
Article:
Storey, R. orcid.org/0000-0002-6677-6229 (2025) Cardiometabolic outcomes with dapagliflozin after myocardial infarction by baseline ejection fraction: DAPA-MI. ESC heart failure. ISSN: 2055-5822

https://doi.org/10.1002/ehf2.15420

ESC HEART FAILURE
ESC Heart Failure (2025)
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.15420

ORIGINAL ARTICLE

Cardiometabolic outcomes with dapagliflozin after myocardial infarction by baseline ejection fraction: DAPA-MI

David Erlinge[1]*, Stefan James[2,3], John Deanfield[4], Niclas Eriksson[2], Mark de Belder[5], Monér Alchay[6], David Austin[7,8], Daniel A. Jones[9,10], Annica Ravn-Fischer[11,12], Sofia Sederholm Lawesson[13,14], Nikunj Shah[15], Julian W. Strange[16,17], Karolina Szummer[18,19], Wilhelm Ridderstråle[20], Ehsan Parvaresh Rizi[20], Anna Maria Langkilde[20], Peter A. Johansson[20], Darren K. McGuire[21,22], Jonas Oldgren[2,3] and Robert F. Storey[23,24]

[1]*Department of Cardiology, Clinical Sciences, Lund University, Lund, Sweden;* [2]*Uppsala Clinical Research Center, Uppsala, Sweden;* [3]*Department of Medical Sciences, Cardiology, Uppsala University, Uppsala, Sweden;* [4]*Institute of Cardiovascular Sciences, University College London, London, UK;* [5]*National Institute for Cardiovascular Outcomes Research (NICOR), NHS Arden and Greater East Midlands Commissioning Support Unit, Leicester, UK;* [6]*North Älvsborg County Hospital, Trollhättan, Sweden;* [7]*Academic Cardiovascular Unit, The James Cook University Hospital, South Tees Hospitals NHS Foundation Trust, Middlesbrough, UK;* [8]*Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne, UK;* [9]*William Harvey Research Institute, Barts and The London Faculty of Medicine and Dentistry, Queen Mary University of London, London, UK;* [10]*Department of Cardiology, St Bartholomew's Hospital, West Smithfield, London, UK;* [11]*Institute of Medicine, Department of Molecular and Clinical Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden;* [12]*Department of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden;* [13]*Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden;* [14]*Department of Cardiology, Linköping University Hospital, Linköping, Sweden;* [15]*Queen Alexandra Hospital, Portsmouth, UK;* [16]*Department of Cardiology, Bristol Heart Institute, University Hospital Bristol NHS Foundation Trust, Bristol, UK;* [17]*Weston Area Health NHS Trust, Bristol, UK;* [18]*Department of Cardiology, Karolinska University Hospital, Huddinge, Stockholm, Sweden;* [19]*Department of Medicine, Karolinska Institutet, Stockholm, Sweden;* [20]*Late-Stage Development, Cardiovascular, Renal and Metabolism, Bio-Pharmaceuticals Research and Development, AstraZeneca, Gothenburg, Sweden;* [21]*Division of Cardiology, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, USA;* [22]*Division of Cardiology, Parkland Health System, Dallas, Texas, USA;* [23]*Division of Clinical Medicine, University of Sheffield, Sheffield, UK; and* [24]*NIHR Sheffield Biomedical Research Centre, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK*

Abstract

Aims In the randomized DAPA-MI clinical trial, 10 mg of dapagliflozin once daily improved cardiometabolic outcomes versus placebo after acute myocardial infarction (MI) in patients without established diabetes or heart failure (HF). We assessed associations between baseline left ventricular ejection fraction (LVEF) and cardiometabolic outcomes in DAPA-MI.

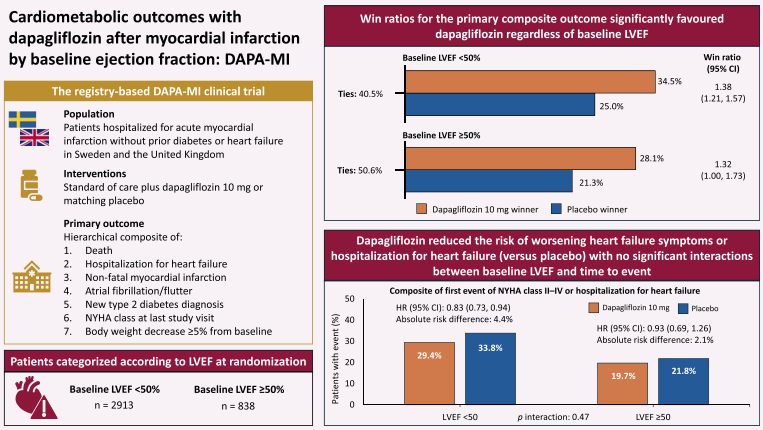
Methods The primary outcome, assessed using the win ratio method, was the hierarchical composite of death, hospitalization for HF, non-fatal MI, atrial fibrillation/flutter, Type 2 diabetes, New York Heart Association classification at last visit and body weight decrease of ≥5% from baseline to last visit. For the present analysis, patients were categorized using LVEF at randomization (<50% or ≥50%).

Results Of the DAPA-MI participants with available LVEF data who received ≥1 dose of study drug (n = 3751), 2913 (77.7%) had LVEF <50% and 838 (22.3%) had LVEF ≥50%. The primary hierarchical composite outcome resulted in a win ratio favouring dapagliflozin of 1.38 (95% CI: 1.21, 1.57; $P < 0.001$) in patients with LVEF <50% and 1.32 (1.00, 1.73; $P = 0.048$) in patients with LVEF ≥ 50% (P interaction = 0.76). In a sensitivity analysis excluding patients with LVEF <30%, the primary hierarchical composite outcome resulted in a win ratio favouring dapagliflozin of 1.40 (95% CI: 1.22, 1.61; $P < 0.001$). There were no significant interactions between baseline LVEF and any secondary outcomes.

Conclusions Regardless of baseline LVEF, dapagliflozin resulted in significant cardiometabolic benefits versus placebo, although there was no impact on the composite of cardiovascular death or hospitalization for HF.

Graphical Abstract

We investigated cardiometabolic outcomes in patients treated with dapagliflozin 10 mg once daily or placebo after acute myocardial infarction according to LVEF at randomisation in the registry-based, randomised DAPA-MI trial. Regardless of baseline LVEF, dapagliflozin resulted in significant cardiometabolic benefits versus placebo, suggesting that dapagliflozin could be a useful complement in early myocardial infarction treatment irrespective of heart function.



Keywords dapagliflozin; heart failure; left ventricular ejection fraction; myocardial infarction; sodium–glucose cotransporter-2 inhibitors

Received: 8 May 2025; Revised: 31 July 2025; Accepted: 19 August 2025
**Correspondence to: David Erlinge, Department of Cardiology, Clinical Sciences, Lund University, Lund, Sweden. Email: david.erlinge@gmail.com*
Anna Maria Langkilde was an employee of AstraZeneca, Gothenburg, Sweden at the time this research was conducted.

Introduction

After acute myocardial infarction (MI), patients are at an elevated risk of adverse cardiometabolic outcomes, including heart failure (HF), recurrent MI, and death.[1–3] Although cardiovascular mortality has declined in developed countries in recent years,[4] the long-term risk of cardiometabolic outcomes after acute MI remains high.[5] This highlights the need for improvements in available treatments and management options.

Sodium–glucose cotransporter-2 (SGLT2) inhibitors have emerged as valuable options to support cardiovascular, renal, and metabolic health in a wide range of chronic disease settings.[6] Dapagliflozin and empagliflozin are recommended by major international guidelines as foundational therapies for the treatment of HF with reduced, mildly reduced, or preserved ejection fractions.[7–9] Results from the dapagliflozin in patients with MI clinical trial (DAPA-MI; NCT04564742) showed that, in patients with acute MI without previous diabetes or chronic symptomatic HF, the SGLT2 inhibitor dapagliflozin was associated with significant improvements in cardiometabolic outcomes.[10] Such improvements in the primary hierarchical composite outcome in DAPA-MI were seen in subgroups of patients with a baseline left ventricular ejection fraction (LVEF) of 30%–49% and ≥50%.[10] Dapagliflozin has also been shown in the DAPA-HF and DELIVER trials to reduce the risk of cardiovascular death or worsening HF in patients with symptomatic chronic HF across the spectrum of LVEF, independent of diabetes status.[11] After acute MI, LVEF is often reduced,[12] and reduced LVEF in this setting has been associated with substantially higher risk of sudden cardiac arrest and death.[12,13] Similarly, the presence of pathological Q-waves is associated with worse prognosis after MI.[14] The DAPA-MI trial enrolled patients with impaired regional or global left ventricular systolic function or pathological Q-waves, resulting in enrolment of patients with a range of LVEFs.

The objective of these analyses of data from the DAPA-MI trial was to investigate further the effects of dapagliflozin on cardiometabolic outcomes according to LVEF at the point of randomization.

Methods

DAPA-MI was a multicentre, parallel-group, registry-based, randomized, double-blind, placebo-controlled Phase 3 clinical trial to evaluate the use of dapagliflozin 10 mg in patients presenting with acute MI but without previous diabetes or established HF. Full methods for the DAPA-MI trial have been reported previously[10,15] and are summarized below.

Data were collected using population-based registries in Sweden (the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies [SWEDEHEART])[16] and the UK (the National Institute for Cardiovascular Outcomes Research [NICOR] registries including the Myocardial Ischaemia National Audit Project [MINAP]).[17] The trial was conducted in accordance with the provisions of the Declaration of Helsinki. The trial and its modifications were approved by the Ethical Review Authority of both participating countries (Swedish Ethical Review Authority Dnr 2020-03087, 2021-03037, 2022-00101-02, and 2023-01452-02; UK Research Ethics Committee reference number 20/NW/0312).

Clinically stable adult patients (aged ≥18 years) who were hospitalized for acute MI in Sweden or the United Kingdom were considered for inclusion in DAPA-MI. Patients were treated with standard therapies for MI according to local and international guidelines and were enrolled in the SWEDEHEART or MINAP registries. Key exclusion criteria included either an established diagnosis of Type 1 or Type 2 diabetes or chronic symptomatic HF with a previous hospitalization for HF associated with a documented LVEF ≤40% within the year before the current MI hospitalization. Patients with a history of chronic symptomatic HF were eligible for inclusion if they did not have a previous hospitalization for HF associated with an LVEF ≤40% within the last year. Eligible patients who provided written informed consent for trial participation were randomized in a 1:1 ratio to receive either dapagliflozin 10 mg once daily or matching placebo, in addition to standard of care therapy. Baseline data at the point of randomization were collected from automatic exports from the registries. Follow-up visits were scheduled after 2 months (±2 weeks), 12 months (±1 month), and 22 months (±1 month), then every 10 months (±1 month) thereafter.

The present study provides *post hoc* subgroup analyses of patients who received at least one dose of study drug (dapagliflozin or placebo) in DAPA-MI. Patients were included in the present analyses if they had a recorded LVEF measurement at randomization (baseline) and received at least one dose of study drug. Baseline LVEF measurements were taken prior to randomization and within 10 days following hospitalization for MI. Echocardiography was performed and interpreted as part of routine clinical care at each site. Patients were categorized according to their baseline LVEF: <50% and ≥50%. The cut-off point of 50% was chosen to accommodate the differing LVEF categories in the two registries used in the DAPA-MI trial. The UK MINAP registry recorded LVEF as 'good' (≥50%), 'moderate' (≥30% to <50%), and 'poor' (<30%), whereas the SWEDEHEART registry recorded LVEF as 'normal' (≥50%), 'slightly reduced' (≥40% to <50%), 'moderately reduced' (≥30% to <40%), and 'severely reduced' (<30%). As a result, the only LVEF cut-offs that could be used to align the data from both databases were 30% and 50%. However, the number of patients in this analysis with an LVEF <30% was modest (n = 128 and n = 137 in the dapagliflozin and placebo groups, respectively). It was therefore decided to pool all LVEF <50% subgroups in both databases. This categorization reflects the consensus that a global LVEF ≥50% is considered normal despite regional impairment, and a global LVEF <50% is reduced.[18]

The primary outcome was the hierarchical composite, by order of perceived clinical importance, of death, hospitalization for HF, non-fatal MI, atrial fibrillation/flutter event, new diagnosis of Type 2 diabetes, NYHA functional class at last study visit, and body weight decrease of ≥5% from baseline to the last trial visit using win ratio analyses. The key secondary outcome was the same hierarchical composite as the primary outcome, excluding the body weight component. Secondary outcomes of special interest for these analyses included time to first event of NYHA Class II–IV or hospitalization for HF and time to first event of NYHA Class III–IV or hospitalization for HF.

All potential hospitalizations for HF and death events (cardiovascular, non-cardiovascular, or undetermined) were adjudicated by an independent, blinded clinical endpoint committee. Patients who died with cause of death undetermined were considered as cardiovascular death.

Statistical analysis

The primary composite outcome was assessed using the win ratio method.[19] This method compares each patient in the dapagliflozin 10 mg arm with each patient in the placebo arm to determine wins, losses, and ties across the component outcomes. Shared follow-up time within each pair was considered to account for the difference in time used for data collection. A win ratio of 1.20 corresponds to a 20% higher likelihood of a better cardiometabolic outcome with dapagliflozin compared with placebo (derived from non-tied pairs).[20]

Because randomization in DAPA-MI was stratified by country, country was included as a variable in all statistical models used in this analysis. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox proportional hazards models including stratification by country. The main subgroup variable (baseline LVEF <50% or ≥50%), treatment, and the subgroup interaction with treatment (P interaction) were also included. Odds ratios (ORs) for associations between dapagliflozin treatment (versus placebo) and NYHA class were calculated using ordinal logistic regression including the variables country, treatment, subgroup, and the interaction between the subgroup and treatment. The analyses of body weight change were performed using a mixed model, assuming an unstructured covariance structure including the variables baseline weight, country, all main terms and interactions between visit (as factors), the subgroup and treatment. Overall estimates and estimates by time point were determined using least-squares means as implemented in SAS software version 9.4 (SAS Institute, Cary, NC, USA). To investigate the potential impact of a subgroup of patients with severely

reduced LVEF (<30%) on the results from the subgroup of patients with an LVEF <50%, a sensitivity analysis was performed excluding these patients.

All analyses were performed with SAS software, version 9.4 and R version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Of the 4017 patients randomly assigned to either treatment arm in DAPA-MI, 3751 (93.4%) had an LVEF measurement at baseline, as well as having received at least one dose of study medication, and were included in the present analyses. Of these patients, 2913 (77.7%) had an LVEF <50% (median age 63.0 years, 80.6% male) and 838 (22.3%) had an LVEF ≥50% (median age 62.0 years, 77.9% male, *Table 1*). Baseline characteristics of the dapagliflozin-assigned groups and the corresponding placebo groups are presented in *Table S1*.

Table 1 Demographic and clinical characteristics of patients in the DAPA-MI trial according to baseline LVEF.

Characteristic	LVEF <50% (*n* = 2913)	LVEF ≥50% (*n* = 838)
Age, years, mean (SD)	63.1 (11.0)	62.3 (10.3)
Age group, *n* (%)		
≤65 years	1697 (58.3)	530 (63.2)
>65 years	1216 (41.7)	308 (36.8)
Male, *n* (%)	2348 (80.6)	653 (77.9)
Country, *n* (%)		
Sweden	922 (31.7)	249 (29.7)
United Kingdom	1991 (68.3)	589 (70.3)
BMI, kg/m^2, mean (SD)	28.2 (4.8)	28.5 (4.8)
Systolic blood pressure, mmHg, mean (SD)	117.9 (16.3)	122.1 (16.5)
Index MI, *n* (%)		
STEMI	2161 (74.2)	550 (65.6)
NSTEMI	738 (25.3)	286 (34.1)
eGFR, mL/min/1.73 m^2, mean (SD)	83.4 (17.3)	84.4 (15.8)
HbA_{1c}, %, mean (SD)	5.7 (0.5)	5.6 (0.6)
Medical history, *n* (%)[a]		
Heart failure[b]	19 (1.0)	2 (0.3)
Hypertension	1079 (37.0)	321 (38.4)
MI	286 (9.8)	67 (8.0)
Stroke	72 (2.5)	18 (2.2)
Baseline therapy, *n* (%)[a]		
ACE inhibitor/ARB	2746 (94.4)	749 (90.0)
Acetylsalicylic acid	2709 (93.1)	784 (93.9)
Aldosterone receptor blocker	833 (28.7)	49 (5.9)
Beta-blockers	2691 (92.5)	703 (84.5)
Thienopyridine/ticagrelor	2719 (93.5)	758 (91.0)
Statins	2802 (96.3)	801 (96.2)
Any antiplatelet	2854 (98.1)	817 (97.8)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST elevation MI; SD, standard deviation; STEMI, ST elevation MI.

[a]Percentages calculated from all patients with non-missing data.

[b]Data for the history of heart failure collected only for the United Kingdom. No patients with a history of heart failure had a hospitalization for heart failure associated with an LVEF ≤40% in the previous year, consistent with study protocol and exclusion criteria.

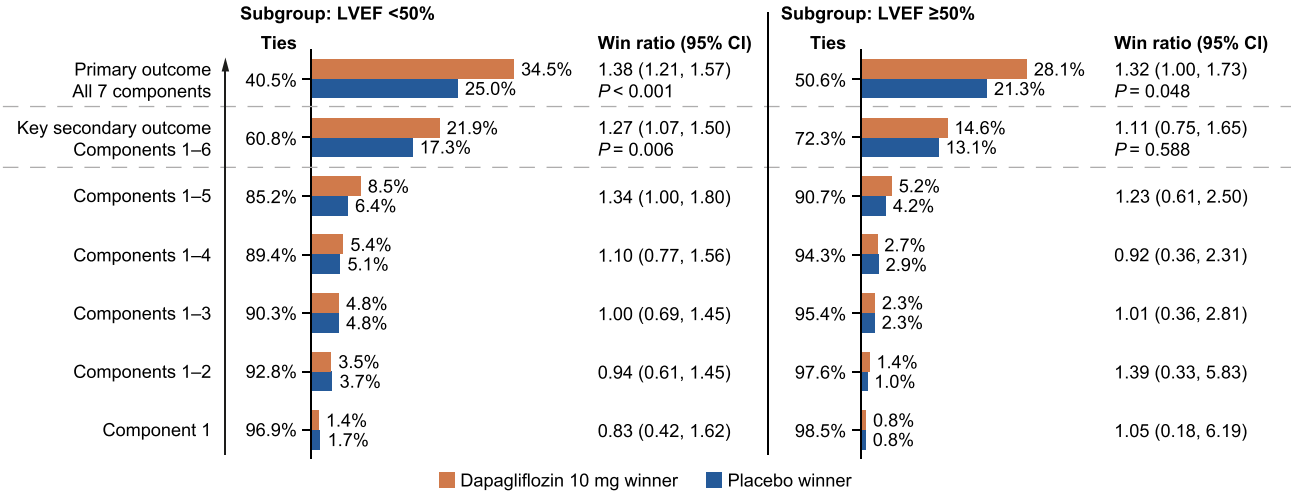
The primary hierarchical composite outcome resulted in a win ratio of 1.38 (95% CI: 1.21, 1.57; $P < 0.001$) for patients with an LVEF <50% and 1.32 (1.00, 1.73; $P = 0.048$) for patients with an LVEF ≥50% (P interaction = 0.76; *Figure 1*). In both groups, this win ratio was primarily driven by the greater incidence of a 5% decrease in body weight from baseline and the improvement in NYHA classification at the last trial visit. A full breakdown of win ratio estimates for each component of the primary composite outcome is presented in *Table S2*. In the sensitivity analysis that excluded patients with a baseline LVEF <30%, the primary hierarchical composite outcome still favoured dapagliflozin (win ratio: 1.40 [95% CI: 1.22, 1.61]; $P < 0.001$) (*Figure S1*).

In a time-to-event analysis, absolute event rates were generally higher in patients with an LVEF <50% than in patients with an LVEF ≥50%. However, there were no statistically significant interactions between LVEF and the impact of dapagliflozin on any of the secondary outcomes investigated (*Table 2*). In patients with an LVEF <50%, dapagliflozin was associated with statistically significant reductions (versus placebo) in the risk of NYHA Class II–IV (HR [95% CI]: 0.83 [0.73, 0.95]; $P < 0.01$), NYHA Class III–IV (0.58 [0.42, 0.79]; $P < 0.01$), and first diagnosis of Type 2 diabetes (0.46 [0.30, 0.72]; $P < 0.01$) (*Table 2*). However, numerical reductions in these outcomes were not statistically significant in patients with an LVEF ≥50%. When excluding patients with an LVEF <30% from the subgroup of patients with an LVEF <50%, dapagliflozin was still associated with statistically significant reductions (versus placebo) in the risk of NYHA Class II–IV (HR [95% CI]: 0.82 [0.71, 0.94]; $P < 0.01$), NYHA Class III–IV (0.56 [0.40, 0.80]; $P < 0.01$), and first diagnosis of Type 2 diabetes (0.54 [0.33, 0.87]; $P = 0.01$) (*Table S3*).

In an ordinal logistic regression analysis of NYHA class during study follow-up, there was no significant interaction between baseline LVEF group and the effect of dapagliflozin on NYHA class at any time point (*Figure 2*). In patients with a baseline LVEF <50%, dapagliflozin was associated with significantly better NYHA class from baseline to last available follow-up date compared with placebo (OR [95% CI]: 0.80 [0.66, 0.97]; $P = 0.03$). However, dapagliflozin was associated with no significant differences in NYHA class values in patients with a baseline LVEF ≥50% (OR [95% CI]: 0.82 [0.55, 1.23]; $P = 0.33$; P interaction = 0.94).

Dapagliflozin was associated with significant body weight reduction compared with placebo, regardless of LVEF subgroup (*Figure 3*). Overall estimates for the effect of dapagliflozin (versus placebo) on body weight across all three time points were a difference in change from baseline of −1.40 kg (95% CI: −1.92, −0.89; $P < 0.01$) for patients with an LVEF <50% and −1.72 kg (−2.93, −0.50; $P < 0.01$) for patients with an LVEF ≥50%.

Figure 1 Primary and key secondary hierarchical composite outcomes according to LVEF baseline, assessed by the win ratio method. Arrow indicates order of endpoint hierarchy. Estimates include the components on the *y*-axis. Percentages are per cent comparisons resulting in a win for dapagliflozin 10 mg, a tie, or a win for placebo. Percentages may not add up to 100% owing to rounding. The components in hierarchical order are: (1) death; (2) hospitalization for heart failure; (3) non-fatal MI; (4) atrial fibrillation/flutter; (5) new diagnosis of Type 2 diabetes; (6) NYHA class; and (7) weight decrease ≥5%. CI, confidence interval; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association.



Discussion

The DAPA-MI trial enrolled participants with impaired regional or global left ventricular systolic function or pathological Q-waves, with approximately 20% of patients enrolled having a global LVEF ≥50%.[10] The primary results of the DAPA-MI trial showed that the primary hierarchical composite win ratio favoured dapagliflozin in patients with a baseline LVEF of 30%–49% and ≥50%, and the present analyses build upon these results by providing an in-depth view of the effects of dapagliflozin on cardiometabolic outcomes stratified by baseline LVEF. We saw that the number of wins in the primary composite outcome with dapagliflozin (versus placebo) was consistent regardless of baseline LVEF. Across all secondary endpoints, there was no significant interaction between baseline LVEF and the effect of dapagliflozin. Consistent with existing evidence on the effects of SGLT2 inhibitors on body weight,[21,22] dapagliflozin was associated with significantly greater incidence of 5% body weight loss from baseline compared with placebo.

Patients with chronic symptomatic HF associated with LVEF ≤40% and hospitalization for HF within the last year were not eligible for enrolment in DAPA-MI. However, reduced LVEF after MI is associated with a higher risk of subsequent HF.[2] This was echoed by results from the present time-to-event analyses, in which the absolute reduction in the risk of worse HF symptoms or hospitalization for HF was driven by a reduction in HF symptoms assessed by NYHA class, and overall event rates in patients with an LVEF <50% were typically higher than in patients with an LVEF ≥50%. Patients with a reduced LVEF after acute MI are at a higher risk of adverse outcomes,[12,13] so the more pronounced effects of dapagliflozin on HF symptom burden in this subgroup are not unexpected. To investigate whether the impact of dapagliflozin was driven by patients with severely reduced LVEF, a sensitivity analysis excluding patients with a baseline LVEF <30% from the group of patients with LVEF <50% was performed. The positive impact of dapagliflozin on the primary hierarchical composite outcome was preserved when excluding these patients, indicating that the results observed were not solely a result of patients with severely reduced LVEF. Furthermore, the ordinal regression analysis in the present study showed that dapagliflozin was associated with significantly reduced HF symptom burden over the full available follow-up period compared with placebo in patients with a baseline LVEF <50%. Given that left ventricular remodelling and associated changes in ejection fraction are prevalent following MI,[23] it is possible that the mechanism underpinning the effects of dapagliflozin after MI may be different according to baseline LVEF. However, it should be noted that dapagliflozin has established cardioprotective effects in patients with HF across the LVEF spectrum.[24,25] Our findings therefore suggest that initiation of dapagliflozin after acute MI may provide symptomatic benefit for patients who present with reduced LVEF during hospitalization.

Recently, results from the EMPACT-MI trial (NCT04509674), in which the use of the SGLT2 inhibitor empagliflozin was investigated in patients with acute MI, LVEF <45%, and an increased risk of HF, found no significant improvement with empagliflozin (versus placebo) in the primary composite time-to-event endpoint of hospitalization for HF or all-cause death.[26] In EMPACT-MI, all-cause death comprised 52% of primary

Table 2 Analysis of time-to-event outcomes according to treatment group and baseline LVEF.

	LVEF <50%				LVEF ≥50%				
Outcome, *n* patients with event (%)	Dapagliflozin 10 mg (*n* = 1478)	Placebo (*n* = 1435)	HR (95% CI)[a]	*P* value	Dapagliflozin 10 mg (*n* = 411)	Placebo (*n* = 427)	HR (95% CI)[a]	*P* value	*P* interaction
Composite of CV death/hospitalization for HF	44 (3.0)	38 (2.6)	1.12 (0.72, 1.73)	0.61	3 (0.7)	7 (1.6)	0.45 (0.12, 1.74)	0.25	0.21
Composite of CV death/hospitalization for HF and MI	69 (4.7)	64 (4.5)	1.04 (0.74, 1.46)	0.82	10 (2.4)	13 (3.0)	0.81 (0.36, 1.86)	0.63	0.59
All-cause mortality	31 (2.1)	26 (1.8)	1.14 (0.68, 1.92)	0.62	4 (1.0)	4 (0.9)	1.07 (0.27, 4.28)	0.92	0.93
MACE[b]	52 (3.5)	53 (3.7)	0.96 (0.65, 1.41)	0.83	11 (2.7)	14 (3.3)	0.83 (0.38, 1.84)	0.65	0.75
MI	32 (2.2)	28 (2.0)	1.10 (0.66, 1.82)	0.72	10 (2.4)	8 (1.9)	1.34 (0.53, 3.39)	0.54	0.71
Stroke	7 (0.5)	11 (0.8)	0.66 (0.25, 1.74)	0.40	1 (0.2)	5 (1.2)	0.21 (0.02, 1.83)	0.16	0.35
CV death	21 (1.4)	16 (1.1)	1.26 (0.66, 2.42)	0.48	3 (0.7)	4 (0.9)	0.80 (0.18, 3.56)	0.77	0.58
New diagnosis of Type 2 diabetes	29 (2.0)	60 (4.2)	0.46 (0.30, 0.72)	<0.01	9 (2.2)	13 (3.0)	0.74 (0.31, 1.72)	0.48	0.34
New diagnosis of AF	10 (0.7)	13 (0.9)	0.75 (0.33, 1.70)	0.49	3 (0.7)	3 (0.7)	1.06 (0.21, 5.26)	0.94	0.70
All-cause hospitalization	314 (21.2)	271 (18.9)	1.13 (0.96, 1.33)	0.13	70 (17.0)	71 (16.6)	1.06 (0.76, 1.47)	0.74	0.71
Adjudicated hospitalization for HF	27 (1.8)	25 (1.7)	1.04 (0.61, 1.80)	0.87	0 (0)	3 (0.7)	0.00 (0.00, N/A)	0.99	0.99
First event of NYHA Class II–IV	429 (29.6)	478 (33.9)	0.83 (0.73, 0.95)	<0.01	81 (20.2)	92 (22.1)	0.94 (0.70, 1.27)	0.70	0.46
First event of NYHA Class III and IV	62 (4.3)	102 (7.2)	0.58 (0.42, 0.79)	<0.01	14 (3.5)	18 (4.3)	0.85 (0.42, 1.71)	0.64	0.33
Composite of first event of NYHA Class II–IV/ hospitalization for HF	435 (29.4)	485 (33.8)	0.83 (0.73, 0.94)	<0.01	81 (19.7)	93 (21.8)	0.93 (0.69, 1.26)	0.66	0.47
Composite of first event of NYHA Class III and IV/ hospitalization for HF	77 (5.2)	115 (8.0)	0.64 (0.48, 0.85)	<0.01	14 (3.4)	19 (4.4)	0.80 (0.40, 1.60)	0.53	0.55

Abbreviations: AF, atrial fibrillation/flutter; CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular event; MI, myocardial infarction; N/A, not available; NYHA, New York Heart Association.
[a]HRs lower than 1 favour dapagliflozin 10 mg.
[b]MACE includes MI, stroke (any kind), and CV death.

Figure 2 Ordinal logistic regression analysis of NYHA class during study follow-up according to LVEF at baseline. OR estimates are for dapagliflozin 10 mg versus placebo for the odds of having a higher NYHA class value (indicating more severe HF symptoms and limitations) at a given time point. [a]OR estimates for patients with baseline LVEF ≥50% after 22 months were unavailable owing to the low number of observations. CI, confidence interval; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OR, odds ratio.

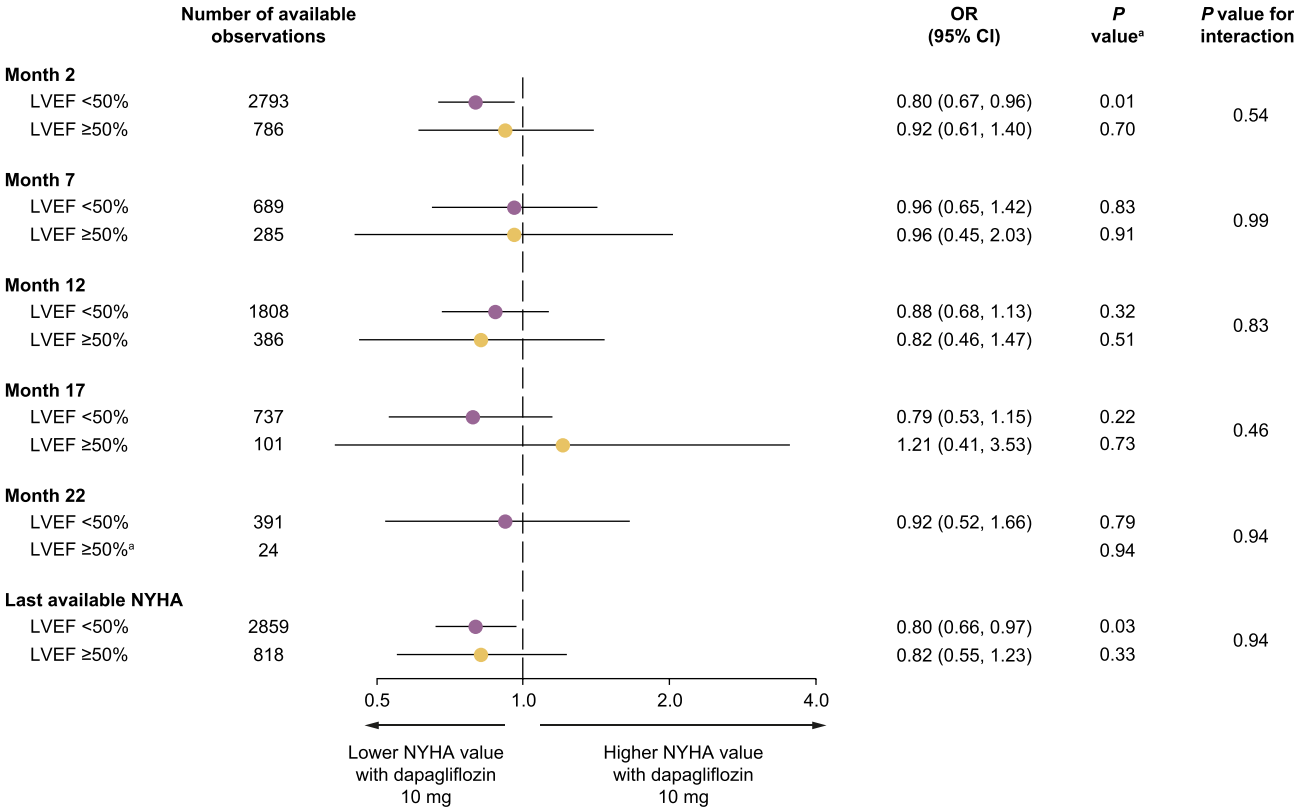
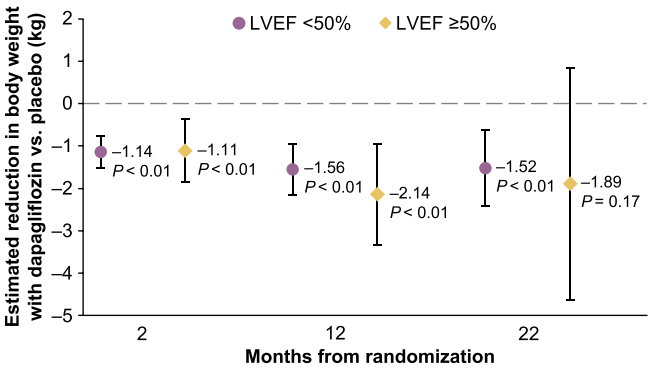


Figure 3 Estimated mean body weight change with dapagliflozin versus placebo during follow-up, by LVEF at baseline. Error bars represent 95% CIs. *P* values represent the statistical significance of the effect of dapagliflozin on body weight versus placebo. CI, confidence interval; LVEF, left ventricular ejection fraction.



No. observations

	Month 2	Month 12	Month 22
LVEF <50%			
Dapagliflozin	1390	1067	413
Placebo	1346	1014	381
LVEF ≥50%			
Dapagliflozin	392	244	30
Placebo	399	260	42

endpoint events, occurring in similar proportions in both the treatment and placebo arms. Similarly, there was no difference in all-cause death in DAPA-MI in the overall cohort or the LVEF subgroups examined in the present analysis. The present results are also in agreement with results from the EMMY trial (NCT03087773), in which empagliflozin was associated with a greater reduction in N-terminal pro-hormone of brain natriuretic peptide and improvement in echocardiographic functional and structural parameters post-MI.[27]

As explained in previous publications,[10,15] the DAPA-MI trial was adapted to use a primary hierarchical composite outcome to account for the low rate of accrual of events for the original primary composite of time to first cardiovascular death or hospitalization for HF. The different components of the composite win ratio outcome were chosen to represent a spectrum of clinically relevant cardiometabolic outcomes in patients who have recently experienced an MI ranked by perceived clinical importance, using the win ratio method for analysis.[15] Similar drivers of the primary composite outcome (new diagnosis of Type 2 diabetes, NYHA class and body weight decrease of ≥5%) were observed in the full DAPA-MI trial population and in both LVEF subgroups in the present analysis. The key secondary outcome excluded the body weight component owing to the known effects of SGLT2 inhibitors on body weight. Significant improvements in this key secondary outcome were observed with dapagliflozin in the primary DAPA-MI results,[10] and in the subgroup of patients with an LVEF <50% in the present analysis.

The present study has limitations. While the win ratio composite outcome is suitable for evaluating the overall cardiometabolic effects of dapagliflozin, it is not able to determine the mechanisms that underlie these effects. The trial was only conducted in two European countries, limiting the generalizability of data to other countries with different demographics. While the DAPA-MI trial was randomized, randomization was not stratified by baseline LVEF, leading to some differences between the baseline characteristics of LVEF subgroups in the present analysis. The subgroup of patients with a baseline LVEF ≥50% had a relatively small sample size that restricted the evaluation of statistical significance of observed results, particularly for time points late in the follow-up. Furthermore, the low accrual of individual events, such as cardiovascular death and hospitalization for HF, coupled with restrictive sample sizes, makes interpretation of individual time-to-event endpoints difficult. It should be noted that the population analysed in the present study included a subset of the intention-to-treat population analysed in the primary DAPA-MI population, namely those with available baseline LVEF and who received at least one dose of study medication, further restricting sample sizes for this analysis. As explained previously, it was necessary to separate LVEF subgroups using 50% as a cut-off point so that data could be pooled effectively between both registries in the DAPA-MI trial. However, this limitation meant that the present analysis could not investigate possible differences between subgroups of patients with reduced LVEF, for example, those with a mildly reduced LVEF (41–49%).

Conclusions

In the registry-based, randomized DAPA-MI clinical trial, treatment with dapagliflozin 10 mg once daily resulted in significant benefit in cardiometabolic outcomes compared with placebo, regardless of baseline LVEF (<50% or ≥50%). These improvements were primarily driven by new diagnoses of Type 2 diabetes, NYHA class, and body weight decrease from baseline. However, no significant benefits were seen on the composite of cardiovascular death or hospitalization for HF in either LVEF subgroup. There were no significant interactions between baseline LVEF subgroup and the effects of dapagliflozin on any of the outcomes investigated. Dapagliflozin could be a useful complement in the early treatment of patients with MI to improve cardiometabolic outcomes, regardless of heart function.

Acknowledgements

Medical writing support was provided by Bobby Thompson, MSc (Res), of Oxford PharmaGenesis, Oxford, UK and was funded by AstraZeneca. We thank the cardiologists and nurses involved in the trial, and the staff at the Uppsala Clinical Research Centre (UCR).

Conflict of interest

David Erlinge reports consulting fees from AstraZeneca for his input on the DAPA-MI study. Stefan James reports grants from AstraZeneca, Novartis, Janssen, and Amgen. John Deanfield reports grants from Alzheimer's Research UK and the British Heart Foundation, consulting fees from Amgen, Boehringer Ingelheim, Merck, Pfizer, Aegerion, Novartis, Sanofi, Takeda, Novo Nordisk, and Bayer, and honoraria from Amgen, Boehringer Ingelheim, Merck, Pfizer, Aegerion, Novartis, Sanofi, Takeda, Novo Nordisk, and Bayer. Niclas Eriksson reports institutional research grants from AstraZeneca. Mark de Belder has received grants from AstraZeneca as a member of the DAPA-MI executive steering group. David Austin reports research grants from TA Sciences, Kancera, and AstraZeneca, speaker fees from Philips Volcano, and support for attending conferences from Novartis. Annica Ravn-Fischer reports honoraria from Amarin, Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Janssen, Novartis, Novo Nordisk, Orion Pharma, Pfizer, and Sanofi, and advisory board fees from Amarin, Amgen, Boehringer Ingelheim, Novartis, Novo Nordisk, and Sanofi. Sofia Sederholm

Lawesson has no financial conflicts of interest to disclose. Julian W. Strange reports honoraria from Boston Scientific. Karolina Szummer reports honoraria from Bayer. Wilhelm Ridderstråle is an employee of AstraZeneca. Ehsan Parvaresh Rizi is an employee of AstraZeneca and holds stock options. Anna Maria Langkilde was a full-time employee and shareholder of AstraZeneca during the conduct of the study. Peter A. Johansson is an employee of AstraZeneca. Darren K. McGuire reports consulting fees from Novo Nordisk, AstraZeneca, Pfizer, Altimmune, Ventyx Pharmaceuticals, Bayer, Lexicon, Applied Therapeutics, Intercept Pharmaceuticals, Esperion, Eli Lilly and Company, Boehringer Ingelheim, New Amsterdam, CSL Behring, Amgen, and Neurotronics. Jonas Oldgren reports institutional research grants from Amgen, AstraZeneca, Bayer, Novartis, and Roche Diagnostics. Robert F. Storey reports institutional research grants from AstraZeneca and Cytosorbents, consulting fees from Alfasigma, AstraZeneca, Boehringer Ingelheim/Lilly, Pfizer, Daiichi Sankyo, Chiesi, Cytosorbents, Idorsia, Novartis, Novo Nordisk, and PhaseBio, and honoraria from AstraZeneca, Pfizer, and Tabuk. Monér Alchay, Daniel A. Jones, and Nikunj Shah report no conflicts of interest.

Funding

This work was supported by AstraZeneca.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Demographic and clinical characteristics of patients in the DAPA-MI trial according to baseline LVEF and treatment group.

Table S2. Components of the primary composite outcome according to baseline LVEF.

Table S3. Sensitivity analysis of time-to-event outcomes according to treatment group in patients with a baseline LVEF <50%, excluding those with a baseline LVEF <30%.

Figure S1. Sensitivity analysis of primary and key secondary hierarchical composite outcomes among DAPA-MI participants with a baseline LVEF <50%, excluding patients with a baseline LVEF <30%. Arrow indicates order of endpoint hierarchy. Estimates include the components on the y-axis. Percentages are per cent comparisons resulting in a win for dapagliflozin 10 mg, a tie, or a win for placebo. Percentages may not add up to 100% owing to rounding. The components in hierarchical order are: 1. Death; 2. Hospitalization for heart failure; 3. Non-fatal MI; 4. Atrial fibrillation/flutter; 5. New diagnosis of Type 2 diabetes; 6. NYHA class; and 7. Weight decrease ≥5%. CI, confidence interval; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association.

References

1. Li S, Peng Y, Wang X, Qian Y, Xiang P, Wade SW, *et al*. Cardiovascular events and death after myocardial infarction or ischemic stroke in an older Medicare population. *Clin Cardiol* 2019;**42**:391-399. doi:10.1002/clc.23160
2. Jenča D, Melenovský V, Stehlik J, Staněk V, Kettner J, Kautzner J, *et al*. Heart failure after myocardial infarction: incidence and predictors. *ESC Heart Fail* 2021;**8**:222-237. doi:10.1002/ehf2.13144
3. Law MR, Watt HC, Wald NJ. The underlying risk of death after myocardial infarction in the absence of treatment. *Arch Intern Med* 2002;**162**:2405-2410. doi:10.1001/archinte.162.21.2405
4. Mensah GA, Wei GS, Sorlie PD, Fine LJ, Rosenberg Y, Kaufmann PG, *et al*. Decline in cardiovascular mortality: possible causes and implications. *Circ Res* 2017;**120**:366-380. doi:10.1161/CIRCRESAHA.116.309115
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. Fatima A, Rasool S, Devi S, Talha M, Waqar F, Nasir M, *et al*. Exploring the cardiovascular benefits of sodium-glucose cotransporter-2 (SGLT2) inhibitors: expanding horizons beyond diabetes management. *Cureus* 2023;**15**:e46243. doi:10.7759/cureus.46243
7. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al*. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2021;**42**:3599-3726. doi:10.1093/eurheartj/ehab670
8. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al*. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2023;**44**:3627-3639. doi:10.1002/ejhf.3024
9. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, *et al*. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. *JACC* 2022;**79**:e263-e421. doi:10.1016/j.jacc.2021.12.012
10. James S, Erlinge D, Storey RF, McGuire DK, Belder M, Eriksson N, *et al*. Dapagliflozin in myocardial infarction without diabetes or heart failure. *NEJM Evid* 2024;**3**:EVIDoa2300286. doi:10.1056/EVIDoa2300286
11. Jhund PS, Kondo T, Butt JH, Docherty KF, Claggett BL, Desai AS, *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
12. Chew DS, Heikki H, Schmidt G, Kavanagh KM, Dommasch M, Bloch Thomsen PE, *et al*. Change in left ventricular ejection fraction following first myocardial infarction and outcome. *JACC: Clin Electrophysiol* 2018;**4**:672-682. doi:10.1016/j.jacep.2017.12.015
13. White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. *Circulation* 1987;**76**:44-51. doi:10.1161/01.cir.76.1.44
14. Siha H, Das D, Fu Y, Zheng Y, Westerhout CM, Storey RF, *et al*. Baseline Q waves as a prognostic modulator in patients with ST-segment elevation: insights from the PLATO trial. *CMAJ* 2012;**184**:1135-1142. doi:10.1503/cmaj.111683
15. James S, Erlinge D, Storey RF, McGuire DK, de Belder M, Björkgren I, *et al*. Rationale and design of the DAPA-MI trial: dapagliflozin in patients without diabetes mellitus with acute myocardial infarction. *Am Heart J* 2023;**266**:188-197. doi:10.1016/j.ahj.2023.08.008
16. Jernberg T, Attebring MF, Hambraeus K, Ivert T, James S, Jeppsson A, *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. Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, *et al*. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. *Eur J Heart Fail* 2021;**23**:352-380. doi:10.1002/ejhf.2115
19. 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* 2011;**33**:176-182. doi:10.1093/eurheartj/ehr352
20. Redfors B, Gregson J, Crowley A, McAndrew T, Ben-Yehuda O, Stone GW, *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
21. Sugiyama S, Jinnouchi H, Kurinami N, Hieshima K, Yoshida A, Jinnouchi K, *et al*. Dapagliflozin reduces fat mass without affecting muscle mass in type 2 diabetes. *J Atheroscler Thromb* 2018;**25**:467-476. doi:10.5551/jat.40873
22. Cho YK, Kim YJ, Jung CH. Effect of sodium-glucose cotransporter 2 inhibitors on weight reduction in overweight and obese populations without diabetes: a systematic review and a meta-analysis. *J Obes Metab Syndr* 2021;**30**:336-344. doi:10.7570/jomes21061
23. Leancă SA, Crișu D, Petriș AO, Afrăsânie I, Genes A, Costache AD, *et al*. Left ventricular remodeling after myocardial infarction: from physiopathology to treatment. *Life (Basel)* 2022;**12**:1111. doi:10.3390/life12081111
24. Solomon SD, McMurray JJV, Claggett B, Boer RA, DeMets D, Hernandez AF, *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
25. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, *et al*. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;**381**:1995-2008. doi:10.1056/NEJMoa1911303
26. Butler J, Jones WS, Udell JA, Anker SD, Petrie MC, Harrington J, *et al*. Empagliflozin after acute myocardial infarction. *N Engl J Med* 2024;**390**:1455-1466. doi:10.1056/NEJMoa2314051
27. von Lewinski D, Kolesnik E, Tripolt NJ, Pferschy PN, Benedikt M, Wallner M, *et al*. Empagliflozin in acute myocardial infarction: the EMMY trial. *Eur Heart J* 2022;**43**:4421-4432. doi:10.1093/eurheartj/ehac494