NEJM Evidence

Published November 11, 2023
NEJM Evid 2024;3(2)
DOI: 10.1056/EVIDoa2300286

ORIGINAL ARTICLE

Dapagliflozin in Myocardial Infarction without Diabetes or Heart Failure

Stefan James, M.D., Ph.D.,[1,2] David Erlinge, M.D., Ph.D.,[3] Robert F. Storey, M.D., D.M.,[4,5] Darren K. McGuire, M.D.,[6,7] Mark de Belder, B.A. Cantab, M.B.B.S., M.A., M.D., F.R.C.P.,[8] Niclas Eriksson, Ph.D.,[1] Kasper Andersen, M.D., Ph.D.,[2,9] David Austin, M.D., F.R.C.P.,[10,11] Gabriel Arefalk, M.D., Ph.D.,[9,12] David Carrick, M.B.Ch.B., Ph.D., F.R.C.P.,[13,14] Robin Hofmann, M.D., Ph.D.,[15] Stephen P. Hoole, M.D., D.M.,[16] Daniel A. Jones, M.D., Ph.D.,[17,18] Kelvin Lee, M.R.C.P., Ph.D.,[19,20] Hans Tygesen, M.D., Ph.D.,[21,22] Peter A. Johansson, M.Sc.,[23] Anna Maria Langkilde, M.D., Ph.D.,[23] Wilhelm Ridderstråle, M.D., Ph.D.,[23] Ehsan Parvaresh Rizi, M.D., Ph.D.,[23] John Deanfield, C.B.E. F.Med.Sci. B.A. Hons. (Cantab), M.B., B.Chir., F.R.C.P., F.E.S.C., F.A.C.C.,[24] and Jonas Oldgren, M.D., Ph.D.,[1,2] for the DAPA-MI investigators*

Abstract

BACKGROUND In patients with acute myocardial infarction (MI), therapies that could further reduce the risk of adverse cardiovascular and metabolic outcomes are needed.

METHODS In this international registry-based, randomized, double-blind trial, patients without prior diabetes or chronic heart failure, presenting with acute MI and impaired left ventricular systolic function, were randomly assigned 10 mg of dapagliflozin or placebo, given once daily. The primary outcome was the hierarchical composite of death, hospitalization for heart failure, nonfatal MI, atrial fibrillation/flutter, type 2 diabetes mellitus, New York Heart Association Functional Classification at the last visit, and body weight decrease of 5% or greater at the last visit using the win ratio analysis method. The key secondary outcome was the same hierarchical composite excluding the body weight component.

RESULTS We enrolled 4017 patients of whom 2019 were assigned to dapagliflozin and 1998 to placebo. The analysis of the primary hierarchical composite outcome resulted in significantly more wins for dapagliflozin than for placebo (win ratio, 1.34; 95% confidence interval [CI], 1.20 to 1.50; P<0.001). The win ratio outcome, which was adopted in a change of analysis during trial performance because of low event accrual, was mainly driven by the added cardiometabolic outcomes. The composite of time to cardiovascular death/hospitalization for heart failure occurred in 50/2019 (2.5%) patients assigned to dapagliflozin and 52/1998 (2.6%) patients assigned to placebo (hazard ratio, 0.95; 95% CI, 0.64 to 1.40). The rates of other cardiovascular events were low, with differences between the groups not reaching nominal statistical significance. No safety concerns were identified.

A complete list of the DAPA-MI investigators is provided in the Supplementary Appendix, available at evidence.nejm.org.

The author affiliations are listed at the end of the article.

Dr. James can be contacted at Stefan.James@ucr.uu.se or at Uppsala Clinical Research Center, Dag Hammarskjölds väg 38, Box 6363, SE-751 85 Uppsala, Sweden.

CONCLUSIONS In patients with acute MI as noted above, after approximately 1 year of treatment with dapagliflozin there were significant benefits with regard to improvement in cardiometabolic outcomes but no impact on the composite of cardiovascular death or hospitalization for heart failure compared with placebo. (Funded by AstraZeneca; ClinicalTrial.gov number, NCT04564742.)

Introduction

The outcomes of patients with acute myocardial infarction (MI) have improved with consistent implementation of early invasive management, effective antiplatelet therapy, and use of evidence-based secondary prevention therapies.[1-3] However, in recent years improvements in prognosis have slowed, with limited new treatment options and continued high risk of cardiovascular and metabolic events.[4,5] Sodium-glucose cotransporter-2 (SGLT2) inhibitors have been shown to favorably affect a broad range of cardiovascular and metabolic parameters (i.e., cardiometabolic outcomes) including cardiovascular death, hospitalization for heart failure (HF), body weight reduction, and glucose levels in patients with type 2 diabetes with established or at high risk for atherosclerotic cardiovascular disease.[6-8] Reduction in cardiovascular death and hospitalization for HF have also been proven in patients with symptomatic chronic HF, with or without diabetes, across a wide range of left ventricular (LV) ejection fractions.[9-14]

We studied the effect of 10 mg of dapagliflozin once daily on a broad range of cardiometabolic outcomes when added to standard of care in patients hospitalized for MI with impaired LV systolic function, but without known diabetes or chronic symptomatic HF.

Methods

TRIAL DESIGN AND OVERSIGHT

We conducted the DAPA-MI (Dapagliflozin in patients with MI) trial as a registry-based, randomized, double-blind, placebo-controlled trial at 39 sites in Sweden and 64 sites in the United Kingdom.

The trial was originally designed to evaluate the effect of 10 mg of dapagliflozin versus placebo, given once daily in addition to standard of care therapy in patients hospitalized for MI and with impaired LV function without known diabetes or established HF on the composite of cardiovascular death and hospitalization for HF. We estimated that for a true hazard ratio of 0.80 between dapagliflozin and placebo, using a two-sided alpha of 0.0498, that 722 patients with primary end point events would provide a statistical power of 85% for the test of the primary composite end point. However, during the course of the trial, it became evident that the number of collected primary end point events of cardiovascular death and hospitalization for HF in our trial was substantially lower than anticipated, requiring an unfeasible sample size.[15] Thus, in February 2023, with no interim analysis other than a total blinded event count for the primary outcome, the trial was modified from an event-driven time-to-event approach, based on the total number of hospitalizations for HF and cardiovascular death events, to a hierarchical composite outcome approach to be analyzed with the win ratio method. The new hierarchical composite outcome included noncardiovascular death, investigator-reported HF event, nonfatal MI, atrial fibrillation/flutter, type 2 diabetes mellitus, New York Heart Association (NYHA) Functional Classification at the last visit, and body weight decrease of 5% or greater at the last visit, in addition to cardiovascular death and adjudicated hospitalization for HF, which were included in the original composite outcome.

Data were collected using two national population-based quality registries: the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART)[16] and the U.K.-based National Institute for Cardiovascular Research (NICOR) registries including the Myocardial Ischaemia National Audit Project (MINAP).[17] Further information on data management in DAPA-MI has been published previously[15] and is available in the Supplementary Appendix.

The DAPA-MI executive committee designed the trial and oversaw its conduct and analysis of the data in collaboration with the sponsor, AstraZeneca. Details of the original and updated trial design and methods have been described previously[15] and are provided in the protocol provided with the full text of this article, available at evidence.nejm.org. The trial and its modifications were approved by the Ethical Review Authority of each country (Swedish Ethical Review Authority Dnr 2020-03087, 2021-03037, 2022-00101-02, and 2023-01452-02; U.K. Research Ethics Committee reference number 20/NW/0312). Information

on the trial leadership, committees, and investigators is provided in the Supplementary Appendix. An independent data monitoring committee was responsible for assessing the safety of the intervention during the trial and reviewing the overall conduct of the trial. AstraZeneca provided the trial drug (dapagliflozin) and placebo. All results presented herein derive from analyses conducted by statisticians at Uppsala Clinical Research Center, Sweden. S.J., who had full access to the data, wrote the first draft of the manuscript and managed all revisions together with the executive committee, with no writing assistance from the sponsor. All authors vouch for the accuracy and completeness of the data, for the adherence of the trial to the trial protocol and statistical analysis plan, and for full reporting of serious adverse events.

TRIAL PATIENTS

Patients eligible for the DAPA-MI trial were clinically stable adults (≥18 years of age) hospitalized for acute MI, including ST-segment or non-ST-segment elevation MI in Sweden and the United Kingdom. They were treated with standard therapies according to established international and local guidelines for MI and enrolled in the SWEDEHEART or MINAP registries. One of the primary inclusion criteria was imaging evidence of regional or global impairment of LV systolic function, or if imaging of LV was not available, definite evidence of Q-wave MI on an electrocardiogram. The exclusion criteria included an established diagnosis of diabetes and chronic symptomatic HF with hospitalization for HF within the last year associated with reduced LV ejection fraction of 40% or less. Patients currently on treatment with an SGLT2 inhibitor, or with an indication for treatment in the opinion of the investigator, were also excluded. The complete set of inclusion and exclusion criteria has been published previously[15] and is provided in Table S1.

TRIAL PROCEDURES

All patients who met eligibility criteria and provided written informed consent were randomly assigned in a 1:1 ratio to receive either 10 mg of dapagliflozin once daily or matching placebo, in addition to standard of care therapy. Randomization was stratified by country (Sweden and the United Kingdom) and performed during the hospitalization for the index MI event or within 10 days from index MI, using a computerized randomization functionality supported by the registry-based, randomized controlled trial (R-RCT) framework, which is a Web application providing a unique link between the patient's registry file and the trial electronic data capture system.[15]

Baseline data at the time point of randomization were collected by automatic exports from the registries. In Sweden, the SWEDEHEART registry was used to collect data from the first two protocol-mandated follow-up visits at week 8 (±2 weeks) and month 12 (±1 month) after randomization. Thereafter, visits continued every 10 months with data entered directly in the electronic data capture system. In the United Kingdom, follow-up data were collected directly in the electronic data capture system. Throughout the trial, vital status was collected from the Swedish and U.K. population registries by automatic exports to SWEDEHEART and requested linkage with the MINAP registry, respectively. More information on the SWEDEHEART and MINAP registries can be found in the Supplementary Appendix.

OUTCOMES

The primary outcome was the hierarchical composite, by order of perceived clinical importance, of death, hospitalization for HF, nonfatal MI, atrial fibrillation/flutter event, new diagnosis of type 2 diabetes, NYHA Functional Classification at the last trial visit, and body weight decrease of 5% or more from baseline to the last trial visit (detailed definitions are presented in the Supplementary Appendix and Table S2). The key secondary outcome was the same composite as the primary outcome, excluding the body weight component. Other secondary outcomes included time to the first occurrence of cardiovascular death or hospitalization for HF. The safety event assessments consisted of serious adverse events leading to hospitalization or death.

An independent, blinded clinical end point committee adjudicated all potential hospitalization for HF and death events. Deaths were classified as either cardiovascular, noncardiovascular, or undetermined cause of death by the clinical end point committee. Patients whose cause of death was undetermined were considered as cardiovascular death in the analyses. Outcome definitions and a complete list of additional secondary outcomes have been published previously[15] and can be found in the Supplementary Appendix and Table S2.

STATISTICAL ANALYSIS

As noted above, after it was determined that the rate of cardiovascular death or hospitalization for HF was less than anticipated, the primary objective of the trial was

changed to determine the clinical effect of 10 mg of dapagliflozin versus placebo assessed using a hierarchical composite outcome and analyzed by the win ratio method where each patient in the treatment group was compared with each patient in the control group to determine the win/loss/tie within each pair across the multiple outcomes.[18] To account for the difference in time used for data collection, the shared follow-up time within each pair was considered.

Assuming a true win ratio of 1.20 in favor of dapagliflozin and a minimum follow-up of 3 months with an approximate trial duration of 30 months, 4000 patients would provide the trial with 80% statistical power for the comparison of dapagliflozin and placebo with respect to the primary outcome, at a two-sided alpha level of 5%. The assumed win ratio of 1.20 corresponds to a 20% higher likelihood of a better cardiometabolic outcome with dapagliflozin versus placebo (derived from nontied pairs), which is considered clinically relevant.[19]

Cox proportional-hazards models, including stratification by country, were used for all secondary time-to-event outcome analyses. The change in body weight from baseline to last visit was analyzed using a mixed-effects model.

The intention-to-treat population, consisting of all randomly assigned patients irrespective of their protocol adherence and continued participation in the trial, was used for the primary and secondary efficacy outcome analyses. The analysis of body weight change was performed for the on-treatment period and included measurements on or after the first dose of randomized trial drug and on or before 30 days after the last dose of trial drug. All randomly assigned patients who received at least one dose of trial treatment were included in the safety analysis set. Numbers presented for safety events are for the on-treatment analysis, as prespecified in the statistical analysis plan, including serious adverse events with onset date while on trial drug or within 30 days of last dose. The primary and secondary analyses were performed according to the prespecified closed confirmatory testing procedure controlling the type 1 error. The widths of the confidence intervals for secondary outcomes and subgroup analyses outside the confirmatory testing procedure have not been adjusted for multiplicity and should not be considered clinically directive. For additional information see the statistical analysis plan, available in the protocol provided with the full text of this article, available at evidence.nejm.org. All analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, NC) and R version 4.2.3 (R Foundation for Statistical Computing, Vienna).

Table 1. Baseline Characteristics.*

Variable	Dapagliflozin 10 mg (n=2019)	Placebo (n=1998)
Age (yr)	63.0±11.06	62.8±10.64
Male sex — no. (%)	1631 (80.8)	1579 (79.0)
Country — no. (%)		
Sweden	584 (28.9)	594 (29.7)
United Kingdom	1435 (71.1)	1404 (70.3)
Weight (kg)	85.5±15.87	85.5±16.54
Systolic blood pressure (mm Hg)	119.1±16.23	118.7±16.62
Baseline LVEF — no. (%)		
<30	130 (6.4)	137 (6.9)
30–49	1363 (67.5)	1311 (65.6)
≥50	416 (20.6)	432 (21.6)
Index MI — no. (%)		
STEMI	1465 (72.6)	1428 (71.5)
NSTEMI	544 (26.9)	562 (28.1)
eGFR (ml/min/1.73 m^2)	83.5±17.12	83.4±16.91
HbA_1c (%)	5.7±0.58 [209]	5.7±0.51 [217]
Baseline therapy — no. (%)		
ACE inhibitor/ARB	1868 (92.5)	1835 (91.8)
Acetylsalicylic acid	1873 (92.8)	1854 (92.8)
Aldosterone receptor blocker	459 (22.7)	464 (23.2)
Beta-blockers	1805 (89.4)	1797 (89.9)
Thienopyridine/ticagrelor	1857 (92.0)	1819 (91.0)
Statins	1938 (96.0)	1897 (94.9)
Any antiplatelet	1970 (97.6)	1938 (97.0)
Medical history — no. (%)		
MI	178 (8.8)	189 (9.5) [1]
Stroke	46 (2.3)	50 (2.5) [1]

* Plus–minus values are means ±SD. [M] represents number of missing values. ACE denotes angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; eGFR, estimated glomerular ejection fraction; HbA_1c, glycated hemoglobin; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-elevation MI; and STEMI, ST-elevation MI.

Results

PATIENTS

A total of 4098 patients were found eligible and gave informed consent between December 2020 and March 2023 at 103 sites in Sweden and the United Kingdom. Of these, 4017 patients were randomly assigned to receive 10 mg of dapagliflozin daily (n=2019) or matching placebo

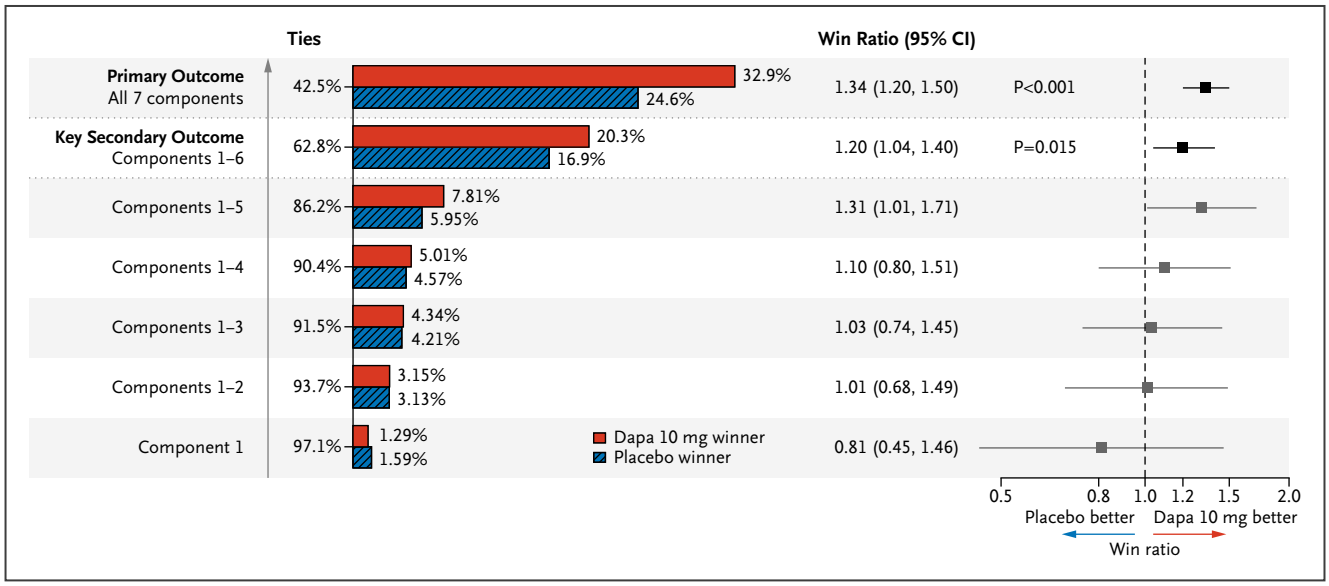

Figure 1. Primary and Key Secondary Hierarchical Composite Outcome, Assessed by the Win Ratio Method.

The results are presented as cumulative estimates where the number of components in the estimate is increased by one component at each step, according to the end point hierarchy, from the bottom and up (for per-component estimates in the hierarchy see Fig. S2). The gray arrow indicates the order of the end point hierarchy. Percentages are percent of 4,033,962 comparisons resulting in a win for Dapa 10 mg, tie, or win for placebo. The components in hierarchical order are as follows: 1. Death, 2. Hospitalization for heart failure, 3. Nonfatal MI, 4. Atrial fibrillation/flutter, 5. New diagnosis of type 2 diabetes, 6. NYHA class, and 7. Weight decrease of 5% or more. CIs for component combinations below the key secondary outcome (gray intervals) have not been adjusted for multiplicity and the inferences drawn may not be reproducible. CI denotes confidence interval; Dapa, dapagliflozin; MI, myocardial infarction; and NYHA, New York Heart Association.

(n=1998) (Fig. S1). The median time from hospital admission to random assignment was 3 days and the mean enrollment rate was two patients per site per month. The two groups did not differ in baseline characteristics, with a mean age of 62.9 years and mean body-mass index of 28.3 (body-mass index is the weight in kilograms divided by the square of the height in meters); 9.1% had prior MI and 2.4% prior stroke (Table 1 and Table S3). On admission, 72.0% had ST-elevation MI. Among patients with ST-elevation MI, 94.2% underwent primary percutaneous coronary intervention, and among those with non-ST-elevation MI, 76.6% underwent percutaneous coronary intervention. The mean estimated glomerular filtration rate at admission was 83.5 ml/min/1.73 m^2. The mean glycated hemoglobin (HbA_1c) at index hospitalization was 5.7% and the LV ejection fraction was below 50% in the majority of participants (73.2%). Patients were treated with guideline-directed therapies comprising more than 90% use of each of aspirin, $P2Y_{12}$ receptor inhibitors, renin-angiotensin-aldosterone system inhibitors, and statins at randomization (Table 1). During the trial, treatment with dapagliflozin and placebo was discontinued for reasons other than death in 304/1995 (15.2%) and 256/1977 (12.9%) patients, respectively (Fig. S1). The median duration of follow-up was 11.6 months (Q1 Q3, 6.8 to 16.9) with a maximum duration of 29.0 months. Vital status at the end of the trial was known for 99.9% of the patients.

EFFICACY

The primary hierarchical composite outcome including all seven components resulted in 32.9% wins for dapagliflozin and 24.6% wins for placebo (win ratio, 1.34; 95% confidence interval [CI], 1.20 to 1.50; P<0.001) (Fig. 1 and Fig. S2). This benefit was mainly driven by the cardiometabolic components adjudicated hospitalization for HF, new diagnosis of type 2 diabetes, NYHA Functional Classification at the last trial visit, and body weight decrease of 5% or more from baseline to the last trial visit.

Table 2. Secondary Outcomes.

Other Secondary and Exploratory End Points	Dapagliflozin 10 mg (n=2019)	Placebo (n=1998)	Hazard Ratio* (95% CI)
Composite of CV death/hospitalization for HF — n (%)	50 (2.5)	52 (2.6)	0.95 (0.64, 1.40)
CV death/hospitalization for HF/MI — n (%)	82 (4.1)	85 (4.3)	0.95 (0.70, 1.29)
MACE (MI, stroke, or CV death) — n (%)	68 (3.4)	72 (3.6)	0.94 (0.67, 1.31)
All-cause death — n (%)	41 (2.0)	33 (1.7)	1.22 (0.77, 1.92)
CV death — n (%)	27 (1.3)	23 (1.2)	1.15 (0.66, 2.01)
MI — n (%)	44 (2.2)	39 (2.0)	1.11 (0.72, 1.71)
Stroke — n (%)†	10 (0.5)	17 (0.9)	0.61 (0.28–1.34)
New diagnosis of type 2 diabetes — n (%)	42 (2.1)	78 (3.9)	0.53 (0.36, 0.77)
New diagnosis of atrial fibrillation/flutter — n (%)†	16 (0.8)	18 (0.9)	0.88 (0.45, 1.73)
All-cause hospitalization — n (%)	418 (20.7)	372 (18.6)	1.12 (0.98, 1.29)
Adjudicated hospitalization for HF — n (%)†	27 (1.3)	32 (1.6)	0.83 (0.50–1.39)
			Placebo-Corrected
Change in body weight — kg (mean)‡	–1.41 (–1.75, –1.07)	0.24 (–0.11, 0.58)	–1.65 (–2.12, –1.18)

* Hazard ratios less than unity favor dapagliflozin. The confirmatory testing procedure stops at the third outcome in the prespecified order of primary and secondary outcomes, which is the composite of CV death/hospitalization for HF that did not reach statistical significance. Other CIs have not been adjusted for multiplicity and the inferences drawn may not be reproducible. CI denotes confidence interval; CV, cardiovascular; HF, heart failure; MACE, major adverse cardiovascular event; and MI, myocardial infarction.

† Exploratory outcome.

‡ Estimate with 95% CI. Number of patients with body weight measurement at baseline and, at least, one additional measurement over time was 1846 (91.4%) for dapagliflozin and 1850 (92.6%) for placebo.

The composite of time to cardiovascular death/hospitalization for HF occurred in 50/2019 (2.5%) patients assigned to dapagliflozin and 52/1998 (2.6%) patients assigned to placebo (hazard ratio, 0.95; 95% CI, 0.64 to 1.40) (Table 2). For the full seven-component win ratio analysis, outcomes were consistent across all prespecified subgroups, including subgroups based on LV function or median level of troponin elevation (Fig. 2). For the key secondary outcome including six of the components, the win ratio was 1.20 (95% CI, 1.04 to 1.40; P=0.015) (Fig. 1 and Fig. S2). A new diagnosis of type 2 diabetes occurred in 42/2019 (2.1%) patients assigned to dapagliflozin and 78/1998 (3.9%) patients assigned to placebo (hazard ratio, 0.53; 95% CI, 0.36 to 0.77) (Table 2 and Fig. 3A). The rates of other prespecified secondary and selected exploratory cardiovascular events were low, with differences between the groups not reaching nominal statistical significance (Table 2). The placebo-corrected mean change from baseline in body weight with dapagliflozin was –1.65 kg (95% CI, –2.12 to –1.18) (Table 2 and Fig. 3B).

SAFETY

Serious adverse events leading to hospitalization occurred in 373/1995 (18.7%) patients treated with dapagliflozin and in 340/1997 (17.2%) treated with placebo. Serious adverse events on treatment leading to death occurred in 30/1995 (1.5%) in the dapagliflozin group and in 29/1997 (1.5%) in the placebo group. The most commonly reported serious adverse events are listed in Table S4. There was no increase in serious adverse events related to adverse reactions that could potentially be associated with SGLT2 inhibitors, such as ketoacidosis, hypovolemia, hypotension, amputations, or genital infections. Kidney function during follow-up was measured in the United Kingdom for safety reasons on request by the regulatory authority. The median change in estimated glomerular filtration rate (n=1440) from baseline to 7 months was –4 ml/min (Q1 Q3, –12.0 to 2.0) as compared with –4 ml/min (Q1 Q3, –11.0 to 3.0) in patients randomized to dapagliflozin versus placebo, respectively.

Discussion

In this international, registry-based, double-blind, randomized controlled trial, enrolling patients with a recent MI with impaired LV function but without prior diabetes and without chronic HF associated with LV systolic dysfunction, dapagliflozin resulted in a significant benefit in terms of cardiometabolic outcomes compared with

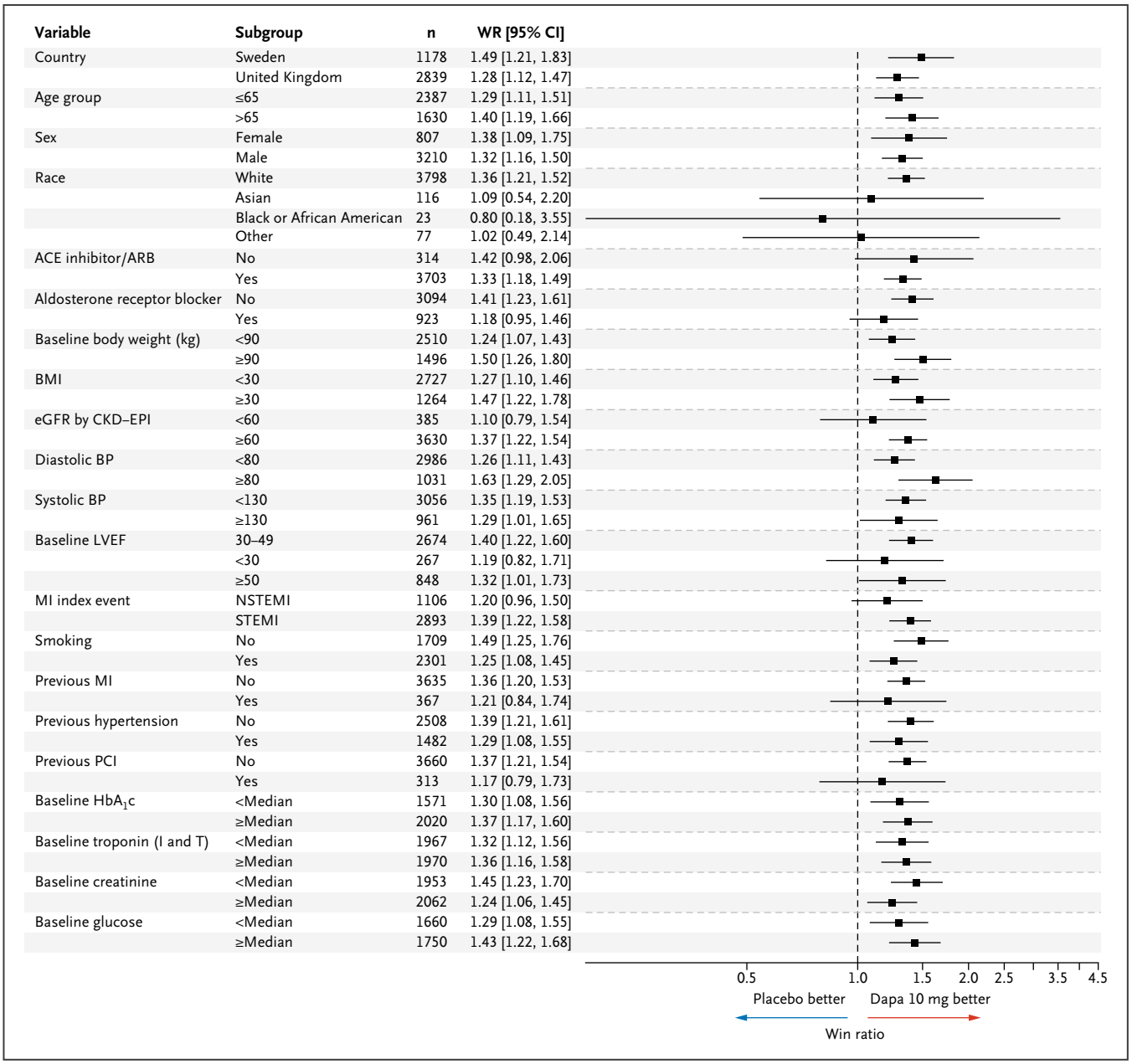

Figure 2. Forest Plot of the Primary Win Ratio Outcome in Prespecified and Clinically Important Subgroups.

CIs have not been adjusted for multiplicity and the inferences drawn may not be reproducible. ACE denotes angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body-mass index; BP, blood pressure; CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; Dapa, dapagliflozin; eGFR, estimated glomerular filtration rate; HbA_1c, glycated hemoglobin; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-elevation MI; PCI, percutaneous coronary intervention; STEMI, ST-elevation MI; and WR, win ratio.

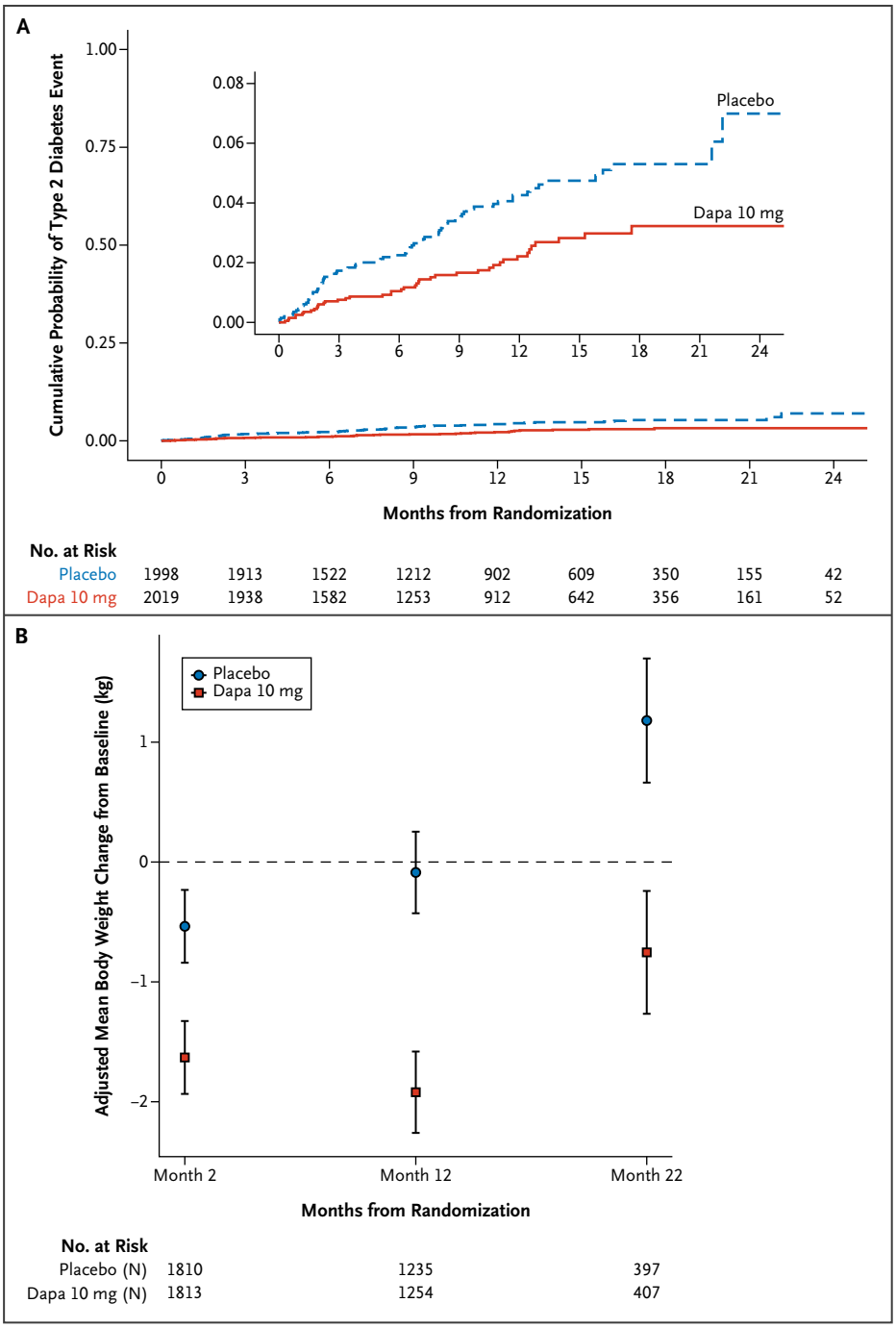

Figure 3. Diabetes and Body Weight by Randomized Groups.

Panel A shows Kaplan–Meier estimates of cumulative probability for new diagnosis of type 2 diabetes by randomized group. Panel B shows adjusted mean body weight change from baseline and 95% CIs from repeated-measures model–on treatment. CI denotes confidence interval; and Dapa, dapagliflozin.

placebo, with 34% more wins in the primary outcome. The win ratio outcome, which was adopted in a change of analysis during trial performance because of low event accrual, was mainly driven by the added cardiometabolic outcomes whereas the rates of the composite of time to cardiovascular death/hospitalization for HF were similar in both treatment groups. The full win ratio benefit was consistent across all prespecified subgroups. Dapagliflozin

also resulted in 20% more wins in the key secondary outcome excluding the body weight component. The rates of other prespecified secondary and exploratory individual and composite clinical end points were low, with limited power to show any difference between the randomized groups. Treatment with dapagliflozin resulted in a lower incidence of new diagnosis of type 2 diabetes and a reduced mean body weight.

Patients with acute MI have an increased risk of consequent adverse cardiometabolic outcomes even with currently available management options. The DAPA-MI trial extends the evidence from prior SGLT2 inhibitor trials and shows clinically relevant, largely cardiometabolic, benefits of dapagliflozin in patients hospitalized for acute MI with impaired LV function and without diabetes or prior chronic HF. Importantly, patients with any degree of globally or regionally impaired LV function were included and approximately 20% of patients had global LV ejection fraction greater than 50%. The primary outcome did not differ based on different degrees of LV function or level of troponin elevation. At the conception of the DAPA-MI trial, it had been demonstrated that SGLT2 inhibitors consistently improved outcomes in patients with diabetes and established or with high risk for atherosclerotic cardiovascular disease, as well as in patients with HF and reduced LV function.[6-10,13,14,20,21] Therefore, based on the evidence and guideline-recommended treatment with SGLT2 inhibitors, patients with prior diabetes or chronic symptomatic HF were excluded.

By the exclusion of patients with diabetes and chronic HF, the enrolled population was at lower risk of cardiovascular events as compared with other MI trials.[22] Patients enrolled in the trial received background treatment that was in accordance with recommendations in European Society of Cardiology guidelines[23,24] with near-complete use of dual antiplatelet therapy, renin-angiotensin-aldosterone system inhibition, statin therapy, and revascularization. In addition, the trial was conducted during the coronavirus disease 2019 (Covid-19) pandemic and postpandemic time periods with generally fewer hospitalizations than in previous periods.[25,26] All of these factors potentially contributed to the lower incidence of cardiovascular death and hospitalization for HF and MI (1.2%, 1.6%, and 2.0% respectively, in the placebo group) relative to preceding MI trials.[22] Without power to evaluate the effect on individual or composite clinical end points, still, dapagliflozin resulted in relevant cardiometabolic benefits in this low-risk population.

The safety profile of dapagliflozin is well-established in patients with chronic cardiovascular and kidney disease.[27,28] In this trial, patients were enrolled in the acute MI setting and no new safety concerns were identified.

The trial design of DAPA-MI used an R-RCT framework, a trial concept that has been used in many prior trials,[29,30] that we have now extended in a double-blind, placebo-controlled, randomized trial. By allowing collection of patient data and outcomes from clinical registries already incorporated into routine health care practice, the DAPA-MI trial was a robust yet streamlined trial that yielded high-quality evidence with a high enrollment rate. Over 4000 patients could be included in this pragmatic trial in only two countries over 26 months, partly during the Covid-19 pandemic.

Trial limitations include that the trial was conducted in two countries with patients predominantly of European descent, which might affect the generalizability to the findings of other populations, as noted in Table S5. The observed event rate for cardiovascular death and hospitalization for HF were substantially lower than initially expected, resulting in major revision to the primary outcome and analysis plan and limited power for evaluation of any composite or individual clinical outcomes. The use of win ratio with a hierarchical order as the revised prespecified statistical method for the primary and key secondary outcomes allowed all patients to contribute with clinical, or biomarker, events to the analyses, but we acknowledge that many of the outcomes considered in the win ratio analysis in the revised approach were ones that could be perceived as favoring dapagliflozin.

The lower incidence of new-onset diabetes and greater weight reduction were important contributors to the primary outcome. These results are consistent with known effects of SGLT2 inhibition on blood glucose and weight. Prior trials including the Prediabetes Lifestyle Intervention Study recently showed that a weight loss of 5% or more can induce metabolic benefits including reversal of prediabetes and enhanced insulin sensitivity.[31] The durability of these effects and the impact on long-term outcomes cannot be evaluated by the trial design. However, the registry-based design makes an extended follow-up of clinical events possible in future research.

In summary, the DAPA-MI trial demonstrated a significant benefit of dapagliflozin in terms of cardiometabolic outcomes as compared with placebo in patients without

diabetes or chronic HF presenting with acute MI and impaired LV systolic function during the index MI hospitalization with no new safety concerns. The clinical event rates were low with limited power for evaluation of individual or composite cardiovascular events that occurred at similar rates in both groups.

Disclosures

Author disclosures and other supplementary materials are available at evidence.nejm.org.

Funded by AstraZeneca.

We thank Prof. Keith A. A. Fox (data monitoring committee [DMC] chair) and all other DMC members; Prof. Claes Held (clinical events committee [CEC] chair) and all other CEC members; Anna Gustavsson (Senior Project Leader), Åsa Eck (Lead Data Manager), Ulrika Andersson, Nermin Hadziosmanovic (Biostatisticians), and Ida Björkgren (Publications Manager) at Uppsala Clinical Research Center; Simon Foulcer (Global Publications Lead) and Jennifer Ostridge (Safety Physician) at AstraZeneca; and all cardiologists and nurses involved in the trials in Sweden and the United Kingdom.

Author Affiliations

[1] Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden

[2] Department of Medical Sciences, Cardiology, Uppsala University, Uppsala, Sweden

[3] Department of Cardiology, Clinical Sciences, Lund University, Skåne University Hospital, Lund, Sweden

[4] Cardiovascular Research Unit, Division of Clinical Medicine, School of Medicine and Population Health, University of Sheffield, Sheffield, United Kingdom

[5] NIHR Sheffield Biomedical Research Centre, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom

[6] Division of Cardiology, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas

[7] Division of Cardiology, Parkland Health and Hospital System, Dallas

[8] National Institute for Cardiovascular Outcomes Research (NICOR), NHS Arden & GEM Commissioning Support Unit, Leicester, United Kingdom

[9] Department of Medical Sciences, Clinical Epidemiology, Uppsala University, Uppsala, Sweden

[10] Academic Cardiovascular Unit, The James Cook University Hospital, South Tees NHS FT, Middlesbrough, United Kingdom

[11] Population Health Science Institute, Newcastle University, Newcastle, United Kingdom

[12] Thoracic Center, Blekinge Hospital, Karlskrona, Sweden

[13] Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom

[14] Department of Cardiology, University Hospital Hairmyres, East Kilbride, United Kingdom

[15] Department of Clinical Science and Education, Division of Cardiology, Karolinska Institutet, Södersjukhuset, Stockholm

[16] Department of Interventional Cardiology, Royal Papworth Hospital, Cambridge, United Kingdom

[17] William Harvey Research Institute, Barts & The London Faculty of Medicine & Dentistry, Queen Mary University of London, London

[18] Department of Cardiology, St. Bartholomew's Hospital, West Smithfield, London

[19] Lincolnshire Heart Centre, United Lincolnshire Hospitals NHS Trust, Lincoln, United Kingdom

[20] School of Life Sciences, University of Lincoln, Lincoln, United Kingdom

[21] Department of Medicine, South Älvsborg Hospital, Borås, Sweden

[22] Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden

[23] Late-Stage Development, Cardiovascular, Renal and Metabolism, BioPharmaceuticals Research and Development, AstraZeneca, Gothenburg, Sweden

[24] Institute of Cardiovascular Sciences, University College London, London

References

1. Szummer K, Wallentin L, Lindhagen L, et al. Improved outcomes in patients with ST-elevation myocardial infarction during the last 20 years are related to implementation of evidence-based treatments: experiences from the SWEDEHEART registry 1995–2014. Eur Heart J 2017;38:3056-3065. DOI: 10.1093/eurheartj/ehx515.

2. Szummer K, Wallentin L, Lindhagen L, et al. Relations between implementation of new treatments and improved outcomes in patients with non-ST-elevation myocardial infarction during the last 20 years: experiences from SWEDEHEART registry 1995 to 2014. Eur Heart J 2018;39:3766-3776. DOI: 10.1093/eurheartj/ehy554.

3. Townsend N, Nichols M, Scarborough P, Rayner M. Cardiovascular disease in Europe 2015: epidemiological update. Eur Heart J 2015; 36:2673-2674. DOI: 10.1093/eurheartj/ehv428.

4. Desta L, Jernberg T, Spaak J, Hofman-Bang C, Persson H. Risk and predictors of readmission for heart failure following a myocardial infarction between 2004 and 2013: a Swedish nationwide observational study. Int J Cardiol 2017;248:221-226. DOI: 10.1016/j.ijcard.2017.05.086.

5. Jernberg T, Hasvold P, Henriksson M, Hjelm H, Thuresson M, Janzon M. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. Eur Heart J 2015;36:1163-1170. DOI: 10.1093/eurheartj/ehu505.

6. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015; 373:2117-2128. DOI: 10.1056/NEJMoa1504720.

7. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347-357. DOI: 10.1056/NEJMoa1812389.

8. Furtado RHM, Bonaca MP, Raz I, et al. Dapagliflozin and cardiovascular outcomes in patients with type 2 diabetes mellitus and

previous myocardial infarction. Circulation 2019;139:2516-2527. DOI: 10.1161/CIRCULATIONAHA.119.039996.

9. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381:1995-2008. DOI: 10.1056/NEJMoa1911303.
10. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 2020;383:1413-1424. DOI: 10.1056/NEJMoa2022190.
11. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med 2021;385:1451-1461. DOI: 10.1056/NEJMoa2107038.
12. McGuire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. JAMA Cardiol 2021;6:148-158. DOI: 10.1001/jamacardio.2020.4511.
13. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med 2022;387:1089-1098. DOI: 10.1056/NEJMoa2206286.
14. Jhund PS, Kondo T, Butt JH, et al. Dapagliflozin across the range of ejection fraction in patients with heart failure: a patient-level, pooled meta-analysis of DAPA-HF and DELIVER. Nat Med 2022;28:1956-1964. DOI: 10.1038/s41591-022-01971-4.
15. James S, Erlinge D, Storey RF, et al. Rationale and design of the DAPA-MI trial: dapagliflozin in patients without diabetes mellitus with acute myocardial infarction. Am Heart J 2023 August 25 (Epub ahead of print).
16. Jernberg T, Attebring MF, Hambraeus K, et al. The Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). Heart 2010;96:1617-1621. DOI: 10.1136/hrt.2010.198804.
17. Herrett E, Smeeth L, Walker L, Weston C. The Myocardial Ischaemia National Audit Project (MINAP). Heart 2010;96:1264-1267. DOI: 10.1136/hrt.2009.192328.
18. Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. Eur Heart J 2012;33:176-182. DOI: 10.1093/eurheartj/ehr352.
19. Redfors B, Gregson J, Crowley A, et al. The win ratio approach for composite endpoints: practical guidance based on previous experience. Eur Heart J 2020;41:4391-4399. DOI: 10.1093/eurheartj/ehaa665.
20. Ostrominski JW, Vaduganathan M, Claggett BL, et al. Dapagliflozin and New York Heart Association functional class in heart failure with mildly reduced or preserved ejection fraction: the DELIVER trial. Eur J Heart Fail 2022;24:1892-1901. DOI: 10.1002/ejhf.2652.
21. von Lewinski D, Kolesnik E, Tripolt NJ, et al. Empagliflozin in acute myocardial infarction: the EMMY trial. Eur Heart J 2022;43:4421-4432. DOI: 10.1093/eurheartj/ehac494.
22. Pfeffer MA, Claggett B, Lewis EF, et al. Angiotensin receptor-neprilysin inhibition in acute myocardial infarction. N Engl J Med 2021;385:1845-1855. DOI: 10.1056/NEJMoa2104508.
23. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39:119-177. DOI: 10.1093/eurheartj/ehx393.
24. Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J 2023;44:3720-3826.
25. Mafham MM, Spata E, Goldacre R, et al. Covid-19 pandemic and admission rates for and management of acute coronary syndromes in England. Lancet 2020;396:381-389. DOI: 10.1016/S0140-6736(20)31356-8.
26. Wu J, Mamas MA, de Belder MA, Deanfield JE, Gale CP. Second decline in admissions with heart failure and myocardial infarction during the Covid-19 pandemic. J Am Coll Cardiol 2021;77:1141-1143. DOI: 10.1016/j.jacc.2020.12.039.
27. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383:1436-1446. DOI: 10.1056/NEJMoa2024816.
28. Rossing P, Inzucchi SE, Vart P, et al. Dapagliflozin and new-onset type 2 diabetes in patients with chronic kidney disease or heart failure: pooled analysis of the DAPA-CKD and DAPA-HF trials. Lancet Diabetes Endocrinol 2022;10:24-34. DOI: 10.1016/S2213-8587(21)00295-3.
29. Erlinge D, Omerovic E, Fröbert O, et al. Bivalirudin versus heparin monotherapy in myocardial infarction. N Engl J Med 2017;377:1132-1142. DOI: 10.1056/NEJMoa1706443.
30. Hofmann R, James SK, Jernberg T, et al. Oxygen therapy in suspected acute myocardial infarction. N Engl J Med 2017;377:1240-1249. DOI: 10.1056/NEJMoa1706222.
31. Sandforth A, von Schwartzenberg RJ, Arreola EV, et al. Mechanisms of weight loss-induced remission in people with prediabetes: a post-hoc analysis of the randomised, controlled, multicentre Prediabetes Lifestyle Intervention Study (PLIS). Lancet Diabetes Endocrinol 2023;11:798-810.