DAPA-MI – A Pragmatic Registry-Based Double-Blind RCT Trial Designed For Regulatory Evaluation

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DAPAMI

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 heart failure
- Reduce mortality
- Reduce myocardial infarction (?)
- 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*

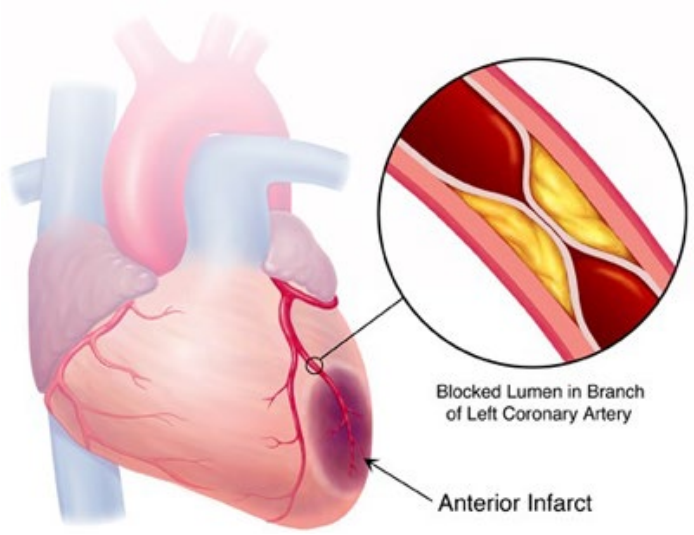
SG

Rationale and unmet medical need

Myocardial infarction (MI) affects approximately 7 million individuals each year

✓Previously observed improvements in post MI prognosis have reached a plateau in recent years

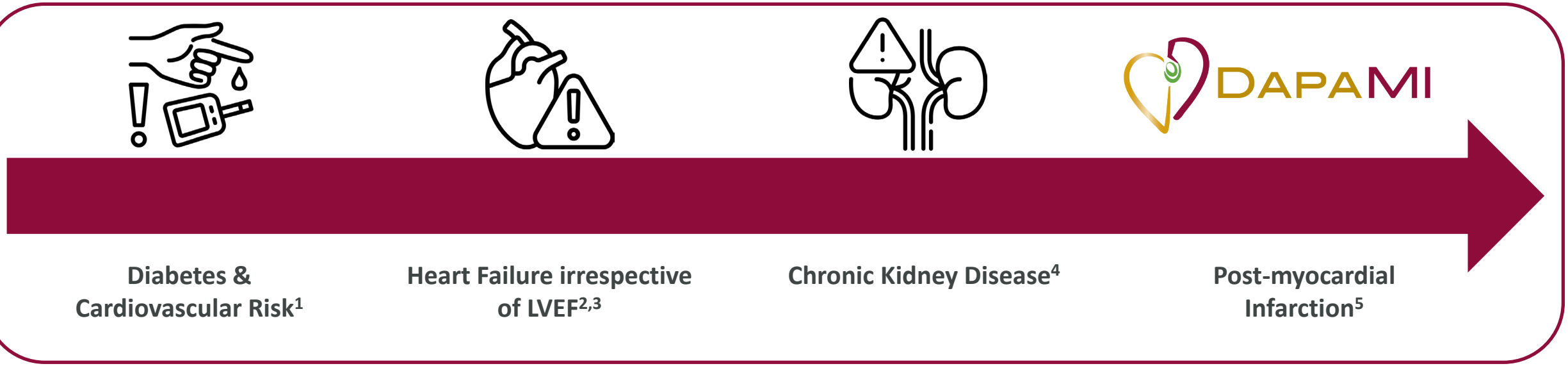
✓Novel approaches need to tackle post MI heart failure development: the strongest predictor of mortality



✓Due to mode of action, dapagliflozin is hypothesized to reduce the risk for development of heart failure following MI

✓ SGLT-2 inhibition may become the first new beneficial pharmacological treatment concept for patients with MI in over a decade

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

DAPA-MI Objectives

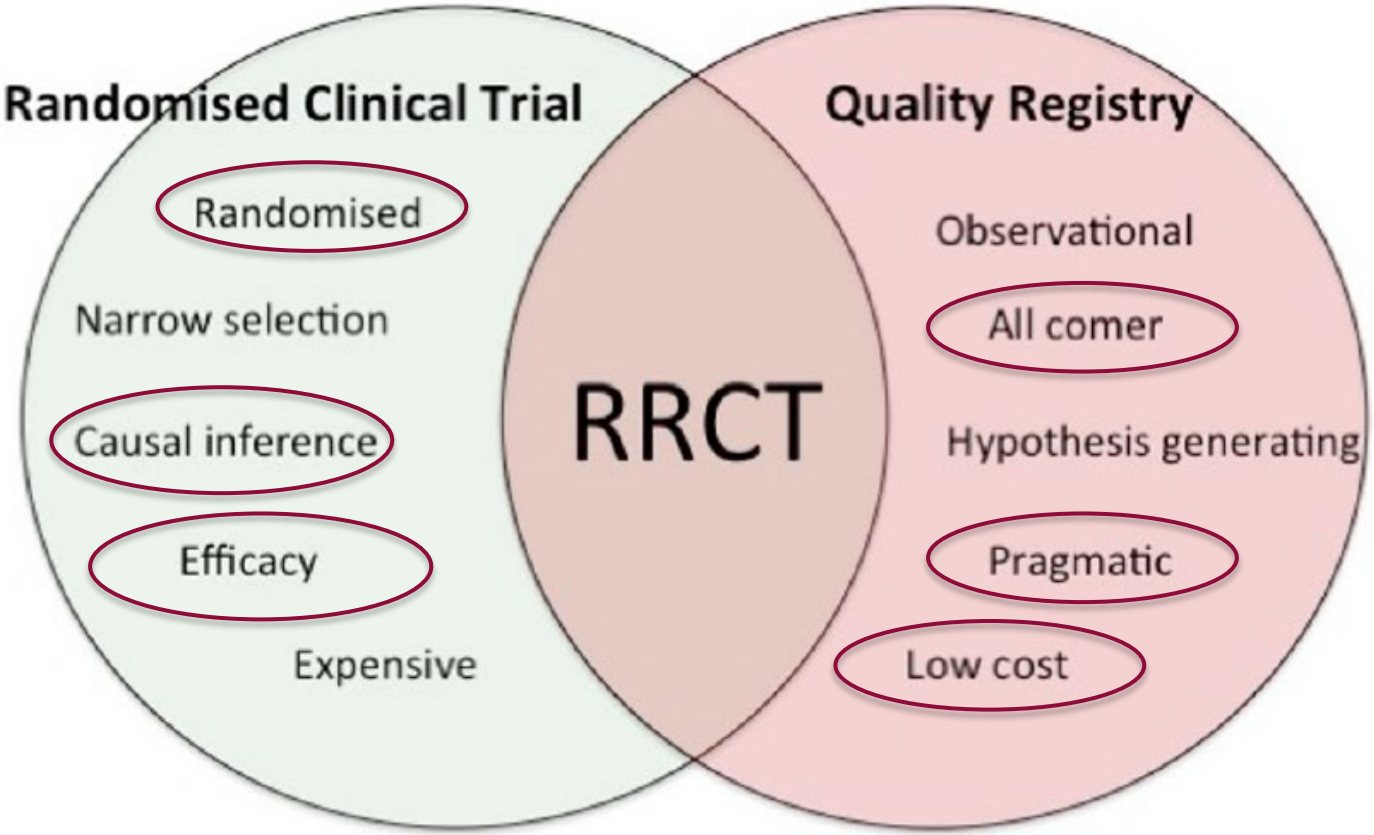
- To evaluate the possibility to conduct registrational clinical trials in a new way for marketed products with a known safety profile

- By combining “gold standard” RCT elements:
  - Randomization
  - Double-blinding
  - Placebo control

- With innovative trial elements using clinical registries in routine health care:
  - Broad population
  - Point of care data collection
  - Alignment of study visits and clinical routine
  - High proportion of eligible patients recruited

Synergy of RCTs and Clinical quality registries

R-RCT: A prospective randomized controlled trial that uses a clinical quality registry for one or several major functions for trial conduct and outcomes reporting



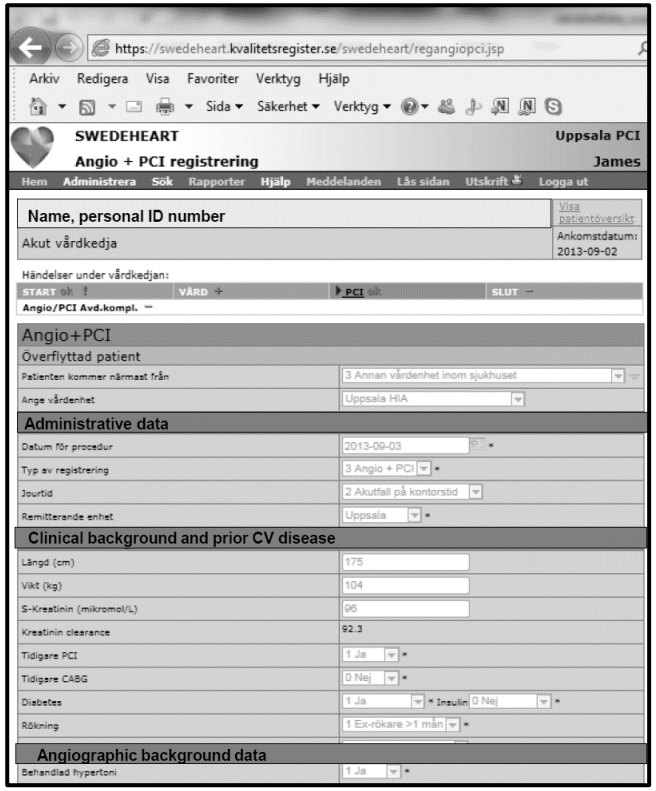
Yndigegn T, et al. Heart 2018;0:1–6. doi:10.1136/heartjnl-2017-312322

The DAPA-MI SWEDEHEART/MINAP registry framework

1. NATIONAL DATA
cover the entire populations

**Note: The MINAP Registry covers England and Wales but not Scotland.

2. STRUCTURED DATA
”eCRF-like”



3. PROSPECTIVELY COLLECTED DATA
As part of clinical routine

4. SHARED TECHNICAL PLATFORM

SWEDEHEART

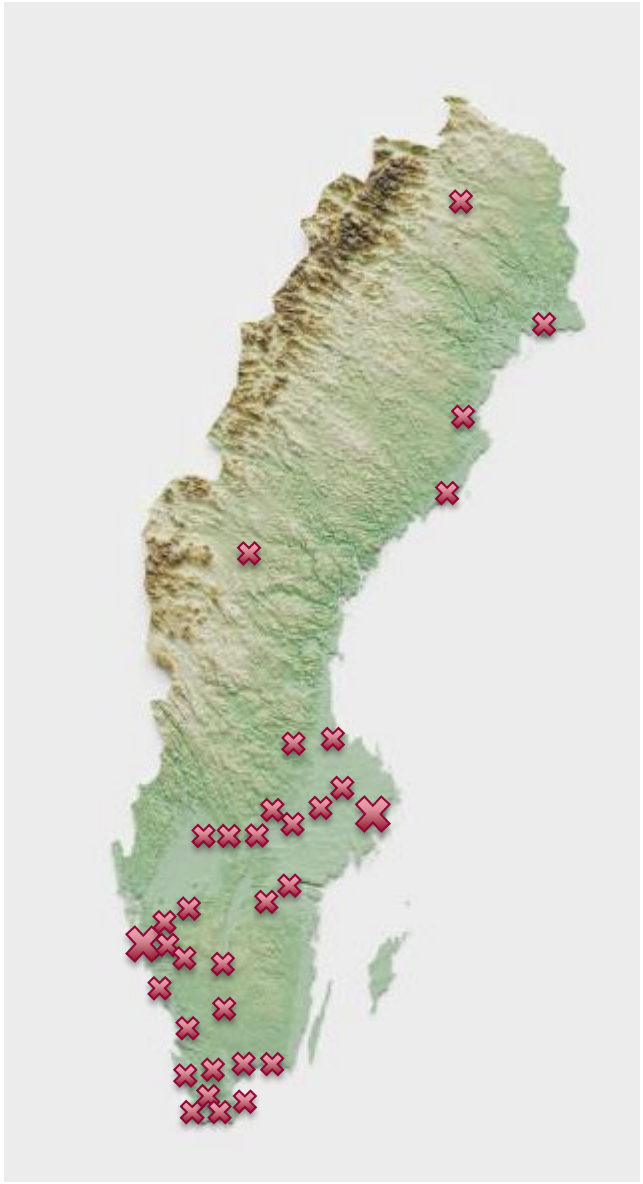
MINAP

SWEDEHEART – Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies

MINAP – Myocardial Infarction National Audit Project

UCR

Covering the population in Sweden



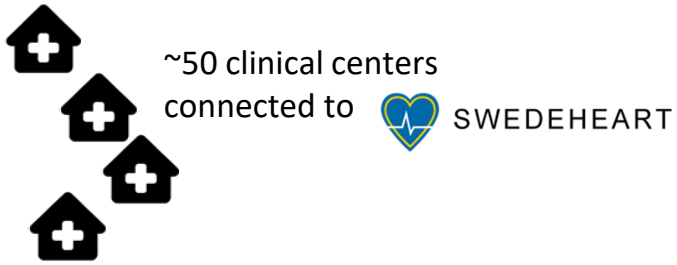
39 sites participated in Sweden across the whole country – both large and small hospitals

- 5 sites in Stockholm
- 3 sites in Göteborg/Mölndal

DAPA-MI Health Authority Formal Interactions

				
UK	**US**	**Sweden**	**Germany**	**EU**
MHRA	**FDA**	**MPA**	**BfArM**	**EMA**
18 Nov 2019	17 Dec 2019	22 Jan 2020	15 June 2020	26 Oct 2020

Study design



~50 clinical centers
connected to SWEDEHEART

- Myocardial infarction (STEMI & NSTEMI) within 10 d
- Reduced LVEF or Q wave MI
- No T1 or T2 Diabetes
- No Chronic symptomatic heart failure*
- WRITTEN INFORMED CONSENT

R

Dapagliflozin 10 mg once daily on top of SoC

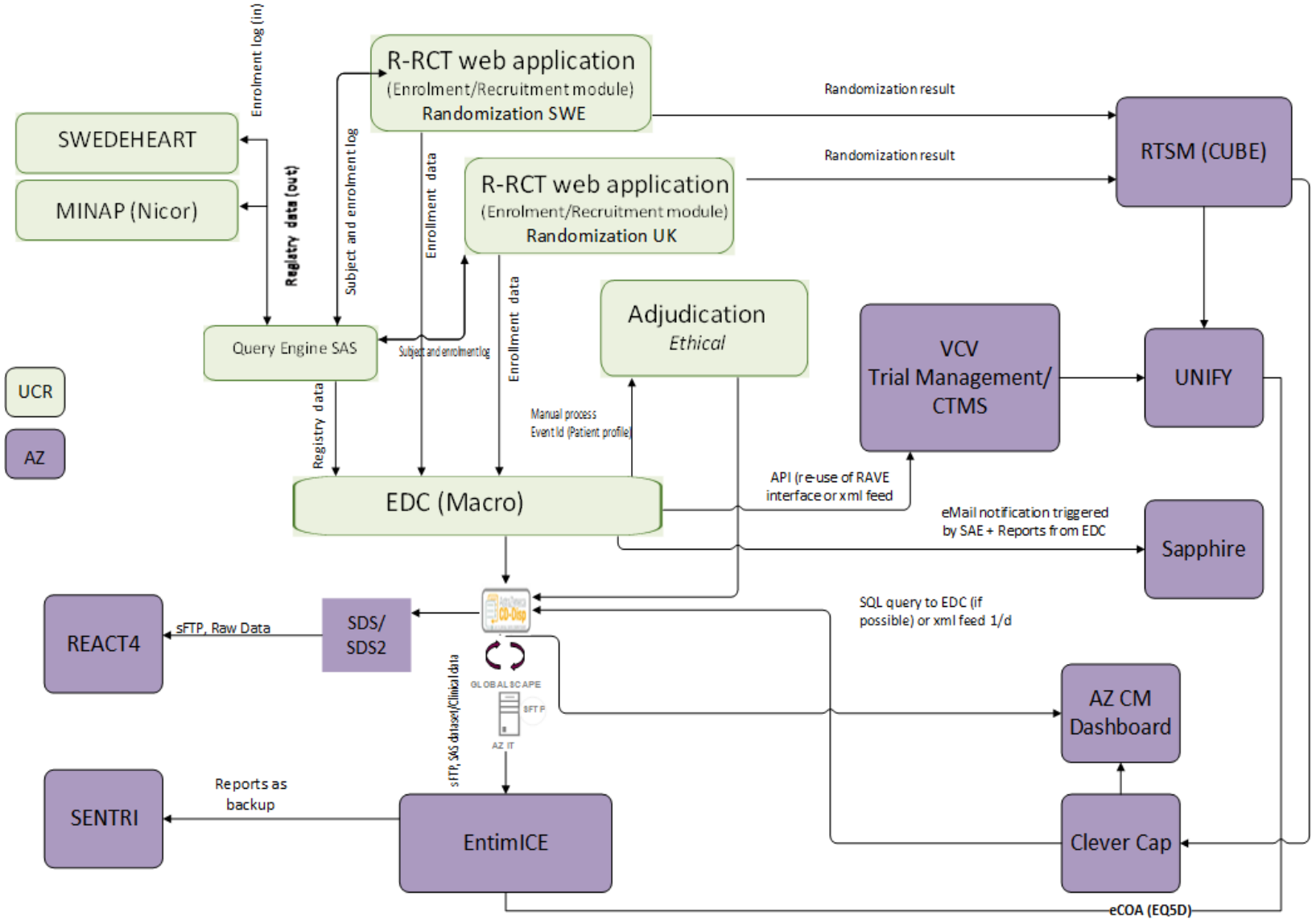
Placebo once daily on top of SoC

~50 clinical centers
connected to MINAP

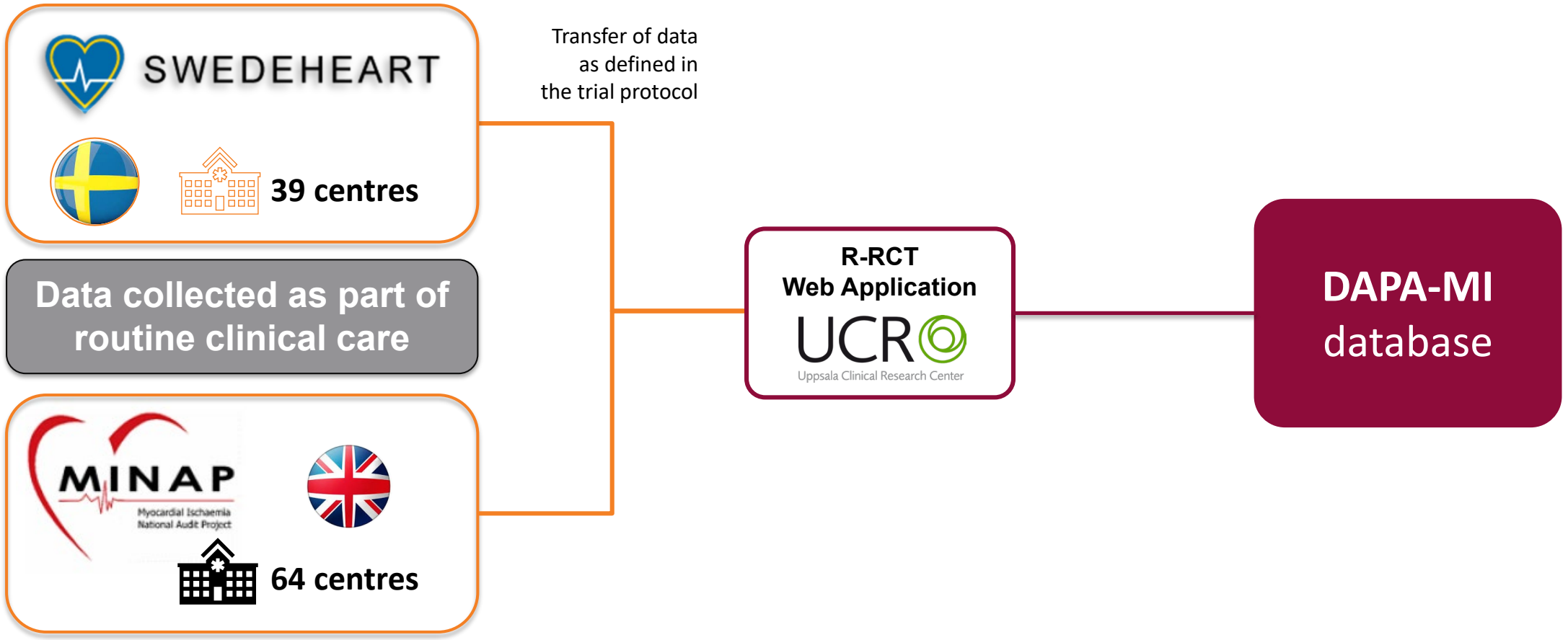
Visits @ 6-10 weeks post-randomization (on-site) and at 1 year; thereafter every 10th month until end of treatment
In UK, additional local lab samples will be collected for serum creatinine, glucose and HbA1c tests at 5 month intervals

*with a prior hospitalization for heart failure within the last year and known reduced ejection fraction (LVEF≤40 %), documented before the current MI

Data Flow (simplified)

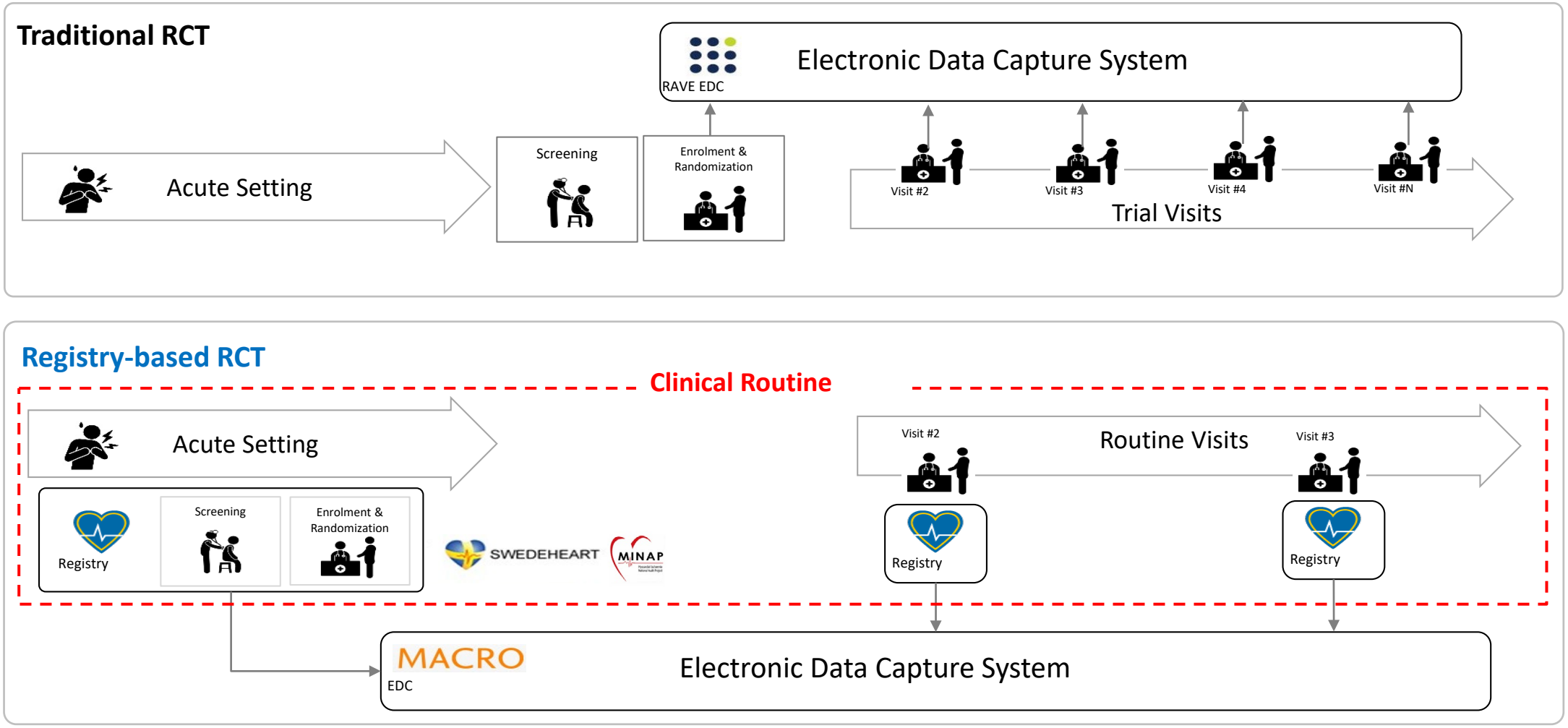


Data flow overview



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

DAPA-MI study drives innovation in clinical trials



Innovative Design and Digital Technologies

Reduced patient and investigator burden

Streamlined trial design with automated data transfer from routine clinical practice

✓

Remote patient monitoring

Patient app for information sharing and signalling of events

+/-

Advancing drug adherence

Use of CleverCap adherence monitoring technology

✓

Original study design

~50 clinical centres in Sweden connected to

SWEDEHEART

6400* patients with

- MI (STEMI & NSTEMI) within 7 d
- Reduced LVEF or Q wave MI
- No T1DM or T2DM
- WRITTEN INFORMED CONSENT

R

Dapagliflozin 10 mg once daily on top of SoC

Placebo once daily on top of SoC

~50 clinical centres in UK connected to

MINAP

Visits @ 6-10 weeks post-randomisation (on-site) and at 1 y; thereafter every 10th month until EoT

Primary composite endpoint: Time to first event of hospitalisation for heart failure or CV death

Key assumptions

- Primary annual event rate: 7.5%
- RRR: 20%
- Power: 85%
- P: <0.05

Event-driven trial (722 events)
Recruitment time: 18 months
Total trial duration: 30 months

Comparison of patients in DAPA-MI vs. Observational database

VARIABLE	OBSERVATIONAL DATABASE	DAPA-MI*
Female	32%	20%
Smoker current	24%	23%
Smoker former	34%	24%
MI previous	11%	8%
Hypertension	46%	32%
Stroke previous	6%	2%
Age median	72 years	64 years
Age mean		64 years
SBP median	143 mmHg	117 mmHg
DBP median	85 mmHg	72 mmHg
BMI median	25.8 kg/m2	27.7 kg/m2
Weight mean	78 kg	85 kg
MI index event STEMI	50%	63%
LVEF <30	10%	7%
LVEF 30-49	80%	78%
LVEF >=50	10%	15% (up to 17% in August 2022)

*June 2022

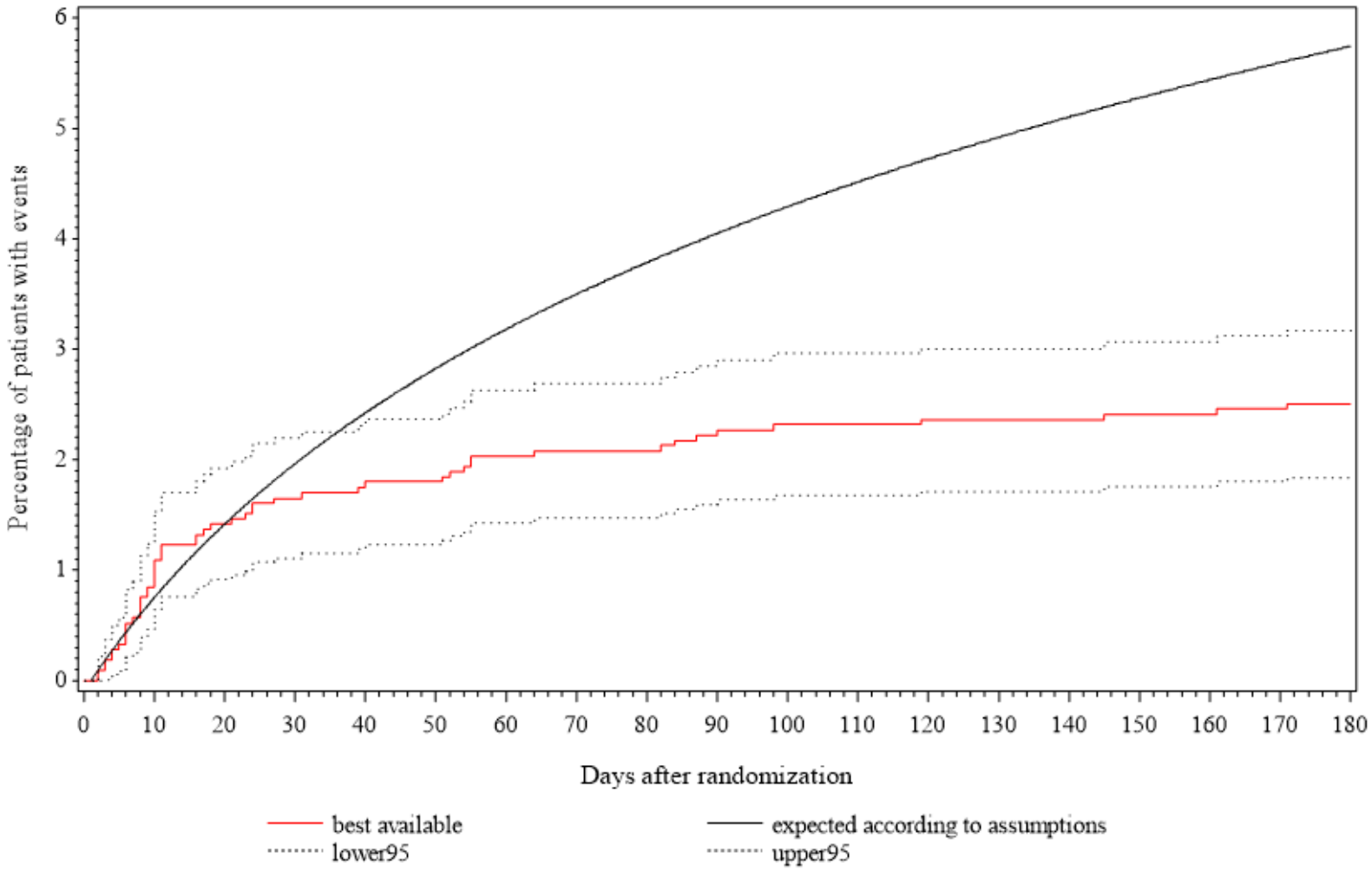
Endpoints

Primary

Time to the first occurrence of any of the components of the composite:

- Hospitalization for heart failure (hHF)
- Cardiovascular (CV) death

Event rate (KM-estimates) for primary composite endpoint at 6 months Nov 2022; N= 2,116



Learnings

Patients were very well treated according to guidelines and with timely revascularization

Broad inclusion criteria led to recruitment of patients in the lower risk spectrum

In addition, the trial was partly performed during the Covid pandemic with generally fewer hospitalisations

Endpoints

Primary

Time to the first occurrence of any of the components of the composite:

- Hospitalisation for heart failure (hHF)
- Cardiovascular (CV) death

During the course of the trial, it became evident that the number of collected primary composite outcomes in the DAPA-MI trial was substantially lower than anticipated.

Endpoints

Primary

The hierarchical (win ratio) composite endpoint:

- Death (first CV death, followed by non-CV death)
- Hospitalisation due to heart failure (first adjudicated, followed by investigator reported)
- Non-fatal MI
- AF/flutter event
- New onset of type 2 diabetes
- NYHA class at last visit
- Body weight decrease at least 5% at last visit

Key Secondary

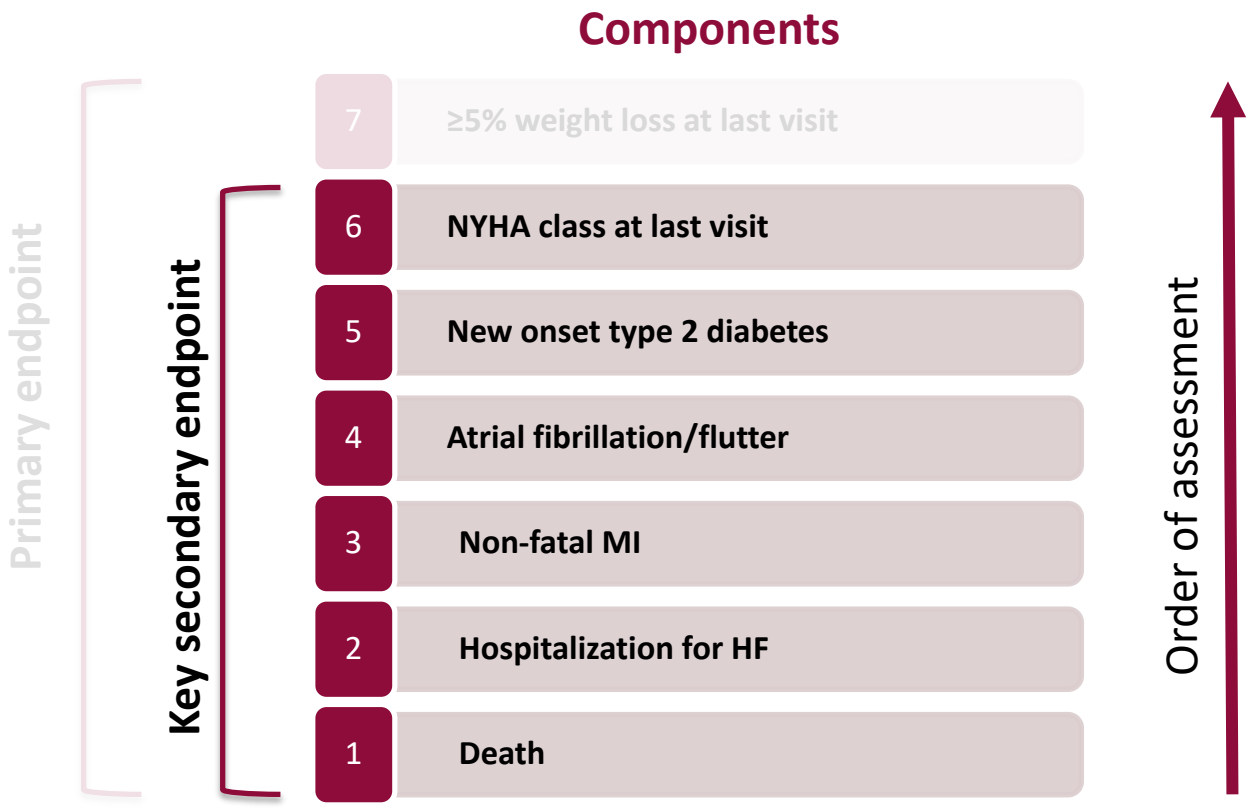
- Primary endpoint excluding body weight decrease at least 5% at last visit component
- Time to the first occurrence of any of the components of the composite:
  - Hospitalisation for heart failure (hHF)
  - Cardiovascular (CV) death

In February 2023, the trial was modified from an event-driven time-to-event approach to a hierarchical composite outcome approach including clinically relevant cardiometabolic outcomes.

Key assumptions

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

Primary Hierarchical Composite Endpoint (HCE)



HF: heart failure. MI: myocardial infarction. NYHA: New York Heart Association

Patient Characteristics were Balanced Between Treatment Groups

Summary of key demographic and baseline characteristics		Dapa 10 mg (N=2019)	Placebo (N=1998)
Age (years)	Mean	63.0	62.8
	>65 years n (%)	831 (41.2)	799 (40.0)
Sex n (%)	Female	388 (19.2)	419 (21.0)
Race n (%)	White	1905 (94.4)	1893 (94.7)
	Black or African American	8 (0.4)	15 (0.8)
	Asian	64 (3.2)	52 (2.6)
	Other	40 (2.0)	37 (1.9)
Country n (%)	Sweden	584 (28.9)	594 (29.7)
	United Kingdom	1435 (71.1)	1404 (70.3)

N: Number of subjects in the treatment group. Dapa: Dapagliflozin.

Patient Characteristics were Balanced Between Treatment Groups

Summary of key demographic and baseline characteristics		Dapa 10 mg (N=2019)	Placebo (N=1998)
Body Mass Index (kg/m^2)	Mean	28.2	28.3
	≥30 n (%)	626 (31.0)	638 (31.9)
Diastolic Blood Pressure (mmHg)	Mean	73.0	72.4
	≥80 n (%)	538 (26.6)	493 (24.7)
Systolic Blood Pressure (mmHg)	Mean	119.1	118.7
	≥130 n (%)	494 (24.5)	467 (23.4)
Baseline LVEF (%)	<30	130 (6.4)	137 (6.9)
	30-49	1363 (67.5)	1311 (65.6)
	≥50	416 (20.6)	432 (21.6)
	Missing	110 (5.4)	118 (5.9)
MI Index event	STEMI	1465 (72.6)	1428 (71.5)
	NSTEMI	544 (26.9)	562 (28.1)
Smoking	Current and former	1170 (57.9)	1131 (56.6)
	Never	843 (41.8)	866 (43.3)
eGFR (ml/min/1.73m^2)	Mean	83.5	83.4
	≥ 60 n (%)	1828 (90.5)	1802 (90.2)

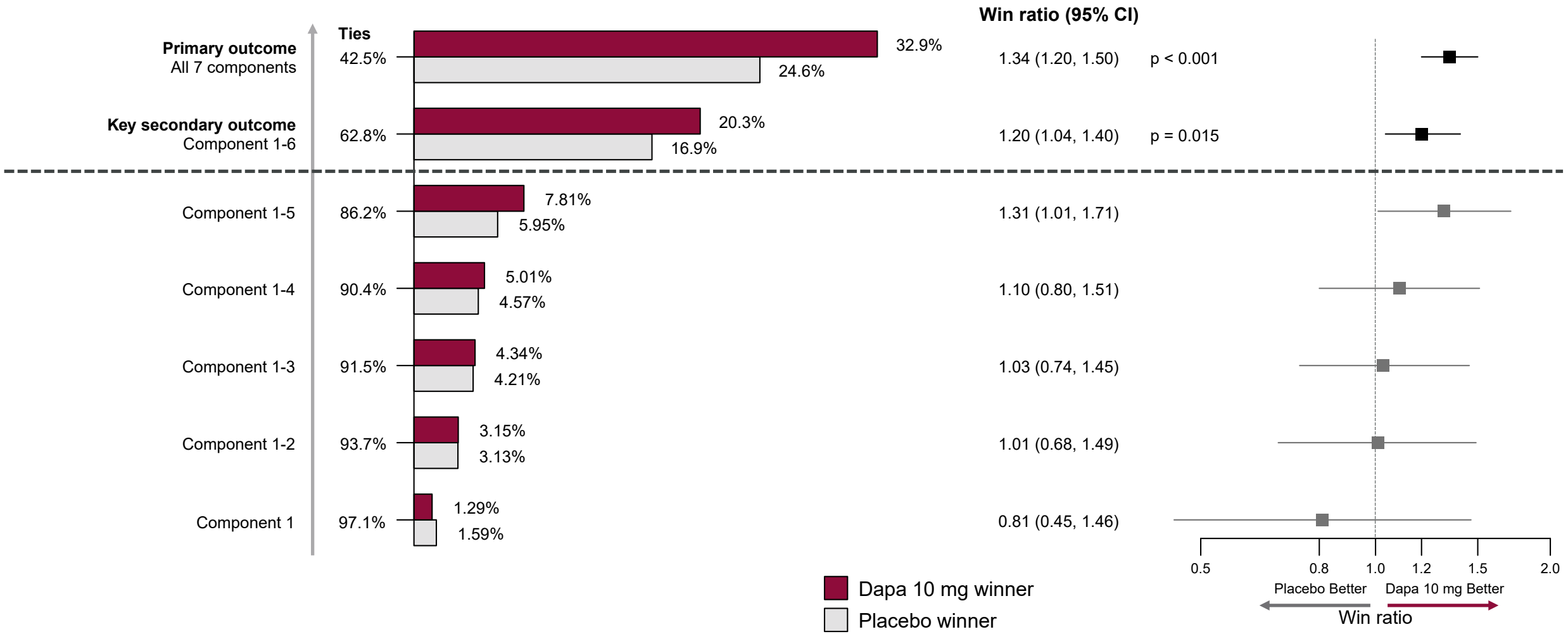
eGFR: Estimated glomerular filtration rate. LVEF: Left ventricular ejection fraction. MI: Myocardial infarction. STEMI: ST Elevation MI. NSTEMI: Non-ST Elevation MI. N: Number of subjects in the treatment group. Dapa: Dapagliflozin.

Baseline Medications were Balanced, and Patients were Well-treated

Summary of key medications at discharge	Dapa 10 mg (N=2019)	Placebo (N=1998)
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)
Oral Anticoagulants	252 (12.5)	269 (13.5)
Thienopyridine/Ticagrelor	1857 (92.0)	1819 (91.0)
Statins	1938 (96.0)	1897 (94.9)
Anti-hyperglycemic agents	31 (1.5)	36 (1.8)
Any Antiplatelet	1970 (97.6)	1938 (97.0)

ACE: Angiotensin-converting enzyme. ARB: Angiotensin II receptor blockers. Dapa: Dapagliflozin. N: Number of subjects in the treatment group

Primary and Key Secondary Hierarchical Composite Endpoint (HCE)



The gray arrow indicates the order of the endpoint 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 hierachical order are:
1. Death, 2. Hospitalization for heart failure, 3. non-fatal MI event, 4. Atrial fibrillation/flutter, 5. New onset type 2 diabetes, 6. NYHA class and 7. Weight decrease >= 5%

Secondary Endpoints Hazard ratio

	Dapa 10 mg (N=2019)	Placebo (N=1998)	HR	95% CI	p-value
Composite of CV death/hospitalisations for HF	50	52	0.95	(0.64, 1.40)	0.781
Composite of CV death/hospitalisations for HF/MI	82	85	0.95	(0.70, 1.29)	0.742
MACE	68	72	0.94	(0.67, 1.31)	0.715
CV Death	27	23	1.15	(0.66, 2.01)	0.612
MI	44	39	1.11	(0.72, 1.71)	0.633
New onset of T2DM	42	78	0.53	(0.36, 0.77)	<0.001
Hospitalisation for any cause	418	372	1.12	(0.98, 1.29)	0.108
All-cause mortality	41	33	1.22	(0.77, 1.92)	0.402

CV: Cardiovascular. HF: Heart failure. MACE: Myocardial infarction, stroke or CV death. MI: Myocardial infarction. N: Number of subjects in each arm. T2DM Type 2 diabetes mellitus

	Mean change difference	95% CI	p-value
Change in body weight (kg)	-1.64	(-2.06, -1.23)	<0.001

SAEs on treatment most commonly reported (≥1%)
On treatment deaths

	Number (%) of subjects	
Preferred term	**Dapa 10 mg (N=1995)**	**Placebo (N=1977)**
Subjects with any SAE	407 (20.4)	376 (19.0)
Non-cardiac chest pain	38 (1.9)	29 (1.5)
Cardiac failure	34 (1.7)	33 (1.7)
Acute myocardial infarction	33 (1.7)	30 (1.5)
Angina pectoris	30 (1.5)	32 (1.6)
Angina unstable	20 (1.0)	17 (0.9)
	Number (%) of subjects	
On treatment deaths	**Dapa 10 mg (N=1995)**	**Placebo (N=1977)**
Subjects	30 (1.5)	29 (1.5)

Dapa: Dapagliflozin. N: Number of subjects in the treatment group. On treatment: AE onset date while on study drug or within 30 days from last dose.

- The percentage of subjects on treatment with any SAE was similar in the dapagliflozin and placebo groups (20.4% vs. 19.0%)
- The most commonly reported SAEs on treatment by PT were in-keeping with the medical profile of the population studied
- The percentage of subjects in the safety analysis set (on treatment) who died was low and balanced between the dapagliflozin and placebo groups (1.5% vs 1.5%)

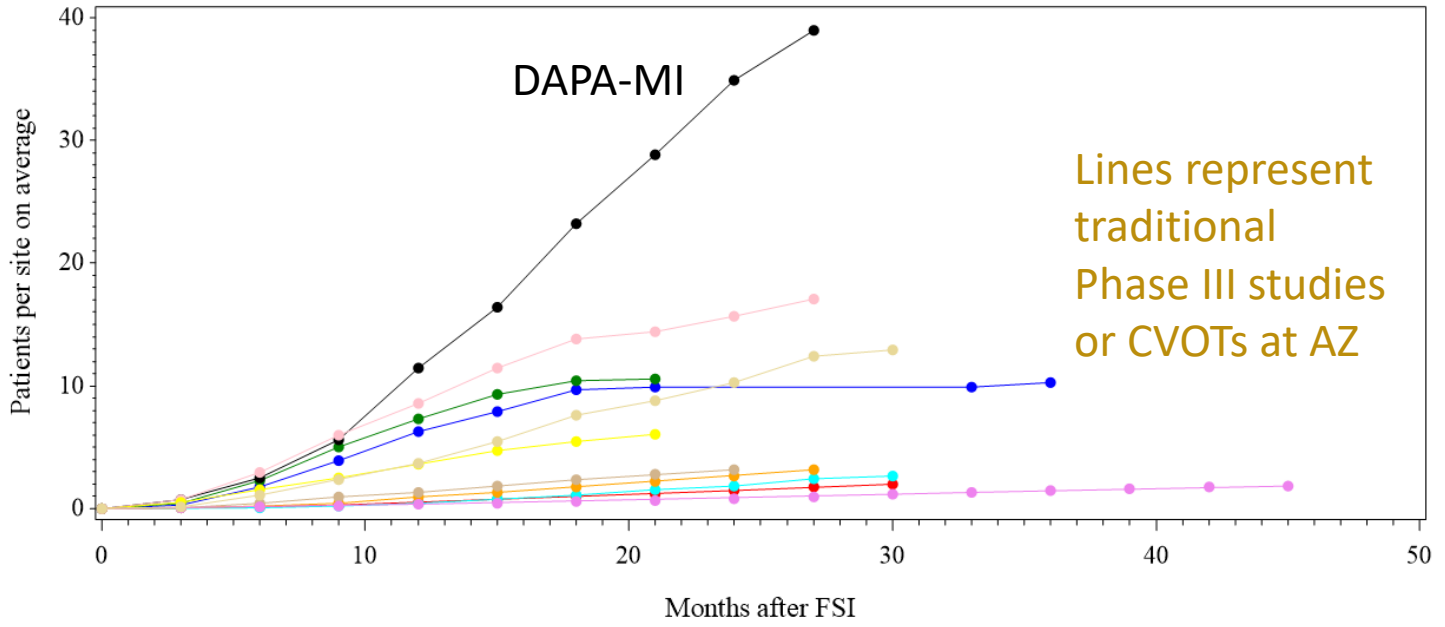
Summary of Study Conduct, Efficacy and Safety

- Feasibility of R-RCT design was confirmed with the recruitment of 4017 patients with acute MI without diabetes and chronic HF in only two countries and 103 sites
- Baseline characteristics were balanced between treatment groups
- Patients were well treated according to the standard of care
- High-quality study conduct led to only 4 patients with missing vital status at the study end
- DAPA-MI met the primary endpoint and dapagliflozin treatment demonstrated significant clinical benefit compared to placebo
  - With a Win ratio of 1.34, the likelihood for a better cardiometabolic outcome with dapagliflozin is 34% higher compared to placebo (Win ratio: 1.34; 95% CI 1.20-1.50; $p<0.001$)
  - Clinical benefit was consistent across pre-specified subgroups
  - The clinical benefit was also significant for the key secondary endpoint (primary endpoint without weight component)
- No new safety or tolerability concerns were identified in this study

R-RCT key learnings

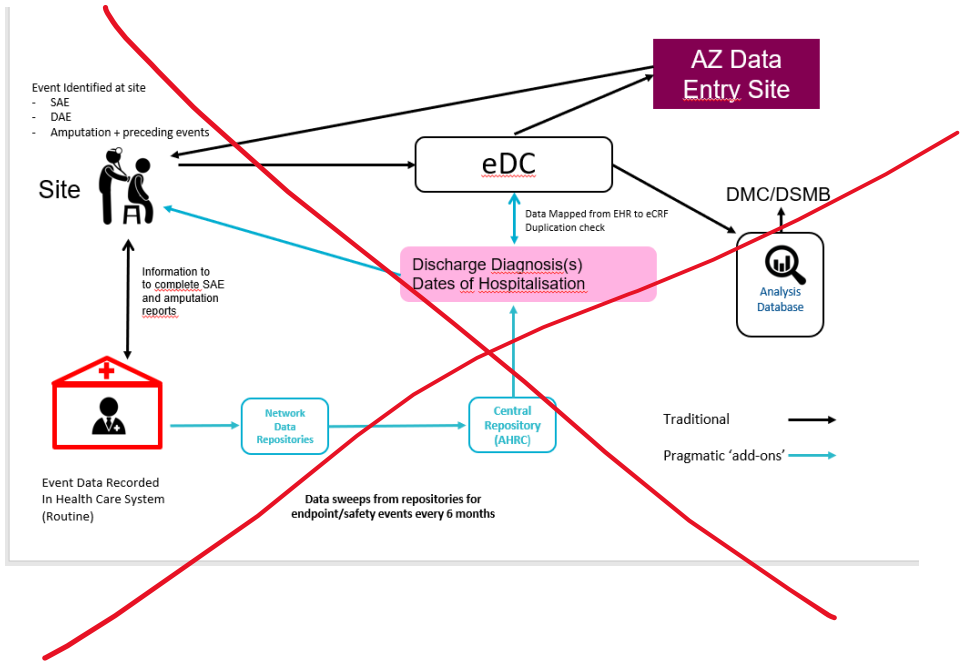
- Recruitment speed was high (see graph)
- Cost reduction vs conventional CVOTs due to fewer visits and assessments
- Use of registry data and visits aligned with clinical routine reduced site and patient burden
- High recruitment numbers at both large and small hospitals
- Regulatory approvability - not fully tested, however approached agencies agreed to the R-RCT design (with original endpoints)

Number of randomized patients versus time. Divided by the total number of activated sites. March 2023.



- Broad inclusion criteria led to recruitment of patients in the lower risk spectrum
- Suitable registries only in the UK and Sweden limits the possibility to expand with additional countries right now

Safety data collection in DAPA-MI



Learnings from previous discussions

- In most registers, limited information about safety events is available
- Difficult to assess seriousness and relatedness for SAE reporting

Safety data collected at visits (ordinary way)

Safety data collection in DAPA-MI cont.

Given Forxiga's well-established safety profile, limited safety data collection with low frequency was specified in the protocol:

- AEs leading to hospitalization and death* (Sweden)
- SAEs and creatinine initially (UK)

Learnings:

- Limited data collection may be sufficient for drugs with well established safety profiles
- Difficult to phrase questions in an app. that can't identify reportable SAEs

*Events leading to hospitalization and death often available in registers for future studies

DAPA-MI Study conduct from an operational perspective

DAPA-MI study was a collaboration between AstraZeneca and Uppsala Clinical Research Centre

DAPA-MI was conducted according to conventional Clinical Trial procedures

- The study was delivered with high quality according to GCP
- UCR was responsible for Data Management and Registries set-up
- Risk-based Monitoring was used and described in the Monitoring Plan
- Patients had to provide informed consent before any transfer of data from Quality Registries to the study

New technical solutions:

- Data was transferred automatically from quality registries, SwedeHeart and MINAP to the electronic data capture system (EDC), MACRO – validated process

DAPA-MI site survey 103 responses

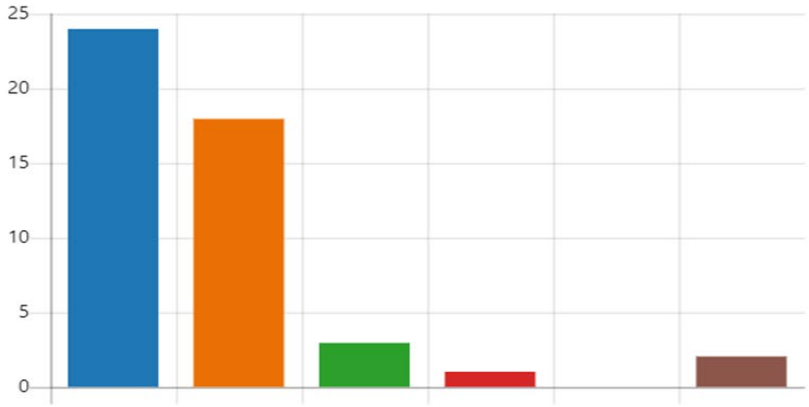
Using clinical registry data for the conduction of a randomized clinical trial is feasible and innovative compared to the traditional way of conducting outcome trials.

Strongly agree	38
Agree	46
No strong opinion	18
Disagree	1
Strongly disagree	0

2. *Only applicable for Sweden:*

Alignment of study visits with the SEPHIA follow up schedule made the trial easier and less burdensome for the site staff compared to traditional trials.

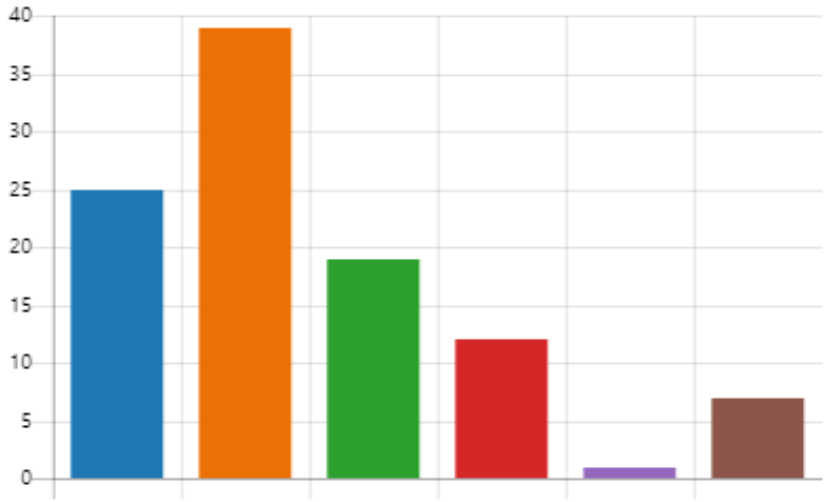
Strongly agree	24
Agree	18
No strong opinion	3
Disagree	1
Strongly disagree	0
N/A as this was my first experience	2



DAPA-MI site survey 103 responses

I believe recruiting patients in DAPA-MI was easier than similar types of outcome trials.

Strongly agree	25
Agree	39
No strong opinion	19
Disagree	12
Strongly disagree	1
Not applicable, as this was my...	7



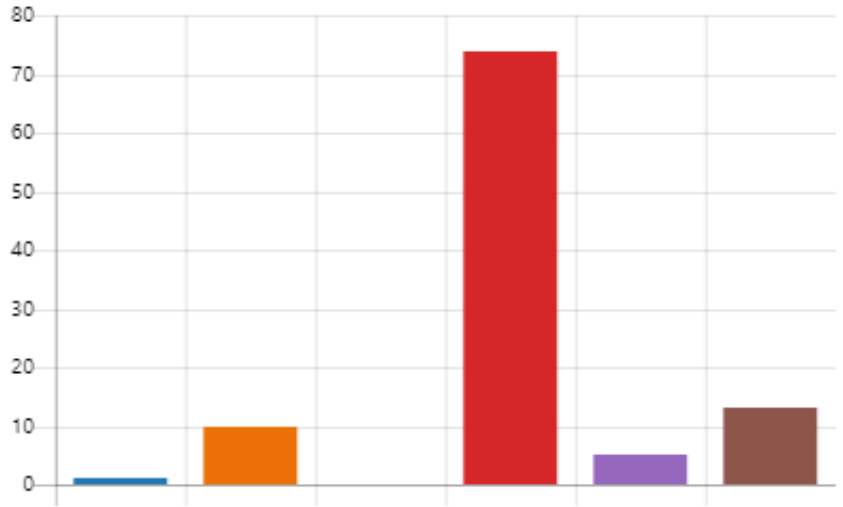
Due to broad inclusion criteria, patients with higher risk profile was not prioritized to be recruited.

Strongly agree	10
Agree	41
No strong opinion	33
Disagree	16
Strongly disagree	3

DAPA-MI site survey 103 responses

In your opinion what was the main reason why the expected number of patients did not want to participate in the study?

- ..didn't know site staff/investigator 1
- ..afraid taking part in a clinical trial 10
- ..didn't want to use/ were afraid using clever c**ap** 0
- ..didn't want an additional drug 74
- ..didn't see any benefits to participate 5
- Other 13



DAPA-MI site survey 103 responses

. I believe using Clever Caps is easier, faster, and less burdensome for the site staff compared to manual Investigational Product (IP) accountability (manually counting of study drugs)

Strongly agree	16
Agree	30
No strong opinion	15
Disagree	21
Strongly disagree	21

. I would like to be considered as an investigator for a similar future trial sponsored by AstraZeneca.

Agree	89
Disagree	14

Summary

- Collaboration with UCR and NICOR enabled successful Registry-based randomized controlled trial confirming this concept for future studies

- Excellent data quality confirming regulatory-grade of R-RCT design

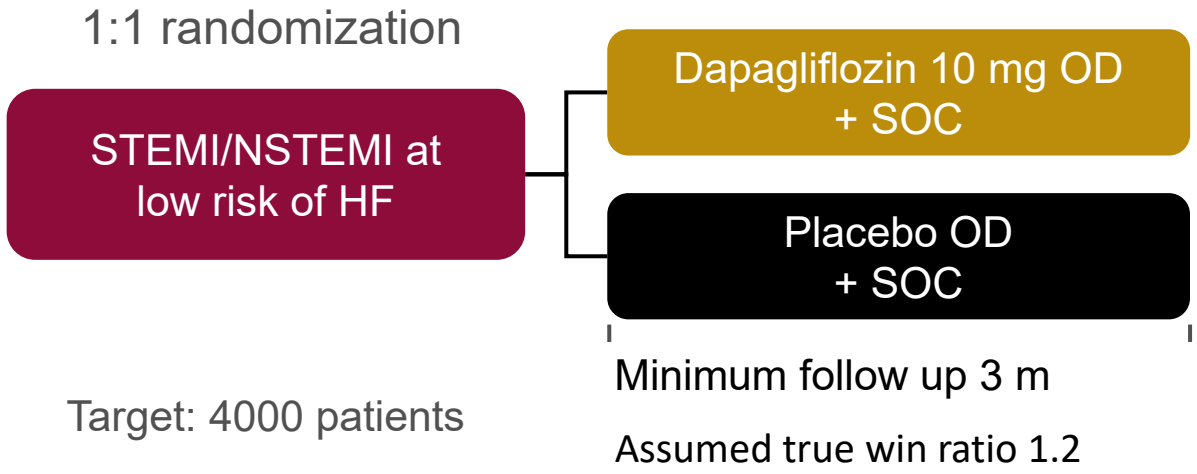
- The registry-based approach was appreciated and attracted Investigators all over Sweden and the UK representing both large and small hospitals

Backup

DAPA MI phase III study to assess efficacy and safety of empagliflozin in patients after acute MI

Pragmatic, multicentre, two country, randomized, double-blind, phase III, placebo-controlled superiority trial

Primary endpoint: Win ratio including 7 outcomes of perceived clinical importance



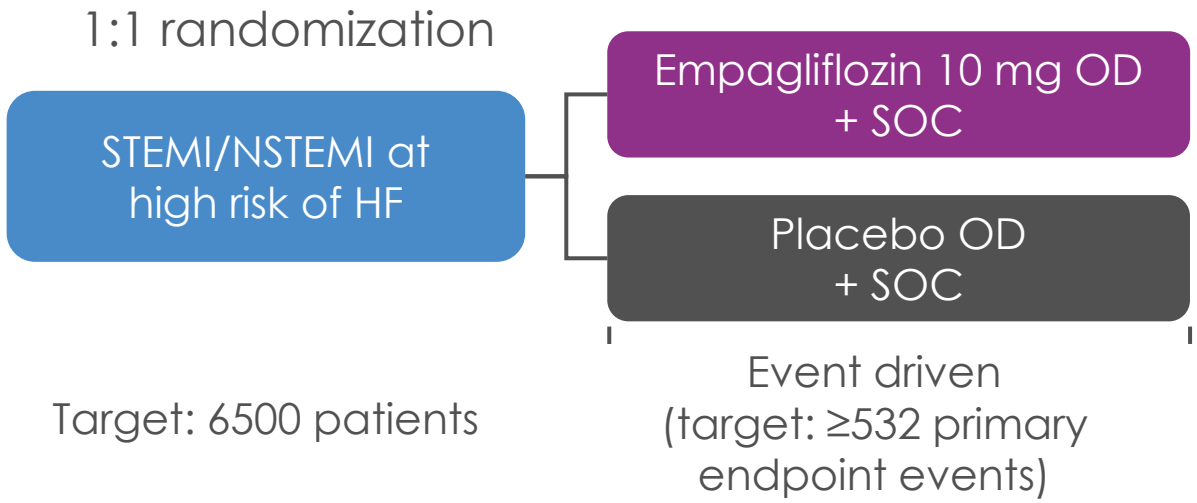
DAPA-MI was a pragmatic registry based trial:

- Use of inclusion/exclusion criteria readily available in routine care
- Linked to clinical registry
- No trial FU visits the first 12 months
- Blinded central adjudication of Cv death and hospitalization for heart failure

EMPACT-MI is phase III study to assess efficacy and safety of empagliflozin in patients after acute MI

Streamlined, multicentre, multinational, randomized, double-blind, phase III, placebo-controlled superiority trial

Primary endpoint: time to first heart failure hospitalization or all-cause mortality



EMPACT-MI was a streamlined trial:

- Use of inclusion/exclusion criteria readily available in routine care
- Mainly remote follow-up visits
- Streamlined data collection incl. focused collection of safety information
- Blinded investigator review instead of central adjudication, additionally supported by structured data collection

NSTEMI, non-ST-segment elevation myocardial infarction; OD, once daily; SOC, standard of care; STEMI, ST-segment elevation myocardial infarction.

DAPA-MI

Inclusion criteria

1. **STEMI or NSTEMI < 10 days and on SoC**
2. **Impaired LV systolic function or Q-wave MI**
3. **Hemodynamically stable**

Exclusion criteria

1. T1 and T2 Diabetes mellitus
2. Chronic symptomatic HF with hospitalization for HF the last year and known LVEF≤40 % before the current MI hospitalization.
3. Symptomatic hypotension or systolic BP <95 mmHg
4. eGFR ≤20 mL/min/1.73 m2

EMPACT-MI

Inclusion criteria

1. **STEMI or NSTEMI ≤14 days**
2. **High risk of HF**, defined as either:
   a. Signs/symptoms of congestion requiring treatment, or
   b. Newly developed LVEF <45%
3. **≥1 HF risk factor**: age ≥65 years; LVEF <35%; prior MI; eGFR<60;* AFib;† type 2 diabetes; elevated NT-proBNP/BNP;‡ elev. uric acid;§ PASP (RVSP) ≥40 mmHg;¶ no revascularization for the index MI; 3-vessel coronary artery disease; peripheral artery disease

Exclusion criteria

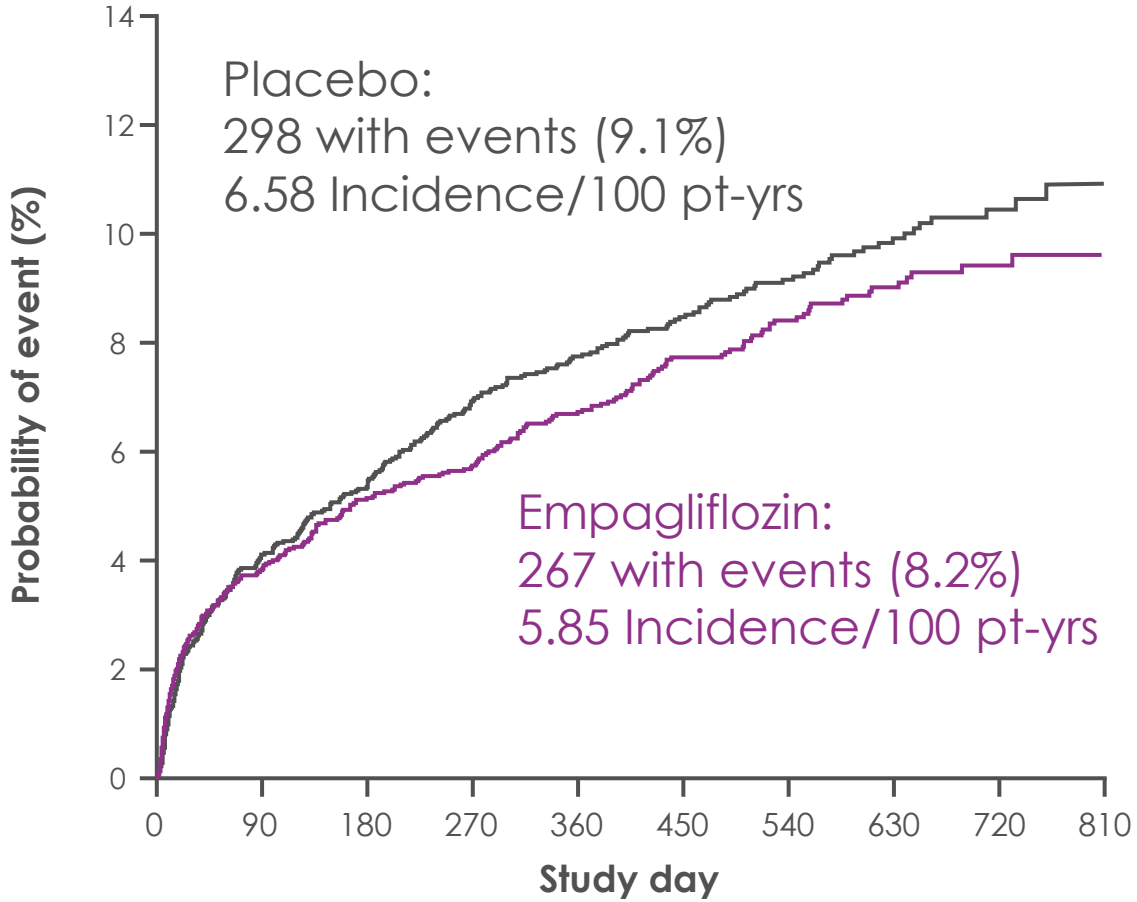
1. Type 1 diabetes mellitus
2. Diagnosis of chronic HF prior to index MI
3. Cardiogenic shock or IV inotropes in last 24 h before randomization
4. eGFR <20 mL/min/1.73 m^2

*Using CKD-EPI formula based on creatinine from local lab at any time during index hospitalization. †Persistent or permanent, if paroxysmal, only valid if associated with index MI; ‡NT-proBNP ≥1400 pg/mL for patients in sinus rhythm, ≥2800 pg/mL if atrial fibrillation; BNP ≥350 pg/mL for patients in sinus rhythm, ≥700 pg/mL if atrial fibrillation, measured at any time during hospitalization. §Uric acid ≥7.5 mg/dL (≥446 µmol/L), measured at any time during hospitalization. ¶Pulmonary Artery Systolic Pressure [or right ventricular systolic pressure].

Key characteristics		DAPA-MI	EMPACT-MI
Number of countries		2	22
Number of sites		103	451
Number of patients		4017	6522
Age, years	Mean	63	64
Sex (%)	Female	20	25
STEMI (%)		72	74
Body Mass Index (kg/m^2)	Mean	28	28
	< 50	79	
	< 45		79
Type 2 diabetes		0	32
eGFR ($ml/min/1.73m^3$)	Mean	83	
Co-morbidities, n (%)	Hypertension	37	70
	Prior myocardial infarction	9	13
Key medications, n (%)	Platelet inhibitor	98	98
	ACE inhibitor/ARB	92	82
	Aldosterone receptor blocker	23	48
	Beta blockers	90	87
	Statins	95	95

Primary Endpoint

Tme to heart failure hospitalization or all-cause mortality



No. at risk										
Placebo	3262	3092	3044	2832	2486	2071	1556	1040	551	137
Empagliflozin	3260	3111	3060	2881	2532	2107	1566	1048	531	134

HR 0.90 (95% CI: 0.76, 1.06)
p=0.21

565 primary endpoint events

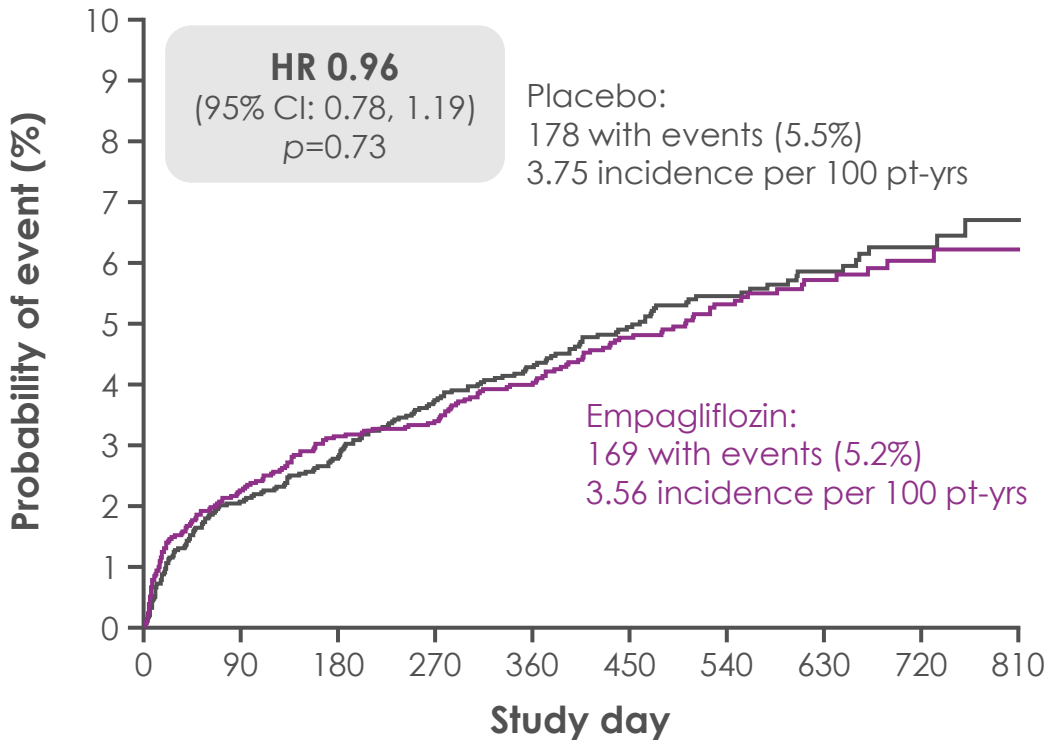
- **271 (48%) first events: HHF**
- **294 (52%) first events: death**

CI, confidence interval; HHF, hospitalization for heart failure; HR, hazard ratio; pt-yrs, patient-years.

Components of primary endpoint

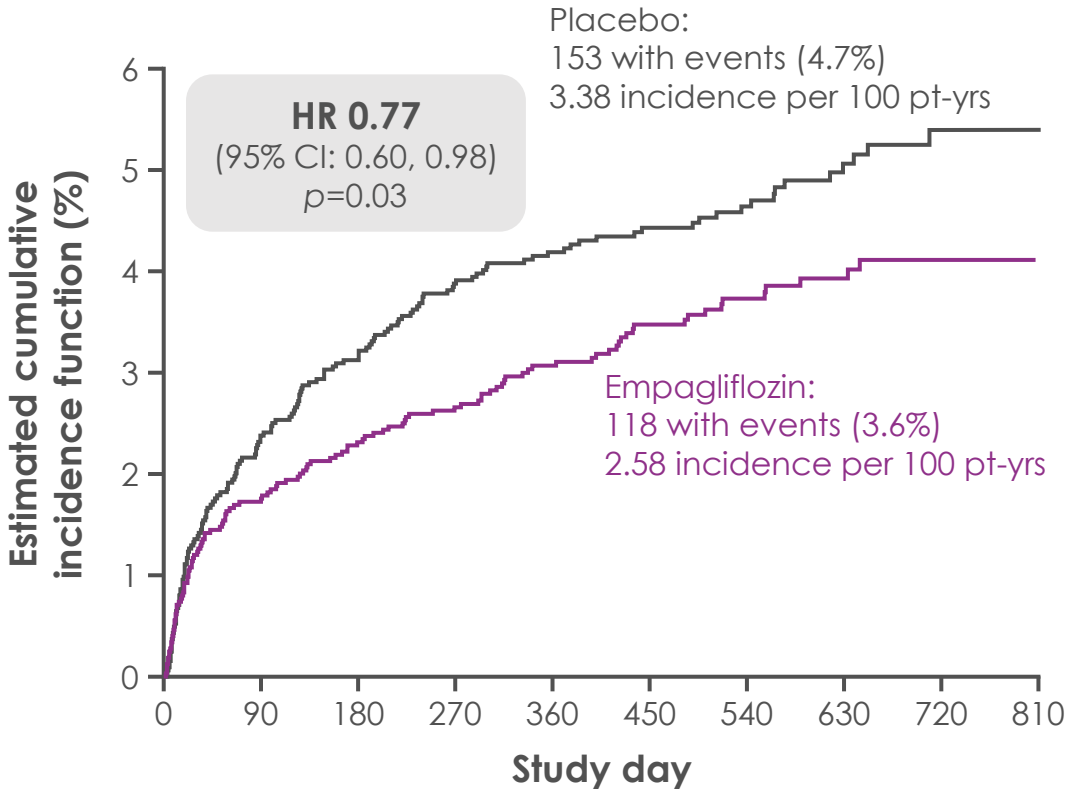
Time to all-cause mortality

347 deaths: 263 (76%) CV death; 84 (24%) non-CV death



No. at risk										
Placebo	3262	3186	3159	2975	2632	2207	1660	1111	593	148
Empagliflozin	3260	3177	3148	2995	2639	2218	1658	1119	572	153

Time to first HHF



	3262	3092	3044	2832	2486	2071	1556	1040	551	137
	3260	3111	3060	2881	2532	2107	1566	1048	531	134

CV, cardiovascular.

EMPACT-MI