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Article

Higher-Dose Sitagliptin and the Risk of Congestive Heart Failure in Older Adults with CKD

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Abstract

Background and objectives Sitagliptin, a dipeptidyl peptidase-4 inhibitor, is commonly prescribed to patients with type 2 diabetes. As this drug is primarily eliminated by the kidney, a reduced dose is recommended for patients with CKD. Some evidence suggests that sitagliptin is associated with a higher risk of congestive heart failure, particularly at higher doses. We compare the 1-year risk of death or hospitalization with congestive heart failure in patients with CKD newly prescribed sitagliptin at >50 versus ≤50 mg/d.

Design, setting, participants, & measurements This population-based cohort study included older adults (>66 years) with type 2 diabetes and an eGFR<45 ml/min per 1.73 m² (but not receiving dialysis) who were newly prescribed sitagliptin between 2010 and 2017 in Ontario, Canada. We used inverse probability of treatment weighting on the basis of propensity scores to balance baseline characteristics. The primary composite outcome was death or hospitalization with congestive heart failure. Secondary outcomes included hospitalization with pancreatitis or hypoglycemia, all-cause hospitalization, and glycemic control. Weighted hazard ratios were obtained using Cox proportional hazards regression, and 95% confidence intervals were obtained using bootstrap variance estimators.

Results Of 9215 patients, 6518 started sitagliptin at >50 mg/d, and 2697 started sitagliptin at ≤50 mg/d. The 1-year risk of death or hospitalization with congestive heart failure did not differ significantly between groups (79 versus 126 events per 1000 person-years; weighted hazard ratio, 0.88; 95% confidence interval, 0.67 to 1.14); hospitalization with pancreatitis (weighted hazard ratio, 0.98; 95% confidence interval, 0.32 to 3.03) and hypoglycemia (weighted hazard ratio, 1.10; 95% confidence interval, 0.64 to 1.90) also did not differ significantly between groups. Patients starting sitagliptin at >50 mg/d had lower mean glycated hemoglobin concentrations (weighted between-group difference, −0.12%; 95% confidence interval, −0.19 to −0.06) and a lower risk of all-cause hospitalization (weighted hazard ratio, 0.81; 95% confidence interval, 0.66 to 0.98).

Conclusions The risk of death or congestive heart failure was not higher in older adults with CKD starting sitagliptin at >50 versus ≤50 mg/d.

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Introduction

Sitagliptin is an oral dipeptidyl peptidase-4 (DPP-4) inhibitor used to improve glycemic control in patients with type 2 diabetes mellitus (1–4). In patients with contraindications or intolerance to metformin, sitagliptin may be prescribed in monotherapy or as an add-on to insulin (1–4). In the United States, 8 million sitagliptin prescriptions were filled in 2016, and in Ontario, Canada, nearly 20% of all antihyperglycemic medication prescriptions are for sitagliptin (5).

Sitagliptin is eliminated primarily by the kidney (2,3). In a pharmacokinetic study, plasma concentrations of sitagliptin were two to four times higher in patients with moderate to severe CKD than in patients with normal kidney function after receipt of one oral dose of 50 mg sitagliptin (6). For this reason, the product monograph recommends starting sitagliptin at a lower dose in patients with an eGFR below 45 ml/min per

1.73 m² (Supplemental Table 1) (2). However, no clinical studies have compared outcomes in patients with CKD who start sitagliptin at a higher versus lower dose (Supplemental Table 2). Although results are mixed, DPP-4 inhibitor use has been linked to a higher risk of congestive heart failure in meta-analyses of clinical trials and some observational studies (7–12). A higher risk of congestive heart failure was observed in sitagliptin users versus nonusers in three population-based studies (10,11,13). DPP-4 inhibitors may exert deleterious cardiovascular effects by increasing the production of endogenous peptides (Glucagon-like peptide-1 and stroma cell–derived factor-1), which can increase cardiac muscle contraction and promote cardiac fibrosis (14).

Approximately 40% of older adults with type 2 diabetes and CKD have an eGFR between 15 and 59 ml/min per 1.73 m² (15). In practice, sitagliptin is

rarely started at a lower dose in these patients (16). We conducted a population-based study of older adults with an eGFR below 45 ml/min per 1.73 m^2 (excluding those receiving dialysis) to compare the 1-year risk of death or hospitalization with congestive heart failure in outpatients starting oral sitagliptin at >50 versus ≤50 mg/d. We hypothesized that starting sitagliptin at >50 mg/d would be associated with a higher risk of congestive heart failure.

Materials and Methods
Study Design and Setting
We conducted a population-based cohort study using linked administrative health care databases in the province of Ontario, Canada (2010–2018). All Ontario residents (approximately 14 million) have universal access to hospital care and physician services through a government-funded single-payer system (17). Those aged 65 years and older (approximately 2.2 million) also receive universal prescription drug coverage. The use of data in this study was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a research ethics board. Study reporting follows recommended guidelines for observational studies that use routinely collected health data (Supplemental Table 3) (18,19).

Data Sources
Eight health care databases housed at ICES (ices.on.ca) were used to obtain information on patient characteristics, prescription drug use, covariates, and the outcomes (20). The datasets were linked using unique encoded identifiers and analyzed at ICES. We used the following databases: the Canadian Institute for Health Information Discharge Abstract Database, ICES-derived Physician Database, the National Ambulatory Care Reporting System, the Ontario Drug Benefit Database, the Ontario Health Insurance Plan database, the Ontario Laboratories Information System, the Ontario Mental Health Reporting System, and the Registered Persons Database. Hospital admissions and diagnoses are coded by trained personnel using the International Classification of Diseases 10th revision system; personnel only consider physician-recorded diagnoses in a patient's medical chart when assigning codes and do not review or interpret symptoms or test results. These databases have been used previously to study adverse drug events and health outcomes (21–25). Except for prescriber data (7% missing; defined as a separate category) and neighborhood income quintile (0.3% missing; recorded as the middle quintile), the databases were complete for all variables used in this study. Emigration from the province, which occurs at a rate of 0.5%/yr, was the only reason for loss to follow-up (26). The codes used to ascertain comorbidities and outcomes are detailed in Supplemental Table 4.

The date sitagliptin was dispensed from the pharmacy served as each patient's cohort entry date. Baseline comorbidities were assessed in the 5-year period before cohort entry and health care use in the 1-year period before cohort entry. A 120-day look-back period was used to ascertain prescription drug exposure because the Ontario Drug Benefits program allows a maximum prescription duration of 100 days.

Patients
We assembled a primary cohort of adults aged 66 years and older who had an eGFR<45 ml/min per 1.73 m^2 and were newly dispensed oral sitagliptin from an outpatient pharmacy between June 2010 (when sitagliptin was first openly listed on the province's formulary) and December 2017. We restricted the cohort to patients aged 66 years and older to ensure that all patients had at least 1 year of prior prescription drug coverage.

We calculated the eGFR for each patient using the Chronic Kidney Disease Epidemiology equation; the justification to use this equation for dose prescribing is provided in Supplemental Table 5 (27). We used the most recent outpatient serum creatinine measurement (using the isotope dilution mass spectroscopy–traceable enzymatic method) recorded before the cohort entry date (27). In Ontario, many older adults have at least one outpatient serum creatinine measured in routine care each year, and we have shown that single creatinine values are representative of chronic values (28). We excluded patients with no serum creatinine measurement in the year before the cohort entry date, kidney transplant recipients, and patients receiving dialysis at or before cohort entry.

To ensure that patients were new sitagliptin users, those with any evidence of sitagliptin use, including combination drug prescriptions (i.e., sitagliptin-metformin for example) and other DPP-4 inhibitors, in the 180-day period before the cohort entry date were excluded. We also excluded those who were discharged from the hospital or emergency department within 2 days before the cohort entry date (in Ontario, patients who start a sitagliptin prescription during a hospital admission would have their outpatient prescription dispensed on the same day or the day after hospital discharge). Patients could only enter the cohort once.

Sitagliptin Dose
The recommended dose of sitagliptin when the eGFR is between 30 and 45 ml/min per 1.73 m^2 is 50 mg/d (Supplemental Table 1). We categorized patients as those who started oral sitagliptin at >50 mg/d and those who started at ≤50 mg/d. The sample was too small to include an additional category of 25 mg/d, which is the dose recommended in patients with eGFR below 30 ml/min per 1.73 m^2 (Supplemental Table 1) (2).

Outcomes
The outcomes were prespecified. The diagnostic codes for all outcomes, their validation, and their interpretation are provided in Supplemental Table 6.

Primary Outcome. The primary outcome was a composite of time to death or first hospitalization with congestive heart failure within 1 year of initiating sitagliptin. This time frame was defined on the basis of the The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 trial (SAVOR-TIMI 53 trial), which showed a higher 1-year risk of congestive heart failure in patients with type 2 diabetes who received saxagliptin (a DPP-4 inhibitor) versus placebo (29). Components of the primary outcome were defined using codes proven to

have good validity when compared with chart review (Supplemental Table 6).

Secondary Outcomes. The first two secondary outcomes were the two components of the primary outcome analyzed separately. The remaining three secondary outcomes were time to first hospitalization or emergency department visit with pancreatitis (a potential DPP-4 inhibitor–related side effect) (12), time to first hospitalization or emergency department visit with hypoglycemia, and time to first hospitalization for any reason. (Supplemental Table 6).

Statistical Analyses

Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). We used inverse probability of treatment weighting on the propensity score to balance comparison groups on indicators of baseline health (30–32). We estimated the propensity score using multivariable logistic regression with 162 covariates chosen *a priori* (defined in Supplemental Table 7) because they are known confounders or risk factors for congestive heart failure (32–34). We weighted patients in the reference group (≤50 mg/d of sitagliptin) using average treatment effect for the treated weights defined as [propensity score/(1− propensity score)], with patients in the exposed group (>50 mg/d of sitagliptin) receiving weights of one (3–32). This method produces a weighted pseudosample of patients in the reference group with a similar distribution of measured covariates as the exposed group (>50 mg/d of sitagliptin) (30, 31). We compared between-group differences in baseline characteristics using standardized differences in both the unweighted and weighted samples (differences >10% were considered meaningful) (35). We obtained weighted hazard ratios using a Cox proportional hazards regression and 95% confidence intervals (95% CIs) using a bootstrap variance estimator (36). We assessed the proportional hazards assumption using a time-dependent covariate test, which was met for all outcomes. We conducted all primary analyses according to the intention-to-treat principle (*i.e.*, patients were not censored if they discontinued sitagliptin or if their dose changed in follow-up). Death was treated as a censoring event when it was not part of an outcome. We interpreted two-tailed *P* values of 0.05 as statistically significant.

Additional Analyses

We conducted seven additional analyses. We recalculated the propensity scores (as done in the primary analysis) and used inverse probability of treatment weighting on the propensity score to balance comparison groups on indicators of baseline health.

1. In patients with blood glycated hemoglobin (HbA1c) concentrations available at baseline and within 1 year after cohort entry (the most recent measurement), we analyzed the between-group difference in the absolute change in HbA1c to determine if starting sitagliptin at higher dose was associated with better glycemic control. The between-group difference was analyzed using a binomial regression model with an identity link function (we assumed the data were normally distributed).

2. We compared the two groups of sitagliptin users (*i.e.*, those prescribed >50 and ≤50 mg/d) with new linagliptin users on the 1-year risk of death or hospitalization with congestive heart failure. Unlike sitagliptin, which is eliminated primarily by the kidney, linagliptin is primarily eliminated by the enterohepatic system, and there is no recommendation to reduce the dose of linagliptin in patients with CKD.

3. We examined effect modification by baseline eGFR (≥30 versus <30 ml/min per 1.73 m^2) and history of congestive heart failure (interaction terms were included in the models).

4. We performed an as-treated analysis censoring follow-up at sitagliptin discontinuation. A patient was considered to be continuously exposed during a series of prescriptions if the gap between prescriptions was within a period equivalent to 150% of the number of days of the previous prescription.

5. We extended the washout period before the cohort entry date from 180 to 365 days to reduce incident user misclassification.

6. We extended the follow-up period from 1 to 2 years after sitagliptin initiation in long-term users (*i.e.*, patients with continuous sitagliptin use ≥180 days since the initiation). The median duration of continuous sitagliptin dispensing was 711 days (interquartile range [IQR], 400–1280.5) in the high-dose group and 738 days (IQR, 370–1252) in the low-dose group (Supplemental Table 8).

7. We excluded patients who received any antidiabetic prescriptions other than sitagliptin on the cohort entry date to isolate the effect of sitagliptin from the effect of other antidiabetic medications.

Results
Patients

The flow diagram for the cohort build is shown in Supplemental Figure 1. The primary cohort included 9215 older adults with an eGFR<45 ml/min per 1.73 m^2 (median age 78 years; IQR, 73–83; 56% women) who were newly dispensed sitagliptin at an outpatient pharmacy. The outpatient serum creatinine to estimate baseline GFR was measured a median of 23 (IQR, 8–73) days prior to cohort entry. Overall, 77% of patients had an eGFR between 30 and 45 ml/min per 1.73 m^2, and 23% had an eGFR<30 ml/min per 1.73 m^2.

Patients received sitagliptin prescriptions primarily from primary care physicians (75%), endocrinologists (7%), and nephrologists (3%). Sitagliptin was prescribed by 4342 different physicians, and it was dispensed by 3139 different pharmacies. Most patients filled prescriptions for 100 mg/d, resulting in a median dose in each eGFR category of 100 mg/d (IQR, 50–100); 6518 (71%) started at >50 mg/d (median 100 mg/d; IQR, 100–100), and 2697 (29%) started at ≤50 mg/d (median 50 mg/d; IQR, 25.7–50).

Characteristics of patients who started sitagliptin at >50 versus ≤50 mg/d are shown in Table 1 (the full set of 173 characteristics is shown in Supplemental Table 9). After weighting, the standardized differences were <10% for 172 of 173 variables (99%), including prescriber specialty, comorbidities, baseline eGFR, diabetes characteristics, and diabetes medications (Supplemental Table 9).

Table 1. Baseline characteristics of older adults with CKD who were newly prescribed sitagliptin in Ontario, Canada (2010–2017)

Baseline Characteristics	Unweighted Data, n=9215[a]			Weighted Data, n=12,828[b]		
	Sitagliptin Dose >50 mg/d, n=6518	Sitagliptin Dose ≤50 mg/d, n=2697	Standardized Difference,[c] %	Sitagliptin Dose >50 mg/d, n=6518	Sitagliptin Dose ≤50 mg/d, n=6310	Standardized Difference,[c] %
Demographics						
Women, no. (%)	3653 (56)	1475 (55)	3	3653 (56)	3470 (55)	2
Age, mean (SD), yr	78 (7)	80 (8)	24	78 (7)	78 (11)	3
Residence, no. (%)						
Urban	5833 (90)	2398 (89)	2	5833 (90)	5575 (88)	4
Rural	685 (11)	299 (11)	2	685 (11)	735 (12)	4
Long-term care	240 (4)	257 (10)	24	240 (4)	250 (4)	2
Income quintile, no. (%)[d]						
1 (lowest)	1519 (23)	665 (25)	3	1519 (23)	1776 (28)	11
2	1492 (23)	613 (23)	0	1492 (23)	1259 (20)	7
3 (middle)	1363 (21)	584 (22)	2	1363 (21)	1050 (17)	11
4	1153 (18)	440 (16)	4	1153 (18)	1293 (21)	7
5 (highest)	992 (15)	395 (15)	2	992 (15)	932 (15)	1
Kidney function						
eGFR, mean (SD),[e] ml/ min per 1.73 m^2	36 (7)	33 (8)	37	36 (7)	36 (11)	1
eGFR category, no. (%), ml/min per 1.73 m^2						
<30	1264 (19)	859 (32)	29	1264 (19)	1234 (20)	1
30 to <45	5254 (81)	1838 (68)	29	5254 (81)	5076 (80)	1
Sitagliptin prescriber, no. (%)						
General practitioner	5125 (79)	1784 (66)	28	5125 (79)	4900 (78)	2
Endocrinologist	403 (6)	246 (9)	11	403 (6)	458 (7)	4
Nephrologist	62 (1)	220 (8)	35	62 (1)	64 (1)	0
Internist	267 (4)	128 (5)	3	267 (4)	237 (4)	2
Cardiologist	86 (1)	21 (0.8)	5	86 (1)	59 (0.9)	4
Other	152 (2)	49 (2)	4	152 (2)	122 (2)	3
Missing	423 (7)	249 (9)	10	423 (7)	475 (7)	4
Comorbidities, no. (%)[f]						
Alcohol-related disorder	40 (0.6)	20 (0.7)	1	40 (0.6)	86 (1)	8
Atrial fibrillation or flutter	575 (9)	298 (11)	7	575 (9)	500 (8)	3
Cancer	2119 (33)	941 (35)	5	2119 (33)	2055 (33)	0
Chronic obstructive pulmonary disease	1592 (24)	665 (25)	1	1592 (24)	1780 (28)	9
Coronary artery disease	2396 (37)	993 (37)	0	2396 (37)	2222 (35)	3
Dyslipidemia	1726 (27)	629 (23)	7	1726 (27)	1823 (29)	5
Hypertension	6118 (94)	2503 (93)	4	6118 (94)	5884 (93)	2
Peripheral vascular disease	124 (2)	45 (2)	2	124 (2)	126 (2)	1
Acute myocardial infarction	364 (6)	155 (6)	0	364 (6)	342 (5)	1
Ischemic stroke	153 (2)	64 (2)	1	153 (2)	244 (4)	9
Diabetic neuropathy	100 (2)	60 (2)	5	100 (2)	124 (2)	4
Diabetic retinopathy	115 (2)	39 (1)	3	115 (2)	105 (2)	1
Prior pancreatitis	50 (0.8)	32 (1)	4	50 (0.8)	62 (1)	2
Prior hypoglycemia	184 (3)	84 (3)	2	184 (3)	140 (2)	4
Prior congestive heart failure	1439 (22)	665 (25)	6	1439 (22)	1299 (21)	4
Charlson comorbidity index, mean (SD)[g]	3 (1.7)	3.2 (1.8)	11	3 (1.7)	3.1 (2.6)	2
Health care visits/tests[h]						
Primary care visits, mean (SD)	10.9 (9.7)	11.3 (11.0)	3	10.9 (9.7)	10.7 (13.9)	2
Emergency department visits, mean (SD)	0.7 (1.3)	0.7 (1.4)	5	0.7 (1.3)	0.8 (2.8)	8
Serum creatinine tests, no. (%)	3.4 (2.5)	4.0 (2.8)	22	3.4 (2.5)	3.5 (3.5)	1
Medication use, no. (%)[i]						
Insulin	745 (11)	499 (20)	20	745 (11)	730 (12)	1
Metformin	4014 (62)	1335 (50)	25	4014 (62)	3942 (63)	2
Glyburide	1471 (23)	286 (11)	33	1471 (23)	1403 (22)	1
Gliclazide	2146 (33)	875 (32)	1	2146 (33)	2230 (35)	5
Pioglitazone	603 (9)	79 (3)	27	603 (9)	495 (8)	5

Table 1. (Continued)

Baseline Characteristics	Unweighted Data, n=9215[a]			Weighted Data, n=12,828[b]		
	Sitagliptin Dose >50 mg/d, n=6518	Sitagliptin Dose ≤50 mg/d, n=2697	Standardized Difference,[c] %	Sitagliptin Dose >50 mg/d, n=6518	Sitagliptin Dose ≤50 mg/d, n=6310	Standardized Difference,[c] %
Rosiglitazone	159 (2.4)	16 (0.6)	15	159 (2.4)	219 (3.5)	7
Repaglinide	56 (0.9)	29 (1)	2	56 (0.9)	38 (0.6)	3
Laboratory test values[j]						
Urine ACR available	4293 (66)	1770 (66)	1	4293 (66)	4256 (67)	3
Baseline ACR categories, μg/mg						
Missing	2225 (34)	927 (34)	1	2225 (34)	2054 (33)	3
_<30_	1998 (31)	657 (24)	14	1998 (31)	1783 (28)	5
_30–300_	1617 (25)	695 (26)	2	1617 (25)	1638 (26)	3
_>300_	678 (10)	418 (16)	15	678 (10)	835 (13)	9
Test for glycosylated hemoglobin levels available	6211 (95)	2577 (96)	1	6211 (95)	6023 (96)	1
Glycosylated hemoglobin level, mean (SD), %	7.9 (1.4)	7.9 (1.4)	4	7.9 (1.4)	7.8 (2.0)	5

ACR, urine albumin-creatinine ratio.

[a]Unless otherwise specified in the footnotes, baseline characteristics were assessed on the date that the patient filled the sitagliptin prescription—the cohort entry date.

[b]Weighted using inverse probability of treatment weighting on the basis of propensity scores. The propensity score was estimated using multivariable logistic regression with 162 covariates chosen _a priori_ (defined in Supplemental Table 7). Patients in the reference group were weighted as [propensity score/(1− propensity score)] (30–32). This method produces a weighted pseudosample of patients in the reference group with the same distribution of measured covariates as the exposure group (30,31).

[c]Standardized difference is the difference between the groups divided by the pooled SD; a value >10% is interpreted as a meaningful difference (35).

[d]Income was categorized into fifths of average neighborhood income on the cohort entry date; missing data on this variable (0.3%) were recorded as the middle quintile.

[e]The most recent eGFR measurement in the 365-day period before the cohort entry date (including the cohort entry date); eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation: $141 \times \min$ ([serum creatinine concentration in micromoles per liter per 88.4]/κ, 1)$\alpha \times \max$ ([serum creatinine concentration in micromoles per liter per 88.4]/κ, 1)-1.209×0.993 age $\times 1.018$ [if a woman] $\times 1.159$ [if Black] (κ=0.7 if a woman and 0.9 if a man; α=−0.329 if a woman and −0.411 if a man; min = the minimum of serum creatinine concentration/κ or 1; max = the maximum of serum creatinine concentration/κ or 1. Information on race was not available in our data sources, and all patients were assumed not to be of African-Canadian race; African Canadians represented <5% of the population of Ontario in 2006. The lowest eGFR value was 15.1 ml/min per 1.73 m^2.

[f]Baseline comorbidities were assessed in the 5-year period before the cohort entry date.

[g]Presence of kidney disease is a variable in the Charlson comorbidity index, which automatically results in all individuals receiving a minimum score of two.

[h]Total number of health care visits/tests in the 12-month period before the cohort entry date.

[i]Medication use was examined in the 120-day period before the cohort entry date (the Ontario Drug Benefit program dispenses a maximum 100-day supply). Some of these medications may have been discontinued after the initiation of sitagliptin.

[j]Most recent laboratory test values in the 1- to 365-day period before the cohort entry date.

Although standardized differences were 11% for the lowest- and middle-income categories, this difference is unlikely to be clinically meaningful (Table 1, Supplemental Table 9).

Additional details about the duration of sitagliptin use, rate of sitagliptin discontinuation, and the person-years of follow-up for sitagliptin users are presented in Supplemental Tables 10–12.

Primary Outcome

The primary outcome of death or hospitalization with congestive heart failure occurred in 495 of 6518 patients who started sitagliptin at >50 mg/d (7.6%; 79.2 events per 1000 person-years) and in 318 of 2697 patients who started sitagliptin ≤50 mg/d (11.8%; 126.1 events per 1000 person-years). Starting sitagliptin at >50 mg/d compared with ≤50 mg/d was not associated with a higher risk of death or a hospital admission with congestive heart failure within 1 year (weighted hazard ratio, 0.88; 95% CI, 0.67 to 1.14) (Figure 1, Table 2).

Secondary Outcomes

Starting sitagliptin at >50 versus ≤50 mg/d was not associated with a higher 1-year risk of a hospital encounter with pancreatitis (weighted hazard ratio, 0.98; 95% CI, 0.32 to 3.03), a hospital encounter with hypoglycemia (weighted hazard ratio, 1.10; 95% CI, 0.64 to 1.90), death (weighted hazard ratio, 0.90; 95% CI, 0.68 to 1.20), or hospitalization with congestive heart failure (weighted hazard ratio, 0.86; 95% CI, 0.52 to 1.40). The risk of hospitalization for any cause was lower in patients starting sitagliptin at >50 versus ≤50 mg/d (weighted hazard ratio, 0.81; 95% CI, 0.66 to 0.98) (Figure 2, Table 2).

Additional Analyses

(1) A total of 7820 patients had both baseline and follow-up HbA1C measurements (5594 sitagliptin >50 mg/d, 2226

sitagliptin ≤50 mg/d). After weighting, the two groups were balanced on all baseline characteristics. Starting sitagliptin at >50 versus ≤50 mg/d was associated with a greater decrement in HbA1c (the weighted mean between-group difference was −0.12%; 95% CI, −0.19 to −0.06) (Table 3). (2) In comparison with linagliptin users, both groups of sitagliptin users (≤50 and >50 mg/d) did not have a higher 1-year risk of death or hospitalization with congestive heart failure: weighted hazard ratios were 0.93 (95% CI, 0.74 to 1.04) and 1.05 (95% CI, 0.92 to 1.19), respectively (Supplemental Tables 13 and 14). (3) Neither baseline eGFR category nor history of congestive heart significantly modified the association between starting sitagliptin at >50 versus ≤50 mg/d and the risk of death or hospitalization with congestive heart failure (Figure 2, test for interaction $P=0.25$ and $P=0.14$, respectively). (4–7) Results were consistent in the remaining additional analyses: when the follow-up time was censored at sitagliptin discontinuation (Supplemental Table 15), when the washout period was extended to 1 year (Supplemental Table 16), when the follow-up period was extended to 2 years (Supplemental Table 8), and after excluding patients who received antidiabetic prescriptions other than sitagliptin on the cohort entry date (Supplemental Table 17).

Discussion

In this population-based cohort study of 9215 older adults with moderate to severe CKD, the 1-year risk of death or hospitalization with congestive heart failure was not significantly different in patients starting sitagliptin at ≤50 versus >50 mg/d. Furthermore, there was no association with the sitagliptin dose and the risk of other outcomes, including hospital encounters with pancreatitis or hypoglycemia. These findings were consistent across multiple additional analyses. The risk of congestive heart failure in sitagliptin users (*i.e.*, those prescribed >50 mg/d and those prescribed ≤50 mg/d) was similar to that in linagliptin users. Our findings suggest that sitagliptin poses no higher risk of congestive heart failure at higher than recommended doses in patients with CKD.

To our knowledge, no previous studies have examined the safety of high- versus low-dose sitagliptin use in patients with type 2 diabetes and CKD; however, our results are consistent with findings from The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS), which studied 3000 patients (mean age 69 years) with CKD (eGFR between 30 and 60 ml/min per 1.73 m²) (37,38). The TECOS trial examined the effect of sitagliptin versus placebo on major adverse cardiovascular outcomes (a composite of cardiovascular death, myocardial infarction, stroke, unstable angina, and congestive heart failure as a separate outcome) and adverse clinical events (hypoglycemia and acute pancreatitis). Sitagliptin was provided at a dose of 50 mg/d (or 100 mg if eGFR was >50 ml/min per 1.73 m²). Patients had a median follow-up time of 2.8
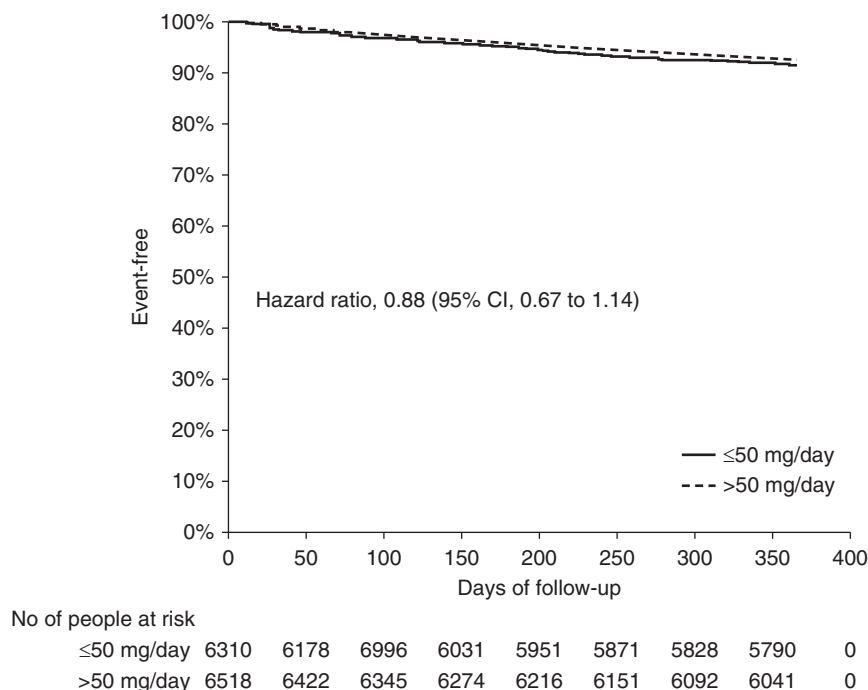

Figure 1. | The risk of death or congestive heart failure was not higher in older adults with CKD starting sitagliptin at >50 mg/d versus ≤50 mg/d. Kaplan–Meier estimates of survival probability without death or hospital admission with heart failure in older adults with moderate to severe CKD who started a new prescription for sitagliptin >50 versus ≤50 mg/d (weighted results). Inverse probability of treatment weighting on the propensity score was used to balance comparison groups on indicators of baseline health (30–32). The propensity score was estimated using multivariable logistic regression with 162 covariates chosen *a priori* (defined in Supplemental Table 7). Patients in the reference group were weighted as [propensity score/(1 − propensity score)] (30–32). This method produces a weighted pseudosample of patients in the reference group with the same distribution of measured covariates as the exposed group (30,31). Weighted hazard ratios and 95% confidence intervals (95% CIs) were obtained using a Cox proportional hazards regression, and 95% CIs were obtained using a bootstrap variance estimator (36). The proportional hazards assumption was assessed using a time-dependent covariate test and was met for all outcomes.

Table 2. Risk of death or heart failure in older adults with moderate to severe CKD who started a new prescription for sitagliptin >50 versus ≤50 mg/d

Baseline Characteristics	Unweighted[a]				Weighted[b]				Hazard Ratio (95% Confidence Interval)
	No. of Events (%)		No. of Events per 1000 person-yr		No. of Events (%)		No. of Events per 1000 person-yr		
	Sitagliptin Dose >50 mg/d, n=6518	Sitagliptin Dose ≤50 mg/d, n=2697	Sitagliptin Dose >50 mg/d	Sitagliptin Dose ≤50 mg/d	Sitagliptin Dose >50 mg/d, n=6518	Sitagliptin Dose ≤50 mg/d, n=6310	Sitagliptin Dose >50 mg/d	Sitagliptin Dose ≤50 mg/d	
Primary outcome									
Death or hospital admission with heart failure	495 (7.6)	318 (11.8)	79.2	126.1	495 (7.6)	543 (8.6)	79.2	90.6	0.88 (0.67 to 1.14)
Secondary outcomes									
Death	404 (6.2)	271 (10.1)	63.9	105.6	404 (6.2)	432 (6.9)	63.9	71.0	0.90 (0.68 to 1.20)
Hospital admission with heart failure	126 (1.9)	67 (2.5)	20.1	26.4	126 (1.9)	141 (2.2)	20.1	23.4	0.86 (0.52 to 1.40)
Hospital encounter with pancreatitis	25 (0.4)	11 (0.4)	4.0	4.3	25 (0.4)	24 (0.4)	4.0	4.0	0.98 (0.32 to 3.03)
Hospital encounter with hypoglycemia	140 (2.2)	55 (2.0)	22.4	21.7	140 (2.2)	122 (1.9)	22.4	20.3	1.10 (0.64 to 1.90)
All-cause hospitalization	1614 (24.8)	754 (28.0)	284.5	331.3	1614 (24.8)	1879 (29.8)	284.5	352.4	0.81 (0.66 to 0.98)

[a]Reference group: sitagliptin dose ≤50 mg/d.
[b]Inverse probability of treatment weighting on the propensity score was used to balance comparison groups on indicators of baseline health (30–32). The propensity score was estimated using multivariable logistic regression with 162 covariates chosen *a priori* (defined in Supplemental Table 7). Patients in the reference group were weighted as [propensity score/(1− propensity score)] (30–32). This method produces a weighted pseudosample of patients in the reference group with the same distribution of measured covariates as the exposed group (30,31). Weighted hazard ratios and 95% confidence intervals were obtained using a Cox proportional hazards regression, and 95% confidence intervals were obtained using a bootstrap variance estimator (36). The proportional hazards assumption was assessed using a time-dependent covariate test and was met for all outcomes.

Subgroup	Number of events / Number of individuals		Event rate per 1000 person-years			Hazard Ratio (95% CI)	P-value for interaction
	>50 mg/day	≤ 50 mg/day	> 50 mg/day	≤ 50 mg/day			
Baseline eGFR (mL/min per 1.73 m^2)							
30-44	361/5254	354/5076	71.3	72.5		0.99 (0.70-1.38)	
							0.14
<30	134/1264	189/1234	112.9	170.1		0.67 (0.42-1.06)	
History of heart failure							
No	250/5079	265/5011	50.5	54.5		0.93 (0.64-1.36)	
							0.25
Yes	245/1439	278/1299	188.3	245.5		0.77 (0.51-1.16)	

0.2   2.0
Hazard ratio

Lower risk with sitagliptin use at   Higher risk with sitagliptin use at
dose **>50 mg/day**   dose **>50 mg/day**

Figure 2. | **Neither baseline eGFR category or history of congestive heart significantly modified the association between starting sitagliptin at >50 versus ≤50 mg/day and the risk of death or hospitalization with congestive heart failure.** Subgroup analysis for risk of death of heart failure by eGFR category and by history of heart failure (weighted results). Inverse probability of treatment weighting on the propensity score was used to balance comparison groups on indicators of baseline health (30–32). The propensity score was estimated using multivariable logistic regression with 162 covariates chosen a priori (defined in Supplemental Table 7). Patients in the reference group were weighted as [propensity score/(1 − propensity score)] (30–32). This method produces a weighted pseudosample of patients in the reference group with the same distribution of measured covariates as the exposed group (30,31). Weighted hazard ratios and 95% CIs were obtained using a Cox proportional hazards regression, and 95% CIs were obtained using a bootstrap variance estimator (36). The proportional hazards assumption was assessed using a time-dependent covariate test and was met for all outcomes.   *Cont.*

(2.2–3.6) years; no significant differences in outcomes were observed between patients receiving sitagliptin versus placebo (37,38). Other trials of DPP-4 inhibitors have shown neutral effects on cardiovascular outcomes overall, including congestive heart failure (39–41), although the SAVOR-TIMI 53 trial reported an increased risk of congestive heart failure in patients randomized to receive the DPP-4 inhibitor saxagliptin (29). In three prior observational studies, a higher risk of congestive heart failure was observed in patients receiving sitagliptin (including patients with kidney failure) compared with nonusers (10,11,13). The biologic plausibility of a deleterious cardiovascular effect of sitagliptin is unclear but may involve a hyperproduction of endogenous peptides, which can increase cardiac muscle contraction and promote cardiac fibrosis. Reconciling findings from these observational studies is challenging because the study population, exposures, patient characteristics, and outcomes differ across studies. For example, none of these studies used an active comparator. Furthermore, we based our hypothesis on the pharmacokinetics of sitagliptin, but these data are often derived from volunteers who receive a single dose of the drug, and results may not reflect the true pharmacokinetics of the drug in clinical practice nor in patients with CKD

who often have multiple comorbidities. Our data do not support the hypothesis that starting a higher than recommended dose of sitagliptin in older adults with CKD is associated with significant harm. In fact, our findings suggest a possible benefit to patients with CKD who started a higher versus lower dose of sitagliptin. It is possible that patients who start at a higher dose achieve better glycemic control and have a lower risk of being admitted to the hospital; however, residual confounding cannot be ruled out—before weighting, sicker patients were less likely to be prescribed a higher dose of sitagliptin, and these results need to be replicated in other studies.

Our study has several strengths. It is the first population-based study to examine the risk of death or congestive heart failure associated with the use of sitagliptin in patients with moderate to severe CKD in routine practice. The findings of this study are likely generalizable to older adults because it was conducted in the setting of usual clinical care and included a representative sample of older adults with moderate to severe CKD in Ontario, Canada, where all residents aged 66 and older have universal prescription drug coverage. The results were consistent across multiple additional analyses, including when linagliptin (a DPP-4 inhibitor with a biliary excretion and a neutral effect on

Table 3.   Changes in glycated hemoglobin within 365 days of new sitagliptin use

Baseline Characteristics	Unweighted[a]		Weighted[b]		Weighted Mean Differences (95% Confidence Interval)
	Sitagliptin Dose >50 mg/d, n=5594	Sitagliptin Dose ≤50 mg/d, n=2226	Sitagliptin Dose >50 mg/d, n=5594	Sitagliptin Dose ≤50 mg/d, n=5413	
Change in Hba1c (%), mean (95% CI)[c]	−0.46 (−0.50 to −0.43)	−0.45 (−0.51 to −0.40)	−0.46 (−0.50 to −0.43)	−0.34 (−0.39 to −0.28)	−0.12 (−0.19 to −0.06)

HbA1c, glycated hemoglobin; 95% CI, 95% confidence interval.
[a]Reference group: sitagliptin dose ≤50 mg/d.
[b]Inverse probability of treatment weighting on the propensity score was used to balance comparison groups on indicators of baseline health (30–32). The propensity score was estimated using multivariable logistic regression with 162 covariates chosen *a priori* (defined in Supplemental Table 7). Patients in the reference group were weighted as [propensity score/(1 − propensity score)] (30–32). This method produces a weighted pseudosample of patients in the reference group with the same distribution of measured covariates as the exposed group (30,31).
[c]Change in HbA1c was defined as the most recent serum HbA1c measurement in the 365 days after the index date minus the baseline serum HbA1c measurement. The most recent serum HbA1c level may have been measured in an outpatient laboratory, emergency department, or hospital setting.

cardiovascular outcomes) was used as an active comparator group. By using inverse probability of treatment weighting, we were able to produce comparison groups that were balanced on a comprehensive set of baseline characteristics.

This study has some limitations. First, although we used an active comparator group and a robust statistical technique to control for confounding by indication, we are aware that residual confounding may be a factor in interpreting our results. For example, physicians who were aware of the association between sitagliptin and adverse cardiac events may have been more likely to prescribe sitagliptin at a lower dose to at-risk patients. Second, despite the use of highly accurate information on sitagliptin dispensing, the use of administrative data cannot provide information on the proportion of patients who took their pills as prescribed. This may introduce a nondifferential misclassification of the exposure, which may underestimate the true risk of death or congestive heart failure. Third, we studied only patients who were aged 66 and older, so our findings may not apply to younger patients. Fourth, because of the small sample size, we could not examine the 1-year risk of death or congestive heart failure in patients with an eGFR<30 ml/min per 1.73 m^2 who started sitagliptin at a dose ≤25 mg/d (the recommended dose in these patients). Fifth, we did not censor patients when sitagliptin dose changed during follow-up. In health care databases, we have access to outpatient prescriptions only; therefore, any change in sitagliptin dose occurring during a hospital stay or emergency room visit would not be captured in the databases. However, the daily dose in each group did not change when we compared a pre- and a posthospitalization sitagliptin prescription (Supplemental Table 18), and thus, not censoring patients when their sitagliptin dose changed during follow-up is unlikely to affect our main conclusions.

In summary, we found that starting a higher than recommended dose of sitagliptin in older adults with CKD was not associated with significant harm. These findings suggest that sitagliptin dose reductions may not be needed in patients with CKD; however, our findings should be confirmed in future population-based studies using health care administrative databases in other jurisdictions.

Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.08310520/-/DCSupplemental.

Supplemental Figure 1. Flow diagram of cohort build.

Supplemental Table 1. Recommendations for sitagliptin dosing in patients with normal kidney function and in those with kidney impairment

Supplemental Table 2. Literature search.

Supplemental Table 3. Checklist of recommendations for reporting of observational studies using the Reporting of Studies Conducted Using Observational Routinely Collected Health Data guidelines.

Supplemental Table 4. Coding definitions for demographic and comorbid conditions.

Supplemental Table 5. Justification for the equation used to estimate the GFR for drug dosing adjustments.

Supplemental Table 6. Operating characteristics of hospital diagnosis codes used to define primary and secondary outcomes.

Supplemental Table 7. Variables included in the propensity score model.

Supplemental Table 8. *Post hoc* analysis comparing the 2-year risk of death or heart failure in older adults with moderate to severe CKD who started a new prescription for sitagliptin >50 versus ≤50 mg/d in patients with prolonged exposure.

Supplemental Table 9. Baseline characteristics of older adults with CKD newly prescribed sitagliptin in Ontario, Canada (2010–2018).

Supplemental Table 10. Dose and duration of continuous sitagliptin dispensing during the years 2010–2018.

Supplemental Table 11. Rate of sitagliptin discontinuation within 1 year after initiation of the medication.

Supplemental Table 12. Total follow-up (person-years) for sitagliptin users.

Supplemental Table 13. Risk of death or heart failure in older adults with moderate to severe CKD who started a new prescription for sitagliptin (>50 mg/d) versus linagliptin.

Supplemental Table 14. Risk of death or heart failure in older adults with moderate to severe CKD who started a new prescription for sitagliptin (≤50 mg/d) versus linagliptin.

Supplemental Table 15. *Post hoc* analysis comparing the risk of death or heart failure in older adults with moderate to severe CKD who started a new prescription for sitagliptin >50 versus ≤50 mg/d, censoring the follow-up time at sitagliptin discontinuation.

Supplemental Table 16. *Post hoc* analysis comparing the risk of death or heart failure in older adults with moderate to severe CKD who started a new prescription for sitagliptin >50 versus ≤50 mg/d when we extended the washout period to 1 year.

Supplemental Table 17. *Post hoc* analysis comparing the risk of death or heart failure in older adults with moderate to severe CKD who started a new prescription for sitagliptin >50 versus ≤50 mg/d after exclusion of patients who received any antidiabetic prescription on the cohort entry date.

Supplemental Table 18. Median dose of sitagliptin prescribed to patients with moderate to severe CKD who had a hospital admission for any reason within 1 year after sitagliptin initiation: A dose comparison between a pre- and a posthospitalization sitagliptin prescription.

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