Metformin Use and Cardiovascular Events in Patients with Type 2 Diabetes and Chronic Kidney Disease

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Abstract

Aims—Metformin could have benefits on cardiovascular disease and kidney disease progression but is often withheld from individuals with diabetes and chronic kidney disease (CKD) out of concern that it may increase the risk of lactic acidosis.

Materials and Methods—All-cause mortality, cardiovascular death, cardiovascular events (death, heart failure hospitalization, myocardial infarction, stroke, or myocardial ischemia), end stage renal disease (ESRD), and the kidney disease composite (ESRD or death) were compared in metformin users and non-users with diabetes and CKD enrolled in the Trial to Reduce Cardiovascular Events with Aranesp (darbepoeitin-alfa) Therapy (TREAT, NCT00093015). Outcomes were compared after propensity matching users and non-users and in multivariable proportional hazards models. .

Results—There were 591 individuals who used metformin at baseline and 3447 non-users. Among propensity matched users, the crude incidence rate for mortality, cardiovascular mortality, cardiovascular events and the combined endpoint was lower in metformin users than non-users, but ESRD was marginally higher (4.0% vs. 3.6%). Metformin use was independently associated with a reduced risk of all-cause mortality (HR 0.49, 95% CI:0.36-0.69), cardiovascular death (HR 0.49, 95% CI: 0.32-0.74),the cardiovascular composite (HR 0.66, 95% CI: 0.51-0.86), and the kidney disease composite (HR 0.77, 95% CI: 0.61-0.98). Associations with ESRD (HR 1.01, 95% CI: 0.65-1.55) were not significant. Results were qualitatively similar in adjusted analyses of the full population. Two cases of lactic acidosis were observed.

Conclusions—Metformin may be safer for use in CKD than previously considered and may lower the risk of death and cardiovascular events in individuals with stage 3 CKD.

Research in Context

Evidence Before This Study

In 2016, the Food and Drug Administration reviewed the safety of metformin utilization in the setting of impaired kidney function. This review concluded that metformin could be used safely in the setting of mild kidney impairment and in some patients with moderate kidney impairment. As a result, the US labelling was changed to recommend that metformin could be safely used in patients with mild to moderate renal impairment, but that metformin should not be started when estimated glomerular filtration rate is <45 mL/min/1.73m^2. Despite these recommendations, data on safety of metformin in the setting of ≥stage 3 chronic kidney disease (CKD) remains sparse and whether metformin improves survival, cardiovascular or kidney outcomes in this setting is uncertain.

Added Value of This Study

We assessed all-cause mortality, cardiovascular death, cardiovascular events (death, heart failure hospitalization, myocardial infarction, stroke, or myocardial ischemia), end stage renal disease (ESRD), and the kidney disease composite (ESRD or death) in users and non-users of metformin with chronic kidney disease and diabetes who were enrolled in the Trial to Reduce Cardiovascular Events with Aranesp (darbepoeitin-alfa) Therapy (TREAT, NCT00093015). Among 591 individuals who used metformin at baseline and 3447 non-users, metformin use was independently associated with a reduced risk of all-cause mortality (HR 0.68, 95% CI: 0.52-0.89), cardiovascular death (HR 0.65, 95% CI: 0.46-0.91) and the cardiovascular composite (HR 0.79, 95% CI: 0.65-0.97). Associations with ESRD (HR 0.94, 95% CI: 0.70-1.26), or the kidney disease composite (HR 0.82, 95% CI: 0.66-1.00) were not significant. Only 2 cases of lactic acidosis were observed.

Implications of all the Available Evidence

Our analysis suggests that metformin can be utilized safely in individuals with stage 3 CKD. Use may be associated with survival and cardiovascular benefits in the setting of CKD but may not slow progression of CKD. Further studies are warranted to confirm these findings and assess the impact on CKD progression and the appropriate asses role for metformin in the CKD population.

Introduction

Approximately 43% of individuals with type 2 diabetes have evidence of chronic kidney disease (CKD), and among individuals ≥65 years with diabetes, CKD prevalence is 61%.[1] Recent trends in diet, lifestyle and obesity suggest that the incidence of stage 5 CKD with diabetes is likely to grow by more than 3% annually in the coming decade.[2] Given associations of diabetes and CKD with cardiovascular morbidity and mortality as well as other important health outcomes it is likely that this degree of growth in the prevalence of diabetic CKD, will be associated with profound increases in the burden of cardiovascular morbidity and health-care spending.[3, 4]

In this context, there is an increasing need for effective therapies that improve glycemic control while reducing the risk of death, cardiovascular events and ESRD in the setting of CKD. Although older hypoglycemic agents could provide benefits when used in the setting of CKD, the role of metformin, the most widely used glucose lowering agent has not been adequately investigated in patients with impaired kidney function.

Experimental studies suggest that metformin may have anti-fibrotic effects[5, 6] with the potential for beneficial kidney and cardiovascular disease effects independent of the direct effect on glycemic control. However, until recently metformin was considered unsafe for use in individuals with moderate or severe CKD due to the potential to induce lactic acidosis.[7] Despite these warnings metformin may be used by more than 15% of patients with stage 3 CKD.[8] This warning was recently revised to permit more liberal use of metformin in individuals with stage 3-4 CKD with recommendations suggesting that the dose be individualized and reduced in accordance with the underlying eGFR,[9, 10], but whether metformin has specific cardiovascular or kidney disease benefits in the setting of CKD is uncertain. We therefore compared cardiovascular and kidney disease outcomes among patients with type 2 diabetes and CKD enrolled in the Trial to Reduce Cardiovascular Events with Aranesp (darbepoeitin-alfa) Therapy (TREAT, NCT00093015).

Methods

Study Cohort

We analyzed data from the TREAT trial which enrolled 4038 subjects with diabetes and CKD to darbepoetin alfa or placebo.[11] TREAT was approved by local institutional review boards, and all subjects provided written informed consent. The study was conducted in accordance with Declaration of Helsinki. An estimated glomerular filtration rate (eGFR) between 20-60 mL/min/1.73 m^2 using the non-IDMS traceable, 4-variable MDRD Study equation,[12, 13] was required for inclusion. Other key inclusion criteria included a hemoglobin ≤11.0 g/dL, and transferrin saturation ≥15%.

Randomization and Masking

Patients in TREAT were randomized using a computer generated permuted block schema according to study site, baseline proteinuria and history of cardiovascular disease. The study was conducted in a double blind fashion between August 2004 and August 2009 as reported previously.[11]

Data Elements

eGFR was estimated using the CKD-EPI 2009 equation.[14] and pre-specified an analysis based on the presence or absence of stage ≥G4 CKD (eGFR<30mL/min/1.73m^2)[15] at baseline. The ratio of urinary protein to creatinine concentration (U_{PCR}) at baseline was analyzed using a binary classification above or below the median.

Outcomes

Pre-selected outcomes of interest were based on the pre-specified endpoints from TREAT and included death, cardiovascular death, ESRD, a kidney disease composite of ESRD or death, and a cardiovascular disease composite which included heart failure hospitalization, myocardial infarction, stroke, or myocardial ischemia or death. Deaths, cardiovascular events, and ESRD were adjudicated by a blinded events committee according to standardized definitions.[16] ESRD required initiation of dialysis for >30 days, refusal/non-availability of dialysis and transplantation, and kidney transplantation. Death within 30 days of dialysis initiation could be considered ESRD after committee review. Lactic acidosis was not adjudicated and was assessed on the basis of adverse events reports.

Statistical Analysis

Baseline characteristics were compared in metformin users and non-users using chi-squared, t-tests, or Kruskal-Wallis tests according to the distribution. Differences in event rates across quartiles of hemoglobin A1C were tested using chi-squared tests. Survival analyses utilized Kaplan-Meir estimates of incident rates per 100 patient-years with hazard ratios (HR) and 95% confidence intervals (CI) calculated using crude and adjusted Cox models.
A propensity score was calculated using logistic regression to predict use of metformin at baseline. All baseline factors listed in Table 1 were included in the calculation of the score and metformin users and non-users were matched using a caliper distance of 0.05. Crude and adjusted hazard ratios or sub-hazard ratios for the matched pairs were calculated using Cox or competing risk models as described below.

Multivariable models included well-established kidney and cardiovascular disease risk factors and were based on a model (M1) previously validated for prediction of outcomes in TREAT and adjusted for age, sex, race, body mass index, insulin use, baseline eGFR, blood urea nitrogen, c-reactive protein, ferritin, hemoglobin, proteinuria, serum albumin, and history of stroke, coronary disease, heart failure, arrhythmia, atrial fibrillation, and acute kidney injury.[17] Proportional hazards assumptions were inspected using standard techniques. In addition, we tested for interaction of metformin use with CKD stage at baseline comparing stage G 1-3 with stage G 4-5.
Sensitivity analyses included assessing for effect modification according to the stage of CKD by testing for binary interactions between the presence of metformin use with CKD stage G 4-5 compared with CKD stage G 1-3 and testing for effect modification by the randomized therapy assignment (placebo or darbepoetin) within the overall cohort. Competing-risk models to account for possibility of death prior to ESRD, kidney or cardiovascular disease events. Fine and Gray models[18] were used to provide cause-specific sub-hazards with death as the competing risk. These models included the same covariates as the primary Cox analyses. To assess the impact of model specification on the outcomes of interest, we constructed a second set of models (M2) adjusted for a broader set of covariates implicated in cardiovascular and kidney outcomes including age, sex, race, body mass index, insulin use, baseline eGFR, blood urea nitrogen, c-reactive protein, proteinuria, serum albumin, and history of stroke, coronary disease, heart failure, arrhythmia, atrial fibrillation, and acute kidney injury, angiotensin converting enzyme inhibitor or receptor blocker use, and duration of diabetes. Lastly, we investigated exploratory, post-hoc kidney endpoints using a non-adjudicated endpoint of doubling of serum creatinine from baseline and its combination with ESRD or the

kidney disease composite endpoint. Analyses were conducted using STATA version 13 (STATA, College Station, TX) with P<0.05 considered significant.

Role of the Funding Source

TREAT was funded by Amgen. The authors designed and conducted all analyses and were solely responsible for drafting, editing, and submitting this manuscript. Dr Charytan had access to the data and responsibility for the decision to submit for publication.

Results

Baseline Characteristics

We identified 591 individuals who received metformin at baseline and 3447 who were not using metformin at baseline (Table 1). Metformin users were less likely to be male (34.5% vs. 44.2%), and more likely to be of white race (69.2% vs. 62.7%), have a shorter duration of diabetes (178 ± 109 vs. 194 ±120 months, P<0.01), and tended to have fewer comorbid conditions including a less frequent history of heart failure, coronary disease, and peripheral vascular disease (P<0.01 for each). Although 386 metformin users had ≥stage G 3b CKD, they were less likely to have stage 4-5 CKD (23.0% vs. 40.8).

Diabetes control was marginally better in metformin users at baseline in whom A1C levels were 6.8% compared to 7.0% in non-users (P=0.047). Consistent with this trend, metformin users were also less likely to utilize insulin (29.4% vs. 52.7%). However, differences in glycemic control over time were marginally different (0.15%) through week 25 of follow-up and were non-significant thereafter (Supplementary Table 1).

We matched 508 out of 597 (85%) of metformin users to a propensity-score matched control subject. After matching, differences in baseline characteristics were markedly attenuated and there were no significant differences in baseline characteristics. (Table 1).

Overall Outcomes

In the propensity matched-analysis, metformin users had lower rates of all-cause mortality (4.6 vs. 8.5/100 patient-years), cardiovascular death (2.8 vs. 5.2/100 patient-years), the kidney disease composite (8.0 vs. 10.9/100 patient-

years) as well as the cardiovascular disease composite (8.6 vs. 11.9/100 patient-years) whereas ESRD was slightly more frequent in the metformin users (4.0 vs. 3.6/100 patient years, Table 2, Figure 1). Results were similar in the non-matched data except that the crude rate of ESRD was lower among metformin users than non-users (3.8 vs. 8.0/100 patient-years, Table 2, Supplementary Figure 1). Crude estimates were consistent with reduction of ≥45% in the hazard of all-cause mortality, cardiovascular, and the kidney disease composite events and were highly significant. The crude risk of ESRD was higher in metformin users than non-users hazard ratio (HR) 1.12 (95% CI: 0.74-1.69) but the difference was non-significant (Table 3). Results for secondary endpoints including doubling of creatinine, combined doubling of creatine and ESRD, and the kidney composite combined with doubling of creatinine were qualitatively similar to the primary kidney outcomes Metformin use remained independently associated with a reduced risk of all-cause mortality (HR 0.49, 95% CI: 0.36-0.69, cardiovascular death (HR 0.49, 95% CI: 0.32-0.74) and the cardiovascular disease composite (HR 0.66, 95% CI: 0.51-0.86). In contrast, associations with ESRD (HR 1.01, 95% CI: 0.65-1.55), and the kidney disease composite (HR 0.67, 95% CI:0.51-0.88) were not significant in adjusted models. Adjusted results were qualitatively similar in the unmatched data (Table 3).

Results according to CKD stage

Regardless of CKD stage, ESRD, cardiovascular disease, and the combined outcomes occurred less frequently among metformin users compared with non-users (Supplementary Figure 2, Supplementary Table 2). Point estimates of associations with metformin use with outcomes were attenuated in individuals with stage G 4-5 compared to stage G 1-3 CKD for all-cause mortality (HR 0.83, 95% CI: 0.54-1.27 vs. HR 0.61, 95% CI:0.44-0.85), cardiovascular death (HR 0.80, 95% CI: 0.46-1.39 vs. HR 0.59, 95% CI: 0.38-0.90), and the kidney disease composite (HR 0.95, 95% CI: 0.70-1.29 vs. 0.70, 95% CI: 0.53-0.92). However, tests of interaction were not suggestive of significant effect modification by CKD stage ($P_{interaction}$≥0.19). For the combined, cardiovascular disease endpoint, metformin was associated with a lower risk compared with alternatives therapies among individuals with CKD stages G 1-3 (HR 0.70, 95% CI: 0.53-0.90) but not among individuals with CKD stage G 4-5 (HR 0.99, 95% CI: 0.71-1.39); however, the interaction did not achieve significance ($P_{interaction}$=0.06). Lactic acidosis was rare. It was reported in only 2 patients taking metformin (0.3%) and was not reported in any non-users during

the study period. The most recent eGFR was 40.8 ml/min/1.73m^2 (39 days prior to the event) and 36.2 ml/min/1.73m^2 (20 days prior to the event) in these 2 individuals.

Sensitivity Analyses Results from model M2 were similar to those from the primary outcomes model as shown in Supplementary Table 3. Kidney and cardiovascular disease outcomes were similar in analyses accounting for the competing risk of all-cause mortality. In crude analyses, use of metformin was associated with significantly lower risks of cardiovascular death, and the kidney and cardiovascular disease composites (P<0.01 for all outcomes). In contrast, neither the risk of ESRD (HR 1.17, 95% CI: 0.78-1.76) as of creatinine doubling and combined ESRD and doubling were significantly increased. In adjusted analyses the associations with the risk of cardiovascular mortality (HR 0.54, 95% CI: 0.35-0.83), the cardiovascular disease composite (HR 0.66, 95% CI: 0.50-0.86), the kidney disease composite (HR 0.67, 95% CI: 0.51-0.88), and the combined kidney disease composite plus doubling of creatinine (HR 0.77, 95% CI: 0.61-0.98) demonstrated independent associations with metformin use following adjustment for clinical and demographic risk factors. Results were similar in the overall data set except that associations with the kidney disease composite (HR 0.82, 95% CI: 0.65-1.02) and combined kidney disease composite and doubling of creatinine were non-significant Supplementary Table 4).

Discussion

We analyzed associations of metformin use with survival, cardiovascular and kidney disease outcomes among 4038 individuals with diabetes and CKD enrolled in the TREAT trial including 591metformin users among whom 386 had ≥stage G 3b CKD. Compared with use of regimens not including metformin, metformin use was associated with significantly lower risks of all-cause mortality, cardiovascular mortality, and a combined cardiovascular disease endpoint that were robust across statistical techniques and that persisted after adjustment for established clinical and demographic risk factors. In contrast, there was no evidence of significant kidney-specific benefits from metformin use and associations with a reduced risk of the combination of death or ESRD were primarily due to effects on overall survival, although confidence intervals for this endpoint were wide despite a large number of ESRD events.

Several studies have previously examined associations of metformin use with kidney and cardiovascular disease outcomes. In the randomized United Kingdom Prospective Diabetes Study, metformin treatment was associated with reduced risks of death and stroke compared to sulfonylurea use, but was not associated with a reduction in progression of CKD.[19] More recently, Hung studied 95,577 US Veterans with eGFR ≥60 mL/min/1.73m^2 and found that compared with initial treatment with metformin, sulfonylurea therapy was associated with a 20% increase in the risks of both combined ESRD or 25% sustained decrease in eGFR and in the combined endpoint of ESRD, sustained decreased in eGFR or death.[20] This group subsequently found that among individuals with serum creatinine <1.5 mg/dL in men or 1.4 mg/dL in women, metformin use was associated with reduced risks of both heart failure and cardiovascular death compared to sulfonylurea therapy.[21]

Despite these encouraging data and recent suggestions to liberalize use of metformin in individuals with CKD stage 3 and stage 4 [10], relatively few studies have analyzed outcomes of metformin use in this population. A 2010 meta-analysis of data including 70,490 patient-years of metformin use found no convincing evidence that its use increases risk of lactic acidosis in the overall population, although there were insufficient data on the underlying kidney function of included subjects to investigate the impact of reduced eGFR per se.[22] Indeed, a rise in lactate levels has been observed in patients with diabetes independent of their use of metformin suggesting that initial report associating diabetes and lactic acidosis may have been confounded [23]. Whether the high frequency of acidosis native to CKD and absence of a uniform definition of lactic acidosis have similarly confounded assessments of the association of CKD with lactic acidosis is uncertain. However, it is interesting that a recent meta-analysis found that drug levels and lactate generally remain within the therapeutic range in individuals with eGFR between 30-60 mL/min/1.73m^2 and that rates of lactic acidosis were generally similar in patients with and without CKD, although there were minimal reliable data.[7] Similarly, a recent pharmacologic study showed that serial blood metformin levels never exceed the upper limit of normal and that lactate levels remained ≤5.0 mmol/L in stage 3b CKD patients treated with 1000 mg daily and stage 3 patients administered 500 mg/day for 4 months.[24]

In contrast, a Danish national registry, found that metformin use was associated with an increased risk of acute dialysis both among individuals with eGFR above and below 60 mL/min/1.73m^2.[25] An analysis of 813 Taiwanese patients with stage G 5 CKD and matched controls also found a significant and dose-dependent increase in the risk

of death among metformin users compared to controls and a non-significant increase in the risk of lactic acidosis.[26] In contrast, several recent studies found that metformin was associated with protective effects in individuals with CKD. Among patients with diabetes and atherosclerosis, metformin was associated with significantly reduced mortality among 4960 stage 3 CKD patients, but was not associated with mortality among 563 stage G 4-5 CKD patients.[27] Similarly, an analysis of the Swedish National Diabetes Register registry found that metformin-based regimens were associated with reduced risks of death in individuals with stage G 3a CKD but not in stage G 3b CKD. There was no association with a combined cardiovascular endpoint.[28] Finally, a recent analysis of US Veterans showed that metformin was associated with a reduced risk of death compared to sulfonylurea therapy among individuals with stage G 3a CKD. Results were qualitatively similar in stage G 3b CKD but did not achieve significance.[29]

Our analysis is consistent with these recent analyses and with the concept that lactic acidosis is a rare event among metformin users with CKD and that metformin could reduce mortality in individuals with CKD. Although our analysis suggests that metformin may be associated with greater reduction in risk of the combined cardiovascular disease outcome among individuals with CKD stages G 1-3 than CKD stages G 4-5, we did not identify significant differences in efficacy by CKD stage for the other outcomes, and there was no evidence of harm in CKD stages G 4-5. Nevertheless, our point-estimates were consistent with the attenuation of mortality benefits at CKD stages G 4-5 as seen previously.[27-29] Our analysis extends these findings in several ways. First, we specifically demonstrated associations between metformin use and a lower risk of cardiovascular mortality and cardiovascular events in individuals with CKD. None of the prior studies analyzed cause-specific mortality and our results suggest for the first time that the reduction in mortality arises primarily from a reduction in fatal cardiovascular events. Regarding non-fatal events, our results differ from those of Ekstrom who did not identify associations with cardiovascular disease events.[28] Differences in the underlying populations could explain differences between our study and Ekstrom's findings.[28] In addition, all cardiovascular disease events in TREAT were adjudicated by a committee using standardized definitions.

To our knowledge, ours is among the first analyses of associations of metformin use with progression to ESRD in a population of individuals with diabetes and CKD in whom there was a substantial rate of progression to ESRD.

Despite the apparent reduction in cardiovascular disease events and a large number of ESRD events, we did not identify a significant association with progression to ESRD. The confidence intervals were wide, and this finding should be interpreted cautiously. However, in the context of prior studies, the lack of an impact on ESRD incidence suggests that the experimental reductions in renal fibrosis observed with metformin[6] may not translate into a reduction in progressive GFR loss in diabetes. However, it is possible that fibrosis present in some stage 4 CKD patients enrolled was advanced and resistant to anti-fibrotic treatment. Whether earlier stages of CKD would be likely to respond merits further study.

It is unclear why metformin would have cardiovascular-specific benefits, but interference with cardiac hypertrophy through disruption of mTOR signaling and activation of AMPK signaling is one possibility.[30] Alternatively, the lower likelihood of hypoglycemia with metformin compared with insulin-based therapy for diabetes may be a key factor since hypoglycemia can stimulate inflammation and secretion of counter-regulatory hormones with adverse cardiovascular effects.[31] We were unable to investigate the role of hypoglycemia in our cohort, but this may be an important area of focus for subsequent studies. Regardless of the underlying mechanism, our findings suggest that metformin may have significant benefits for individuals with moderate CKD and should not be withheld on the basis of kidney function in those with stage G 3 CKD. However, in contrast to SGLT-2 inhibitors and glucagon-like peptide 1 agonists, metformin may not prevent CKD progression.[32-34] Our study supports that hypothesis that metformin may nevertheless have an important role as an agent with the potential to reduce cardiovascular morbidity and mortality which are among the most serious threats to individuals with CKD. Randomized trials to confirm these benefits and to assess whether they extend to later stages of CKD is warranted.

An important strength of our study is the inclusion and long-term follow-up of a large cohort of patients with diabetes and clinically diagnosed CKD, confirmation of eGFR between 20-60 mL/min/1.73m^2 (using the MDRD Study formula) by a central lab during a stable outpatient visit, and use of metformin despite prevailing guidelines at the time of the study recommending against prescription of this drug in individuals with eGFR <60 mL/min/1.73m^2. In addition, as noted above, cardiovascular and kidney disease events were adjudicated by a central committee using standard definitions and clinical records rather than on the basis of extraction from diagnostic codes. Finally, there

were a large number of ESRD events which provided a unique ability to specifically analyze kidney failure rather than surrogate markers of CKD progression.

Several limitations should also be acknowledged. We studied prevalent users of metformin at baseline and use was not randomized. Results were consistent in 2-different multi-variable models in addition to the propensity matched analysis, but we cannot rule out the possibility of residual confounding or inherent bias in the selection of patients to receive metformin. Our study was conducted prior to the availability of several new agents for diabetes, albeit some of these newer agents such as SGLT2i are not generally used in low GFR subjects, and thus we were unable to assess the relative effects of metformin compared to these agents. We were unable to determine cause of CKD with certainty. However, all patients were clinically diagnosed to have CKD due to diabetes and were required to have evidence of stage G 3 or higher (using the MDRD Study formula) on central lab measurement done while the patients were clinically stable. In addition, the large number of missing values precluded adjustment for time updated measure of glycemic control. However, in those with available values differences in glycemic control between groups were generally small and non-significant. Furthermore, given that lactic acidosis is an uncommon event, the precision of our safety analysis could potentially be low. In addition, the use of a population of prevalent metformin users for this analysis, would have selected those CKD patients most likely to tolerate its use. Larger, preferably randomized, trials, are clearly warranted to provide more precise and generalizable risk estimates. Lastly, lactate levels were not collected uniformly, and cases of lactic acidosis were identified clinically using adverse events reports rather than with a standardized definition.

In conclusion, we studied associations of metformin use with clinical outcomes among individuals in the TREAT study with diabetes and CKD. Despite concerns about lactic acidosis that have limited use of metformin in CKD, our data suggest that metformin may be safer than previously considered for use in CKD. Lactic acidosis was rare and non-fatal, and, although not definitive, our results suggest that metformin may lower the risk of death and cardiovascular events albeit not ESRD in individuals with stage G 3 CKD. These data may be useful to inform decisions to utilize or withhold metformin in the setting of diabetes with late-stage CKD and suggest the need for randomized studies to better assess the appropriate role for metformin in this population.

Conflict of Interest Statement

David Charytan- Research grant Janssen Pharmaceuticals (significant). Funds for service DSMB-Astra Zeneca

Scott Solomon- Research grants from Alnylam, Amgen, AstraZeneca, Bellerophon, BMS, Celladon, Gilead, GSK, Ionis, Lone Star Heart, Mesoblast, MyoKardia, NIH/NHLBI, Novartis, Sanofi Pasteur, Theracos. Consulting: r Akros, Alnylam, Amgen, AstraZeneca, Bayer, BMS, Corvia, Gilead, GSK, Ironwood, Merck, Novartis, Pfizer, Roche, Takeda, Theracos, Quantum Genetics, , Cardurion, Abiomed, Janssen

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Author Contributions

SDS, PI, GR, MEC, JBM, HHP, PP, AKS, EAB, ASL, KUE, JJVM, EFL, LAW and MAP, contributed to patient recruitment and study conduct, of TREAT. DMC, JL, BC and MAP contributed to the design of this analysis. BC and JL performed the statistical analyses. DMC and MAP drafted the manuscript. All authors contributed to data interpretation, critical revision of the manuscript, and final approval. DMC, JL, BC and MAP take responsibility for all aspects of the report and all authors take responsibility for their contributions.

Data Sharing Statement

Data collected for this study is not publicly available. Collaborative analyses may be considered after emailing a written research proposal including mechanism of support to Dr. Marc Pfeffer at mpfeffer@rics.bwh.harvard.edu.

Table 1. Baseline characteristics according to use of metformin at baseline

	Overall			Matched Cohort		
	Non-Users (N=3447)	**Metformin Users** (N=591)	**P Value**	**Non-Users** (N=508)	**Metformin Users** (N=508)	**P Value**
Demographics						
Age (years)	67 ± 11	67 ± 10	0.55	67 ± 10	68 ± 10	0.68
Male	1522 (44.2%)	204 (34.5%)	<0.001	184 (36.2%)	180 (35.4%)	0.79
Race			<0.001			0.47
Black	747 (21.7%)	68 (11.5%)		50 (9.8 %)	62 (12.2%)	
Other	539 (15.6%)	114 (19.3%)		100 (19.7%)	94 (18.5%)	
White	2161 (62.7%)	409 (69.2%)		358 (70.5%)	352 (69.3%)	
Physical Exam						
Systolic pressure (mm Hg)	136 ± 19	136 ± 18	0.53	137 ± 18	137 ± 18	0.98
Diastolic pressure (mm Hg)	72 ± 11	73 ± 11	0.03	74 ± 11	73 ± 12	0.56
Body mass index (kg/m^2)	31.5 ± 7.4	31.5 ± 7.4	0.97	31.5 ± 7.4	31.3 ± 7.3	0.75
Medical History						
Duration of DM (Months)	194.1 ± 119.8	177.7 ± 108.9	0.002	170.0 [90.6, 261.3]	168.3 [97.6, 247.6]	0.73
Cardiovascular disease	2309 (67.0%)	333 (56.3%)	<0.001	294 (57.9%)	290 (57.1%)	0.80
Coronary disease	1508 (43.7%)	210 (35.5%)	<0.001	204 (40.2%)	183 (36.0%)	0.17
Heart Failure	1206 (35.0%)	141 (23.9%)	<0.001	121 (23.8%)	117 (23.0%)	0.77
Myocardial infarction	643 (18.7%)	98 (16.6%)	0.23	100 (19.7%)	85 (16.7%)	0.22
Stroke	390 (11.3%)	57 (9.6 %)	0.23	50 (9.8 %)	49 (9.6 %)	0.92
Peripheral vascular disease	691 (20.0%)	88 (14.9%)	0.003	87 (17.1%)	83 (16.3%)	0.74
Current Smoker	181 (5.3 %)	23 (3.9 %)	0.16	18 (3.5 %)	17 (3.3 %)	0.86
CKD Stage			<0.001			0.49
Stage 1-2	79 (2.3 %)	29 (4.9 %)		26 (5.1 %)	25 (4.9 %)	
Stage 3a	505 (14.7%)	176 (29.8%)		128 (25.2%)	150 (29.5%)	
Stage 3b	1455 (42.2%)	250 (42.3%)		230 (45.3%)	217 (42.7%)	
Stage 4-5	1405 (40.8%)	136 (23.0%)		124 (24.4%)	116 (22.8%)	
Medications						
Randomized to darbepoetin	1720 (49.9%)	292 (49.4%)	0.83	252 (49.6%)	257 (50.6%)	0.75
Insulin	1815 (52.7%)	174 (29.4%)	<0.001	152 (29.9%)	144 (28.3%)	0.58
Sulfonamides	1144 (33.2%)	285 (48.2%)	<0.001	251 (49.4%)	245 (48.2%)	0.71
Thiazolidinediones	822 (23.8%)	162 (27.4%)	0.06	122 (24.0%)	140 (27.6%)	0.20
DPP-IV Inhibitors	23 (0.7 %)	3 (0.5 %)	0.65	3 (0.6 %)	3 (0.6 %)	1.00
Other diabetic agents	10 (0.3 %)	2 (0.3 %)	0.84	3 (0.6 %)	2 (0.4 %)	0.65
ACEi or ARB	2718 (78.9%)	505 (85.4%)	<0.001	441 (86.8%)	433 (85.2%)	0.47
Beta blockers	1721 (49.9%)	269 (45.5%)	0.05	248 (48.8%)	231 (45.5%)	0.29
Aldosterone blockers	181 (5.3 %)	28 (4.7 %)	0.60	22 (4.3 %)	21(4.1 %)	0.88
Statin	2002 (58.1%)	362 (61.3%)	0.15	306 (60.2%)	315 (62.0%)	0.56
Other antiplatelet agents	455 (13.2%)	58 (9.8 %)	0.02	54 (10.6%)	48 (9.4 %)	0.53
Vitamin K antagonists	238 (6.9 %)	39 (6.6 %)	0.79	38 (7.5 %)	36 (7.1 %)	0.81

Labs						
Creatinine (mg/dL)	168.0 [141.4, 212.2]	141.4 [114.9, 176.8]	<0.001	38.0 [30.4, 47.4]	40.0 [31.1, 48.0]	0.17T
eGFR (mL/min/1.73m^2)	32.7 [25.5, 41.3]	39.8 [30.9, 48.4]	<0.001	38.0 [30.4, 47.4]	40.0 [31.1, 48.0]	0.17
Urine protein creatinine ratio	0.5 [0.1, 2.0]	0.3 [0.1, 1.5]	<0.001	0.3 [0.1, 1.6]	0.3 [0.1, 1.4]	0.15
CRP (μg/mL)*	5.0 [4.9, 5.1]	4.6 [4.3, 4.8]	0.01	4.7 [4.4, 4.9]	4.6 [4.3, 4.9]	0.71
Albumin (g/L)	40.0 [37.0, 42.0]	41.0 [38.0, 43.0]	<0.001	41.0 [39.0, 43.0]	41.0 [38.0, 43.0]	0.89
A1C (%)	7.0 [6.2, 8.0]	6.8 [6.3, 7.7]	0.05	6.9 [6.2, 7.9]	6.8 [6.3, 7.7]	0.77
Potassium (mE/L)	4.7 [4.3, 5.1]	4.7 [4.4, 5.1]	0.04	4.7 [4.3, 5.1]	4.7 [4.4, 5.1]	0.74
Hemoglobin (g/L)	104 [99, 109]	105 [99, 110]	0.02	106 [100, 110]	105 [99, 110]	0.30
Ferritin (ug/L)	139.0 [71.0, 269.0]	98.0 [48.0, 197.0]	<0.001	114.5 [56.5, 196.0]	98.0 [49.5, 192.0]	0.08
LDL (mg/dL)	2.2 [1.7, 2.9]	2.1 [1.6, 2.7]	0.32	1.2 [1.0, 1.5]	1.2 [1.0, 1.5]	0.22
HDL (mg/dL)	1.2 [1.0, 1.4]	1.2 [1.0, 1.5]	0.03	152 (29.9%)	144 (28.3%)	0.58

Table 1— Baseline characteristics of the TREAT population. Data are shown as n (%), mean ± standard deviation or median [25th, 75th percentile] according to distribution. ACEi-ace inhibitor, ARB-angiotensin receptor blocker. CKD-chronic kidney disease. CRP-C reactive protein. DPP-Dipeptidyl peptidase. *CRP is presented as geometric mean and 95% confidence interval.

Table 2—Incidence and Incidence rate of clinical events

Outcome	N (%)	Incidence Rate	N (%)	Incidence Rate	P Value
		Overall			
	Non-Users (N=3447)		Metformin Users (N=591)		
Death	741 (21.5)	8.7	66 (11.2)	4.5	< 0.001
Cardiovascular death	469 (13.6)	5.5	40 (6.8)	2.7	< 0.001
ESRD	615 (17.8)	8.0	53 (9.0)	3.8	< 0.001
Kidney disease Composite	1161 (33.7)	14.9	109 (18.4)	7.8	< 0.001
Creatinine Doubling	364 (11.8)	5.5	64 (11.5)	5.3	0.87
Doubling of creatinine plus ESRD	779 (22.6)	11.5	92 (15.6)	7.5	<0.001
Kidney disease composite and doubling of creatinine					
Cardiovascular disease composite	1119 (32.5)	14.6	115 (19.5)	8.4	< 0.001
		Propensity Matched			
	Non-Users (N=508)		Metformin Users (N=508)		
Death	105 (20.7)	8.5	58 (11.4)	4.6	<0.001
Cardiovascular death	64 (12.6)	5.2	35 (6.9)	2.8	0.004
ESRD	43 (8.5)	3.6	48 (9.5)	4.0	0.59
Kidney disease Composite	131 (25.8)	10.9	96 (18.9)	8.0	0.02
Creatinine Doubling	51 (10.9)	5.5	56 (11.7)	5.3	0.68
Doubling of creatinine plus ESRD	76 (15.0)	7.3	81 (15.9)	7.6	0.64
Kidney disease composite and doubling of creatinine	156 (30.7)	14.9	125 (24.6)	11.7	0.03
Cardiovascular disease composite	138 (27.2)	11.9	101 (19.9)	8.6	0.01

Incidence and incidence rate for all-cause mortality, cardiovascular mortality, end stage renal disease and renal and cardiovascular composite events. Incidence rate is provided as number per 100-patient years. P value for comparison on incidence rates.

Table 3—Crude and adjusted associations of metformin use with outcomes

Outcome	Crude HR (95% CI)	P Value	Adjusted HR (95% CI)	P Value
		Overall		
Death	0.52 (0.40 – 0.67)	< 0.001	0.68 (0.52-0.89)	0.004
CV Death	0.50 (0.36 – 0.69)	< 0.001	0.65 (0.46-0.91)	0.01
ESRD	0.48 (0.36 – 0.63)	< 0.001	0.94(0.70-1.26)	0.69
Kidney Disease Composite	0.52 (0.43 – 0.64)	< 0.001	0.82(0.66-1.00)	0.05
Doubling of creatinine	0.97 (0.75-1.27)	0.85	1.04 (0.78-1.38)	0.80
Doubling of creatinine and ESRD	0.65 (0.52-0.81)	<0.001	0.99 (0.79-1.24)	0.91
Kidney disease composite and doubling creatinine	0.61 (0.52-0.73)	<0.001	0.88 (0.73-1.05)	0.15
Cardiovascular Disease Composite	0.58 (0.48 – 0.70)	< 0.001	0.79(0.65-0.97)	0.02
		Propensity Matched		
Death	0.55 (0.40 – 0.75)	< 0.001	0.49 (0.36-0.69)	<0.001
CV Death	0.54 (0.36 – 0.82)	0.004	0.49 (0.32-0.74)	<0.001
ESRD	1.12 (0.74 – 1.69)	0.59	1.01 (0.65 – 1.55)	0.98
Kidney Disease Composite	0.73 (0.56 – 0.96)	0.02	0.67 (0.51 – 0.88)	0.004
Doubling of creatinine	1.09 (0.74-1.59)	0.67	1.25 (0.84-1.86)	0.28
Doubling of creatinine and ESRD	1.05 (0.77-1.43)	0.77	1.02 (0.73-1.41)	0.92
Kidney disease composite and doubling creatinine	0.79 (0.62-1.00)	0.050	0.77 (0.61-0.98)	0.037
Cardiovascular Disease Composite	0.72 (0.56 – 0.94)	0.01	0.66 (0.51 – 0.86)	0.002

Crude and adjusted associations with all-cause mortality, cardiovascular (CV) mortality, end stage renal disease (ESRD), renal and cardiovascular composites. Results are shown for model M1—details of adjusted models are provided in the methods.

Figure 1—Event-Free Survival according to metformin use in matched cohort

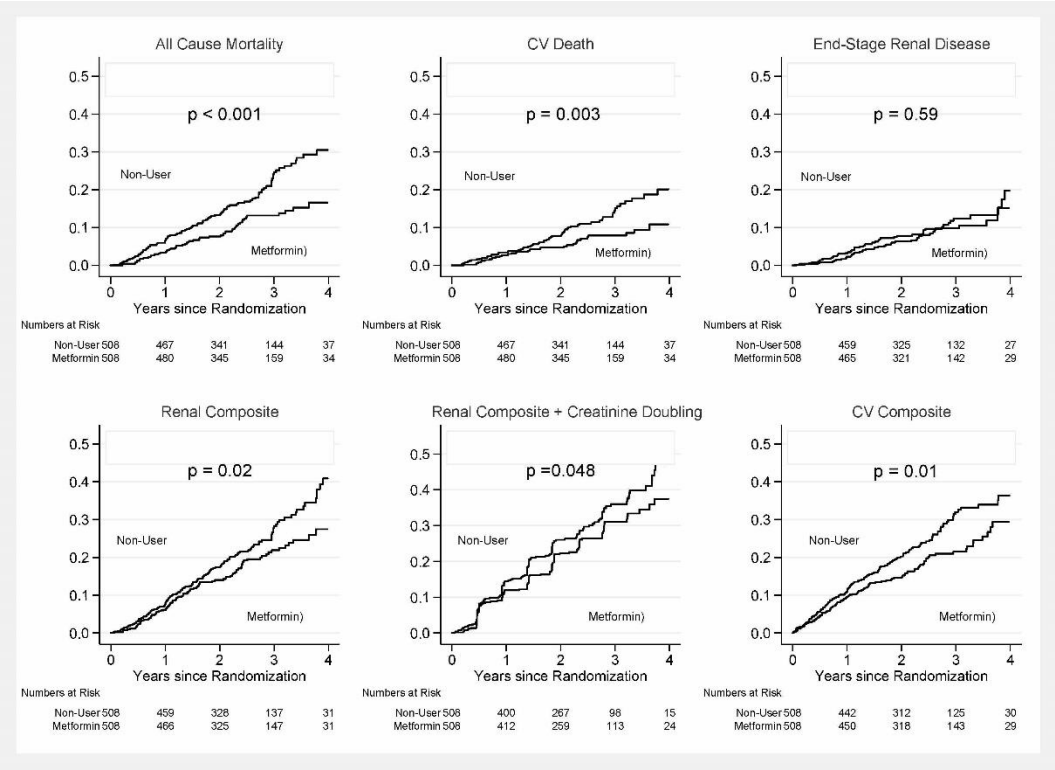

Figure 1—Crude and adjusted outcomes according to metformin use in matched cohort.

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