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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RobotReviewer report

Risk of bias table

trial	design	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment
Mcmurray JJ, 2019	RCT	+	+	+	+

Trial summaries

n	Participants	Interventions	Outcomes	punchline	finding
4744	patients with established heart failure, patients with heart failure, Patients with Heart Failure and Reduced Ejection Fraction, 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, 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, patients with diabetes	dapagliflozin, Dapagliflozin, placebo	Death from cardiovascular causes, worsening heart failure event, composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death, risk of worsening heart failure or death from cardiovascular causes, volume depletion, renal dysfunction, and hypoglycemia	The incidence of the prespecified renal compos- ite outcome did not differ between the treatment groups (Table 2).	‚Äï no diff

Characteristics of studies

Mcmurray JJ, 2019

Population	1. 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. 2. 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 pres- sure 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 rap- idly declining renal function). 3. 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.
Interventio n	1. 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. 2. Dose reduction (to 5 mg daily of dapagliflozin or pla- cebo) 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. 3. Fr action 10 mg once daily) or matching placebo, in accor- dance with the sequestered, fixed-randomization schedule, with the use of balanced blocks to en- sure an approximate 1:1 ratio of the two regimens.
Outcomes	1. 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 potassi- um levels. 2. na l o f m e dicine 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 mean- ingful 14 ; a composite of worsening renal func- tion, which was defined as a sustained decline in the eGFR of 50% or greater, end-stage renal disease (defined as a sustained [,â•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. 3. The additional secondary outcomes were the total number of hospitalizations for heart fail- ure (including repeat admissions) and cardiovascu- lar deaths; the change from baseline to 8 months in the total symptom score on the Kansas City Cardiomyopathy Questionnaire, which is scored All the patients who underwent randomization were included in the primary analysis.

Bias	Judgement	Support for judgement
Random sequence generation	low	1. Fr action 10 mg once daily) or matching placebo, in accor- dance with the sequestered, fixed-randomization schedule, with the use of balanced blocks to en- sure an approximate 1:1 ratio of the two regimens. 2. Patients From February 15, 2017, through August 17, 2018, a total of 4744 patients were randomly assigned to receive either dapagliflozin or matching pla- cebo at 410 centers in 20 countries (Fig. 1). 3. Randomization was stratified on the basis of a diagnosis of type 2 diabetes (i.e., an estab- lished diagnosis or a glycated hemoglobin level of ,â•6.5% [,â•48 mmol per mole]) confirmed at screening.
Allocation	low	1. Fr action 10 mg once daily) or matching placebo, in accor- dance

concealment		with the sequestered, fixed-randomization schedule, with the use of balanced blocks to en- sure an approximate 1:1 ratio of the two regimens. 2. Randomization was stratified on the basis of a diagnosis of type 2 diabetes (i.e., an estab- lished diagnosis or a glycated hemoglobin level of ,â•6.5% [,â•48 mmol per mole]) confirmed at screening. 3. The analyses conducted by the sponsor were replicated by an independent academic group at the Univer- sity of Glasgow.
Blinding of participants and personnel	low	1. Most of the patients in our trial were already being treated with a loop di- uretic and a mineralocorticoid receptor antago- nist, and we did not know whether dapagliflozin would cause the initial diuresis seen in other patient groups. 2. The safety analyses were performed in patients who had undergone randomization and received at least one dose of dapa- gliflozin or placebo. 3. Patients who did not receive a dose of either dapagliflozin or placebo were excluded from the safety analysis.
Blinding of outcome assessment	low	1. 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). 2. The safety of patients in the trial was overseen by an indepen- dent data and safety monitoring committee. 3. Most of the patients in our trial were already being treated with a loop di- uretic and a mineralocorticoid receptor antago- nist, and we did not know whether dapagliflozin would cause the initial diuresis seen in other patient groups.

References

1. Mcmurray JJ et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction N. Engl. J. Med. 2019. 21(23); 1995-2008 PMID: 19001508