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ORIGINAL RESEARCH

Impact of Dapagliflozin on Cardiometabolic Outcomes After Acute Myocardial Infarction According to Baseline Glycemic Status and Body Mass Index: Subanalyses of the DAPA-MI Trial

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BACKGROUND: Dapagliflozin improved cardiometabolic outcomes following myocardial infarction in patients without prior type-2 diabetes (T2DM) in the DAPA-MI (dapagliflozin in patients with myocardial infarction) trial. The effect of glycemic status and body mass index (BMI) post–myocardial infarction requires elucidation.

METHODS: Participants with T2DM diagnosis, without baseline hemoglobin A1c, or not receiving any study medication, were excluded. Eligible participants were categorized, according to baseline hemoglobin A1c, as normoglycemic (<5.7% [39 mmol/mol]) or prediabetes (5.7 to <6.5% [48 mmol/mol]) and according to baseline BMI (<25, 25 to <30, and ≥30 kg/m^2). Hazard ratios (HRs) with 95% CIs and 1-year Kaplan–Meier rates were determined for new-onset T2DM (investigator-reported or hemoglobin A1c ≥6.5%) and New York Heart Association symptom classification during follow-up.

RESULTS: Of 4017 DAPA-MI participants, 3425 were eligible. In 1926 with baseline normoglycemia, new-onset T2DM occurred in 0.6% and 1.6% assigned to dapagliflozin and placebo, respectively (hazard ratio, 0.40 [95% CI, 0.15–1.03]); in 1499 with prediabetes at baseline, new-onset T2DM occurred in 10.1% and 13.1%, respectively (hazard ratio, 0.74 [05% CI, 0.55–0.99]; *P* interaction 0.23). One-year absolute risk reduction for new-onset T2DM was 8.1% in those with both prediabetes and BMI ≥30. Dapagliflozin reduced the occurrence of New York Heart Association class III–IV symptoms, with greater effect in those with prediabetes versus normoglycemia (*P* interaction 0.009). One-year absolute risk reduction for New York Heart Association class III–IV symptoms was 10.0% in those with both prediabetes and BMI ≥30.

CONCLUSIONS: Dapagliflozin reduced the occurrence of new-onset T2DM following myocardial infarction, regardless of baseline hemoglobin A1c or BMI. Dapagliflozin provided greater reduction in heart failure symptom burden in those with prediabetes compared with normoglycemia.

Key Words: dapagliflozin ■ diabetes ■ myocardial infarction ■ obesity ■ prediabetes

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CLINICAL PERSPECTIVE

What Is New?

- Dapagliflozin improved glycemia and reduced the risk of new-onset type-2 diabetes following myocardial infarction in individuals without diabetes or chronic heart failure, regardless of baseline glycemic status or body mass index.
- Dapagliflozin reduced the development of heart failure symptoms following myocardial infarction in individuals without diabetes or chronic heart failure, with particular benefit seen in those with prediabetes at baseline.
- The most marked cardiometabolic benefits of dapagliflozin, in terms of absolute risk reduction for new-onset type-2 diabetes and progressive heart failure symptoms, were seen in those with both prediabetes and obesity.

What Are the Clinical Implications?

- In the absence of prevalent type-2 diabetes or chronic heart failure, a low threshold for commencing sodium glucose transporter-2 inhibition may be appropriate following myocardial infarction in those with evidence of dysglycemia and/or excess adiposity.
- Dapagliflozin appears to be a reasonable option for reducing the risk of progressive heart failure symptoms following myocardial infarction in those without type-2 diabetes or chronic heart failure, particularly in those with prediabetes and/or obesity.

Nonstandard Abbreviations and Acronyms

ARR	absolute risk reduction
DAPA-MI	dapagliflozin in patients with myocardial infarction
NYHA	New York Heart Association
SGLT2	sodium glucose transporter-2
T2DM	type-2 diabetes

Sodium glucose transporter-2 (SGLT2) inhibitors improve glycemic control and help with weight reduction in persons with type-2 diabetes (T2DM).[1–3] Additionally, SGLT2 inhibitors reduce the risk of hospitalization for heart failure (HF) or cardiovascular death in patients with either T2DM or chronic HF associated with reduced or preserved left ventricular ejection fraction,[4–8] and also provide kidney protection in patients with chronic kidney disease.[9,10] In the DAPA-MI (Dapagliflozin in Patients with Myocardial Infarction) double-blind randomized controlled trial (https://www.clinicaltrials.gov: NCT04564742), the SGLT2 inhibitor dapagliflozin was compared with placebo following acute myocardial infarction (MI) in patients with impaired left ventricular function but without a prior history of T2DM or chronic HF.[11,12] Dapagliflozin demonstrated significant cardiometabolic benefits, including lower risk of new-onset T2DM or poor New York Heart Association (NYHA) class of HF symptoms and improved chances of achieving 5% or more weight loss, but without a significant impact on the composite of cardiovascular death or hospitalization for HF.[12] New diagnoses of T2DM and identification of individuals with prediabetes (elevated fasting glucose or impaired glucose tolerance) are common in patients with acute MI without a history of T2DM,[13] and these metabolic abnormalities are associated with adverse clinical outcomes.[14–18] The effects of dapagliflozin in this subgroup of patients, compared with those with normoglycemia, have yet to be fully addressed. Moreover, the associations between weight and the cardiometabolic responses to dapagliflozin require further evaluation. Therefore, the aims of the present subanalyses were to investigate the cardiometabolic effects of dapagliflozin in the DAPA-MI trial according to baseline normoglycemia and prediabetes status, assessed by hemoglobin A1c (HbA1c), as well as body mass index (BMI), focusing on a prespecified analysis of new-onset T2DM.

METHODS

Data underlying the findings described in this article may be obtained in accordance with AstraZeneca's data-sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli can be requested through Vivli at https://vivli.org/members/enquiries-aboutstudies-not-listed-on-the-vivli-platform/. The AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

Participant Cohort

The trial design and principal results of the DAPA-MI trial have been previously published.[11,12] All trial activities were approved by relevant ethics committees and regulatory authorities with participants providing written informed consent. In brief, the trial included patients with acute MI within the last 7 to 10 days who had evidence of global or regional impairment of left ventricular systolic function, and did not have a history of diabetes or chronic HF with reduced ejection fraction requiring hospitalization within the last year. Participants in the DAPA-MI trial were included in these subanalyses if they had a baseline HbA1c

measurement recorded and did not have a baseline HbA1c ≥6.5% or an in-hospital diagnosis of T2DM. In addition, participants who did not receive any dose of study medication were excluded from the principal subanalyses but included in sensitivity intention-to-treat subanalyses. Eligible participants were divided into post-hoc subgroups according to baseline HbA1c and/or BMI: participants were classified as being normoglycemic if baseline HbA1c was <5.7% [39 mmol/mol] and as having prediabetes if baseline HbA1c was 5.7 to <6.5% [48 mmol/mol][19] and 3 categories of BMI were assessed: <25 kg/m^2; ≥25 to <30 kg/m^2; and ≥30 kg/m^2.

Cardiometabolic Outcomes

Clinical events, NYHA classification of symptoms, HbA1c and random plasma glucose levels, and body weight were assessed at study follow-up visits. The key outcome for these subanalyses was new-onset T2DM during follow-up, which was prespecified in the academic statistical analysis plan as being defined as either an investigator-reported T2DM event or occurrence of an HbA1c measurement ≥6.5%. Further outcomes assessed were as follows: occurrence of NYHA class II–IV symptoms; occurrence of NYHA class III–IV symptoms; attainment of 5% or more weight loss; a composite of hospitalization for HF or a major adverse cardiovascular event; a composite of cardiovascular death or hospitalization for HF; hospitalization for HF alone; major adverse cardiovascular event alone; cardiovascular death alone.

Statistical Methods

Continuous variables are expressed as mean±SD or median and interquartile range. The percentage of subjects with events was assessed and participants were censored if they had no event, with the time of censoring set according to the rules in the main trial (the earliest of withdrawn consent date, death date, or last study visit date). Hazard ratios (HRs) with 95% CIs were calculated using Cox proportional hazards models. All analyses included the treatment variable, whereas all subgroup analyses included the subgroup variable and the interaction between subgroup and treatment. Subgroup effects were estimated by applying appropriate contrasts to the previously mentioned model. The Kaplan–Meier cumulative incidence for the survival analyses was calculated at 360 days ("1-year KM%"). Mixed model analyses were performed for continuous measurements over time prioritizing an unstructured covariance structure. When the algorithm did not converge, alternative covariance structures were used in the order Toeplitz, first order auto regressive and compound symmetric. The mixed-model analyses of HbA1c change were estimated in subgroups of baseline HbA1c using a first-order autoregressive covariance structure including baseline HbA1c, treatment, visit (as factor), and the interaction between treatment and visit. The analyses of plasma glucose change were

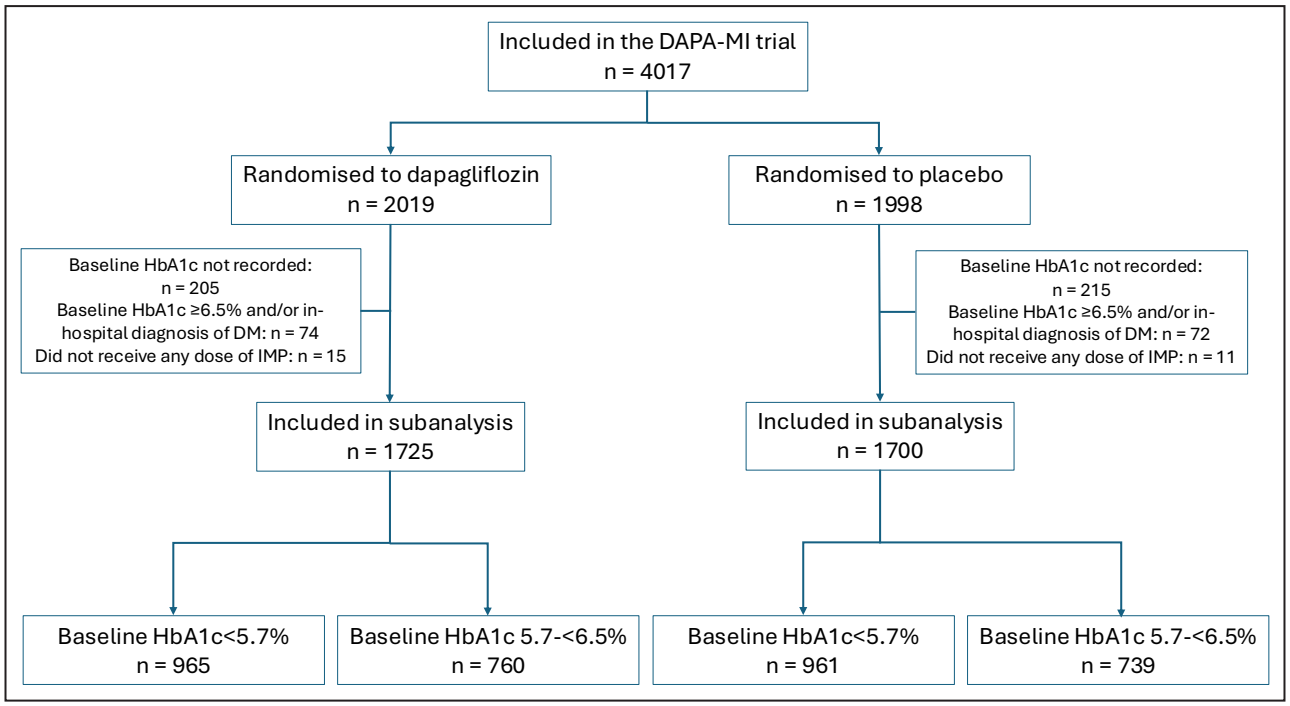

Figure 1. CONSORT diagram of the subanalyses cohort.
CONSORT indicates Consolidated Standards of Reporting Trials; DAPA-MI, dapagliflozin in patients with myocardial infarction; DM, diabetes; HbA1c, hemoglobin A1c; and IMP, investigational medicinal product (study medication).

Table Baseline Characteristics and Duration of Follow-Up for the Subanalyses Cohort

	Dapagliflozin n=1725	Placebo n=1700
Age, y, mean (SD)	62.9 (10.9)	62.8 (10.5)
Female sex, n (%)	327 (19%)	348 (20%)
Baseline HbA1c values		
HbA1c value, %, mean (SD)	5.6 (0.34)	5.6 (0.34)
HbA1c value, mmol/mol, mean (SD)	38.0 (3.7)	38.0 (3.7)
HbA1c <5.7% at baseline, n (%)	965 (56%)	961 (57%)
HbA1c 5.7 to <6.5% at baseline, n (%)	760 (44%)	739 (43%)
Baseline body mass index		
kg/m^2, n (%)	423 (24%)	440 (26%)
25 to <30 kg/m^2, n (%)	763 (44%)	727 (43%)
≥30 kg/m^2, n (%)	539 (31%)	533 (31%)
Country, n (%)		
United Kingdom	1201 (70%)	1154 (68%)
Sweden	524 (30%)	546 (32%)
Duration of follow-up, mo, median (IQR)	11.6 (6.9–17.0)	11.6 (6.7–17.0)

HbA1c indicates hemoglobin A1c; and IQR, interquartile range.

performed using a mixed model with an unstructured covariance matrix including baseline glucose, treatment, visit (as factor), and the interaction between treatment and visit, excluding those who had discontinued study medication for more than 30 days. The analyses of body weight change were performed using a mixed model assuming an unstructured covariance structure including the variables baseline weight and all main terms and interactions between visit (as factor), treatment, and the subgroup. In all mixed model analyses, overall estimates and estimates by time point were estimated using least-squared means as implemented in SAS. Sensitivity analyses for the HbA1c baseline subgroups and missing values were performed in the intention-to-treat population. Restricted cubic splines, with 3 knots placed at the 10th, 50th, and 90th percentile of the HbA1c distribution, were generated for HRs according to baseline HbA1c. In order to include participants with missing baseline HbA1c, imputations were performed using the R-package MICE using 10 imputed sets (default imputation methods) with a model that included randomized treatment, HbA1c, sex, age, systolic and diastolic blood pressure, height, weight, smoking history, and creatinine. The interaction effect when HbA1c was modeled as a spline was illustrated with HR (95% CI) for the contrast of dapagliflozin versus placebo for varying values of HbA1c ranging from 1% to 99% percent of the HbA1c distribution. Since no adjustment was made for multiple testing and the subanalyses were performed post-hoc, the results should be considered hypothesis-generating.

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).

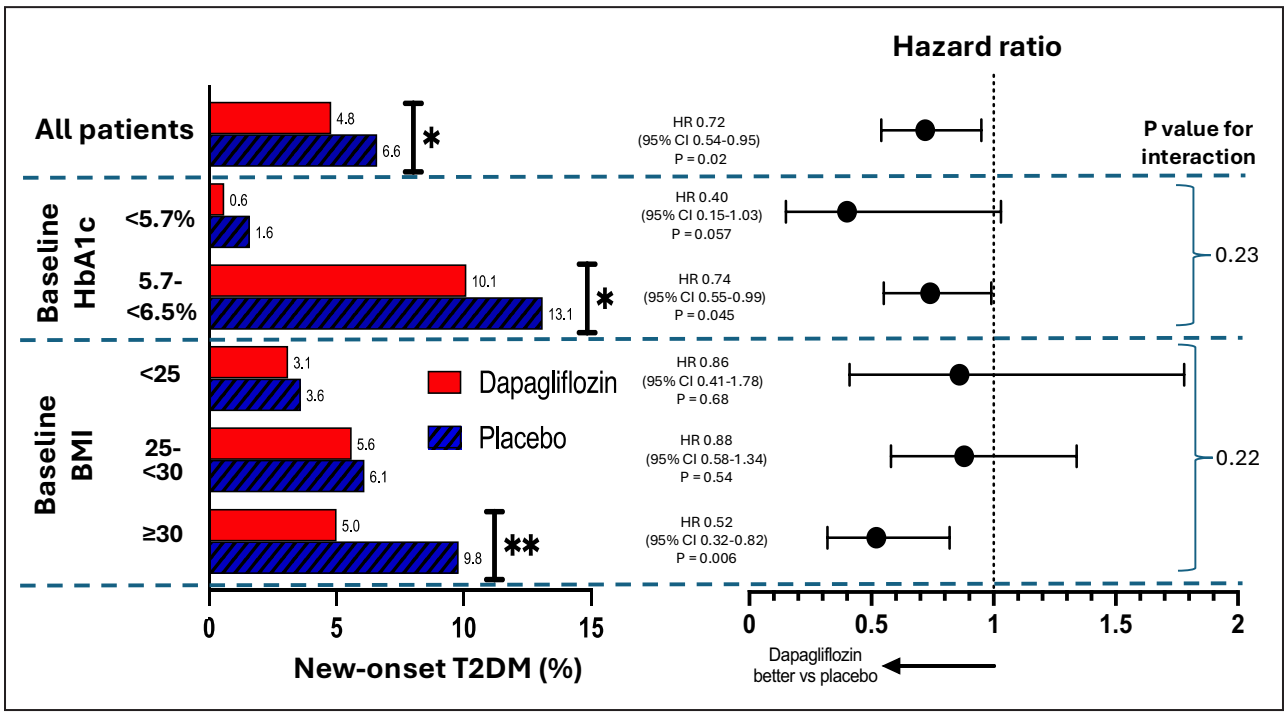

Figure 2. New-onset type-2 diabetes occurring during follow-up in dapagliflozin and placebo groups according to baseline HbA1c or body mass index.

Bars represent percentage of subjects with events. BMI indicates body mass index; HbA1c, hemoglobin A1c; HR, hazard ratio; and T2DM, type-2 diabetes. *P <0.05; **P <0.01.

RESULTS

Subanalyses Cohort

Out of 4017 participants in the DAPA-MI trial, 3425 participants were eligible for these subanalyses, of whom 1926 were normoglycemic and 1499 had prediabetes at baseline (Figure 1). Median follow-up was 11.6 months. Details of the treatment groups are shown in the Table .

Occurrence of New-Onset T2DM

New-onset T2DM occurred in 83 (4.8%) participants in the dapagliflozin group compared with 112 (6.6%)

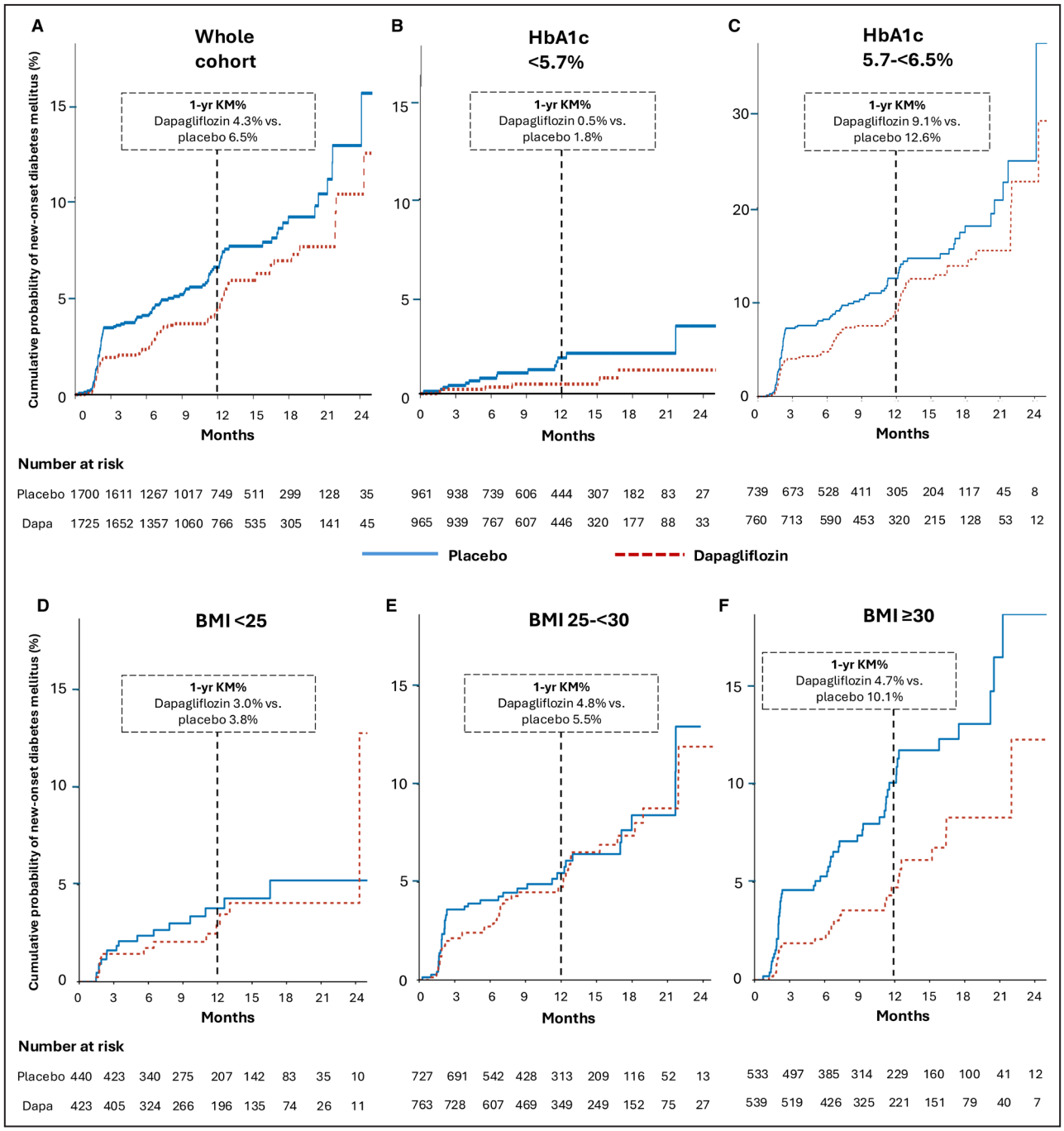

Figure 3. Cumulative probability of new-onset type-2 diabetes occurring during follow-up in dapagliflozin and placebo groups according to baseline HbA1c or body mass index.

New-onset type-2 diabetes in (A) the whole subanalysis cohort and (B-F) subgroups of this cohort with the following baseline characteristics: (B) HbA1c <5.7%, (C) HbA1c 5.7 to <6.5%, (D) BMI <25, (E) BMI 25 to <30, and (F) BMI ≥30. BMI indicates body mass index; HbA1c, hemoglobin A1c; 1-yr KM%, Kaplan–Meier cumulative incidence at 1 year; and Dapa, dapagliflozin.

participants in the placebo group (HR, 0.72 [95% CI, 0.54–0.95]) (Figure 2 and 3A), with no significant interaction according to baseline glycemic status or BMI (Figure 2). The 1-year absolute risk reduction (ARR) for new-onset-T2DM was 1.4% in those with normoglycemia and 3.5% in those with prediabetes (Figure 3B and 3C). The 1-year ARR for new-onset T2DM was 0.8% in those with BMI <25, 0.7% in those with BMI ≥25 to <30, and 5.3% in those with BMI ≥30 (Figure 3D through 3F).Similar results were obtained with intention-to-treat sensitivity analysis (Table S1). Analysis of baseline HbA1c as a continuous variable did not suggest a strong effect of baseline HbA1c on relative risk reduction with dapagliflozin versus placebo (Figure S1).

In the 576 participants with both prediabetes and BMI ≥30 at baseline, dapagliflozin reduced new-onset T2DM (HR, 0.50 [95% CI, 0.31–0.81]; *P*=0.005) with a particularly large 1-year ARR of 8.1% reflecting a high event rate in this group (1-year KM%: dapagliflozin 8.6% versus placebo 16.7%) (Table S2, Figure S2A).

In the group with pre-T2DM at baseline, 24.1% in the dapagliflozin group compared with 18.5% in the placebo group achieved an HbA1c measurement <5.7% during follow-up (HR, 1.35 [95% CI, 1.08–1.69]; *P*=0.008).

Twelve participants (0.6%) in the dapagliflozin group and 14 (0.8%) in the placebo group received open-label SGLT2 inhibitor therapy during follow-up, and very few (4 in each group) received other glucose-lowering therapies.

Change in HbA1c and Glucose Over Time

HbA1c levels increased from baseline to month 2 and subsequent time points in the overall subanalyses cohort, with similar increases seen in those with either normoglycemia or prediabetes at baseline (Figure 4). Dapagliflozin, compared with placebo, led to a lesser increase in HbA1c that was most notable at month 2 in those with either normoglycemia or prediabetes at baseline. A similar effect was seen when including only HbA1c measurements performed within 30 days of last dose of study medication (Figure S3).

In those with available plasma glucose levels in the subanalyses cohort, mean±SD plasma glucose levels were 129.1±32.8 mg/dL (n=1022) and 129.9±31.9 mg/dL (n=994) at baseline and fell to 97.5±17.9 mg/dL (n=1106) and 99.8±19.2 mg/dL (n=1063) at month 2 in the dapagliflozin and placebo groups, respectively (estimated difference in change from baseline: –2.0 mg/dL; *P*=0.02).

NYHA Class

Three thousand three hundred and seventy-one out of 3425 patients had available NYHA classification during follow-up and were included in this analysis. During follow-up, fewer participants in the dapagliflozin group reported NYHA class II or above symptoms (Figure 5A) or NYHA class III–IV symptoms (Figure 5B and 6A) compared with the placebo group. The reduction in symptoms was significantly greater in those

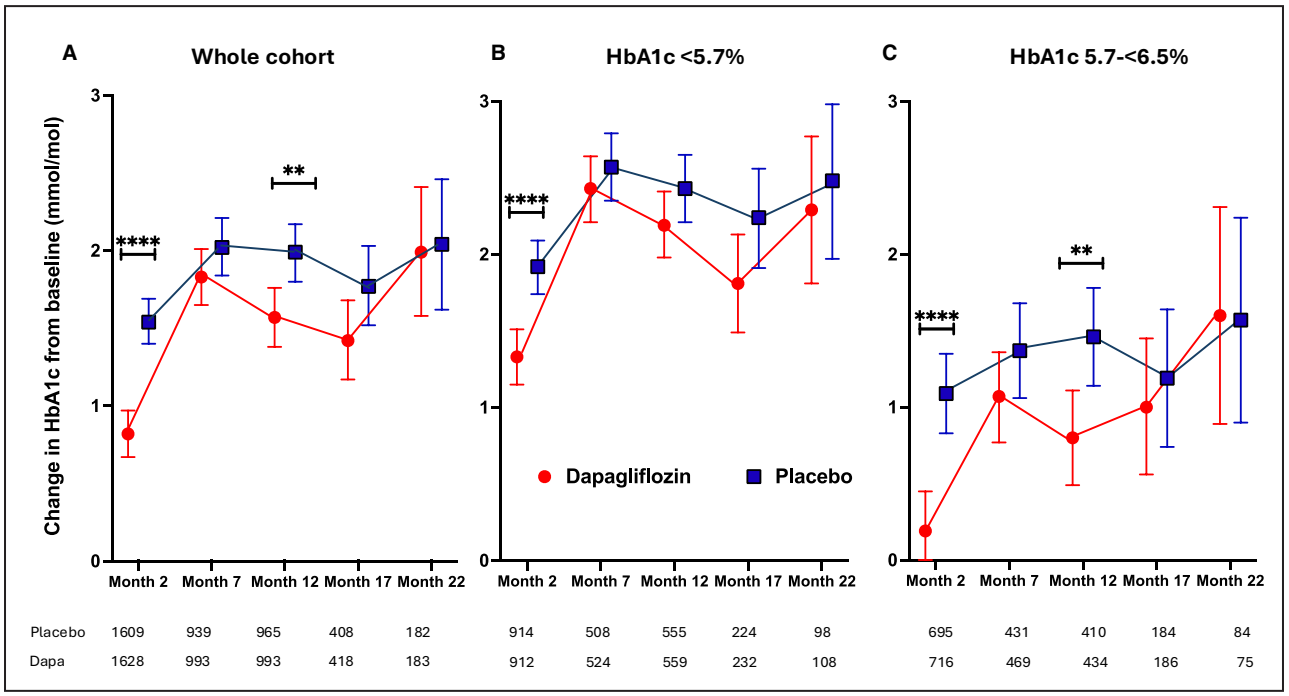

Figure 4. Mean change in HbA1c values during follow-up according to treatment group in (A) the whole cohort, (B) participants with normoglycemia at baseline, and (C) prediabetes at baseline.
Data are least-squares mean and error bars show 95% CIs of estimates. Dapa indicates dapagliflozin; and HbA1c, hemoglobin A1c. ***P* <0.01, *****P* <0.0001.

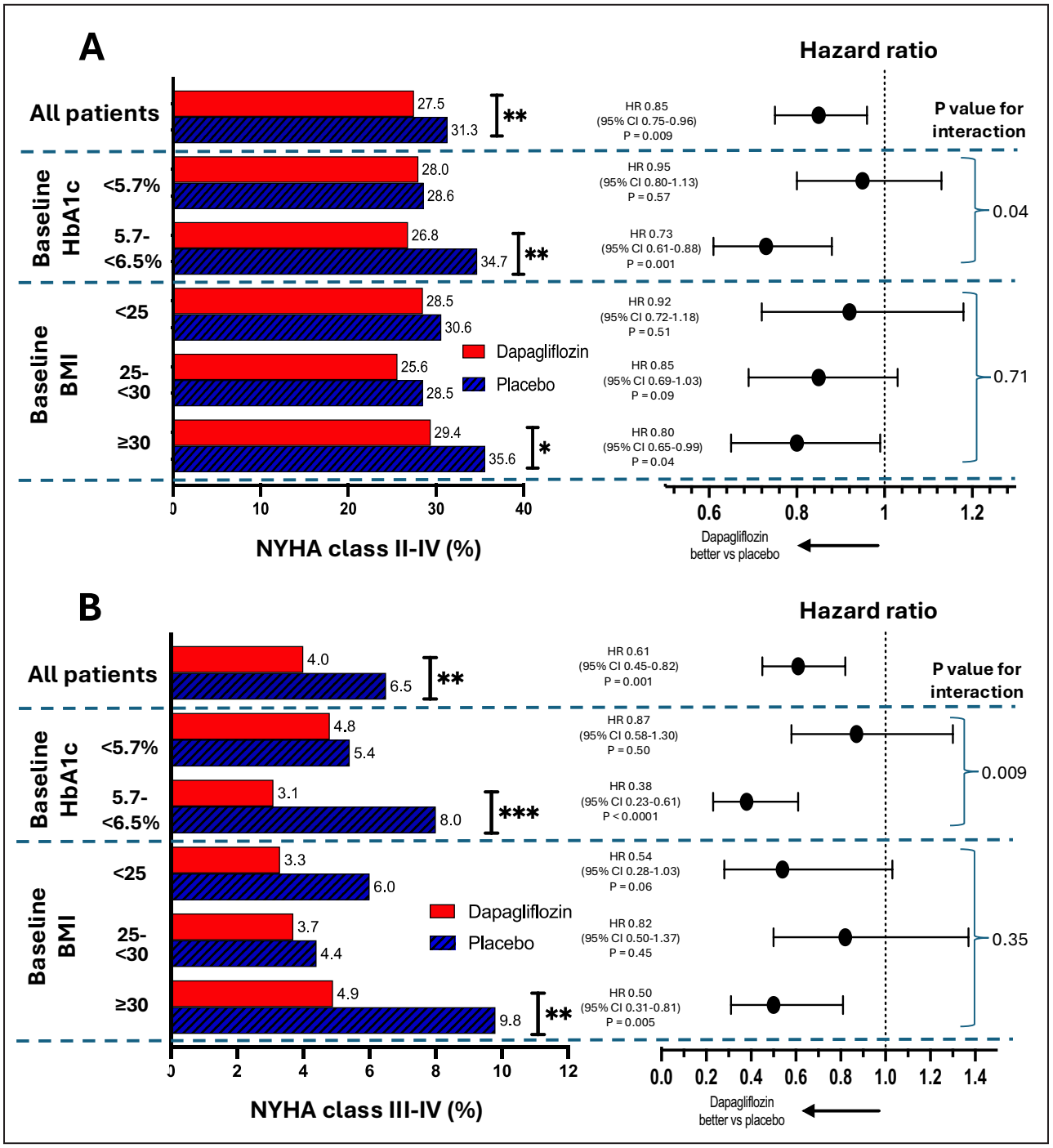

Figure 5. New York Heart Association heart failure symptoms of (A) class II to IV or (B) class III to IV occurring during follow-up in the dapagliflozin and placebo groups according to baseline HbA1c or body mass index.
Bars represent percentage of subjects with events. BMI indicates body mass index; CI, confidence intervals; HbA1c, hemoglobin A1c; HR, hazard ratio; and NYHA, New York Heart Association. **P* <0.05, ***P* <0.01, *****P* <0.0001.

with prediabetes at baseline compared with those with normoglycemia, particularly for NYHA class III–IV symptoms (interaction *P*=0.009). One-year ARR for NYHA class III–IV symptoms was 4.6% in those with prediabetes and 0.7% in those with normoglycemia at baseline (Figure 6B and 6C).There was no significant interaction according to BMI subgroup for either NYHA class II–IV or NYHA class III–IV symptoms (Figure 5A and 5B). One-year ARR for NYHA class III–IV symptoms was 1.6% in those with BMI <25, 0% in those with BMI ≥25 to <30, and 6.4% in those with BMI ≥30 (Figure 6D through 6F).

Similar results were obtained with intention-to-treat sensitivity analysis (Table S3). Analysis of baseline

HbA1c as a continuous variable showed consistent findings for relative risk reduction of the occurrence of NYHA class II–IV or class III–IV symptoms with dapagliflozin versus placebo (Figure S4).

In the 576 participants with both prediabetes and BMI ≥30 at baseline, dapagliflozin reduced the occurrence of NYHA class III–IV symptoms (HR, 0.29 [95% CI, 0.15–0.58]; *P*=0.005) with a particularly large 1-year ARR of 10.0% reflecting a high event rate in the placebo-treated participants in this group (1-year KM%: dapagliflozin 3.9% versus placebo 13.9%) (Table S4, Figure S2B).

Weight Loss

Dapagliflozin was similarly effective in achieving 5% or more weight loss in those with baseline normoglycemia or prediabetes and in all the BMI categories (all *P* ≤0.001;

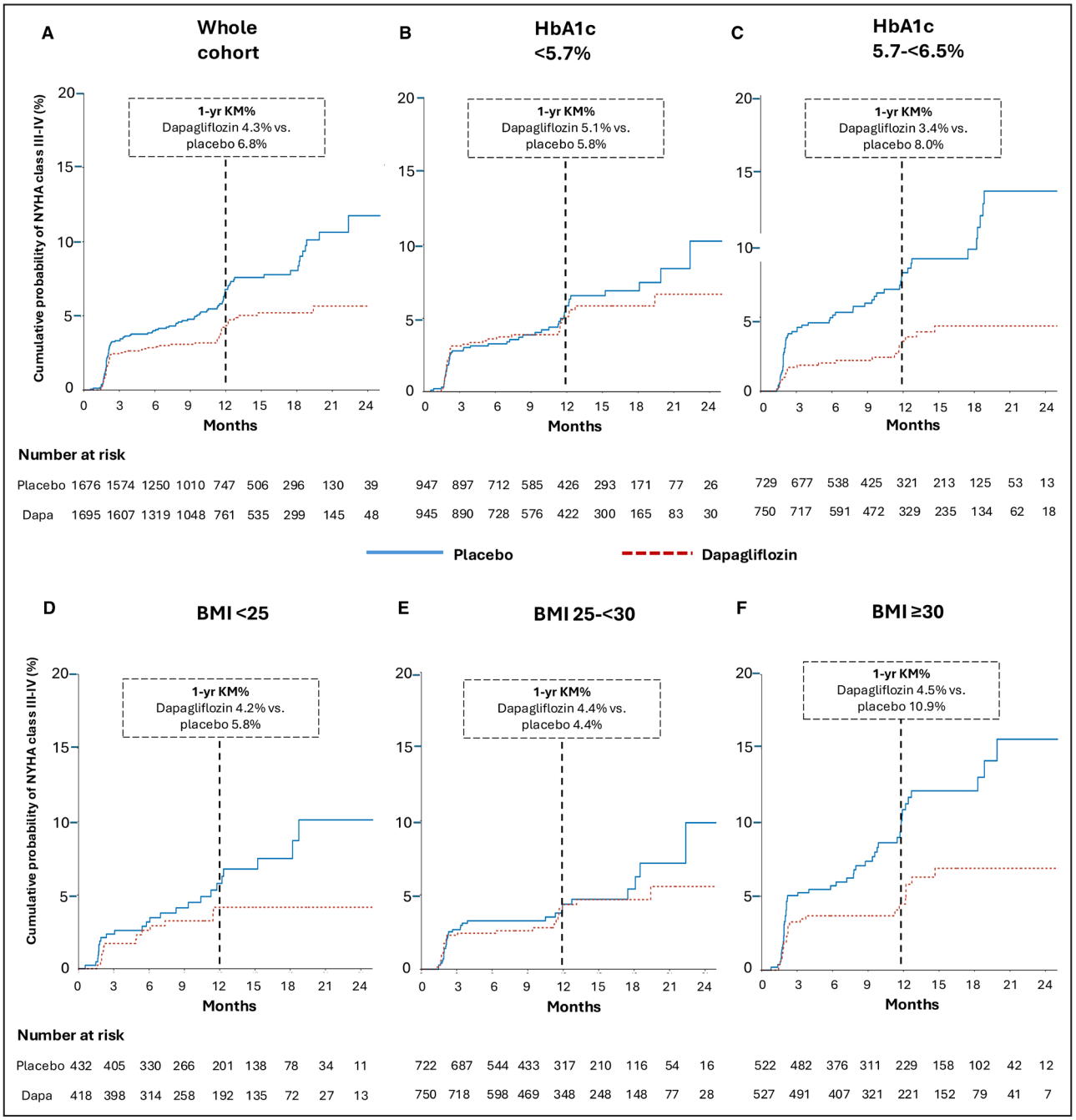

Figure 6. Cumulative probability of New York Heart Association class III to IV symptoms occurring during follow-up in dapagliflozin and placebo groups according to baseline HbA1c or body mass index.
NYHA class III-IV symptoms in (A) the whole subanalysis cohort and (B-F) subgroups of this cohort with the following baseline characteristics: (B) HbA1c <5.7%, (C) HbA1c 5.7 to <6.5%, (D) BMI <25, (E) BMI 25 to <30, and (F) BMI ≥30. BMI indicates body mass index; 1-yr KM% indicates Kaplan–Meier cumulative incidence at 1 year; Dapa, dapagliflozin; HbA1c, hemoglobin A1c; and NYHA, New York Heart Association.

both interaction P >0.7; Figure S5). Mean (±SD) weight change at 1 year in the dapagliflozin group was –1.5±6.9 kg and –1.6±8.2 kg in those with baseline normoglycemia and prediabetes, respectively, compared with 0.0±7.5 kg and –0.3±7.8 kg in the placebo group, respectively (both P <0.001 for dapagliflozin versus placebo).

Cardiovascular Events

There were no significant differences in cardiovascular events between the dapagliflozin and placebo groups, either in the entire subanalyses cohort or in any of the baseline glycemic status or BMI subgroups (Tables S5 through S7).

DISCUSSION

The results of these subanalyses of the DAPA-MI trial provide novel insights into the cardiometabolic benefits of dapagliflozin following acute myocardial infarction (MI) in those with evidence of impaired left ventricular function and no history of diabetes or chronic HF. The principal cardiometabolic benefits seen in the entire study cohort were reduction in new-onset T2DM events, reduced risk of limiting HF symptoms, and greater chance of achieving 5% or more weight loss.[12] The results from the present subanalyses show that these benefits were achieved regardless of baseline glycemic status or BMI, although an enhanced clinical gain was evident in some patient subgroups.

The ARR with dapagliflozin for new-onset T2DM was particularly marked in those with prediabetes, obesity (BMI ≥30) or both at baseline, reflecting high event rates in these participants. The highest incidence of new-onset T2DM was seen in participants with both prediabetes and obesity at baseline with a 1-year risk of 16.7% in the placebo group, which was halved with the use of dapagliflozin in this subgroup. HbA1c tended to increase following the index MI event, and this increase was attenuated by dapagliflozin, particularly after 2 months of treatment, accompanied by a marginal yet significant reduction in random plasma glucose levels. These HbA1c data suggest that early administration of an SGLT2 inhibitor following acute MI helps to avoid hyperglycemia within the first 2 months of the ischemic event in those with normoglycemia and prediabetes, although this glycemic benefit appears to be diminished during longer follow-up, possibly related to progression of T2DM and/or reduced adherence to study medication over time.

Similarly, the highest ARRs with dapagliflozin for the incidence of NYHA class II–IV or III–IV symptoms were seen in those with either prediabetes or obesity (BMI ≥30) at baseline, including a significant interaction according to baseline glycemic status. The reduced risk of worsening HF symptoms was seen within 3 months of commencing dapagliflozin, and this benefit was sustained during follow-up compared with placebo. This early benefit is consistent with previous studies of dapagliflozin in patients with HF with reduced or preserved ejection fraction.[5,6,20] The findings of the present subanalyses support having a low threshold for commencing SGLT2 inhibition following acute MI in those with evidence of dysglycemia and/or obesity.

These subanalyses have the following limitations. Firstly, the post-hoc definition of the subgroups may have created bias, despite a prespecified plan to assess new-onset T2DM as defined within the present work. Secondly, all assessments were made during the period of intended study medication administration, and it is unknown whether any glycometabolic effects would have been sustained after cessation of study medication. Thirdly, the study had negligible ability to detect any impact of dapagliflozin on cardiovascular events and mortality in patients with prediabetes or obesity since the follow-up period was relatively short, the event rates were low, and confidence intervals for the hazard ratios were wide.

CONCLUSIONS

New-onset T2DM occurs commonly after acute MI, particularly in those with prediabetes or obesity. This emphasizes the importance of assessing glycemic status in patients with acute MI. The incidence of new-onset T2DM is reduced with dapagliflozin therapy regardless of baseline glycemic status or BMI. Dapagliflozin reduced HF symptom burden, particularly in those with prediabetes or obesity, suggesting there should be a low threshold for initiation of SGLT2 inhibition in these individuals. Dapagliflozin was associated with reduced body weight regardless of baseline glycemic status or BMI.

ARTICLE INFORMATION

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Disclosures

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Supplemental Material

Tables S1–S7
Figures S1–S5

REFERENCES

1. Bolinder J, Ljunggren O, Kullberg J, Johansson L, Wilding J, Langkilde AM, Sugg J, Parikh S. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. *J Clin Endocrinol Metab*. 2012;97:1020–1031. doi: 10.1210/jc.2011-2260
2. Ferrannini E, Seman L, Seewaldt-Becker E, Hantel S, Pinnetti S, Woerle HJ. A phase IIb, randomized, placebo-controlled study of the SGLT2 inhibitor empagliflozin in patients with type 2 diabetes. *Diabetes Obes Metab*. 2013;15:721–728. doi: 10.1111/dom.12081
3. Stenlöf K, Cefalu WT, Kim K-A, Alba M, Usiskin K, Tong C, Canovatchel W, Meininger G. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetes Obes Metab*. 2013;15:372–382. doi: 10.1111/dom.12054
4. Patel SM, Kang YM, Im K, Neuen BL, Anker SD, Bhatt DL, Butler J, Cherney DZI, Claggett BL, Fletcher RA, et al. Sodium-glucose cotransporter-2 inhibitors and major adverse cardiovascular outcomes: a SMART-C collaborative meta-analysis. *Circulation*. 2024;149:1789–1801. doi: 10.1161/CIRCULATIONAHA.124.069568
5. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381:1995–2008. doi: 10.1056/NEJMoa1911303
6. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, 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
7. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *New Engl J Med*. 2015;373:2117–2128. doi: 10.1056/NEJMoa1504720
8. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Brunner–la Rocca HP, Choi DJ, Chopra V, Chuquiure-Valenzuela E, et al. Empagliflozin in heart failure with a preserved ejection fraction. *New Engl J Med*. 2021;385:1451–1461. doi: 10.1056/NEJMoa2107038
9. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, Mann JFE, McMurray JJV, Lindberg M, Rossing P, et al. Dapagliflozin in patients with chronic kidney disease. *New Engl J Med*. 2020;383:1436–1446. doi: 10.1056/NEJMoa2024816
10. The EMPA-KIDNEY Collaborative Group. Empagliflozin in patients with chronic kidney disease. *New Engl J Med*. 2023;388:117–127. doi: 10.1056/NEJMoa2204233
11. James S, Erlinge D, Storey RF, McGuire DK, de Belder M, Björkgren I, Johansson PA, Langkilde AM, Ridderstråle W, Parvaresh Rizi E, 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
12. James S, Erlinge D, Storey RF, DK MG, de Belder M, Eriksson N, Andersen K, Austin D, Arefalk G, Carrick D, et al. Dapagliflozin in myocardial infarction without diabetes or heart failure. *NEJM Evid*. 2023;3:EVIDoa2300286. doi: 10.1056/EVIDoa2300286
13. Norhammar A, Tenerz A, Nilsson G, Hamsten A, Efendíc S, Rydén L, Malmberg K. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. *Lancet*. 2002;359:2140–2144.
14. Ali MK, Bullard KM, Saydah S, Imperatore G, Gregg EW. The cardiorenal burdens of prediabetes in the US: data from serial cross-sectional surveys over 1988–2014. *Lancet Diabetes Endocrinol*. 2018;6:392–403.
15. Alabas OA, Hall M, Dondo TB, Rutherford MJ, Timmis AD, Batin PD, Deanfield JE, Hemingway H, Gale CP. Long-term excess mortality associated with diabetes following acute myocardial infarction: a population-based cohort study. *J Epidemiol Community Health*. 2017;71:25–32. doi: 10.1136/jech-2016-207402
16. Rocca B, Fox K, Ajjan R, Andreotti F, Baigent C, Collet JP, Grove EL, Halvorsen S, Huber K, Morais J, et al. Antithrombotic therapy and body mass: an expert position paper of the ESC working group on thrombosis. *Eur Heart J*. 2018;39:1672–1686.
17. Rentsch CT, Garfield V, Mathur R, Eastwood SV, Smeeth L, Chaturvedi N, Bhaskaran K. Sex-specific risks for cardiovascular disease across the glycaemic spectrum: a population-based cohort study using the UK biobank. *Lancet Regional Health*. 2023;32:100693. doi: 10.1016/j.lanepe.2023.100693
18. Laichuthai N, Abdul-Ghani M, Kosiborod M, Parksook WW, Kerr SJ, DeFronzo R. Newly discovered abnormal glucose tolerance in patients

with acute myocardial infarction and cardiovascular outcomes: a meta-analysis. *Diabetes Care*. 2020;43:1958–1966. doi: 10.2337/dc20-0059

19. American Diabetes Association Professional Practice Committee. 2. Classification and diagnosis of diabetes: standards of medical Care in Diabetes—2022. *Diabetes Care*. 2022;45:S17–S38. doi: 10.2337/dc22-S002

20. Peikert A, Chandra A, Kosiborod MN, Claggett BL, Desai AS, Jhund PS, Lam CSP, Inzucchi SE, Martinez FA, de Boer RA, et al. Association of Dapagliflozin vs placebo with individual Kansas City cardiomyopathy questionnaire components in patients with heart failure with mildly reduced or preserved ejection fraction: a secondary analysis of the DELIVER trial. *JAMA Cardiol*. 2023;8:684–690. doi: 10.1001/jamacardio.2023.1342