Effect of Dapagliflozin on Atrial Fibrillation in Patients with Type 2 Diabetes Mellitus: Insights from the DECLARE-TIMI 58 Trial

Running Title: Zelniker et al.; Dapagliflozin and Atrial Fibrillation in T2DM

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Abstract

Background: Atrial fibrillation (AF) and atrial flutter (AFL) are associated with both diabetes and its related comorbidities including hypertension, obesity, and heart failure (HF). SGLT2i have been shown to lower blood pressure, reduce weight, have salutary effects on left ventricular remodeling and reduce hospitalization for HF and cardiovascular death in patients with type 2 diabetes (T2DM). We therefore investigated whether SGLT2i may also reduce the risk of AF/AFL.

Methods: DECLARE-TIMI 58 studied the efficacy and safety of the SGLT2i dapagliflozin versus placebo in 17160 patients with T2DM and either multiple risk factors for (MRF, n=10186) or known atherosclerotic cardiovascular disease (ASCVD, n=6974). Here, we explore the effect of dapagliflozin on the first and total number of AF/AFL events in patients with (n=1,116) and without prevalent AF/AFL using Cox and negative binomial models, respectively. AF/AFL events were identified by search of the safety database using the MedDRA Preferred Terms (“atrial fibrillation”, “atrial flutter”).

Results: Dapagliflozin reduced the risk of AF/AFL events by 19% (264 versus 325 events, 7.8 versus 9.6 events per 1000 patient-years, hazard ratio 0.81, 95% CI 0.68 to 0.95, P=0.009). The reduction in AF/AFL events was consistent regardless of presence or absence of a history of AF/AFL at baseline (Prior AF/AFL: HR 0.79, 95% CI 0.58-1.09, No AF/AFL: HR 0.81, 95% CI 0.67-0.98; P-INT 0.89). Similarly, presence of ASCVD (HR 0.83, 95% CI 0.66-1.04) versus MRF (HR 0.78, 95% CI 0.62-0.99; P-INT 0.72), or a history of HF (HF: HR 0.81, 95% CI 0.68-0.97; P-INT 0.88) did not modify the reduction in AF/AFL events observed with dapagliflozin. Moreover, there was no effect modification by sex, history of ischemic stroke, HbA1c, body mass index, blood pressure, or eGFR (all P-INT>0.20).

Dapagliflozin also reduced the total number (first and recurrent) of AF/AFL events (337 versus 432; incidence rate ratio 0.77, 95% CI 0.64-0.92, P=0.005).

Conclusions: Dapagliflozin decreased the incidence of reported episodes of AF/AFL adverse events in high-risk patients with T2DM. This effect was consistent regardless of the patients’ prior history of AF, ASCVD, or HF.

Clinical Trial Registration: URL: https://clinicaltrials.gov Unique Identifier: NCT01730534

Key Words: SGLT2i; dapagliflozin; atrial fibrillation; atrial flutter

Nonstandard Abbreviations and Acronyms

AF  atrial fibrillation
AFL  atrial flutter
ASCVD  atherosclerotic cardiovascular disease
BMI  body mass index
CV  cardiovascular
eGFR  estimated glomerular filtration rate
HbA1c  glycated hemoglobin A1c
HF  heart failure
HHF  hospitalization for heart failure
MACE  major adverse cardiovascular events
SGLT2i  sodium-glucose cotransporter 2 inhibitors
T2DM  type 2 diabetes mellitus
TIMI  Thrombolysis in Myocardial Infarction
Clinical Perspective

What is new?

• The sodium-glucose co transporter 2 inhibitor dapagliflozin reduced the risk of atrial fibrillation/flutter (AF/AFL) events during follow-up as well as the total number of AF/AFL events in patients with type 2 diabetes mellitus.

• These reductions were consistent across major subgroups including sex, presence of atherosclerotic cardiovascular disease, history of AF/AFL, history of heart failure, history of ischemic stroke, HbA1c, body mass index, blood pressure, or eGFR that are well established to have associations with the risk of AF/AFL.

What are the clinical implications?

• In addition to the known beneficial effects of dapagliflozin to reduce hospitalization for heart failure and renal adverse outcomes, dapagliflozin appears to lower the risk of AF/AFL events in a broad population of patients with type 2 diabetes mellitus including those with and without CAD or HF at baseline.
Introduction

Diabetes and diabetes-related comorbidities including obesity, hypertension, chronic kidney disease, and heart failure (HF) are associated with an increased incidence of atrial fibrillation (AF) and atrial flutter (AFL).\textsuperscript{1-3} Diabetes-induced myocardial remodeling and changes in the electrical properties of the heart are associated with a propensity to develop these common cardiac arrhythmias.\textsuperscript{3,4}

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) block glucose and sodium reabsorption in the proximal tubule of the kidney and thereby lower glucose without increasing the risk of hypoglycemia in patients with type 2 diabetes mellitus (T2DM).\textsuperscript{5} Moreover, SGLT2i lower blood pressure without increasing the heart rate, reduce body weight, have protective effects on atherosclerotic cardiovascular disease (ASCVD) and heart failure-related outcomes, and prevent the progression of chronic kidney disease.\textsuperscript{5-8} We have shown that the SGLT2i dapagliflozin reduces the composite of cardiovascular (CV) death and hospitalization for heart failure (HHF) by 17%, primarily driven by a 27% reduction in HHF, and was non-inferior with regard to major adverse CV events (MACE), the composite of myocardial infarction, ischemic stroke, and CV death in patients with T2DM.\textsuperscript{9} The \textit{Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure} (DAPA-HF) trial showed that dapagliflozin reduced the risk of the composite of worsening of HF or CV death by 26% in patients with and without T2DM who had HF and reduced ejection fraction.\textsuperscript{10} These findings suggest glucose-independent, direct cardiac protective effects of SGLT2i.\textsuperscript{11} Although the exact mechanisms of the non-glycemic benefit of SGLT2i are incompletely understood, in addition to the aforementioned favorable metabolic effects (including lowering of HbA1c, blood pressure, weight) multiple pleiotropic properties including a modest diuretic effect, improved myocardial efficiency, improved oxygen delivery, a
reduction of inflammation and oxidative stress, and restoration of the tubuloglomerular feedback have been suggested to contribute to the salutary cardiorenal effects.\textsuperscript{5,12-14} In addition, mitigation of inflammation, endothelial and left ventricular dysfunction, and improved glucose control may improve atrial remodeling and thereby favorably impact the incidence of AF/AFL. We, therefore, sought to investigate the effect of the SGLT2i dapagliflozin on the incidence and total number of AF/AFL events in post-hoc analyses.

Methods

We encourage parties interested in collaboration and data sharing to contact the corresponding author directly for further discussions.

Study Population

The design and primary results of the \textit{Dapagliflozin Effect on Cardiovascular Events (DECLARE)} – \textit{Thrombolysis in Myocardial Infarction (TIMI)} 58 trial have been published previously (ClinicalTrials.gov Identifier: NCT01730534).\textsuperscript{9,15,16} In brief, DECLARE-TIMI 58 studied the CV efficacy and safety of dapagliflozin in 17,160 patients with type 2 diabetes mellitus (T2DM) and either multiple risk factors for or established atherosclerotic CV disease over a median duration of 4.2 years.

Outcomes of interest

The primary outcomes of interest of the present post-hoc analyses were AF/AFL events that were identified by search of the adverse event reporting safety clinical trial database using the Medical Dictionary of Regulatory Affairs (MedDRA) Preferred Terms (“atrial fibrillation”, “atrial flutter”). As described previously,\textsuperscript{9} serious adverse events, adverse events of special interest, and adverse events leading to discontinuation of study drug were mandated to be reported by
protocol, while all other adverse events could be reported at the discretion of the caring physician. We performed several sensitivity analyses including the analysis of 1) only AF/AFL events that met criteria as serious adverse events; 2) only AF/AFL events that were associated with hospitalization; 3) AF/AFL events which were not followed or preceded by an HHF event within 14 days; and 4) patients who were not hospitalized for HF at any point during the trial. Major subgroups of interest were presence or absence of atherosclerotic CV disease, history of HF, history of known AF/AFL, age (<70 vs. ≥70 years), sex, glycated hemoglobin A1c (HbA1c, <8 vs. ≥8%), body mass index (BMI, <30 vs. ≥30 kg/m²), systolic blood pressure (<135 vs. ≥135 mmHg), and by baseline estimated glomerular filtration rate (eGFR) using the following strata <60, 60-90, >90 ml/min/1.73 m².

History of AF/AFL (either paroxysmal, persistent, or permanent AF, and/or AFL) was reported by local investigators in the electronic case report. Baseline ECG’s were not mandated by the study protocol and therefore were not available.

**Statistical Analysis**

Baseline characteristics are reported using means (and standard deviation) or medians (and interquartile range) as appropriate. Outcomes are presented using 4-year Kaplan Meier event rates and examined using Cox regression models. All Cox models were stratified according to presence or absence of known ASCVD and hematuria at baseline. The proportional hazards assumption was confirmed using statistical tests and visual inspection based on the scaled Schoenfeld residuals. Interaction terms were included to test for heterogeneity of the relative treatment effect across subgroups. Negative binomial regression models were used to compare the total (i.e., first and recurrent) number of AF/AFL events between patients randomized to dapagliflozin with those to placebo. The incidence rate ratio (IRR) and the corresponding 95%
confidence intervals are reported from the negative binomial regression models. The Wei-Lin-Weissfeld” model considering the first 3 events (since the number of subjects with >3 events was small) was used as a sensitivity analysis. All effects were analyzed using an intention-to-treat approach.

All analyses were planned post hoc. Statistical significance was assessed at a nominal alpha level of 0.05. All reported P values are two-sided and no adjustments for multiple testing are performed. Statistical analyses were carried out using SAS, version 9.4 (SAS Institute Inc) and Stata/IC, version 14.2 (StataCorp LP).

Compliance with ethical standards

DECLARE-TIMI 58 conformed to the recommendations of the Declaration of Helsinki and the International Council on Harmonization Good Clinical Practice norms with regard to medical research in humans. The study protocol was approved by all institutional review boards of participating sites before starting enrollment. All patients provided written informed consent form before participation.

Results

Effect of dapagliflozin on AF/AFL

During the trial, 769 AF/AFL events occurred in 589 patients over a median follow-up of 4.2 years. Among these, 124 patients had 2 events, 36 patients had 3 events and 20 patients had ≥4 events. The maximum number of events experienced were 6 and 7 events in 1 patient each. Overall, 1,116 (6.5%) patients had known history of AF/AFL at baseline (Supplemental Table 1). Patients with AF/AFL were more likely to be older, have a higher body mass index, a history of ASCVD and HF, lower baseline eGFR, and higher UACR at baseline (Supplemental Table 1).
Dapagliflozin reduced the risk of first AF/AFL event during follow-up by 19% (264 versus 325 events; 7.8 versus 9.6 events per 1000 patient years, hazard ratio (HR) 0.81, 95% CI 0.68 to 0.95, P=0.009, Figure 1). The effect of dapagliflozin was consistent when restricting to AF/AFL events that met criteria as serious adverse events (132 versus 166 events, HR 0.79, 95% CI 0.63 to 0.99) and those that were associated with hospitalization (114 versus 147 events, HR 0.77, 95% CI 0.60 to 0.98). Similar point estimates were observed when extending the PT search to include “atrial tachycardia” (264 versus 326 events, HR 0.80, 95% CI 0.68 to 0.94), and “supraventricular tachyarrhythmia/ tachycardia” (280 versus 336 events, HR 0.83, 95% CI 0.71 to 0.97). Dapagliflozin also reduced the total number of AF/AFL events (337 versus 432; incidence rate ratio 0.77, 95% CI 0.64 to 0.92, P=0.005; Figure 2). A sensitivity analysis using the Wei-Lin-Weissfeld model supported a treatment effect for the first event as well as for the subsequent events (First event: HR 0.81, 95% CI 0.68 to 0.95, P=0.009; Second Event: HR 0.69, 95% CI 0.49 to 0.99, P=0.045; Third Event: HR 0.50, 95% CI 0.25 to 0.99, P=0.048; Average HR: 0.81, 95% CI 0.68 to 0.95, P=0.009).

We performed several sensitivity analyses to investigate the effect of dapagliflozin on HHF and AF/AFL. Exclusion of all AF/AFL events that were within 14 days of an HHF event provided similar results (238 versus 288 events, HR 0.82, 95% CI 0.69 to 0.97; Table 1). Similar findings were seen when restricting the patient cohort to patients that did not experience HHF at any time during the trial (215 versus 246 events; HR 0.86, 95% CI 0.72 to 1.03; Supplemental Table 1). Similarly, a consistent treatment effect was seen when restricting the patient cohort to patients that did not experience myocardial infarction within 14 days of an AF/AFL event (232 versus 297 events; HR 0.77, 95% CI 0.65 to 0.92) or at any time during the trial (215 versus 273 events; HR 0.77, 95% CI 0.65 to 0.92; Table 1).
Effect of dapagliflozin on the incidence of AF/AFL by major subgroups

The reduction in AF/AFL events was consistent regardless of presence or absence of a history of AF/AFL at baseline (Prior AF/AFL: 68 (12.4%) vs. 86 (15.2%) events, HR 0.79, 95% CI 0.58 to 1.09; No AF/AFL: 196 (2.4%) vs. 239 (3.0%) events, HR 0.81, 95% CI 0.67 to 0.98; Figure 3). Similarly, presence of ASCVD (141 (4.1%) vs. 170 (4.9%) events, HR 0.83, 95% CI 0.66 to 1.04) versus multiple risk factors for ASCVD (123 (2.4%) vs 155 (3.1%) events, HR 0.78, 95% CI 0.62 to 0.99), or a history of HF (HF: 55 (6.5%) vs. 70 (8.0%) events, HR 0.78, 95% CI 0.55 to 1.11; No HF: 209 (2.7%) vs 255 (3.3%) events, HR 0.81, 95% CI 0.68 to 0.97) did not modify the reduction in AF/AFL events observed with dapagliflozin. Moreover, the treatment effect of dapagliflozin on AF/AFL was not modified by age, sex, HbA1c, BMI, systolic blood pressure, or eGFR (Figure 3).

Discussion

In the present subgroup analyses from the DECLARE-TIMI 58 trial, we found that dapagliflozin reduced the risk of AF/AFL events by significantly lowering the risk of time to the first AF/AFL event during follow-up by 19%. Dapagliflozin did not only reduce the risk of the first event but also significantly lowered the total number of AF/AFL events that were observed in the trial. Importantly, these reductions were found to be consistent in patients with and without known history of AF/AFL. Similarly, presence of ASCVD or a history of HF did not modify the reduction in AF/AFL events observed in patients randomized to dapagliflozin. AF/AFL commonly occur in the presence of HHF and SGLT2i are well known to reduce the risk of HHF. However, the favorable effects on reducing the incidence of AF/AFL persisted even when
restricting the analysis to patients who did not experience HHF or to AF/AFL events that were not preceded or followed by HHF within 14 days.

T2DM was identified to be an independent risk factor for the development of atrial fibrillation more than three decades ago in the Framingham Heart Study, a finding that has been confirmed in more contemporary registries as well. Patients with T2DM and AF/AFL are at high risk of cardiovascular complications. Underlying heart diseases such as hypertensive heart disease and heart failure, both commonly observed in patients with diabetes, are associated with a higher incidence of AF. The pathophysiology that may causally link diabetes with risk for AF/AFL is complex with several mechanisms proposed including structural, electromechanical, mechanical myocardial remodeling, and an imbalance in the sympathetic-parasympathetic tone.

There are several mechanisms how SGLT2i may modify the risk of AF/AFL in patients with T2DM. SGLT2i promote natriuresis and diuresis and thus may reduce atrial dilation. Experimental and clinical data suggest that SGLT2i reduce cardiac remodeling. Empagliflozin has been recently shown to reduce left ventricular mass as measured by cardiac magnetic resonance imaging in 97 patients with T2DM and ASCVD after a treatment duration of 6 months. SGLT2i have also been shown to lower blood pressure and body weight, and reduce inflammation, oxidative stress, and the sympathetic overdrive, all of which play important roles in fostering of AF/AFL. Furthermore, SGLT2i have been linked to a reduction in epicardial fat, a biologically highly-active tissue that has been associated with an increase in incidence and severity of AF. Moreover, glycemic variations and specifically hypoglycemia have been linked to an increased risk of AF in patients with T2DM. The glycemic lowering of SGLT2i is insulin independent and related to decreased glucose reabsorption in the kidney, with urinary...
glucose excretion ceasing once circulating levels get to or below the kidney urinary excretion threshold. As such, the risk of hypoglycemia with SGLT2i is low unless used with other agents that can cause hypoglycemia (e.g. insulin, sulphonylureas). Therefore, SGLT2i may have a favorable impact on both triggering effects as well as maintenance mechanisms of AF/AFL.

Several diabetes drug classes have been linked to a reduction in risk of AF/AFL. Experimental data suggest anti-inflammatory and anti-oxidative effects of thiazolidinediones may reduce structural an electrophysiological remodeling. A randomized controlled trial of 146 patients with T2DM and persistent AF reported that a smaller proportion of patients progressed to permanent AF with pioglitazone. However, no difference in incident AF was observed in the Prospective Pioglitazone Clinical Trial in macrovascular events (PROactive) or the Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD) trial.

Members of the glucagon-like peptide 1 receptor agonist (GLP1-RA) class significantly reduce the risk of the composite of myocardial infarction, stroke, and CV death but are associated with an increase in heart rate. A meta-analysis of randomized controlled GLP1-RA trials including 33271 patients did not find any association between the incidence of AF and GLP1-RA except for albiglutide that is possibly associated with a higher risk.

The results from the present analyses provides the first clinical trial evidence for a favorable effect of SGLT2i on the incidence of AF/AFL with consistent findings in patients with and without known AF/AFL. These results offer another potential benefit of the use of SGLT2i for the management of patients with T2DM given the frequent clinical occurrence of T2DM and AF/AFL in the same patients.
Limitations

Although this study benefits from analyses from a large dataset of a well characterized, and broad patient cohort, several limitations including its exploratory nature should be addressed. ECGs were not systematically collected nor independently reviewed and AF/AFL events were not confirmed by central adjudication. Also, serial ECGs and Holter monitoring were not available. AF/AFL were not prespecified outcomes of the trial and AF/AFL events that did not qualify as an SAE or led to drug discontinuation were not mandated to be reported. Furthermore, the lack of serial ECGs and available Holter monitoring do not allow us to quantify the burden of AF/AFL. This study also does not allow to determine whether the observed reductions in AF/AFL events in patients with known AF manifests as an increase in frequency or worsening of sustained arrhythmia.

Conclusions

In conclusion, dapagliflozin reduced the risk of both the first as well as the total number of reported episodes of AF/AFL adverse events in patients with T2D irrespective of the prevalence of AF, ASCVD, or HF.

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References


Table 1. Sensitivity analyses

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dapagliflozin n (%)</th>
<th>4yr KM</th>
<th>Events/1000 Ptyrs</th>
<th>Placebo n (%)</th>
<th>4yr KM</th>
<th>Events/1000 Ptyrs</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF/AFL in patients who did not experience HHF within 14 days of AF/AFL</td>
<td>238 (2.8%)</td>
<td>2.7</td>
<td>7.0</td>
<td>288 (3.4%)</td>
<td>3.3</td>
<td>8.6</td>
<td>0.82 (0.69, 0.97)</td>
<td>0.023</td>
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<tr>
<td>AF/AFL in patients who did not experience HHF</td>
<td>215 (2.6%)</td>
<td>2.5</td>
<td>6.5</td>
<td>246 (3.0%)</td>
<td>2.9</td>
<td>7.5</td>
<td>0.86 (0.72, 1.03)</td>
<td>0.105</td>
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<tr>
<td>AF/AFL in patients who did not experience MI within 14 days of AF/AFL</td>
<td>232 (2.7%)</td>
<td>2.6</td>
<td>6.8</td>
<td>297 (3.5%)</td>
<td>3.4</td>
<td>8.8</td>
<td>0.77 (0.65, 0.92)</td>
<td>0.003</td>
</tr>
<tr>
<td>AF/AFL in patients who did not experience MI</td>
<td>215 (2.6%)</td>
<td>2.5</td>
<td>6.6</td>
<td>273 (3.4%)</td>
<td>3.3</td>
<td>8.5</td>
<td>0.78 (0.65, 0.93)</td>
<td>0.005</td>
</tr>
</tbody>
</table>
Figures Legends

Figure 1. Effect of dapagliflozin versus placebo on atrial fibrillation and atrial flutter (AF/AFL)

Figure 2. First, additional and total events of atrial fibrillation and atrial flutter (AF/AFL).

Figure 3. Effect of dapagliflozin versus placebo on atrial fibrillation and atrial flutter (AF/AFL) by major subgroups.

Legend: AF = atrial fibrillation; AFL = atrial flutter; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin A1c; HF = heart failure, MRF = multiple risk factors; SBP = systolic blood pressure
KM Event Rate at 4 yrs: 3.0% vs 3.7%
Hazard Ratio 0.81, 95% CI 0.68 to 0.95, P=0.009
Total Events
IRR 0.77, 95% CI 0.64 to 0.92, P=0.005

Placebo
325

Dapagliflozin
264

Additional Events
IRR 0.67 (0.44-1.01)
1st Event
HR 0.81 (0.68-0.95)
<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Daplan (%)</th>
<th>Placebo (%)</th>
<th>HR (95%CI)</th>
<th>P interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AF/AFL</strong></td>
<td>264 (3.1)</td>
<td>325 (3.8)</td>
<td>0.81 (0.68, 0.95)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.66</td>
</tr>
<tr>
<td>Age &lt; 70</td>
<td>192 (2.8)</td>
<td>228 (3.3)</td>
<td>0.83 (0.68, 1.00)</td>
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<tr>
<td>Age &gt;= 70</td>
<td>72 (4.3)</td>
<td>97 (5.6)</td>
<td>0.76 (0.56, 1.03)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Male</td>
<td>186 (3.4)</td>
<td>226 (4.2)</td>
<td>0.80 (0.66, 0.98)</td>
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<tr>
<td>Female</td>
<td>78 (2.5)</td>
<td>99 (3.0)</td>
<td>0.80 (0.60, 1.08)</td>
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<tr>
<td><strong>ASCVD vs. MRF</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.72</td>
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<tr>
<td>ASCVD</td>
<td>141 (4.1)</td>
<td>170 (4.9)</td>
<td>0.83 (0.66, 1.04)</td>
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<tr>
<td>MRF</td>
<td>123 (2.4)</td>
<td>155 (3.1)</td>
<td>0.78 (0.62, 0.99)</td>
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<tr>
<td><strong>HF</strong></td>
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<td></td>
<td></td>
<td>0.88</td>
</tr>
<tr>
<td>HF</td>
<td>55 (6.5)</td>
<td>70 (8.0)</td>
<td>0.78 (0.55, 1.11)</td>
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</tr>
<tr>
<td>No HF</td>
<td>209 (2.7)</td>
<td>255 (3.3)</td>
<td>0.81 (0.68, 0.97)</td>
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</tr>
<tr>
<td><strong>Ischemic stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.88</td>
</tr>
<tr>
<td>Prior ischemic stroke</td>
<td>21 (3.8)</td>
<td>27 (4.8)</td>
<td>0.84 (0.47, 1.48)</td>
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</tr>
<tr>
<td>No prior ischemic stroke</td>
<td>243 (3.0)</td>
<td>298 (3.7)</td>
<td>0.81 (0.68, 0.96)</td>
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<tr>
<td><strong>AF/AFL</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.89</td>
</tr>
<tr>
<td>Hx of AF/AFL</td>
<td>68 (12.4)</td>
<td>86 (15.2)</td>
<td>0.79 (0.58, 1.09)</td>
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<tr>
<td>No Hx of AF/AFL</td>
<td>196 (2.4)</td>
<td>239 (3.0)</td>
<td>0.81 (0.67, 0.98)</td>
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<tr>
<td><strong>SBP</strong></td>
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<td>SBP &lt;135</td>
<td>123 (2.9)</td>
<td>135 (3.2)</td>
<td>0.91 (0.71, 1.16)</td>
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<tr>
<td>SBP &gt;=135</td>
<td>141 (3.2)</td>
<td>190 (4.4)</td>
<td>0.73 (0.59, 0.91)</td>
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<tr>
<td><strong>HbA1c</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.54</td>
</tr>
<tr>
<td>HbA1c &lt;8%</td>
<td>135 (3.3)</td>
<td>174 (4.3)</td>
<td>0.77 (0.61, 0.96)</td>
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<tr>
<td>HbA1c &gt;=8%</td>
<td>129 (2.9)</td>
<td>151 (3.4)</td>
<td>0.85 (0.67, 1.07)</td>
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</tr>
<tr>
<td><strong>BMI</strong></td>
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<tr>
<td>BMI &gt;=30 kg/m2</td>
<td>199 (3.9)</td>
<td>246 (4.88)</td>
<td>0.78 (0.65, 0.94)</td>
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<tr>
<td>BMI &lt;30 kg/m2</td>
<td>64 (1.9)</td>
<td>79 (2.24)</td>
<td>0.83 (0.60, 1.15)</td>
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<tr>
<td><strong>eGFR</strong></td>
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<td>0.88</td>
</tr>
<tr>
<td>eGFR &gt;=90 ml/min/1.73m2</td>
<td>95 (2.3)</td>
<td>107 (2.7)</td>
<td>0.85 (0.65, 1.12)</td>
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<tr>
<td>eGFR 60-90 ml/min/1.73m2</td>
<td>136 (3.5)</td>
<td>176 (4.5)</td>
<td>0.78 (0.62, 0.98)</td>
<td></td>
</tr>
<tr>
<td>eGFR &lt;60 ml/min/1.73m2</td>
<td>32 (5.3)</td>
<td>42 (6.4)</td>
<td>0.82 (0.52, 1.30)</td>
<td></td>
</tr>
</tbody>
</table>