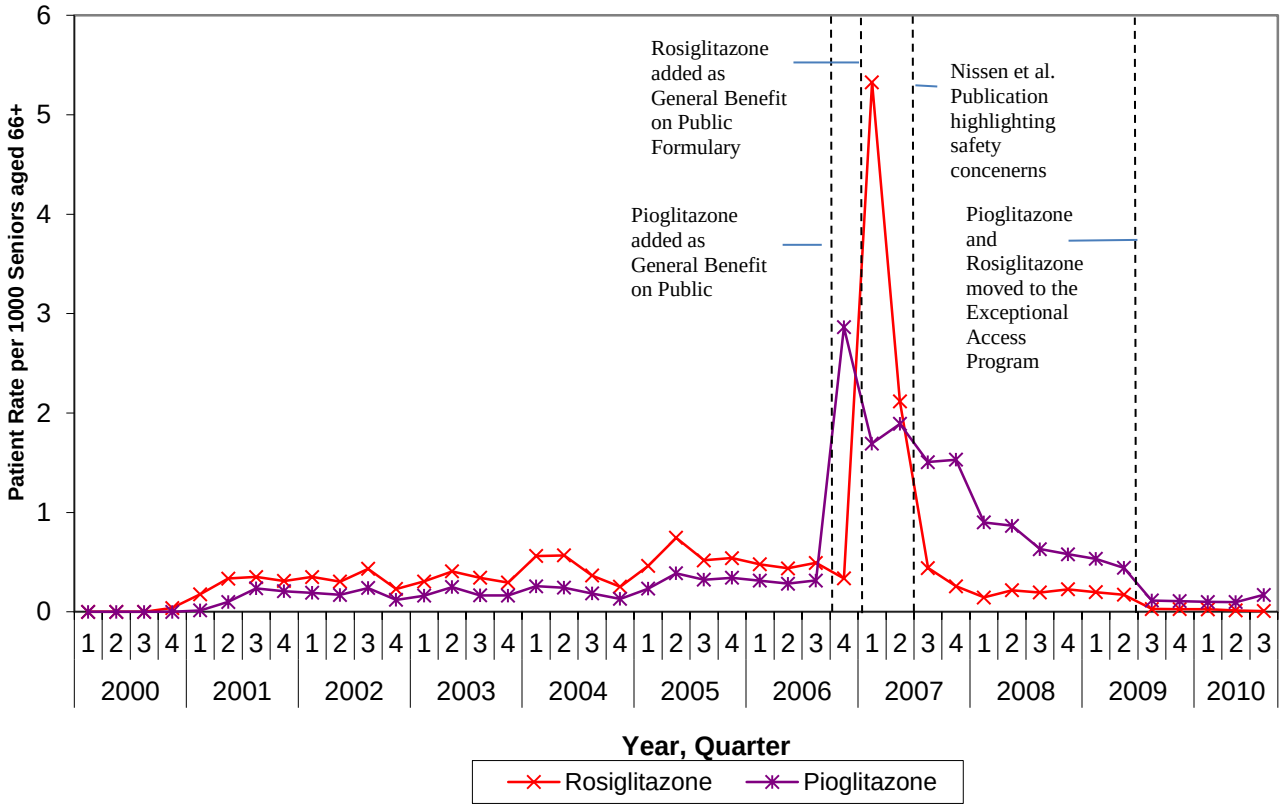
The incident use of the TZDs was significantly influenced by drug policy decisions as well as published evidence regarding their safety. These findings are consistent with those observed in previous studies studying the effects of formulary changes[23] as well as studies examining the effect of clinical evidence – particularly safety evidence – on drug utilization.[24-26] The impact of the Nissen study on pioglitazone initiation is unclear. Reliable statistical models could not be developed given the close temporality of events with respect to rosiglitazone approval and publication of the Nissen study. However, while the introduction of rosiglitazone impacted use of pioglitazone, the initiation of therapy with pioglitazone continued to decline significantly following publication of the Nissen study which focused exclusively on rosiglitazone. This may suggest a cautionary mindset of physicians by negatively grouping a class of drugs rather than treating two drugs differently in light of adverse effects shown by only one of those drugs.

Our study also suggests that the impact of high profile clinical evidence highlighting safety concerns may have significant effects on utilization independent of drug reimbursement decisions. This may indicate the vigilance of physicians regarding a relatively novel diabetes medication and any new data on its safety.

Several study limitations warrant discussion. This study was limited to elderly patients and publicly reimbursed prescriptions only. As a result, the generalizability of our findings to a younger population is unknown. A series of events that occurred in 2007, such as FDA safety alerts and black box warnings, as well as the introduction of novel diabetes therapies, may have had a cumulative influence on the decline of both TZDs. The influence of these events on our findings is uncertain. Lastly, the generic formulation of pioglitazone was available in Canada in November 2008, possibly contributing to a decline in pioglitazone use, since promotional efforts for branded products typically decline following generic drug availability. The impact of generic pioglitazone on our findings is unknown.

The findings of this study highlight the possible influences of clinical evidence and drug policy on the initiation of TZD therapy. Once drugs are approved for reimbursement, the clinical community may be particularly sensitive to safety concerns, especially when alternative therapies are available.

Figure 1: Trends in Diabetes TZD Therapy Incidence: 2000 to 2010



Acknowledgements

We thank Brogan Inc., Ottawa for use of their Drug Product and Therapeutic Class Database.

Conflicts of Interest

Over the past 3 years MMM has served on advisory boards for Hoffmann-La Roche, GlaxoSmithKlein, Pfizer, Novartis, Lilly, Astra Zeneca, BoehringerIngelheim, and Novo-Nordisk.

Funding Source

This study was supported by a grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC) Drug Innovation Fund and the Institute for Clinical Evaluative Sciences (ICES), a non-profit research institute sponsored by the Ontario MOHLTC. The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred.

REFERENCES

1. Stafford RS, Furberg CD, Finkelstein SN, Cockburn IM, Alehegn T, Ma J. Impact of clinical trial results on national trends in a-blocker prescribing, 1996–2002. JAMA 2004;291(1):54-62.
2. Goldman DP, Joyce GF, Zheng Y. Prescription drug cost sharing: associations with medication and medical utilization and spending and health. JAMA 2007;298.1:61-69.
3. Hollon MF. Direct-to-consumer marketing of prescription drugs. JAMA 1999;281.4:382-384.
4. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspectivepioglitAzone Clinical Trial In macroVascular Events): a randomized controlled trial. The Lancet 2005;366:1279-1289.
5. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006;355:2427-2443.

6. Hernandez AV, Usmani A, Rajamanickam A, Moheet A. Thiazolidinediones and risk of heart failure in patients with or at high risk of type 2 diabetes mellitus: a meta-analysis and meta-regression analysis of placebo-controlled randomized clinical trials. Am J Cardiovasc Drugs 2011;11(2):115-128.
7. Shah ND, Montori VM, Krumholz HM, Tu K, Alexander C, Jackevicius CA. Responding to an FDA warning- geographic variation in the use of rosiglitazone. N Engl J Med 2010;363:2081-2084.
8. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:2457-2471.
9. US Department of Health and Human Services: US Food and Drug Administration: FDA significantly restricts access to the diabetes drug Avandia [article online], 2010. Available from: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm226956.htm Accessed 30 March 2011
10. European Medicines Agency: Questions and answers on the suspension of rosiglitazone-containing medicines, Sept 2010. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2010/09/WC500097003.pdf
11. Ministry of Health and Long-Term Care: Change in Funding Status Rosiglitazone (Avandia®) and Pioglitazone (Actos® and Generics). Ontario Public Drug Programs.
12. Ministry of Health and Long-Term Care. Exceptional Access Program, Telephone Request Service: Reimbursement Criteria, Sept 2011. Available from: http://www.health.gov.on.ca/english/public/pub/drugs/trs/trs_guide.pdf
13. Starner CI, Schafer JA, Heaton AH, Gleason PP. Rosiglitazone and pioglitazone utilization from January 2007 through May 2008 associated with five risk-warning events. J Manag Care Pharm 2008; Jul-Aug;14(6):523-31.
14. Stewart KA, Natzke BM, Williams T, Granger E, Casscells SW, Croghan TW. Temporal trends in anti-diabetes drug use in TRICARE following safety warnings in 2007 about rosiglitazone. Pharmacoepidemiol Drug Saf 2009 Nov;18(11):1048-52.
15. Shi L, Zhao Y, Szymanski K, Yau L, Fonseca V. Impact of thiazolidinedione safety warnings on medication use patterns and glycemic control among veterans with diabetes mellitus. J Diabetes Complications 2011;May-Jun 25(3):143-50.
16. Jain R, Mullins CD, Lee H, Wong W. Use of rosiglitazone and pioglitazone immediately after the cardiovascular risk warnings. Res Social Adm Pharm 2012 Jan;8(1):47-59.
17. Morrow RL, Carney G, Wright JM, Bassett K, Sutherland J, Dormuth CR. Impact of rosiglitazone meta-analysis on use of glucose-lowering medications. Open Med 2010;4(1):e50-9.
18. Shah ND, Montori VM, Krumholz HM, Tu K, Alexander GC, Jackevicius CA. Responding to an FDA warning--geographic variation in the use of rosiglitazone. N Engl J Med 2010 Nov 25;363(22):2081-4.
19. Shah BR, Juurlink DN, Austin PC, Mamdani MM. New use of rosiglitazone decreased following publication of a meta-analysis suggesting harm. Diabet Med 2008 Jul;25(7):871-4.
20. Levy AR, O'Brien BJ, Sellors C, Grootendorst P, Willison D. Coding accuracy of administrative drug claims in the Ontario Drug Benefit database. Can J Clin Pharmacol 2003;10:67-71.
21. Statistics Canada. Percentage of the Population aged 65 years and over – Ontario Censuses, 2009. Available from:http://www12.statcan.gc.ca/census-recensement/2006/dp-pd/92-596/figure1.cfm?STID=203&Lang=eng&T=PR&PRCODE=35&GEOCODE=35&GEOLVL=PR&TID=0. Accessed on September 2011.
22. Pindyck RS, Rubinfeld DL. Econometric models and economic forecasts. Boston: Irwin/McGraw-Hill, 1998.
23. Huskamp HA, Deverka PA, Epstein AM, Epstein RS, McGuigan KA, Frank RG. The effect of incentive-based formularies on prescription-drug utilization and spending. N Engl J Med 2003;349:2224-2232.
24. Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the randomized aldactone evaluation study. N Engl J Med 2004;351(6):543-51.
25. Majumdar SR, McAlister FA, Soumerai SB. Synergy between publication and promotion: comparing adoption of new evidence in Canada and the United States. Am J Med 2003;115:467-72.
26. Beatriz CC, Rubinstein A. Influence of new evidence on prescription patterns. J Am Board Fam Pract 2002;15:457-62.