Metformin use and cardiovascular events in patients with type 2 diabetes and chronic kidney disease

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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) because of a concern that it may increase the risk of lactic acidosis.

Materials and methods: All-cause mortality, cardiovascular death, cardiovascular events (death, hospitalization for heart failure, 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 of 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 in 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, 0.67, 95% CI, 0.51-0.88) 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.

KEYWORDS
cardiovascular disease, diabetes complications, diabetic nephropathy, metformin
INTRODUCTION

Approximately 43% of individuals with type 2 diabetes show evidence of chronic kidney disease (CKD) and, among individuals 65 years of age or older with diabetes, the prevalence of CKD is 61%. 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. Given the 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.

In this context, there is an increasing need for effective therapies that improve glycaemic control while reducing the risk of death, cardiovascular events and ESRD in the setting of CKD. Although older hypoglycaemic 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 with the potential for beneficial effects on kidney and cardiovascular disease independent of the direct effect on glycaemic control. However, until recently, metformin was considered unsafe for use in individuals with moderate or severe CKD because of the potential to induce lactic acidosis. Despite these warnings, metformin may be used by more than 15% of patients with stage 3 CKD. 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, but whether metformin has specific benefits for cardiovascular or kidney disease 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 (darbepoetin-alfa) Therapy (TREAT) (NCT00093015).

1 METHODS

1.1 Study cohort

We analysed data from the TREAT trial which enrolled 4038 participants with diabetes and CKD and randomized them to darbepoetin alfa or placebo. TREAT was approved by local institutional review boards, and all participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki. An estimated glomerular filtration rate (eGFR) of 20-60 mL/min/1.73 m² using the non-IDMS traceable, 4-variable MDRD study equation was required for inclusion in the study. Other key inclusion criteria included hemoglobin less than or equal to 11.0 g/dL and transferrin saturation greater than or equal to 15%.

1.2 Randomization and masking

Patients in the TREAT trial 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.

1.3 Data elements

eGFR was estimated using the CKD-EPI 2009 equation and a pre-specified analysis based on the presence or absence of stage G4 CKD or higher (eGFR < 30 mL/min/1.73m²) at baseline.

1.4 Outcomes

Pre-selected outcomes of interest were based on the pre-specified endpoints from the TREAT trial and included death, cardiovascular death, ESRD, a kidney disease composite of ESRD or death, and a cardiovascular disease composite which included hospitalization for heart failure, myocardial infarction, stroke, myocardial ischemia or death. Deaths, cardiovascular events and ESRD were adjudicated by a blinded events committee according to standardized definitions. ESRD required initiation of dialysis for more than 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 event reports.

1.5 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 haemoglobin A1C were tested using chi-squared tests. Survival analyses utilized Kaplan-Meier 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 calculation of the score, and metformin users and non-users were matched using a caliper distance of 0.05. Crude and
## TABLE 1  Baseline characteristics according to use of metformin at baseline

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Metformin non-users (N = 3447)</th>
<th>Metformin users (N = 591)</th>
<th>P value</th>
<th>Matched cohort</th>
<th>Metformin non-users (N = 508)</th>
<th>Metformin users (N = 508)</th>
<th>P value</th>
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<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
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<tr>
<td>Age (years)</td>
<td>67 ± 11</td>
<td>67 ± 10</td>
<td></td>
<td>0.55</td>
<td>67 ± 10</td>
<td>68 ± 10</td>
<td></td>
<td>0.68</td>
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<tr>
<td>Male</td>
<td>1522 (44.2%)</td>
<td>204 (34.5%)</td>
<td></td>
<td>&lt;0.001</td>
<td>184 (36.2%)</td>
<td>180 (35.4%)</td>
<td></td>
<td>0.79</td>
</tr>
<tr>
<td>Race</td>
<td>747 (21.7%)</td>
<td>68 (11.5%)</td>
<td></td>
<td>&lt;0.001</td>
<td>50 (9.8%)</td>
<td>62 (12.2%)</td>
<td></td>
<td>0.47</td>
</tr>
<tr>
<td>Black</td>
<td>539 (15.6%)</td>
<td>114 (19.3%)</td>
<td></td>
<td>0.03</td>
<td>100 (19.7%)</td>
<td>94 (18.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>2161 (62.7%)</td>
<td>409 (69.2%)</td>
<td></td>
<td>0.97</td>
<td>358 (70.5%)</td>
<td>352 (69.3%)</td>
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<tr>
<td><strong>Physical exam</strong></td>
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<tr>
<td>Systolic pressure (mm Hg)</td>
<td>136 ± 19</td>
<td>136 ± 18</td>
<td></td>
<td>0.53</td>
<td>137 ± 18</td>
<td>137 ± 18</td>
<td></td>
<td>0.98</td>
</tr>
<tr>
<td>Diastolic pressure (mm Hg)</td>
<td>72 ± 11</td>
<td>73 ± 11</td>
<td></td>
<td>0.03</td>
<td>74 ± 11</td>
<td>73 ± 12</td>
<td></td>
<td>0.56</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>31.5 ± 7.4</td>
<td>31.5 ± 7.4</td>
<td></td>
<td>0.97</td>
<td>31.5 ± 7.4</td>
<td>31.3 ± 7.3</td>
<td></td>
<td>0.75</td>
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<tr>
<td><strong>Medical history</strong></td>
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<tr>
<td>Duration of DM (months)</td>
<td>194.1 ± 119.8</td>
<td>177.7 ± 108.9</td>
<td></td>
<td>0.002</td>
<td>170.0 [90.6, 261.3]</td>
<td>168.3 [97.6, 247.6]</td>
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<td>0.73</td>
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<tr>
<td>Cardiovascular disease</td>
<td>2309 (67.0%)</td>
<td>333 (56.3%)</td>
<td></td>
<td>&lt;0.001</td>
<td>294 (57.9%)</td>
<td>290 (57.1%)</td>
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<td>0.80</td>
</tr>
<tr>
<td>Coronary disease</td>
<td>1508 (43.7%)</td>
<td>210 (35.5%)</td>
<td></td>
<td>&lt;0.001</td>
<td>204 (40.2%)</td>
<td>183 (36.0%)</td>
<td></td>
<td>0.17</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1206 (35.0%)</td>
<td>141 (23.9%)</td>
<td></td>
<td>&lt;0.001</td>
<td>121 (23.8%)</td>
<td>117 (23.0%)</td>
<td></td>
<td>0.77</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>643 (18.7%)</td>
<td>98 (16.6%)</td>
<td></td>
<td>0.23</td>
<td>100 (19.7%)</td>
<td>85 (16.7%)</td>
<td></td>
<td>0.22</td>
</tr>
<tr>
<td>Stroke</td>
<td>390 (11.3%)</td>
<td>57 (9.6%)</td>
<td></td>
<td>0.23</td>
<td>50 (9.8%)</td>
<td>49 (9.6%)</td>
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<td>0.92</td>
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<td>Peripheral vascular disease</td>
<td>691 (20.0%)</td>
<td>88 (14.9%)</td>
<td></td>
<td>0.003</td>
<td>87 (17.1%)</td>
<td>83 (16.3%)</td>
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<td>Current smoker</td>
<td>181 (5.3%)</td>
<td>23 (3.9%)</td>
<td></td>
<td>0.16</td>
<td>18 (3.5%)</td>
<td>17 (3.3%)</td>
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<td><strong>CKD stage</strong></td>
<td></td>
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<td>&lt;0.001</td>
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<td></td>
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<td>0.49</td>
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<tr>
<td>Stage 1-2</td>
<td>79 (2.3%)</td>
<td>29 (4.9%)</td>
<td></td>
<td>0.16</td>
<td>26 (5.1%)</td>
<td>25 (4.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 3a</td>
<td>505 (14.7%)</td>
<td>176 (29.8%)</td>
<td></td>
<td>0.21</td>
<td>128 (25.2%)</td>
<td>150 (29.5%)</td>
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<tr>
<td>Stage 3b</td>
<td>1455 (42.2%)</td>
<td>250 (42.3%)</td>
<td></td>
<td>0.65</td>
<td>230 (45.3%)</td>
<td>217 (42.7%)</td>
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<tr>
<td>Stage 4-5</td>
<td>1405 (40.8%)</td>
<td>136 (23.0%)</td>
<td></td>
<td>0.84</td>
<td>124 (24.4%)</td>
<td>116 (22.8%)</td>
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<td></td>
</tr>
<tr>
<td><strong>Medications</strong></td>
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<tr>
<td>Randomized to darbepoetin</td>
<td>1720 (49.9%)</td>
<td>292 (49.4%)</td>
<td></td>
<td>0.83</td>
<td>252 (49.6%)</td>
<td>257 (50.6%)</td>
<td></td>
<td>0.75</td>
</tr>
<tr>
<td>Insulin</td>
<td>1815 (52.7%)</td>
<td>174 (29.4%)</td>
<td></td>
<td>&lt;0.001</td>
<td>152 (29.9%)</td>
<td>144 (28.3%)</td>
<td></td>
<td>0.58</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>1144 (33.2%)</td>
<td>285 (48.2%)</td>
<td></td>
<td>&lt;0.001</td>
<td>251 (49.4%)</td>
<td>245 (48.2%)</td>
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<tr>
<td>Thiazolidinediones</td>
<td>822 (23.8%)</td>
<td>162 (27.4%)</td>
<td></td>
<td>0.06</td>
<td>122 (24.0%)</td>
<td>140 (27.6%)</td>
<td></td>
<td>0.20</td>
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<tr>
<td>DPP-IV inhibitors</td>
<td>23 (0.7%)</td>
<td>3 (0.5%)</td>
<td></td>
<td>0.65</td>
<td>3 (0.6%)</td>
<td>3 (0.6%)</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Other diabetic agents</td>
<td>10 (0.3%)</td>
<td>2 (0.3%)</td>
<td></td>
<td>0.84</td>
<td>3 (0.6%)</td>
<td>2 (0.4%)</td>
<td></td>
<td>0.65</td>
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<tr>
<td>ACEi or ARB</td>
<td>2718 (78.9%)</td>
<td>505 (85.4%)</td>
<td></td>
<td>&lt;0.001</td>
<td>441 (86.8%)</td>
<td>433 (85.2%)</td>
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<td>0.47</td>
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<tr>
<td>Beta blockers</td>
<td>1721 (49.9%)</td>
<td>269 (45.5%)</td>
<td></td>
<td>0.05</td>
<td>248 (48.8%)</td>
<td>231 (45.5%)</td>
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<td>0.29</td>
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<td>Aldosterone blockers</td>
<td>181 (5.3%)</td>
<td>28 (4.7%)</td>
<td></td>
<td>0.60</td>
<td>22 (4.3%)</td>
<td>21(4.1%)</td>
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<td>0.88</td>
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<td>Statin</td>
<td>2002 (58.1%)</td>
<td>362 (61.3%)</td>
<td></td>
<td>0.15</td>
<td>306 (60.2%)</td>
<td>315 (62.0%)</td>
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<td>0.56</td>
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<tr>
<td>Other antiplatelet agents</td>
<td>455 (13.2%)</td>
<td>58 (9.8%)</td>
<td></td>
<td>0.02</td>
<td>54 (10.6%)</td>
<td>48 (9.4%)</td>
<td></td>
<td>0.53</td>
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<td>Vitamin K antagonists</td>
<td>238 (6.9%)</td>
<td>39 (6.6%)</td>
<td></td>
<td>0.79</td>
<td>38 (7.5%)</td>
<td>36 (7.1%)</td>
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<td>0.81</td>
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Table 1 (Continued)

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Metformin non-users (N = 3447)</th>
<th>Metformin users (N = 591)</th>
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<th>Metformin users (N = 508)</th>
<th>P value</th>
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<td>Labs</td>
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<tr>
<td>Creatinine (mg/dL)</td>
<td>168.0 [141.4, 212.2]</td>
<td>141.4 [114.9, 176.8]</td>
<td>&lt;0.001</td>
<td>38.0 [30.4, 47.4]</td>
<td>40.0 [31.1, 48.0]</td>
<td>0.17 T</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td>32.7 [25.5, 41.3]</td>
<td>39.8 [30.9, 48.4]</td>
<td>&lt;0.001</td>
<td>38.0 [30.4, 47.4]</td>
<td>40.0 [31.1, 48.0]</td>
<td>0.17</td>
<td></td>
<td></td>
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<tr>
<td>Urine protein creatinine ratio</td>
<td>0.5 [0.1, 2.0]</td>
<td>0.3 [0.1, 1.5]</td>
<td>&lt;0.001</td>
<td>0.3 [0.1, 1.6]</td>
<td>0.3 [0.1, 1.4]</td>
<td>0.15</td>
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<tr>
<td>CRP (μg/mL)</td>
<td>5.0 [4.9, 5.1]</td>
<td>4.6 [4.3, 4.8]</td>
<td>0.01</td>
<td>4.7 [4.4, 4.9]</td>
<td>4.6 [4.3, 4.9]</td>
<td>0.71</td>
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<tr>
<td>Albumin (g/L)</td>
<td>40.0 [37.0, 42.0]</td>
<td>41.0 [38.0, 43.0]</td>
<td>&lt;0.001</td>
<td>41.0 [39.0, 43.0]</td>
<td>41.0 [38.0, 43.0]</td>
<td>0.89</td>
<td></td>
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<tr>
<td>A1C (%)</td>
<td>7.0 [6.2, 8.0]</td>
<td>6.8 [6.3, 7.7]</td>
<td>0.05</td>
<td>6.9 [6.2, 7.9]</td>
<td>6.8 [6.3, 7.7]</td>
<td>0.77</td>
<td></td>
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<tr>
<td>Potassium (mEq/L)</td>
<td>4.7 [4.3, 5.1]</td>
<td>4.7 [4.4, 5.1]</td>
<td>0.04</td>
<td>4.7 [4.3, 5.1]</td>
<td>4.7 [4.4, 5.1]</td>
<td>0.74</td>
<td></td>
<td></td>
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<tr>
<td>Haemoglobin (g/L)</td>
<td>104 [99, 109]</td>
<td>105 [99, 110]</td>
<td>0.02</td>
<td>106 [100, 110]</td>
<td>105 [99, 110]</td>
<td>0.30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferritin (μg/L)</td>
<td>139.0 [71.0, 269.0]</td>
<td>98.0 [48.0, 197.0]</td>
<td>&lt;0.001</td>
<td>114.5 [56.5, 196.0]</td>
<td>98.0 [49.5, 192.0]</td>
<td>0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>2.2 [1.7, 2.9]</td>
<td>2.1 [1.6, 2.7]</td>
<td>0.32</td>
<td>1.2 [1.0, 1.5]</td>
<td>1.2 [1.0, 1.5]</td>
<td>0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>1.2 [1.0, 1.4]</td>
<td>1.2 [1.0, 1.5]</td>
<td>0.03</td>
<td>152 (29.9%)</td>
<td>144 (28.3%)</td>
<td>0.58</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ACEi, ace inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; CRP, C-reactive protein; DPP, dipeptidyl peptidase. Data are shown as n (%), mean ± standard deviation or median [25th, 75th percentile] according to distribution.

* CRP is presented as geometric mean and 95% confidence interval.

adjusted HRs or sub-HRs 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 the TREAT trial and adjusted for age, sex, race, body mass index, insulin use, baseline eGFR, blood urea nitrogen, C-reactive protein, ferritin, haemoglobin, proteinuria, serum albumin and history of stroke, coronary disease, heart failure, arrhythmia, atrial fibrillation or acute kidney injury. Proportional hazards assumptions were inspected using standard techniques. In addition, we tested for interaction of metformin use with CKD stage at baseline, comparing stage G1-3 with stage G4-5.

Sensitivity analyses included assessment for effect modification according to stage of CKD by testing for binary interactions between the presence of metformin use with CKD stage G4-5 and CKD stage G1-3 and by testing for effect modification by the randomized therapy assignment, darbepoetin or placebo, within the overall cohort. Competing-risk models using the Fine and Gray approach were used to account for the possibility of death prior to ESRD, kidney or cardiovascular disease and to provide cause-specific sub-HRs 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 the 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, acute kidney injury, use of angiotensin-converting enzyme inhibitors or receptor blockers, 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, Texas) with P < 0.05 considered to be significant.

2 | RESULTS

2.1 | Baseline characteristics

We identified 591 individuals who were receiving 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 ethnicity (69.2% vs 62.7%), and to have had a shorter duration of diabetes (178 ± 109 vs 194 ± 120 months; P < 0.01), and they 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 G3b CKD or higher, they were less likely to have stage G4-5 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 glycaemic control over time were marginally different (0.15%) through week 25 of the follow-up period and were non-significant thereafter (Supporting Information Table S1).

We matched 508 out of 597 (85%) 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).

2.2 | 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 among metformin users (4.0 vs 3.6/100 patient years) (Table 2 and Figure 1). Results were similar in the non-matched data, with the exception that the crude rate of ESRD was lower among metformin users than among non-users (3.8 vs 8.0/100 patient-years) (Table 2 and Supporting Information Figure S1). Crude estimates were consistent with a reduction in the hazard of all-cause mortality, cardiovascular and the kidney disease composite events, and these were highly significant. The crude risk of ESRD was higher in metformin users than in non-users (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 those of the primary kidney outcomes. Metformin use remained independently associated with a lower risk compared with alternatives therapies among individuals with CKD stages G1-3 (HR, 0.70; 95% CI, 0.53-0.92) but not among individuals with CKD stage G4-5 (HR, 0.99; 95% CI, 0.71-1.39); however, the interaction did not reach significance ($P_{interaction} = 0.06$). Lactic acidosis was rare, reported in only two patients using 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 two individuals.

### 2.3 | Results according to CKD stage

Regardless of CKD stage, ESRD, cardiovascular disease and the composite outcomes occurred less frequently among metformin users compared with non-users (Supporting Information Figure S2 and Table S2). Point estimates of association with metformin use and outcomes were attenuated in individuals with stage G4-5 compared to stage G1-3 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 HR, 0.70; 95% CI, 0.53-0.92). However, tests of interaction were not suggestive of significant effect modification by CKD stage ($P_{interaction} \geq 0.19$). For the combined, cardiovascular disease endpoint, metformin was associated with a lower risk compared with alternatives therapies among individuals with CKD stages G1-3 (HR, 0.70; 95% CI, 0.53-0.90) but not among individuals with CKD stage G4-5 (HR, 0.99; 95% CI, 0.71-1.39); however, the interaction did not reach significance ($P_{interaction} = 0.06$). Lactic acidosis was rare, reported in only two patients using 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 two individuals.

### 2.4 | Sensitivity analyses

Results from model M2 were similar to those from the primary outcomes model (Supporting Information Table S3). 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

<p>| TABLE 2 | Incidence and incidence rate of clinical events |
|---|---|---|---|---|---|---|---|</p>
<table>
<thead>
<tr>
<th>Outcome</th>
<th>N (%)</th>
<th>Incidence rate</th>
<th>N (%)</th>
<th>Incidence rate</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin non-users (N = 3447)</td>
<td>Metformin users (N = 591)</td>
<td>Metformin non-users (N = 508)</td>
<td>Metformin users (N = 508)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>741 (21.5)</td>
<td>8.7</td>
<td>66 (11.2)</td>
<td>4.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>469 (13.6)</td>
<td>5.5</td>
<td>40 (6.8)</td>
<td>2.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESRD</td>
<td>615 (17.8)</td>
<td>8.0</td>
<td>53 (9.0)</td>
<td>3.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Kidney disease composite</td>
<td>1161 (33.7)</td>
<td>14.9</td>
<td>109 (18.4)</td>
<td>7.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine doubling</td>
<td>364 (11.8)</td>
<td>5.5</td>
<td>64 (11.5)</td>
<td>5.3</td>
<td>0.87</td>
</tr>
<tr>
<td>Doubling of creatinine plus ESRD</td>
<td>779 (22.6)</td>
<td>11.5</td>
<td>92 (15.6)</td>
<td>7.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Kidney disease composite and doubling of creatinine</td>
<td>1119 (32.5)</td>
<td>14.6</td>
<td>115 (19.5)</td>
<td>8.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Propensity matched</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin non-users (N = 508)</td>
<td>Metformin users (N = 508)</td>
<td>Metformin non-users (N = 508)</td>
<td>Metformin users (N = 508)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>105 (20.7)</td>
<td>8.5</td>
<td>58 (11.4)</td>
<td>4.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>64 (12.6)</td>
<td>5.2</td>
<td>35 (6.9)</td>
<td>2.8</td>
<td>0.004</td>
</tr>
<tr>
<td>ESRD</td>
<td>43 (8.5)</td>
<td>3.6</td>
<td>48 (9.5)</td>
<td>4.0</td>
<td>0.59</td>
</tr>
<tr>
<td>Kidney disease composite</td>
<td>131 (25.8)</td>
<td>10.9</td>
<td>96 (18.9)</td>
<td>8.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Creatinine doubling</td>
<td>51 (10.9)</td>
<td>5.5</td>
<td>56 (11.7)</td>
<td>5.3</td>
<td>0.68</td>
</tr>
<tr>
<td>Doubling of creatinine plus ESRD</td>
<td>76 (15.0)</td>
<td>7.3</td>
<td>81 (15.9)</td>
<td>7.6</td>
<td>0.64</td>
</tr>
<tr>
<td>Kidney disease composite and doubling of creatinine</td>
<td>156 (30.7)</td>
<td>14.9</td>
<td>125 (24.6)</td>
<td>11.7</td>
<td>0.03</td>
</tr>
<tr>
<td>Cardiovascular disease composite</td>
<td>138 (27.2)</td>
<td>11.9</td>
<td>101 (19.9)</td>
<td>8.6</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Incidence and incidence rate for all-cause mortality, cardiovascular mortality, end stage renal disease and renal and cardiovascular composite events. Incidence rate are provided as number per 100-patient years. P value is given for comparison on incidence rates. Abbreviation: ESRD, end stage renal disease.
**TABLE 3**  Crude and adjusted associations of metformin use with outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Crude HR (95% CI)</th>
<th>P value</th>
<th>Adjusted HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0.52 (0.40-0.67)</td>
<td>&lt;0.001</td>
<td>0.68 (0.52-0.89)</td>
<td>0.004</td>
</tr>
<tr>
<td>CV death</td>
<td>0.50 (0.36-0.69)</td>
<td>&lt;0.001</td>
<td>0.65 (0.46-0.91)</td>
<td>0.01</td>
</tr>
<tr>
<td>ESRD</td>
<td>0.48 (0.36-0.63)</td>
<td>&lt;0.001</td>
<td>0.94 (0.70-1.26)</td>
<td>0.69</td>
</tr>
<tr>
<td>Kidney disease composite</td>
<td>0.52 (0.43-0.64)</td>
<td>&lt;0.001</td>
<td>0.82 (0.66-1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>Doubling of creatinine</td>
<td>0.97 (0.75-1.27)</td>
<td>0.85</td>
<td>1.04 (0.78-1.38)</td>
<td>0.80</td>
</tr>
<tr>
<td>Doubling of creatinine and ESRD</td>
<td>0.65 (0.52-0.81)</td>
<td>&lt;0.001</td>
<td>0.99 (0.79-1.24)</td>
<td>0.91</td>
</tr>
<tr>
<td>Kidney disease composite and doubling of creatinine</td>
<td>0.61 (0.52-0.73)</td>
<td>&lt;0.001</td>
<td>0.88 (0.73-1.05)</td>
<td>0.15</td>
</tr>
<tr>
<td>Cardiovascular disease composite</td>
<td>0.58 (0.48-0.70)</td>
<td>&lt;0.001</td>
<td>0.79 (0.65-0.97)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**Propensity matched**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Crude HR (95% CI)</th>
<th>P value</th>
<th>Adjusted HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0.55 (0.40-0.75)</td>
<td>&lt;0.001</td>
<td>0.49 (0.36-0.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV death</td>
<td>0.54 (0.36-0.82)</td>
<td>0.004</td>
<td>0.49 (0.32-0.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESRD</td>
<td>1.12 (0.74-1.69)</td>
<td>0.59</td>
<td>1.01 (0.65-1.55)</td>
<td>0.98</td>
</tr>
<tr>
<td>Kidney disease composite</td>
<td>0.73 (0.56-0.96)</td>
<td>0.02</td>
<td>0.67 (0.51-0.88)</td>
<td>0.004</td>
</tr>
<tr>
<td>Doubling of creatinine</td>
<td>1.09 (0.74-1.59)</td>
<td>0.67</td>
<td>1.25 (0.84-1.86)</td>
<td>0.28</td>
</tr>
<tr>
<td>Doubling of creatinine and ESRD</td>
<td>1.05 (0.77-1.43)</td>
<td>0.77</td>
<td>1.02 (0.73-1.41)</td>
<td>0.92</td>
</tr>
<tr>
<td>Kidney disease composite and doubling of creatinine</td>
<td>0.79 (0.62-1.00)</td>
<td>0.050</td>
<td>0.77 (0.61-0.98)</td>
<td>0.037</td>
</tr>
<tr>
<td>Cardiovascular disease composite</td>
<td>0.72 (0.56-0.94)</td>
<td>0.01</td>
<td>0.66 (0.51-0.86)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Crude and adjusted associations with all-cause mortality, cardiovascular mortality, end stage renal disease renal and cardiovascular composites. Results are shown for model M1; details of adjusted models are provided in the Methods section. Abbreviations: CI, confidence interval; CV, cardiovascular; ESRD, end stage renal disease; HR, hazard ratio.
death and of 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) nor of combined ESRD and doubling of creatinine were significantly increased. In adjusted analyses, associations with the risk of cardiovascular mortality (HR, 0.54; 95% CI, 0.35-0.83), of the cardiovascular disease composite (HR, 0.66; 95% CI, 0.50-0.86), of the kidney disease composite (HR, 0.67; 95% CI, 0.51-0.88) and of 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, with the exception that associations with the kidney disease composite (HR, 0.82; 95% CI, 0.65-1.02) and with the combined kidney disease composite plus doubling of creatinine were non-significant (Supporting Information Table S4).

3 | DISCUSSION

We analysed associations between metformin use and survival as well as cardiovascular and kidney disease outcomes among 4038 individuals with diabetes and CKD enrolled in the TREAT trial, including 591 metformin users, among whom 386 had stage G3b CKD or higher. Compared with regimens that did not include 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 the result of 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 between metformin use and kidney and cardiovascular disease outcomes. In the randomized United Kingdom Prospective Diabetes Study, metformin treatment was associated with reduced risk of death and stroke compared to sulfonylurea use, but was not associated with a reduction in progression of CKD. More recently, Hung et al. studied 95 577 US veterans with eGFR above or equal to 60 mL/min/1.73m² and found that, compared with initial treatment with metformin, sulfonylurea use was associated with a 20% increase in the risk of both combined ESRD or with a 25% sustained decrease in eGFR and in the combined endpoint of ESRD, sustained decrease in eGFR or death. This group subsequently found that, among individuals with serum creatinine below 1.5 mg/dL in men or 1.4 mg/dL in women, metformin use was associated with reduced risk of both heart failure and cardiovascular death compared to sulfonylurea use. Despite these encouraging data and recent suggestions to liberalize the use of metformin in individuals with stage G3 and stage G4 CKD, relatively few studies have analysed the outcomes of metformin use in this population. A 2010 meta-analysis of data, including 70 490 patient-years of metformin use, revealed no convincing evidence that its use increases the risk of lactic acidosis in the overall population, although there were insufficient data concerning the underlying kidney function of participants to investigate the impact of reduced eGFR per se. Indeed, a rise in lactate levels has been observed in patients with diabetes, independent of metformin use, suggesting that initial reports associating diabetes and lactic acidosis may have been confounded. Whether the high frequency of acidosis native to CKD, and the absence of a uniform definition of lactic acidosis, have similarly confounded assessments of the association between CKD and lactic acidosis is uncertain. However, it is interesting that a recent meta-analysis revealed that drug and lactate levels generally remain within the therapeutic range in individuals with an eGFR of 30-60 mL/min/1.73m² and that rates of lactic acidosis were generally similar in patients with and without CKD, although there were minimal reliable data. Similarly, a recent pharmacological study showed that serial blood metformin levels never exceed the upper limit of normal and that lactate levels remained at 5.0 mmol/L or less in stage 3b CKD patients treated with 1000 mg daily and stage G4 CKD patients who received 500 mg/d for 4 months.

In contrast, information from a Danish national registry revealed that metformin use was associated with an increased risk of acute dialysis, among individuals with eGFR both above and below 60 mL/min/1.73m². An analysis of 813 Taiwanese patients with stage G5 CKD and matched controls also revealed 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. 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 patients with stage G3 CKD, but was not associated with mortality among 563 patients with stage G4-5 CKD. Similarly, an analysis of the Swedish National Diabetes Register revealed that metformin-based regimens were associated with reduced risk of death in individuals with stage G3a CKD but not in individuals with stage G3b CKD. There was no association with a combined cardiovascular endpoint. Finally, a recent analysis of US veterans showed that metformin use was associated with a reduced risk of death compared to sulfonylurea use among individuals with stage G3a CKD. Results were qualitatively similar in stage G3b CKD but did not reach significance.

Our analysis is consistent with other 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 stage G1-3 CKD than with stage G4-5 CKD, we did not identify significant differences in efficacy by CKD stage for other outcomes, and there was no evidence of harm in CKD stages G4-5. Nevertheless, our point-estimates were consistent with the attenuation of mortality benefits at CKD stages G4-5, as reported previously. 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 analysed 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 et al. who did not identify associations with cardiovascular disease events. Differences in the underlying populations could explain the differences between our study and that of Ekstrom et al. In addition, all cardiovascular disease events in the TREAT trial 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 use may not translate into a reduction in progressive GFR loss in diabetes. However, it is possible that the fibrosis present in some enrolled patients with stage G4 CKD 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 use of metformin would have cardiovascular-specific benefits, but interference with cardiac hypertrophy through disruption of mTOR signaling and activation of AMPK signaling is one possibility. Alternatively, the lower likelihood of hypoglycaemia with metformin use compared with insulin-based therapy for diabetes may be a key factor as hypoglycaemia can stimulate inflammation and secretion of counter-regulatory hormones with adverse cardiovascular effects. We were unable to investigate the role of hypoglycaemia in our cohort, but this may be an important area of focus for subsequent studies. Regardless of the underlying mechanism, our findings suggest that treatment with 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 G3 CKD. However, in contrast to SGLT-2 inhibitors and glucagon-like peptide 1 agonists, metformin may not prevent the progression of CKD.

Our study supports the 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, the confirmation of eGFR of 20-60 mL/min/1.73m² using the MDRD study formula by a central lab during a stable outpatient visit, and the use of metformin despite prevailing guidelines at the time of the study that advised against prescription of this drug in individuals with eGFR less 60 mL/min/1.73m². 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, the number of ESRD events was large, which provided a unique ability to specifically analyse 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 two 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 treatment of diabetes, albeit some of these newer agents, such as SGLT2i, are not generally used in low-GFR patients, and thus, we were unable to assess the relative effects of metformin compared to these agents. We were unable to determine the cause of CKD with certainty. However, all patients were clinically diagnosed to have CKD as a consequence of diabetes and were required to have evidence of stage G3 or higher, using the MDRD study formula, and serum creatinines drawn while the patients were clinically stable. In addition, the large number of missing values precluded adjustment for time-updated measure of glycaemic control. However, in those for whom values were available, differences in glycaemic 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 event reports rather than with a standardized definition.

In conclusion, we studied associations of metformin use with clinical outcomes among individuals with diabetes and CKD in the TREAT trial. Despite the concerns about lactic acidosis that have limited the use of metformin in patients with CKD, our data suggest that metformin may be safer than previously considered for use in these patients. 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 G3 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

D. C. has received a research grant from Janssen Pharmaceuticals (significant) and funds for service from DSMB-AstraZeneca.

S. S. has received research grants from Aplylam, Amgen, AstraZeneca, Bellerophon, BMS, Celladon, Gilead, GSK, Ionis, Lone Star Heart, Mesoblast, MyoKardia, NIH/NHLBI, Novartis, Sanofi Pasteur and Theracos; and has received consulting fees from Akros, Aplylam, Amgen, AstraZeneca, Bayer, BMS, Corvia, Gilead, GSK, Ironwood, Merck, Novartis, Pfizer, Roche, Takeda, Theracos, Quantum Genetics, Cardurion, Abiomed and Janssen.

A. K. S. has received a research grant from Glaxo Smith Kline (significant).

A. L. has received a research grant from Amgen as a member of the TREAT Steering Committee.

E. B. has received fees for consultancy and Advisory Board membership from Fresenius (modest).
Author contributions

S. D. S., P. I., G. R., M. E. C., J. B. M., H. H. P., P. P., A. K.S, E. A. B., A. S. L., K. U. E., J. J. V. M., E. F. L., L. A. W. and M. A. P. contributed to patient recruitment for and conduct of the TREAT trial. D. M. C., J. L., B. C. and M. A. P. contributed to the design of the analysis. B. C. and J. L. performed statistical analyses. D. M. C. and M. A. P. drafted the manuscript. All authors contributed to data interpretation, critical revision of the manuscript and final approval. D. M. C., J. L., B. C. and M. A. P. take responsibility for all aspects of the report and all authors take responsibility for their contributions. D. M. C. had access to the data and takes responsibility for the decision to submit for publication.

Data sharing statement

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

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.