Dapagliflozin In Patients Undergoing Transcatheter Aortic Valve Implantation

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Abstract

BACKGROUND

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors reduce heart failure admissions in high-risk patients. However, patients with valvular heart disease, including those undergoing transcatheter aortic valve intervention (TAVI) have been systematically excluded from randomized trials.

METHODS

We conducted an independent, pragmatic, prospective randomized open blinded end point trial in Spain to evaluate the efficacy of dapagliflozin 10mg daily compared to standard care among patients with aortic stenosis undergoing TAVI who had a prior episode of heart failure and renal insufficiency or diabetes or left ventricular systolic dysfunction. The primary outcome was a composite of all-cause death or worsening heart failure defined as hospitalization or urgent visit from the time of hospital discharge to 1 year follow-up.

RESULTS

A total of 620 patients were randomly assigned to dapagliflozin and 637 to standard care after TAVI; after exclusions, a total of 1,222 patients were included in the primary analysis. The primary outcome occurred in 91 patients (15.0%) in the dapagliflozin group and in 124 patients (20.1%) in the standard care group (hazard ratio, 0.72; 95% confidence interval [CI], 0.55 to 0.95; P=0.018). All-cause death occurred in 47 patients (7.8%) in the dapagliflozin group and in 55 (8.9%) in the standard care group (hazard ratio, 0.87; 95% CI, 0.59 to 1.28). Worsening heart failure occurred in 9.4% of patients in the dapagliflozin group compared to 14.4% in the standard care group (hazard ratio, 0.63; 95% CI, 0.45 to 0.88). Genital infections and hypotension were significantly more common in the dapagliflozin group.

CONCLUSION

Among older adults with aortic stenosis undergoing TAVI and at high risk for future heart failure events, dapagliflozin resulted in a significantly lower incidence of a composite of all-cause death or worsening heart failure.

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Aortic stenosis is the most common valvular heart disease in Western countries, and its prevalence is increasing due to aging of the population. The advent of transcatheter aortic valve intervention (TAVI) has changed how aortic stenosis is managed; TAVI has become the standard of care for most of patients, especially older patients.[1,2] Many patients with aortic stenosis who are treated with TAVI still face high rates of hospitalization for heart failure ,[3-5] which is associated with high rates of mortality in these patients. [6]

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors have been proven effective in reducing heart failure-related admissions across a wide spectrum of high-risk patients. [7-14]Both American and European clinical practice guidelines recommend the use of SGLT-2 inhibitors in patients with heart failure regardless of their left ventricular ejection fraction or diabetes status .[15,16] However, the supporting evidence for this recommendation is less robust when it comes to patients with heart failure attributable to reversible conditions, such as aortic stenosis.

People with severe valvular heart disease and those undergoing transcatheter interventions have been systematically excluded from randomized controlled trials investigating SGLT-2 inhibitors.[17] Furthermore, patients undergoing TAVI are typically of advanced age,[18,19] and patients more than 80 years of age are underrepresented in clinical trials evaluating SGLT-2 inhibitors.[20] As a result, the prescription of SGLT-2 inhibitors for older adults remains low.[21]

Given the limited evidence about the efficacy of SGLT-2 inhibitors in elderly patients with aortic stenosis undergoing TAVI, we conducted the DapaTAVI trial (Dapagliflozin In Patients Undergoing Transcatheter Aortic Valve Implantation), a randomized controlled trial to assess the efficacy and safety of dapagliflozin in this patient population.

Methods

TRIAL OVERSIGHT

The Dapagliflozin In Patients Undergoing Transcatheter Aortic Valve Implantation (DapaTAVI) trial was a multicenter, independent, pragmatic, prospective randomized open blinded endpoint (PROBE) controlled trial conducted at 39 centers across Spain. The DapaTAVI trial was designed to assess the effectiveness of oral dapagliflozin 10 mg once daily in patients with severe aortic stenosis undergoing TAVI. The trial design and baseline characteristics of the patients enrolled have been previously reported and are available online at NEJM.org with the full text of this article.[22] This investigator-initiated clinical trial was sponsored by the Spanish Society of Cardiology and the Spanish National Center of Cardiovascular Research (CNIC). DapaTAVI was an independent trial designed and overseen by a steering committee. The protocol was approved by the Galician Clinical Research Ethics Committee (approval number 2020/434), the Spanish Agency of Medicines and Medical Devices (AEMPS 20-0748), and the investigational review boards at each of the participating sites. The trial adhered to the principles outlined in the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. The authors take full responsibility for the accuracy and completeness of the data and analyses, as well as for ensuring that the trial and this report faithfully reflect the protocol. Data was analyzed by Xavier Rosselló (cardiologist and statistician). The first and last author, who had unrestricted access to the data, drafted the manuscript, which was then revised by all authors. All authors made the decision to submit the manuscript and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

PATIENTS

Patients with severe aortic stenosis undergoing TAVI were eligible for enrollment if they had a prior episode of aortic stenosis-related heart failure, including any hospitalization for heart failure or urgent heart failure visit requiring intravenous diuretic prior to TAVI, and either moderate renal insufficiency (estimated glomerular filtrate rate [eGFR] of 25 to 75 ml/min/1.73m^2), diabetes mellitus, or a left ventricular ejection fraction ≤40%. Exclusion criteria were any contraindication to dapagliflozin, current therapy with sulfonylurea or SGLT-2 inhibitors, systolic blood pressure<100 mmHg, diastolic blood pressure<50 mmHg, eGFR<25 ml/min/1.73 m^2, chronic cystitis or recurrent urinary tract infections (≥2 in the last year). A complete list of the inclusion and exclusion criteria is provided in the Supplementary Appendix available online at NEJM.org. All participants provided written informed consent.

TRIAL PROCEDURES

Participants were randomly assigned in a 1:1 ratio to either dapagliflozin 10 mg daily and standard care or standard care alone. Randomization was performed at the time of hospital discharge after TAVI or within 14 days of discharge and was carried out using a secure web-based system; randomization was stratified according to the presence of absence of diabetes mellitus, left ventricular ejection fraction ≤40%, and eGFR between 25 and 75 ml/min/1.73 m^2. Treatment began at the time of randomization. The assessment of clinical outcomes, and adherence to dapagliflozin or standard care treatment was conducted at 3 and 12 months after randomization through telephone interviews and review of medical records and national vital status registries. Clinical outcomes were adjudicated externally by a clinical panel blinded to treatment allocation.

OUTCOMES

The primary outcome was a composite of all-cause death or worsening heart failure defined as either hospitalization for heart failure or urgent heart failure visit requiring intravenous diuretics. Key secondary outcomes included: the incidence rate of the individual components of the primary outcome; cardiovascular mortality; the composite of hospitalization for heart failure or cardiovascular death; and the total number of heart failure rehospitalizations. Safety end points, including symptomatic hypotension, major hypoglycemia, ketoacidosis, genital or urinary infections, necrotizing fasciitis, and non-traumatic amputations were also reported. All other safety outcomes were based on adverse event reporting.

STATISTICAL ANALYSIS

The study was designed to have 80% power to detect a relative risk reduction of 30% with dapagliflozin in the primary end point during a 1-year follow-up, considering a primary end point event rate of 30% per year in the standard care group, and an estimated loss during follow-up of 5%. The initial planned total sample size was 1,020 patients (510 per group). According to the study protocol, a blinded examination of the overall event rate (i.e. no unblinding of treatment allocation) and an assessment of the percentage of patients according to the inclusion criteria took place 3 months before closing recruitment. The data was evaluated by the Data Safety Monitoring Board. As prespecified in the protocol, we applied the Haybittle–Peto stopping rule in the interim analysis: using this approach, the trial stops early only if a $P \leq 0.001$ is observed without an alpha penalty. At the time of the blinded examination, the overall event rate projection at the end of the trial was expected to be lower than 25%, so the Data and Safety Monitoring Board recommended the sample size be increased by 20% or approximately 200 patients to a total of 1,220 participants.

Baseline characteristics assessed at the time of randomization were reported using frequencies and percentages, or means and standard deviations, as appropriate. Given that the missing data appeared evenly distributed between groups, the data are most likely missing at random. For the primary analysis, no imputation of missing data was performed. The primary end point was assessed through the log rank test and reported by study arm using a Kaplan-Meier plot. A Cox proportional hazards model was used to estimate treatment effect through hazard ratios and their corresponding 95% confidence intervals (CI). All patients without an event were censored at the end of their 1-year follow-up, whereas patients that withdrew from follow-up were censored on the day of withdrawal. The prespecified subgroups were analyzed with the use of the Cox regression model with an interaction term for the subgroup.

All secondary end points, except the total number of heart failure hospitalizations or cardiovascular deaths, were evaluated using the same statistical approach as for the primary end point. For outcomes that were subject to competing risks, treatment effects were estimated with the use of a competing risks model using a direct likelihood approach for the cause-specific cumulative incidence function, with all-cause mortality (for those outcomes not including any type of cause-specific mortality), or non- cardiovascular mortality (for those outcomes including cardiovascular death) as the competing risk. [23] Results were presented as subhazard ratios with their corresponding 95% CI. A negative binomial regression was used to estimate treatment effect for the total number of heart failure hospitalizations or cardiovascular deaths. The widths of the CIs have not been adjusted for multiplicity, and the intervals may not be used in place of hypothesis testing. [24]

The primary analysis was performed according to the intention-to-treat principle. A pre-specified analysis was performed on the per protocol set of patients without crossovers: crossovers were censored at the time of their switch of arm group.

A 2-sided P-value with an alpha ≤0.05 level of significance was used for all tests. Analyses were performed with Stata 16.1.

Results

PATIENTS

From January 2021, through December 2023, a total of 1,257 patients underwent randomization; 620 were randomly assigned to dapagliflozin and 637 to standard care at 39 centers in Spain (**Table S1**). After exclusions due to randomization in error, withdrawal, and loss to follow-up, there were 605 patients assigned to the dapagliflozin group and 617 to the standard care group, which formed the population included in the intention to treat analysis (**Figure S1**). Patient characteristics and baseline therapies appeared balanced between the groups with the exception of coronary artery disease, which was more prevalent in the dapagliflozin group and mean N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, which were higher in the dapagliflozin group (**Table 1** and Table S2). The mean (±SD) age was 82.4±5.6 years and 49.4% of patients were women. A total of 43.9% of the patients had diabetes mellitus, 17% had a left ventricular ejection fraction ≤40%, and 88.6% had an eGFR between 25 and 75ml/min/1.73 m^2. The mean eGFR was 56.2±16.4mL/min/1.73m^2. The representativeness of the trial population is shown in Table S3.

The median time from the TAVI procedure to randomization was 2 days (interquartile range, 1 to 4 days). In the dapagliflozin arm, 103 patients (17%) stopped dapagliflozin treatment during follow-up, while in the standard care group, 43 patients (7%) were initiated on dapagliflozin

therapy for reasons other than heart failure. At 1-year follow-up, 496 patients (82.0%) in the dapagliflozin group and 554 patients (89.8%) in the standard care group remained on their assigned study treatment. Only one patient in the standard care group was lost to follow-up.

OUTCOMES

The primary composite outcome of all-cause death or worsening heart failure occurred in 91 patients (15.0%) in the dapagliflozin group and in 124 patients (20.1%) in standard care group (hazard ratio, 0.72; 95% CI, 0.55 to 0.95; P=0.018) (**Table 2** and **Figure 1A**). All-cause death occurred in 47 patients (7.8%) and 55 patients (8.9%) in the dapagliflozin and standard care groups, respectively (hazard ratio, 0.87; 95% CI, 0.59 to 1.28) (**Figure 1B**). Worsening heart failure occurred in 57 patients (9.4%) and 89 patients (14.4%) in dapagliflozin and the standard care groups, respectively (subhazard ratio, 0.63; 95% CI, 0.45 to 0.88) (**Figure 1C**). With respect to the individual components of the worsening heart failure end point, hospitalization for heart failure occurred in 45 (7.4%) and in 66 (10.7%) patients in the dapagliflozin and standard care groups, respectively (subhazard ratio, 0.68; 95% CI, 0.46 to 0.99), while urgent heart failure visits resulting in intravenous diuretic therapy occurred in 17 patients (2.8%) and 37 patients (6.0%), respectively (subhazard ratio, 0.46; 95% CI, 0.26 to 0.82) (Fig. S2). Death from cardiovascular causes occurred in 27 patients (4.5%) and in 33 patients (5.3%) in the dapagliflozin and standard care groups, respectively (subhazard ratio, 0.81; 95% CI, 0.49 to 1.35) (Figure S2). Causes of death are shown in Table S4.

Results appeared similar when including those patients randomized in error without performing a competing risk analysis (Table S5). Analysis in the per-protocol population (Figure S3 and Table S6) and across prespecified subgroups also appeared consistent across prespecified subgroups (**Figure 2**).

The incidence of the secondary composite outcome of hospitalization for heart failure or death from cardiovascular causes occurred in 61 patients (10.1%) in the dapagliflozin group and 85 (13.8%) in the standard care group (hazard ratio, 0.71; 95% CI, 0.51 to 0.98) (**Table 2**, Figure S2). There were a total number of 79 recurrent heart failure hospitalizations or cardiovascular death (52 hospitalizations for heart failure and 27 deaths from cardiovascular causes) that occurred among 61 patients in the dapagliflozin group and 121 total events (88 hospitalizations for heart failure and 33 deaths from cardiovascular causes) among 85 patients in the standard care group (rate ratio, 0.67; 95% CI, 0.47 to 0.95).

SAFETY

Safety end points are shown in **Table 3**. The rates of non-traumatic amputation, major hypoglycemia, and cancer appeared balanced between the groups. There were no cases of diabetic ketoacidosis in the study population. Genital infections occurred in 1.8% of patients assigned to dapagliflozin and 0.5% assigned to standard care (P=0.03) and hypotension occurred in 6.6% of patients assigned to dapagliflozin and 3.6% of patients assigned to standard care (P=0.01). There were no apparent differences found in rates of urinary tract infections, bacteremia, or syncope between dapagliflozin and standard care groups. Adverse events led to a discontinuation of dapagliflozin in 37 patients (6.1%).

Discussion

Among patients with severe aortic stenosis undergoing TAVI with a high-risk for future heart failure events, defined as a prior episode of aortic stenosis-related heart failure and either diabetes mellitus, a left ventricular ejection fraction ≤40% or moderate renal insufficiency, SGLT-2 inhibition with dapagliflozin led to a resulted in a 28% relative risk reduction in the composite end point of all-cause death or worsening heart failure. The effects on the incidence

of primary outcome events appeared consistent across all prespecified subgroups, including among patients with or without diabetes, chronic kidney disease, and reduced or preserved left ventricular ejection fraction.

Patients with aortic stenosis undergoing TAVI usually have high rates of mortality and readmissions for heart failure despite undergoing the TAVI procedure, approximately 20% in the first year after intervention[4,5]. The DapaTAVI trial extends the evidence from prior SGLT-2 inhibitor trials and includes older patients undergoing aortic valve replacement, showing clinically relevant benefits of dapagliflozin in this patient population after TAVI. In the DapaHF and DELIVER clinical trials[7,8], dapagliflozin demonstrated a 30% and 21% reduction in worsening heart failure, respectively, in a population of patients with reduced (≤40%) and mid-range or preserved left ventricular ejection fraction. In the DECLARE–TIMI 58 trial, dapagliflozin was associated with a 27% reduction in heart failure hospitalization in patients with diabetes.[9] Results from our trial on the reduction of worsening heart failure are consistent with the results of these previous trials. SGLT-2 inhibitors are known to promote natriuresis and glycosuria, exerting a hemodynamic effect through a reduction in preload and afterload. [25]

The DapaTAVI trial examined SGLT-2 inhibitors in a population of older patients (mean age, 82 years; 72% of the participants were older than 80 years and 7.5% were older than 90 years). In randomized clinical trials evaluating the cardiovascular benefits of SGLT-2 inhibitors, fewer than 10% of participants were over 75 years of age. [7-14] The mean age of patients enrolled in the DECLARE-TIMI 58, DapaHF and DELIVER trials was 64, 66, and 72 years, respectively. [7-9] The VERTIS-CV trial in patients with diabetes included a pre-specified analysis among adults 65 years of age and older and a post-hoc analysis in 903 patients 75 years of age and older, finding

similar cardiovascular and renal outcomes with ertugliflozin across all age groups.[26] Our results appear to confirm that SGLT-2 inhibitors are safe in older patients in our trial and associated with clinical benefits, which is important since SGLT-2 inhibitors are underprescribed in older patients.[27] Another relevant aspect of the present DapaTAVI trial is that almost half of the patients were women. In prior trials of SGLT-2 inhibitors, women have been underrepresented[7-14]. In the present trial, genital infections and hypotension were the most common adverse events associated with dapagliflozin. Although urinary tract infections were frequent, the rates appeared similar in both groups, similar to prior clinical trials with SGLT-2 inhibitors.[28] Rates of bacteremia appeared similar between patients assigned to dapagliflozin and standard care.

Our study has limitations. This includes the pragmatic and open-label trial design and the fact that only limited effectiveness and safety data were collected. Although masking was not implemented for patients and care providers, end point events were adjudicated centrally, with evaluators blinded to treatment allocation. The observed event rate for death and worsening heart failure events was substantially lower than initially expected. However, the increase in sample size upon observing an overall lower event rate partially mitigated this limitation. The trial was conducted only in Spain; data on race and ethnic groups are not available, but based on the population of Spain, it is expected that more than 90% of participants were Caucasian.

In conclusion, among patients with aortic stenosis undergoing TAVI and at high risk for future heart failure events, dapagliflozin reduced the incidence of a composite of all-cause death or worsening heart failure compared to standard care.

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Table 1. Characteristics of the Patients at Baseline*

Characteristic	Dapagliflozin Group (N = 605)	Standard care Group (N = 618)‖
Age — yr	82.4±5.6	82.4±5.5
Female sex — no. (%)	299 (49.4)	305 (49.4)
Cardiovascular disease history and risk factors — no. (%)		
Diabetes mellitus type 2	264 (43.6)	273 (44.2)
Hypertension	518 (85.6)	519 (84.0)
Coronary artery disease	237 (39.2)	197 (31.9)
Previous myocardial infarction	51 (8.4)	52 (8.4)
Prior stroke	61 (10.1)	69 (11.2)
Peripheral artery disease	51 (8.4)	43 (7.0)
Atrial fibrillation	250 (41.3)	274 (44.3)
Echocardiographic data — no. (%)		
Mean gradient — mmHg†	47.8±13.7	46.6±13.5
Left ventricular ejection fraction — %	54.9±12.3	54.8±12.1
Left ventricular ejection fraction ≤ 40%	109 (18.0)	103 (16.7)
Moderate-severe left ventricular hypertrophy	368 (60.8)	367 (59.3)
Mitral regurgitation grade 3+ or higher	99 (16.4)	99 (16.0)
Laboratory data— no. (%)		
Hemoglobin — g/dL‡	11.9±1.7	12.0±1.7
Estimated glomerular filtrate rate — ml/min/1.73 m2 §	56.0±16.4	56.4±16.3
Glomerular filtrate rate (25-75 ml/min/1.73 m2) no. (%)	529 (87.4)	555 (89.8)
NTproBNP — pg/ml ¶	6,324.0±19,948.9	5,301.1±6,622.0
In-hospital complications after TAVI — no. (%)		
Myocardial infarction	2 (0.3)	1 (0.2)
Stroke	10 (1.7)	15 (2.4)
New-onset bundle branch block	151 (32.0)	146 (32.6)
Pacemaker implantation	105 (19.3)	103 (19.0)
Post-TAVI aortic regurgitation grade 3+ or higher	27 (4.5)	37 (6.0)
Baseline therapy — no. (%)		
Acetylsalicylic acid	318 (52.6)	298 (48.2)
P2Y12 inhibitor	125 (20.7)	118 (19.1)
Oral anticoagulation	280 (46.3)	300 (48.5)
Beta-blockers	219 (36.2)	230 (37.2)
Renin-angiotensin system inhibitor	380 (62.8)	364 (58.9)
Aldosterone receptor blocker	84 (13.9)	97 (15.7)
Diuretic	441 (72.9)	473 (76.5)
Insulin therapy	53 (8.8)	60 (9.7)

* Plus–minus values are means ±SD. Percentages may not sum to 100% due to rounding. Baseline variable data were available for all patients except the 3 variables specifically indicated (mean transaortic gradient, hemoglobin, NTproBNP). There were no significant differences between the two groups for any variable except for coronary artery disease. HbA1c denotes glycated hemoglobin, NT-proBNP N-terminal pro–B-type natriuretic peptide, and TAVI transcatheter aortic valve implantation.

† Data were missing for 198 patients in the dapagliflozin group and 178 patients in the standard care group.

‡ Data were missing for 40 patients in the dapagliflozin group and 33 patients in the standard care group.

§ Estimated glomerular filtrate rate according to the CKD-EPI creatinine-based estimation equation.

¶ Data were missing for 298 patients in the dapagliflozin group and 276 patients in the standard care group.

‖ At baseline, 618 patients in the standard care group were randomized and initiated the follow-up period, but one patient was lost to follow-up (thus, the final ITT population for standard care was 617)

Table 2. Primary, Secondary, and Other End Points.

End Point	Dapagliflozin Group (N = 605)		Standard care Group (N = 617)		95% CI*
	No.	%	No.	%	
Primary composite end point	91	15.0	124	20.1	0.72 (0.55–0.95)‡
Components of the primary outcome					
All-cause death	47	7.8	55	8.9	0.87 (0.59–1.28)
Worsening heart failure	57	9.4	89	14.4	0.63 (0.45-0.88) §
Hospitalization for heart failure	45	7.4	66	10.7	0.68 (0.46–0.99) §
Urgent heart failure visit	17	2.8	37	6.0	0.46 (0.26–0.82) §
Key secondary end points					
Death from cardiovascular causes	27	4.5	33	5.3	0.81 (0.49-1.35) §
Hospitalization for heart failure or death from cardiovascular causes	61	10.1	85	13.8	0.71 (0.51–0.98) §
Total no. of hospitalizations for heart failure or death from cardiovascular causes	79	13.1	121	19.6	0.67 (0.47-0.95) ¶

* The effects are presented as hazard ratios estimated with the use of a Cox proportional-hazards model unless indicated otherwise. All confidence intervals for secondary and exploratory outcomes are exploratory since no prespecified multiplicity adjustment was performed.

‡ P =0.018 for the comparison of the dapagliflozin group with the standard care group.

§ The effects are presented as subhazard ratio with the use of a competing risks model, with all-cause mortality (for those outcomes not including any type of cause-specific mortality), or non- cardiovascular mortality (for those outcomes including cardiovascular death) as the competing risk.

¶ The effect is presented as rate ratio with the use of a negative binomial regression

Table 3. Safety End Points.

End Point	Dapagliflozin Group (N = 605)		Standard care Group (N = 617)		P-value
	No.	%	No.	%	
Genitourinary infections	94	15.5	71	11.5	0.04
Genital infections	11	1.8	3	0.5	0.03
Urinary infections	83	13.7	68	11.0	0.15
Relevant urinary infections*	17	2.8	11	1.8	0.23
Bacteremia	31	5.1	32	5.2	0.96
Hypotension	40	6.6	22	3.6	0.01
Syncope	22	3.6	13	2.1	0.11
Ketoacidosis	0	0	0	0	-
Major Hypoglycemia	4	0.7	8	1.3	0.26
Necrotizing fasciitis	0	-	0	-	-
Non-traumatic amputation	5	0.8	4	0.6	0.72
Cancer	30	5	22	3.6	0.23

* Requiring hospital admission or complicated with urinary sepsis.

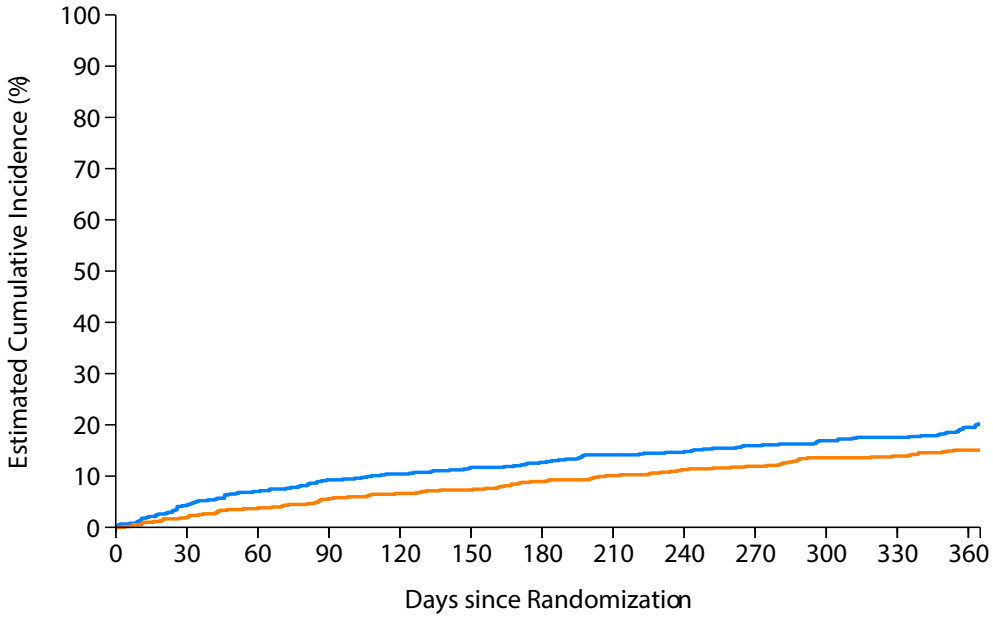
FIGURE LEGENDS.

Figure 1. Kaplan–Meier Estimates and Cumulative Incidence Functions for the Composite Primary End Point and Its Components.

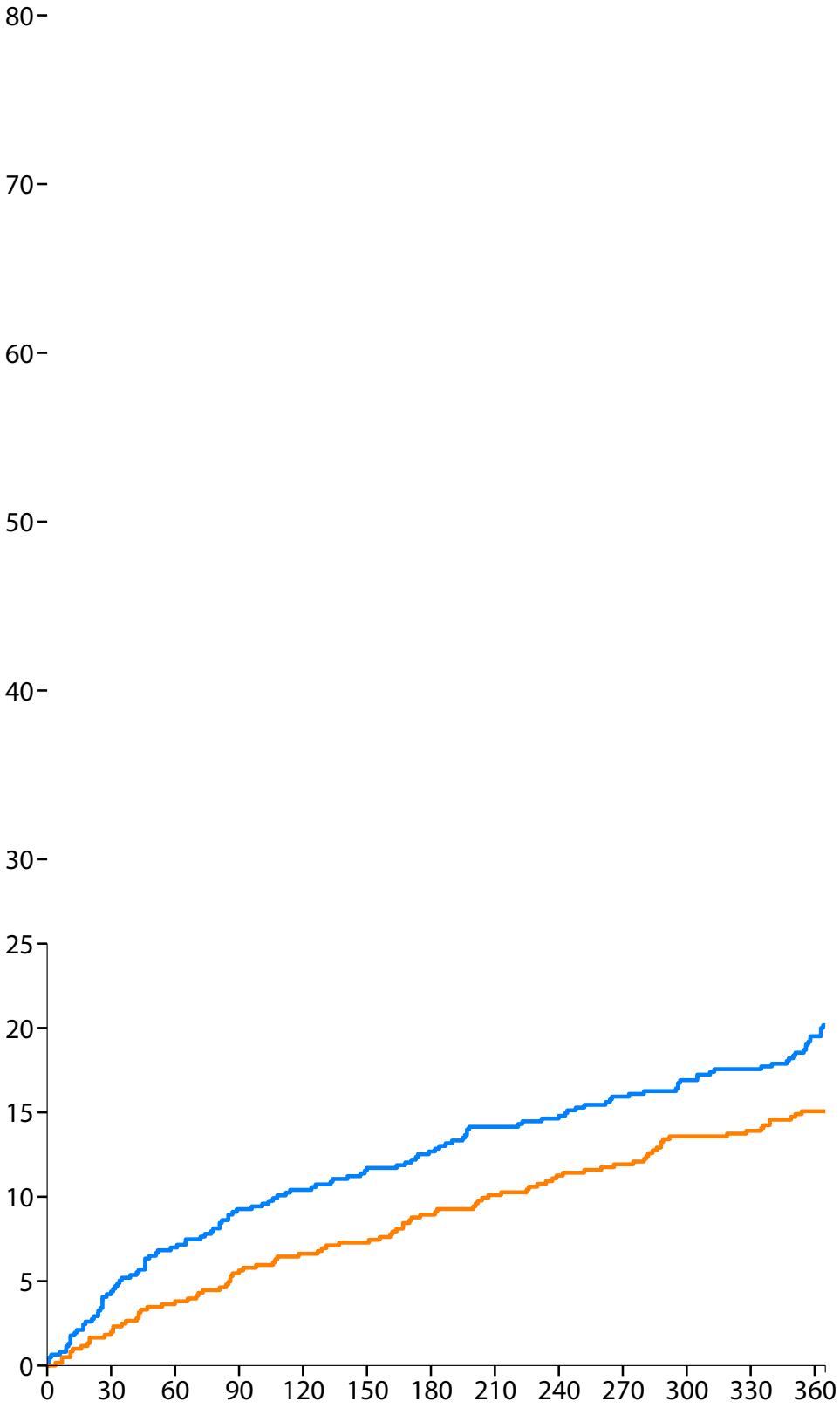
Panel A shows the time to first all-cause death or worsening heart failure. Panels B and C show the time to a first all-cause death and the time to a first worsening heart failure. The insets display the same data on an expanded Y-axis. Hazard ratios and 95% confidence intervals were estimated using Cox regression models. The widths of the confidence intervals have not been adjusted for multiple comparisons and should not be used in place of hypothesis testing.

Figure 2. Primary Outcome in Prespecified Subgroups.

The primary outcome was a composite of all-cause death or worsening heart failure defined as either an unplanned hospitalization or an urgent visit. eGFR denotes estimated glomerular filtrate rate and RAAS Renin-angiotensin system inhibitor.



No. at Risk													
Control	617	588	572	558	551	543	537	528	524	517	511	507	493
Dapagliflozin	605	592	581	570	564	560	550	543	536	532	522	520	514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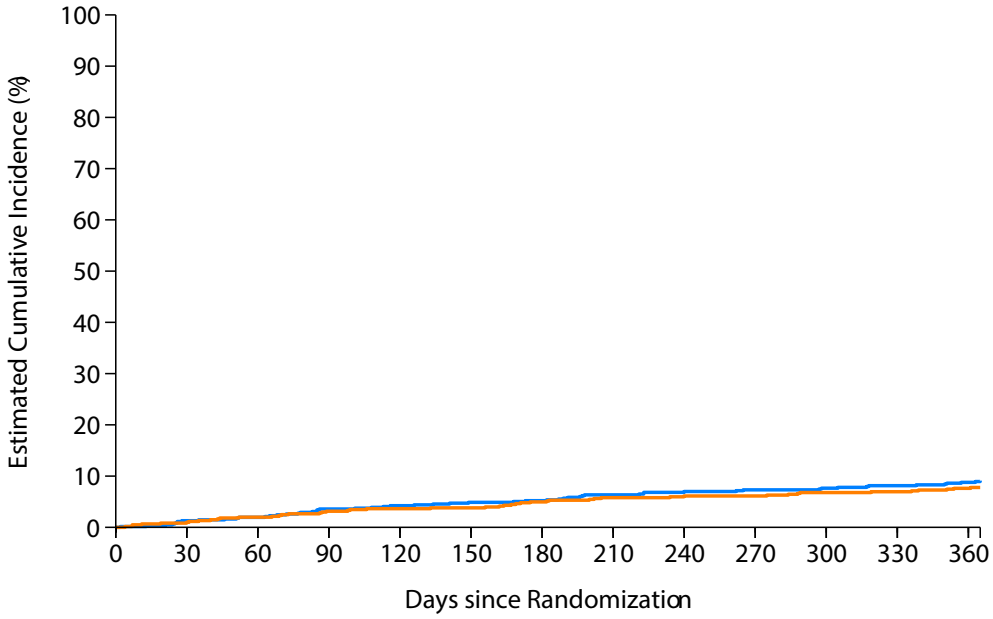
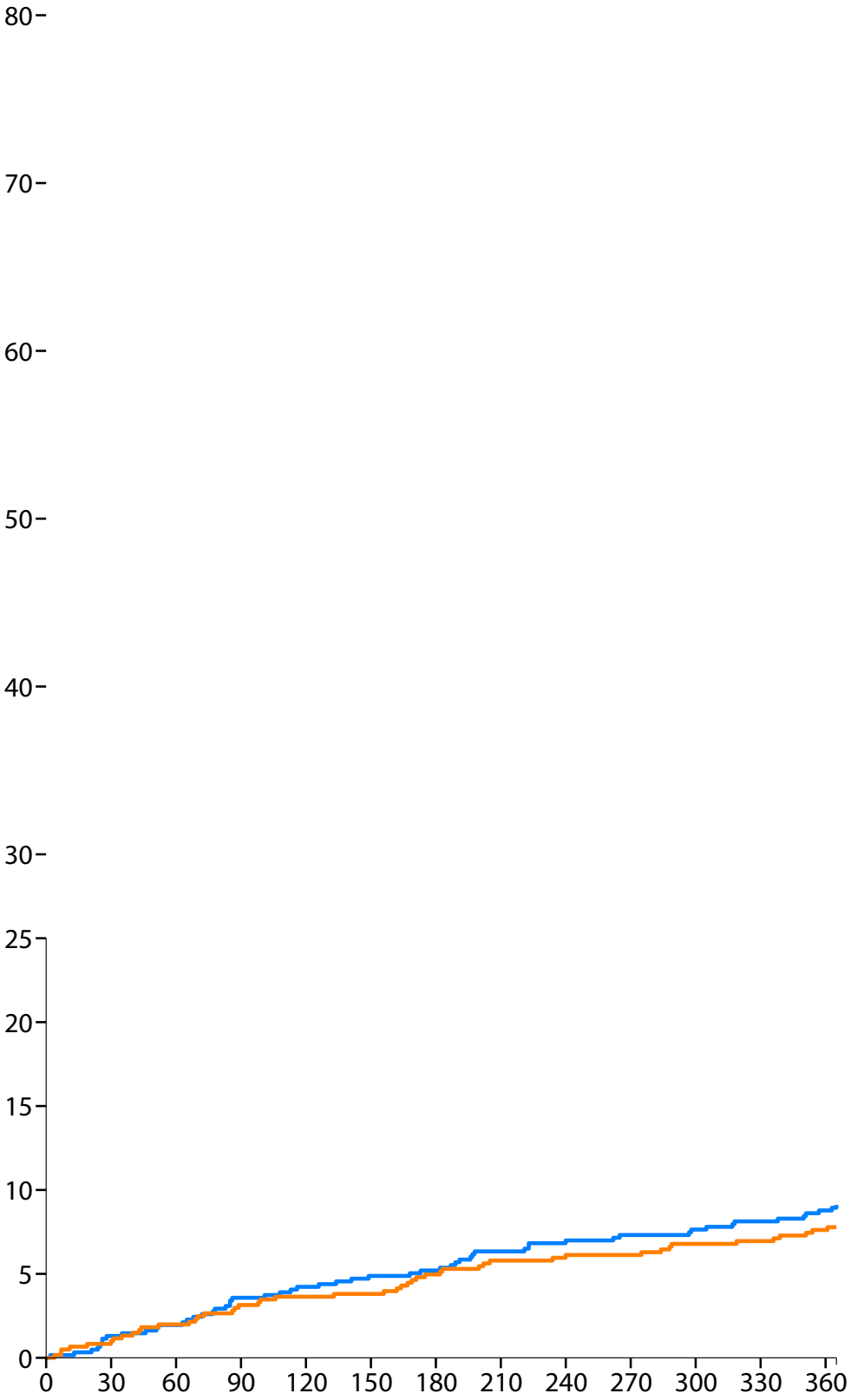


No. at Risk													
Control	617	607	603	593	589	585	583	576	572	570	568	565	562
Dapagliflozin	605	598	592	585	582	581	574	569	567	567	563	562	558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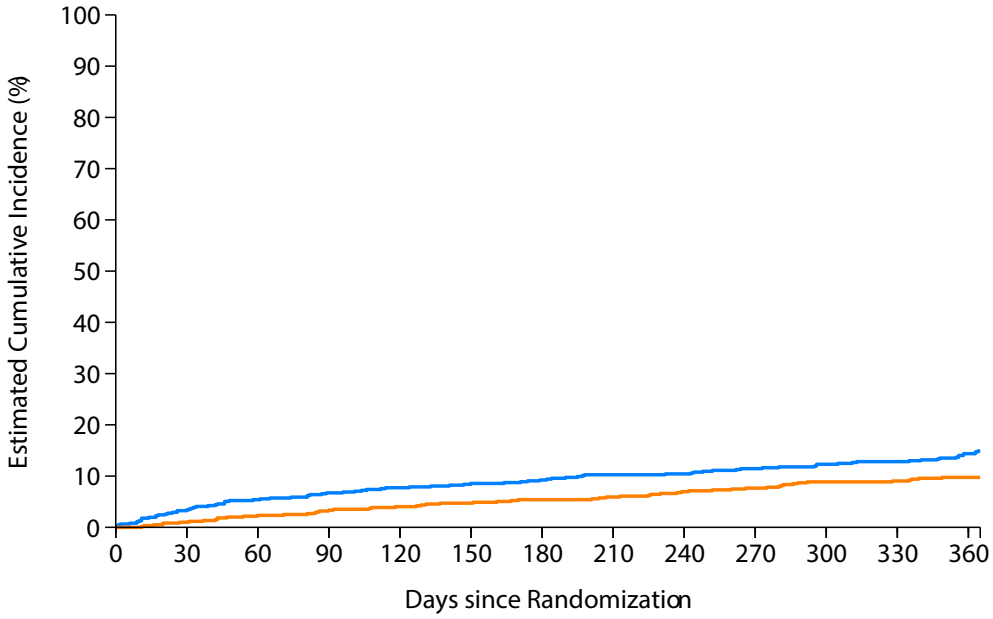
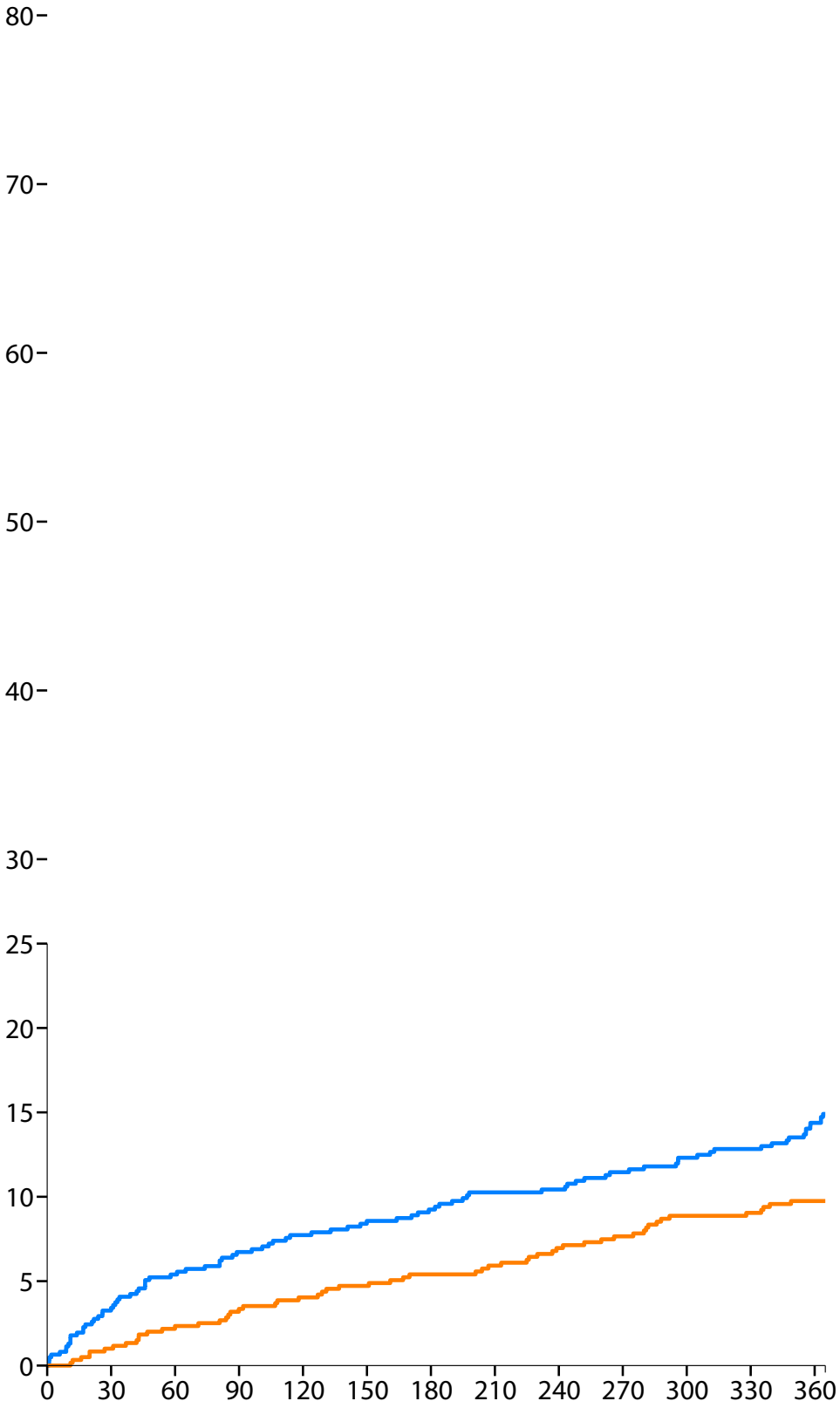


No. at Risk													
Control	617	588	572	558	551	543	537	528	524	517	511	507	493
Dapagliflozin	605	592	581	570	564	560	550	543	536	532	522	520	514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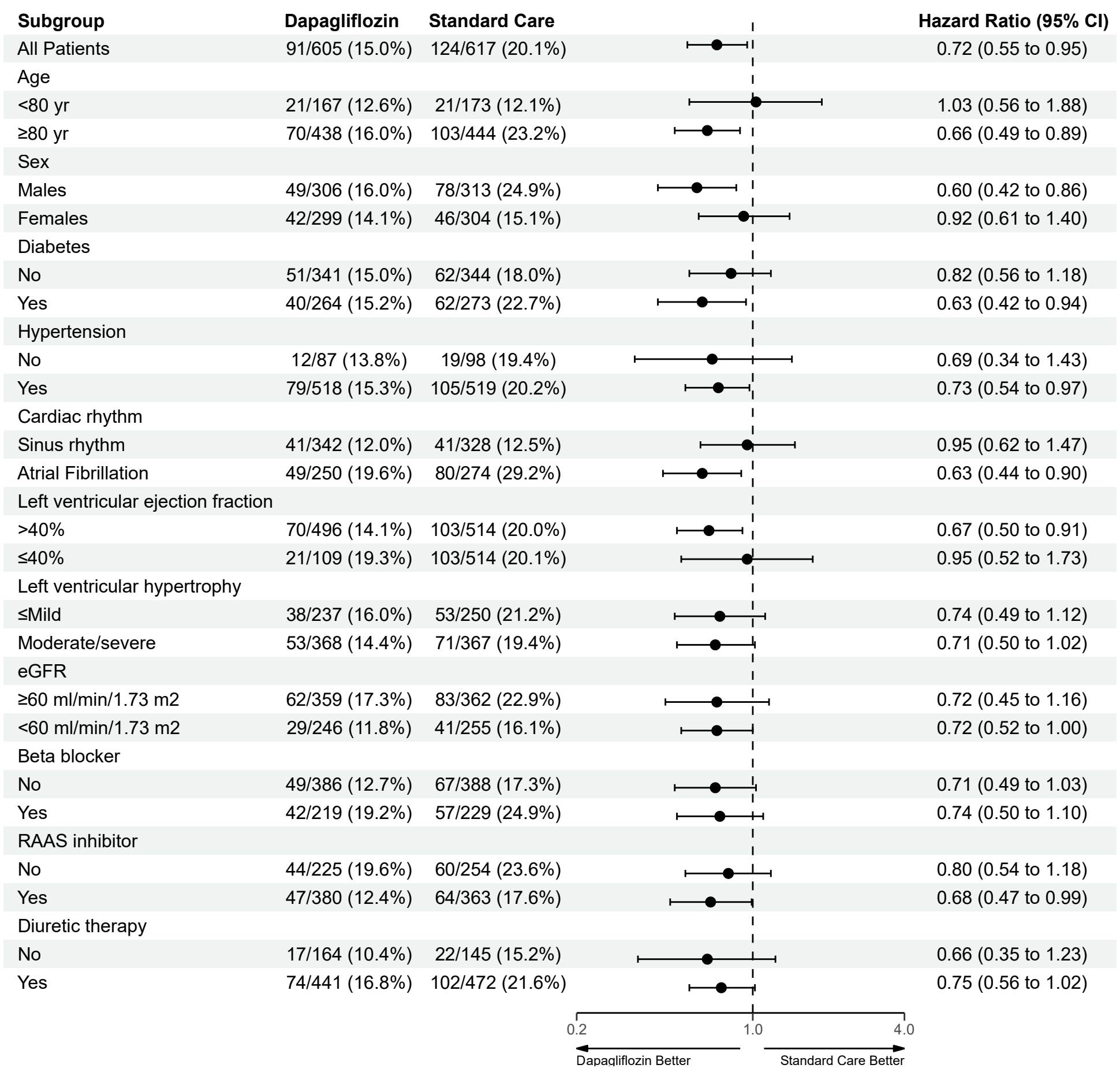
Subgroup
Dapagliflozin
Standard Care
Hazard Ratio (95% CI)
All Patients 91/605 (15.0%) 124/617 (20.1%) 0.72 (0.55 to 0.95)
Age
<80 yr 21/167 (12.6%) 21/173 (12.1%) 1.03 (0.56 to 1.88)
≥80 yr 70/438 (16.0%) 103/444 (23.2%) 0.66 (0.49 to 0.89)
Sex
Males 49/306 (16.0%) 78/313 (24.9%) 0.60 (0.42 to 0.86)
Females 42/299 (14.1%) 46/304 (15.1%) 0.92 (0.61 to 1.40)
Diabetes
No 51/341 (15.0%) 62/344 (18.0%) 0.82 (0.56 to 1.18)
Yes 40/264 (15.2%) 62/273 (22.7%) 0.63 (0.42 to 0.94)
Hypertension
No 12/87 (13.8%) 19/98 (19.4%) 0.69 (0.34 to 1.43)
Yes 79/518 (15.3%) 105/519 (20.2%) 0.73 (0.54 to 0.97)
Cardiac rhythm
Sinus rhythm 41/342 (12.0%) 41/328 (12.5%) 0.95 (0.62 to 1.47)
Atrial Fibrillation 49/250 (19.6%) 80/274 (29.2%) 0.63 (0.44 to 0.90)
Left ventricular ejection fraction
>40% 70/496 (14.1%) 103/514 (20.0%) 0.67 (0.50 to 0.91)
≤40% 21/109 (19.3%) 103/514 (20.1%) 0.95 (0.52 to 1.73)
Left ventricular hypertrophy
≤Mild 38/237 (16.0%) 53/250 (21.2%) 0.74 (0.49 to 1.12)
Moderate/severe 53/368 (14.4%) 71/367 (19.4%) 0.71 (0.50 to 1.02)
eGFR
≥60 ml/min/1.73 m2 62/359 (17.3%) 83/362 (22.9%) 0.72 (0.45 to 1.16)
<60 ml/min/1.73 m2 29/246 (11.8%) 41/255 (16.1%) 0.72 (0.52 to 1.00)
Beta blocker
No 49/386 (12.7%) 67/388 (17.3%) 0.71 (0.49 to 1.03)
Yes 42/219 (19.2%) 57/229 (24.9%) 0.74 (0.50 to 1.10)
RAAS inhibitor
No 44/225 (19.6%) 60/254 (23.6%) 0.80 (0.54 to 1.18)
Yes 47/380 (12.4%) 64/363 (17.6%) 0.68 (0.47 to 0.99)
Diuretic therapy
No 17/164 (10.4%) 22/145 (15.2%) 0.66 (0.35 to 1.23)
Yes 74/441 (16.8%) 102/472 (21.6%) 0.75 (0.56 to 1.02)
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1.0
4.0
Dapagliflozin Better
Standard Care Better