Sitagliptin, pancreatitis and older adults: a population-based cohort study

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Abstract

Background: The risk of pancreatitis with sitagliptin in routine care remains to be established in elderly patients with type 2 diabetes.

Methods: In a population-based retrospective cohort study of older adults in Ontario from 2010 until 2012, we studied those who were newly prescribed sitagliptin (n=57 689) or an alternative hypoglycemic agent to sitagliptin (metformin, glyburide, gliclazide or insulin; n=83 405) in the outpatient setting. Our primary outcome was a hospital encounter (emergency room visit or hospitalization) with acute pancreatitis assessed within 90 days of a new prescription for the relevant hypoglycemic agent. We used inverse probability of treatment weighting to balance the two groups in the analysis.

Results: There were no significant differences in 68 measured baseline characteristics and 34 medications between the sitagliptin and the alternative hypoglycemic agent group. A prescription for sitagliptin was not associated with an increased risk of a hospital encounter with pancreatitis compared with a prescription for an alternative hypoglycemic agent (weighted total 46 of 57 689 sitagliptin users [0.08%] vs 48 of 55 705 alternative hypoglycemic agent

users [0.09%], absolute risk difference −0.01% [95% CI −0.05%–0.02%], odds ratio [OR] 0.92 [95% CI 0.55–1.55]).

Interpretation: Older adults who were prescribed sitagliptin in routine care were not at a substantially higher risk of acute pancreatitis compared with those prescribed alternative oral hypoglycemic agents. These findings are reassuring for those who use or prescribe sitagliptin in the management of type 2 diabetes.

Introduction

Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, reduces blood glucose by blocking the breakdown of glucagon-like peptide-1 (GLP-1), an incretin hormone that stimulates insulin secretion in a glucose-dependent fashion. [1] Because of its relative potency (decreases glycated hemoglobin by up to 1% as monotherapy) and low risk of hypoglycemia, [2] sitagliptin use has increased significantly over recent years (there were over 700 000 prescriptions for sitagliptin in Ontario alone from June 2010 to June 2012). [3]

Despite its benefits, DPP-4 inhibitor use has been linked with pancreatitis in case reports, animal studies and post-marketing drug surveillance studies. It has been postulated that sitagliptin might promote pancreatitis by increasing the mass of the pancreas, modifying enzyme secretion, disturbing acinar architecture, promoting pancreatic inflammation, or increasing ductal turnover and ductal metaplasia. [4, 5] As pancreatitis can be a significant cause of morbidity and mortality, warnings of the association have been published by regulatory agencies, pharmaceutical companies and diabetes association guidelines (pancreatitis warnings outlined in eTable 1 of the Supplement).

However, in real-practice observational studies, the link between DPP-4 inhibitor use and pancreatitis has been inconsistently described and studies have been limited in their collection of baseline covariates, drug use and health care utilization. [6, 7] Further, there has been a reliance on self-reported outcomes, [6, 8, 9] and studies have often been limited to younger populations, making results less generalizable to the elderly. [7, 10] In the current study we aimed to examine the risk of acute pancreatitis with sitaglipin use in routine care in a large, representative population of older adults in Ontario, Canada.

Methods

Study Design and Setting

We conducted a population-based retrospective cohort study of older adults from June 2010 to December 2012 using linked health care databases in Ontario, Canada. Ontario has approximately 1.8 million adults aged 65 years or older who have comprehensive universal healthcare. This includes coverage for outpatient prescription medications, physician services, hospitalizations and diagnostic testing. [11]

The study was conducted at the Institute for Clinical Evaluative Sciences (ICES) according to a pre-specified protocol that was approved by the research ethics board at Sunnybrook Health Sciences Centre (Toronto, Canada). This

board waived informed consent. The reporting of the study follows guidelines for the reporting of observational studies (checklist of recommendations in eTable 2 of the Supplement). [12]

Data Sources

We obtained patient characteristics, drug use, covariate information, and outcome data using records from five databases. We ascertained vital statistics from the Registered Persons Database of Ontario, which contains demographic information on all Ontario residents who have been issued a health card. The Ontario Drug Benefit Program database was used to identify prescription drug use. This database contains accurate records of all outpatient prescriptions dispensed to those aged 65 years or older, with an error rate of less than 1%. [13] Diagnostic and procedural information on hospitalizations and emergency room visits were abstracted from the Canadian Institute for Health Information's Discharge Abstract Database and the National Ambulatory Care Reporting System database, respectively. Covariate information was derived from the Ontario Health Insurance Plan database, which includes health claims for inpatient and outpatient physician services. We used the ICES Physician Database to abstract hypoglycemic agent prescriber information. In several previous studies, we have used these databases to research adverse drug events and health outcomes. [14-18] A

subpopulation in Southwestern Ontario had outpatient glycated hemoglobin measurements available before a new hypoglycemic agent prescription. [19]

With the exception of prescriber information (missing in approximately 9.6% in the study), and income quintile (missing in approximately 0.4% of the study) the databases were complete for all variables used. *International Classification of Diseases 10th revision* (*ICD-10*; post-2002) and *Canadian Classification of Health Interventions* (*CCI*; post-2002) codes were utilized to assess baseline comorbidities and investigations in the five years prior to the hypoglycemic agent prescription (coding definitions listed in eTable 3 in the Supplement). Codes used to assess the outcome of acute pancreatitis and their validity are detailed in eTable 4 in the Supplement.

Patient Selection

Patient selection is presented in eFigure 1 and eFigure 2 in the Supplement. To mimic routine practice, we studied older adults newly prescribed sitagliptin or an alternative hypoglycemic agent to sitagliptin (metformin, glyburide, gliclazide or insulin) between June 2010 and December 2012. The date of their hypoglycemic drug prescription served as the index date (referred to as the cohort entry date or start time for follow-up).

In the sitagliptin group we excluded the following patients from the analysis: 1) those in their first year of eligibility for prescription drug coverage (aged 65 years) to avoid incomplete medication records, 2) those with evidence of a hospital discharge in the two days prior to or on the index date to ensure these were new sitagliptin prescriptions (because in Ontario patients continuing a medication initiated in hospital would have their medication dispensed on the same day or the day after hospital discharge), 3) those who had evidence of a code for anesthesia or an epidural in the 30 days prior to the index date to exclude those with a recent surgery, a risk factor for pancreatitis, 4) those with evidence of a pancreas transplant or pancreatectomy in the five years prior to the index date, to exclude those with previous surgical manipulation of the pancreas, 5) those with a prescription for one or more DPP-4 inhibitors in the one year prior (to define new use), 6) those prescribed saxagliptin (an alternative DPP-4 inhibitor) or a sitagliptin-metformin combination pill (to restrict to sitagliptin use only).

In those prescribed an alternate hypoglycemic agent we excluded patients from analysis for similar reasons as in the sitagliptin cohort, with differences as follows: we excluded 1) those initiated on metformin without evidence of a code for diabetes in the Ontario Diabetes Database [20] as diabetes itself is a risk factor for pancreatitis and

metformin can be prescribed for indications other than diabetes), [6, 7] 2) those with a prescription for the same alternative hypoglycemic agent in the one year prior (to define new use), 3) those with a prescription for a DPP-4 inhibitor in the one year prior (to compare mutually exclusive groups). In both the sitagliptin and alternative hypoglycemic agent groups, a patient could enter the cohort only once.

Outcomes

The outcome was a hospital encounter (emergency room visit or hospital admission) with acute pancreatitis (diagnostic codes and their validation presented in eTable 4 in the Supplement). In the primary analysis the outcome was assessed within 90 days of the index date. We chose 90 days of follow-up to avoid crossover in drug therapy that could occur with longer periods of follow up, and because prescriptions covered by Ontario's drug plan are prescribed at no more than 100-day intervals.

Statistical Analysis

We compared baseline characteristics between the sitagliptin and the alternative hypoglycemic agent group using standardized differences. This metric describes differences between group means relative to the pooled standard deviation and is considered a meaningful difference if greater than 10%. [21]

The propensity score was derived from a logistic regression model with 29 baseline covariates incorporated into the score based on prior recommended methods (variables listed in eTable 5 in the Supplement). [22] Inverse probability of treatment weights (IPTW) were calculated using the propensity model to create a sample in which the distribution of measured baseline covariates was independent of treatment assignment. [22]

For the referent group, we considered older adults prescribed an alternative hypoglycemic agent to sitagliptin (metformin, glyburide, gliclazide, or insulin). We expressed the risk for developing acute pancreatitis in both relative and absolute terms. To calculate odds ratios and 95% confidence intervals, a logistic regression model was fit using a robust variance estimate, accounting for IPTW.

We conducted all analyses with SAS version 9.3 (SAS Institute, Cary, North Carolina). This includes additional analyses we undertook after knowledge of the primary results (see Results section). In all outcome analyses we interpreted 2-tailed *p* values lower than 0.05 as statistically significant.

Results

Baseline Characteristics

We identified 57 689 patients initiated on sitagliptin and 83 405 patients initiated on an alternative hypoglycemic agent. The baseline characteristics of the two groups before and after propensity weighting are presented in Table 1 and in eTable 6 and eTable 7 of the Supplement. After weighting, we had weighted totals of 57 689 in the sitagliptin group and 55 705 in the alternative hypoglycemic agent group, and characteristics were similar between the groups (with standardized differences less than 10% for 68 characteristics and 34 medications).

Outcomes

Results for the primary outcome of pancreatitis are presented in Table 2. Prescribing sitagliptin was not associated with a higher 90-day risk of a hospital encounter with pancreatitis compared with prescribing an alternative hypoglycemic agent (weighted total 46 of 57 689 sitagliptin users [0.08%] vs 48 of 55 705 alternative hypoglycemic agent users [0.09%], absolute risk difference −0.01% [95% CI −0.05%–0.02%], odds ratio [OR] 0.92 [95% CI 0.55–1.55], p=0.76).

Additional Analysis

We conducted a time to event analysis and our findings remained robust. Specifically, we extended the follow-up beyond 90 days, terminating the observation period for

reasons of death, study hypoglycemic agent discontinuation, receipt of a non-study hypoglycemic agent, or the last date of available records (March 31, 2013) (details presented in eTable 8 of the Supplement). Prescribing sitagliptin was not associated with a higher risk of a hospital encounter with acute pancreatitis compared with prescribing an alternative hypoglycemic agent (Cox proportional hazards model with IPTW; hazard ratio [HR] 1.18 [95% CI 0.94–1.49], p=0.15).

Discussion

Study Findings

In our study of older adults, the initiation of sitagliptin was not associated with a higher 90-day risk of hospital encounters with acute pancreatitis compared with the initiation of metformin, glyburide, gliclazide or insulin in routine care.

Results in Relation to Other Studies

The findings of our routine practice study are consistent with the results of randomized controlled trials. In a systematic review and meta-analysis of the risk of pancreatitis with DPP-4 inhibitor use in patients with type 2 diabetes (109 studies of 26 732 DPP-4 inhibitor users and 18 507 individuals using placebo or alternative hypoglycemic agents), Monami et al noted no increase in the incidence of pancreatitis in DPP-4 inhibitor users (20 of 11 553 DPP-4

inhibitor users vs 16 of 8973 placebo/alternative hypoglycemic agent users; adjusted odds ratio [OR] 0.93 [CI 0.52–1.69], *p*=0.83). [23] In a recent study of patients with type 2 diabetes (mean age 65 years) randomized to saxagliptin (a DPP-4 inhibitor) or placebo and followed for a median of 2.1 years for cardiovascular outcomes, in secondary analysis, rates of adjudicated cases of acute pancreatitis were similar in both groups (22 of 8280 saxagliptin users [0.3%] vs 16 of 8212 placebo users [0.2%], *p*=0.42). [24]

Our results are also consistent with a smaller active drug surveillance study of adults and older adults which noted that in 16 276 initiators of sitagliptin and 16 281 matched initiators of metformin or glyburide, the risk of acute pancreatitis was comparable (RR 1.0 [95% CI 0.5–2.0]). [25] Recognizing that their study excluded older adults and that they collected fewer baseline characteristics, we also note similar findings to a population-based cohort study of adults which found that when compared with those prescribed a new sulphonylurea, biguanide or thiazolidendione, sitagliptin or exenatide (a GLP-1 agonist) use was not associated with a higher risk of acute pancreatitis (adjusted HR 1.0 [95% CI 0.7–1.3]). [7]

Our results do differ from other published studies that report a higher risk of pancreatitis with sitagliptin use. A

United States Food and Drug Administration database (U.S. FDA) study of patient or physician reported adverse events from 2004–2009 noted that users of sitagliptin or exanatide had a higher odds of pancreatitis (OR 6.74 [95% CI 4.61–10], $p<0.0001$) compared with users of rosiglitazone, nateglinide, repaglinide, and glipizide. [6] In an additional U.S. FDA study, the odds of pancreatitis in DPP-4 inhibitor users was found to be 20.8 times (95% CI 12.6–34.5) the odds of pancreatitis in users of other hypoglycemic agents in an adjusted analysis. [8] A recent study of serious adverse events reported to the French Pharmacovigilance system noted that the rate of exposure to incretin-based drugs was higher in cases of pancreatitis vs non-cases of pancreatitis (67 DPP-4 inhibitor users in 147 cases of pancreatitis vs 421 DPP-4 inhibitor users in 2962 non-cases of pancreatitis; adjusted reporting OR 12.1 [95% CI 7.3–20.0], $p<0.0001$). These studies however may have been subject to reporting bias as events were self-reported and there is no certainty that the reported event was due to the product itself. Reporting results may also have been inflated by external factors. [6, 9]

In an additional study, Singh et al using a case-control design found that the adjusted odds of acute pancreatitis in those who were currently (OR 2.24 [95% CI 1.36–3.68]) and who had recently used a DPP-4 inhibitor was higher (OR 2.01 [95% CI 1.37–3.18]) than those who had not. [10] This study

performed a more limited assessment of baseline covariates and health care utilization indices, and as it was completed in a younger population, may not be fully generalizable to older adults (mean age 52 years).

Strengths and Limitations

Our study has several strengths. Using a large, representative sample of elderly patients who use sitagliptin in a routine setting (with multiple comorbidities, and on multiple medications), our study complements information generated from randomized clinical trials by studying an uncommon but significant adverse drug reaction with adequate statistical power and inclusive of patients not enrolled in randomized clinical trials.

Compared with previous observational studies we accounted for a number of confounders including baseline comorbidities and medications associated with acute pancreatitis and comprehensively examined health care utilization, investigations and concomitant hypoglycemic drug prescriptions in both groups. Using propensity weighting, we were able to balance the two groups on 68 characteristics and 34 medications.

Further, our new-user design allowed us to observe outcomes after the initiation of treatment. Where previous studies included self-reported pancreatitis, in our study

pancreatitis was documented in hospital records by the treating health care team. Additionally, to echo routine care and make our findings interpretable in clinical practice, we studied patients who were newly prescribed current hypoglycemic alternatives to sitagliptin as a comparison group (metformin, a sulphonylurea or insulin).

Our study does have some limitations. Prospective data collection with independent outcome adjudication is a preferred methodology to a retrospective database study. We were also not able to detect asymptomatic pancreatitis or pancreatitis that did not result in a hospital presentation, although such outcomes are less severe hospital encounters for pancreatitis. We were further only able to accurately ascertain medications dispensed with no information on medication use.

As in previous studies, the statistical power of our study warrants attention. Given the low event rate of pancreatitis in both our sitagliptin and alternative hypoglycemic agent groups we were able to rule out a greater than 1.7-fold increase in the risk of pancreatitis in new users of sitagliptin compared with the alternative hypoglycemic agent group with adequate statistical power (upper bound of the confidence interval). We could not rule out a smaller increase in risk. Also, the limited number of events also precluded meaningful subgroup analysis.

Confounding is an additional consideration in all observational studies and in the current study we had limited information on factors including obesity, body mass index, and smoking status which are known to influence the risk of pancreatitis. However, using propensity score weighting we obtained good balance on a large number of measured baseline characteristics between the two groups.

Conclusions

In older adults, the initiation of sitagliptin did not result in a higher risk of a hospital encounter with pancreatitis compared with an alternative diabetic medication (any of metformin, glyburide, gliclazide or insulin). These findings are reassuring for those who use or prescribe sitagliptin in the management of type 2 diabetes.

Authors Contributions: EM was responsible for the acquisition of data and the study analysis. KC drafted the manuscript. All authors contributed to the conception and design of the work, its interpretation, revised the manuscript critically for important intellectual content, gave final approval of the version to be published and agree to act as guarantor of the work. AG and EM had full access to the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Disclaimer: The opinions, results, and conclusions are those of the authors, and no endorsement by the Institute for Clinical Evaluative Sciences, Ontario Ministry of Health and Long-Term Care, or Academic Medical Organization of Southwestern Ontario is intended or should be inferred.

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Table 1: Key baseline characteristics prior to and after propensity weighting in patients initiated on sitagliptin or an alternative hypoglycemic agent.

	Prior to Weighting			After Weighting #		
	Sitagliptin (n=57 689)	Other (n=83 405)	Standardized Difference*	Sitagliptin (Weighted n=57 689)	Other (Weighted n=55 705)	Standardized Difference*
Mean age at index date	73.98 (6.25)	75.07 (6.93)	17%	73.98 (6.25)	74.07 (5.2)	2%
Female	27 584 (47.82)	40 312 (48.33)	1%	27 584 (47.82)	26 279 (47.18)	1%
Comorbidities||						
Gallstones/ biliary stones	2163 (3.75)	3152 (3.78)	0%	2163 (3.75)	2059 (3.70)	0%
Calcium disorder	123 (0.21)	273 (0.33)	2%	123 (0.21)	154 (0.28)	1%
Alcoholism	240 (0.42)	659 (0.79)	5%	240 (0.42)	338 (0.61)	3%
ERCP	281 (0.49)	561 (0.67)	2%	281 (0.49)	334 (0.60)	2%
Charlson cormorbidity index score §	1.13	1.22	5%	1.13	1.23	7%
Pancreatitis	216 (0.37)	467 (0.56)	3%	216 (0.37)	267 (0.48)	2%
Medications ##						
Diuretics	18 516 (32.10)	28 090 (33.68)	3%	18 516 (32.10)	18 644 (33.47)	3%
Anti-inflammatories	10 816 (18.75)	13 157 (15.77)	8%	10 816 (18.75)	10 268 (18.43)	1%
Glucocorticoids	11 297 (19.58)	16 121 (19.33)	1%	11 297 (19.58)	11 350 (20.38)	2%
Sulphonamides	859 (1.49)	1647 (1.97)	4%	859 (1.49)	1029 (1.85)	3%
Lipid lowering drugs	43 829 (75.97)	51 532 (61.79)	31%	43 829 (75.97)	42 210 (75.77)	0%
Estrogen therapy	601 (1.04)	886 (1.06)	0%	601 (1.04)	689 (1.24)	2%
Omeprazole	2343 (4.06)	3519 (4.22)	1%	2343 (4.06)	2639 (4.74)	3%
Hypoglycemic agents prescribed in the 120 days prior to index date **						
Insulin	4505 (7.81)	3164 (3.79)	17%	4505 (7.81)	4091 (7.34)	2%
Gliclazide	17 142 (29.71)	4566 (5.47)	67%	17 142 (29.71)	14 734 (26.45)	7%
Glyburide	13 807 (23.93)	12 681 (15.20)	22%	13 807 (23.93)	14 847 (26.65)	6%
Metformin	43 135 (74.77)	20 987 (25.16)	14%	43 135 (74.77)	41 592 (74.66)	0%

Pioglitazone	5812 (10.07)	1863 (2.23)	33%	5812 (10.07)	5949 (10.68)	2%
Repaglinde	341 (0.59)	194 (0.23)	6%	341 (0.59)	228 (0.41)	3%
Rosiglitazone	2015 (3.49)	524 (0.63)	20%	2015 (3.49)	1956 (3.51)	0%
Hemoglobin A1c				0.077 (0.013)	0.078 (0.012)	8%

Full table of demographics, comorbidities, medications, laboratory data and health care utilization available in eTable 6 and eTable 7 of the Supplement.
Data presented as number (percent) with the exception of age which is presented as mean (SD), Charlson comorbidity score (mean) and hemoglobin A1c which is presented as mean (SD).
Abbreviations: ERCP endoscopic retrograde cholangiopancreatography.
Cell sizes less than six were not reported for reasons of privacy.
All patients identified prior to weighting were included in the analyses. The number of patients indicated represents a weighted total.
* Standardized differences are less sensitive to sample size than traditional hypothesis tests. They provide a measure of the difference between groups divided by the pooled standard deviation; a value greater than 10% (0.1) is interpreted as a meaningful difference between the groups.
§ Charlson Comorbidity Index was calculated using five years of hospitalization data. “No hospitalizations” received a score of 0. [26]
|| Comorbidities were assessed by administrative database codes in the previous five years.
Baseline medication use was assessed in the previous 120 days.
** Hypoglycemic agent use in the previous 120 days includes hypoglycemic drugs prescribed from −120 to −1 day prior to the index date where days supply covered the prescription date.

Table 2: Ninety-day risk of a hospital encounter with acute pancreatitis

	Number of Events (%)		Absolute Risk Difference(%) (95% CI)	Odds ratio (95% CI)
	Sitagliptin Weighted n=57 689	Alternative hypoglycemic agent Weighted n=55 705		
Hospital encounter with acute pancreatitis	46 (0.08)	48.26 (0.09)	-0.01% (-0.05-0.02)	0.92 (0.53-1.61)

Patients prescribed glyburide, gliclazide, metformin or insulin served as the referent group.
Abbreviations: confidence interval (CI).
All patients identified prior to weighting were included in the analysis. The number of patients indicated represents a weighted total.

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Supplementary Online Content

eTable 1. DPP-4 inhibitor and pancreatitis warnings

Food and Drug Administration 2009	Information for Healthcare Professionals – Acute pancreatitis and sitagliptin (marketed as Januvia and Janumet) "FDA is revising the prescribing information for Januvia (sitagliptin) and Janumet (sitagliptin/metformin) to include information on reported cases of acute pancreatitis in patients using these products." "Eighty-eight post-marketing cases of acute pancreatitis, including two cases of hemorrhagic or necrotizing pancreatitis in patients using sitagliptin, were reported to the Agency between October 16, 2006 and February 9, 2009. Based on these reports, FDA is working with the manufacturer of sitagliptin and sitagliptin/metformin to revise the prescribing information…" to include: "Based on the temporal relationship of initiating sitagliptin or sitagliptin/metformin and development of acute pancreatitis in the reviewed cases, FDA believes there may be an association between these events. Because acute pancreatitis is associated with considerable morbidity and mortality, and early recognition is important in reducing adverse health outcomes, FDA is recommending revisions to the prescribing information to alert healthcare professionals to this potentially serious adverse drug event."
MERCK Januvia Drug monograph 2013	"There have been reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking JANUVIA®. After initiation of JANUVIA®, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, JANUVIA® should promptly be discontinued and appropriate management should be initiated. Risk factors for pancreatitis include a history of: pancreatitis, gallstones, alcoholism, or hypertriglyceridemia."
Canadian Diabetes Association Guidelines 2013	"DPP-4 inhibitor: Sitagliptin (Januvia) Saxagliptin (Onglyza) Linagliptin (Trajenta): Negligible risk of hypoglycemia as monotherapy, weight neutral, Improved postprandial control, rare cases of pancreatitis "

Harper W, Clement M, Goldenberg R, Hanna A, Main A, Retnakaran R, Sherifali D, Woo V, Yale JF. Canadian Diabetes Associaton Guidelines – Pharmacologic management of type 2 diabetes. 2013. Available from: http://guidelines.diabetes.ca/Browse/Chapter13. Accessed 03/13, 2014.

Januvia Sitagliptin tablets 25mg, 50mg, 100mg. Merck Sharp & Dohme Limited; 2013. Available from: http://www.merck.ca/assets/en/pdf/products/JANUVIA-PM_E.pdf. Accessed 03/13, 2014.

U.S. Food and Drug Administration. Information for Healthcare Professionals – Acute pancreatitis and sitagliptin (marketed as Januvia and Janumet). 2009. Available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm183764.htm. Accessed 03/13, 2014.

eTable 2. Checklist of recommendations for reporting of observational studies using the STROBE guidelines

	Item No	Recommendation	Reported
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Abstract
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction
Objectives	3	State specific objectives, including any pre-specified hypotheses	Introduction
Methods			
Study design	4	Present key elements of study design early in the paper	Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods
		(b) For matched studies, give matching criteria and number of exposed and unexposed	Methods
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods
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	Supplementary Materials eTable 3, 4
Bias	9	Describe any efforts to address potential sources of bias	Discussion
Study size	10	Explain how the study size was arrived at	Methods, based on availability of the data
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Methods
		(b) Describe any methods used to examine subgroups and interactions	Not Applicable
		(c) Explain how missing data were addressed	Not Applicable
		(d) If applicable, explain how loss to follow-up was addressed	Not Applicable
		(e) Describe any sensitivity analyses	Not Applicable

Results			
Participants	13	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	Results, Supplementary Materials eFigure 1, 2
		(b) Give reasons for non-participation at each stage	Methods, Supplementary Materials eFigure 1, 2
		(c) Consider use of a flow diagram	Supplementary Materials eFigure 1, 2
Descriptive data	14	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders	Results, Table 1, Supplementary Materials eTable 6, 7
		(b) Indicate number of participants with missing data for each variable of interest	Results
		(c) Summarise follow-up time (e.g. average and total amount)	Results
Outcome data	15	Report numbers of outcome events or summary measures over time	Results
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results, Table 3
		(b) Report category boundaries when continuous variables were categorized	Table 1, Supplementary Materials eTable 6, 7
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Results, Table 3
Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	Results
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion
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	Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion
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	Cover page, Disclosures

eTable 3. Coding definitions for demographic and comorbid conditions

Characteristics/Condition	Database	Codes
Age	RPDB	
Sex	RPDB	
Socioeconomic Status	Statistics Canada	
Rural Location	Statistics Canada	
Long Term Care Utilization	ODB	
Charlson Comorbidity Index	CIHI-DAD	
Health Care Visits	OHIP IPDB	
Prescribing Physician	IPDB	
Pancreatectomy/Pancreas Transplant	CIHI-DAD OHIP	CCI: “1OA85VCXXK", "1OJ85", "1OJ87", "1OJ89", "1OK58", "1OK85", "1OK87", "1OK91", "1OJ83" ICD10: "T8681" OHIP FEE: "S297", "S298", "S299", "S300", "S301", "S303", "S308", "S309"
Gallstones/Biliary stones	CIHI-DAD OHIP	ICD10: "K563", "K800", "K801", "K802", "K803", "K804", "K805" OHIP DX: "574"
Calcium disorder	CIHI-DAD	ICD10: "E835"
Alcoholism	CIHI-DAD	ICD10: "E512", "F10", "G312", "G621", "G721", "I426", "K292", "K70", "K860", "T510", "X45", "X65", "Y15", "Y573", "Z502", "Z714", "Z721"
Tobacco Use	CIHI-DAD OHIP	ICD10: "F17", "T652", "Z587", "Z716", "Z720", "Z8642" OHIP DX: "305" OHIP Fee: "E079, "K039", "Q041", "Q042", "Q622"
Pancreatic Neoplasm	CIHI-DAD OHIP	ICD10: "C250", "C251", "C252", "C253", "C254", "C257", "C258", "C259" OHIP DX: "157"
ERCP	CIHI-DAD OHIP	CCI: "1OE50BA", "1OE50BAAG", "1OE52BATS", "1OE54BATS", "1OJ52BA", "1OJ52BATS", "3OG10WZ" OHIP FEE: "E662", "E668", "Z760"

Chronic Kidney Disease	CIHI-DAD OHIP	ICD10: "E102", "E112", "E132", "E142", "I12", "I13", "N08", "N18", "N19" OHIP DX: "403", "585"
Bile Duct Neoplasm	CIHI-DAD OHIP	ICD10: "C221", "C240", "C248", "C249", "C787", "D015", "D135", "D376", "81600", "81610", "81613" OHIP DX: "156"
HIV	CIHI-DAD OHIP	ICD10: "B20", "B21", "B22", "B23", "B24", "Z21", "C46" OHIP DX: "042", "043", "044"
Systemic Lupus Erythematosis	CIHI-DAD OHIP	ICD10: "L93", "M32" OHIP DX: "695"
Polyarteritis Nodosa	CIHI-DAD OHIP	ICD10: "M300" OHIP DX: "446"
Celiac Disease	CIHI-DAD OHIP	ICD10: "K900" OHIP DX: "579"
Obesity	CIHI-DAD OHIP	ICD10: "E660", "E661", "E662", "E668", "E669" OHIP DX: "278"
Charlson Comorbidity Index	CIHI-DAD	
Diabetic Retinopathy	CIHI-DAD	ICD10: "E1030", "E1031", "E1032", "E1033", "E1130", "E1131", "E1132", "E1133", "E1330", "E1331", "E1332", "E1333", "E1430", "E1431", "E1432", "E1433", "H360"
Diabetic Neuropathy	CIHI-DAD	ICD10: "E1040", "E1041", "E1042", "E1048", "E1049", "E1440", "E1441", "E1442", "E1448", "E1140", "E1141", "E1142", "E1148", "E1340", "E1341", "E1342", "E1348", "E1349", "G590", "G632", "G990"
Peripheral Vascular Disease	CIHI-DAD OHIP	ICD 10: "I700", "I702", "I708", "I709", "I731", "I738", "I739", "K551" CCI: "1KA76", "1KA50", "1KE76", "1KG26", "1KG50", "1KG57", "1KG76MI", "1KG87"

		OHIP fee codes: "R787", "R780", "R797", "R804", "R809", "R875", "R815", "R936", "R783", "R784","R785", "E626", "R814", "R786", "R937", "R860", "R861", "R855", "R856", "R933", "R934", "R791", "E672", "R794", "R813", "R867", "E649"
Heart Failure	CIHI-DAD OHIP	ICD10: "I500", "I501", "I509", "I255", "J81" CCI: "1HP53", "1HP55", "1HZ53GRFR", "1HZ53LAFR", "1HZ53SYFR" OHIP FEE: "R701", "R702", "Z429" OHIP DX: "428"
Coronary Artery Bypass Graft	CIHI-DAD OHIP	CCI: 1IJ50, 1IJ76 CCP: 4802, 4803, 4809, 4811, 4812, 4813, 4814, 4815, 4816, 4817, 4819 OHIP FEE: Z434, R742, R743
Hypertension	ODB	
Coronary Artery Disease, Excluding Angina	CIHI-DAD	ICD10: "I21", "I22", "Z955", "T822" CCI: "1IJ50", "1IJ76" OHIPFee: "R741", "R742", "R743", "G298", "E646", "E651", "E652", "E654", "E655", "Z434", "Z448" OHIPDx: "410", "412"
Myocardial Infarction	CIHI-DAD	ICD9: “410” ICD10: “I21”, “I22”
Stroke/Transient Ischemic Attack	CIHI-DAD	ICD10: "I630", "I631", "I632", "I633", "I634", "I635", "I638", "I639", "I64", "H341", "I600", "I601", "I602", "I603", "I604", "I605", "I606", "I607", "I609", "I61", "G450", "G451", "G452", "G453", "G458", "G459"
Dialysis	CIHI-DAD OHIP	ICD10: "T824", "Y602", "Y612", "Y622", "Y841", "Z49", "Z992", "N180", "E1022", "E1023", "E1122", "E1123", "E1322", "E1323", "E1422", "E1423" CCI: "1OT53DATS", "1OT53HATS", "1OT53LATS", "1SY55LAFT", "7SC59QD", "1KY76", "1PZ21" OHIP FEE: "R850", "G324", "G336", "G327", "G862", "G865", "G099", "R825", "R826", "R827", "R833", "R840", "R841", "R843", "R848", "R851", "Z450", "Z451", "Z452", "G864", "R852", "R853", "R854", "R885", "G333", "H540", "H740", "R849", "G323", "G325", "G326", "G860", "G863", "G866", "G330", "G331", "G332", "G861", "G082", "G083", "G085", "G090", "G091", "G092", "G093", "G094", "G095", "G096", "G294", "G295"

Renal Transplant	CIHI-DAD OHIP	ICD10: "T861", "N165", "Z940" CCI: "1PC85" OHIP FEE: "E762", "S435", "E769", "S434", "E771", "Z631", "G347", "G348", "G412", "G408", "
Hypoglycemic Episode	CIHI-DAD	ICD10: "E15", "E160", "E161", "E162", "E1063", "E1163", "E1363", "E1463"
Acute or Chronic Pancreatitis	CIHI-DAD	ICD 10: "K85", "B252", "B263", "K860", "K861"
Hyperglycemic Emergency	CIHI-DAD	ICD10: "E1410", "E1412", "E1010", "E1012", "E1110", "E1112", "E1300", "E140"
Glycated Hemoglobin Value	Gamma Dynacare	
Number of Physician Visits	OHIP	
Glycated Hemoglobin Tests	OHIP	OHIP FEE: "L093"
Glucose Tests	OHIP	OHIP FEE: "L111", "L112", "G002"
Cholesterol Tests	OHIP	OHIP Fee: "G001", "G013", "L117", "Q183"
TSH Tests	OHIP	OHIP FEE: "G016", "G399", "L341"
Carotid Ultrasound	CIHI-DAD OHIP	CCI: "3JE30" OHIP FEE: "J201", "J501", "J189", "J489', "J190", "J191", "J490", "J491", "J492"
Cardiac Catheterization	CIHI-DAD OHIP	CCI: "3IJ30GP", "3HZ30GP", "2HZ24GPKJ", "2HZ24GPKL", "2HZ24GPKM", "2HZ24GPXJ", "2HZ28GPPL", "2HZ71GP" OHIP FEE: "G296", "G297", "G299", "G300", "G301", "G304", "G305", "G306"
Coronary Revascularization	CIHI-DAD OHIP	CCI: "1IJ50", "1IJ26", "IIJ27", "1IJ57", "1IJ76" OHIP FEE: "R741", "R742", "R743", "E651", "E652", "E654", "E646", "G298", "Z434", "G262"
Echocardiography	CIHI-DAD OHIP	CCI: "3IP30" OHIP FEE: "G560", "G561", "G562", "G566", "G567", "G568", "G570", "G571", "G572", "G574", "G575", "G576", "G577", "G578", "G579", "G580", "G581"
Holter Monitor	CIHI-DAD OHIP	CCI: "2HZ24JAKH" OHIP FEE: "G650", "G651", "G652", "G653", "G654", "G655", "G656", "G657", "G658", "GG59", "G660", "G661", "G682", "G683", "G684", "G685", "G686", "G687", "G688", "G689", "G690", "G692", "G693"

Cardiac Stress Test	CIHI-DAD OHIP	CCI: "2HZ08", "3IP70" OHIP FEE: "G315", "G174", "G111", "G112", "G319", "J604", "J606", "J607", "J608", "J611", "J612", "J613", "J667", "J807", "J808", "J809", "J804", "J811", "J812", "J813", "J867", "J609", "J666", "J866"
Influenza Vaccine	OHIP	OHIP FEE: "G590", "G591"
Colorectal Cancer Screening	OHIP	OHIP FEE: "G004", "L179", "L181", "Q043", "Q152", "X112", "X113", "Z535", "Z536", "Z555", "Z580"
Prostate Specific Antigen Testing	OHIP	OHIP FEE: "L354", "L358"
Mammography	OHIP	OHIP FEE: "X172", "X178", "X184", "X185", "X201"
Diabetes Management Code	OHIP	OHIP FEE: "K030"
Diabetes Incentive Code	OHIP	OHIP FEE: "Q040"
Bone Mineral Density	OHIP	OHIP FEE: "J654", "J688", "J854", "J888", "X149", "X152", "X153", "X155", "Y654", "Y688", "Y854", "Y888"

CCI, Canadian Classification of Health Interventions; CCP, Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures; CIHI, Canadian Institute for Health Information hospital discharge abstract database; *ICD-9, International Classification of Disease, Ninth Revision*; *ICD-10, International Classification of Disease, Tenth Revision*; RPDB, Registered Persons Database of Ontario; IPDB, ICES Physician Database.

eTable 4. Coding definitions for hospital presentation with pancreatitis

Condition	Database	Codes
Acute pancreatitis*	CIHI-DAD	ICD 10: "K85", "B252", "B263"

* Using the Swedish National Patient Register, in a cohort of patients in an inpatient setting Razavi et al performed a validation study of acute pancreatitis codes (K85.0, 85.1, 85.2, 85.3, K85.8 and K85.9) using clinical diagnostic criteria (definitive acute pancreatitis if 2 of 3 of: upper abdominal pain, elevated blood levels of amylase, pancreatic amylase or lipase at least three times the upper limit of normal or typical signs of acute pancreatitis on medical imaging; probable acute pancreatitis if combination or clinical signs of acute pancreatitis and enzyme levels elevated but not greater than three times the upper limit of normal or a combination of clinical signs and medical imaging indicating acute pancreatitis). Among 530 patients with a diagnosis code of acute pancreatitis in the registry, 442 (83%) had definitive acute pancreatitis and another 80 (15%) had probable acute pancreatitis. Eight (2%) had no acute pancreatitis. The number of false-negative cases of pancreatitis was 23 (32%) (those registered with a non-malignant pancreatitis disorder apart from acute pancreatitis). The positive predictive value of codes ranged from 83 to 98% if not all formal criteria for acute pancreatitis were fulfilled. See Razavi D, Ljung R, Lu Y, Andren-Sandberg A, Lindblad M. Reliability of acute pancreatitis diagnostic coding in a National Patient Register: a validation study in Sweden. Pancreatology 2011; 11: 525-532.

Code B252 (cytomegalovirus pancreatitis) and B263 (mumps pancreatitis) were added to coding definition as both represent acute forms of pancreatitis.

CIHI, Canadian Institute for Health Information Discharge Abstract Database; *ICD 10, International Classification of Disease, Tenth Revision*

eTable 5. Propensity score variables

Demographics
Age
Rural location
Long term care
Prescribing physician of relevant hypoglycemic agent
Comorbidities *
Chronic kidney disease
Hypertension
Charlson comorbidity index
Medication use #
Diuretic use
Lipid lowering drug
ACE inhibitor use
ARB use
Insulin use
Gliclazide use
Glyburide use
Metformin use
Rosiglitazone use
Health care utilization ||
Number of unique drug identifier numbers
Number of unique drug names
Number of hospitalizations
Number of emergency room visits
Number of endocrinologist visits
Number of nephrologist visits
Number of glycated hemoglobin tests
Number of glucose tests
Number of serum creatinine tests
Number of thyroid stimulating hormone tests
Flu vaccine
Diabetes management code

* Comorbidities were assessed in the previous 5 years
# Medication use was assessed in the previous 120 days
|| Health care utilization was assessed in the previous 1 year

eTable 6. Demographics, comorbidities, medications and laboratory data prior to and after propensity weighting in patients initiated on sitagliptin or an alternative hypoglycemic agent.

	Prior to Weighting			After Weighting #		
	Sitagliptin (n=57 689)	Other n=83 405)	Standardized Difference*	Sitagliptin (Weighted n=57 689)	Other (Weighted n=55 705)	Standardized Difference*
Age at Index Date						
Mean	73.98	75.07	17%	73.98	74.07	2%
Median	73	74		73	73	
SD	6.25	6.93		6.25	5.2	
66-70 years	21 105 (36.58)	26 880 (32.23)	9%	21 105 (36.58)	20 171 (36.21)	1%
71-75 years	15 829 (27.44)	21 282 (25.52)	4%	15 829 (27.44)	15 199 (27.28)	0%
76-80 years	11 228 (19.46)	16 397 (19.66)	0%	11 228 (19.46)	10 661 (19.14)	1%
81-85 years	6431 (11.15)	11 112 (13.32)	7%	6431 (11.15)	6350 (11.40)	1%
86-90 years	2461 (4.27)	5828 (6.99)	12%	2461 (4.27)	2678 (4.81)	3%
>90	635 (1.10)	1906 (2.29)	9%	635 (1.10)	646 (1.16)	1%
Female	27 584 (47.82)	40 312 (48.33)	1%	27 584 (47.82)	26 279 (47.18)	1%
Rural location	5997 (10.40)	12 396 (14.86)	13%	5997 (10.40)	6275 (11.26)	3%
Long term care facility	1446 (2.51)	5581 (6.69)	20%	1446 (2.51)	1594 (2.86)	2%
Income quintile †						
Quintile 1	12 582 (21.81)	18 233 (21.86)	0%	12 582 (21.81)	12 447 (22.34)	1%
Quintile 2	13 048 (22.62)	18 029 (21.62)	2%	13 048 (22.62)	12 134 (21.78)	2%
Quintile 3	11 601 (20.11)	16 572 (19.87)	1%	11 601 (20.11)	11 150 (20.02)	0%
Quintile 4	10 860 (18.83)	16 320 (19.57)	2%	10 860 (18.83)	10 845 (19.47)	2%
Quintile 5	9419 (16.33)	13 878 (16.64)	1%	9419 (16.33)	8894 (15.97)	1%
Missing	179 (0.31)	373 (0.45)	2%	179 (0.31)	234 (0.42)	2%
Prescribing Physician						
Endocrinology	4813 (8.34)	3042 (3.65)	20%	4813 (8.34)	5047 (9.06)	3%
General Practitioner	42 925 (74.41)	66 305 (79.50)	12%	42 925 (74.41)	40 948 (73.51)	2%
Internal	2454 (4.25)	2281	8%	2454 (4.25)	2407 (4.32)	0%

Medicine		(2.73)				
Nephrology	342 (0.59)	778 (0.93)	4%	342 (0.59)	360 (0.65)	1%
Other	1830 (3.17)	2252 (2.70)	3%	1830 (3.17)	1727 (3.10)	0%
Missing	5325 (9.23)	8169 (9.79)	2%	5325 (9.23)	5216 (9.36)	0%
Comorbidities ||						
Gallstones/ biliary stones	2163 (3.75)	3152 (3.78)	0%	2163 (3.75)	2059 (3.70)	0%
Calcium disorder	123 (0.21)	273 (0.33)	2%	123 (0.21)	154 (0.28)	1%
Alcoholism	240 (0.42)	659 (0.79)	5%	240 (0.42)	338 (0.61)	3%
Tobacco Use	3128 (5.42)	4662 (5.59)	1%	3128 (5.42)	3222 (5.78)	2%
Pancreatic neoplasm	101 (0.18)	250 (0.30)	3%	101 (0.18)	178 (0.32)	3%
ERCP	281 (0.49)	561 (0.67)	2%	281 (0.49)	334 (0.60)	2%
Chronic kidney disease¶	6069 (10.52)	10321 (12.37)	6%	6069 (10.52)	6714 (12.05)	5%
Bile duct neoplasm	118 (0.20)	272 (0.33)	2%	118 (0.20)	158 (0.28)	2%
HIV	50 (0.09)	67 (0.08)	0%	50 (0.09)	33 (0.06)	1%
SLE	739 (1.28)	1107 (1.33)	0%	739 (1.28)	659 (1.18)	1%
Polyarteritis nodosa	216 (0.37)	429 (0.51)	2%	216 (0.37)	248 (0.45)	1%
Celiac disease	78 (0.14)	158 (0.19)	1%	78 (0.14)	103 (0.18)	1%
Obesity	4219 (7.31)	5468 (6.56)	3%	4219 (7.31)	3696 (6.63)	3%
Charlson cormorbidity index §						
Mean	1.13	1.22	5%	1.13	1.23	7%
0–1	40 624 (70.42)	57 156 (68.53)	4%	40 624 (70.42)	37 816 (67.89)	5%
2	7861 (13.63)	10 430 (12.51)	3%	7861 (13.63)	8053 (14.46)	2%
>3	9204 (15.95)	15 819 (18.97)	8%	9204 (15.95)	9836 (17.66)	5%
Diabetic retinopathy	636 (1.10)	842 (1.01)	1%	636 (1.10)	783 (1.41)	3%
Diabetic neuropathy	576 (1.00)	843 (1.01)	0%	576 (1.00)	597 (1.07)	1%
Peripheral vascular disease	679 (1.18)	1259 (1.51)	3%	679 (1.18)	740 (1.33)	1%
Heart failure	6606 (11.45)	11 932 (14.31)	9%	6606 (11.45)	7068 (12.69)	4%
Coronary artery bypass graft	1766 (3.06)	2553 (3.06)	0%	1766 (3.06)	1781 (3.20)	1%

Hypertension	49 934 (86.56)	64 828 (77.73)	23%	49 934 (86.56)	48 277 (86.67)	0%
Coronary artery disease	16 299 (28.25)	23 740 (28.46)	0%	16 299 (28.25)	16 144 (28.98)	2%
Myocardial infarction	1243 (2.15)	2479 (2.97)	5%	1243 (2.15)	1381 (2.48)	2%
Stroke/TIA	1377 (2.39)	3011 (3.61)	7%	1377 (2.39)	1535 (2.76)	2%
Dialysis	1251 (2.17)	2992 (3.59)	8%	1251 (2.17)	1545 (2.77)	4%
Renal transplant	30 (0.05)	118 (0.14)	3%	30 (0.05)	62 (0.11)	2%
Hypoglycemia	770 (1.33)	1354 (1.62)	2%	770 (1.33)	818 (1.47)	1%
Pancreatitis	216 (0.37)	467 (0.56)	3%	216 (0.37)	267 (0.48)	2%
Hyperglycemic emergency	117 (0.20)	245 (0.29)	2%	117 (0.20)	162 (0.29)	2%
Medication use prior to the index date ##						
Diuretics	18 516 (32.10)	28 090 (33.68)	3%	18 516 (32.10)	18 644 (33.47)	3%
Anti-inflammatories	10 816 (18.75)	13 157 (15.77)	8%	10 816 (18.75)	10 268 (18.43)	1%
Glucocorticoids	11 297 (19.58)	16 121 (19.33)	1%	11 297 (19.58)	11 350 (20.38)	2%
Sulphonamides	859 (1.49)	1647 (1.97)	4%	859 (1.49)	1029 (1.85)	3%
Tetracyclines	85 (0.15)	152 (0.18)	1%	85 (0.15)	128 (0.23)	2%
Lipid lowering drugs	43 829 (75.97)	51 532 (61.79)	31%	43 829 (75.97)	42 210 (75.77)	0%
Estrogen therapy	601 (1.04)	886 (1.06)	0%	601 (1.04)	689 (1.24)	2%
Beta blockers	18 780 (32.55)	25 985 (31.16)	3%	18 780 (32.55)	19 343 (34.72)	5%
Azathioprine	74 (0.13)	139 (0.17)	1%	74 (0.13)	67 (0.12)	0%
Acetaminophen	2981 (5.17)	4455 (5.34)	1%	2981 (5.17)	2871 (5.15)	0%
Methyldopa	92 (0.16)	129 (0.15)	0%	92 (0.16)	111 (0.20)	1%
Tamoxifen	65 (0.11)	84 (0.10)	0%	65 (0.11)	42 (0.08)	1%
ACE inhibitors	26 098 (45.24)	32 599 (39.09)	12%	26 098 (45.24)	25 536 (45.84)	1%
ARB's	19 645 (34.05)	21 037 (25.22)	19%	19 645 (34.05)	18 335 (32.91)	2%
Aliskiren	1394 (2.42)	951 (1.14)	10%	1394 (2.42)	979 (1.76)	5%
Codeine	5667 (9.82)	7468 (8.95)	3%	5667 (9.82)	5693 (10.22)	1%
Mesalamine	55 (0.10)	63 (0.08)	1%	55 (0.10)	43 (0.08)	1%
Metronidazole	730 (1.27)	1129 (1.35)	1%	730 (1.27	774 (1.39)	1%
Sulindac	37 (0.06)	41 (0.05)	1%	37 (0.06)	28 (0.05)	1%

Valproic Acid	41 (0.07)	94 (0.11)	1%	41 (0.07)	53 (0.10)	1%
Amiodarone	336 (0.58)	639 (0.77)	2%	336 (0.58)	377 (0.68)	1%
Lamivudine	12 (0.02)	12 (0.01)	0%	12 (0.02)	<=5	---
Omeprazole	2343 (4.06)	3519 (4.22)	1%	2343 (4.06)	2639 (4.74)	3%
Erythromycin	43 (0.07)	54 (0.06)	0%	43 (0.07)	32 (0.06)	1%
Hypoglycemic agents prescribed in the 120 days prior to index date **						
Insulin	4505 (7.81)	3164 (3.79)	17%	4505 (7.81)	4091 (7.34)	2%
Gliclazide	17 142 (29.71)	4566 (5.47)	67%	17 142 (29.71)	14 734 (26.45)	7%
Glyburide	13 807 (23.93)	12 681 (15.20)	22%	13 807 (23.93)	14 847 (26.65)	6%
Metformin	43 135 (74.77)	20 987 (25.16)	14%	43 135 (74.77)	41 592 (74.66)	0%
Pioglitazone	5812 (10.07)	1863 (2.23)	33%	5812 (10.07)	5949 (10.68)	2%
Repaglinde	341 (0.59)	194 (0.23)	6%	341 (0.59)	228 (0.41)	3%
Rosiglitazone	2015 (3.49)	524 (0.63)	20%	2015 (3.49)	1956 (3.51)	0%
Hypoglycemic agents prescribed on the index date ††						
Insulin	1010 (1.75)	<=5	---	1010 (1.75)	0	19%
Gliclazide	6232 (10.80)	5578 (6.69)	15%	6232 (10.80)	0	49%
Glyburide	2982 (5.17)	6198 (7.43)	9%	2982 (5.17)	0	33%
Metformin	14174 (24.57)	1324 (1.59)	73%	14174 (24.57)	0	81%
Pioglitazone	652 (1.13)	409 (0.49)	7%	652 (1.13)	771 (1.38)	2%
Repaglinde	61 (0.11)	27 (0.03)	3%	61 (0.11)	13 (0.02)	3%
Rosiglitazone	89 (0.15)	51 (0.06)	3%	89 (0.15)	105 (0.19)	1%
Hypoglycemic agents prescribed in the 1 year to 120 days prior to the index date §§						
Insulin	4671 (8.10)	5272 (6.32)	37%	4671 (8.10)	4213 (7.56)	2%
Gliclazide	17 175 (29.77)	5886 (7.06)	61%	17 175 (29.77)	14 249 (25.58)	9%
Glyburide	17 038 (29.53)	15 101 (18.11)	27%	17 038 (29.53)	17 053 (30.61)	2%
Metformin	45 376 (78.66)	27 777 (33.30)	103%	45 376 (78.66)	41 580 (74.64)	9%
Pioglitazone	7023 (12.17)	2918 (3.50)	33%	7023 (12.17)	6493 (11.66)	2%
Repaglinde	450 (0.78)	372 (0.45)	4%	450 (0.78)	353 (0.63)	2%
Rosiglitazone	2981 (5.17)	1123 (1.35)	22%	2981 (5.17)	2447 (4.39)	4%
Hemoglobin A1c						

No. with recent test (%)				16 413 (28.45)	14 837 (26.63)	4%
	Mean			0.077	0.078	8%
	Median			0.074	0.075	
	25th Percentile			0.069	0.069	
	75th Percentile			0.082	0.084	
	SD			0.013	0.012	

Data presented as number (percent) with the exception of age and hemoglobin A1c (presented as mean, median, 25th and 75th percentile and SD standard deviation).
Abbreviations: ERCP endoscopic retrograde cholangiopancreatography, HIV human immunodeficiency virus, SLE systemic lupus erythematosis, TIA transient ischemic attack, ACE angiotensin converting enzyme inhibitor, ARB angiotensin receptor blocker.
Cell sizes less than six were not reported for reasons of privacy.
All patients identified prior to weighting were included in the analyses. The number of patients indicated represents a weighted total.
* Standardized differences are less sensitive to sample size than traditional hypothesis tests. They provide a measure of the difference between groups divided by the pooled standard deviation; a value greater than 10% (0.1) is interpreted as a meaningful difference between the groups.
† Income was categorized into fifths of average neighborhood income on the index date.
§ Charlson Comorbidity Index was calculated using five years of hospitalization data. “No hospitalizations” received a score of 0. See Charlson M, Pompei P, Alex K, Mackenzie C. A new method for classifying prognostic co morbidity in longitudinal studies: development and validation. J Chron Dis. 1877; 40: 373-383.
|| Comorbidities were assessed by administrative database codes in the previous five years.
¶ We identified individuals with chronic kidney disease using a validated algorithm of diagnosis and physician claim codes. In Ontario, this algorithm identifies patients with a median estimated glomerular filtration rate (eGFR) of 38 mL/min per 1.73 m^2 (interquartile range 27 to 52). Its absence identifies patients with a median eGFR of 69 mL/min per 1.73 m^2 (interquartile range 56 to 82). See Fleet JL, Dixon SN, Shariff SZ, et al. Detecting chronic kidney disease in population-based administrative databases using an algorithm of hospital encounter and physician claim codes. BMC Nephrol. 2013; 14(1):81.
Baseline medication use was assessed in the previous 120 days.
** Hypoglycemic agent use in the previous 120 days includes hypoglycemic drugs prescribed from -120 to -1 day prior to the index date where days supply covered the index date.
†† Hypoglycemic agent use on the index date refers to hypoglycemic drugs prescribed on the same day as study drug (index date).
§§ Hypoglycemic agent use in the previous 365 to 120 days includes those hypoglycemic drugs prescribed from -365 to -120 days prior to the index date.
There were no prescriptions for pentamidine, flucytosine, clomiphene, clozapine, acarbose, acetohexamide, chlorpropramide, glimiperide, nateglinide, tobultamide.
There were fewer than 1% prescriptions for dapsone, isoniazid, procainamide, methimazole, nelfinavir.

eTable 7. Health care utilization prior to and after propensity weighting in patients initiated on sitagliptin or an alternative hypoglycemic agent.

	Prior to Weighting			After Weighting #		
	Sitagliptin (n=57 689)	Other (n=83 405)	Standardized Difference*	Sitagliptin (Weighted n=57 689)	Other (Weighted n=55 705)	Standardized Difference*
Number of unique drug identifier numbers †						
Mean	10.6	8.97	28%	10.6	10.78	4%
SD	5.51	6.22		5.51	4.67	
Median	10	8		10	10	
25th Percentile	7	5		7	7	
75th Percentile	13	15		13	14	
0	725 (1.26)	4957 (5.94)	25%	725 (1.26)	775 (1.39)	1%
1–4	4632 (8.03)	15 092 (18.09)	30%	4632 (8.03)	4678 (8.40)	1%
5–8	17 181 (29.78)	24 599 (29.49)	1%	17 181 (29.78)	15 977 (28.68)	2%
9–12	17 849 (30.94)	19 091 (22.89)	18%	17 849 (30.94)	16 536 (29.68)	3%
12–15	8001 (13.87)	8460 (10.14)	11%	8001 (13.87)	8000 (14.36)	1%
>16	9301 (16.21)	11 206 (13.44)	8%	9301 (16.12)	9738 (17.48)	4%
Number of unique drug names †						
Mean	9.56	8	32%	9.56	9.69	3%
SD	4.65	5.2		4.65	3.94	
Median	9	7		9	9	
25th Percentile	6	4		6	6	
75th Percentile	12	11		12	12	
0	725 (1.26)	4957 (5.94)	25%	725 (1.26)	775 (1.39)	1%
1–4	5284 (9.16)	16787 (20.13)	31%	5284 (9.16)	5363 (9.63)	2%
5–8	20 344 (35.26)	27 678 (33.19)	4%	20 344 (35.26)	18 882 (33.90)	3%
9–12	18 377 (31.86)	19 284 (23.12)	20%	18 377 (31.86)	17 236 (30.94)	2%
12–15	7042 (12.21)	7641 (9.16)	10%	7042 (12.21)	7151 (12.84)	2%

>16	5917 (10.26)	7058 (8.46)	6%	5917 (10.26)	6298 (11.31)	3%
Health care use ||						
Number of any hospitalization						
Mean	0.17	0.25	13%	0.17	0.19	4%
SD	0.54	0.68		0.54	0.46	
Median	0	0		0	0	
25th Percentile	0	0		0	0	
75th Percentile	0	0		0	0	
0	50 874 (88.19)	69 546 (83.38)	14%	50 874 (88.19)	48 013 (86.19)	6%
1	4954 (8.59)	9561 (11.46)	10%	4954 (8.59)	5647 (10.14)	5%
2	1270 (2.20)	2748 (3.29)	7%	1270 (2.20)	1468 (2.64)	3%
>=3	591 (1.02)	1550 (1.86)	7%	591 (1.02)	577 (1.04)	0%
Number of emergency room visits						
Mean	0.55	0.72	12%	0.55	0.6	4%
SD	1.28	1.5		1.28	1.01	
Median	0	0		0	0	
25th Percentile	0	0		0	0	
75th Percentile	1	1		1	1	
0	40 910 (70.91)	54 459 (65.29)	12%	40 910 (70.91)	37 731 (67.73)	7%
1	9734 (16.87)	15 573 (18.67)	5%	9734 (16.87)	10 372 (18.62)	5%
2	3700 (6.41)	6510 (7.81)	5%	3700 (6.41)	4034 (7.24)	3%
>=3	3345 (5.80)	6863 (8.23)	10%	3345 (5.80)	3569 (6.41)	3%
Number of general practitioner visits						
Mean	9.78	10.21	4%	9.78	9.8	0%
SD	8.38	11.87		8.38	7.32	
Median	8	7		8	8	
25th Percentile	5	4		5	5	
75th Percentile	12	12		12	12	
0	1218 (2.11)	3242 (3.89)	10%	1218 (2.11)	1468 (2.64)	3%

1	1418 (2.46)	3537 (4.24)	10%	1418 (2.46)	1560 (2.80)	2%
2	2344 (4.06)	4719 (5.66)	7%	2344 (4.06)	2384 (4.28)	1%
>=3	52 709 (91.37)	71 907 (86.21)	16%	52 709 (91.37)	50 293 (90.28)	4%
Number of endocrinologist visits						
Mean	0.32	0.22	9%	0.32	0.34	2%
SD	1.06	1.14		1.06	1	
Median	0	0		0	0	
25th Percentile	0	0		0	0	
75th Percentile	0	0		0	0	
0	49 228 (85.33)	75 945 (91.06)	18%	49 228 (85.33)	47 358 (85.02)	1%
1	3398 (5.89)	3457 (4.14)	8%	3398 (5.89)	3605 (6.47)	2%
2	2609 (4.52)	1911 (2.29)	12%	2609 (4.52)	2348 (4.22)	2%
>=3	2454 (4.25)	2092 (2.51)	10%	2454 (4.25)	2393 (4.30)	0%
Number of nephrologist visits						
Mean	0.23	0.51	8%	0.23	0.28	3%
SD	2.12	4.29		2.12	1.65	
Median	0	0		0	0	
25th Percentile	0	0		0	0	
75th Percentile	0	0		0	0	
0	52 827 (91.57)	75 493 (90.51)	4%	52 827 (91.57)	50 209 (90.13)	5%
1	2393 (4.15)	3476 (4.17)	0%	2393 (4.15)	2534 (4.55)	2%
2	1275 (2.21)	1892 (2.27)	0%	1275 (2.21)	1490 (2.67)	3%
3	1194 (2.07)	2544 (3.05)	6%	1194 (2.07)	1472 (2.64)	4%
Number of gastro-enterologist visits						
Mean	0.19	0.23	4%	0.19	0.23	4%
SD	0.96	1.28		0.96	0.86	
Median	0	0		0	0	
25th Percentile	0	1		0	0	

75th Percentile	0	0		0	0	
0	52 637 (91.24)	75 695 (90.76)	2%	52 637 (91.24)	50 171 (90.07)	4%
1	2438 (4.23)	3628 (4.35)	1%	2438 (4.23)	2598 (4.66)	2%
2	1291 (2.24)	1828 (2.19)	0%	1291 (2.24)	1363 (2.45)	1%
3	1323 (2.29)	2254 (2.70)	3%	1323 (2.29)	1573 (2.82)	3%
Number of opthalmologist visits						
Mean	1.08	0.92	7%	1.08	1.1	1%
SD	2.3	2.13		2.3	1.91	
Median	0	0		0	0	
25th Percentile	0	0		0	0	
75th Percentile	1	1		1	1	
0	36 786 (63.77)	57 776 (69.27)	12%	36 786 (63.77)	35 506 (63.74)	0%
1	8735 (15.14)	10626 (12.74	7%	8735 (15.14)	8527 (15.31)	0%
2	4367 (7.57)	5282 (6.33)	5%	4367 (7.57)	4022 (7.22)	1%
3	7801 (13.52)	9721 (11.66)	6%	7801 (13.52)	7650 (13.73)	1%
Number of internist visits						
Mean	0.88	1.09	7%	0.88	0.94	2%
SD	2.65	3.62		2.65	2.4	
Median	0	0		0	0	
25th Percentile	0	0		0	0	
75th Percentile	1	1		1	1	
0	41 733 (72.34)	60 445 (72.47)	0%	41 733 (72.34)	40 129 (72.04)	1%
1	6926 (12.01)	9728 (11.66)	1%	6926 (12.01)	6882 (12.35)	1%
2	3116 (5.40)	4098 (4.91)	2%	3116 (5.40)	2927 (5.25)	1%
3	5914 (10.25)	9134 (10.95)	2%	5914 (10.25)	5768 (10.35)	0%
Number of HbA1c tests						
Mean	10.48	7.8	43%	10.48	10.7	4%
SD	6.34	6.06		6.34	5.51	
Median	10	7		10	10	

0	1368 (2.37)	5927 (7.11)	22%	1368 (2.37)	1686 (3.03)	4%
1–2	3349 (5.81)	12 197 (14.62)	29%	3349(5.81)	3316 (5.95)	1%
3–4	5043 (8.74)	11688 (14.01)	17%	5043 (8.74)	4797 (8.61)	0%
>4	47 929 (83.08)	53 593 (64.26)	44%	47 929 (83.08)	45 907 (82.41)	2%
Number of glucose tests						
Mean	12.36	9.6	30%	12.36	12.38	0%
SD	9.78	8.36		9.78	8.2	
Median	11	8		11	11	
0	1282 (2.22)	4416 (5.29)	16%	1282 (2.22)	1620 (2.91)	4%
1–2	2753 (4.77)	7631 (9.15)	17%	2753 (4.77)	2693 (4.83)	0%
3–4	4315 (7.48)	9819 (11.77)	15%	4315 (7.48)	4229 (7.59)	0%
>4	49 339 (85.53)	61 539 (73.78)	29%	49 339 (85.53)	47 163 (84.67)	2%
Number of creatinine tests						
Mean	10.54	9	21%	10.54	10.73	3%
SD	7.24	7.63		7.24	6.19	
Median	9	7		9	9	
0	1178 (2.04)	4165 (4.99)	16%	1178 (2.04)	1420 (2.55)	3%
1–2	2847 (4.94)	8060 (9.66)	18%	2847 (4.94)	2737 (4.91)	0%
3–4	5377 (9.32)	11 099 (13.31)	13%	5377 (9.32)	5192 (9.32)	0%
>4	48 287 (83.70)	60 081 (72.04)	28%	48 287 (83.70)	46 355 (83.22)	1%
Number of lipid tests						
Mean	7.43	5.84	35%	7.43	7.24	4%
SD	4.75	4.3		4.75	3.93	
Median	7	5		7	6	
0	1847 (3.20)	6504 (7.80)	20%	1847 (3.20)	2237 (4.02)	4%
1–2	5128 (8.89)	13 137 (15.75)	21%	5128 (8.89)	5162 (9.27)	1%
3–4	50 714 (87.91)	63 764 (76.45)	30%	50 714 (87.91)	48 306 (86.72)	4%
Number of TSH tests						
Mean	4.82	4.18	17%	4.82	4.77	1%

SD	3.88	3.65		3.88	3.34	
Median	4	3		4	4	
0	4781 (8.29)	10 033 (12.03)	12%	4781 (8.29)	5236 (9.40)	4%
1–2	12 462 (21.60)	21 610 (25.91)	10%	12 462 (21.60)	12 482 (22.41)	2%
3–4	40 446 (70.11)	51 762 (62.06)	17%	40 446 (70.11)	37 986 (68.19)	4%
Carotid ultrasound	9358 (16.22)	13 505 (16.19)	0%	9358 (16.22)	9472 (17.00)	2%
Cardiac catheterization	5037 (8.73)	6909 (8.28)	2%	5037 (8.73)	5065 (9.09)	1%
Coronary revascularization	3000 (5.20)	4280 (5.13)	0%	3000 (5.20)	3068 (5.51)	1%
Echocardiography	27 738 (48.08)	38 656 (46.35)	3%	27 738 (48.08)	26 551 (47.66)	1%
Holter monitoring	11 059 (19.17)	15 445 (18.52)	2%	11 059 (19.17)	10 490 (18.83)	1%
Cardiac stress test	23 137 (40.11)	30 200 (36.21)	8%	23 137 (40.11)	22 232 (39.91)	0%
Influenza vaccine	46 035 (79.80)	61 324 (73.53)	15%	46 035 (79.80)	44 662 (80.18)	1%
Colorectal cancer screening	36 721 (63.65)	48 271 (57.88)	12%	36 721 (63.65)	35 512 (63.75)	0%
Prostate specific antigen test	7875 (13.65)	10 403 (12.47)	3%	7875 (13.65)	7279 (13.07)	2%
Mammography	10 204 (17.69)	13 221 (15.85)	5%	10 204 (17.69)	9369 (16.82)	2%
Diabetes management §	31 928 (55.35)	36 713 (44.02)	23%	31 928 (55.35)	31 902 (57.27)	4%
Diabetes incentive ¶	31 057 (53.84)	35 608 (42.69)	22%	31 057 (53.84)	30 491 (54.74)	2%
Bone mineral density test	17 129 (29.69)	22 387 (26.84)	6%	17 129 (29.69)	15 681 (28.15)	3%

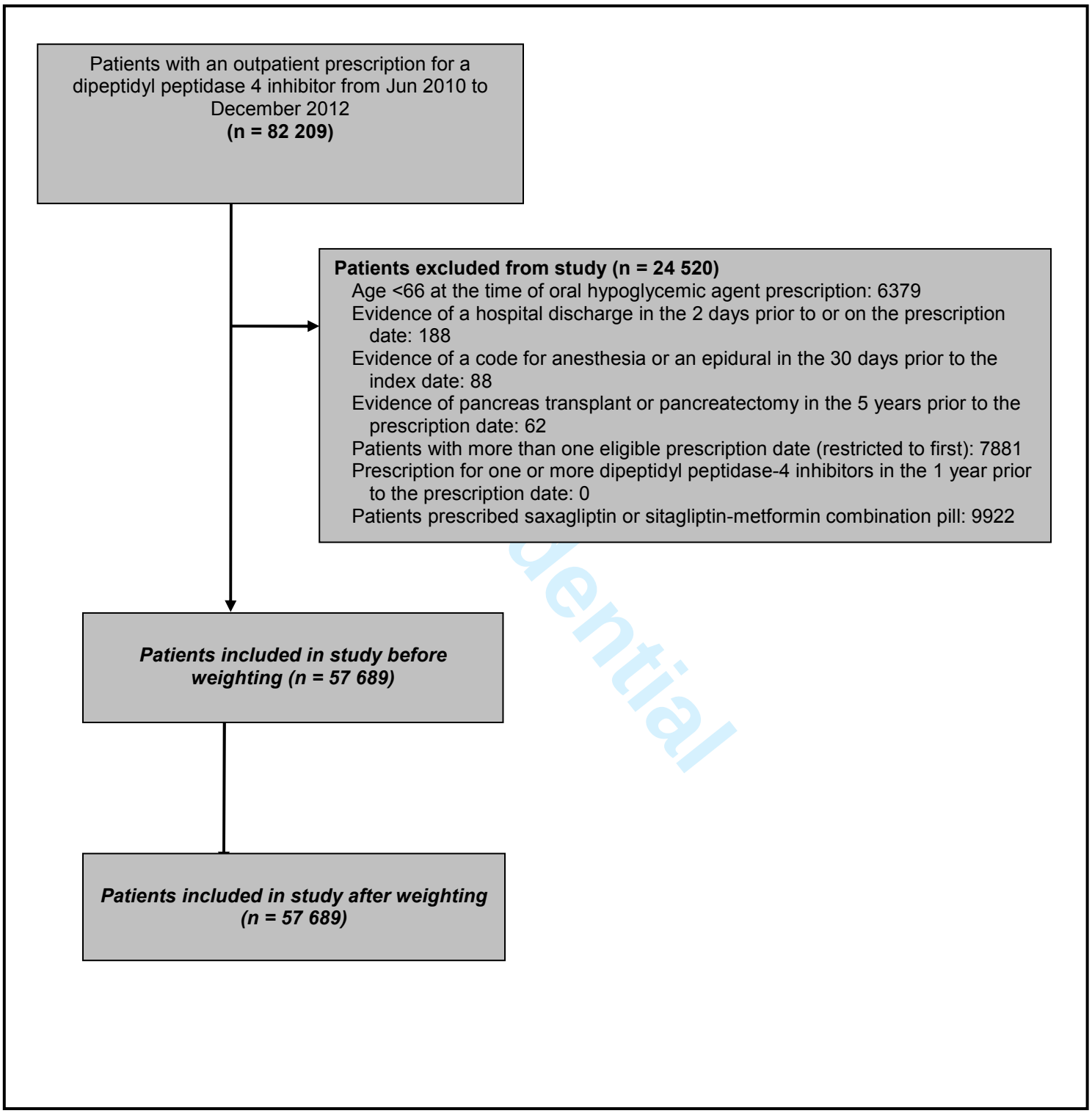
Data presented as number (percent) with the exception of number of investigations and health care visits (presented as mean, median, 25th percentile, 75th percentile, SD standard deviation).
Abbreviations: TSH thyroid stimulating hormone.
Cell sizes less than six were not reported for reasons of privacy.
#All patients identified prior to weighting were included in the analyses. The number of patients indicated represents a weighted total.
*Standardized differences are less sensitive to sample size than traditional hypothesis tests. They provide a measure of the difference between groups divided by the pooled standard deviation; a value greater than 10% (0.1) is interpreted as a meaningful difference between the groups.
†Prescribed medication use was assessed in the 120 days prior to the index date.
||Health care use was assessed in the 1 year previous.
§Diabetes management is an all-inclusive service payable to the most responsible physician for providing continuing management and support of a diabetic patient. The service must include assessments focusing on diabetic target organ systems, relevant counseling and maintenance of a diabetic flow sheet retained on the patient's permanent medical record. The flow sheet must track lipids, cholesterol, HbA1C, urinalysis, blood pressure, fundal examination, peripheral vascular examination, weight, BMI and medication dosage. See Schedule of benefits for physician services under the health insurance act – consultations and visits. A1-128. Available from: http://www.health.gov.on.ca/english/providers/program/ohip/sob /physserv/a_consul.pdf. Accessed 12/30, 2013.
¶Diabetes management incentive is a fee rendered to a general practitioner providing ongoing management of a diabetic patient consistent with the requirements of the Canadian Diabetes Association including a minimum of lipid, HbA1C, blood pressure, BMI measurement, albumin:creatinine, preventative measures and health promotion, referral for dilated eye exam, foot and neurological exam over the

previous 12 months. See Schedule of benefits for physician services under the health insurance act – consultations and visits. A1-128. Available from: http://www.health.gov.on.ca/english/providers/program/ohip/sob /physserv/a_consul.pdf. Accessed 12/30, 2013.

eTable 8. Time to event analysis

Censoring events	**Sitagliptin** **Weighted n=57 689** **14 988 person years of follow-up** **Median (IQR) days of follow-up, 65 (30, 125)**	**Other** **Weighted n=55 705** **16 972 person years of follow-up** **Median (IQR) days of follow-up, 75 (30, 129)**
Hospital encounters with pancreatitis	260 (0.45%)	224 (0.4%)
Hazard ratio (95% CI)	1.18 (0.94 to 1.49)	1.00 (reference)
Event rate per 1000 person years	17.35	13.18
Censoring events		
Death	9 (0.02%)	20.95 (0.04%)
Study hypoglycemic agent discontinued	8579 (14.87%)	17485 (31.39%)
Prescription for a non-study hypoglycemic agent	48 841 (84.66%)	37 976 (68.17%)

eFigure 1. Flow diagram representing sitagliptin cohort inclusions and exclusions



eFigure 2. Flow diagram representing alternative hypoglycemic agent cohort inclusions and exclusions