Efficacy and Safety of Dapagliflozin in Patients With Heart Failure and Previous Myocardial Infarction: A Participant-level Pooled Analysis of DAPA-HF and DELIVER

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BACKGROUND

- Patients with heart failure (HF) and history of myocardial infarction (MI) may represent a distinct subpopulation with unique pathways of disease progression and elevated risk of clinical events.
- Sodium-glucose co-transporter 2 (SGLT2) inhibitors have been shown to reduce cardiovascular death and HF events in a broad range of patients with HF.
- Whether SGLT2 inhibitors may modify clinical trajectory in such individuals is uncertain.

OBJECTIVES

- This pooled participant-level analysis, we examined the efficacy and safety of dapagliflozin according to history of MI in patients with HF across the spectrum of ejection fraction.

METHODS

- The DAPA-HF and DELIVER trials compared dapagliflozin with placebo in patients with symptomatic HF with left ventricular ejection fraction (LVEF) ≤40% and >40%, respectively.
- Patients were categorized by history of MI at baseline.
- Event rates across the LVEF spectrum according to history of MI were examined by Poisson regression using restricted cubic splines.
- The association between history of MI and clinical events was examined using Cox proportional hazard models.
- Treatment effects of dapagliflozin compared with placebo were analyzed by Cox proportional hazard models.
- Additional models further analyzed treatment effect modifications as a continuous function of LVEF using Poisson regression models with baseline LVEF expressed by restricted cubic splines.
- Safety outcomes according to history of MI were examined by logistic regression models with interaction terms.

RESULTS

Table 1. Baseline Characteristics

Characteristic	No previous Myocardial Infarction (n=7276)	Previous Myocardial Infarction (n=3731)	*P*-value
Age	69.7 ± 10.8	68.7 ± 9.7	<0.001
Men	4326 (59.5%)	2825 (75.7%)	<0.001
Race, n (%)			<0.001
White	4958 (68.1%)	2814 (75.4%)	
Asian	1707 (23.5%)	683 (18.3%)	
Black Or African American	285 (3.9 %)	100 (2.7 %)	
American Indian Or Alaska Native	125 (1.7 %)	68 (1.8 %)	
Other	201 (2.8 %)	66 (1.8 %)	
Atrial Fib/Flutter	4125 (56.7%)	1312 (35.2%)	<0.001
Stroke	622 (8.5 %)	441 (11.8%)	<0.001
Dyslipidemia	4059 (55.8%)	2801 (75.1%)	<0.001
Type 2 Diabetes Mellitus	2954 (40.6%)	1835 (49.2%)	<0.001
Hypertension	5961 (81.9%)	3114 (83.5%)	0.045
Prior HF Hospitalization	3135 (43.1%)	1655 (44.4%)	0.20
Coronary Artery Bypass Graft	557 (7.7 %)	1019 (27.3%)	<0.001
Body Mass Index (kg/m^2)	29.4 ± 6.4	28.6 ± 5.5	<0.001
Systolic Blood Pressure (mmHg)	126.1 ± 16.4	124.3 ± 15.5	<0.001
Pulse (beats/min)	72.5 ± 12.0	69.5 ± 10.9	<0.001
NYHA Class at Baseline, n (%)			0.05
I	1 (0.0 %)	0 (0.0 %)	
II	5277 (72.5%)	2639 (70.7%)	
III	1952 (26.8%)	1077 (28.9%)	
IV	46 (0.6 %)	15 (0.4 %)	
KCCQ-TSS	71.4 ± 22.2	71.9 ± 21.7	0.28
LVEF category, n (%)			<0.001
≤ 40 (%)	2654 (36.5%)	2093 (56.1%)	
41-49 (%)	1280 (17.6%)	833 (22.3%)	
≥ 50 (%)	3342 (45.9%)	805 (21.6%)	
NT-proBNP in AFF (ECG)	1509 [1009, 2438]	1728 [1137, 2765]	<0.001
NT-proBNP when no AFF (ECG)	926 [547, 1772]	1015 [602, 1898]	<0.001
Baseline eGFR (mL/min/1.73m2)	63.2 ± 19.7	62.9 ± 18.8	0.45
HbA1c (%)	6.5 ± 1.3	6.7 ± 1.5	<0.001

Figure 1. Incidence Rates of Key Outcomes Across the LVEF Spectrum by History of Myocardial Infarction

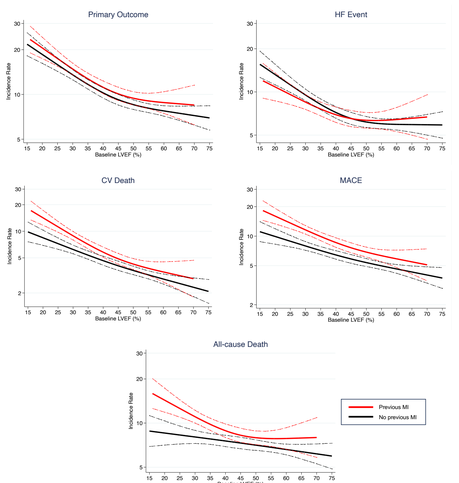


Figure 2. Effect of Dapagliflozin according to History of Myocardial Infarction

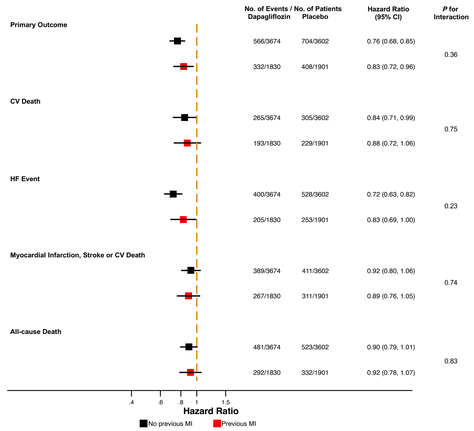


Figure 3. Effect of Dapagliflozin according to History of Myocardial Infarction across the LVEF Spectrum

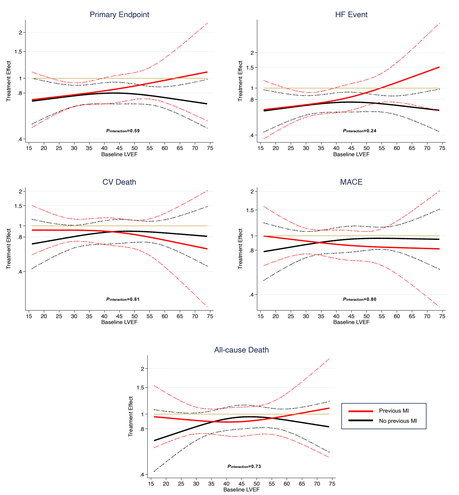
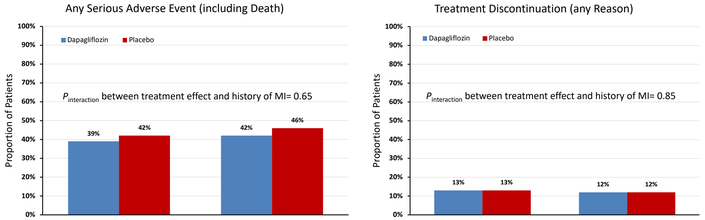


Figure 4. Serious Adverse Events and Treatment Discontinuation According to History of Myocardial Infarction



CONCLUSION

- History of MI confers increased risks of adverse cardiovascular outcomes in patients with HF across the LVEF spectrum, even among those with preserved ejection fraction.
- Dapagliflozin consistently and safely reduces the risk of cardiovascular death or worsening HF, regardless of previous MI.
- Ongoing trials are actively examining SGLT2 inhibitors when introduced early after acute MI.

DISCLOSURE INFORMATION

Dr Peikert receives a research grant from the German Research Foundation. Dr Vaduganathan has received research grant support, served on advisory boards, or had speaker engagements with American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Boehringer Ingelheim, Chiesi, Cytokinetics, Lexicon Pharmaceuticals, Merck, Novartis, Novo Nordisk, Pharmacosmos, Relypsa, Roche Diagnostics, Sanofi, and Tricog Health, and participates on clinical trial committees for studies sponsored by AstraZeneca, Galmed, Novartis, Bayer AG, Occlutech, and Impulse Dynamics. Dr Claggett has received consulting fees from Alnylam, Cardurion, Corvia, Cytokinetics, and Intellia, Rocket. Dr Desai has received institutional research grants from Abbott, AstraZeneca, Alnylam, Bayer, Novartis, and Pfizer; and has received personal consulting fees from Abbott, AstraZeneca, Alnylam, Avidity, Axon Therapeutics, Bayer, Biofourmis, GlaxoSmithKline, Medpace, Merck, Novartis, Parexel, Regeneron, RiverZRenal, Veristat, Verily, and Zydus. Dr Jhund has received speakers' fees from AstraZeneca, Novartis, Aileen Metabolics, ProMaVitae Communications, Sun Pharmaceuticals; has received advisory board fees from AstraZeneca, Boehringer Ingelheim, Analog Devices Inc; and personal fees from Roche and Intas Pharma; has served as Director of Global Clinical Trial Partners (GCTP); and his employer, the University of Glasgow, has been remunerated for clinical trial work from AstraZeneca, Bayer AG, Novartis, and NovoNordisk. Dr Lam is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Bayer and Roche Diagnostics; has served as consultant or on the Advisory Board/Steering Committee/Executive Committee for Actelion, Alleviant Medical, Alyata Pharma, Amgen, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Cytokinetics, Darma Inc, EchoNous Inc, Eli Lilly, Impulse Dynamics, Ionis Pharmaceutical, Janssen Research and Development LLC, Medscape/WebMD Global LLC, Merck, Novartis, Novo Nordisk, Prosciento Inc, Radcliffe Group Ltd, Roche Diagnostics, Sanofi, Siemens Healthcare Diagnostics, and ViiJ Jc; and has served as cofounder and non-executive director of ViiJ Jc. Dr Kosiborod has received research grant support from AstraZeneca, Boehringer Ingelheim, and Pfizer; has served as a consultant or on an advisory board for 35 Pharma, Alnylam, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Dexcom, Eli Lilly, Esperion Therapeutics, Imbria Pharmaceuticals, Janssen, Lexicon, Merck (Diabetes and Cardiovascular), Novo Nordisk, Pharmacosmos, Pfizer, scPharmaceuticals Structure Therapeutics, Vifor Pharma, and Youngene Therapeutics; has received other research support from AstraZeneca; and has received honoraria from AstraZeneca, Boehringer Ingelheim, and Novo Nordisk. Dr Desai has received institutional research grants from Abbott, AstraZeneca, Alnylam, Bayer, Novartis, and Pfizer; and has received personal consulting fees from Abbott, AstraZeneca, Alnylam, Avidity, Axon Therapeutics, Bayer, Biofourmis, GlaxoSmithKline, Medpace, Merck, Novartis, Parexel, Regeneron, RiverZRenal, Veristat, Verily, and Zydus. Dr Inzucchi has served on clinical trial committees or as a consultant to AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Lexicon, Merck, and Pfizer, and has given lectures sponsored by AstraZeneca and Boehringer Ingelheim. Dr Martinez has received personal fees from AstraZeneca. Dr de Boer has received research grants and/or fees from AstraZeneca, Abbott, Boehringer Ingelheim, Cardior Pharmaceuticals GmbH, Ionis Pharmaceuticals Inc, Novo Nordisk, and Roche; and has had speaker engagements with Abbott, AstraZeneca, Bayer, Bristol Myers Squibb, Novo Nordisk, and Roche. Dr Hernandez has received research grants from American Regent, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Merck, Novartis, Somologic and Verily; and has served as a consultant or on the Advisory Board for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cytokinetics, Eidos, Intercept, Merck, and Novartis. Dr Shah has received research grants from the National Institutes of Health (USA HL160273, R01 HL157077, R01 HL127028, R01 HL140731, and R01 HL149423), Actelion, AstraZeneca, Corvia, Novartis, and Pfizer; and has received consulting fees from Abbott, Actelion, AstraZeneca, Amgen, Aria CV, Axon Therapies, Bayer, Boehringer-Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cardiora, Coridea, CVRx, Cyclerion, Cytokinetics, Edwards Lifesciences, Eidos, Elixi, Imara, Impulse Dynamics, GlaxoSmithKline, Intellia, Ionis, Ironwood, Eli Lilly, Merck, MyoKardia, Novartis, Novo Nordisk, Pfizer, Prothena, Regeneron, Rivus, Sanofi, Sardocor, Shifamed, Tenax, Tenaya, and United Therapeutics. Dr Kaber reports speakers' honorariums from AstraZeneca, Bayer, Boehringer, Novartis and Novo Nordisk. Dr Ponikowski reports receiving consulting fees, fees for serving on a speakers bureau, and fees (paid to himself and to his institution) for serving as an investigator and steering or executive committee member for clinical trials from Boehringer Ingelheim, lecture fees from Pfizer, fees (paid to himself and to his institution) for serving as an investigator and steering or executive committee member for clinical trials from Amgen, grant support (paid to his institution), fees for serving on a speakers bureau, consulting fees, and fees (paid to himself and to his institution) for serving as an investigator and steering or executive committee member for clinical trials from Vifor Pharma, fees for serving on a speakers bureau and consulting fees from Servier, fees for serving on a speakers bureau, consulting fees, and fees (paid to himself and to his institution) for serving as an investigator and steering or executive committee member for clinical trials from Bayer, fees for serving on a speakers bureau, consulting fees, and fees (paid to himself and to his institution) for serving as an investigator and steering or executive committee member for clinical trials from Bristol-Myers Squibb, fees for serving on a speakers bureau and consulting fees from Respicardia, fees for serving on a speakers bureau, consulting fees, and fees (paid to himself and to his institution) for serving as an investigator and steering or executive committee member for clinical trials from Cibiem, fees for serving on a speakers bureau, consulting fees, and fees (paid to himself and to his institution) for serving as an investigator and steering or executive committee member for clinical trials from Novartis, and fees for serving on a speakers bureau, consulting fees, and fees (paid to himself and to his institution) for serving as an investigator and steering or executive committee member for clinical trials from RenalGuard. Dr Sabatine reports research grant support through Brigham and Women's Hospital from: Abbott; Amgen; Anthos Therapeutics; AstraZeneca; Boehringer Ingelheim; Daiichi-Sankyo; Eisai; Intarcia; Ionis; Merck; Novartis; Pfizer; Saghmos Therapeutics; Verve Therapeutics, and consulting for: Amgen; Anthos Therapeutics; AstraZeneca; Beren Therapeutics; Boehringer Ingelheim; Dr. Reddy's Laboratories; Fibrogen; Intarcia; Merck; Moderna; Novo Nordisk; Precision BioSciences; Silence Therapeutics. Additionally, Dr. Sabatine is a member of the TIMI Study Group, which has also received institutional research grant support through Brigham and Women's Hospital from: ARCA Biopharma, Inc., Janssen Research and Development, LLC, Pfizer, Regeneron Pharmaceuticals, Inc., Roche, Siemens Healthcare Diagnostics, Inc., Softcell Medical Limited, and Zora Biosciences. Dr Petersson and Langkilde are employees and shareholders of AstraZeneca. Dr McMurray reports payments through Glasgow University from work on clinical trials, consulting and other activities from: Amgen, AstraZeneca, Bayer, Cardurion, Cytokinetics, GSK, KBP Biosciences, and Novartis. Personal consultancy fees from: Alnylam Pharma., Bayer, BMS, George Clinical PTY Ltd, Ionis Pharma., Novartis, Regeneron Pharma., River 2 Renal Corporation; Personal lecture fees from Abbott, Aiken Metabolics, Astra Zeneca, Blue Ocean Scientific Solutions Ltd, Boehringer Ingelheim, Canadian Medical and Surgical Knowledge, Encure Pharma Ltd, Eris Lifesciences, European Academy of CME, Hikma Pharmaceuticals, Imagica health, Intas Pharma, J.B. Chemicals & Pharma. Ltd, Lupin Pharma, Medscape/HeartOrg, ProMaVitae Communications, Radcliffe Cardiology, Sun Pharma., The Corpus, Translation Research Group, Translational Medicine Academy. Dr McMurray is a director of Global Clinical Trial Partners Ltd. Dr Solomon has received research grants (paid to institution) from Actelion, Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, Bristol-Myers Squibb, Celladon, Cytokinetics, Eidos, Gilead, GlaxoSmithKline, Ionis, Eli Lilly, MesoblastL MyoKardia, National Institutes of Health/NHLBI, Neurotronik, Novartis, NovoNordisk, Respicardia, Sanofi Pasteur, Theracos, US2.AI; and has consulted for Abbott, Action, Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GlaxoSmithKline, Eli Lilly, Merck, MyoKardia, Novartis, Roche, Theracos, Quantum Genomics, Cardurion, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellProThera, Moderna, American Regent, Sarepta, Lexicon, Anacardio, and Valo. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.