Received: 10 April 2018 | Revised: 6 June 2018 | Accepted: 19 June 2018

DOI: 10.1111/dom.13448

WILEY

ORIGINAL ARTICLE

Acute vs cumulative benefits of metformin use in patients with type 2 diabetes and heart failure

Daniala L. Weir MSc[1,2] | Michal Abrahamowicz PhD[2,3] | Marie-Eve Beauchamp PhD[3] | Dean T. Eurich PhD[4,5]

[1]Clinical and Health Informatics Research Group, Department of Medicine, McGill University, Montreal, Canada

[2]Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Canada

[3]Centre for Health Outcomes Research, Research Institute of the McGill University Health Centre, Montreal, Canada

[4]School of Public Health, University of Alberta, Edmonton, Canada

[5]Alliance for Canadian Health Outcomes Research in Diabetes, University of Alberta, Edmonton, Canada

Correspondence
Dean T. Eurich, PhD, 2-040 Li Ka Shing Center for Health Research Innovation, University of Alberta, Edmonton, Alberta, T6G 2E1, Canada.
Email: deurich@ualberta.ca

Funding information
Government of Canada; Canadian Institutes for Health Research, Grant/Award Number: #PJT-148946

Aims: To evaluate the association between metformin use and heart failure (HF) exacerbation in people with type 2 diabetes (T2D) and pre-existing HF using alternative exposure models.

Materials and methods: We analysed data for patients with T2D and incident HF from a national US insurance claims database. We compared the results of several multivariable Cox models where time-varying use of metformin was modelled as: (1) current use; (2) total duration of past use; and (3) use within the past 30 days or 10 days. The outcome was defined as time to HF-related hospitalization. We then re-analysed the data using flexible weighted cumulative exposure (WCE) models.

Results: A total of 7620 patients with diabetes and incident HF were analysed. The mean (SD) patient age was 54 (8) years, and 58% (n = 4440) were men. In all, 3799 individuals (50%) were exposed to metformin, and 837 HF hospitalizations (11%) occurred (mean follow-up 1.7 years). Results of conventional models suggested potential acute benefits in reducing HF exacerbation with metformin use in the past 10 days (adjusted hazard ratio [aHR] 0.76, 95% confidence interval [CI] 0.60-0.97), while WCE models, which provided a better fit for the data, suggested lack of a systematic effect (aHR 0.91, 95% CI 0.69-1.20).

Conclusions: Our results suggest that cumulative metformin exposure does not decrease the risk of HF-related exacerbation. Use of other anti-hyperglycaemic agents with proven efficacy in patients with HF should also be considered as treatment options in this population.

KEYWORDS

antidiabetic drug, metformin, observational study, pharmaco-epidemiology, type 2 diabetes

1 | INTRODUCTION

Heart failure (HF) is a serious and common comorbidity in patients with type 2 diabetes mellitus. The prevalence of HF in patients with diabetes aged ≥65 years has been reported to be as high as 22%[1] and HF in patients with diabetes is associated with 3-year mortality of 40%, 10-fold higher than that of similar patients with diabetes alone.[2]

Although it remains uncertain whether or not intensive glucose-lowering affects HF outcomes,[3,4] studies have suggested that the choice of glucose-lowering agent appears to play an important role in patients with existing HF. Subgroup analyses in randomized trials evaluating incretin-based therapies including dipeptidyl peptidase-4 (DPP-4) inhibitors (EXAMINE, SAVOR-TIMI and TECOS) and glucagon-like peptide 1 (GLP-1) receptor agonists (ELIXA and LEADER) have not observed a significant benefit or risk related to treatment with these medications in patients with existing HF[5–9]; however, two DPP-4 inhibitors (saxagliptin and alogliptin) have subsequently received US Food and Drug Administration warnings with respect to the potential risk of development of incident HF.[10] Most recently, exploratory analyses of the EMPA-REG study have suggested that substantial benefits are associated with empagliflozin in patients both with and without pre-existing HF.[11] The evidence for older agents, such as metformin and sulphonylureas, in particular, is based on far less rigorous studies and thus, reliance on clinical experience and observational evidence has been required to judge the safety and effectiveness of older anti-hyperglycaemic drugs in patients with diabetes and comorbid HF.[12]

In the absence of randomized trial evidence, current observational evidence suggests that, in patients with HF, metformin is safe and its use may be associated with improved outcomes.[13] Accordingly, metformin has been considered as first-line therapy in this patient population, similarly to other populations with type 2 diabetes.[14] Nonetheless, observational studies related to the safety and effectiveness of metformin have faced a number of important methodological challenges, including how best to model time-varying drug exposure because treatment with metformin varies considerably both between patients and within-patients over time.[15] Metformin use has typically been modeled using a range of time-fixed measures (ever-use or total days of use),[13] which do not fully account for the time-varying nature of the treatment regimens and also largely misclassify exposed person-time. Indeed, these biased measures can induce immortal time bias which tends to overestimate the benefits of treatment.[16]

To address the inherent challenges associated with how best to represent dynamic treatment regimens, novel analytical methods have been developed, and extensively validated, to flexibly model the effects of a time-varying cumulative history of drug use.[17–19] We hypothesize that this approach may be useful, compared with the conventional methods used in previously published studies, for more accurately modelling the association between metformin use and HF exacerbation in patients with pre-existing HF. The objective of the present study, therefore, was to compare alternative, flexible methods with conventional methods for modelling the association between metformin use and HF exacerbation in patients with diabetes and pre-existing HF.

2 | METHODS

2.1 | Data source

We used a large US claims and integrated laboratory database that included employed, commercially insured individuals from all 50 states, which had been de-identified for privacy and compliance reasons (Clinformatics Data Mart; OptumInsight, Eden Prairie, Minnesota). Patient-level data included administrative and demographic information (type of insurance plan, sex, age, dates of eligibility and income) and billable medical services claims including inpatient and outpatient visits and medical procedures (physician and facility identifier, date and place of service, cost of service, admission and discharge dates, procedures and diagnostic codes), all laboratory tests and results (including fasting lipids, renal function, liver function, blood glucose [glycated haemoglobin] and complete blood count) and pharmacy claims data (prescribing physician, drug dispensed based on national drug codes, quantity and date dispensed, drug strength, days' supply, and cost of service). All clinical diagnoses were recorded according to International Classification of Disease, 9th revision Clinical Modification (ICD-9-CM) codes and procedure codes.

2.2 | Study population

We identified those individuals who had a prescription claim for either metformin or sulphonylurea therapy from January 1, 2003 to December 31, 2009, and subsequently developed incident HF (ie, any claim with an ICD-9 CM code of 428.XX) with no previous history of a diagnosis of HF in 1 year prior to incident HF event).[20] These agents were chosen because they are the most commonly prescribed first-line oral antidiabetic agents in patients with diabetes and would provide a more homogenous study population. Moreover, this time period would avoid confounding by the newer anti-hyperglycaemic agents (sodium-glucose co-transporter-2 drugs), which were mostly unavailable on the market at this time. As thiazolidinedione therapy has been shown to increase the risk of HF, is contraindicated in patients with established HF, and was used extensively during this period of time, all patients were excluded if they has received a thiazolidinedione after diagnosis of HF. Patients also had to be aged ≥20 years and had to have at least 1 year of continuous medical insurance before diagnosis of HF (so we could be certain any cases of HF were new diagnoses) to be included in our cohort.[21] The patients were followed from the date of incident HF until death, termination of medical insurance, or December 31, 2010 (study exit date) (Figure 1).

2.3 | Exposure

As patterns of glucose-lowering treatment are quite complex, we used a time-varying exposure measure to model metformin use. We established time-varying exposure to metformin on the basis of the expected duration of each prescription by using the "days' supplied" field in the prescription drug dispensations database. Use of metformin was updated on a daily basis from date of incident HF until the end of follow-up for each person. Current metformin use was represented by a time-varying binary indicator ("1" indicated metformin use on a given day and "0" indicated non-use). Patients were considered unexposed to metformin for the period of time from the end of the last expected day of metformin use to either the end of the study or until they restarted the drug.

2.4 | Outcome

The time-to-event was defined as the time from the incident HF (time 0) to the first subsequent HF-related hospital admission, based on any ICD-9 code of 428.XX occurring in hospital.

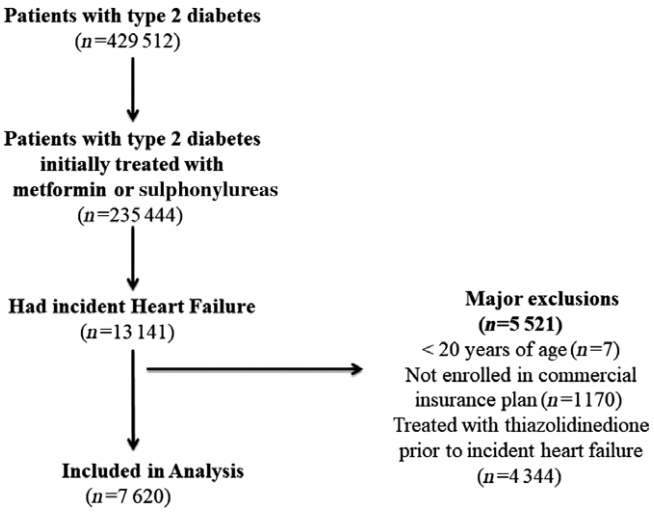

FIGURE 1 Flow chart of patient exclusions

2.5 | Confounders

Covariates in our models included demographics (age and sex), history of cardiovascular disease (ischaemic heart disease, myocardial infarction, dyslipidaemia, hypertension, arrhythmia or valve disease), and a time-varying indicator of the current use of any other antidiabetic medication (sulphonylureas, incretins and insulin). We also evaluated the time-varying use of common HF drugs (ie, agents effecting the angiotensin system, β blockers, spironolactone, loop diuretics, hydralazine, digoxin and amiodarone). To further control for the clinical complexity of patients, we used specific variables and adjusted clinical groups derived from the Johns Hopkins Adjusted Clinical Group system.[22] More specifically, we adjusted for a frailty flag calculated based on patient characteristics including malnutrition, difficulty walking, dementia, incontinence and barriers to access of care. This measure of frailty has been previously validated and found accurately to identify elderly populations who have the clinical characteristics of frailty as well as to predict adverse outcomes.[23] To further control for comorbidities, we also calculated a mortality risk score based on the weighted components of the 32 adjusted diagnostic groups from the Johns Hopkins System, which has previously been shown to perform as well as or better than other comorbidity scores such as the Charlson or Elixhauser scores.[24] Additionally, we adjusted for a time-varying propensity score for metformin use that evaluates the conditional probability of metformin use based on a set of observed patient characteristics including patient demographics, healthcare service utilization, comorbidity level, and concomitant drug use (anti-hyperglycaemic and cardiovascular).

2.6 | Statistical analysis

2.6.1 | Conventional models

To address the concerns associated with modelling metformin using time-fixed measures, our main analyses relied on time-varying models, which accounted for within-patient changes in metformin exposure over time. First, three separate conventional time-varying exposure models were estimated. Our preliminary analyses suggested that including metformin exposure that occurred more than 1 month prior to the time at which the risk is evaluated provided a worse fit to the data (data not shown); therefore, only time-varying exposure that occurred during the acute time windows of the preceding ≤30 days were evaluated in the main analyses. Firstly, we evaluated a binary time-varying indicator (1 vs 0) of the *current use* of metformin, updated for every day of follow-up. Secondly, we evaluated the impact of time-varying *total duration of past use* of metformin from the beginning of follow-up until the current day. Thirdly, we considered a binary time-varying indicator of any recent use of metformin within two alternative time-varying "acute" windows of the past (model 3a) 30 days and (model 3b) 10 days. See Figure 2 for an illustration of how metformin use was represented in these models, at any time during the follow-up time, using a single patient's metformin exposure pattern during their follow-up period.

2.6.2 | Flexible weighted cumulative exposure modelling

The novel analytical method used weighted cumulative exposure (WCE), whereby metformin exposure was modelled using a time-varying variable representing the weighted sum of the binary indicator

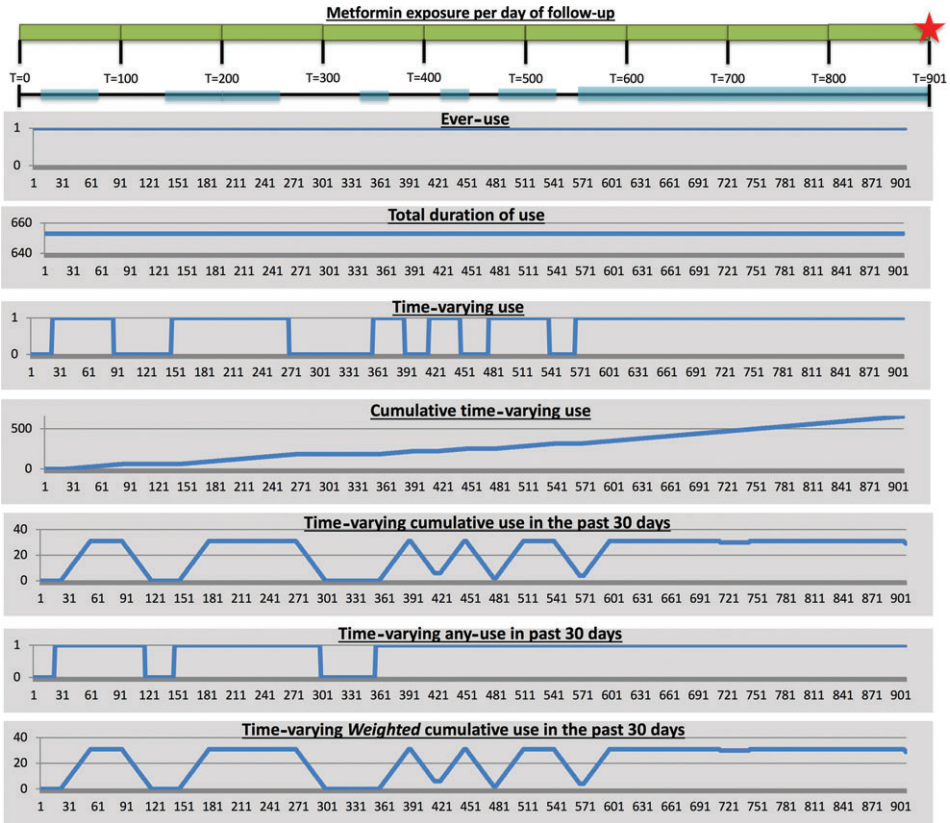

FIGURE 2 Illustration of how metformin use was represented in conventional and weighted cumulative exposure models using a single patient's metformin exposure patterns during their follow-up period

of use at each day in the relevant window of past exposure, with weights estimated to reflect the relative importance of medication taken at different times (eg, 2 days vs 10 days ago) on the current risk of events.[17] The weights assigned to past doses were estimated using a flexible cubic spline technique that avoided a priori assumptions regarding the shape of the weight function.[19] To enhance consistency with the conventional models, alternative WCE models assuming a different relevant window of past exposures of (1) 30 days and (2) 10 days were fit. For example, the 30-day window implies that metformin taken more than 1 month previously could not affect the current risk of HF exacerbation. The goodness of fit of each model were compared based on the minimum Akaike information criterion (AIC).[25] Any AIC difference > 10 was considered important, but a difference < 4 was not.

2.6.3 | Sensitivity analyses

A post hoc sensitivity analysis was conducted related to conventional model 3b above, where we evaluated use of metformin in the past 10 days, while also including an additional, binary, time-varying covariate which indicated if the patient had filled their first metformin prescription since the beginning of the follow-up period (ie, since incident HF diagnosis) in the last 7 days. This approach allowed us to separate the (mutually adjusted) effects of (1) any use in the past 10 days (regardless of the duration of previous exposure) vs (2) recent initiation of metformin treatment.

To improve the clinical interpretability of our results, the comparison between metformin and sulphonylurea monotherapy and its impact on HF exacerbation was conducted for the conventional time-varying current use model. This model was also re-run using metformin vs no antidiabetic agent as the comparator (the reference group in the primary analysis was metformin vs no metformin, where the no-metformin group could include any other antidiabetic agent or no antidiabetic agent [ie, diet controlled]).

3 | RESULTS

For the 7620 patients with diabetes with incident HF included in the present study, the mean follow-up was 604 days (1.7 years), resulting in a total of 4 606 057 person-days at risk (Figure 2). Their mean (SD) age was 54 (8) years, 4440 (58%) of them were men, and 6448 (85%) had three or more chronic conditions (Table 1).

Overall, 3799 individuals (50.0%) were exposed to metformin at any point following incident HF. Table 1 shows the characteristics of

TABLE 1 Characteristics of study cohort at time of incident heart failure (baseline[a]) according to those who were exposed to metformin over the follow-up period and those who were not exposed to metformin (n = 7620)

	Not exposed to metformin over follow-up (n = 3821)	Exposed to metformin over follow-up (n = 3799)	P^b
Baseline characteristics			
Mean (SD) age, years	54.5 (9.0)	54.3 (8.3)	0.41
Men, *n* (%)	2237 (58.5)	2203 (58.0)	0.62
Mean (SD) income, US$	48 526 (64313)	48 181 (6223)	
Type of insurance, *n* (%)			
Point of service	2235 (58.5)	2256 (59.4)	0.3
Exclusive provider	651 (17.0)	688 (18.1)	
Preferred provider	351 (9.2)	314 (8.3)	
Health maintenance	504 (13.2)	462 (12.2)	
Independent	80 (2.1)	78 (2.1.)	
Clinical variables			
Mean (SD) mortality risk score	48.0 (13.3)	44.5 (12.6)	<0.001
History of cardiovascular disease, *n* (%)			
Ischaemic heart disease	1606 (42.0)	1522 (40.1)	0.08
Myocardial infarction	267 (7.0)	208 (5.5)	0.006
Dyslipidaemia	2698 (68.0)	2679 (70.5)	0.017
Hypertension	3202 (83.8)	3119 (82.1)	0.05
Arrhythmia	722 (18.9)	622 (16.4)	0.004
Valve disease	359 (9.4)	304 (8.0)	0.03
History of diabetes complications, *n* (%)	1412 (37.0)	1639 (43.1)	<0.001
Estimated glomerular filtration rate category, *n* (%)			<0.001
<30 mL/min	279 (7.3)	12 (0.3)	
30 to <60 mL/min	709 (18.6)	363 (9.6)	
≥60 mL/min	1597 (41.8)	2080 (54.8)	
Mean (SD) total cholesterol, mmol/L	4.7 (1.4)	4.6 (1.4)	0.006
Mean (SD) triglycerides, mmol/L	2.2 (3.0)	2.2 (3.5)	0.39

TABLE 1 (Continued)

	Not exposed to metformin over follow-up (*n* = 3821)	Exposed to metformin over follow-up (*n* = 3799)	*P*[b]
Mean (SD) HDL cholesterol, mmol/L	1.2 (0.4)	1.1 (0.3)	<0.001
Mean (SD) LDL cholesterol, mmol/L	2.6 (1.0)	2.5 (1.0)	0.38
Mean (SD) HbA1c, % mmol/mol	7.8 (1.9) 61.7 (-)	7.5 (1.7) 58.5 (-)	<0.001
Mean (SD) haemoglobin, mmol/L	8.1 (1.2)	8.4 (1.0)	<0.001
Drug use, *n* (%)			
Antidiabetic			
No oral antidiabetic agent or insulin	525 (13.7)	184 (4.8)	<0.001
Metformin	957 (25.1)	3228 (85.0)	<0.001
Metformin monotherapy	294 (7.7)	1213 (31.9)	<0.001
Acarbose	20 (.5)	21 (0.6)	0.86
Pramlin	44 (1.2)	18 (0.5)	0.001
Incretin	344 (9.0)	413 (10.1)	0.006
Sulphonylurea	1226 (32.1)	1688 (44.4)	<0.001
Insulin	1967 (51.5)	806 (21.1)	<0.001
Cardiovascular			
Agents acting on the renin-angiotensin system	2568 (67.2)	2868 (70.7)	0.001
Statins	2022 (52.9)	2172 (57.2)	<0.001
β-Blockers	2013 (52.7)	1843 (48.5)	<0.001
Dihydro calcium channel blockers	1025 (26.8)	797 (21.0)	<0.001
Non-dihydro calcium channel blockers	425 (11.1)	346 (9.1)	0.004
Nitrates	507 (13.3)	512 (13.5)	0.8
Diuretics (loop)	1398 (36.6)	938 (24.7)	<0.001
Anticoagulants	448 (11.7)	340 (9.0)	0.001
Antiplatelet agents	761 (19.9)	636 (16.7)	<0.001
Anti-arrhythmic	101 (2.6)	94 (2.5)	0.64
Healthcare use			
Inpatient hospital admission in year before baseline date, *n* (%)			<0.001
0	2463 (64.5)	2840 (74.8)	
1	929 (24.3)	744 (19.6)	
2+	429 (11.2)	215 (5.7)	
Frailty, *n* (%)	393 (10.3)	324 (8.5)	0.009
Chronic conditions before index date, *n* (%)			<0.001
≥1	265 (6.9)	286 (7.5)	
2	240 (6.3)	346 (9.1)	
≥3	3316 (86.8)	3176(83.4)	

Abbreviation: HbA1c, glycated haemoglobin.

[a] Baseline characteristics are measured in the 1 year prior to incident heart failure (HF) or are based on the most recent value of a given characteristics prior to incident HF.

[b] For difference in baseline characteristics between those exposed to metformin over the follow-up period and those not exposed to metformin over the follow-up period.

metformin users vs never-users; those exposed to metformin at any point during the follow-up period were healthier at baseline (ie, at time of incident HF) than those never exposed to metformin during the follow-up. Metformin users had a lower overall mortality risk score, were less likely to have valve disease or arrhythmia, had a lower mean glycated haemoglobin (HbA1c) value, were less likely to be insulin users, were less likely to be treated with most cardiovascular medications, and were less likely to have two or more inpatient hospital admissions in the 1 year prior to incident HF. Metformin users were, however, more likely to have dyslipidaemia, or a history of diabetes complications at baseline. A total of 837 HF hospitalizations occurred over the follow-up period; the event rate for metformin ever-users was 1.3 HF-related hospitalizations per 10 000 person-years and 2.57 HF-related hospitalizations per 10 000 person-years of follow-up in metformin never-users.

Among the conventional time-varying models, current use of metformin, updated for every day of follow-up, was associated with a nonsignificant 16% reduction in HF events compared with non-use (adjusted hazard ratio [aHR] 0.84, 95% confidence interval [CI] 0.66-1.07; $P = 0.17$). This model had the best fit for the data

TABLE 2 Adjusted hazard ratios for different patterns of metformin use and impact on heart failure exacerbation in conventional and weighted cumulative exposure models

Patterns of metformin use	HR (95% CI)[a]	AIC
Conventional models		
Time varying: current use updated daily	0.84 (0.66-1.07)	14 610
Time varying: cumulative duration past use updated daily, unweighted	1.00 (0.99-1.01)	14 621
Time varying: any use in past 30 days, unweighted	0.71 (0.56-0.91)	14 613
Time varying: any use in past 10 days, unweighted	0.76 (0.60-0.97)	14 616
WCE model		
Time varying: use in past 30 days, weighted	0.85 (0.63-1.18)	14 604
Time varying: use in past 10 days, weighted	0.91 (0.69-1.20)	14 599

Abbreviations: AIC, Akaike Information Criterion HR, hazard ratio; WCE, weighted cumulative exposure.
[a] Adjusted for age, sex, pre-existing cardiovascular conditions, presence of diabetes complications, time-varying cardiovascular medication use, time-varying antidiabetic medication use, frailty, time-varying propensity score for conditional metformin use.

(AIC = 14 610) among the conventional time-varying models. Adjusted models including time-varying cumulative duration of past metformin use provided a worse fit for the data (AIC = 14 621), and suggested no association with the risk of HF-related hospitalization (aHR for each additional day of metformin exposure: 1.00, 95% CI 0.99-1.01; P = 0.80), whereas the "acute" time-varying models that accounted only for recent use suggested statistically significant protective effects (but had an AIC slightly worse than the current use model, by 3 and 6 points). In particular, any metformin use, in the past 30-day and 10-day windows, compared with non-use within the same window, was associated with, respectively, 29% and 21% reductions in HF-related hospital admissions (aHR 0.71, 95% CI 0.56-0.91 and aHR 0.76, 95% CI 0.60-0.97) (Table 2).

The novel WCE models provided the best fit for the data compared with the conventional time-varying models (AIC = 14 599 vs AIC = 14 610 for the best-fitting models in either category). The estimated weight function for the 30-day window is shown in Figure 3, in which the horizontal axis shows the number of days elapsed (t) between past metformin use and the time when the risk was assessed, and the vertical axis shows the corresponding estimated weights (negative weights indicate a protective effect), reflecting the relative strength of the impact of metformin use "t days ago" on the current risk of HF

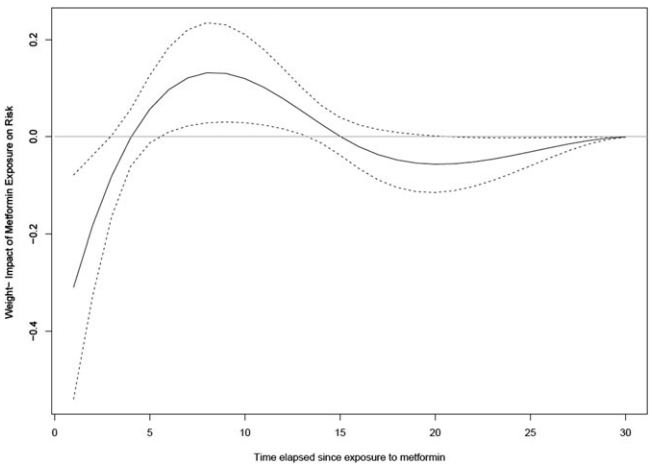

FIGURE 3 Spline-based estimated weight function: demonstrates the impact of metformin use on risk of heart failure exacerbation (ie, the weight) up to 30 days ago, with 95% confidence interval

hospitalization. Specifically, Figure 3 suggests that very recent metformin use, in the past 3 to 4 days, may confer acute benefits in reducing HF-related exacerbation, when the risk reduction appears statistically significant, as even the upper bound of the 95% confidence bands for the estimated weight fall below weight = 0. These benefits dissipate, however, for exposures that occurred more than 3 to 4 days ago, when the estimated weights become positive. Considering the net balance of these short- vs medium-term effects, the WCE models suggest that metformin use in the past 30 days is associated with a 15% lower risk of HF exacerbation compared with non-use in the same time period (aHR 0.85, 95% CI 0.63-1.18), and a 9% lower risk for patients who used it only in the past 10 days (aHR 0.91, 95% CI 0.69-1.20), with both estimates being statistically non-significant (Table 2).

The results of our first post hoc sensitivity analysis suggested that when adjusted for the first use of metformin (since incident HF) in the past week, the effect of any use in the past 10 days lost both clinical relevance and statistical significance (aHR 0.95, 95% CI 0.72-1.24). These results, in addition to the finding of improved fit over other conventional time-varying models (AIC = 14 606 vs 14 610 for the best-fitting conventional model) suggest that the protective effect of recent metformin exposure may be limited to those subjects who recently started using the medication since their HF diagnosis and does not apply to longer-time users.

The results of further sensitivity analyses suggest that metformin does not confer additional benefits in preventing HF exacerbations when directly compared with sulphonylurea therapy (based on the time-varying current use model, which was the best-fitting conventional model). Compared with time-varying sulphonylurea monotherapy updated daily, metformin monotherapy was associated with a very small decreased risk of HF exacerbation, which was statistically nonsignificant (aHR 0.94, 95% CI 0.50-1.50). Additionally, there was no appreciable difference in the results of our model when the reference group was changed to no antidiabetic drug use rather than no metformin use (data not shown).

4 | DISCUSSION

We evaluated the relationship between metformin use and HF-related hospitalization in patients with diabetes and pre-existing HF using

both conventional models and novel, flexible weighted cumulative exposure models. We observed potential acute benefits for metformin exposure in reducing HF exacerbations which dissipated after a few days of non-use. In other words, patients who continue to use metformin may experience acute cardiovascular benefits, but, these benefits are not amplified by cumulative use; however, we found that any protective effect of acute metformin exposure may be limited to those who had just started using the medication during follow-up.

Our results highlight the importance of evaluating a number of different exposure definitions for metformin, or indeed any dynamic treatment regimen. While previous studies have detected a benefit for metformin ever-use (usually as a monotherapy) in decreasing the risk of adverse cardiovascular outcomes,[13] our results suggest a statistically nonsignificant and clinically unimportant benefit of its overall cumulative impact and weighted cumulative impact on HF-related hospitalization. Additionally, our results suggest that the risk of HF hospitalization may be lowest during initial metformin use after incident HF diagnosis.

Indeed, pharmacokinetic and pharmacodynamic characteristics of different drugs, as well as different physiological responses to different pharmacological agents imply that drug exposure-risk associations may vary substantially across different medications and various adverse effects.[26] Such differences may reflect the pharmacokinetics/pharmacodynamics of the drug and/or latency of the biological mechanism linking its use with a given clinical endpoint.[19] With respect to metformin's impact in HF, there are a number of biological mechanisms which suggest acute use of this drug may have the greatest impact on cardiovascular outcomes.[27]

The arbitrary choice of the time window over which metformin exposure has been assessed in the past implies that prior knowledge regarding relative importance of exposures that occurred at different points in the past is relatively imprecise, and suggests a more data-driven approach may be required.[19] Furthermore, conventional binary indicators of any use in a particular time window (or ever-use) ignores information on dosage and duration of treatment. Although the "true" model for a particular exposure-outcome association is rarely known, statistical goodness-of-fit criteria can help identify model(s) that approximate reasonably well the underlying mechanisms.[28] It is important to emphasize again, however, that any time-fixed measures of exposure tend to induce immortal time bias which is known to produce an under-estimation of the relative risk of harm or benefit among users of a time-varying treatment.[16]

There are a number of limitations to keep in mind when interpreting the results of the present study. Although WCE models provided new insights regarding the associations between exposure to metformin and the risk of HF-related hospital admission in patients with diabetes and pre-existing HF, they produced slightly wider 95% CIs than the conventional models. This is common to more complex models, where additional coefficients help to increase the accuracy of the estimated association, at the cost of increased variance.[29] Additionally, we cannot be certain whether or not this potential acute benefit with metformin use is a true association or artifact of the data. Indeed, the potential remains for metformin (or any other antidiabetic medication) exposure to be misclassified around the time of an event given the patient is experiencing a significant decline in their health state and unable to visit their pharmacy to fill their medication. Thus, this would make metformin appear more protective than it actually is in preventing HF-related hospitalization. The potential impact of medication adherence on our results should also be acknowledged. Sub-optimal adherence to cardiovascular medications can lead to HF exacerbations, reduced physical functioning and a higher risk of hospitalization.[30] Given that patients who are non-adherent to cardiovascular medications are also less likely to adhere to antidiabetic medications, it is plausible that those who are not exposed to metformin may actually be non-adherent to their antidiabetic medications, and thus, more likely to experience HF exacerbations compared with those who filled metformin prescriptions. This would, in turn, make it appear as though metformin use is beneficial when it is simply a marker of a patient who tends to fill their medications as directed. Last, similarly to most studies evaluating the safety of antidiabetic medications, the potential impact of confounding by indication must be considered. This is especially true when evaluating the safety of metformin given that it is typically considered as first-line therapy and its discontinuation usually indicates it is not well tolerated by the patient or the patient has more advanced diabetes (has likely progressed to insulin), both of which may be associated with poorer health outcomes. In our propensity score models, we were able to account for markers of advanced diabetes, such as insulin use in the baseline period, history of diabetes complications, HbA1c and frailty, therefore, we have balanced metformin users and non-users with respect to important confounders given the data available within the observational design. We were unable to fully account for some differences between patients, however, such as HF severity, and acknowledge that residual confounding still may be an issue.

In summary, by using alternative flexible techniques to model the impact of metformin exposure on risk of HF-related hospital admission in those with pre-existing HF and diabetes, we were able to uncover important new relationships which previous studies have not been able to elucidate and added to the literature surrounding the safety of metformin in this patient population. Indeed, our results suggest that the benefits of metformin may have been overstated in previous observational studies. While metformin was observed to be safe in this population and should be considered as an option for blood glucose control in patients with type 2 diabetes it was not found to confer the level of benefit suggested by previous studies which supported its use as a first-line agent. After considering the broader clinical context for a given patient, such as blood glucose levels, lifestyle and potential for other diabetes-related complications, use of other anti-hyperglycaemic agents with proven efficacy in patients with HF should also be considered as treatment options.

ACKNOWLEDGMENTS

D.L.W. is supported by a doctoral award from the Canadian Institutes of Health Research, M.A. is a James McGill Professor at McGill University and is supported by the Canadian Institutes for Health Research (grant #PJT-148946) and D.T.E. is a Canada Research Chair supported by the Government of Canada.

Conflict of interest

None declared.

Author contributions

All authors conceived and designed the study. DTE acquired the data. DLW and MEB conducted the statistical analysis. All authors interpreted the data. DLW wrote the manuscript and all authors critically revised it. All authors approved the final version of the manuscript and agree to be accountable for the accuracy of the work. DTE supervised the study and is the guarantor.

ORCID

Daniala L. Weir http://orcid.org/0000-0001-7044-2443

REFERENCES

1. Bertoni AG, Hundley WG, Massing MW, Bonds DE, Burke GL, Goff DC Jr. Heart failure prevalence, incidence, and mortality in the elderly with diabetes. *Diabetes Care*. 2004;27:699-703.
2. Bertoni AG, Kirk JK, Goff DC Jr, Wagenknecht LE. Excess mortality related to diabetes mellitus in elderly Medicare beneficiaries. *Ann Epidemiol*. 2004;14:362-367.
3. Hemmingsen B, Lund SS, Gluud C, et al. Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. *BMJ*. 2011;343:d6898.
4. Mannucci E, Dicembrini I, Lauria A, Pozzilli P. Is glucose control important for prevention of cardiovascular disease in diabetes? *Diabetes Care*. 2013;36:S259-S263.
5. White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med*. 2013;369:1327-1335.
6. Green JB, Bethel MA, Armstrong PW, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2015;373:232-242.
7. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013;369:1317-1326.
8. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med*. 2015;373:2247-2257.
9. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375:311-322.
10. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin [Internet]; 2016. https://www.fda.gov/Drugs/DrugSafety/ucm486096.htm. Accessed November 1, 2016.
11. Barnett AH, Mithal A, Manassie J, et al. Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2014;2:369-384.
12. Patil HR, Al Badarin FJ, Al Shami HA, et al. Meta-analysis of effect of dipeptidyl peptidase-4 inhibitors on cardiovascular risk in type 2 diabetes mellitus. *Am J Cardiol*. 2012;110:826-833.
13. Eurich DT, Weir DL, Majumdar SR, et al. Comparative safety and effectiveness of metformin in patients with diabetes mellitus and heart failure. *Circ Heart Fail*. 2013;6:395-402.
14. American Diabetes Association. Standards of medical care in diabetes-2017 [Internet]; 2017. http://care.diabetesjournals.org/content/diacare/suppl/2016/12/15/40.Supplement_1.DC1/DC_40_S1_final.pdf. Accessed November 1, 2016.
15. Patorno E, Garry EM, Patrick AR, et al. Addressing limitations in observational studies of the association between glucose-lowering medications and all-cause mortality: a review. *Drug Saf*. 2015;38:295-310.
16. Suissa S. Immortal time bias in pharmacoepidemiology. *Am J Epidemiol*. 2008;167:492-499.
17. Abrahamowicz M, Bartlett G, Tamblyn R, du Berger R. Modeling cumulative dose and exposure duration provided insights regarding the associations between benzodiazepines and injuries. *J Clin Epidemiol*. 2006;59:393-403.
18. Dixon WG, Abrahamowicz M, Beauchamp M-E, et al. Immediate and delayed impact of oral glucocorticoid therapy on risk of serious infection in older patients with rheumatoid arthritis: a nested case-control analysis. *Ann Rheum Dis*. 2012;71:1128-1133.
19. Sylvestre M-P, Abrahamowicz M. Flexible modeling of the cumulative effects of time-dependent exposures on the hazard. *Stat Med*. 2009;28:3437-3453.
20. Eurich DT, Weir DL, Simpson SH, Senthilselvan A, McAlister FA. Risk of new-onset heart failure in patients using sitagliptin: a population-based cohort study. *Diabet Med*. 2016;33(5):621-630.
21. Weir DL, McAlister FA, Senthilselvan A, Minhas-Sandhu JK, Eurich DT. Sitagliptin use in patients with diabetes and heart failure. *JACC Heart Fail*. 2014;2:573-582.
22. Johns Hopkins University. The Johns Hopkins ACG System; 2012.
23. Poudel A, Hubbard RE, Nissen L, Mitchell C. Frailty: a key indicator to minimize inappropriate medication in older people. *QJM*. 2013;106:969-975.
24. Austin PC, Walraven C. The mortality risk score and the ADG score: two points-based scoring systems for the Johns Hopkins aggregated diagnosis groups to predict mortality in a general adult population cohort in Ontario, Canada. *Med Care*. 2011;49:940-947.
25. Akaike H. A new look at the statistical model identification. *IEEE Trans Autom Control*. 1974;19:716-723.
26. Csajka C, Verotta D. Pharmacokinetic–pharmacodynamic modelling: history and perspectives. *J Pharmacokinet Pharmacodyn*. 2006;33:227-279.
27. Foretz M, Guigas B, Bertrand L, Pollak M, Viollet B. Metformin: from mechanisms of action to therapies. *Cell Metab*. 2014;20:953-966.
28. Abrahamowicz M, Beauchamp M-E, Sylvestre M-P. Comparison of alternative models for linking drug exposure with adverse effects. *Stat Med*. 2012;31:1014-1030.
29. Abrahamowicz M, MacKenzie T, Esdaile JM. Time-dependent hazard ratio: modeling and hypothesis testing with application in lupus nephritis. *J Am Stat Assoc*. 1996;91:1432-1439.
30. Ruppar TM, Cooper PS, Mehr DR, Delgado JM, Dunbar-Jacob JM. Medication adherence interventions improve heart failure mortality and readmission rates: systematic review and meta-analysis of controlled trials. *J Am Heart Assoc*. 2016;5:e002606.

How to cite this article: Weir DL, Abrahamowicz M, Beauchamp M-E, Eurich DT. Acute vs cumulative benefits of metformin use in patients with type 2 diabetes and heart failure. *Diabetes Obes Metab*. 2018;1–8. https://doi.org/10.1111/dom.13448