ORIGINAL ARTICLE

# Dapagliflozin in Patients Undergoing Transcatheter Aortic-Valve Implantation

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## ABSTRACT

### BACKGROUND

Sodium–glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of heart-failure admission among high-risk patients. However, most patients with valvular heart disease, including those undergoing transcatheter aortic-valve implantation (TAVI), have been excluded from randomized trials.

### METHODS

We conducted this randomized, controlled trial in Spain to evaluate the efficacy of dapagliflozin (at a dose of 10 mg once daily) as compared with standard care alone in patients with aortic stenosis who were undergoing TAVI. All the patients had a history of heart failure plus at least one of the following: renal insufficiency, diabetes, or left ventricular systolic dysfunction. The primary outcome was a composite of death from any cause or worsening of heart failure, defined as hospitalization or an urgent visit, at 1 year of follow-up.

### RESULTS

A total of 620 patients were randomly assigned to receive dapagliflozin and 637 to receive standard care alone after TAVI; after exclusions, a total of 1222 patients were included in the primary analysis. A primary-outcome event 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=0.02). Death from any cause 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 of heart failure occurred in 9.4% and 14.4% of the patients, respectively (subhazard ratio, 0.63; 95% CI, 0.45 to 0.88). Genital infection and hypotension were significantly more common in the dapagliflozin group.

### CONCLUSIONS

Among older adults with aortic stenosis undergoing TAVI who were at high risk for heart-failure events, dapagliflozin resulted in a significantly lower incidence of death from any cause or worsening of heart failure than standard care alone. (Funded by Instituto de Salud Carlos III and others; ClinicalTrials.gov number, NCT04696185.)

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

Sodium–glucose cotransporter 2 (SGLT2) inhibitors have been shown to be effective in reducing heart-failure–related admissions across a wide spectrum of high-risk patients.[7-14] Both U.S. and European clinical practice guidelines recommend the use of SGLT2 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.

Most patients with severe valvular heart disease and those undergoing transcatheter interventions have been excluded from randomized, controlled trials investigating SGLT2 inhibitors.[17] Furthermore, patients who are undergoing TAVI are typically of advanced age,[18,19] and those who are older than 80 years of age are underrepresented in clinical trials evaluating SGLT2 inhibitors.[20] As a result, the frequency of prescriptions for SGLT2 inhibitors among older adults remains low. Given the limited evidence about the efficacy of SGLT2 inhibitors in older patients with aortic stenosis undergoing TAVI, we conducted the randomized, controlled DapaTAVI (Dapagliflozin in Patients Undergoing Transcatheter Aortic-Valve Implantation) trial to assess the efficacy and safety of dapagliflozin in this patient population.

## Methods

### Trial Oversight

The DapaTAVI trial was conducted at 39 centers across Spain. The trial was designed to assess the effectiveness of oral dapagliflozin (at a dose of 10 mg once daily) in patients with severe aortic stenosis undergoing TAVI. Details regarding the trial design and baseline characteristics of the patients have been reported previously and are available in the protocol with the full text of this article at NEJM.org.[21] This investigator-initiated clinical trial was financed by the Instituto de Salud Carlos III, the Gerencia Regional de Salud de la Junta de Castilla y León y Fondos, the Spanish Society of Cardiology, and the Galician Society of Cardiology.

The trial was designed and overseen by a steering committee. The protocol was approved by the Galician clinical research ethics committee, the Spanish Agency of Medicines and Medical Devices, and the institutional review board at each of the participating sites. The trial adhered to the principles outlined in the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines.

The first and last author, who had unrestricted access to the data, prepared the first draft of the manuscript, which was then revised by all the authors. The authors made the decision to submit the manuscript for publication 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 had a previous episode of aortic stenosis–related heart failure, including any hospitalization for heart failure or urgent heart-failure visit that led to the administration of an intravenous diuretic before TAVI and any of the following conditions: moderate renal insufficiency (estimated glomerular filtrate rate [eGFR], 25 to 75 ml per minute per 1.73 $m^2$ of body-surface area), diabetes mellitus, or a left ventricular ejection fraction of 40% or less. Exclusion criteria were any contraindication to dapagliflozin, current therapy with a sulfonylurea or SGLT2 inhibitor, a systolic blood pressure of less than 100 mm Hg, a diastolic blood pressure of less than 50 mm Hg, an eGFR of less than 25 ml per minute per 1.73 $m^2$, and chronic cystitis or recurrent urinary tract infection (≥2 in the past year). A complete list of the inclusion and exclusion criteria is provided in the Supplementary Appendix, available at NEJM.org. All the patients provided written informed consent.

### Trial Procedures

The patients were randomly assigned in a 1:1 ratio to receive either dapagliflozin (at a dose of 10 mg once daily) and standard care or standard

**Table 1. Characteristics of the Patients at Baseline.***

| Characteristic | Dapagliflozin (N=605) | Standard Care (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) |
| Previous 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 | | |
| Mean gradient — mm Hg‡ | 47.8±13.7 | 46.6±13.5 |
| Left ventricular ejection fraction | | |
| Percentage | 54.9±12.3 | 54.8±12.1 |
| Value ≤40% — no. (%) | 109 (18.0) | 103 (16.7) |
| Moderate or severe left ventricular hypertrophy — no. (%) | 368 (60.8) | 367 (59.4) |
| Mitral regurgitation of grade ≥3 — no. (%) | 99 (16.4) | 99 (16.0) |
| Laboratory data | | |
| Hemoglobin — g/dl§ | 11.9±1.7 | 12.0±1.7 |
| Estimated glomerular filtration rate | | |
| Mean — ml/min/1.73 $m^2$ of body-surface area¶ | 56.0±16.4 | 56.4±16.3 |
| Value of 25 to 75 ml/min/1.73 $m^2$ — no. (%) | 529 (87.4) | 555 (89.8) |
| NT-proBNP — pg/ml‖ | 6324.0±19,948.9 | 5301.1±6622.0 |
| In-hospital complications after TAVI — no./total no. (%) | | |
| Myocardial infarction | 2/605 (0.3) | 1/618 (0.2) |
| Stroke | 10/605 (1.7) | 15/618 (2.4) |
| New-onset bundle-branch block** | 151/471 (32.1) | 146/448 (32.6) |
| Pacemaker implantation†† | 105/544 (19.3) | 103/543 (19.0) |
| Post-TAVI aortic regurgitation grade ≥3 | 27/605 (4.5) | 37/618 (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-blocker | 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% because of rounding. Baseline variable data were available for all the patients except for the three variables that are footnoted (mean transaortic gradient, hemoglobin, and N-terminal pro–B-type natriuretic peptide [NT-proBNP]). P2Y12 denotes platelet P2Y12 receptor, and TAVI transcatheter aortic-valve implantation.

† Of the 618 patients who were assigned to the standard-care group in the intention-to-treat population, 1 was lost to follow-up.

‡ 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.

¶ The estimated glomerular filtrate rate was calculated according to the Chronic Kidney Disease Epidemiology Collaboration creatinine-based equation.

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

** Patients who had bundle-branch block before undergoing TAVI — 134 in the dapagliflozin group and 170 in the standard-care group — were not included in the new-onset analysis.

†† Patients who had undergone pacemaker implantation before TAVI — 61 in the dapagliflozin group and 75 in the standard-care group — were not included in the new-implantation analysis.

**Table 2. Primary, Secondary, and Other Outcomes.**

| Outcome | Dapagliflozin (N=605) | Standard Care (N=617) | Treatment Effect (95% CI)* |
|---|---|---|---|
| Primary composite outcome — no. (%) | 91 (15.0) | 124 (20.1) | 0.72 (0.55–0.95)†‡ |
| Components of the primary outcome — no. (%) | | | |
| Death from any cause | 47 (7.8) | 55 (8.9) | 0.87 (0.59–1.28)‡ |
| Worsening of 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 outcomes | | | |
| Death from cardiovascular causes — no. (%) | 27 (4.5) | 33 (5.3) | 0.81 (0.49–1.35)§ |
| Any hospitalization for heart failure or death from cardiovascular causes — no. (%) | 61 (10.1) | 85 (13.8) | 0.71 (0.51–0.98)§ |
| Total no. of hospitalizations for heart failure or deaths from cardiovascular causes | 79 | 121 | 0.67 (0.47–0.95)¶ |

* The widths of the confidence intervals for secondary outcomes have not been adjusted for multiple comparisons and should not be used in place of hypothesis testing.
† P=0.02 for the comparison of the dapagliflozin group with the standard-care group.
‡ The effect is reported as a hazard ratio as estimated with the use of a Cox proportional-hazards model.
§ The effect is presented as a subhazard ratio as calculated by means of a competing-risks model, with death from any cause and death from a noncardiovascular cause as the competing risks.
¶ The effect is presented as a rate ratio with the use of a negative binomial regression model.

care alone. Randomization was performed at the time of hospital discharge after TAVI (or within 14 days after discharge) with the use of a secure Web-based system. Randomization was stratified according to the presence or absence of diabetes mellitus, a left ventricular ejection fraction 40% or less, and an eGFR of 25 to 75 ml per minute per 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 months and 12 months after randomization through telephone interviews and a review of medical records and national vital statistics registries. Clinical outcomes were adjudicated externally by a clinical panel whose members were unaware of the trial-group assignments.

### OUTCOMES

The primary outcome was a composite of death from any cause or worsening of heart failure, with the latter defined as either hospitalization for heart failure or an urgent heart-failure visit leading to the administration of intravenous diuretics. Key secondary outcomes were the incidence of the individual components of the primary outcome, death from cardiovascular causes, a composite of hospitalization for heart failure or cardiovascular death, and the total number of repeat hospitalizations for heart failure. Safety end points — including symptomatic hypotension, major hypoglycemia, ketoacidosis, genital or urinary tract infection, necrotizing fasciitis, and nontraumatic amputation — were also reported. All other safety outcomes were based on adverse event reporting.

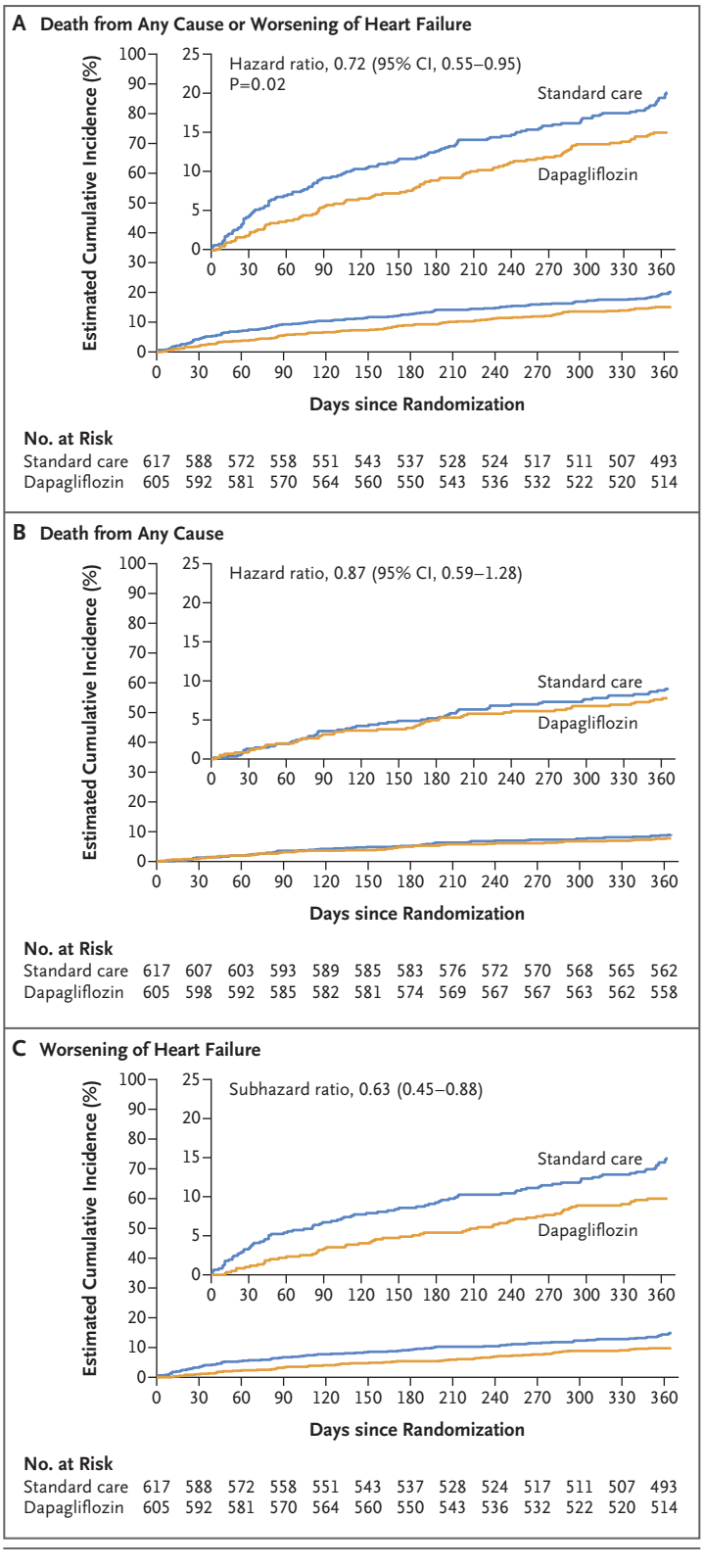
### STATISTICAL ANALYSIS

The trial was designed to have 80% power to detect a relative reduction of 30% in the risk of a primary-outcome event with dapagliflozin, as compared with standard therapy, at 1 year. This calculation was based on an assumption of an event rate of 30% per year in the standard-care group with an estimated loss to follow-up of 5%. The initial planned total sample size was 1020 patients (510 per group).

A prespecified, blinded interim analysis of the event rate for the primary outcome was per-

**Figure 1. Kaplan–Meier Estimates and Cumulative Incidence of the Primary Outcome and Its Components.**

Panel A shows the time until the composite primary outcome of death from any cause or worsening of heart failure; the latter was defined as either an unplanned hospitalization or an urgent medical visit. Panels B and C show the time until death from any cause and first worsening of heart failure, respectively. The insets show the same data on an expanded y axis. Hazard ratios and 95% confidence intervals were estimated with the use of 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.




formed 3 months before the end of recruitment. The data were evaluated by the data and safety monitoring board. In this interim analysis, we applied the Haybittle–Peto stopping rule, which mandates an early trial discontinuation only if a P value of 0.001 or less is observed without an alpha penalty. At the time of the blinded examination, the overall event rate at the end of the trial was projected to be lower than 25%, so the data and safety monitoring board recommended that the sample size be increased by 20% (i.e., by approximately 200 patients) to a total enrollment of 1220 patients.

The characteristics of the patients were assessed at the time of randomization and are reported as frequencies and percentages or means and standard deviations, as appropriate. Given that the missing data appeared to be evenly distributed between groups, we determined that data were most likely missing at random. For the primary analysis, no imputation of missing data was performed.

The primary outcome was assessed by means of the log-rank test and reported according to trial group with the use of Kaplan–Meier analysis. A Cox proportional-hazards model was used to estimate the treatment effect with the use of hazard ratios and their corresponding 95% confidence intervals. Data for all the patients without an event were censored at the end of the 1-year follow-up, whereas data for those who had withdrawn 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.

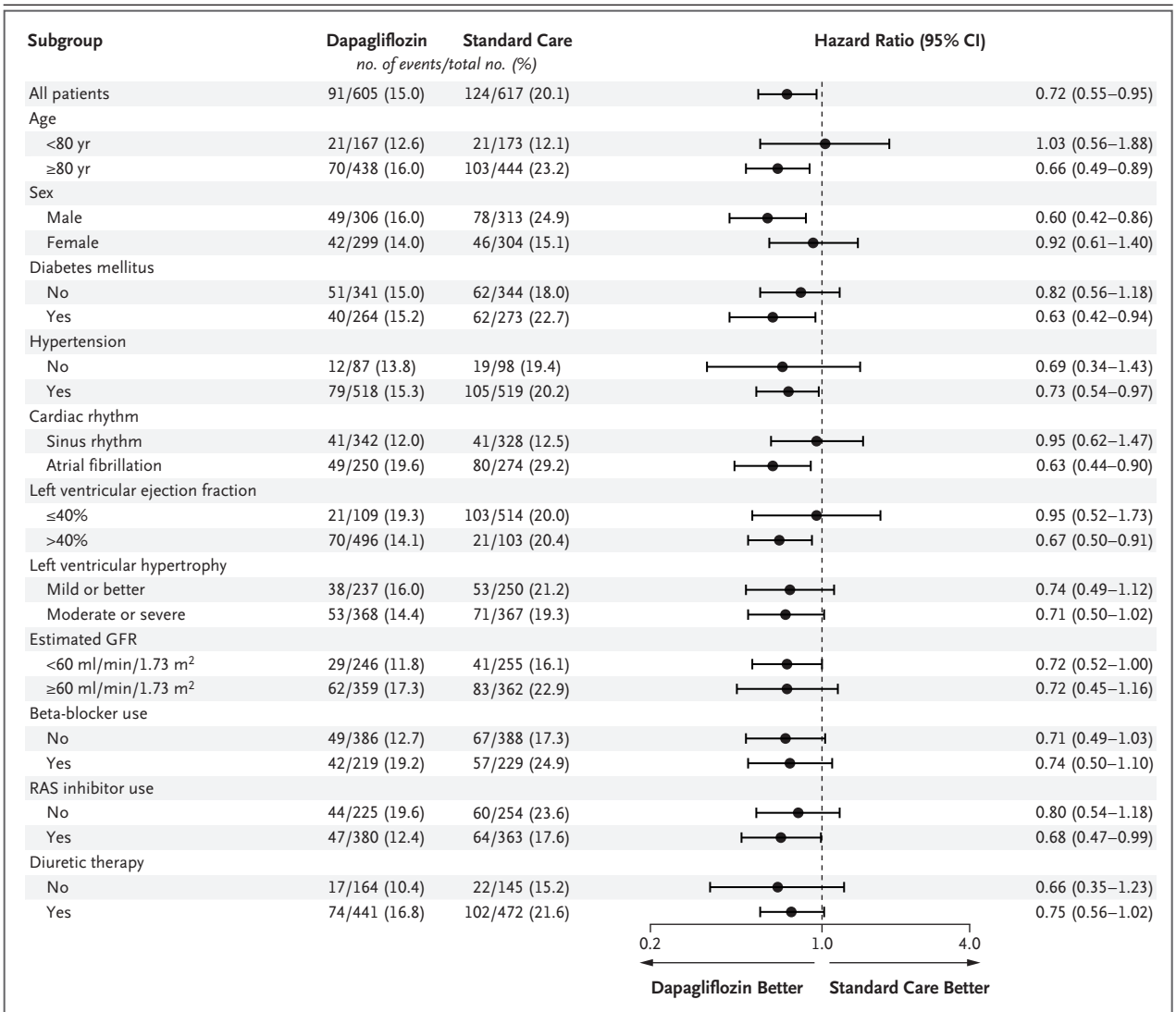



**Figure 2. Primary Outcome in Prespecified Subgroups.**

The forest plot shows the primary outcome (a composite of death from any cause or worsening of heart failure) in prespecified subgroups of patients. In the cardiac rhythm category, a rhythm other than sinus rhythm or atrial fibrillation was identified in 13 patients in the dapagliflozin group and in 15 patients in the standard-care group. The abbreviation eGFR denotes estimated glomerular filtration rate, and RAS renin–angiotensin system.

All secondary outcomes with the exception of the total number of heart-failure hospitalizations or cardiovascular deaths were evaluated by means of the same statistical approach that was used for the primary analysis. For outcomes that were subject to competing risks, we estimated the treatment effects using a competing-risks model with a direct-likelihood approach for the cause-specific cumulative incidence function, with the competing risk of death from any cause (for outcomes that did not include any calculation of cause-specific mortality) or death from noncardiovascular causes (for outcomes that included cardiovascular death).[22] Such results were presented as subhazard ratios with their corresponding 95% confidence intervals. 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 confidence inter-

**Table 3. Safety End Points.**

| End Point | Dapagliflozin (N=605) | Standard Care (N=617) | P Value |
|---|---|---|---|
| | *number (percent)* | | |
| Genitourinary infection | 94 (15.5) | 71 (11.5) | 0.04 |
| Genital infection | 11 (1.8) | 3 (0.5) | 0.03 |
| Urinary tract infection | 83 (13.7) | 68 (11.0) | 0.15 |
| Relevant urinary tract infection* | 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 | — |
| Major hypoglycemia | 4 (0.7) | 8 (1.3) | 0.26 |
| Necrotizing fasciitis | 0 | 0 | — |
| Nontraumatic amputation | 5 (0.8) | 4 (0.6) | 0.72 |
| Cancer | 30 (5.0) | 22 (3.6) | 0.23 |

* A relevant urinary tract infection was defined as one that led to hospital admission or was complicated by urinary sepsis.

vals have not been adjusted for multiplicity, so they may not be used in place of hypothesis testing.[23]

The primary analysis was performed according to the intention-to-treat principle. A prespecified analysis was performed on the per-protocol set of patients without trial-group crossovers; crossover data were censored at the time of the crossover.

A two-sided P value of 0.05 or less was considered to indicate statistical significance for all tests. All analyses were performed with the use of Stata software, version 16.1 (StataCorp).

## RESULTS

### PATIENTS

From January 2021 through December 2023, a total of 1257 patients underwent randomization; 620 were assigned to receive dapagliflozin and 637 to receive standard care at 39 centers in Spain (Table S1 in the Supplementary Appendix). After exclusions because of randomization in error, withdrawal, or loss to follow-up, the primary intention-to-treat analysis included 605 patients in the dapagliflozin group and 617 in the standard-care group (Fig. S1).

The characteristics of the patients and their therapies at baseline appeared to be generally balanced between the groups, with the exception that the incidence of coronary artery disease and the mean N-terminal pro–B-type natriuretic peptide (NT-proBNP) level were both higher in the dapagliflozin group (Table 1 and Table S2). The mean (±SD) age of the patients was 82.4±5.6 years, and 49.4% of the patients were women. A total of 43.9% of the patients had diabetes mellitus, 17.0% had a left ventricular ejection fraction of 40% or less, and 88.6% had an eGFR of 25 to 75 ml per minute per 1.73 $m^2$. The mean eGFR was 56.2±16.4 ml per minute per 1.73 $m^2$. 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). In the dapagliflozin group, dapagliflozin treatment was stopped during follow-up in 103 patients (17.0%), whereas dapagliflozin treatment was initiated in 43 patients (7.0%) in the standard-care group for reasons other than heart failure. At the 1-year follow-up, adherence to the assigned trial therapy was reported in 496 patients (82.0%) in the dapagliflozin group and in 554 patients (89.8%) in the standard-care group. Only 1 patient in the standard-care group was lost to follow-up.

### OUTCOMES

The primary composite outcome of death from any cause or worsening of heart failure 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=0.02) (Table 2 and Fig. 1A). Death from any cause was reported in 47 patients (7.8%) in the dapagliflozin group and in 55 patients (8.9%) in the standard-care group (hazard ratio, 0.87; 95% CI, 0.59 to 1.28) (Fig. 1B). Worsening of heart failure occurred in 57 patients (9.4%) and 89 patients (14.4%) in the dapagliflozin and standard-care groups, respectively (subhazard ratio, 0.63; 95% CI, 0.45 to 0.88) (Fig. 1C).

With respect to the individual components of the outcome of worsening of heart failure, hospitalization for heart failure occurred in 45 patients (7.4%) in the dapagliflozin group and in 66 patients (10.7%) in the standard-care group (subhazard ratio, 0.68; 95% CI, 0.46 to 0.99); urgent visits for heart failure that resulted 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%) with dapagliflozin and in 33 patients (5.3%) with standard care (subhazard ratio, 0.81; 95% CI, 0.49 to 1.35). Causes of death are shown in Table S4.

Results appeared to be similar with the inclusion of patients who had undergone randomization in error without the performance of a competing-risk analysis (Table S5). Results appeared to be consistent with the primary findings in the per-protocol analysis (Fig. S3 and Table S6) and across prespecified subgroups (Fig. 2).

A secondary-composite-outcome event of hospitalization for heart failure or death from cardiovascular causes occurred in 61 patients (10.1%) in the dapagliflozin group and in 85 patients (13.8%) in the standard-care group (subhazard ratio, 0.71; 95% CI, 0.51 to 0.98) (Table 2 and Fig. S2). A total number of 79 recurrent heart-failure hospitalizations or cardiovascular deaths (52 hospitalizations for heart failure and 27 deaths from cardiovascular causes) occurred in 61 patients in the dapagliflozin group, and 121 total events (88 hospitalizations for heart failure and 33 deaths from cardiovascular causes) occurred in 85 patients in the standard-care group (rate ratio, 0.67; 95% CI, 0.47 to 0.95).

### SAFETY

Adverse events are listed in Table 3. The risks of nontraumatic amputation, major hypoglycemia, and cancer appeared to be balanced between the two groups. No cases of diabetic ketoacidosis were diagnosed in the trial population. Genital infection occurred in 1.8% of patients in the dapagliflozin group and in 0.5% of those in the standard-care group (P=0.03); hypotension occurred in 6.6% and 3.6%, respectively (P=0.01). No apparent between-group differences were reported in the frequency of urinary tract infection, bacteremia, or syncope. Adverse events (genital and urinary tract infections, bacteremia, and hypotension or syncope) led to a discontinuation of dapagliflozin in 37 patients (6.1%).

## DISCUSSION

Among patients with severe aortic stenosis undergoing TAVI who were at high risk for future heart-failure events, SGLT2 inhibition with dapagliflozin resulted in a 28% relative reduction in the risk of the composite outcome of death from any cause or worsening of heart failure, as compared with standard care alone. The effects on the incidence of a primary-outcome event appeared to be consistent across all prespecified subgroups, regardless of the presence or absence of renal insufficiency, diabetes, or left ventricular systolic dysfunction.

Patients with aortic stenosis who undergo TAVI have a risk of death or readmission for heart failure of approximately 20% during the first year after the intervention.[4,5] Our current findings extend the evidence from previous trials of SGLT2 inhibitors. By including older patients undergoing aortic-valve replacement, we found clinically relevant benefits of dapagliflozin in this patient population after TAVI. In the DapaHF[7] and DELIVER[8] clinical trials, dapagliflozin resulted in 30% and 21% reductions in the risk of worsening of heart failure, respectively, in a population of patients with reduced (≤40%) and midrange or preserved left ventricular ejection fraction. In the DECLARE–TIMI 58 trial,[9] dapagliflozin was associated with a 27% reduction in the risk of heart-failure hospitalization among patients with diabetes. Results from

our trial regarding the reduction in worsening of heart failure are consistent with the findings of the previous trials. SGLT2 inhibitors are known to promote natriuresis and glycosuria, thereby exerting a hemodynamic effect through a reduction in preload and afterload.[24]

Our current trial examined SGLT2 inhibitors in a population of older patients with a mean age of 82 years; 72% of the patients were older than 80 years, and more than 7% were older than 90 years. In randomized clinical trials evaluating the cardiovascular benefits of SGLT2 inhibitors, less than 10% of the patients were older than 75 years of age.[7-14] The mean age of patients enrolled in the DapaHF, DELIVER, and DECLARE-TIMI 58 trials was 66 years, 72 years, and 64 years, respectively.[7-9] The VERTIS-CV trial[25] involving patients with diabetes included a prespecified analysis among adults who were 65 years of age or older and a post hoc analysis involving 903 patients who were 75 years of age or older — analyses that showed cardiovascular and renal outcomes similar to those with another SGLT2 inhibitor, ertugliflozin, across all age groups.

Our results appear to confirm that SGLT2 inhibitors are safe in older patients and are associated with clinical benefits, which is important given the low frequency of prescriptions for SGLT2 inhibitors among older patients.[26] Another relevant aspect of our current trial is that almost half the patients were women. In previous trials of SGLT2 inhibitors, women have been underrepresented.[7-14] In the present trial, genital infection and hypotension were the most common adverse events associated with dapagliflozin. Although urinary tract infections were frequent, the incidence appeared to be similar in the two groups, findings that have been reported in previous clinical trials of SGLT2 inhibitors.[27] The incidence of bacteremia appeared to be similar in the two groups.

Our trial has several limitations. We used a pragmatic and open-label trial design and collected only limited effectiveness and safety data. Although masking of trial group was not implemented for patients and care providers, outcome events were adjudicated centrally by evaluators in a blinded manner. The observed event rate for death or worsening of heart failure was substantially lower than initially expected. However, after we observed an overall lower event rate in an interim analysis, we increased the sample size, which may have partially mitigated this limitation. The trial was conducted only in Spain. Data regarding race and ethnic group were not collected in the trial, but on the basis of general Spanish population data, it is expected that more than 90% of the patients were White.

Among patients with aortic stenosis undergoing TAVI who were at high risk for future heart-failure events, the addition of dapagliflozin therapy to standard care led to a lower incidence of a composite of death from any cause or worsening of heart failure than standard care alone.

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