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ABSTRACT

Objective

To understand the independent role of thiazolidinediones (TZDs) in delaying progression to parenteral insulin therapy.

Design

Population-based prospective cohort study.

Setting

British Columbia, Canada.

Participants

18,867 Type 2 diabetes patients (mean age 58.9) treated with metformin as first-line therapy who then switched or added a TZD or sulfonylurea as second-line treatment between January 1, 1998 and March 31, 2008.

Outcome Measures

Multivariable Poisson regression models were used to estimate the effect of using TZD compared to sulfonylureas on time to initation of insulin treatment (third-line).

Results

The adjusted rate difference (RD) in women age >= 60 showed 1.18 fewer insulin initiation events per 100 person-years (PYs) in the TZD group versus the SU group (95% CI -2.05 to -0.32). Men in the same age group had 0.80 fewer insulin initiation events per 100 PYs in the TZD group versus the SU group (95% CI -1.51 to -0.08).

Conclusion

Second-line TZD therapy compared to second-line sulfonylurea therapy was associated with a lower incidence of insulin initiation as third-line treatment in patients with type-2 diabetes, with a mean delay of 90 days. This duration of delay must be weighed against the absence of serious morbidity or mortality benefit from TZDs and their known serious cardiovascular harm.

ARTICLE SUMMARY

Article focus

- Previous epidemiological studies indicate a greater delay in progression to insulin therapy in patients treated with metformin in combination with a thiazolidinedione (TZD) compared to those treated with sulfonylurea in combination with a TZD, although the magnitude of the delay is unknown.

- This study examines the incidence and magnitude of the delayed progression of insulin therapy in patients receiving second-line TZD treatment versus those receiving second-line sulfonylurea treatment.

Key messages

- Current treatment guidelines for T2DM in Canada recommend treatment options designed to attain specific target HbA1cs, a strategy weakly associated with morbidity and mortality evidence.
- Second-line TZD therapy compared to second-line sulfonylurea therapy was associated with a lower incidence of insulin initiation as third-line treatment in patients with T2DM, with a mean delay of 90 days.
- Despite these findings, further research is needed to assess the benefits and known cardiovascular risks of TZDs before using this therapeutic option to meet HbA1c goals.

Strengths and limitations of this study

- The comprehensive BC administrative health claims database rates relatively high in data quality.
- Baseline characteristics of the study cohorts indicate some imbalance in income and cardiovascular history which may indicate residual confounding.

- Due to BC PharmaCare's limited coverage reimbursement of TZDs versus full coverage of sulfonylureas, wealthier patients were more likely to pay out-of-pocket for TZDs than lower income patients.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a growing problem in North America,[1] affecting more than 250,000 individuals in British Columbia alone (5.6% of the population). Prescription drug treatment for T2DM is a substantial health care cost burden, especially as patients progress to treatment with insulin.[2] Recent studies found 25% of T2DM patients were prescribed insulin within 6 years of starting oral anti-diabetic drug therapy, rising to 42% after 10 years.[3,4] Current treatment guidelines for T2DM in Canada, which are not without controversy[5], recommend initiating metformin as first-line drug therapy based on a reduction in cardiovascular morbidity and mortality and adding oral anti-diabetic agents and eventually insulin to attain specific target HbA1cs, a strategy weakly associated with morbidity and mortality evidence.[6,7] From 1998 to 2007, approximately 80% of patients with T2DM in British Columbia started metformin as first-line drug therapy.[8]

Thiazolidinediones (TZDs) are a class of drugs that improve cell 'sensitivity' to endogenous insulin. Rosiglitazone and pioglitazone are two TZDs that have been shown to decrease fasting plasma glucose and HbA_{1c} levels in patients with T2DM.[9] Epidemiologic studies have reported a slower progression to insulin in patients receiving metformin in combination with a TZD compared with those receiving a sulfonylurea in combination with a TZD.[10] In a retrospective analysis of the Texas Medicaide database, Rascati et al compared 3 cohorts of

patients who received combination oral anti-diabetic therapy. They showed that patients in the sulfonylurea+TZD cohort had a 40% higher probability of more rapid progression to insulin (203/773) than patients who received combination metformin+TZD (85/438). Further research is needed to understand the magnitude of the delay to insulin initiation, particularly for newly diagnosed patients.

We investigated the association between insulin initiation in patients with T2DM and second-line treatment with rosiglitazone, pioglitazone or sulfonylureas in patients who initiated metformin as first-line pharmacotherapy. We required first-line metformin use as a way of controlling for confounding by indication. Similarly, we chose second-line sulfonylurea patients as a comparison group because the severity and course of their diabetes was expected to be similar to patients who were prescribed a TZD. Confounding by indication is one of the most widespread threats to validity in epidemiologic observational analysis[11], occurring when the exposure is associated with disease severity.

The ACCORD[12] and UGDP[13] trials found intensive hypoglycemic therapy attempting to achieve lower HbA1c levels is associated with an increase in morbidity and mortality. These studies highlight the importance of validating HbA1c targets in terms of serious morbidity and mortality before accepting them as treatment goals. This is particularly important with TZDs where there is a

paradoxical relationship between HbA1c which was significantly decreased while serious cardiovascular morbidity was significantly increased on rosiglitazone.[14]

We expected second-line rosiglitazone and pioglitazone to delay the use of insulin compared to second-line sulfonylureas, in patients with T2DM who initiated metformin as first-line therapy. However, the incidence and magnitude of that delay, especially in newly diagnosed patients, needs to be quantified to better weight that benefit versus known serious harm.

METHODS

Data

All prescriptions dispensed at community pharmacies in British Columbia since the autumn of 1995 are stored in a central database named PharmaNet. The system captures dispensing data and performs quality checks every time prescriptions are filled. It is believed those features keep underreporting and misclassification very low. Prescriptions are linked by unique personal health number to BC Ministry of Health databases for hospitalizations, medical services, and medical services registration. The Canadian Institute for Health Information collects hospital discharge records from all Canadian provinces, including Ontario where the data have been evaluated for accuracy.[15] Similar administrative claims databases in other North American jurisdictions have been studied for accuracy and completeness [16-19] but we are unaware of any such analyses in

British Columbia. We had ethics approval from the University of British Columbia Clinical Research Ethics Board (Certificate No. H02-70020).

Study Population

The source population for the study was all BC residents between January 1998 and March 2008 who were registered in the provincial universal medical services plan (MSP). Federally insured patients such as aboriginals, federal police officers and members of the armed forces and their families were excluded from the source population because we did not have permission to use those data. Excluded patients composed about 7% of the provincial population. The source population numbered 4.01 million in 2007.[20]

Study Design and Cohort

We conducted a prospective cohort study. We extracted patients from the source population who initiated metformin between January 1, 1998 and March 31, 2008 and then added or switched to a thiazolidinedione (rosiglitazone or pioglitazone) or a sulfonylurea (acetohexamide, chlorpropamide, gliclazide, glimepiride, glyburide, tolbutamide) as second-line therapy. We chose second-line sulfonylurea patients as a comparison group because the severity and course of their diabetes was expected to be most similar to other second-line patients who were prescribed a TZD instead. We assigned an index date equal to the first prescription dispensed date of a TZD or sulfonylurea.

Study Outcome

Our outcome was the occurrence of first insulin prescription after exposure to a TZD or sulfonylurea. The outcome was identified by the presence of a dispensing for insulin in the PharmaNet database. Patients were censored at the earliest occurrence of our study outcome, death, end of the study period (March 31, 2008), entry into a long-term care facility, emigration from BC, therapy discontinuation (no further prescriptions for 60 days after the end of a drug dispensing), or crossover to the other treatment arm.

Data Analysis

Multivariable Poisson regression models were used to estimate the effect of TZD therapy on initiation of insulin treatment compared to sulfonylureas. In three regressions with sulfonylurea patients as controls we estimated rates of insulin initiation, and adjusted rate ratios and rate differences for 3 contrasts with sulfonylurea patients: rosiglitazone (RSG), pioglitazone (PIO) and TZD (defined as rosiglitazone or pioglitazone). We constructed a cumulative hazard plot for insulin initiation in each exposure category. Rate differences per 100 person-years were calculated in 4 categories: Men, women, age >=60 and age < 60.

Confounders

Potential confounders were measured before exposure to an SU or TZD using diagnostic codes, procedure codes, prescription claim records, and Ministry of Health Services' patient demographic data. Our analysis included the following potential confounders: age (10-year age groups), sex, family income (quintiles), and index year of treatment initiation. The following covariates were included in the outcome model if within 5 years prior to index date: renal disease (ICD-9 584-586, 403-404), acute myocardial infarction (ICD-9 410 or 412), angina (ICD-9 411, 413), congestive heart failure (hospitalization for ICD-9 425, or 428, or a physician visit for same plus a prescription for furosemide), coronary artery bypass graft (hospitalization for procedure code 410), transient ischemic attack (hospitalization for ICD-9 435), coronary catheterization (hospitalization for procedure codes 4802 or 4803), and percutaneous transluminal coronary angioplasty (hospitalization for procedure codes 4892-4898, or 4995-4997). Prior use of the following covariates was included in the model if within 2 years of the index date: exposure to statins, digoxin, ACE Inhibitors, Cox-2 inhibitors, diuretics, clopidogrel, angiotensin-converting enzyme Inhibitors or angiotensin receptor blockers, spironolactone, or beta blockers. The following covariates were examined but excluded based on p-values greater than 0.2 in univariate tests: prior osteoarthritis (ICD-9 715), peripheral vascular disease (ICD-9 440-440.9), exposure to non-coxib NSAIDs, all NSAIDs, calcium channel blockers, metformin, benzodiazepines, and bisphosphonates.

Sensitivity Analysis

A sensitivity analysis was performed comparing the TZD cohort versus the sulfonylurea cohort using Schneeweiss et al's method of High Dimension Propensity Score (HDPS) comorbidity adjustment. The HDPS methods have been previously described here.[21] Poisson regression was used, adjusting for propensity score deciles.

Results

There were 21,230 patients from the source population who initiated metformin as first-line therapy and then added or switched to either an SU or TZD between January 1, 1998 and March 31, 2008. Of those, 18,867 patients (89%) remained eligible for cohort entry after excluding patients who were admitted to a long-term care facility (n=245), diagnosed with gestational diabetes in the previous 2 years (n=24), had invalid data for sex or date of birth (n=13), or had less than 2 years of provincial health plan coverage prior to index (n=2,098). In total, 2,363 distinct patients were excluded.

Characteristics of cohort patients are shown in **Table 1**. The patients in the study averaged 58.9 years old and TZD patients were 3.7 years younger on average than SU patients. The proportion of patients who were women was similar in all groups (SU 45%, Any TZD 45%, PIO 46%, ROS 45%). Income data was available for 87% of patients in the Any TZD cohort and for 81% of patients

in the SU cohort. 12% of patients in the Any TZD cohort were in the highest income, indicating that TZD patients earned significantly more than SU patients. Mean Romano comorbidity scores indicated that SU patients had slightly more comorbid disease (mean Romano score 1.75) compared to TZD patients (mean Romano score 1.42), however the median diabetes duration was 3 years in each of the four cohorts.

The SU group had higher rates of renal disease, acute myocardial infarction, angina, congestive heart failure, and coronary catherization, in the 5 year period prior to the index date, (absolute range 2–5% higher). Medication history was similar in all groups in the 2 year period prior to the index date. Pioglitazone (PIO) patients had a lower proportion of congestive heart failure (7.5) compared to Rosiglitazone (RSG) patients (9.4). Baseline characteristics were otherwise similar between RSG patients and PIO patients.

The cumulative hazard for starting insulin for SU patients at 12, 24, 36, and 48 months was approximately three times higher in the sulfonylurea group compared to TZD patients (Figure 1). The difference in the cumulative hazard distribution of insulin use between TZD and SU patients suggests the association is not modified over time and is amenable to modeling using Poisson regression.

Table 2 shows the number of events, person-years of follow-up, and event rates for insulin initiation in each of the treatment arms. We identified 563 total

events of insulin initiation in the cohorts during follow-up. The average time in days to initiation on insulin in the SU, RSG and PIO group was 343, 252 and 339, respectively. Average follow-up times were similar among treatment groups (0.90 years SU, 1.09 years TZD, 1.09 years RSG, and 1.04 years PIO).

The incidence rate among women was nearly 3 times higher in the SU group (4.21 events per 100 PYs) compared to PIO (1.42 events per 100 PYs), and was 2.7 times higher than the RSG group (1.56 events per 100 PYs). Men taking SUs were over 2.3 times more likely to initiate insulin than men prescribed TZDs (3.05 events per 100 PYs versus 1.30 events per 100 PYs, respectively).

Adjusted rate differences from our multivariable Poisson regressions for men and women by age group are shown in **Table 3**. The adjusted rate difference (RD) in women age >= 60 showed 1.18 fewer insulin initiation events per 100 person-years (PYs) in the TZD group versus the SU group (95% CI -2.05 to -0.32). Men in the same age group had 0.80 fewer insulin initiation events per 100 PYs in the TZD group versus the SU group (95% CI -1.51 to -0.08). In the under 60 age group, the adjusted RD per 100 PYs in women and men were -2.22 (95% CI -3.46 to -0.99) and -1.50 (95% CI -2.44 to -0.56), respectively, when comparing SU versus TZDs. When exposure to each thiazolidinediones was estimated separately, similar adjusted rate differences in both men and women and in both age groups were found.

The results of the HDPS sensitivity analysis showed a statistically significant 62% lower probability of insulin initiation in the TZD group compared to the sulfonylureas (adjusted HR, 0.38, 95% CI - 0.28 to 0.51). The c-statistic of the HDPS model discrimination was 0.72.

Discussion

This prospective cohort study followed T2DM patients who initiated metformin, then added or switched to second-line SU (n=15,613), second-line PIO (n=1,213), second-line ROS (n=2,041), or second-line PIO or ROS (n=3,254). We found a lower rate of insulin initiation in the PIO, ROS, and any TZD cohorts compared to SU for both men and women, age <60 and age >=60. The results were statistically significant for all comparisons except in men in the PIO versus SU comparison.

We chose second-line SU as our comparator as this cohort is similar in disease duration and severity to the second-line TZD cohorts. This study design minimizes the effect of channeling, a mechanism that leads to confounding by indication, where sicker patients are more likely to be early users of newer drugs. The expected effect of this bias is to increase the association between TZD exposure and insulin use, suggesting that any residual channeling lead to an underestimate of the true effects.

Insulin initiation events per 100 person years (PYs) are 3.57 for SU, 1.37 for TZDs, 1.36 for ROS, and 1.48 for PIO. Our insulin initiation event rates are lower than other studies have reported.[22,23] This is likely because we only include T2DM patients following metformin monotherapy. Other studies included TZDs as third line therapy who likely have a more advanced disease state and are more likely to initiate insulin sooner.

The clinical relevance of our finding, a 90 day delay in initiation of insulin, must be weighed against the growing body of evidence of increased risk of cardiovascular events associated with TZDs. A 2007 meta-analysis of randomized clinical trial data found a statistically significant 43% increase in risk of myocardial infarction (AMI) with rosiglitazone treatment compared to other oral antidiabetic therapies or placebo.[14] The RECORD trial found a 15% higher hazard ratio for AMI comparing rosiglitazone to a metformin/sulfonylurea combination, although the finding was statistically insignificant due to limited statistical power.[24,25] Several population level observational studies have shown that TZD treatment was associated with an increased risk of cardiovascular disease when compared with other oral anti-diabetic therapies.[26,27]

A significant strength of our study was the use of the BC PharmaNet database, which captured all oral anti-diabetic and insulin prescriptions dispensed at a

community pharmacy, regardless of insurance coverage or payer. The completeness of this database allowed for a study design with low misclassification of exposed patients and a high specificity and sensitivity of our outcome, third-line use of insulin.

Limitations

Our study has data limitations and interpretability issues that warrant discussion. As with most observational pharmaco-epidemiological studies, the use of administrative claims databases is subject to data quality issues. We have no reason to believe the quality of the BC administrative health claims database is of inferior data quality compared to similar administrative claims databases in other jurisdictions. The comprehensiveness of the database allows for generalizing results to a wide population.

Residual confounding is a limitation of our study due to its nonrandomized design. Baseline characteristics of the study cohorts indicate comparable diabetes duration, sex ratio, and drug use. The sulfonylurea cohort was older and had higher rates of renal disease and cardiovascular events in the previous 5 years. Family income was unbalanced at the extreme low and high ranges. In the sulfonylurea cohort, 23% were in the lowest income range ($0-$21,250) compared to 12% of the TZD cohort. The highest income range (> $97,500) contained 6% of the sulfonylurea cohort versus 12% of the TZD cohort. This

discrepancy is likely due to B.C. PharmaCare's limited coverage reimbursement of TZD's versus full coverage of sulfonylureas; wealthier patients were more likely to pay out-of-pocket for TZDs.

Conclusion

Our analysis showed second-line TZD therapy compared to second-line sulfonylurea therapy was associated with a lower incidence of insulin initiation as third-line treatment in patients with type-2 diabetes, with a mean of 90 days. This duration of delay must be weighed against the absence of morbidity and mortality benefit from TZDs and known serious cardiovascular risks.

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The study received ethics approval from the University of British Columbia (UBC CREB Number H02-70020). The BC Ministry of Health approved data access.

All authors substantially contributed to the conception, design, analysis and interpretation of data, drafting and revising the article for important intellectual content, and gave approval for the final version. Data analysis was performed by Carney, Dormuth.

Table Legend:

Table 1: Baseline Characteristics of Study Patients by Current Exposure to Thiazolidinediones or Sulfonylureas in British Columbia (1998-2007)

Table 2: Insulin Events with Thiazolidinediones or Sulfonylureas in Patients With Type II Diabetes Mellitus

Table 3: Poisson Regression for Insulin End Points Associated with Thiazolidinediones or Sulfonylureas in Patients With Type II Diabetes Mellitus

Figure Legend:

Figure 1: Cumulative Hazard Distribution for Time to Insulin End Points Associated with Thiazolidinediones or Sulfonylureas in Patients With Type II Diabetes Mellitus

Table 1. Baseline Characteristics of Study Patients by Current Exposure to Glitazones or Sulfonylureas

Variable	Sulfonylurea (N = 15,613)	Any TZD (N = 3,254)	Pioglitazone (N = 1,213)	Rosiglitazone (N = 2,041)
Age, median (IQR*)	60 (50,69)	56 (48,64)	56 (48,64)	56 (48,64)
Women (%)	6,952 (45)	1,479 (45)	556 (46)	923 (45)
Family Income (%)				
0 to $21,250	3,600 (23)	377 (12)	139 (11)	238 (12)
$21,251 to $45,000	4,211 (27)	783 (24)	288 (24)	495 (24)
$45,001 to $70,833	2,634 (17)	761 (23)	280 (23)	481 (24)
$70,834 to $97,500	1,260 (8)	511 (16)	178 (15)	333 (16)
> $97,500	935 (6)	393 (12)	149 (12)	244 (12)
Unknown	2,973 (19)	429 (13)	179 (15)	250 (12)
Romano comorbidity score, median (IQR) †	1.00 (1,3)	1.00 (1,2)	1.0 (1,2)	1.0 (1,2)
Diabetes duration in years, median (IQR)	3 (1,7)	3 (1,6)	3 (1,7)	3 (1,6)
Medical History				
Renal disease ‡	637 (4)	75 (2)	25 (2)	50 (2)
Acute myocardial infarction ‡	912 (6)	104 (3)	40 (3)	64 (3)
Angina ‡	3,693 (24)	639 (20)	241 (20)	398 (20)
Congestive heart failure ‡	2,211 (14)	282 (9)	91 (8)	191 (9)
Coronary catheterization ‡	1,024 (7)	176 (5)	70 (6)	106 (5)
Lab Tests in Past Two Years**				
HbA1c, n	14,525 (93)	3,057 (94)	1,124 (93)	1,933 (95)
HbA1c, median (IQR)	3 (2,5)	3 (2,5)	4 (2,6)	3 (2,5)
Fasting Blood Glucose, n	14,521 (93)	3,041 (93)	1,129 (93)	1,912 (94)
Fasting Blood Glucose, median (IQR)	3 (2,5)	3 (2,5)	3 (2,5)	3 (2,5)
Drug Use in Past Two Years §				
Metformin	15,393 (99)	3,211 (99)	1,193 (98)	2,018 (99)
ACE Inhibitor	6,923 (44)	1,448 (44)	531 (44)	917 (45)
Beta blockers	11,279 (72)	2,512 (77)	940 (77)	1,572 (77)
Calcium channel blockers	2,854 (18)	487 (15)	176 (15)	311 (15)
Coxib NSAIDs	1,260 (8)	334 (10)	111 (9)	223 (11)
NSAIDs	5,511 (35)	1,059 (33)	394 (32)	665 (33)
Digoxin	609 (4)	63 (2)	18 (1)	45 (2)
Spironolactone	609 (4)	100 (3)	36 (3)	64 (3)
Statins	6,682 (43)	1,475 (45)	544 (45)	931 (46)

¶ Net family income in Canadian dollars from the most recent income tax return (1 Canadian dollar ~ 1 US dollar).
† Romano commorbidity score calculated using data one year prior to the index date.
‡ History within five years prior to the index date.
\ Dispensing of drug within 730 days prior to index date.
* IQR refers to the interquartile range.
** MSP fee items used - HbA1c: 91745, Fasting Blood Glucose: 91705-91710, 91715-91717, 91719

Table 2: Insulin Initiation Events with Thiazolidinediones (TZDs) or Sulfonylureas in Patients With Type II Diabetes Mellitus

Sex	Drug Group	Person Years of Follow-up	Insulin Initiation Events	Events per 100 PYs
Men	Sulfonylurea	7,879	240	3.05
	TZDs	2,005	26	1.30
	Rosiglitazone	1,250	15	1.20
	Pioglitazone	722	11	1.52
Women	Sulfonylurea	6,491	273	4.21
	TZDs	1,633	24	1.47
	Rosiglitazone	1,027	16	1.56
	Pioglitazone	562	8	1.42
Men and Women	Sulfonylurea	14,369	513	3.57
	TZDs	3,638	50	1.37
	Rosiglitazone	2,277	31	1.36
	Pioglitazone	1,285	19	1.48

Table 3. Poisson Regression for Insulin Initiation Events Associated with Thiazolidinediones (TZDs) or Sulfonylureas (SU) in Patients With Type II Diabetes Mellitus

	TZDs vs Sulfonylureas				
Cohort	Crude Rate in TZD Group per 100 PYs	Crude Rate in SU Group per 100 PYs	TZD PYs of Follow-up	Crude Rate Ratio	Adjusted Rate Difference per 100 PYs (95% CI)
Men, age >=60	0.54	2.35	734	0.23	-0.80 (-1.51 - -0.08)
Men, age <60	1.73	3.75	1,271	0.46	-1.50 (-2.44 - -0.56)
Women, age >=60	0.76	2.75	656	0.28	-1.18 (-2.05 - -0.32)
Women, age <60	1.94	5.91	977	0.33	-2.22 (-3.46 - -0.99)
	Pioglitazone (PIO) vs Sulfonylureas				
Cohort	Crude Rate in PIO Group per 100 PYs	Crude Rate in SU Group per 100 PYs	PIO PYs of Follow-up	Crude Rate Ratio	Adjusted Rate Difference per 100 PYs (95% CI)
Men, age >=60	0.77	2.35	260	0.33	-0.73 (-1.9 - 0.43)
Men, age <60	1.92	3.75	469	0.51	-1.37 (-2.76 - 0.02)
Women, age >=60	0.42	2.75	240	0.15	-1.09 (-2.08 - -0.11)
Women, age <60	2.05	5.91	341	0.35	-2.04 (-3.79 - -0.29)
	Rosiglitazone (ROS) vs Sulfonylureas				
Cohort	Crude Rate in ROS Group per 100 PYs	Crude Rate in SU Group per 100 PYs	ROS PYs of Follow-up	Crude Rate Ratio	Adjusted Rate Difference per 100 PYs (95% CI)
Men, age >=60	0.42	2.35	474	0.18	-0.81 (-1.57 - -0.06)
Men, age <60	1.62	3.75	802	0.43	-1.52 (-2.59 - -0.45)
Women, age >=60	0.96	2.75	415	0.35	-1.21 (-2.31 - -0.12)
Women, age <60	1.89	5.91	636	0.32	-2.27 (-3.65 - -0.89)

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Contributorship Statement

- All authors substantially contributed to the conception, design, analysis and interpretation of data, drafting and revising the article for important intellectual content, and gave approval for the final version. Data analysis was performed by Carney, Dormuth.

Competing Statement

- No, there are no competing interests

Data Sharing Statement

- Statistical code available from the corresponding author at greg.carney@ti.ubc.ca.

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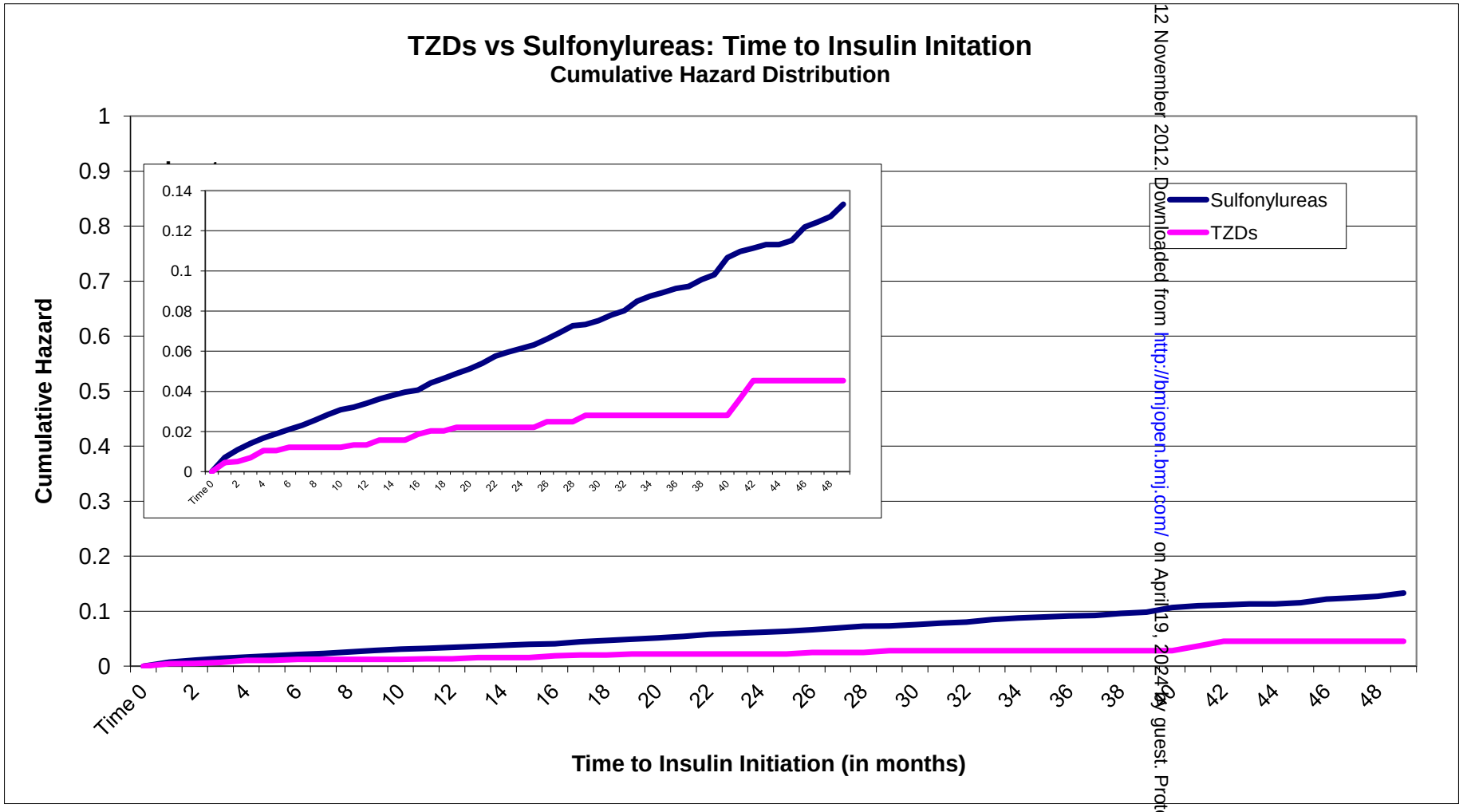

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	p.1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	p.2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	p.6-7
Objectives	3	State specific objectives, including any pre-specified hypotheses	p.7-8
Methods			
Study design	4	Present key elements of study design early in the paper	P.8-9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	p.8-9
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	p.9
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	p.15
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	p.9-11

Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	p.8-9
Bias	9	Describe any efforts to address potential sources of bias	p.7,9,11-12
Study size	10	Explain how the study size was arrived at	p.9,12
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	p.9-12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	p.10-12
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	p.12
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	p.12,15; Table 3
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	p.12-14
		(b) Give reasons for non-participation at each stage	p.12
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	p.12,13; Table 1
		(b) Indicate number of participants with missing data for each variable of interest	p.12-13
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	p.13-14; Table 2

Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	p.13-14; Table 2-3; Figure 1
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	p.13-14
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	p.12,15; Table 3
Discussion			
Key results	18	Summarise key results with reference to study objectives	p.15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	p.15,17-18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	p.16
Generalisability	21	Discuss the generalisability (external validity) of the study results	p.16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	p.18-19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

THIAZOLIDINEDIONES DELAYED THE USE OF INSULIN IN PATIENTS WITH TYPE-2 DIABETES IN BRITISH COLUMBIA

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IS THIAZOLIDINEDIONES USE A FACTOR IN DELAYING THE NEED FOR INSULIN THERAPY IN TYPE-2 DIABETICS? A POPULATION-BASED COHORT STUDY

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ABSTRACT

Objective

To understand the independent role of thiazolidinediones (TZDs) in delaying progression to parenteral insulin therapy.

Design

Population-based retrospective cohort study.

Setting

British Columbia, Canada.

Participants

18,867 Type 2 diabetes patients (mean age 58.9) treated with metformin as first-line therapy who then switched or added a TZD or sulfonylurea as second-line treatment between January 1, 1998 and March 31, 2008.

Outcome Measures

Multivariable Poisson regression models were used to estimate the effect of using TZD compared to sulfonylureas on time to initiation of insulin treatment (third-line).

Results

The adjusted rate difference in women age <60 showed 2.22 fewer insulin initiation events per 100 person-years in the TZD group versus the sulfonylurea group (95% CI -3.46 to -0.99). Men in the same age group had 1.50 fewer insulin initiation events per 100 PYs in the TZD group versus the sulfonylurea group (95% CI -2.44 to -0.56). The average time in days to initiation on insulin in the sulfonylurea, rosiglitazone and pioglitazone group was 343, 252 and 339, respectively. The cumulative hazard for starting insulin for sulfonylurea patients at 12, 24, 36, and 48 months was approximately three times higher compared to TZD patients

Conclusion

Second-line TZD therapy compared to second-line sulfonylurea therapy was associated with a lower incidence of insulin initiation as third-line treatment in patients with type-2 diabetes, with a mean delay of 90 days. This duration of delay must be weighed against the absence of a proven reduction in morbidity or mortality with TZDs and their known serious cardiovascular harm.

ARTICLE SUMMARY

Article focus

- Previous epidemiological studies indicate a greater delay in progression to insulin therapy in patients treated with metformin in combination with a thiazolidinedione (TZD) compared to those treated with sulfonylurea in combination with a TZD, although the magnitude of the delay is unknown.
- This study examines the incidence and magnitude of the delayed progression of insulin therapy in patients receiving second-line TZD treatment versus those receiving second-line sulfonylurea treatment.

Key messages

- Current treatment guidelines for T2DM in Canada recommend treatment options designed to attain specific target HbA1cs, a strategy weakly associated with morbidity and mortality evidence.
- Second-line TZD therapy compared to second-line sulfonylurea therapy was associated with a lower incidence of insulin initiation as third-line treatment in patients with T2DM, with a mean delay of 90 days.
- Despite these findings, further research is needed to assess the benefits and known cardiovascular risks of TZDs before using this therapeutic option to meet HbA1c goals.

Strengths and limitations of this study

- The comprehensive BC administrative health claims database rates relatively high in data quality.

- Baseline characteristics of the study cohorts indicate some imbalance in income and cardiovascular history that may indicate residual confounding.
- Due to BC PharmaCare's limited coverage reimbursement of TZDs versus full coverage of sulfonylureas, wealthier patients were more likely to pay out-of-pocket for TZDs than lower income patients.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a growing problem in North America,[1] affecting more than 250,000 individuals in British Columbia alone (5.6% of the population). Prescription drug treatment for T2DM is a substantial health care cost burden, especially as patients progress to treatment with insulin.[2] Recent studies found 25% of T2DM patients were prescribed insulin within 6 years of starting oral anti-diabetic drug therapy, rising to 42% after 10 years.[3,4] Current treatment guidelines for T2DM in Canada, which are not without controversy[5], recommend initiating metformin as first-line drug therapy based on a reduction in cardiovascular morbidity and mortality and adding oral anti-diabetic agents and eventually insulin to attain specific target HbA1cs, a strategy weakly associated with morbidity and mortality evidence.[6,7] From 1998 to 2007, approximately 80% of patients with T2DM in British Columbia started metformin as first-line drug therapy.[8]

Thiazolidinediones (TZDs) are a class of drugs that improve cell 'sensitivity' to endogenous insulin. Rosiglitazone and pioglitazone are two TZDs that have been shown to decrease fasting plasma glucose and HbA1c levels in patients with T2DM.[9] In addition, Rosiglitazone delayed the time to diagnosis of diabetes compared placebo in patients with mild hyperglycemia and impaired glucose tolerance tests [10]. Rosiglitazone also delayed the time to monotherapy failure

compared to metformin or glyburide, but at the cost of an increased risk of congestive heart failure [11].

In more advanced disease, epidemiologic studies have reported a slower progression to insulin in patients receiving metformin in combination with a TZD compared with those receiving a sulfonylurea in combination with a TZD.[12] In a retrospective analysis of the Texas Medicaide database, Rascati et al compared 3 cohorts of patients who received combination oral anti-diabetic therapy. They showed that patients in the sulfonylurea+TZD cohort had a 40% higher probability of more rapid progression to insulin (203/773) than patients who received combination metformin+TZD (85/438). Further research is needed to understand the magnitude of the delay to insulin initiation, particularly for patients needing second-line therapy.

We investigated the association between insulin initiation in patients with T2DM and second-line treatment with rosiglitazone, pioglitazone or sulfonylureas in patients who initiated metformin as first-line pharmacotherapy. We required first-line metformin use as a way of controlling for confounding by indication. Similarly, we chose second-line sulfonylurea patients as a comparison group because the severity and course of their diabetes was expected to be similar to patients who were prescribed a TZD. Confounding by indication is one of the

most widespread threats to validity in epidemiologic observational analysis[13], occurring when the exposure is associated with disease severity.

The ACCORD[14] and UGDP[15] trials found intensive hypoglycemic therapy attempting to achieve lower HbA1c levels is associated with an increase in morbidity and mortality. These studies highlight the importance of validating HbA1c targets in terms of serious morbidity and mortality before accepting them as treatment goals. This is particularly important with TZDs where paradoxically HbA1c was significantly decreased and serious cardiovascular morbidity was significantly increased in patients taking rosiglitazone.[16]

We expected second-line rosiglitazone and pioglitazone to delay the use of insulin compared to second-line sulfonylureas, in patients with T2DM who initiated metformin as first-line therapy. However, the incidence and magnitude of that delay, especially in newly diagnosed patients, needed to be quantified to better weight that benefit versus known serious harm.

METHODS

Data

All prescriptions dispensed at community pharmacies in British Columbia since the autumn of 1995 are stored in a central database named PharmaNet. The system captures dispensing data and performs quality checks every time prescriptions are filled. It is believed those features keep underreporting and

misclassification very low. Prescriptions are linked by unique personal health number to BC Ministry of Health databases for hospitalizations, medical services, and medical services registration. The Canadian Institute for Health Information collects hospital discharge records from all Canadian provinces, including Ontario where the data have been evaluated for accuracy.[17] Similar administrative claims databases in other North American jurisdictions have been studied for accuracy and completeness [18-21] but we are unaware of any such analyses in British Columbia. We had ethics approval from the University of British Columbia Clinical Research Ethics Board (Certificate No. H02-70020).

Study Population

The source population for the study was all BC residents between January 1998 and March 2008 who were registered in the provincial universal medical services plan (MSP). Federally insured patients such as aboriginals, federal police officers and members of the armed forces and their families were excluded from the source population because we did not have permission to use those data. Excluded patients composed about 7% of the provincial population. The source population numbered 4.01 million in 2007.[22]

Study Design and Cohort

We conducted a retrospective cohort study. We extracted patients from the source population who initiated metformin between January 1, 1998 and March

31, 2008 and then added or switched to a thiazolidinedione (rosiglitazone or pioglitazone) or a sulfonylurea (acetohexamide, chlorpropamide, gliclazide, glimepiride, glyburide, tolbutamide) as second-line therapy. We chose second-line sulfonylurea patients as a comparison group because the severity and course of their diabetes was expected to be most similar to other second-line patients who were prescribed a TZD instead. We assigned an index date equal to the first prescription dispensed date of a TZD or sulfonylurea.

Study Outcome

Our outcome was the occurrence of first insulin prescription after exposure to a TZD or sulfonylurea. The outcome was identified by the presence of a dispensing for insulin in the PharmaNet database. Patients were censored at the earliest occurrence of our study outcome, death, end of the study period (March 31, 2008), entry into a long-term care facility, emigration from BC, therapy discontinuation (no further prescriptions for 60 days after the end of a drug dispensing), or crossover to the other treatment arm.

Data Analysis

Multivariable Poisson regression models were used to estimate the effect of TZD therapy on initiation of insulin treatment compared to sulfonylureas. In three regressions with sulfonylurea patients as controls we estimated rates of insulin initiation, and adjusted rate ratios and rate differences for 3 contrasts with

sulfonylurea patients: rosiglitazone (RSG), pioglitazone (PIO) and TZD (defined as rosiglitazone or pioglitazone). We constructed a cumulative hazard plot for insulin initiation in each exposure category. Rate differences per 100 person-years were calculated in 4 categories: Men, women, age >=60 and age < 60.

Confounders

Potential confounders were measured before exposure to an SU or TZD using diagnostic codes, procedure codes, prescription claim records, and Ministry of Health Services' patient demographic data. Our analysis included the following potential confounders: age (10-year age groups), sex, family income (quintiles), and index year of treatment initiation. The following covariates were included in the outcome model if within 5 years prior to index date: renal disease (ICD-9 584-586, 403-404), acute myocardial infarction (ICD-9 410 or 412), angina (ICD-9 411, 413), congestive heart failure (hospitalization for ICD-9 425, or 428, or a physician visit for same plus a prescription for furosemide), coronary artery bypass graft (hospitalization for procedure code 410), transient ischemic attack (hospitalization for ICD-9 435), coronary catheterization (hospitalization for procedure codes 4802 or 4803), and percutaneous transluminal coronary angioplasty (hospitalization for procedure codes 4892-4898, or 4995-4997). Prior use of the following covariates was included in the model if within 2 years of the index date: exposure to statins, digoxin, ACE Inhibitors, Cox-2 inhibitors, diuretics, clopidogrel, angiotensin-converting enzyme Inhibitors or angiotensin

receptor blockers, spironolactone, or beta blockers. The following covariates were examined but excluded based on p-values greater than 0.2 in univariate tests: prior osteoarthritis (ICD-9 715), peripheral vascular disease (ICD-9 440-440.9), exposure to non-coxib NSAIDs, all NSAIDs, calcium channel blockers, metformin, benzodiazepines, and bisphosphonates.

Sensitivity Analysis

A sensitivity analysis was performed comparing the TZD cohort versus the sulfonylurea cohort using Schneeweiss et al's method of High Dimension Propensity Score (HDPS) comorbidity adjustment. The High Dimensional approach to generating propensity scores is an automated data-driven approach to analyzing the administrative claims database for variables that appear to be confounders. The HDPS algorithm searches the database to find variables that serve as proxies for previously unmeasured confounders by measuring potential to bias the exposure/outcome relationship. The HDPS methods have been previously described in detail here.[23] Poisson regression was used, adjusting for propensity score deciles.

Results

There were 21,230 patients from the source population who initiated metformin as first-line therapy and then added or switched to either an SU or TZD between January 1, 1998 and March 31, 2008. Of those, 18,867 patients (89%) remained

eligible for cohort entry after excluding patients who were admitted to a long-term care facility (n=245), diagnosed with gestational diabetes in the previous 2 years (n=24), had invalid data for sex or date of birth (n=13), or had less than 2 years of provincial health plan coverage prior to index (n=2,098). In total, 2,363 distinct patients were excluded.

Characteristics of cohort patients are shown in **Table 1**. The patients in the study averaged 58.9 years old and TZD patients were 3.7 years younger on average than SU patients. The proportion of patients who were women was similar in all groups (SU 45%, Any TZD 45%, PIO 46%, ROS 45%). Income data was available for 87% of patients in the "Any TZD" cohort and for 81% of patients in the SU cohort. 12% of patients in the "Any TZD" cohort were in the highest income, indicating that TZD patients earned significantly more than SU patients. The Romano Score is a comobidity index based on ICD-9 outpatient and inpatient diagnoses.[24] Mean Romano comorbidity scores indicated that SU patients had slightly more comorbid disease (mean Romano score 1.75) compared to TZD patients (mean Romano score 1.42), however the median diabetes duration was 3 years in each of the four cohorts.

The SU group had higher rates of renal disease, acute myocardial infarction, angina, congestive heart failure, and coronary catherization, in the 5 year period prior to the index date, (absolute range 2–5% higher). Medication history was similar in all groups in the 2 year period prior to the index date. Pioglitazone

(PIO) patients had a lower proportion of congestive heart failure (7.5) compared to Rosiglitazone (RSG) patients (9.4). Baseline characteristics were otherwise similar between RSG patients and PIO patients.

The cumulative hazard for starting insulin for sulfonylurea patients at 12, 24, 36, and 48 months was approximately three times higher compared to TZD patients (Figure 1). The difference in the cumulative hazard distribution of insulin use between TZD and SU patients suggests the association is not modified over time and is amenable to modeling using Poisson regression.

Table 2 shows the number of events, person-years of follow-up, and event rates for insulin initiation in each of the treatment arms. We identified 563 total events of insulin initiation in the cohorts during follow-up. The average time in days to initiation on insulin in the SU, RSG and PIO group was 343, 252 and 339, respectively. Average follow-up times were similar among treatment groups (0.90 years SU, 1.09 years TZD, 1.09 years RSG, and 1.04 years PIO).
The incidence rate among women was nearly 3 times higher in the SU group (4.21 events per 100 PYs) compared to PIO (1.42 events per 100 PYs), and was 2.7 times higher than the RSG group (1.56 events per 100 PYs). Men taking SUs were over 2.3 times more likely to initiate insulin than men prescribed TZDs (3.05 events per 100 PYs versus 1.30 events per 100 PYs, respectively).

Adjusted rate differences from our multivariable Poisson regressions for men and women by age group are shown in **Table 3**. The adjusted rate difference (RD) in women age >= 60 showed 1.18 fewer insulin initiation events per 100 person-years (PYs) in the TZD group versus the SU group (95% CI -2.05 to -0.32). Men in the same age group had 0.80 fewer insulin initiation events per 100 PYs in the TZD group versus the SU group (95% CI -1.51 to -0.08). In the under 60 age group, the adjusted RD per 100 PYs in women and men were -2.22 (95% CI -3.46 to -0.99) and -1.50 (95% CI -2.44 to -0.56), respectively, when comparing SU versus TZDs. When exposure to each thiazolidinedione was estimated separately, similar adjusted rate differences in both men and women and in both age groups were found.

The results of the HDPS sensitivity analysis showed a statistically significant 62% lower probability of insulin initiation in the TZD group compared to the sulfonylureas (adjusted HR, 0.38, 95% CI - 0.28 to 0.51). The c-statistic of the HDPS model discrimination was 0.72.

Discussion

This retrospective cohort study followed T2DM patients who initiated metformin, then added or switched to second-line SU (n=15,613), second-line PIO (n=1,213), second-line ROS (n=2,041), or second-line PIO or ROS (n=3,254).

We found a lower rate of insulin initiation in the PIO, ROS, and any TZD cohorts compared to SU for both men and women, age <60 and age >=60.
The results were statistically significant for all comparisons except in men in the PIO versus SU comparison.

We chose second-line SU as our comparator as this cohort is similar in disease duration and severity to the second-line TZD cohorts. This study design minimizes the effect of channeling, a mechanism that leads to confounding by indication, where sicker patients are more likely to be early users of newer drugs. The expected effect of this bias is to increase the association between TZD exposure and insulin use, suggesting that any residual channeling lead to an underestimate of the true effects.

Insulin initiation events per 100 person years (PYs) are 3.57 for SU, 1.37 for TZDs, 1.36 for ROS, and 1.48 for PIO. Our insulin initiation event rates are lower than other studies have reported.[25,26] This is likely because we only include T2DM patients following metformin monotherapy. Other studies included TZDs as third line therapy who likely have a more advanced disease state and are more likely to initiate insulin sooner.

The clinical relevance of our finding, a 90 day delay in initiation of insulin, must be weighed against the growing body of evidence of increased risk of

cardiovascular events associated with TZDs. The ADOPT Trial raises the same issue in monotherapy, where rosiglitazone reduced the incidence of monotherapy failure compared to metformin and glyburide but increased the risk of cardiovascular events (including congestive heart failure) versus glyburide.[11] A 2007 meta-analysis of randomized clinical trial data found a statistically significant 43% increase in risk of myocardial infarction (AMI) with rosiglitazone treatment compared to other oral antidiabetic therapies or placebo.[14] The RECORD trial found a 15% higher hazard ratio for AMI comparing rosiglitazone to a metformin/sulfonylurea combination, although the finding was statistically insignificant due to limited statistical power.[27,28] Several population level observational studies have shown that TZD treatment was associated with an increased risk of cardiovascular disease when compared with other oral anti-diabetic therapies.[29,30]

A significant strength of our study was the use of the BC PharmaNet database, which captured all oral anti-diabetic and insulin prescriptions dispensed at a community pharmacy, regardless of insurance coverage or payer. The completeness of this database allowed for a study design with low misclassification of exposed patients and a high specificity and sensitivity of our outcome, third-line use of insulin.

Limitations

Our study has data limitations and interpretability issues that warrant discussion. As with most observational pharmaco-epidemiological studies, the use of administrative claims databases is subject to data quality issues. We have no reason to believe the quality of the BC administrative health claims database is of inferior data quality compared to similar administrative claims databases in other jurisdictions. The comprehensiveness of the database allows for generalizing results to a wide population.

Residual confounding is a limitation of our study due to its nonrandomized design. Baseline characteristics of the study cohorts indicate comparable diabetes duration, sex ratio, and drug use. The sulfonylurea cohort was older and had higher rates of renal disease and cardiovascular events in the previous 5 years. Family income was unbalanced at the extreme low and high ranges. In the sulfonylurea cohort, 23% were in the lowest income range ($0-$21,250) compared to 12% of the TZD cohort. The highest income range (> $97,500) contained 6% of the sulfonylurea cohort versus 12% of the TZD cohort. This discrepancy is likely due to B.C. PharmaCare's limited coverage reimbursement of TZD's versus full coverage of sulfonylureas; wealthier patients were more likely to pay out-of-pocket for TZDs.

Conclusion

Our analysis showed second-line TZD therapy compared to second-line sulfonylurea therapy was associated with a lower incidence of insulin initiation as third-line treatment in patients with type-2 diabetes, with a mean of 90 days. This duration of delay must be weighed against the absence of a proven reduction in morbidity and mortality with TZDs and the known serious cardiovascular risks.

Acknowledgments

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The study received ethics approval from the University of British Columbia (UBC CREB Number H02-70020). The BC Ministry of Health approved data access.

All authors substantially contributed to the conception, design, analysis and interpretation of data, drafting and revising the article for important intellectual content, and gave approval for the final version. Data analysis was performed by Carney, Dormuth.

Data Sharing

Statistical code available from the corresponding author at greg.carney@ti.ubc.ca.

Competing Interests

There are no competing interests.

Table Legend:

Table 1: Baseline Characteristics of Study Patients by Current Exposure to Thiazolidinediones or Sulfonylureas in British Columbia (1998-2007)

Table 2: Insulin Events with Thiazolidinediones or Sulfonylureas in Patients With Type II Diabetes Mellitus

Table 3: Poisson Regression for Insulin End Points Associated with Thiazolidinediones or Sulfonylureas in Patients With Type II Diabetes Mellitus

Figure Legend:

Figure 1: Cumulative Hazard Distribution for Time to Insulin End Points Associated with Thiazolidinediones or Sulfonylureas in Patients With Type II Diabetes Mellitus

Table 1. Baseline Characteristics of Study Patients by Current Exposure to Glitazones or Sulfonylureas

Variable	Sulfonylurea (N = 15,613)	Any TZD (N = 3,254)	Pioglitazone (N = 1,213)	Rosiglitazone (N = 2,041)
Age, median (IQR*)	60 (50,69)	56 (48,64)	56 (48,64)	56 (48,64)
Women (%)	6,952 (45)	1,479 (45)	556 (46)	923 (45)
Family Income (%)				
0 to $21,250	3,600 (23)	377 (12)	139 (11)	238 (12)
$21,251 to $45,000	4,211 (27)	783 (24)	288 (24)	495 (24)
$45,001 to $70,833	2,634 (17)	761 (23)	280 (23)	481 (24)
$70,834 to $97,500	1,260 (8)	511 (16)	178 (15)	333 (16)
> $97,500	935 (6)	393 (12)	149 (12)	244 (12)
Unknown	2,973 (19)	429 (13)	179 (15)	250 (12)
Romano comorbidity score, median (IQR) †	1.00 (1,3)	1.00 (1,2)	1.0 (1,2)	1.0 (1,2)
Diabetes duration in years, median (IQR)	3 (1,7)	3 (1,6)	3 (1,7)	3 (1,6)
Medical History				
Renal disease ‡	637 (4)	75 (2)	25 (2)	50 (2)
Acute myocardial infarction ‡	912 (6)	104 (3)	40 (3)	64 (3)
Angina ‡	3,693 (24)	639 (20)	241 (20)	398 (20)
Congestive heart failure ‡	2,211 (14)	282 (9)	91 (8)	191 (9)
Coronary catheterization ‡	1,024 (7)	176 (5)	70 (6)	106 (5)
Lab Tests in Past Two Years**				
HbA1c, n	14,525 (93)	3,057 (94)	1,124 (93)	1,933 (95)
HbA1c, median (IQR)	3 (2,5)	3 (2,5)	4 (2,6)	3 (2,5)
Fasting Blood Glucose, n	14,521 (93)	3,041 (93)	1,129 (93)	1,912 (94)
Fasting Blood Glucose, median (IQR)	3 (2,5)	3 (2,5)	3 (2,5)	3 (2,5)
Drug Use in Past Two Years §				
Metformin	15,393 (99)	3,211 (99)	1,193 (98)	2,018 (99)
ACE Inhibitor	6,923 (44)	1,448 (44)	531 (44)	917 (45)
Beta blockers	11,279 (72)	2,512 (77)	940 (77)	1,572 (77)
Calcium channel blockers	2,854 (18)	487 (15)	176 (15)	311 (15)
Coxib NSAIDs	1,260 (8)	334 (10)	111 (9)	223 (11)
NSAIDs	5,511 (35)	1,059 (33)	394 (32)	665 (33)
Digoxin	609 (4)	63 (2)	18 (1)	45 (2)
Spironolactone	609 (4)	100 (3)	36 (3)	64 (3)
Statins	6,682 (43)	1,475 (45)	544 (45)	931 (46)

¶ Net family income in Canadian dollars from the most recent income tax return (1 Canadian dollar ~ 1 US dollar).
† Romano commorbidity score calculated using data one year prior to the index date.
‡ History within five years prior to the index date.
\ Dispensing of drug within 730 days prior to index date.
* IQR refers to the interquartile range.
** MSP fee items used - HbA1c: 91745, Fasting Blood Glucose: 91705-91710, 91715-91717, 91719

Table 2: Insulin Initiation Events with Thiazolidinediones (TZDs) or Sulfonylureas in Patients With Type II Diabetes Mellitus

Sex	Drug Group	Person Years of Follow-up	Insulin Initiation Events	Events per 100 PYs
Men	Sulfonylurea	7,879	240	3.05
	TZDs	2,005	26	1.30
	Rosiglitazone	1,250	15	1.20
	Pioglitazone	722	11	1.52
Women	Sulfonylurea	6,491	273	4.21
	TZDs	1,633	24	1.47
	Rosiglitazone	1,027	16	1.56
	Pioglitazone	562	8	1.42
Men and Women	Sulfonylurea	14,369	513	3.57
	TZDs	3,638	50	1.37
	Rosiglitazone	2,277	31	1.36
	Pioglitazone	1,285	19	1.48

Table 3. Poisson Regression for Insulin Initiation Events Associated with Thiazolidinediones (TZDs) or Sulfonylureas (SU) in Patients With Type II Diabetes Mellitus

	TZDs vs Sulfonylureas				
Cohort	Crude Rate in TZD Group per 100 PYs	Crude Rate in SU Group per 100 PYs	TZD PYs of Follow-up	Crude Rate Ratio	Adjusted Rate Difference per 100 PYs (95% CI)
Men, age >=60	0.54	2.35	734	0.23	-0.80 (-1.51 - -0.08)
Men, age <60	1.73	3.75	1,271	0.46	-1.50 (-2.44 - -0.56)
Women, age >=60	0.76	2.75	656	0.28	-1.18 (-2.05 - -0.32)
Women, age <60	1.94	5.91	977	0.33	-2.22 (-3.46 - -0.99)
	Pioglitazone (PIO) vs Sulfonylureas				
Cohort	Crude Rate in PIO Group per 100 PYs	Crude Rate in SU Group per 100 PYs	PIO PYs of Follow-up	Crude Rate Ratio	Adjusted Rate Difference per 100 PYs (95% CI)
Men, age >=60	0.77	2.35	260	0.33	-0.73 (-1.9 - 0.43)
Men, age <60	1.92	3.75	469	0.51	-1.37 (-2.76 - 0.02)
Women, age >=60	0.42	2.75	240	0.15	-1.09 (-2.08 - -0.11)
Women, age <60	2.05	5.91	341	0.35	-2.04 (-3.79 - -0.29)
	Rosiglitazone (ROS) vs Sulfonylureas				
Cohort	Crude Rate in ROS Group per 100 PYs	Crude Rate in SU Group per 100 PYs	ROS PYs of Follow-up	Crude Rate Ratio	Adjusted Rate Difference per 100 PYs (95% CI)
Men, age >=60	0.42	2.35	474	0.18	-0.81 (-1.57 - -0.06)
Men, age <60	1.62	3.75	802	0.43	-1.52 (-2.59 - -0.45)
Women, age >=60	0.96	2.75	415	0.35	-1.21 (-2.31 - -0.12)
Women, age <60	1.89	5.91	636	0.32	-2.27 (-3.65 - -0.89)

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IS THIAZOLIDINEDIONES USE A FACTOR IN DELAYING THE NEED FOR INSULIN THERAPY IN TYPE-2 DIABETICS? A POPULATION-BASED COHORT STUDY

~~THIAZOLIDINEDIONES DELAYED THE USE OF INSULIN IN PATIENTS WITH TYPE-2 DIABETES IN BRITISH COLUMBIA~~

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ABSTRACT

Objective

To understand the independent role of thiazolidinediones (TZDs) in delaying progression to parenteral insulin therapy.

Design

Population-based ~~prospective~~ retrospective cohort study.

Setting

British Columbia, Canada.

Participants

18,867 Type 2 diabetes patients (mean age 58.9) treated with metformin as first-line therapy who then switched or added a TZD or sulfonylurea as second-line treatment between January 1, 1998 and March 31, 2008.

Outcome Measures

Multivariable Poisson regression models were used to estimate the effect of using TZD compared to sulfonylureas on time to initiation of insulin treatment (third-line).

Results

The adjusted rate difference in women age <60 showed 2.22 fewer insulin initiation events per 100 person-years in the TZD group versus the sulfonylurea group (95% CI -3.46 to -0.99). Men in the same age group had 1.50 fewer insulin initiation events per 100 PYs in the TZD group versus the sulfonylurea group (95% CI -2.44 to -0.56). The average time in days to initiation on insulin in the sulfonylurea, rosiglitazone and pioglitazone group was 343, 252 and 339, respectively. The cumulative hazard for starting insulin for sulfonylurea patients at 12, 24, 36, and 48 months was approximately three times higher compared to TZD patients

Conclusion

Second-line TZD therapy compared to second-line sulfonylurea therapy was associated with a lower incidence of insulin initiation as third-line treatment in patients with type-2 diabetes, with a mean delay of 90 days. This duration of delay must be weighed against the absence of a proven reduction in morbidity or mortality with TZDs and their known serious cardiovascular harm.

ARTICLE SUMMARY

Article focus

- Previous epidemiological studies indicate a greater delay in progression to insulin therapy in patients treated with metformin in combination with a thiazolidinedione (TZD) compared to those treated with sulfonylurea in combination with a TZD, although the magnitude of the delay is unknown.
- This study examines the incidence and magnitude of the delayed progression of insulin therapy in patients receiving second-line TZD treatment versus those receiving second-line sulfonylurea treatment.

Key messages

- Current treatment guidelines for T2DM in Canada recommend treatment options designed to attain specific target HbA1cs, a strategy weakly associated with morbidity and mortality evidence.
- Second-line TZD therapy compared to second-line sulfonylurea therapy was associated with a lower incidence of insulin initiation as third-line treatment in patients with T2DM, with a mean delay of 90 days.
- Despite these findings, further research is needed to assess the benefits and known cardiovascular risks of TZDs before using this therapeutic option to meet HbA1c goals.

Strengths and limitations of this study

- The comprehensive BC administrative health claims database rates relatively high in data quality.

- Baseline characteristics of the study cohorts indicate some imbalance in income and cardiovascular history that may indicate residual confounding.
- Due to BC PharmaCare's limited coverage reimbursement of TZDs versus full coverage of sulfonylureas, wealthier patients were more likely to pay out-of-pocket for TZDs than lower income patients.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a growing problem in North America,[1] affecting more than 250,000 individuals in British Columbia alone (5.6% of the population). Prescription drug treatment for T2DM is a substantial health care cost burden, especially as patients progress to treatment with insulin.[2] Recent studies found 25% of T2DM patients were prescribed insulin within 6 years of starting oral anti-diabetic drug therapy, rising to 42% after 10 years.[3,4] Current treatment guidelines for T2DM in Canada, which are not without controversy[5], recommend initiating metformin as first-line drug therapy based on a reduction in cardiovascular morbidity and mortality and adding oral anti-diabetic agents and eventually insulin to attain specific target HbA1cs, a strategy weakly associated with morbidity and mortality evidence.[6,7] From 1998 to 2007, approximately 80% of patients with T2DM in British Columbia started metformin as first-line drug therapy.[8]

Thiazolidinediones (TZDs) are a class of drugs that improve cell 'sensitivity' to endogenous insulin. Rosiglitazone and pioglitazone are two TZDs that have been shown to decrease fasting plasma glucose and HbA1c levels in patients with T2DM.[9] In addition, Rosiglitazone delayed the time to diagnosis of diabetes compared placebo in patients with mild hyperglycemia and impaired glucose tolerance tests [10]. Rosiglitazone also delayed the time to monotherapy failure

compared to metformin or glyburide, but at the cost of an increased risk of congestive heart failure [11].

In more advanced disease, epidemiologic studies have reported a slower progression to insulin in patients receiving metformin in combination with a TZD compared with those receiving a sulfonylurea in combination with a TZD.[12] In a retrospective analysis of the Texas Medicaide database, Rascati et al compared 3 cohorts of patients who received combination oral anti-diabetic therapy. They showed that patients in the sulfonylurea+TZD cohort had a 40% higher probability of more rapid progression to insulin (203/773) than patients who received combination metformin+TZD (85/438). Further research is needed to understand the magnitude of the delay to insulin initiation, particularly for patients needing second-line therapy.

We investigated the association between insulin initiation in patients with T2DM and second-line treatment with rosiglitazone, pioglitazone or sulfonylureas in patients who initiated metformin as first-line pharmacotherapy. We required first-line metformin use as a way of controlling for confounding by indication. Similarly, we chose second-line sulfonylurea patients as a comparison group because the severity and course of their diabetes was expected to be similar to patients who were prescribed a TZD. Confounding by indication is one of the

most widespread threats to validity in epidemiologic observational analysis[13], occurring when the exposure is associated with disease severity.

The ACCORD[14] and UGDP[15] trials found intensive hypoglycemic therapy attempting to achieve lower HbA1c levels is associated with an increase in morbidity and mortality. These studies highlight the importance of validating HbA1c targets in terms of serious morbidity and mortality before accepting them as treatment goals. This is particularly important with TZDs where paradoxically HbA1c was significantly decreased and serious cardiovascular morbidity was significantly increased in patients taking rosiglitazone.[16]

We expected second-line rosiglitazone and pioglitazone to delay the use of insulin compared to second-line sulfonylureas, in patients with T2DM who initiated metformin as first-line therapy. However, the incidence and magnitude of that delay, especially in newly diagnosed patients, needed to be quantified to better weight that benefit versus known serious harm.

METHODS

Data

All prescriptions dispensed at community pharmacies in British Columbia since the autumn of 1995 are stored in a central database named PharmaNet. The system captures dispensing data and performs quality checks every time prescriptions are filled. It is believed those features keep underreporting and

misclassification very low. Prescriptions are linked by unique personal health number to BC Ministry of Health databases for hospitalizations, medical services, and medical services registration. The Canadian Institute for Health Information collects hospital discharge records from all Canadian provinces, including Ontario where the data have been evaluated for accuracy.[17] Similar administrative claims databases in other North American jurisdictions have been studied for accuracy and completeness [18-21] but we are unaware of any such analyses in British Columbia. We had ethics approval from the University of British Columbia Clinical Research Ethics Board (Certificate No. H02-70020).

Study Population

The source population for the study was all BC residents between January 1998 and March 2008 who were registered in the provincial universal medical services plan (MSP). Federally insured patients such as aboriginals, federal police officers and members of the armed forces and their families were excluded from the source population because we did not have permission to use those data. Excluded patients composed about 7% of the provincial population. The source population numbered 4.01 million in 2007.[22]

Study Design and Cohort

We conducted a ~~prospective~~ retrospective cohort study. We extracted patients from the source population who initiated metformin between January 1, 1998

and March 31, 2008 and then added or switched to a thiazolidinedione (rosiglitazone or pioglitazone) or a sulfonylurea (acetohexamide, chlorpropamide, gliclazide, glimepiride, glyburide, tolbutamide) as second-line therapy. We chose second-line sulfonylurea patients as a comparison group because the severity and course of their diabetes was expected to be most similar to other second-line patients who were prescribed a TZD instead. We assigned an index date equal to the first prescription dispensed date of a TZD or sulfonylurea.

Study Outcome

Our outcome was the occurrence of first insulin prescription after exposure to a TZD or sulfonylurea. The outcome was identified by the presence of a dispensing for insulin in the PharmaNet database. Patients were censored at the earliest occurrence of our study outcome, death, end of the study period (March 31, 2008), entry into a long-term care facility, emigration from BC, therapy discontinuation (no further prescriptions for 60 days after the end of a drug dispensing), or crossover to the other treatment arm.

Data Analysis

Multivariable Poisson regression models were used to estimate the effect of TZD therapy on initiation of insulin treatment compared to sulfonylureas. In three regressions with sulfonylurea patients as controls we estimated rates of insulin initiation, and adjusted rate ratios and rate differences for 3 contrasts with

sulfonylurea patients: rosiglitazone (RSG), pioglitazone (PIO) and TZD (defined as rosiglitazone or pioglitazone). We constructed a cumulative hazard plot for insulin initiation in each exposure category. Rate differences per 100 person-years were calculated in 4 categories: Men, women, age >=60 and age < 60.

Confounders

Potential confounders were measured before exposure to an SU or TZD using diagnostic codes, procedure codes, prescription claim records, and Ministry of Health Services' patient demographic data. Our analysis included the following potential confounders: age (10-year age groups), sex, family income (quintiles), and index year of treatment initiation. The following covariates were included in the outcome model if within 5 years prior to index date: renal disease (ICD-9 584-586, 403-404), acute myocardial infarction (ICD-9 410 or 412), angina (ICD-9 411, 413), congestive heart failure (hospitalization for ICD-9 425, or 428, or a physician visit for same plus a prescription for furosemide), coronary artery bypass graft (hospitalization for procedure code 410), transient ischemic attack (hospitalization for ICD-9 435), coronary catheterization (hospitalization for procedure codes 4802 or 4803), and percutaneous transluminal coronary angioplasty (hospitalization for procedure codes 4892-4898, or 4995-4997). Prior use of the following covariates was included in the model if within 2 years of the index date: exposure to statins, digoxin, ACE Inhibitors, Cox-2 inhibitors, diuretics, clopidogrel, angiotensin-converting enzyme Inhibitors or angiotensin

receptor blockers, spironolactone, or beta blockers. The following covariates were examined but excluded based on p-values greater than 0.2 in univariate tests: prior osteoarthritis (ICD-9 715), peripheral vascular disease (ICD-9 440-440.9), exposure to non-coxib NSAIDs, all NSAIDs, calcium channel blockers, metformin, benzodiazepines, and bisphosphonates.

Sensitivity Analysis

A sensitivity analysis was performed comparing the TZD cohort versus the sulfonylurea cohort using Schneeweiss et al's method of High Dimension Propensity Score (HDPS) comorbidity adjustment. The High Dimensional approach to generating propensity scores is an automated data-driven approach to analyzing the administrative claims database for variables that appear to be confounders. The HDPS algorithm searches the database to find variables that serve as proxies for previously unmeasured confounders by measuring potential to bias the exposure/outcome relationship. The HDPS methods have been previously described in detail here.[23] Poisson regression was used, adjusting for propensity score deciles.

Results

There were 21,230 patients from the source population who initiated metformin as first-line therapy and then added or switched to either an SU or TZD between January 1, 1998 and March 31, 2008. Of those, 18,867 patients (89%) remained

eligible for cohort entry after excluding patients who were admitted to a long-term care facility (n=245), diagnosed with gestational diabetes in the previous 2 years (n=24), had invalid data for sex or date of birth (n=13), or had less than 2 years of provincial health plan coverage prior to index (n=2,098). In total, 2,363 distinct patients were excluded.

Characteristics of cohort patients are shown in **Table 1**. The patients in the study averaged 58.9 years old and TZD patients were 3.7 years younger on average than SU patients. The proportion of patients who were women was similar in all groups (SU 45%, Any TZD 45%, PIO 46%, ROS 45%). Income data was available for 87% of patients in the "Any TZD" cohort and for 81% of patients in the SU cohort. 12% of patients in the "Any TZD" cohort were in the highest income, indicating that TZD patients earned significantly more than SU patients. The Romano Score is a comobidity index based on ICD-9 outpatient and inpatient diagnoses.[24] Mean Romano comorbidity scores indicated that SU patients had slightly more comorbid disease (mean Romano score 1.75) compared to TZD patients (mean Romano score 1.42), however the median diabetes duration was 3 years in each of the four cohorts.

The SU group had higher rates of renal disease, acute myocardial infarction, angina, congestive heart failure, and coronary catherization, in the 5 year period prior to the index date, (absolute range 2–5% higher). Medication history was similar in all groups in the 2 year period prior to the index date. Pioglitazone

(PIO) patients had a lower proportion of congestive heart failure (7.5) compared to Rosiglitazone (RSG) patients (9.4). Baseline characteristics were otherwise similar between RSG patients and PIO patients.

The cumulative hazard for starting insulin for sulfonylurea patients at 12, 24, 36, and 48 months was approximately three times higher compared to TZD patients (Figure 1). The difference in the cumulative hazard distribution of insulin use between TZD and SU patients suggests the association is not modified over time and is amenable to modeling using Poisson regression.

Table 2 shows the number of events, person-years of follow-up, and event rates for insulin initiation in each of the treatment arms. We identified 563 total events of insulin initiation in the cohorts during follow-up. The average time in days to initiation on insulin in the SU, RSG and PIO group was 343, 252 and 339, respectively. Average follow-up times were similar among treatment groups (0.90 years SU, 1.09 years TZD, 1.09 years RSG, and 1.04 years PIO).
The incidence rate among women was nearly 3 times higher in the SU group (4.21 events per 100 PYs) compared to PIO (1.42 events per 100 PYs), and was 2.7 times higher than the RSG group (1.56 events per 100 PYs). Men taking SUs were over 2.3 times more likely to initiate insulin than men prescribed TZDs (3.05 events per 100 PYs versus 1.30 events per 100 PYs, respectively).

Adjusted rate differences from our multivariable Poisson regressions for men and women by age group are shown in **Table 3**. The adjusted rate difference (RD) in women age >= 60 showed 1.18 fewer insulin initiation events per 100 person-years (PYs) in the TZD group versus the SU group (95% CI -2.05 to -0.32). Men in the same age group had 0.80 fewer insulin initiation events per 100 PYs in the TZD group versus the SU group (95% CI -1.51 to -0.08). In the under 60 age group, the adjusted RD per 100 PYs in women and men were -2.22 (95% CI -3.46 to -0.99) and -1.50 (95% CI -2.44 to -0.56), respectively, when comparing SU versus TZDs. When exposure to each thiazolidinedione was estimated separately, similar adjusted rate differences in both men and women and in both age groups were found.

The results of the HDPS sensitivity analysis showed a statistically significant 62% lower probability of insulin initiation in the TZD group compared to the sulfonylureas (adjusted HR, 0.38, 95% CI - 0.28 to 0.51). The c-statistic of the HDPS model discrimination was 0.72.

Discussion

This ~~prospective~~ retrospective cohort study followed T2DM patients who initiated metformin, then added or switched to second-line SU (n=15,613), second-line PIO (n=1,213), second-line ROS (n=2,041), or second-line PIO or ROS

(n=3,254). We found a lower rate of insulin initiation in the PIO, ROS, and any TZD cohorts compared to SU for both men and women, age <60 and age >=60. The results were statistically significant for all comparisons except in men in the PIO versus SU comparison.

We chose second-line SU as our comparator as this cohort is similar in disease duration and severity to the second-line TZD cohorts. This study design minimizes the effect of channeling, a mechanism that leads to confounding by indication, where sicker patients are more likely to be early users of newer drugs. The expected effect of this bias is to increase the association between TZD exposure and insulin use, suggesting that any residual channeling lead to an underestimate of the true effects.

Insulin initiation events per 100 person years (PYs) are 3.57 for SU, 1.37 for TZDs, 1.36 for ROS, and 1.48 for PIO. Our insulin initiation event rates are lower than other studies have reported.[25,26] This is likely because we only include T2DM patients following metformin monotherapy. Other studies included TZDs as third line therapy who likely have a more advanced disease state and are more likely to initiate insulin sooner.

The clinical relevance of our finding, a 90 day delay in initiation of insulin, must be weighed against the growing body of evidence of increased risk of

cardiovascular events associated with TZDs. The ADOPT Trial raises the same issue in monotherapy, where rosiglitazone reduced the incidence of monotherapy failure compared to metformin and glyburide but increased the risk of cardiovascular events (including congestive heart failure) versus glyburide.[11] A 2007 meta-analysis of randomized clinical trial data found a statistically significant 43% increase in risk of myocardial infarction (AMI) with rosiglitazone treatment compared to other oral antidiabetic therapies or placebo.[14] The RECORD trial found a 15% higher hazard ratio for AMI comparing rosiglitazone to a metformin/sulfonylurea combination, although the finding was statistically insignificant due to limited statistical power.[27,28] Several population level observational studies have shown that TZD treatment was associated with an increased risk of cardiovascular disease when compared with other oral anti-diabetic therapies.[29,30]

A significant strength of our study was the use of the BC PharmaNet database, which captured all oral anti-diabetic and insulin prescriptions dispensed at a community pharmacy, regardless of insurance coverage or payer. The completeness of this database allowed for a study design with low misclassification of exposed patients and a high specificity and sensitivity of our outcome, third-line use of insulin.

Limitations

Our study has data limitations and interpretability issues that warrant discussion. As with most observational pharmaco-epidemiological studies, the use of administrative claims databases is subject to data quality issues. We have no reason to believe the quality of the BC administrative health claims database is of inferior data quality compared to similar administrative claims databases in other jurisdictions. The comprehensiveness of the database allows for generalizing results to a wide population.

Residual confounding is a limitation of our study due to its nonrandomized design. Baseline characteristics of the study cohorts indicate comparable diabetes duration, sex ratio, and drug use. The sulfonylurea cohort was older and had higher rates of renal disease and cardiovascular events in the previous 5 years. Family income was unbalanced at the extreme low and high ranges. In the sulfonylurea cohort, 23% were in the lowest income range ($0-$21,250) compared to 12% of the TZD cohort. The highest income range (> $97,500) contained 6% of the sulfonylurea cohort versus 12% of the TZD cohort. This discrepancy is likely due to B.C. PharmaCare's limited coverage reimbursement of TZD's versus full coverage of sulfonylureas; wealthier patients were more likely to pay out-of-pocket for TZDs.

Conclusion

Our analysis showed second-line TZD therapy compared to second-line sulfonylurea therapy was associated with a lower incidence of insulin initiation as third-line treatment in patients with type-2 diabetes, with a mean of 90 days. This duration of delay must be weighed against the absence of a proven reduction in morbidity and mortality with TZDs and the known serious cardiovascular risks.

Acknowledgments

The authors have no conflicts of interest to declare. The study was funded by a grant to the University of British Columbia from the British Columbia Ministry of Health. Their support is gratefully acknowledged. Carney and Dormuth had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The study received ethics approval from the University of British Columbia (UBC CREB Number H02-70020). The BC Ministry of Health approved data access.

All authors substantially contributed to the conception, design, analysis and interpretation of data, drafting and revising the article for important intellectual content, and gave approval for the final version. Data analysis was performed by Carney, Dormuth.

Table Legend:

Table 1: Baseline Characteristics of Study Patients by Current Exposure to Thiazolidinediones or Sulfonylureas in British Columbia (1998-2007)

Table 2: Insulin Events with Thiazolidinediones or Sulfonylureas in Patients With Type II Diabetes Mellitus

Table 3: Poisson Regression for Insulin End Points Associated with Thiazolidinediones or Sulfonylureas in Patients With Type II Diabetes Mellitus

Figure Legend:

Figure 1: Cumulative Hazard Distribution for Time to Insulin End Points Associated with Thiazolidinediones or Sulfonylureas in Patients With Type II Diabetes Mellitus

Table 1. Baseline Characteristics of Study Patients by Current Exposure to Glitazones or Sulfonylureas

Variable	Sulfonylurea (N = 15,613)	Any TZD (N = 3,254)	Pioglitazone (N = 1,213)	Rosiglitazone (N = 2,041)
Age, median (IQR*)	60 (50,69)	56 (48,64)	56 (48,64)	56 (48,64)
Women (%)	6,952 (45)	1,479 (45)	556 (46)	923 (45)
Family Income (%)				
0 to $21,250	3,600 (23)	377 (12)	139 (11)	238 (12)
$21,251 to $45,000	4,211 (27)	783 (24)	288 (24)	495 (24)
$45,001 to $70,833	2,634 (17)	761 (23)	280 (23)	481 (24)
$70,834 to $97,500	1,260 (8)	511 (16)	178 (15)	333 (16)
> $97,500	935 (6)	393 (12)	149 (12)	244 (12)
Unknown	2,973 (19)	429 (13)	179 (15)	250 (12)
Romano comorbidity score, median (IQR) †	1.00 (1,3)	1.00 (1,2)	1.0 (1,2)	1.0 (1,2)
Diabetes duration in years, median (IQR)	3 (1,7)	3 (1,6)	3 (1,7)	3 (1,6)
Medical History				
Renal disease ‡	637 (4)	75 (2)	25 (2)	50 (2)
Acute myocardial infarction ‡	912 (6)	104 (3)	40 (3)	64 (3)
Angina ‡	3,693 (24)	639 (20)	241 (20)	398 (20)
Congestive heart failure ‡	2,211 (14)	282 (9)	91 (8)	191 (9)
Coronary catheterization ‡	1,024 (7)	176 (5)	70 (6)	106 (5)
Lab Tests in Past Two Years**				
HbA1c, n	14,525 (93)	3,057 (94)	1,124 (93)	1,933 (95)
HbA1c, median (IQR)	3 (2,5)	3 (2,5)	4 (2,6)	3 (2,5)
Fasting Blood Glucose, n	14,521 (93)	3,041 (93)	1,129 (93)	1,912 (94)
Fasting Blood Glucose, median (IQR)	3 (2,5)	3 (2,5)	3 (2,5)	3 (2,5)
Drug Use in Past Two Years §				
Metformin	15,393 (99)	3,211 (99)	1,193 (98)	2,018 (99)
ACE Inhibitor	6,923 (44)	1,448 (44)	531 (44)	917 (45)
Beta blockers	11,279 (72)	2,512 (77)	940 (77)	1,572 (77)
Calcium channel blockers	2,854 (18)	487 (15)	176 (15)	311 (15)
Coxib NSAIDs	1,260 (8)	334 (10)	111 (9)	223 (11)
NSAIDs	5,511 (35)	1,059 (33)	394 (32)	665 (33)
Digoxin	609 (4)	63 (2)	18 (1)	45 (2)
Spironolactone	609 (4)	100 (3)	36 (3)	64 (3)
Statins	6,682 (43)	1,475 (45)	544 (45)	931 (46)

¶ Net family income in Canadian dollars from the most recent income tax return (1 Canadian dollar ~ 1 US dollar).
† Romano commorbidity score calculated using data one year prior to the index date.
‡ History within five years prior to the index date.
\ Dispensing of drug within 730 days prior to index date.
* IQR refers to the interquartile range.
** MSP fee items used - HbA1c: 91745, Fasting Blood Glucose: 91705-91710, 91715-91717, 91719

Table 2: Insulin Initiation Events with Thiazolidinediones (TZDs) or Sulfonylureas in Patients With Type II Diabetes Mellitus

Sex	Drug Group	Person Years of Follow-up	Insulin Initiation Events	Events per 100 PYs
Men	Sulfonylurea	7,879	240	3.05
	TZDs	2,005	26	1.30
	Rosiglitazone	1,250	15	1.20
	Pioglitazone	722	11	1.52
Women	Sulfonylurea	6,491	273	4.21
	TZDs	1,633	24	1.47
	Rosiglitazone	1,027	16	1.56
	Pioglitazone	562	8	1.42
Men and Women	Sulfonylurea	14,369	513	3.57
	TZDs	3,638	50	1.37
	Rosiglitazone	2,277	31	1.36
	Pioglitazone	1,285	19	1.48

Table 3. Poisson Regression for Insulin Initiation Events Associated with Thiazolidinediones (TZDs) or Sulfonylureas (SU) in Patients With Type II Diabetes Mellitus

Cohort	Crude Rate in TZD Group per 100 PYs	Crude Rate in SU Group per 100 PYs	TZD PYs of Follow-up	Crude Rate Ratio	Adjusted Rate Difference per 100 PYs (95% CI)
TZDs vs Sulfonylureas					
Men, age >=60	0.54	2.35	734	0.23	-0.80 (-1.51 - -0.08)
Men, age <60	1.73	3.75	1,271	0.46	-1.50 (-2.44 - -0.56)
Women, age >=60	0.76	2.75	656	0.28	-1.18 (-2.05 - -0.32)
Women, age <60	1.94	5.91	977	0.33	-2.22 (-3.46 - -0.99)
Pioglitazone (PIO) vs Sulfonylureas					
Men, age >=60	0.77	2.35	260	0.33	-0.73 (-1.9 - 0.43)
Men, age <60	1.92	3.75	469	0.51	-1.37 (-2.76 - 0.02)
Women, age >=60	0.42	2.75	240	0.15	-1.09 (-2.08 - -0.11)
Women, age <60	2.05	5.91	341	0.35	-2.04 (-3.79 - -0.29)
Rosiglitazone (ROS) vs Sulfonylureas					
Men, age >=60	0.42	2.35	474	0.18	-0.81 (-1.57 - -0.06)
Men, age <60	1.62	3.75	802	0.43	-1.52 (-2.59 - -0.45)
Women, age >=60	0.96	2.75	415	0.35	-1.21 (-2.31 - -0.12)
Women, age <60	1.89	5.91	636	0.32	-2.27 (-3.65 - -0.89)

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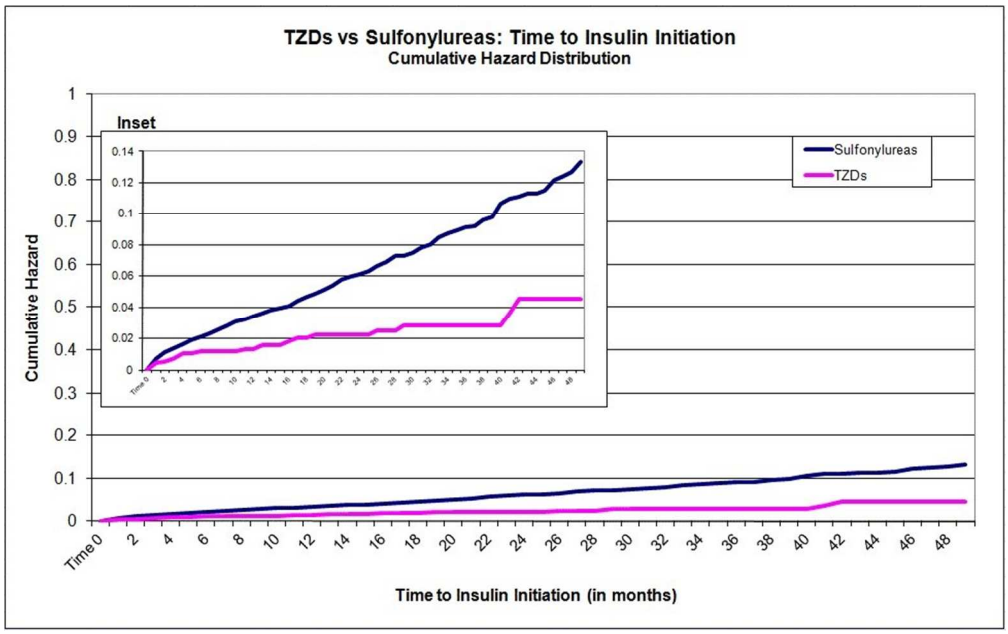

Figure 1: Cumulative Hazard Distribution for Time to Insulin End Points Associated with Thiazolidinediones or Sulfonylureas in Patients With Type II Diabetes Mellitus
82x51mm (300 x 300 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	p.1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	p.2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	p.6-7
Objectives	3	State specific objectives, including any pre-specified hypotheses	p.7-8
Methods			
Study design	4	Present key elements of study design early in the paper	P.8-9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	p.8-9
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	p.9
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	p.15
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	p.9-11

Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	p.8-9
Bias	9	Describe any efforts to address potential sources of bias	p.7,9,11-12
Study size	10	Explain how the study size was arrived at	p.9,12
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	p.9-12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	p.10-12
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	p.12
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	p.12,15; Table 3
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	p.12-14
		(b) Give reasons for non-participation at each stage	p.12
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	p.12,13; Table 1
		(b) Indicate number of participants with missing data for each variable of interest	p.12-13
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	p.13-14; Table 2

Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	p.13-14; Table 2-3; Figure 1
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	p.13-14
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	p.12,15; Table 3
Discussion			
Key results	18	Summarise key results with reference to study objectives	p.15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	p.15,17-18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	p.16
Generalisability	21	Discuss the generalisability (external validity) of the study results	p.16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	p.18-19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.