Empagliflozin after Acute Myocardial Infarction
The EMPACT-MI trial

Javed Butler, MD, MPH, MBA, FACC
on behalf of EMPACT-MI Committees and Investigators

@javedbutler1

Disclosures

Consultant to Abbott, American Regent, Amgen, Applied Therapeutic, AskBio, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cardiac Dimension, Cardiocell, Cardior, CSL Bearing, CVRx, Cytokinetics, Daxor, Edwards, Element Science, Faraday, Foundry, G3P, Innolife, Impulse Dynamics, Imbria, Inventiva, Ionis, Lexicon, Lilly, LivaNova, Janssen, Medtronics, Merck, Occlutech, Owkin, Novartis, Novo Nordisk, Pfizer, Pharmacosmos, Pharmain, Prolaio, Regeneron, Renibus, Roche, Salamandra, Sanofi, SC Pharma, Secretome, Sequana, SQ Innovation, Tenex, Tricog, Ultromics, Vifor, and Zoll

Background

- Despite advances in AMI management, post-MI patients remain at risk for developing HF
  - Up to 30% over the first year [1]
- Prognosis is especially poor in patients who develop congestion or left ventricular dysfunction with AMI [2,3]
- SGLT2 inhibitors have been consistently shown to reduce the risk of HF events
  - In patients at high-risk of developing HF, e.g., CKD or T2D
  - In those with prevalent HF (irrespective LVEF or T2D) [4]

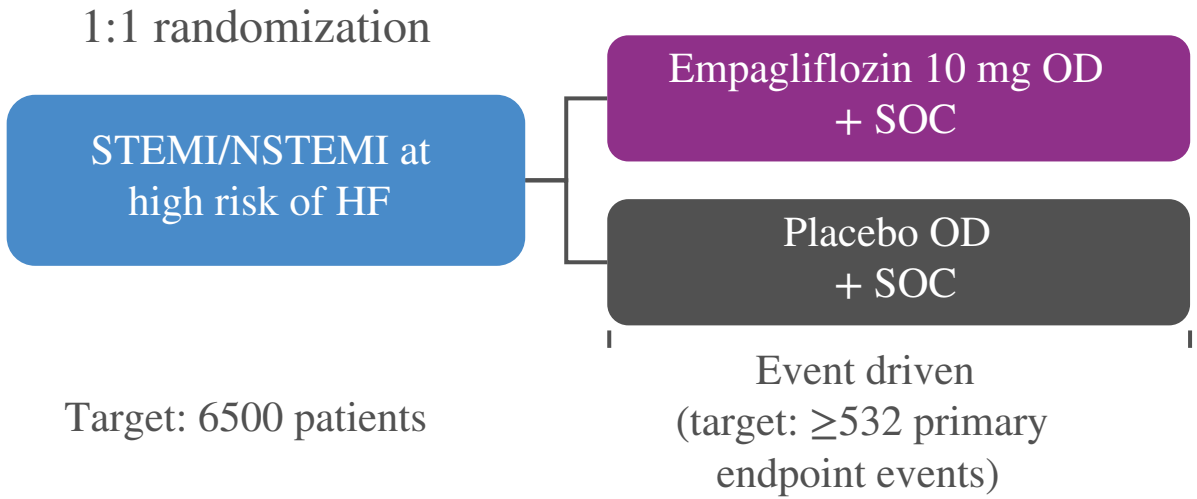
AMI, acute myocardial infarction; CKD, chronic kidney disease; HF, heart failure; LVEF, left ventricular ejection fraction; SGLT2, sodium-glucose co-transporter-2; T2D, type 2 diabetes.

1. Butler J at ESC 2023 https://esc365.escardio.org/presentation/272295; 2. Harrington J et al. JACC Heart Fail 2022;10:404; 3. Hamilton E et al. ESC Heart Fail 2023;10:1347; 4. Usman M et al. J Am Coll Cardiol 2023;81:2377.

EMPACT-MI was conducted to evaluate efficacy and safety of empagliflozin in patients after acute MI

Streamlined, multicentre, 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.

Key eligibility criteria

INCLUSION

Diagnosis of spontaneous acute MI
- **STEMI or NSTEMI**
- Randomization **≤14 days** after hospital admission

High risk of HF, defined as either:
- Signs or symptoms of **congestion** requiring treatment during index hospitalization **OR**
- Newly developed **LVEF <45%**

At least one HF risk factor: Age ≥65 years; LVEF <35%; prior MI; eGFR <60 mL/min/1.73 m ^{2};* atrial fibrillation;† type 2 diabetes; elevated NT-proBNP/BNP; ‡ elevated uric acid; § PASP (RVSP) ≥40 mmHg; ¶ no revascularization for the index MI; 3-vessel coronary artery disease; peripheral artery disease

EXCLUSION

- Diagnosis of chronic HF prior to index MI
- SBP ≤90 mmHg at randomization
- Cardiogenic shock or use of IV inotropes in last 24 hours before randomization
- Current or planned treatment with an SGLT2 inhibitor
- Any current severe (stenotic or regurgitant) valvular heart disease
- eGFR <20 mL/min/1.73 m ^{2}
- Type 1 diabetes mellitus

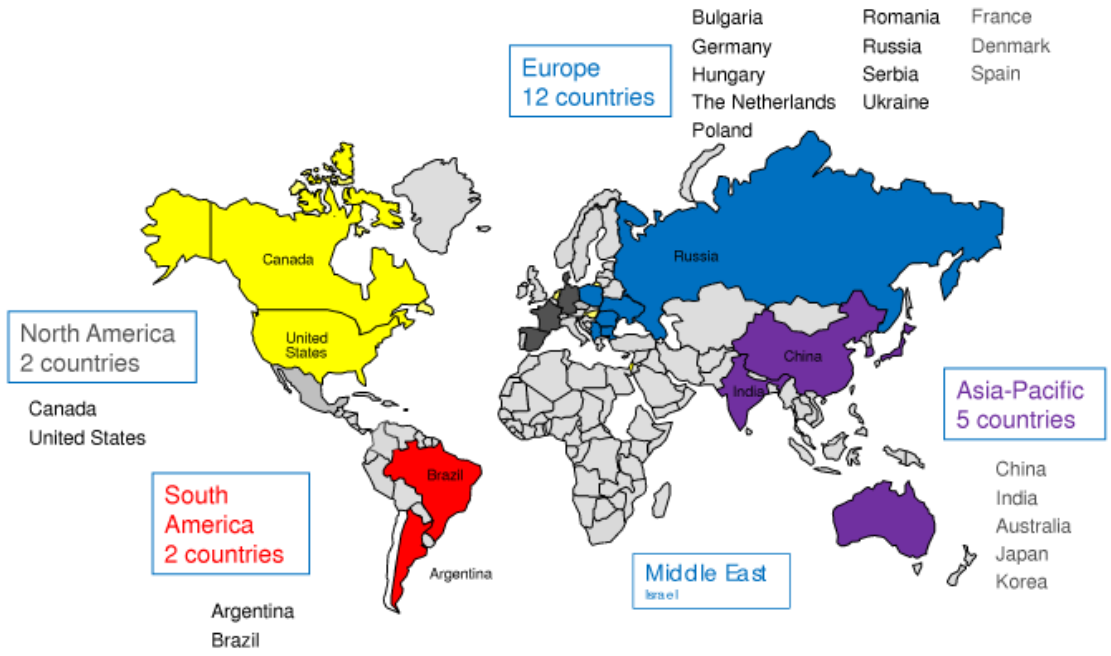
*Using CKD-EPI formula based on creatinine from local lab at any time during index hospitalization. †Persistent or permanent, if paroxysmal, only valid if associated with index MI; ‡NT-proBNP ≥1400 pg/mL for patients in sinus rhythm, ≥2800 pg/mL if atrial fibrillation; BNP ≥350 pg/mL for patients in 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]. eGFR, estimated glomerular filtration rate; IV, intravenous; (NT-pro)BNP, (N-terminal prohormone of) brain natriuretic peptide; SBP, systolic blood pressure.

EMPACT-MI

EMPACT- MI trial is a large-scale, global clinical trial

Global investigator participation

- 22 countries
- 451 sites



Key trial parameters

- 6522 patients randomized
- 565 patients with primary endpoint
- Median follow-up: 17.9 months
- Complete follow-up for vital status: 99.2%

First patient screened: Dec 16, 2020

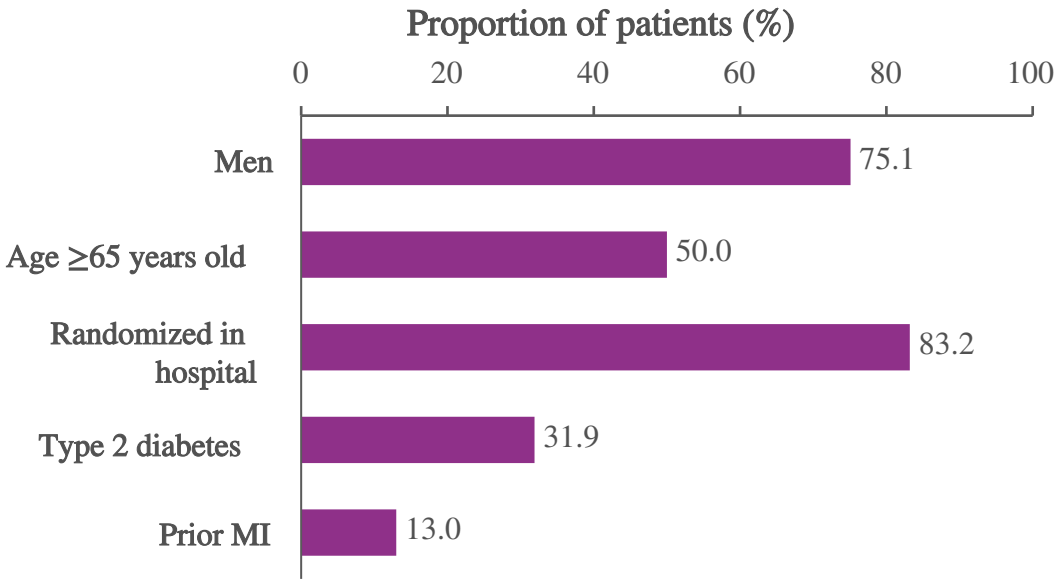
Last patient visit: Nov 05, 2023

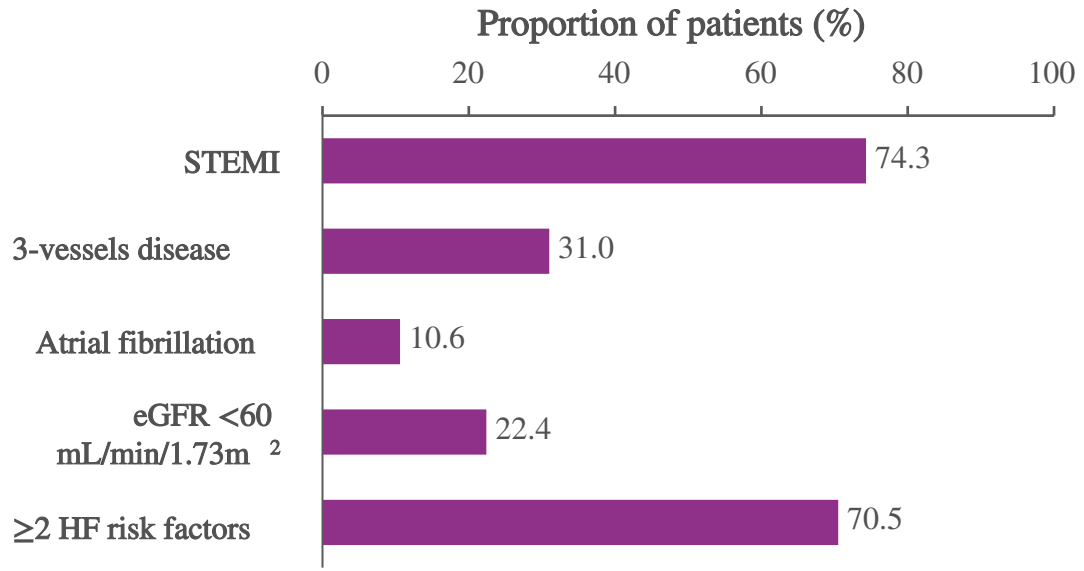
EMPACT-MI: Patient population

Patients with signs and symptoms of congestion requiring treatment: n=3715 (57.0%)

Patients with both: n=2323 (35.6%)

Patients with LVEF <45%;* n=5112 (78.4%)





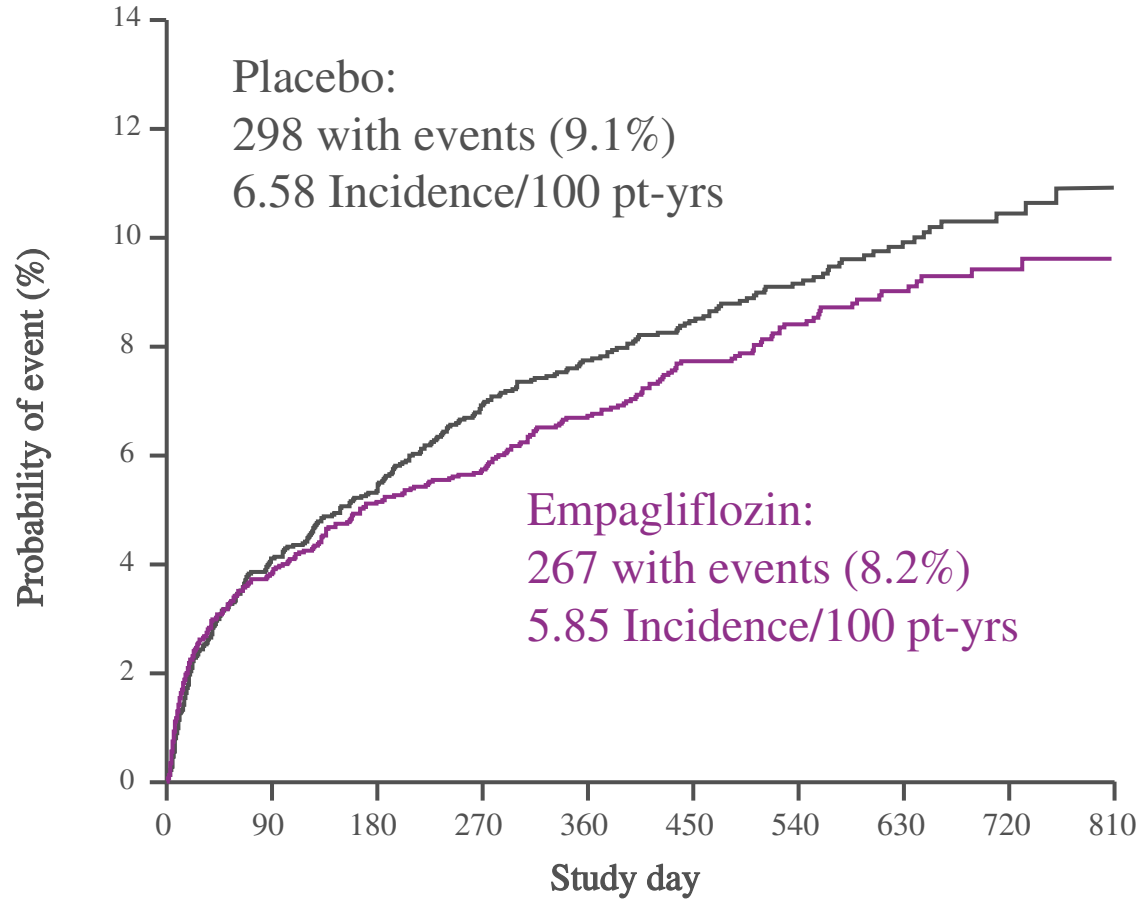
*52 patients had missing LVEF.
≥2 enrichment criteria: Except for eGFR, laboratory values and pulmonary artery pressure have been optional to be reported beyond meeting the inclusion criterion of providing at least 1 enrichment criterion.

Revascularization and medications at discharge

Revascularization for index AMI: 5822 (89.3%)

Treatment	N (%)
Renin-angiotensin modulator	5381 (82.5)
Beta blocker	5655 (86.7)
Mineralocorticoid receptor antagonist	3117 (47.8)
Diuretic	4250 (65.2)
Loop diuretic	2499 (38.3)
Antiplatelet therapy	6399 (98.1)
Statins	6217 (95.3)

Primary Endpoint



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.

EMPACT-MI

Key secondary endpoints

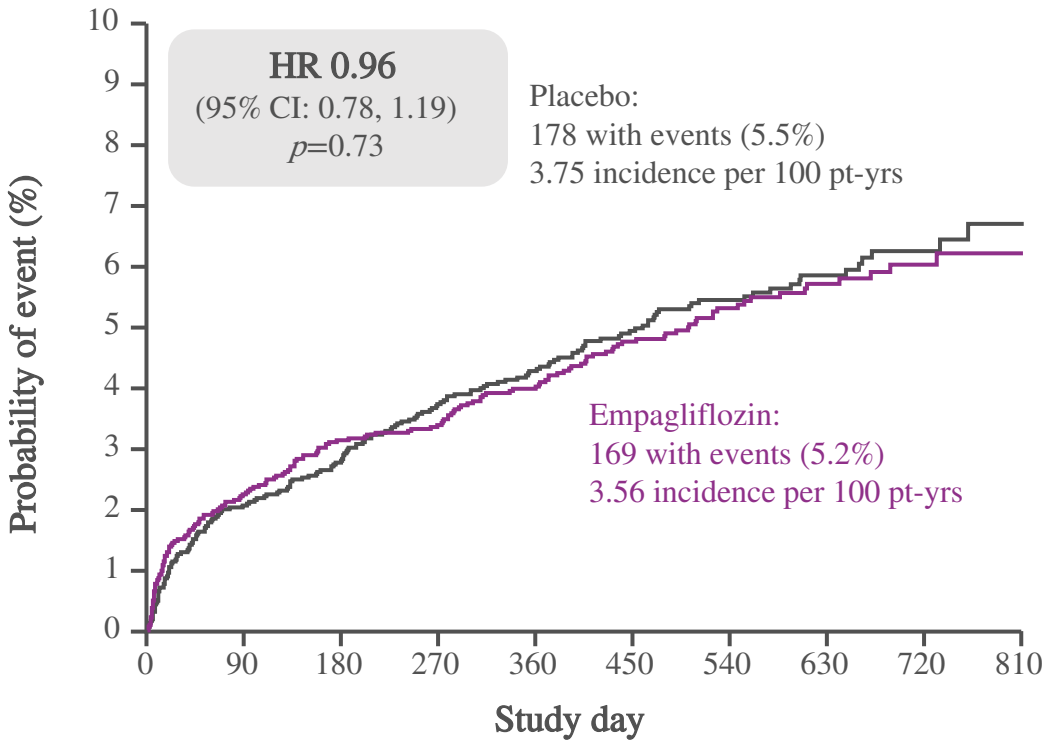
	RR (95% CI) of empagliflozin vs placebo	*p*-value
Total HHF or all-cause mortality	0.87 (0.68, 1.10)	0.24
Total non-elective CV hospitalizations or all-cause mortality	0.92 (0.78, 1.07)	0.29
Total non-elective all-cause hospitalizations or all-cause mortality	0.87 (0.77, 1.00)	0.046
Total MI hospitalizations or all-cause mortality	1.06 (0.83, 1.35)	0.63

CV, cardiovascular; HHF – hospitalization for heart failure, RR, rate ratio; CI confidence interval.

Components of primary endpoint

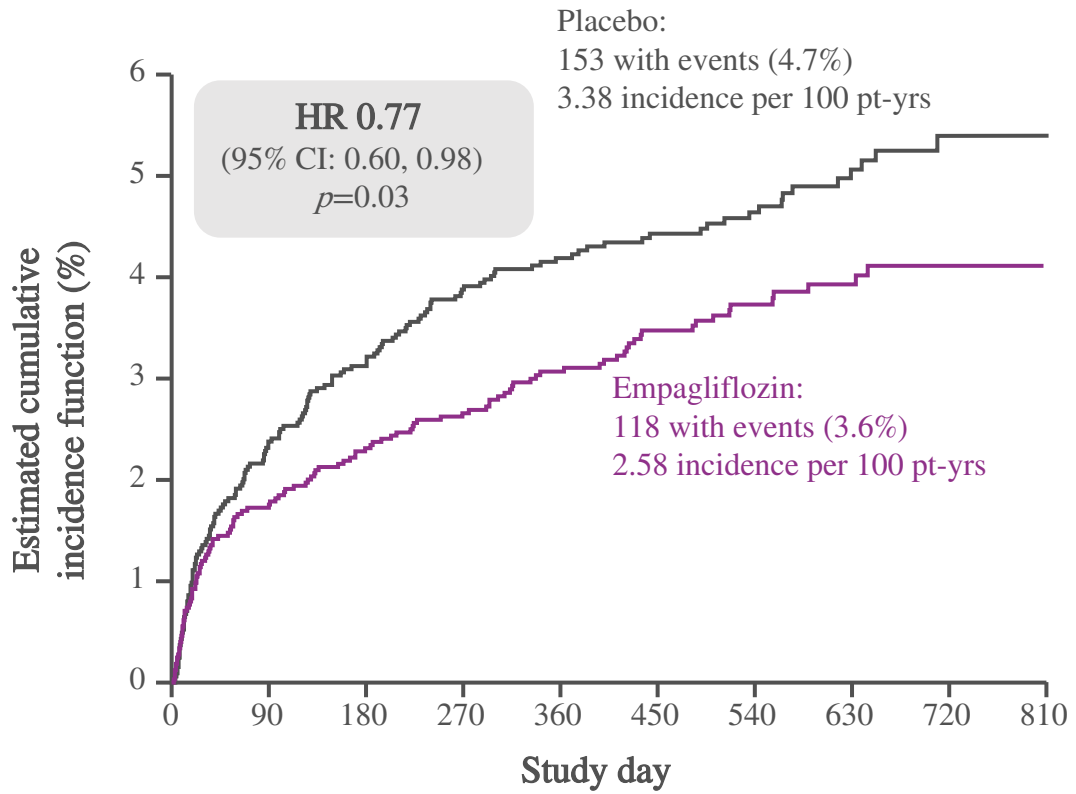
Time to all-cause mortality

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



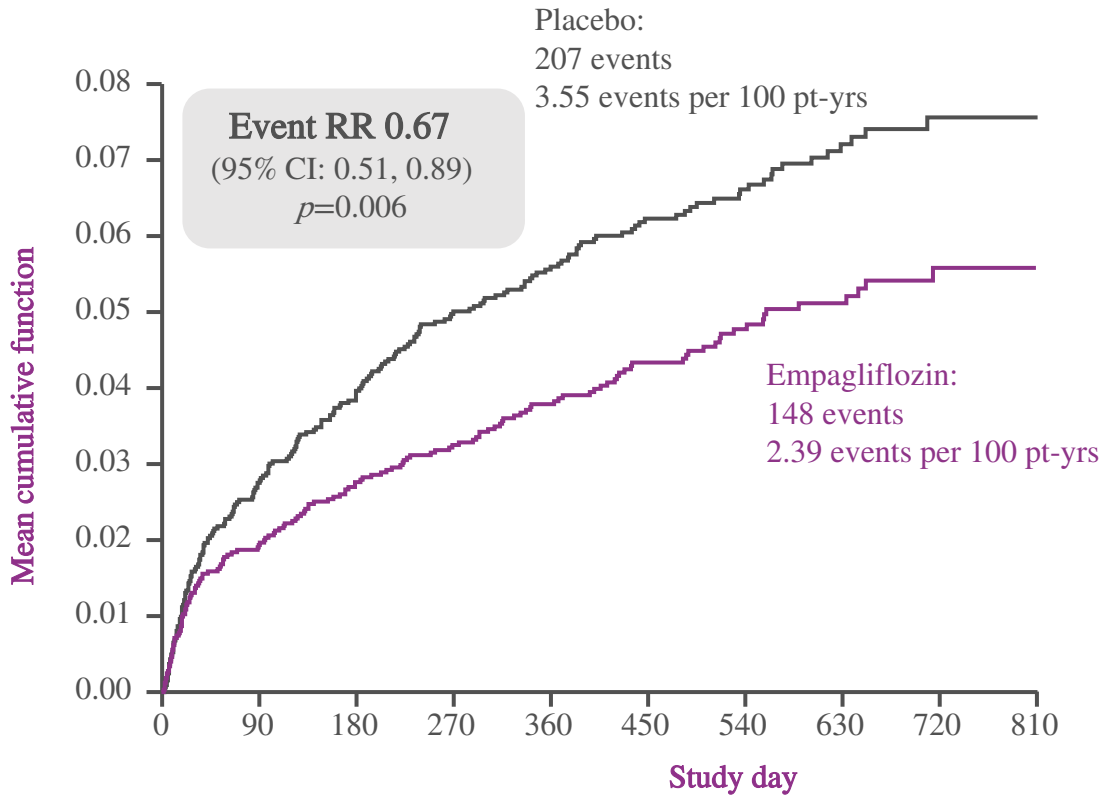
No. at risk										
Placebo	3262	3186	3159	2975	2632	2207	1660	1111	593	148
Empagliflozin	3260	3177	3148	2995	2639	2218	1658	1119	572	153

Time to first HHF



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

Total number of heart failure hospitalizations



No. at risk										
Placebo	3262	3158	3125	2925	2579	2154	1617	1086	581	144
Empagliflozin	3260	3162	3124	2955	2600	2171	1616	1088	552	139

Number of patients with HHF	271
Time from randomization to first HHF , days, median (IQR)*	91 (20, 238)
Time from first HHF to end of follow-up , days, median (IQR) *	354 (160, 503)
Subsequently died, n (%)	53 (20%)

Analysis based on 6522 randomized patients and 355 HHF events. Adjusted event rates and rate ratio (95% CI) based on the negative binomial model. *Based on patients with HHF over pooled treatment groups.
IQR, interquartile range.

EMPACT-MI

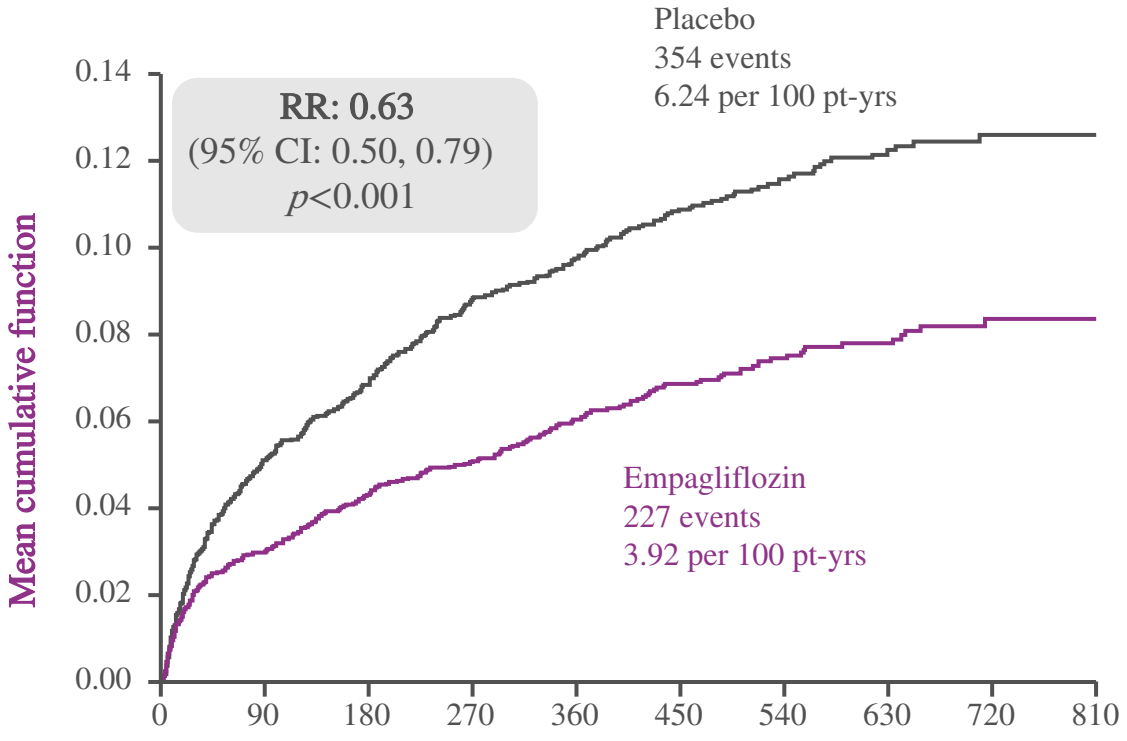
Total heart failure burden: Heart failure adverse events

- Increasing trend to diagnose and treat HF as outpatient
- HF adverse events included
  - Hospitalization
  - Fatal HF events
  - Outpatient events
- The identification of HF AE were pre-defined as serious AEs*
  - All SAEs were reported per protocol

*The list of the PTs of MedDRA narrow SMQ 'cardiac failure' to be always reported in the trial as serious adverse events: Cardiac failure, Cardiac failure congestive, Cardiac failure acute, Acute left ventricular failure, Acute right ventricular failure, Acute pulmonary oedema, Cardiogenic shock, Cardiohepatic syndrome, Cardiopulmonary failure, Cardiorenal syndrome, Cor pulmonale, Cor pulmonale acute, Cor pulmonale chronic, Left ventricular failure, Low cardiac output syndrome, Obstructive shock, Pulmonary oedema, Pulmonary oedema neonatal, Right ventricular failure, Ventricular failure.
The list of PTs of MedDRA narrow SMQ 'of cardiac failure' that were not on the list to be always reported in the trial as serious adverse events and hence not required to be reported at all (unless leading to treatment discontinuation for ≥ 7 consecutive days or other seriousness criteria fulfilled): Cardiac asthma, Cardiac failure chronic, Cardiac failure high output, Chronic left ventricular failure, Chronic right ventricular failure, Congestive hepatopathy, Ejection fraction decreased, Hepatojugular reflux, Neonatal cardiac failure, Radiation associated cardiac failure, Right ventricular ejection fraction decreased.
(S)AE, (serious) adverse event.

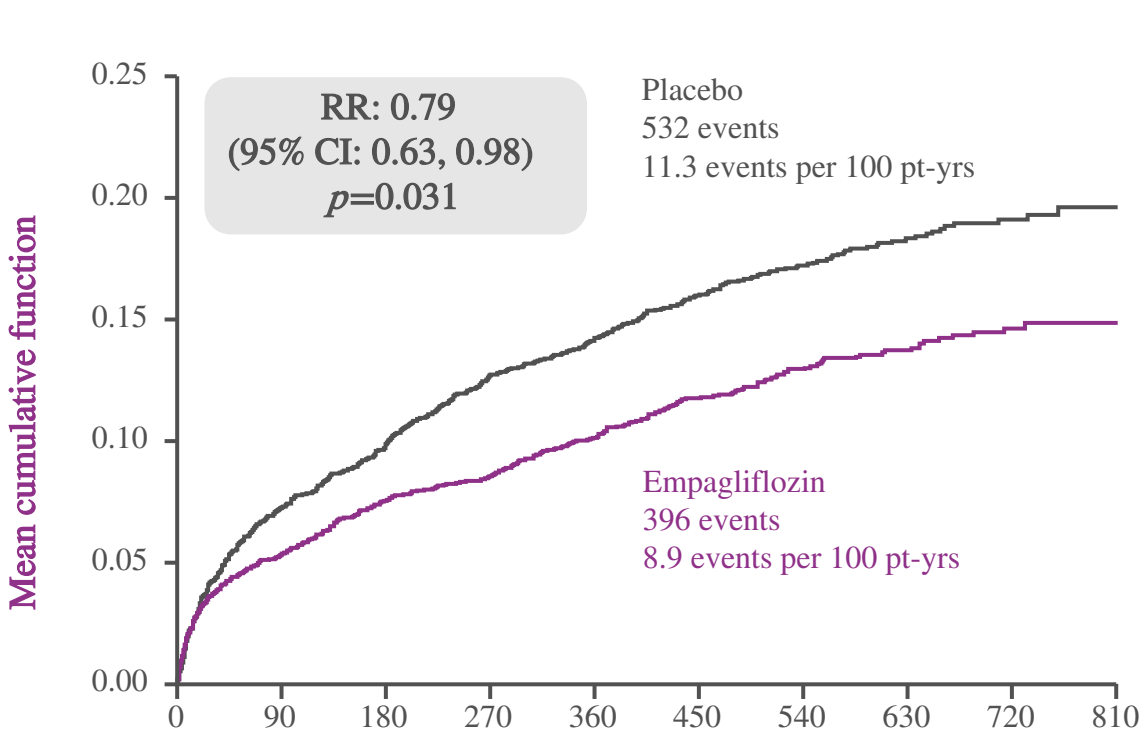
Effect of empagliflozin on total number of HF adverse events

Total number of adverse events of heart failure



No. at risk										
Placebo	3262	3158	3125	2925	2579	2154	1617	1086	581	144
Empagliflozin	3260	3162	3124	2955	2600	2171	1616	1088	552	139

Total number of adverse events of heart failure or all-cause mortality



	3262	3158	3125	2925	2579	2154	1617	1086	581	144
	3260	3162	3124	2955	2600	2171	1616	1088	552	139

Total number of HHF or death due to HF

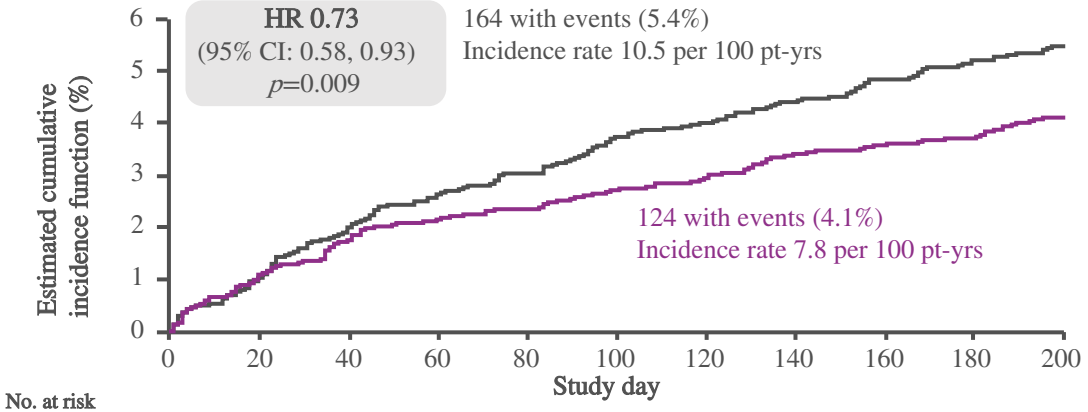
0.69 (0.51, 0.93)

Analyses based on negative binomial regression. Adverse events of heart failure based on narrow Standardized MedDRA query "cardiac failure". All analyses performed post hoc.

EMPACT-MI

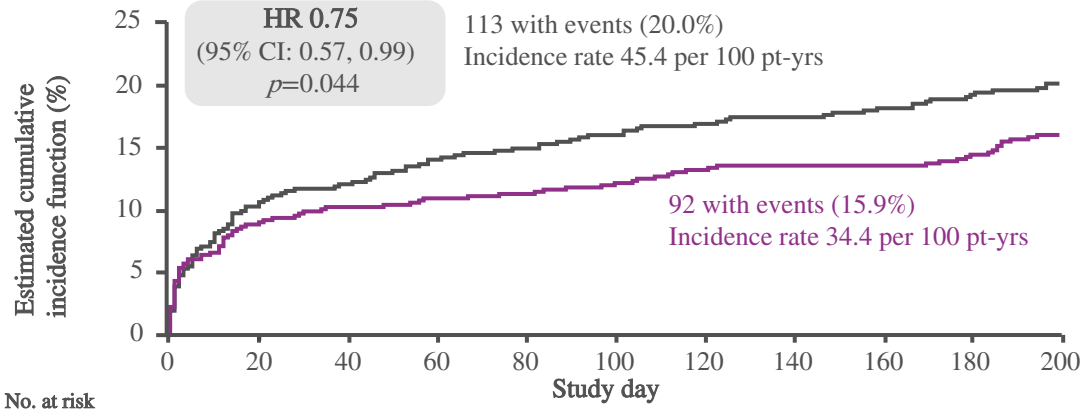
Time to first use * of heart failure therapies

ARNI



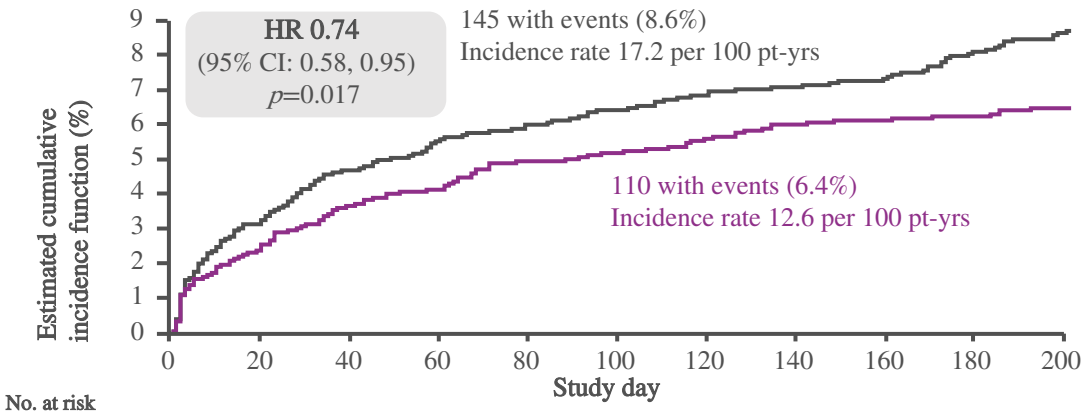
No. at risk											
Placebo	3026	2941	2895	2865	2843	2816	2804	2784	2767	2750	2724
Empagliflozin	3041	2955	2923	2903	2886	2865	2854	2830	2818	2805	2786

RAAS inhibitors †



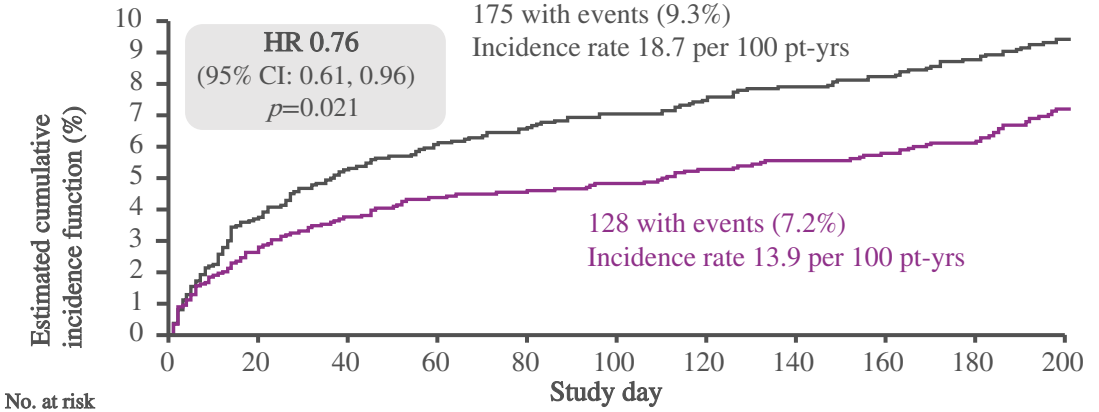
No. at risk											
Placebo	564	490	476	461	454	445	439	435	431	425	415
Empagliflozin	577	511	500	494	490	485	477	472	471	467	455

MRA



No. at risk											
Placebo	1687	1603	1567	1550	1536	1527	1518	1509	1503	1489	1469
Empagliflozin	1717	1650	1623	1609	1589	1582	1571	1560	1553	1548	1541

Diuretics ‡



No. at risk											
Placebo	1873	1771	1737	1720	1707	1695	1686	1677	1669	1657	1639
Empagliflozin	1788	1719	1696	1684	1677	1671	1662	1653	1645	1634	1613

*Relative to discharge, the information about concomitant medication was collected only until month 6.
‡Other than MRA. Analyses based on Cox regression. All analyses post hoc.

†RAAS inhibitors includes: ACE inhibitors, ARB, ARNI.

EMPACT-MI

Safety

	Empagliflozin (N=3234)		Placebo (N=3229)	
	n (%)	Incidence per 100 pt-yrs	n (%)	Incidence per 100 pt-yrs
Patients with any AE	891 (27.6)	25.37	883 (27.3)	25.38
Patients with AE leading to permanent treatment discontinuation	122 (3.8)	2.93	122 (3.8)	2.96

Consistent with the known safety profile of empagliflozin

Of note – no significant difference in the risk of kidney AEs

Acute contrast-induced kidney injury*	8 (0.2%)	0.19	9 (0.3%)	0.22
Acute renal failure ‡	43 (1.3)	1.04	59 (1.8)	1.44
Volume depletion §	35 (1.1)	0.84	40 (1.2)	0.98
Hypotension §	34 (1.1)	0.82	36 (1.1)	0.88
Hypoglycaemia ‡	4 (0.1)	0.10	5 (0.2)	0.12

Shown are adverse events up to 7 days following discontinuation of study medication, except for adverse events of lower limb amputations which are presented up to the end of the trial. The table presents adverse events (AEs) that were to be reported in this trial, i.e., defined as serious AEs, AEs leading to study drug discontinuation of at least 7 days and adverse events of special interest, defined as ketoacidosis, adverse events leading to lower limb amputation, hepatic injury and contrast-induced kidney injury. *AESI (Adverse Events of Special Interest); †A hepatic injury was defined by the following alterations of hepatic laboratory parameters: an elevation of AST (Aspartate Aminotransferase) and/or ALT (Alanine Aminotransferase) ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, or in samples drawn within 30 days of each other, OR, (ALT, and/or AST) elevations ≥10 fold ULN. Among those reported 3 patients in empagliflozin and 0 patients in placebo met these criteria. None of the cases reported met a Hy´s Law criteria: Every case has a cofounding factor, either alternative suspect drug (Statins) or acute gastrointestinal illnesses. ‡Narrow SMQ; §BIcMQ. BIcMQ, Boehringer Ingelheim customized MedDRA Query; ULN, upper limit of normal.

EMPACT-MI

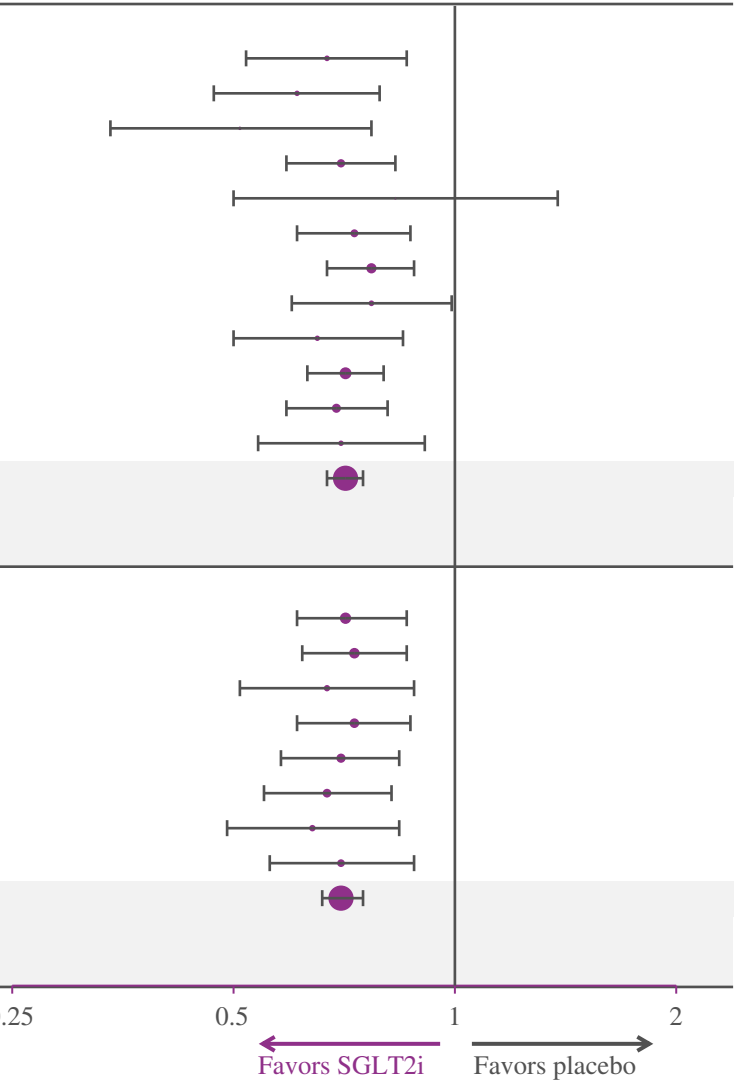
EMPACT -MI: Summary of trial results

- Empagliflozin did not significantly reduce the risk of time to first HHF or all-cause death following AMI
- Empagliflozin demonstrated 23% and 33% relative risk reduction of first HHF* and total HHF, † components of the primary and first key secondary endpoints respectively
- Risk reduction for HHF was consistent in subgroup and sensitivity analyses
- Safety was consistent with known safety profile of empagliflozin

*HR 0.77 (95% CI: 0.60, 0.98). †RR 0.67 (95% CI: 0.51, 0.89).

Effect of SGLT-2 inhibitors on heart failure: meta-analysis

Endpoint and study/subgroup	log[HR]	SE	Weight (%)	HR/RR (95% CI)
Time to first HHF				
CANVAS	-0.4005	0.1293	5.0	0.67 (0.52, 0.86)
CREDENCE	-0.4943	0.133	4.7	0.61 (0.47, 0.79)
DAPA-CKD	-0.6733	0.2059	1.9	0.51 (0.34, 0.77)
DAPA-HF	-0.3567	0.0872	10.9	0.70 (0.59, 0.83)
DAPA-MI	-0.1863	0.2586	1.2	0.83 (0.50, 1.38)
DECLARE-TIMI-50	-0.3147	0.0916	9.9	0.73 (0.61, 0.87)
DELIVER	-0.2614	0.071	16.5	0.77 (0.67, 0.88)
EMPACT-MI	-0.2614	0.1273	5.1	0.77 (0.60, 0.99)
EMPA-REG OUTCOME	-0.4308	0.1339	4.6	0.65 (0.50, 0.85)
EMPEROR-Preserved	-0.3425	0.061	22.3	0.71 (0.63, 0.80)
EMPEROR-Reduced	-0.3711	0.0799	13.0	0.69 (0.59, 0.81)
VERTIS CV	-0.3567	0.1324	4.7	0.70 (0.54, 0.91)
Total	–	–	**100**	**0.71 (0.67, 0.75)**
Heterogeneity Tau ^{2}=0.00; Chi ^{2}=6.81, df=11 (p=0.81); I^2=0%				
Test for overall effect: Z=12.03 (p<0.00001)				
Total HHF				
DAPA-HF	-0.3425	0.0775	20.3	0.71 (0.61, 0.86)
DELIVER	-0.3147	0.0833	17.6	0.73 (0.62, 0.86)
EMPACT-MI	-0.4005	0.1392	6.3	0.67 (0.51, 0.88)
EMPEROR-Preserved	-0.3147	0.0916	14.5	0.73 (0.61, 0.87)
EMPEROR-Reduced	-0.3567	0.0959	13.3	0.70 (0.58, 0.84)
SCORED	-0.4005	0.1007	12.0	0.67 (0.55, 0.82)
SOLOIST-WHF	-0.4463	0.1363	6.6	0.64 (0.49, 0.84)
VERTIS-CV	-0.3567	0.1139	9.4	0.70 (0.56, 0.88)
Total	–	–	**100**	**0.70 (0.66, 0.75)**
Heterogeneity Tau ^{2}=0.00; Chi ^{2}=1.21, df=7 (p=0.99); I^2=0%				
Test for overall effect: Z=10.14 (p<0.00001)				



In press, Lancet Diabetes Endocrinol 2024

Totality of evidence

- The totality of evidence suggests the benefit of empagliflozin for heart failure risk reduction in patients post-AMI without prior heart failure

- Consistent with benefit demonstrated with empagliflozin in other trials in adjacent patient populations

With appreciation to

All 6522 patients participating in the trial

Executive Committee : Javed Butler, Adrian F. Hernandez, Jacob A. Udell, Members: Stefan D. Anker, Deepak L. Bhatt, Mark C. Petrie, Martina Brueckmann, Waheed Jamal, Mikhail Sumin

Duke Clinical Research Institute : W. Schuyler Jones, Maya McKean-Peraza, Meghan Channel and many others

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ORIGINAL ARTICLE

Empagliflozin after Acute Myocardial Infarction

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EMPACT-MI

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Effect of Empagliflozin on Heart Failure Outcomes After Acute Myocardial Infarction: Insights from the EMPACT-MI Trial

Adrian F. Hernandez, MD, MHS; Jacob A. Udell, MD; W. Schuyler Jones, M.D; Stefan D. Anker, M.D, PhD; Mark C. Petrie, MD; Josephine Harrington, MD; Michaela Mattheus, Dipl.Biomath; Svenja Seide Dr. sc hum; Isabella Zwiener, PhD; Offer Amir, MD; M. Cecilia Bahit, MD; Johann Bauersachs, MD; Antoni Bayes-Genis, MD; Yundai Chen, MD; Vijay K. Chopra, MD; Gemma Figtree, MD; Junbo Ge, MD; Shaun Goodman, MD; Nina Gotcheva, MD; Shinya Goto, MD; Tomasz Gasior, MD; Waheed Jamal, MD; James L. Januzzi, MD; Myung Ho Jeong, MD; Yuri Lopatin, MD; Renato D. Lopes, MD, PhD; Béla Merkely, MD; Puja B. Parikh, MD, MPH; Alexander Parkhomenko, MD; Piotr Ponikowski, MD; Xavier Rossello, MD; Morten Schou, MD; Dragan Simic, MD; Philippe Gabriel Steg, MD; Joanna Szachniewicz, MD; Peter van der Meer, MD; Dragos Vinereanu, MD; Shelley Zieroth, MD; Martina Brueckmann, MD; Mikhail Sumin, MD; Deepak L. Bhatt, MD, MPH, MBA; and Javed Butler, MD, MPH, MBA

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Left Ventricular Ejection Fraction, Congestion, and Effect of Empagliflozin on Reducing Heart Failure Risk After Acute Myocardial Infarction: Insights from the EMPACT-MI Trial

Jacob A. Udell*, M.D., M.P.H., Mark C. Petrie*, M.D., W. Schuyler Jones, M.D., Stefan D. Anker, M.D., Ph.D., Josephine Harrington, M.D., Michaela Mattheus, Dipl.Biomath, Svenja Seide, Ph.D., Offer Amir, M.D., M. Cecilia Bahit, M.D., Johann Bauersachs, M.D., Antoni Bayes-Genis, M.D., Yundai Chen, M.D., Vijay K. Chopra, M.D., Gemma Figtree, M.D., Junbo Ge, M.D., Shaun G. Goodman, M.D., Nina Gotcheva, M.D., Shinya Goto, M.D., Tomasz Gasior, M.D. Waheed Jamal, M.D., James L. Januzzi, M.D., Myung Ho Jeong, M.D., Yuri Lopatin, M.D., Renato D. Lopes, M.D., Ph.D., Béla Merkely, M.D., Ph.D., Monica Martinez-Traba, M.D., Puja B. Parikh, M.D., M.P.H., Alexander Parkhomenko, M.D., Piotr Ponikowski, M.D., Xavier Rossello, M.D., Morten Schou, M.D., Dragan Simic, M.D., Philippe Gabriel Steg, M.D., Joanna Szachniewicz, M.D., Peter van der Meer, M.D., Dragos Vinereanu, M.D., Shelley Zieroth, M.D., Martina Brueckmann, M.D., Mikhail Sumin, M.D., Deepak L. Bhatt, M.D., M.P.H., Adrian F. Hernandez, M.D., Javed Butler, M.D., M.P.H., M.B.A.

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Effect of SGLT2 Inhibitors on Heart Failure Outcomes and Cardiovascular Death: A Systematic Review and Meta-Analysis

Muhammad Shariq Usman, MD; Prof Deepak L Bhatt, MD; Ishaque Hameed, MD; Prof Stefan D. Anker, MD; Alice YY Cheng, MD; Prof Adrian F. Hernandez, MD; William Schuyler Jones, MD; Muhammad Shahzeb Khan, MD; Prof Mark C. Petrie, MD; Jacob A. Udell, MD; Prof Tim Friede, PhD; Prof Javed Butler, MD

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