The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 21, 2019 VOL. 381 NO. 21

# Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

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## ABSTRACT

### BACKGROUND

In patients with type 2 diabetes, inhibitors of sodium–glucose cotransporter 2 (SGLT2) reduce the risk of a first hospitalization for heart failure, possibly through glucose-independent mechanisms. More data are needed regarding the effects of SGLT2 inhibitors in patients with established heart failure and a reduced ejection fraction, regardless of the presence or absence of type 2 diabetes.

### METHODS

In this phase 3, placebo-controlled trial, we randomly assigned 4744 patients with New York Heart Association class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either dapagliflozin (at a dose of 10 mg once daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death.

### RESULTS

Over a median of 18.2 months, the primary outcome occurred in 386 of 2373 patients (16.3%) in the dapagliflozin group and in 502 of 2371 patients (21.2%) in the placebo group (hazard ratio, 0.74; 95% confidence interval [CI], 0.65 to 0.85; P<0.001). A first worsening heart failure event occurred in 237 patients (10.0%) in the dapagliflozin group and in 326 patients (13.7%) in the placebo group (hazard ratio, 0.70; 95% CI, 0.59 to 0.83). Death from cardiovascular causes occurred in 227 patients (9.6%) in the dapagliflozin group and in 273 patients (11.5%) in the placebo group (hazard ratio, 0.82; 95% CI, 0.69 to 0.98); 276 patients (11.6%) and 329 patients (13.9%), respectively, died from any cause (hazard ratio, 0.83; 95% CI, 0.71 to 0.97). Findings in patients with diabetes were similar to those in patients without diabetes. The frequency of adverse events related to volume depletion, renal dysfunction, and hypoglycemia did not differ between treatment groups.

### CONCLUSIONS

Among patients with heart failure and a reduced ejection fraction, the risk of worsening heart failure or death from cardiovascular causes was lower among those who received dapagliflozin than among those who received placebo, regardless of the presence or absence of diabetes. (Funded by AstraZeneca; DAPA-HF ClinicalTrials.gov number, NCT03036124.)

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*A complete list of DAPA-HF committee members and investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on September 19, 2019, at NEJM.org.

N Engl J Med 2019;381:1995-2008.
DOI: 10.1056/NEJMoa1911303

A Quick Take is available at NEJM.org

Large clinical trials involving patients with type 2 diabetes have shown that inhibitors of sodium–glucose cotransporter 2 (SGLT2) reduce the risk of hospitalization for heart failure.[1-4] Most patients in these trials did not have heart failure at baseline, so the benefit of treatment with an SGLT2 inhibitor largely reflected the prevention of incident heart failure. The reduction in the risk of hospitalization for heart failure was observed early after randomization, which raised the possibility of mechanisms of action that differed from those usually postulated to explain the cardiovascular benefits of glucose-lowering therapies.[5-9] In addition to diuretic and related hemodynamic actions of SGLT2 inhibitors, effects on myocardial metabolism, ion transporters, fibrosis, adipokines, and vascular function have also been proposed.[5-9] These actions, along with preservation of renal function, would also benefit patients with established heart failure, including those without diabetes, in whom SGLT2 inhibitors have not been tested.[4,10,11] We designed the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial to prospectively evaluate the efficacy and safety of the SGLT2 inhibitor dapagliflozin in patients with heart failure and a reduced ejection fraction, regardless of the presence or absence of diabetes.[12,13]

## Methods

### Trial Design and Oversight

The executive committee designed and oversaw the conduct and analysis of the trial in collaboration with the sponsor, AstraZeneca.[12,13] The trial was conducted and reported in accordance with the protocol and the statistical analysis plan, both of which are available with the full text of this article at NEJM.org. The trial was approved by the ethics committee at each center. The safety of patients in the trial was overseen by an independent data and safety monitoring committee. The analyses conducted by the sponsor were replicated by an independent academic group at the University of Glasgow. The first draft of the manuscript was prepared by the first author, who had unrestricted access to the data, and was reviewed and edited by all the authors. All 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

Eligibility requirements included an age of at least 18 years, an ejection fraction of 40% or less, and New York Heart Association (NYHA) class II, III, or IV symptoms. Patients were required to have a plasma level of N-terminal pro–B-type natriuretic peptide (NT-proBNP) of at least 600 pg per milliliter (or ≥400 pg per milliliter if they had been hospitalized for heart failure within the previous 12 months). Patients with atrial fibrillation or atrial flutter on baseline electrocardiography were required to have an NT-proBNP level of at least 900 pg per milliliter, regardless of their history of hospitalization for heart failure.

Patients were required to receive standard heart-failure device therapy (an implantable cardioverter–defibrillator, cardiac resynchronization therapy, or both) and standard drug therapy, including an angiotensin-converting–enzyme inhibitor, an angiotensin-receptor blocker, or sacubitril–valsartan plus a beta-blocker, unless such use was contraindicated or resulted in unacceptable side effects. In addition, the use of a mineralocorticoid receptor antagonist was encouraged. Drug doses were individually tailored, in accordance with guideline recommendations. Patients with type 2 diabetes continued to take their glucose-lowering therapies, but doses could be adjusted as required. Specifically, the dose of insulin and sulfonylurea could be reduced to minimize the risk of hypoglycemia (e.g., in patients with a glycated hemoglobin level of <7%).

Exclusion criteria included recent treatment with or unacceptable side effects associated with an SGLT2 inhibitor, type 1 diabetes mellitus, symptoms of hypotension or a systolic blood pressure of less than 95 mm Hg, and an estimated glomerular filtration rate (eGFR) below 30 ml per minute per 1.73 $m^2$ of body-surface area (or rapidly declining renal function).

### Trial Procedures

All the patients provided written informed consent and entered a 14-day screening period, during which the trial inclusion and exclusion criteria were checked and baseline information gathered. After this screening, patients were randomly assigned to receive either dapagliflozin (at a dose of

10 mg once daily) or matching placebo, in accordance with the sequestered, fixed-randomization schedule, with the use of balanced blocks to ensure an approximate 1:1 ratio of the two regimens. Investigators used an interactive voice- or Web-response system to determine treatment assignment. Randomization was stratified on the basis of a diagnosis of type 2 diabetes (i.e., an established diagnosis or a glycated hemoglobin level of ≥6.5% [≥48 mmol per mole]) confirmed at screening.

Patients were evaluated at 14 days and 60 days after randomization, with a focus on assessment of heart failure and volume status, adverse events, and an evaluation of renal function and potassium levels. Additional trial visits were scheduled at 4 months and at 4-month intervals thereafter (Fig. S1 in the Supplementary Appendix, available at NEJM.org). The full schedule of assessments is provided in the trial protocol. Dapagliflozin or placebo was to be discontinued if pregnancy or diabetic ketoacidosis occurred. Dose reduction (to 5 mg daily of dapagliflozin or placebo) or temporary discontinuation was permitted in case of an acute, unexpected decline in the eGFR, volume depletion, or hypotension (or to avoid these conditions), with a subsequent increase in dose or restarting of treatment, if possible.

### OUTCOMES

The primary outcome was a composite of worsening heart failure or death from cardiovascular causes. An episode of worsening heart failure was either an unplanned hospitalization or an urgent visit resulting in intravenous therapy for heart failure.

A key secondary outcome was a composite of hospitalization for heart failure or cardiovascular death. The additional secondary outcomes were the total number of hospitalizations for heart failure (including repeat admissions) and cardiovascular deaths; the change from baseline to 8 months in the total symptom score on the Kansas City Cardiomyopathy Questionnaire, which is scored

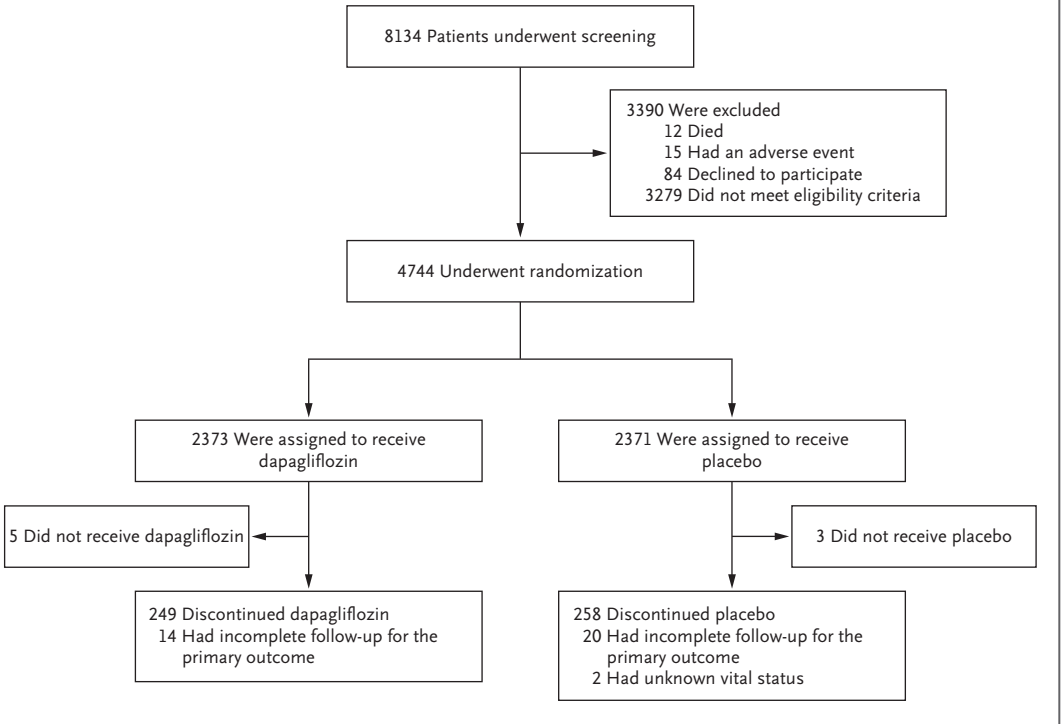


**Figure 1. Enrollment and Follow-up.**

All the patients who underwent randomization were included in the primary analysis. Patients who did not receive a dose of either dapagliflozin or placebo were excluded from the safety analysis.

on a scale from 0 to 100, with a higher score indicating fewer symptoms and a change of 5 or more points considered to be clinically meaningful[14]; a composite of worsening renal function, which was defined as a sustained decline in the eGFR of 50% or greater, end-stage renal disease (defined as a sustained [≥28 days] eGFR of <15 ml per minute per 1.73 $m^2$, sustained dialysis, or renal transplantation), or renal death; and death from any cause.[12] All outcomes were adjudicated by the members of a clinical-events committee, who were unaware of trial-group assignments, according to prespecified criteria (with definitions listed in the Supplementary Appendix).[15]

The prespecified safety analyses included serious adverse events, adverse events associated with the discontinuation of a trial treatment, adverse events of interest (i.e., volume depletion, renal events, major hypoglycemic events, bone fractures, diabetic ketoacidosis, and amputations), a diagnosis of Fournier's gangrene, and laboratory findings of note. Data on other adverse events were not routinely collected in view of the extensive previous collection of safety data regarding dapagliflozin.[3]

### STATISTICAL ANALYSIS

We calculated that 844 primary outcome events would provide the trial with a power of 90% to detect a hazard ratio of 0.80 for the comparison between dapagliflozin and placebo, using a two-sided alpha level of 0.05. With an expected annual event incidence of 11% in the placebo group, we estimated that the enrollment of approximately 4500 patients would provide the required number of primary events, based on an anticipated recruitment period of 18 months and an average follow-up period of approximately 24 months. We used a closed testing procedure, with prespecified hierarchical testing of the primary and secondary outcomes. The type I error was controlled at a two-sided alpha level of 0.0499 for multiple comparisons across primary and secondary outcomes, with one interim efficacy analysis taken into account.

We included data from all the patients who had undergone randomization in the analyses of the primary and secondary outcomes, according to the intention-to-treat principle. Baseline characteristics were summarized as means and standard deviations, medians and interquartile ranges, or percentages. We used a mixed model for repeated measurement to analyze longitudinal measures (e.g., glycated hemoglobin level and body weight) and estimated the least-squares mean differences between treatment groups, together with 95% confidence intervals. Time-to-event data were evaluated with the use of Kaplan–Meier estimates and Cox proportional-hazards models, stratified according to diabetes status, with a history of hospitalization for heart failure and treatment-group assignment as fixed-effect factors; for the renal outcome, the baseline eGFR was included instead of a history of hospitalization for heart failure. We used the Cox models to calculate hazard ratios, 95% confidence intervals, and two-sided P values and used a semiparametric proportional-rates model to calculate total (including recurrent) events.[16]

We analyzed the total symptom score on the Kansas City Cardiomyopathy Questionnaire as a composite, rank-based outcome, incorporating patient vital status at 8 months along with a change in score from baseline to 8 months in surviving patients, using the rank analysis of covariance method, with a corresponding win ratio used to estimate the magnitude of treatment effect.[17] We assessed the consistency of the treatment effect among 14 prespecified subgroups. The safety analyses were performed in patients who had undergone randomization and received at least one dose of dapagliflozin or placebo. We used Fisher's exact test to compare the incidence of adverse events. All the analyses were performed with the use of Stata software, version 15 (StataCorp) and R, version 3.5.1 (R Foundation for Statistical Computing).

## RESULTS

### PATIENTS

From February 15, 2017, through August 17, 2018, a total of 4744 patients were randomly assigned to receive either dapagliflozin or matching placebo at 410 centers in 20 countries (Fig. 1). The characteristics of the patients and the therapies for heart failure were well balanced between the trial groups at baseline (Table 1). At screening, 42% of the patients in each trial group had a history of type 2 diabetes, and an additional 3%

of the patients in each group received a new diagnosis of diabetes.

Dapagliflozin was stopped for reasons other than death in 249 patients and placebo was stopped in 258 patients (10.5% vs. 10.9%, P=0.71). At the last assessment, 2039 of the patients who were still taking dapagliflozin (98.1%) continued to receive the 10-mg daily dose; 1993 patients (98.2%) were receiving the equivalent dose of placebo. No patients in the dapagliflozin group and 2 patients in the placebo group had unknown vital status at the end of the trial (Fig. 1). The median duration of follow-up was 18.2 months (range, 0 to 27.8).

### OUTCOMES

The primary composite outcome of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or death from cardiovascular causes occurred in 386 patients (16.3%) in the dapagliflozin group and in 502 patients (21.2%) in the placebo group (hazard ratio, 0.74; 95% confidence interval [CI], 0.65 to 0.85; P<0.001) (Table 2 and Fig. 2A).

Event rates for all three components of the composite outcome favored dapagliflozin; the largest number of events of worsening heart failure were hospitalizations. Of the patients receiving dapagliflozin, 231 (9.7%) were hospitalized for heart failure, as compared with 318 patients (13.4%) receiving placebo (hazard ratio, 0.70; 95% CI, 0.59 to 0.83) (Fig. 2B). Death from cardiovascular causes occurred in 227 patients (9.6%) who received dapagliflozin and in 273 (11.5%) who received placebo (hazard ratio, 0.82; 95% CI, 0.69 to 0.98) (Fig. 2C). During the trial period, the number of patients who would need to have been treated with dapagliflozin to prevent one primary event was 21 (95% CI, 15 to 38).

The incidence of the secondary composite outcome of hospitalization for heart failure or death from cardiovascular causes was lower in the dapagliflozin group than in the placebo group (hazard ratio, 0.75; 95% CI, 0.65 to 0.85; P<0.001) (Table 2). There were 567 total first and recurrent events (340 hospitalizations for heart failure and 227 deaths from cardiovascular causes in 382 patients) in the dapagliflozin group and 742 total events (469 hospitalizations for heart failure and 273 deaths from cardiovascular causes in 495 patients) in the placebo group, which resulted in a rate ratio of 0.75 (95% CI, 0.65 to 0.88; P<0.001).

The increase in the total symptom score on the Kansas City Cardiomyopathy Questionnaire (indicating fewer symptoms) was greater in the dapagliflozin group than in the placebo group between baseline and month 8 (Table 2). More patients in the dapagliflozin group than in the placebo group had an increase of at least 5 points (the minimally important difference) in the total score (58.3% vs. 50.9%; odds ratio, 1.15; 95% CI, 1.08 to 1.23) and fewer had significant deterioration (25.3% vs. 32.9%; odds ratio, 0.84; 95% CI, 0.78 to 0.90; P<0.001 for both comparisons). The incidence of the prespecified renal composite outcome did not differ between the treatment groups (Table 2).

A total of 276 patients (11.6%) in the dapagliflozin group and 329 patients (13.9%) in the placebo group died from any cause (hazard ratio, 0.83; 95% CI, 0.71 to 0.97) (Fig. 2D). Details regarding the analysis of deaths and hospitalizations for heart failure are summarized in Figure S2.

The effect of dapagliflozin on the primary outcome was generally consistent across prespecified subgroups, including in patients without diabetes at baseline, although the patients in NYHA functional class III or IV appeared to have less benefit than those in class II (Fig. 3). In a post hoc subgroup analysis involving patients taking sacubitril–valsartan at baseline, the hazard ratio for the comparison of dapagliflozin and placebo for the primary outcome was 0.75 (95% CI, 0.50, 1.13), as compared with 0.74 (95% CI, 0.65 to 0.86) among those not taking sacubitril–valsartan.

Changes from baseline to 8 months in values for glycated hemoglobin, hematocrit, creatinine, NT-proBNP, systolic blood pressure, and weight are shown in Table 2.

### SAFETY

A total of 8 patients (5 in the dapagliflozin group and 3 in the placebo group) were excluded from the safety analyses because they did not receive dapagliflozin or placebo (Table 2). Serious adverse events related to volume depletion occurred in 29 patients (1.2%) in the dapagliflozin group and in 40 patients (1.7%) in the placebo group (P=0.23). Serious renal adverse events occurred in 38 patients (1.6%) in the

dapagliflozin group and in 65 patients (2.7%) in the placebo group (P=0.009). Adverse events rarely led to a discontinuation of treatment. All serious adverse events are listed in Table S1; there was no notable excess of any event in the dapagliflozin group.

## DISCUSSION

In this randomized, placebo-controlled trial involving patients with heart failure and a reduced left ventricular ejection fraction, the risk of the primary composite outcome of worsening heart

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

| Characteristic | Dapagliflozin (N=2373) | Placebo (N=2371) |
|---|---|---|
| Age — yr | 66.2±11.0 | 66.5±10.8 |
| Female sex — no. (%) | 564 (23.8) | 545 (23.0) |
| Body-mass index† | 28.2±6.0 | 28.1±5.9 |
| Race — no. (%)‡ | | |
| White | 1662 (70.0) | 1671 (70.5) |
| Black | 122 (5.1) | 104 (4.4) |
| Asian | 552 (23.3) | 564 (23.8) |
| Other | 37 (1.6) | 32 (1.3) |
| Region — no. (%) | | |
| North America | 335 (14.1) | 342 (14.4) |
| South America | 401 (16.9) | 416 (17.5) |
| Europe | 1094 (46.1) | 1060 (44.7) |
| Asia–Pacific | 543 (22.9) | 553 (23.3) |
| NYHA functional classification — no. (%) | | |
| II | 1606 (67.7) | 1597 (67.4) |
| III | 747 (31.5) | 751 (31.7) |
| IV | 20 (0.8) | 23 (1.0) |
| Heart rate — beats/min | 71.5±11.6 | 71.5±11.8 |
| Systolic blood pressure — mm Hg | 122.0±16.3 | 121.6±16.3 |
| Left ventricular ejection fraction — % | 31.2±6.7 | 30.9±6.9 |
| Median NT-proBNP (IQR) — pg/ml | 1428 (857–2655) | 1446 (857–2641) |
| Principal cause of heart failure — no. (%) | | |
| Ischemic | 1316 (55.5) | 1358 (57.3) |
| Nonischemic | 857 (36.1) | 830 (35.0) |
| Unknown | 200 (8.4) | 183 (7.7) |
| Medical history — no. (%) | | |
| Hospitalization for heart failure | 1124 (47.4) | 1127 (47.5) |
| Atrial fibrillation | 916 (38.6) | 902 (38.0) |
| Diabetes mellitus§ | 993 (41.8) | 990 (41.8) |
| Estimated GFR | | |
| Mean — ml/min/1.73 $m^2$ | 66.0±19.6 | 65.5±19.3 |
| Rate of <60 ml/min/1.73 $m^2$ — no./total no. (%) | 962/2372 (40.6) | 964/2371 (40.7) |
| Device therapy — no. (%) | | |
| Implantable cardioverter–defibrillator¶ | 622 (26.2) | 620 (26.1) |
| Cardiac resynchronization therapy‖ | 190 (8.0) | 164 (6.9) |

**Table 1. (Continued.)**

| Characteristic | Dapagliflozin (N=2373) | Placebo (N=2371) |
|---|---|---|
| Heart failure medication — no. (%) | | |
| Diuretic | 2216 (93.4) | 2217 (93.5) |
| ACE inhibitor | 1332 (56.1) | 1329 (56.1) |
| ARB | 675 (28.4) | 632 (26.7) |
| Sacubitril–valsartan | 250 (10.5) | 258 (10.9) |
| Beta-blocker | 2278 (96.0) | 2280 (96.2) |
| Mineralocorticoid receptor antagonist | 1696 (71.5) | 1674 (70.6) |
| Digitalis | 445 (18.8) | 442 (18.6) |
| Glucose-lowering medication — no./total no. (%)** | | |
| Biguanide | 504/993 (50.8) | 512/990 (51.7) |
| Sulfonylurea | 228/993 (23.0) | 210/990 (21.2) |
| DPP-4 inhibitor | 161/993 (16.2) | 149/990 (15.1) |
| GLP-1 receptor agonist | 11/993 (1.1) | 10/990 (1.0) |
| Insulin | 274/993 (27.6) | 266/990 (26.9) |

* Plus–minus values are means ±SD. There were no significant differences between the two groups for any variable. Percentages may not total 100 because of rounding. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, DPP-4 dipeptidyl peptidase 4, GFR glomerular filtration rate, GLP-1 glucagon-like peptide 1, IQR interquartile range, NT-proBNP N-terminal pro–B-type natriuretic peptide, and NYHA New York Heart Association.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Race was reported by the investigators.
§ An additional 82 patients in the dapagliflozin group and 74 in the placebo group had previously undiagnosed diabetes, which was defined as a glycated hemoglobin level of 6.5% or greater (≥48 mmol per mole), as measured in a central laboratory at both screening and randomization.
¶ This category includes either an implantable cardioverter–defibrillator or cardiac resynchronization therapy with a defibrillator.
‖ This category includes cardiac resynchronization therapy with or without a defibrillator.
** Glucose-lowering medications are listed only for the patients who had a history of diabetes at baseline.

failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or death from cardiovascular causes was lower in the dapagliflozin group than in the placebo group. Each of the three components of the composite outcome was less common in the dapagliflozin group, as were the total numbers of hospitalizations for heart failure and deaths from cardiovascular causes. The use of dapagliflozin also resulted in fewer symptoms of heart failure, as measured on the Kansas City Cardiomyopathy Questionnaire. The observed benefits, which were substantial and clinically significant, occurred early after randomization and were seen in patients who were receiving other recommended therapies for heart failure.

Dapagliflozin was as effective in the 55% of patients without type 2 diabetes as in those with diabetes. This demonstration of the cardiovascular benefits of an SGLT2 inhibitor in patients without diabetes provides support for prior suggestions that such treatment has beneficial actions other than glucose lowering.[4-11] Thus, our findings potentially extend the therapeutic role of dapagliflozin beyond patients with diabetes.

The lowering of the risk of the primary outcome was generally consistent across the other prespecified subgroups, although one comparison suggested possible heterogeneity, with less treatment benefit in patients in NYHA functional class III or IV than in class II. However, findings with respect to other subgroups that also reflected more advanced disease (e.g., more reduced ejection fraction, worse renal function, and an increased NT-proBNP level) were not consistent with the finding regarding the NYHA class.

Our population was distinct from the patients in previous trials of SGLT2 inhibitors, since our patients were at much higher risk for hospitalization for heart failure and for death from car-

**Table 2. Primary and Secondary Cardiovascular Outcomes and Adverse Events of Special Interest.***

| Variable | Dapagliflozin (N=2373) | | Placebo (N=2371) | | Hazard or Rate Ratio or Difference (95% CI) | P Value |
|---|---|---|---|---|---|---|
| | *values* | *events/100 patient-yr* | *values* | *events/100 patient-yr* | | |
| **Efficacy outcomes** | | | | | | |
| Primary composite outcome — no. (%)† | 386 (16.3) | 11.6 | 502 (21.2) | 15.6 | 0.74 (0.65 to 0.85) | <0.001 |
| Hospitalization or an urgent visit for heart failure | 237 (10.0) | 7.1 | 326 (13.7) | 10.1 | 0.70 (0.59 to 0.83) | NA |
| Hospitalization for heart failure | 231 (9.7) | 6.9 | 318 (13.4) | 9.8 | 0.70 (0.59 to 0.83) | NA |
| Urgent heart-failure visit | 10 (0.4) | 0.3 | 23 (1.0) | 0.7 | 0.43 (0.20 to 0.90) | NA |
| Cardiovascular death | 227 (9.6) | 6.5 | 273 (11.5) | 7.9 | 0.82 (0.69 to 0.98) | NA |
| Secondary outcomes | | | | | | |
| Cardiovascular death or heart-failure hospitalization — no. (%) | 382 (16.1) | 11.4 | 495 (20.9) | 15.3 | 0.75 (0.65 to 0.85) | <0.001 |
| Total no. of hospitalizations for heart failure and cardiovascular deaths‡ | 567 | — | 742 | — | 0.75 (0.65 to 0.88) | <0.001 |
| Change in KCCQ total symptom score at 8 mo§ | 6.1±18.6 | — | 3.3±19.2 | — | 1.18 (1.11 to 1.26) | <0.001 |
| Worsening renal function — no. (%)¶ | 28 (1.2) | 0.8 | 39 (1.6) | 1.2 | 0.71 (0.44 to 1.16) | NA |
| Death from any cause — no. (%) | 276 (11.6) | 7.9 | 329 (13.9) | 9.5 | 0.83 (0.71 to 0.97) | NA |
| **Safety outcomes**‖ | | | | | | |
| Discontinuation due to adverse event — no./total no. (%) | 111/2368 (4.7) | — | 116/2368 (4.9) | — | — | 0.79 |
| Adverse events of interest — no./total no. (%) | | | | | | |
| Volume depletion | 178/2368 (7.5) | — | 162/2368 (6.8) | — | — | 0.40 |
| Renal adverse event | 153/2368 (6.5) | — | 170/2368 (7.2) | — | — | 0.36 |
| Fracture | 49/2368 (2.1) | | 50/2368 (2.1) | — | — | 1.00 |
| Amputation | 13/2368 (0.5) | — | 12/2368 (0.5) | — | — | 1.00 |
| Major hypoglycemia** | 4/2368 (0.2) | — | 4/2368 (0.2) | — | — | NA |
| Diabetic ketoacidosis†† | 3/2368 (0.1) | — | 0 | — | — | NA |
| Fournier's gangrene | 0 | — | 1/2368 (<0.1) | — | — | NA |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Laboratory and other measures** | | | | | | |
| Change from baseline to 8 mo‡‡ | | | | | | |
| Glycated hemoglobin — %§§ | −0.21±1.14 | — | 0.04±1.29 | — | −0.24 (−0.34 to −0.13) | <0.001 |
| Creatinine — mg/dl | 0.07±0.24 | — | 0.04±0.25 | — | 0.02 (0.01 to 0.03) | <0.007 |
| Hematocrit — % | 2.31±3.90 | — | −0.19±3.81 | — | 2.41 (2.21 to 2.62) | <0.001 |
| NT-proBNP — pg/ml | −196±2387 | — | 101±2944 | — | −303 (−457 to −150) | <0.001 |
| Weight — kg | −0.88±3.86 | — | 0.10±4.09 | — | −0.87 (−1.11 to −0.62) | <0.001 |
| Systolic blood pressure — mm Hg | −1.92±14.92 | — | −0.38±15.27 | — | −1.27 (−2.09 to −0.45) | 0.002 |

* Plus–minus values are means ±SD. NA denotes not applicable because P values for efficacy outcomes are reported only for outcomes that were included in the hierarchical-testing strategy.

† The primary outcome was a composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or death from cardiovascular causes.

‡ The total number of hospitalizations for heart failure and cardiovascular deaths was analyzed by means of the semiparametric proportional-rates model, in which the treatment effect is reported as a rate ratio.

§ The total symptom score on the Kansas City Cardiomyopathy Questionnaire (KCCQ) range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure. The treatment effect is shown as a win ratio, in which a value greater than 1 indicates superiority.

¶ Worsening renal function is a composite outcome of a reduction of 50% or more in the estimated GFR sustained for at least 28 days, end-stage renal disease, or death from renal causes. End-stage renal disease was defined as an estimated GFR of less than 15 ml per minute per 1.73 $m^2$ that was sustained for at least 28 days, long-term dialysis treatment (sustained for ≥28 days), or kidney transplantation. Serious adverse events of acute kidney injury were reported in 23 patients (1.0%) in the dapagliflozin group and in 46 (1.9%) in the placebo group (P=0.007).

‖ The safety population included all the patients who had undergone randomization and received at least one dose of dapagliflozin or placebo.

** Major hypoglycemia was defined as hypoglycemia requiring the assistance of another person to actively administer carbohydrates or glucagon or to take other corrective action. All cases occurred in patients with diabetes at baseline.

†† All cases of diabetic ketoacidosis occurred in patients with diabetes at baseline.

‡‡ The between-group difference in laboratory and other measures is reported as the treatment effect.

§§ Glycated hemoglobin values are listed only for the patients with diabetes.

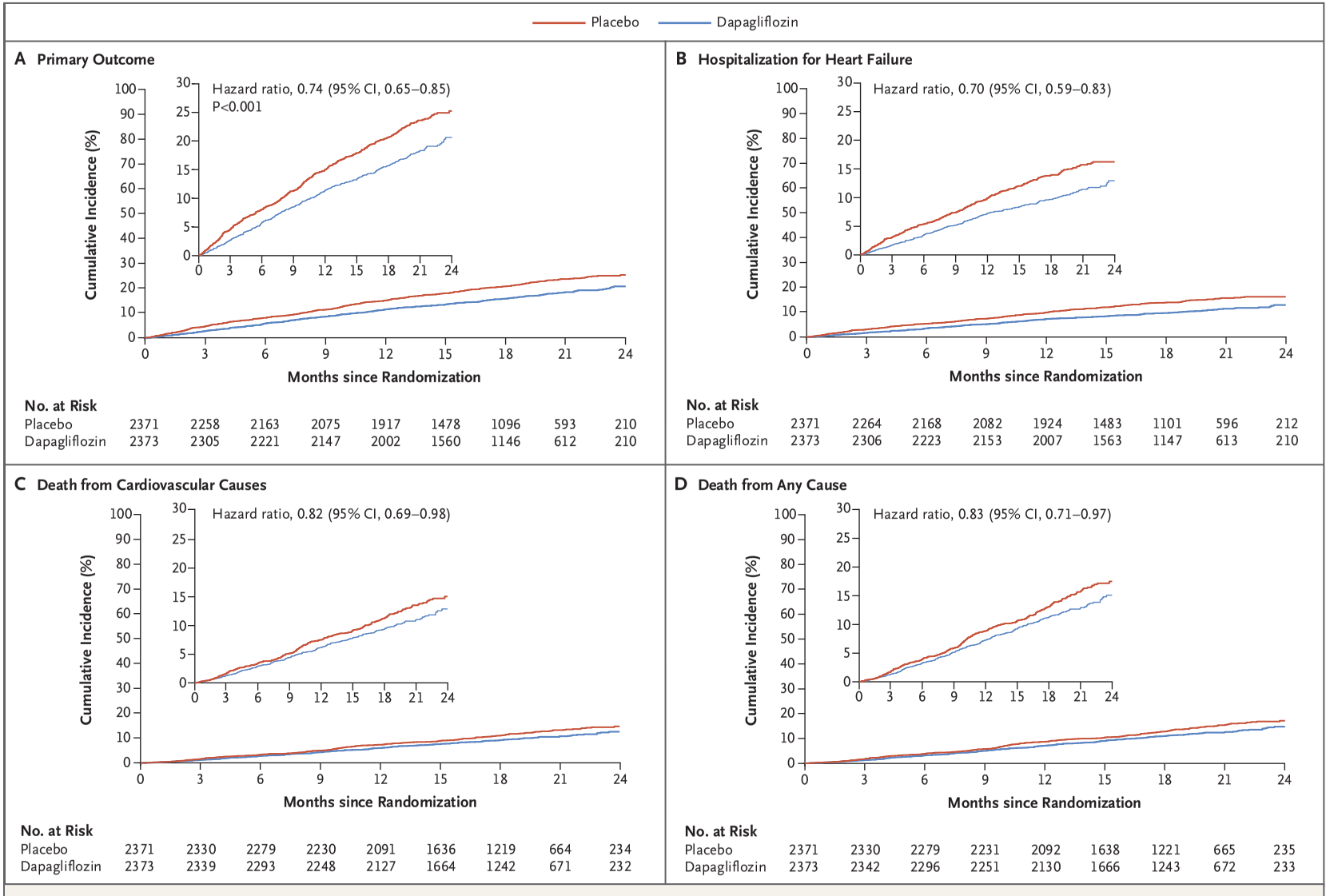


**Figure 2. Cardiovascular Outcomes.**

The primary outcome was a composite of death from cardiovascular causes, hospitalization for heart failure, or an urgent visit resulting in intravenous therapy for heart failure (Panel A). The cumulative incidences of the primary outcome, hospitalization for heart failure (Panel B), death from cardiovascular causes (Panel C), and death from any cause (Panel D) were estimated with the use of the Kaplan–Meier method; hazard ratios and 95% confidence intervals were estimated with the use of Cox regression models, stratified according to diabetes status, with a history of hospitalization for heart failure and treatment-group assignment as explanatory variables. Included in these analyses are all the patients who had undergone randomization. The graphs are truncated at 24 months (the point at which less than 10% of patients remained at risk). The inset in each panel shows the same data on an enlarged y axis.

| Subgroup | Dapagliflozin (N=2373) | Placebo (N=2371) | Hazard Ratio (95% CI) |
|---|---|---|---|
| | *no. of patients/total no.* | | |
| All patients | 386/2373 | 502/2371 | 0.74 (0.65–0.85) |
| Age | | | |
| ≤65 yr | 162/1032 | 196/998 | 0.78 (0.63–0.96) |
| >65 yr | 224/1341 | 306/1373 | 0.72 (0.60–0.85) |
| Sex | | | |
| Male | 307/1809 | 406/1826 | 0.73 (0.63–0.85) |
| Female | 79/564 | 96/545 | 0.79 (0.59–1.06) |
| Race | | | |
| White | 275/1662 | 348/1671 | 0.78 (0.66–0.91) |
| Black | 26/122 | 32/104 | 0.62 (0.37–1.04) |
| Asian | 78/552 | 118/564 | 0.64 (0.48–0.86) |
| Other | 7/37 | 4/32 | |
| Geographic region | | | |
| Asia | 77/543 | 114/553 | 0.65 (0.49–0.87) |
| Europe | 193/1094 | 218/1060 | 0.84 (0.69–1.01) |
| North America | 54/335 | 73/342 | 0.73 (0.51–1.03) |
| South America | 62/401 | 97/416 | 0.64 (0.47–0.88) |
| NYHA class | | | |
| II | 190/1606 | 289/1597 | 0.63 (0.52–0.75) |
| III or IV | 196/767 | 213/774 | 0.90 (0.74–1.09) |
| LVEF | | | |
| ≤Median | 222/1230 | 307/1239 | 0.70 (0.59–0.84) |
| >Median | 164/1143 | 195/1132 | 0.81 (0.65–0.99) |
| NT-proBNP | | | |
| ≤Median | 100/1193 | 155/1179 | 0.63 (0.49–0.80) |
| >Median | 286/1179 | 347/1191 | 0.79 (0.68–0.92) |
| Hospitalization for heart failure | | | |
| Yes | 195/1124 | 279/1127 | 0.67 (0.56–0.80) |
| No | 191/1249 | 223/1244 | 0.84 (0.69–1.01) |
| MRA at baseline | | | |
| Yes | 281/1696 | 361/1674 | 0.74 (0.63–0.87) |
| No | 105/677 | 141/697 | 0.74 (0.57–0.95) |
| Type 2 diabetes at baseline | | | |
| Yes | 215/1075 | 271/1064 | 0.75 (0.63–0.90) |
| No | 171/1298 | 231/1307 | 0.73 (0.60–0.88) |
| Atrial fibrillation or flutter on enrollment ECG | | | |
| Yes | 109/569 | 126/559 | 0.82 (0.63–1.06) |
| No | 277/1804 | 376/1812 | 0.72 (0.61–0.84) |
| Main cause of heart failure | | | |
| Ischemic | 223/1316 | 289/1358 | 0.77 (0.65–0.92) |
| Nonischemic or unknown | 163/1057 | 213/1013 | 0.71 (0.58–0.87) |
| Body-mass index | | | |
| <30 | 259/1537 | 320/1533 | 0.78 (0.66–0.92) |
| ≥30 | 127/834 | 182/838 | 0.69 (0.55–0.86) |
| Baseline eGFR (ml/min/1.73m$^2$) | | | |
| <60 | 191/962 | 254/964 | 0.72 (0.59–0.86) |
| ≥60 | 195/1410 | 248/1406 | 0.76 (0.63–0.92) |

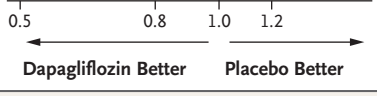


**Figure 3. Primary Composite Outcome, According to Prespecified Subgroup.**

Shown is the primary outcome of the trial — a composite of hospitalization for heart failure, an urgent visit resulting in intravenous therapy for heart failure, or death from cardiovascular causes — according to subgroups that were prespecified in the protocol. Race was reported by the investigators. The body-mass index is the weight in kilograms divided by the square of the height in meters. ECG denotes electrocardiography, eGFR estimated glomerular filtration rate, LVEF left ventricular ejection fraction, MRA mineralocorticoid receptor antagonist, NT-proBNP N-terminal pro–B-type natriuretic peptide, and NYHA New York Heart Association.

diovascular causes than many of the patients in the previous trials. Most of the patients in our trial were already being treated with a loop diuretic and a mineralocorticoid receptor antagonist, and we did not know whether dapagliflozin would cause the initial diuresis seen in other patient groups. We did not know whether such an effect might lead to volume depletion and worsening of renal function, since many of our patients had chronic kidney disease. As it turned out, neither of these adverse effects was common (each occurring in <8% of the patients, with no between-group difference), and serious renal adverse events were generally uncommon and significantly less frequent in the dapagliflozin group. Overall, few patients stopped dapagliflozin or placebo because of any adverse effect (<5% of the patients in either treatment group). Major hypoglycemia was rare, as was diabetic ketoacidosis, and both of these adverse events occurred only in patients with diabetes.

This trial has some limitations. We used specific inclusion and exclusion criteria, which may have limited the generalizability of our findings. Less than 5% of the patients were black, and relatively few were very elderly with multiple coexisting illnesses. The baseline use of sacubitril–valsartan, which is more effective than renin–angiotensin system blockade alone at reducing the incidence of hospitalization for heart failure and death from cardiovascular causes, was low.[18] However, the postulated mechanisms of action of SGLT2 inhibition and neprilysin inhibition are distinct, and in a post hoc subgroup analysis, the benefit of dapagliflozin was similar in patients treated with sacubitril–valsartan and in those who did not receive such treatment.[19,20]

Among patients with heart failure and a reduced ejection fraction, those who received the SGLT2 inhibitor dapagliflozin had a lower risk of worsening heart failure or death from cardiovascular causes and better symptom scores than those who received placebo, regardless of the presence or absence of diabetes.

Supported by AstraZeneca.

Dr. McMurray reports receiving fees (all fees listed paid to Glasgow University) for serving on a steering committee from Bayer, fees for serving on a steering committee, fees for serving on an end-point committee, and travel support from Cardiorentis, fees for serving on a steering committee and travel support from Amgen, fees for serving on a steering committee and travel support from Oxford University–Bayer, fees for serving as principal investigator of a trial and travel support from Theracos, fees for serving on a steering committee and travel support from AbbVie, fees for serving on a steering committee from DalCor Pharmaceuticals, fees for serving on a data and safety monitoring committee from Pfizer, fees for serving on a data and safety monitoring committee from Merck, fees for serving on an executive committee, fees for serving as co-principal investigator of a trial, fees for serving on a steering committee, fees for serving on an executive committee, travel support, and advisory board fees from Novartis, fees for serving as co-principal investigator for a trial, fees for serving on a steering committee, and travel support from GlaxoSmithKline, fees for serving on a steering committee from Bristol-Myers Squibb, and fees for serving on a steering committee, fees for serving on an end-point adjudication committee, and travel support from Vifor Pharma–Fresenius; Dr. Solomon, receiving grant support and consulting fees (all fees listed paid to Brigham and Women's Hospital) from Alnylam Pharmaceuticals, Amgen, AstraZeneca, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, MyoKardia, Novartis, Theracos, Bayer, and Cytokinetics, grant support from Bellerophon Therapeutics, Celladon, Ionis Pharmaceuticals, Lonestar Heart, Mesoblast, Sanofi Pasteur, and Eidos Therapeutics, consulting fees from Akros Pharma, Corvia Medical, Ironwood Pharma, Merck, Roche, Takeda Pharmaceutical, Quantum Genomics, AOBiome, Cardiac Dimensions, Tenaya Therapeutics, and Daiichi Sankyo, and fees for serving on a data and safety monitoring board from Janssen; Dr. Inzucchi, receiving advisory fees from AstraZeneca and Zafgen, lecture fees, consulting fees, fees for serving as a clinical-trial publications committee member, reimbursement for medical writing, and travel support from Boehringer Ingelheim, fees for serving on a steering committee and travel support from Sanofi–Lexicon, lecture fees, consulting fees, and travel support from Merck, and advisory fees and travel support from vIv Therapeutics and Abbott–Alere; Dr. Køber, receiving lecture fees from Novartis and Bristol-Myers Squibb; Dr. Kosiborod, receiving grant support, honoraria, and research support from AstraZeneca, grant support and honoraria from Boehringer Ingelheim, and honoraria from Sanofi, Amgen, Novo Nordisk, Merck (Diabetes), Eisai, Janssen, Bayer, GlaxoSmithKline, Glytec, Intarcia Therapeutics, Novartis, Applied Therapeutics, Amarin, and Eli Lilly; Dr. Ponikowski, receiving consulting fees, fees for serving on a speakers bureau, and fees (paid to himself and to his institution) for serving as an investigator and steering or executive committee member for clinical trials from Boehringer Ingelheim, lecture fees from Pfizer, fees (paid to himself and to his institution) for serving as an investigator and steering or executive committee member for clinical trials from Amgen, grant support (paid to his institution), fees for serving on a speakers bureau, consulting fees, and fees (paid to himself and to his institution) for serving as an investigator and steering or executive committee member for clinical trials from Vifor Pharma, fees for serving on a speakers bureau and consulting fees from Servier, fees for serving on a speakers bureau, consulting fees, and fees (paid to himself and to his institution) for serving as an investigator and steering or executive committee member for clinical trials from Bayer, fees for serving on a speakers bureau, consulting fees, and fees (paid to himself and to his institution) for serving as an investigator and steering or executive committee member for clinical trials from Bristol-Myers Squibb, fees for serving on a speakers bureau and consulting fees from Respicardia, fees for serving on a speakers bureau from Berlin-Chemie, fees for serving on a speakers bureau, consulting fees, and fees (paid to himself and to his institution) for serving as an investigator and steering or executive committee member for clinical trials from Cibiem, fees for serving on a speakers bureau, consulting fees, and fees (paid to himself and to his institution) for serving as an investigator and steering or executive committee member for clinical trials from Novartis, and fees for serving on a speakers bureau, consulting fees, and fees (paid to himself and to his institution) for serving

as an investigator and steering or executive committee member for clinical trials from RenalGuard; Dr. Sabatine, receiving grant support (paid to Brigham and Women's Hospital) and consulting fees from Amgen, AstraZeneca, Intarcia Therapeutics, Janssen Research and Development, the Medicines Company, MedImmune, Merck, and Novartis, receiving consulting fees from Anthos Therapeutics, Bristol-Myers Squibb, CVS Caremark, DalCor Pharmaceuticals, Dyrnamix, Esperion, IFM Therapeutics, and Ionis Pharmaceuticals, receiving grant support (paid to Brigham and Woman's Hospital) from Bayer, Daiichi Sankyo, Eisai, GlaxoSmithKline, Pfizer, Poxel, Quark Pharmaceuticals, and Takeda Pharmaceutical, and serving as a member of the TIMI Study Group, which receives grant support (paid to Brigham and Women's Hospital) from Abbott, Aralez Pharmaceuticals, Roche, and Zora Biosciences; Dr. Anand, receiving fees for serving as United States national leader of a trial from AstraZeneca, fees for serving on a steering committee from ARCA Biopharma, Amgen, LivaNova, and Novartis, fees for serving on an end-point committee from Boehringer Ingelheim, fees for serving as chair of a data and safety monitoring board from Boston Scientific, and advisory board fees from Zensun; Dr. Bělohlávek, receiving advisory board fees from Novartis and Pfizer and lecture fees from Getginge; Dr. Böhm, receiving lecture fees from Amgen, Bayer, Servier, Medtronic, Boehringer Ingelheim, Vifor Pharma, and Bristol-Myers Squibb, grant support and lecture fees from AstraZeneca, and grant support from Deutsche Forschungsgemeinschaft; Dr. Chiang, receiving honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi Sankyo, MSD, Novartis, Pfizer, and Sanofi; Dr. de Boer, receiving grant support (paid to University Medical Center Groningen [UMCG]), consulting fees, and lecture fees from AstraZeneca, grant support (paid to UMCG) from Bristol-Myers Squibb, grant support (paid to UMCG) and consulting fees from Abbott, grant support (paid to UMCG) and lecture fees from Roche, and consulting fees from MandalMed and being a minority shareholder in scPharmaceuticals; Dr. Desai, receiving consulting fees from Abbott, Biofourmis, Boston Scientific, Boehringer Ingelheim, DalCor Pharmaceuticals, and Regeneron, grant support (paid to Brigham and Women's Hospital) and consulting fees from Alnylam Pharmaceuticals and Novartis, and advisory board fees from Corvidia and Relypsa; Dr. Howlett, receiving grant support, consulting fees, and lecture fees from AstraZeneca, Boehringer Ingelheim, Novartis, and Servier, consulting fees and lecture fees from Novo Nordisk, consulting fees from Janssen, and grant support, consulting fees, lecture fees, and provision of drugs from Pfizer; Dr. Katova, receiving fees for serving as national coordinator of a trial from Novartis and AstraZeneca; Dr. Kitakaze, receiving grant support and lecture fees from Astellas Pharma, Sanofi, Pfizer, Ono Pharmaceutical, Novartis, and Mitsubishi Tanabe Pharma, lecture fees from Daiichi Sankyo, Bayer, Boehringer Ingelheim, Kowa Pharmaceutical, Sawai Pharmaceutical, MSD, Shionogi, Kureha, Taisho Toyama Pharmaceutical, Takeda Pharmaceutical, and Toa Eiyo, and manuscript fees from Japan Medical Data Center; Dr. Ljungman, receiving lecture fees and advisory board fees from AstraZeneca, lecture fees from Novartis, and advisory board fees from Pfizer; Dr. Merkely, receiving lecture fees from AstraZeneca, Sanofi Aventis, Servier, and Biotronik and grant support and lecture fees from Abbott and Medtronic; Dr. Nicolau, receiving consulting fees from Amgen, grant support from AstraZeneca, Bristol-Myers Squibb, CSL Behring, DalCor Pharmaceuticals, Janssen, Novo Nordisk, and Vifor Pharma, grant support and fees for serving as principal investigator from Bayer, lecture fees from Daiichi Sankyo, grant support and consulting fees from Novartis, grant support, fees for serving as principal investigator, and advisory board fees from Sanofi, and lecture fees and advisory board fees from Servier; Dr. O'Meara, receiving fees for serving on a clinical trial (paid to her institution), consulting fees, and lecture fees from AstraZeneca, Bayer, Amgen, and Novartis, consulting fees from Merck, fees for serving on a clinical trial (paid to her institution) from American Regent, and consulting fees and lecture fees from Pfizer and Boehringer Ingelheim; Dr. Petrie, receiving lecture fees from AstraZeneca, Novartis, and Eli Lilly, grant support, advisory board fees, and fees for serving on an end-point committee from Boehringer Ingelheim, advisory board fees, lecture fees, and fees for serving on an end-point committee from Novo Nordisk, advisory board fees from Napp Pharmaceuticals, and fees for serving on an end-point committee from Takeda Pharmaceutical and Bayer; Dr. Tereshchenko, receiving lecture fees from Servier, Pfizer, Novartis, and Boehringer Ingelheim; Dr. Verma, receiving grant support, lecture fees, and advisory board fees from AstraZeneca, Boehringer Ingelheim, Bayer, Janssen, and Merck, lecture fees from Sun Pharmaceutical Industries and EOCI Pharmacomm, grant support and advisory board fees from Amgen, and lecture fees and advisory board fees from Sanofi and Eli Lilly; Dr. Held, receiving grant support, advisory board fees, and lecture fees from Bayer, grant support and advisory board fees from Boehringer Ingelheim, grant support from Bristol-Myers Squibb, advisory board fees from Coala Life, and fees for serving on a data and safety monitoring board (paid to his institution) from Idorsia; Dr. DeMets, receiving consulting fees from Frontier Science, Actelion, Bristol-Myers Squibb, Medtronic, Boston Scientific, GlaxoSmithKline, and Merck, and consulting fees and being owner of DL DeMets Consulting; Dr. Docherty, receiving grant support from Novartis; Dr. Jhund, receiving consulting fees, advisory board fees, and lecture fees from Novartis, advisory board fees from Cytokinetics, and grant support from Boehringer Ingelheim; Drs. Bengtsson and Sjöstrand, being employed by AstraZeneca; and Dr. Langkilde, being employed by and holding shares in AstraZeneca. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

## APPENDIX

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(M. Schou), Copenhagen; the Department of Medicine, Saarland University Hospital, Homburg–Saar, Germany (M.B.); Saint Luke's Mid America Heart Institute, University of Missouri, Kansas City (M.N.K.); National University of Cordoba, Cordoba (F.A.M.), and the Division of Cardiology, Instituto Cardiovascular de Buenos Aires, Buenos Aires (M.D.) — both in Argentina; Wroclaw Medical University, Wroclaw (P.P.), and the Department of Cardiology, Medical University of Lodz, Lodz (J.D.) — both in Poland; the Department of Cardiology, University of Minnesota, Minneapolis (I.S.A.); 2nd Department of Internal Medicine, Cardiovascular Medicine, General Teaching Hospital and 1st Faculty of Medicine, Charles University, Prague, Czech Republic (J.B.); the Division of Cardiology, Taipei Veterans General Hospital and National Yang-Ming University, Taipei, Taiwan (C.-E.C.); the Department of Cardiology, Medanta, Gurgaon, India (V.K.C.); the Department of Cardiology, University Medical Center and University of Groningen, Groningen, the Netherlands (R.A.B.); the 5th Department of Internal Medicine, Comenius University in Bratislava, Bratislava, Slovakia (A.D.); the Department of Cardiology, Shanghai Institute of Cardiovascular Disease and Zhongshan Hospital Fudan University, Shanghai, China (J.G.); Cumming School of Medicine and Libin Cardiovascular Institute, University of Calgary, Calgary, AB (J.G.H.), the Department of Cardiology, Montreal Heart Institute, Montreal (E.O.), and the Division of Cardiac Surgery, St. Michael's Hospital, University of Toronto, Toronto (S.V.) — all in Canada; Clinic of Cardiology, National Cardiology Hospital, Sofia, Bulgaria (T.K.); the Cardiovascular Division of Medicine, National Cerebral and Cardiovascular Center, Osaka, Japan (M.K.); the Department of Molecular and Clinical Medicine and Cardiology, Sahlgrenska Academy (C.E.A.L.), and AstraZeneca (O.B., M. Sjöstrand, A.M.L.), Gothenburg, and the Department of Medical Sciences, Cardiology, Uppsala Clinical Research Center, Uppsala University (C.H.), Uppsala — all in Sweden; the Heart and Vascular Center, Semmelweis University, Budapest, Hungary (B.M.); Instituto do Coracao, Hospital das Clinicas da Faculdade de Medicina, Universidade de São Paolo, São Paolo (J.C.N.); the Department of Internal Medicine, Tan Tao University, Tan Duc, Vietnam (P.N.V.); the Department of Myocardial Disease and Heart Failure, National Medical Research Center of Cardiology, Moscow (S.T.); and the Department of Biostatistics and Medical Informatics, University of Wisconsin, Madison (D.L.D.).

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