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Uppsala Clinical Research Center

DAPAGLIFLOZIN IN MYOCARDIAL INFARCTION WITHOUT DIABETES OR HEART FAILURE

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DAPA-MI TRIAL

Dapagliflozin in myocardial infarction without diabetes or heart failure

Conflicts of interest

Institutional research grants/support from AstraZeneca, Novartis, Jansen and Amgen.

The DAPA-MI trial is sponsored by AstraZeneca (AZ)

DAPAMI

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RATIONALE FOR DAPA-MI TRIAL

What we want to achieve with secondary prevention after a myocardial infarction

- Reduce recurrent myocardial infarction
- Reduce heart failure
- Reduce mortality
- Optimize blood pressure
- Improve kidney function
- Optimize glucose levels
- Weight reduction
- Improve lipid profile
- Promote exercise
- Promote smoking cessation

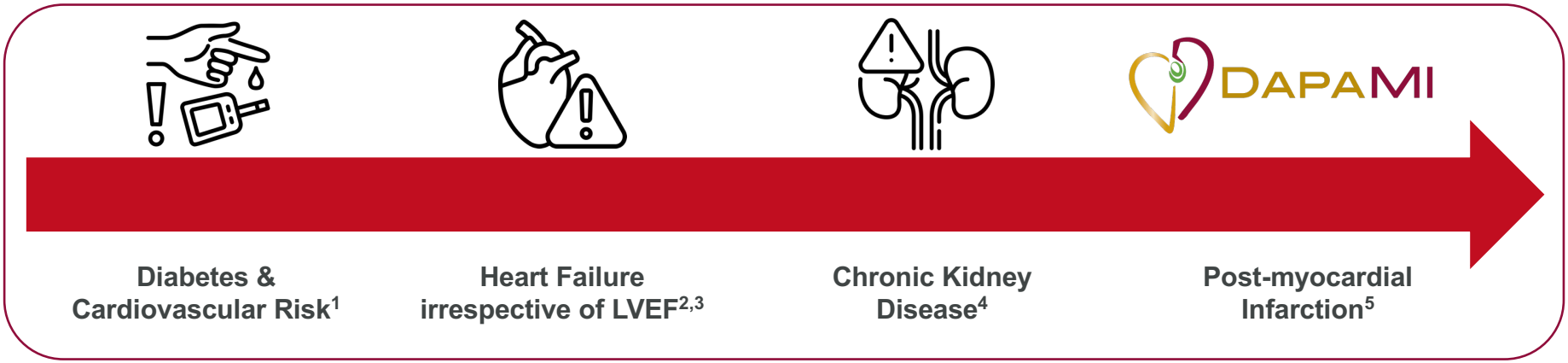
Effects of SGLT2i

- Reduce myocardial infarction
- Reduce heart failure
- Reduce mortality
- Reduce blood pressure
- Improve kidney-related outcomes
- Reduce glucose levels
- Weight reduction
- Slightly lower triglycerides

- *SGLT2i have positive effects on almost all cardiometabolic parameters*
- *It could be an effective secondary prevention medication*

SGLT2i: sodium glucose co-transporter 2 inhibitors

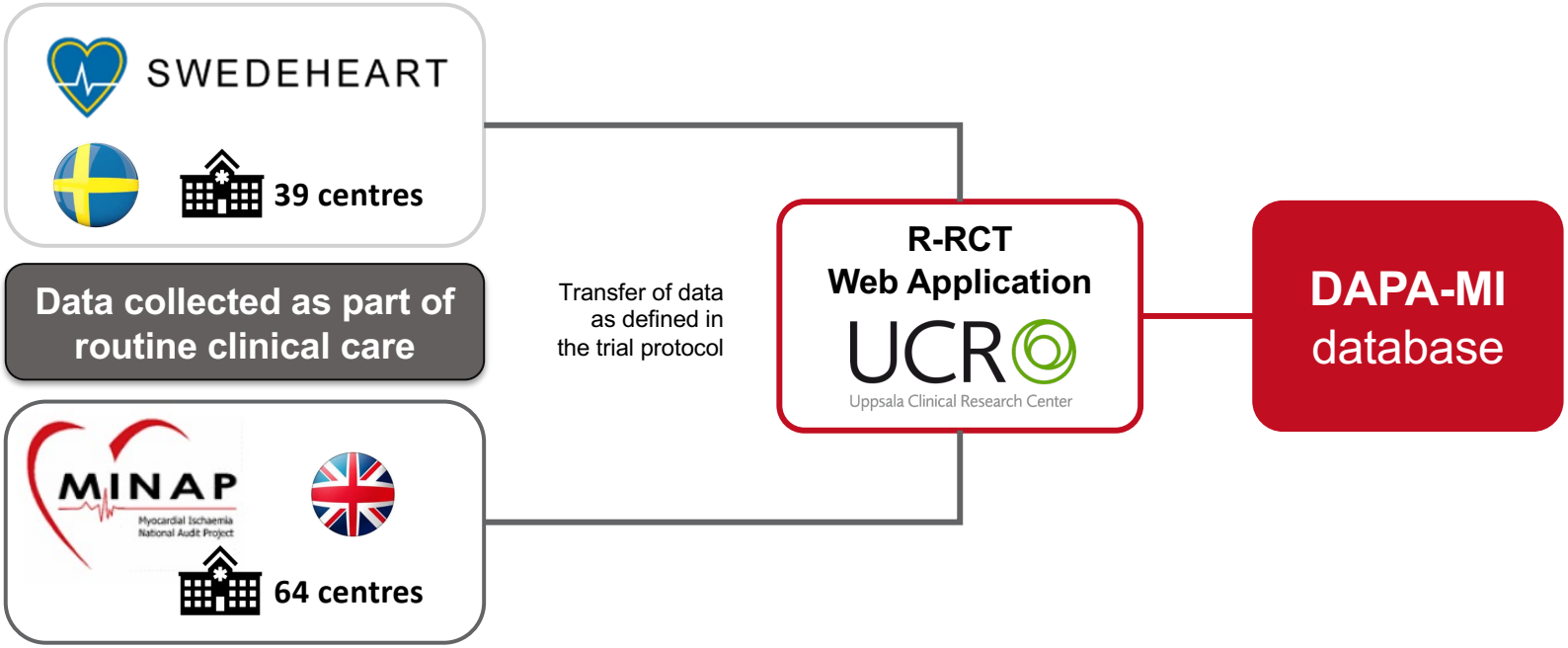
BENEFITS OF SGLT2- INHIBITION



DAPA-MI objective: To evaluate the effect of dapagliflozin on cardiometabolic outcomes in patients with acute myocardial infarction without diabetes or chronic heart failure

1. Wiviott SD et al. *N Engl J Med* 2019;380:347-357; 2. McMurray JJV et al. *N Engl J Med* 2019;381:1995-2008;
3. Solomon SD et al. N Engl J Med 2022;387(12):1089-1098 ; 4. Heerspink HJL et al. N Engl J Med. 2020; 383:1436-14464;
5. James S et al. *Am Heart J* 2023. doi: 10.1016/j.ahj.2023.08.008.
LVEF: left ventricular ejection fraction

REGISTRY-BASED RANDOMIZED CLINICAL TRIAL – R-RCT



SWEDEHEART: Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies. MINAP: Myocardial Ischaemia National Audit Project.

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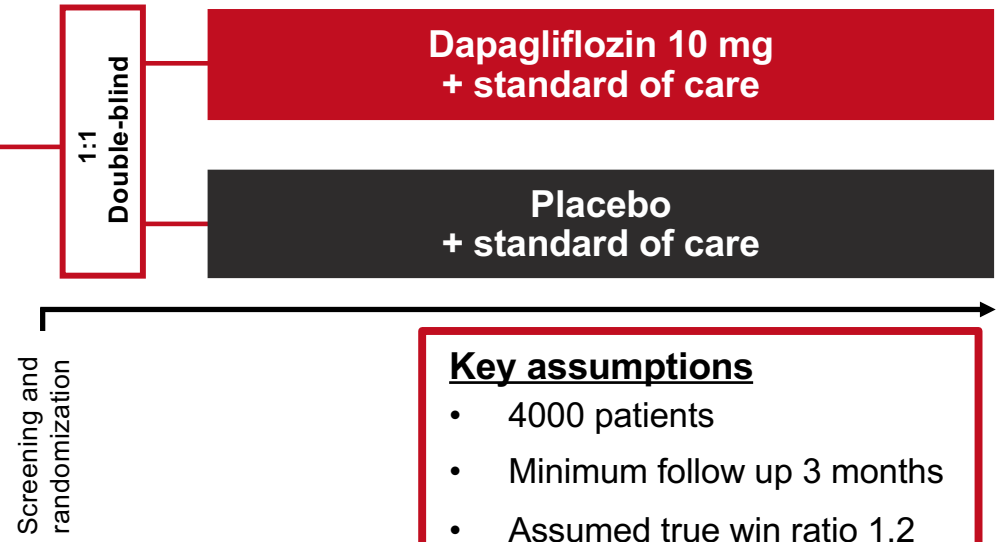
TRIAL DESIGN

Main Inclusion Criteria

- MI (NSTEMI or STEMI) < 10 days
- Impaired LV systolic function or Q-wave MI
- Hemodynamically stable

Main Exclusion Criteria

- Type 1 or type 2 diabetes
- Chronic symptomatic HF with a prior HHF within the last year and known reduced EF (LVEF ≤ 40 %)
- eGFR <20 mL/min/1.73 m^2



Key assumptions

- 4000 patients
- Minimum follow up 3 months
- Assumed true win ratio 1.2
- Total trial duration 2.5 years
- Power 80%, *P*<0.05

MI: myocardial infarction, NSTEMI: non-ST-elevation MI, STEMI: ST-elevation MI, HF: heart failure, HHF: hospitalization for heart failure, EF: ejection fraction
eGFR: estimated glomerular filtration rate

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ENDPOINTS

The composite of CV death and hospitalization for heart failure was initially chosen as the primary outcome.
During the trial, it became evident that the number primary composite outcomes was substantially lower than anticipated.
Thus, in Feb 2023, the trial was modified to a hierarchical composite outcome approach with cardiometabolic outcomes.[1]

Primary

The hierarchical (win ratio) composite outcomes:

- Death (first cardiovascular death, followed by non-cardiovascular death)
- Hospitalization due to heart failure (first adjudicated, followed by investigator reported)
- Non-fatal myocardial infarction
- Atrial fibrillation/flutter event
- New diagnosis of type 2 diabetes
- NYHA functional class at last visit
- Body weight decrease at least 5% at last visit

Key secondary

- Primary outcome excluding body weight component

Other secondary

- Time to the first occurrence of any of the components of the composite:
  - Hospitalization for heart failure
  - Cardiovascular death

1. James S et al. *Am Heart J* 2023. doi: 10.1016/j.ahj.2023.08.008.
NYHA, New York Heart Association

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Summary of key demographic and baseline characteristics		Dapa 10 mg (N=2019)	Placebo (N=1998)
Age, years	Mean	63.0	62.8
Sex, n (%)	Female	388 (19.2)	419 (21.0)
Country, n (%)	Sweden / United Kingdom	584 (28.9) / 1435 (71.1)	594 (29.7) / 1404 (70.3)
Body Mass Index (kg/m^2)	Mean	28.2	28.3
Baseline LVEF, n (%)	<30	130 (6.4)	137 (6.9)
	30-49	1363 (67.5)	1311 (65.6)
	≥50	416 (20.6)	432 (21.6)
Myocardial Infarction Index Event, n (%)	STEMI	1465 (72.6)	1428 (71.5)
eGFR (ml/min/1.73m^3)	Mean	83.5	83.4
Co-morbidities, n (%)	Hypertension	766 (37.9)	716 (35.8)
	Prior myocardial infarction	178 (8.8)	189 (9.5)
	Prior stroke	46 (2.3)	50 (2.5)
Key medications, n (%)	Acetylsalicylic acid	1873 (92.8)	1854 (92.8)
	Thienopyridine/Ticagrelor	1857 (92.0)	1819 (91.0)
	ACE inhibitor/ARB	1868 (92.5)	1835 (91.8)
	Aldosterone receptor blocker	459 (22.7)	464 (23.2)
	Beta blockers	1805 (89.4)	1797 (89.9)
	Statins	1938 (96.0)	1897 (94.9)

N: Number of subjects in the treatment group, Dapa: Dapagliflozin, ACE: Angiotensin-converting enzyme, ARB: angiotensin receptor blocker

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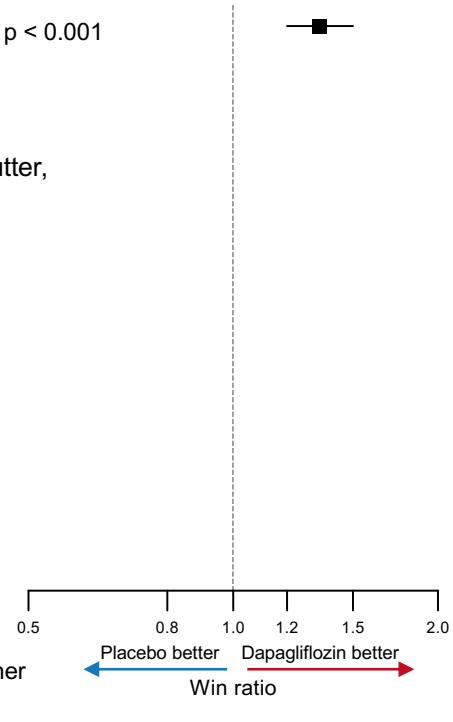
PRIMARY & KEY SECONDARY OUTCOMES

Primary outcome
All 7 components

Win ratio (95% CI)

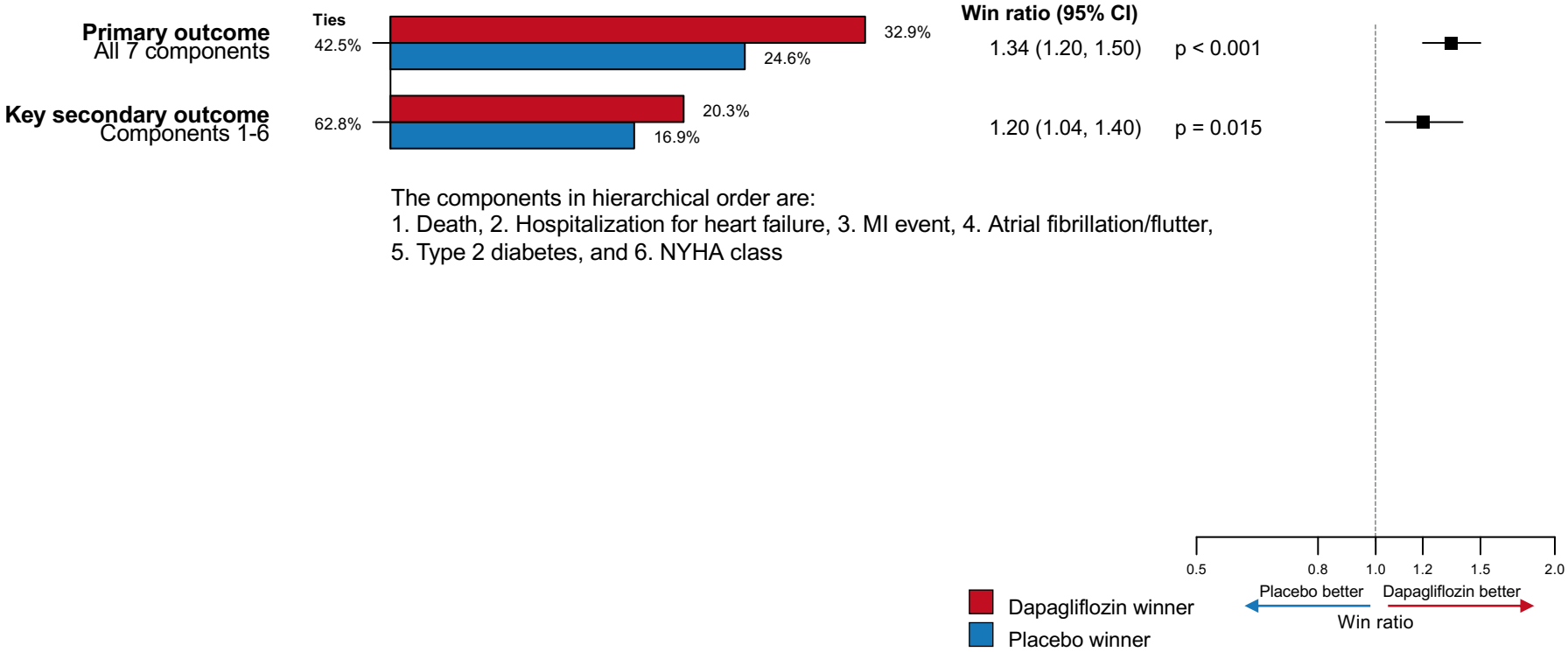
1.34 (1.20, 1.50) p < 0.001



The components in hierarchical order are:
1. Death, 2. Hospitalization for heart failure, 3. MI event, 4. Atrial fibrillation/flutter, 5. Type 2 diabetes, 6. NYHA class, and 7. Weight decrease ≥ 5%

Dapagliflozin winner
Placebo winner

PRIMARY & KEY SECONDARY OUTCOMES



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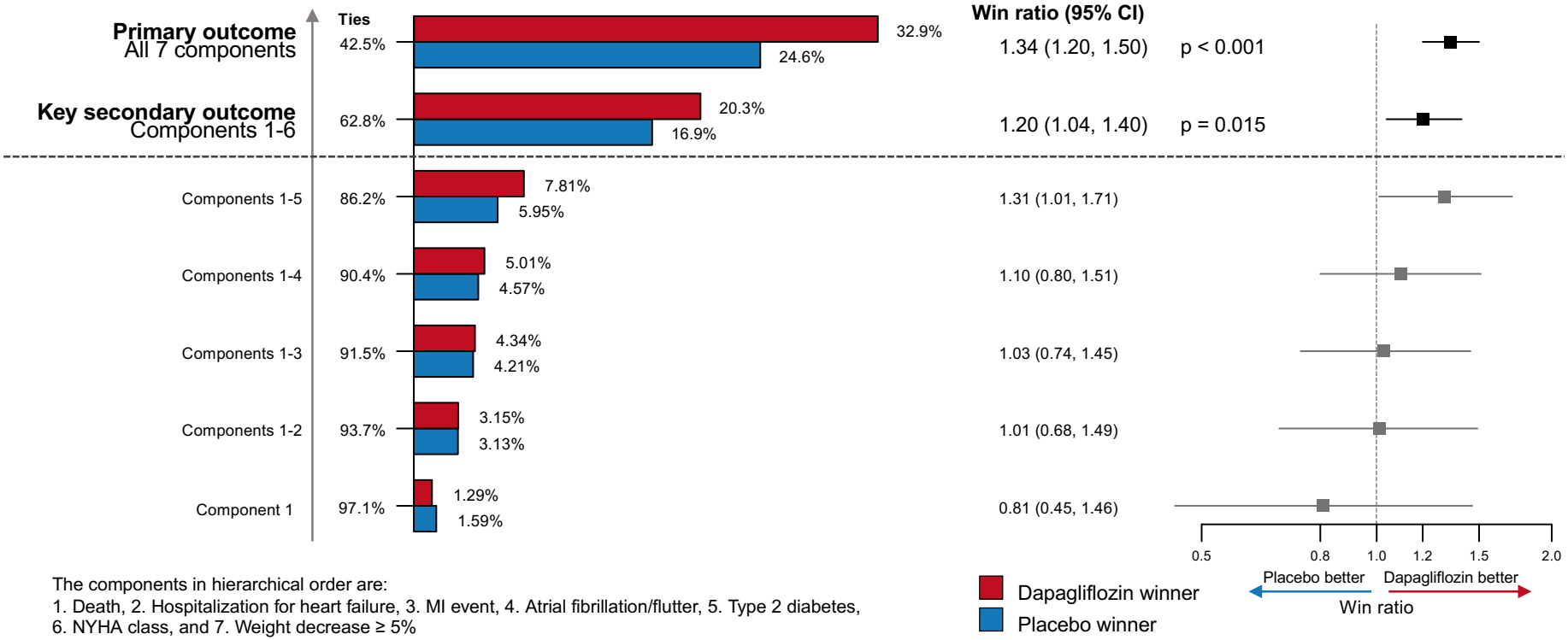
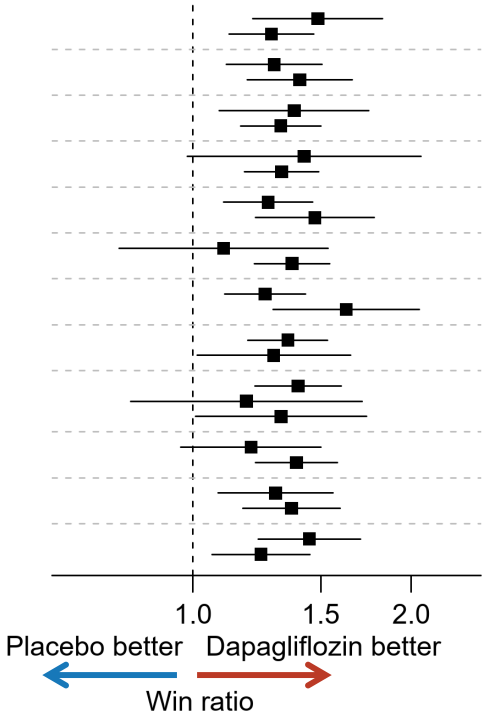
PRIMARY & KEY SECONDARY OUTCOMES



The components in hierarchical order are:
1. Death, 2. Hospitalization for heart failure, 3. MI event, 4. Atrial fibrillation/flutter, 5. Type 2 diabetes, 6. NYHA class, and 7. Weight decrease ≥ 5%

PRIMARY OUTCOME BY SUBGROUPS

Variable	Subgroup	N	WR [95% CI]	p interaction
Country	Sweden	1178	1.49 [1.21,1.83]	0.240
	United Kingdom	2839	1.28 [1.12,1.47]	
Age group	≤65	2387	1.29 [1.11,1.51]	0.477
	>65	1630	1.40 [1.19,1.66]	
Sex	Female	807	1.38 [1.09,1.75]	0.760
	Male	3210	1.32 [1.16,1.50]	
ACEi/ARB	No	314	1.42 [0.98,2.06]	0.720
	Yes	3703	1.33 [1.18,1.49]	
BMI	<30	2727	1.27 [1.10,1.46]	0.216
	≥30	1264	1.47 [1.22,1.78]	
eGFR by CKD−EPI	<60	385	1.10 [0.79,1.54]	0.228
	≥60	3630	1.37 [1.22,1.54]	
Diastolic BP	<80	2986	1.26 [1.11,1.43]	0.057
	≥80	1031	1.63 [1.29,2.05]	
Systolic BP	<130	3056	1.35 [1.19,1.53]	0.750
	≥130	961	1.29 [1.01,1.65]	
Baseline LVEF	30−49	2674	1.40 [1.22,1.60]	0.804
	<30	267	1.19 [0.82,1.71]	
	≥50	848	1.32 [1.01,1.73]	
MI index event	NSTEMI	1106	1.20 [0.96,1.50]	0.273
	STEMI	2893	1.39 [1.22,1.58]	
Baseline HbA_1c	<Median	1571	1.30 [1.08,1.56]	0.679
	≥Median	2020	1.37 [1.17,1.60]	
Baseline Creatinine	<Median	1953	1.45 [1.23,1.70]	0.181
	≥Median	2062	1.24 [1.06,1.45]	



BMI: body mass index, CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration, BP: blood pressure, HbA_1c: glycated hemoglobin

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SECONDARY AND EXPLORATORY OUTCOMES

Secondary and exploratory outcomes	Dapagliflozin 10 mg (N = 2019)	Placebo (N = 1998)	Hazard ratio (95% CI)
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)
Hospitalization due to AF/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 (0.97–1.29)
Adjudicated hospitalization for HF, n (%)*	27 (1.3)	32 (1.6)	0.83 (0.50–1.39)

No unexpected safety concerns were reported during the trial. Serious adverse events leading to death on treatment** occurred in 30/1995 (1.5%) in the dapagliflozin group and in 29/1997 (1.5%) in the placebo group.

*Exploratory outcome, **On-treatment period will include events with an onset date on or after the first dose of randomized study drug and on or before 30 days after the last dose of the study drug

CI: confidence interval, CV: cardiovascular, HF: heart failure, MACE: major adverse cardiovascular event, AF: atrial fibrillation

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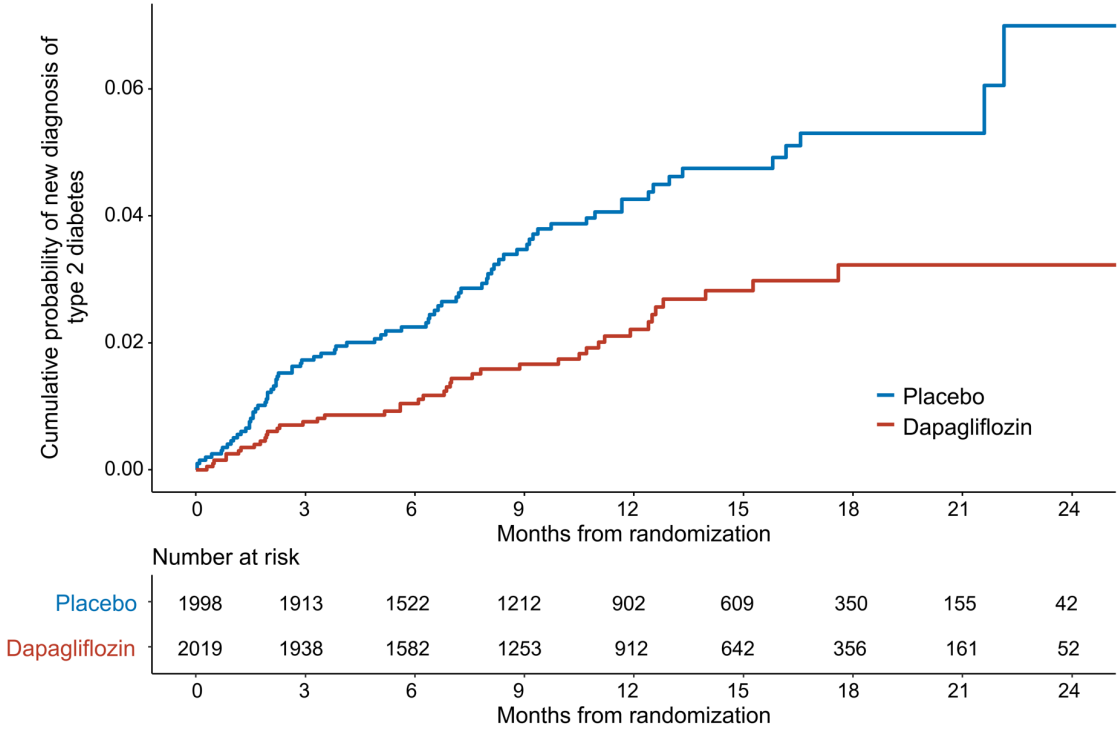
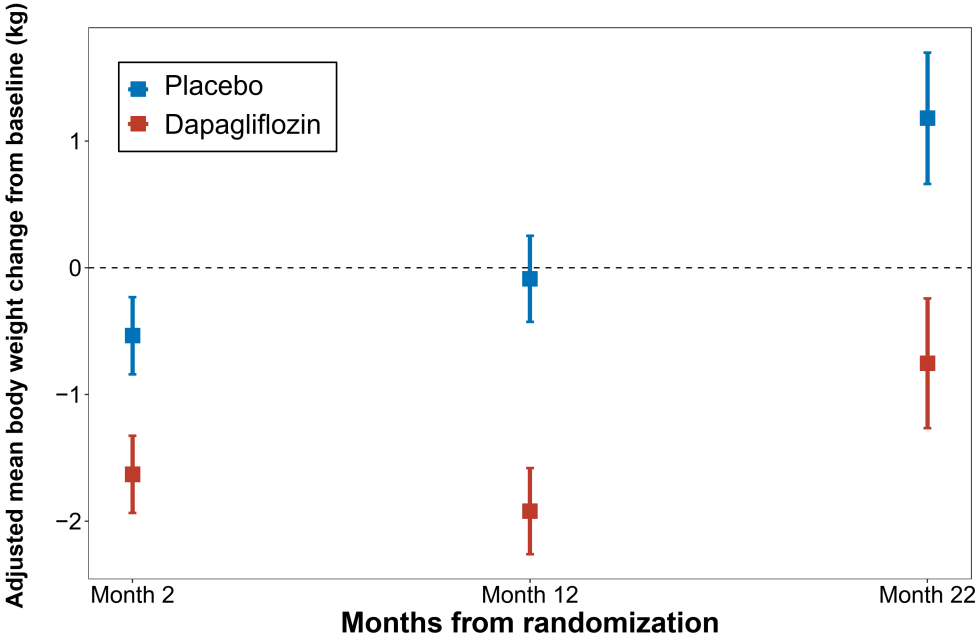
NEW DIAGNOSIS OF TYPE 2 DIABETES



CHANGE IN BODY WEIGHT



Dapagliflozin (N)	1813	1254	407
Placebo (N)	1810	1235	397

Overall treatment effect on change in body weight (kg) for dapagliflozin vs placebo

-1.65 (95% CI, -2.12 to -1.18)

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CONCLUSIONS

- In patients with acute MI and impaired left ventricular systolic function, without prior diabetes or chronic heart failure, dapagliflozin demonstrated significant benefit with regards to improvement in cardiometabolic outcomes compared with placebo.
- The cardiometabolic benefit was consistent across all pre-specified subgroups and there were no new safety concerns.
- Clinical event rates were low with no significant difference between randomized groups.
- The innovative registry-based clinical trial (R-RCT) design, incorporating national clinical registry data, facilitated efficient patient recruitment and outcome ascertainment.

NEJM Evidence

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ORIGINAL ARTICLE

Dapagliflozin in Myocardial Infarction without Diabetes or Heart Failure

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