Efficacy and safety of dapagliflozin in the background of polypharmacy among patients with HFmrEF or HFpEF in the DELIVER Trial

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BACKGROUND

- Patients with heart failure (HF) have a high burden of multimorbidity, often necessitating numerous medications.
- While SGLT2i have been demonstrated to be highly effective in HF, there may be clinical concern about introducing another medication, especially among individuals with polypharmacy.

PURPOSE

- This study examined the efficacy and safety of addition of dapagliflozin according to the number of concomitant medications in HF with mildly reduced or preserved ejection fraction.

METHODS

- The DELIVER trial compared dapagliflozin with placebo in 6,263 participants with HF with left ventricular EF >40%. The primary outcome was worsening HF or cardiovascular death.
- Baseline medication use (including vitamins, supplements) was collected.
- Patients were categorized by the total number of concomitant medications at baseline according to categories of polypharmacy status: 0-4 medications (non-polypharmacy), 5-9 medications (polypharmacy), and ≥10 medications (hyper-polypharmacy).
- Event rates across the total number of baseline medications were examined by Poisson regression using restricted cubic splines.
- The association between polypharmacy categories 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 effects with the number of medications modeled as continuous variable.
- Safety outcomes according to polypharmacy category were examined by logistic regression models with interaction terms.

RESULTS

Table 1. Baseline Characteristics according to Categories of Total Numbers of Medications.

Characteristic	Non-polypharmacy (<5 medications; n=582)	Polypharmacy (5-9 medications; n=3795)	Hyper-polypharmacy (≥10 medications; n=1886)	P-value for Trend
Total Number of Medications	4 ± 1	7 ± 1	13 ± 3	
Age	72 ± 11	71 ± 10	73 ± 9	p<0.001
Men	47 %	57 %	58 %	p<0.001
Race, %				p<0.001
White	57 %	71 %	74 %	
Asian	29 %	19 %	20 %	
Black Or African American	1 %	2 %	4 %	
American Indian Or Alaska Native	6 %	3 %	1 %	
Other	7 %	3 %	1 %	
Total Number of Comorbidities	3 ± 2	4 ± 2	6 ± 2	p<0.001
Prior HF Hospitalization, %	28 %	39 %	47 %	p<0.001
Body Mass Index (kg/m²)	28 ± 6	30 ± 6	31 ± 7	p<0.001
Systolic Blood Pressure (mmHg)	128 ± 15	128 ± 15	128 ± 16	p=0.88
Pulse (beats/min)	71 ± 12	72 ± 12	71 ± 12	p=0.36
NYHA Class , %				p=0.53
I	0 %	0 %	<1 %	
II	79 %	75 %	76 %	
III	21 %	25 %	24 %	
IV	<1 %	<1 %	<1 %	
KCCQ-Total Symptom Score	73 ± 22	71 ± 28	68 ± 23	p<0.001
LVEF(%)	56 ± 9	54 ± 9	55 ± 9	p=0.018
NT-proBNP in AFF [IQR]	1299 [926, 2149]	1394 [968, 2174]	1435 [962, 2348]	p=0.15
NT-proBNP no AFF [IQR]	797 [471, 1438]	714 [461, 1276]	701 [474, 1251]	p=0.34
eGFR (mL/min/1.73m2)	64.7 ± 19.6	62.6 ± 19.1	57 ± 18	p<0.001
HbA1c (%)	6 ± 1	7 ± 1	7 ± 2	p<0.001

Figure 1. Incidence of Key Outcomes by Total Number of Medications.

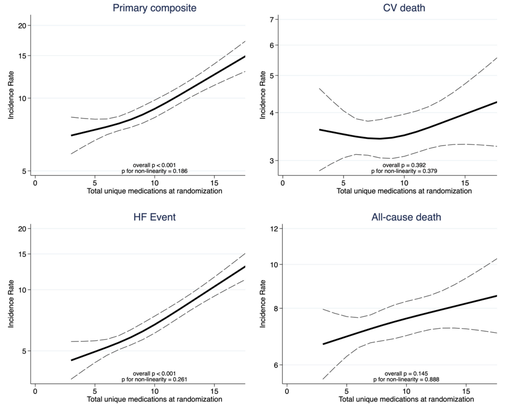


Figure 2. Effect of Dapagliflozin by Categories of Total Numbers of Medications.

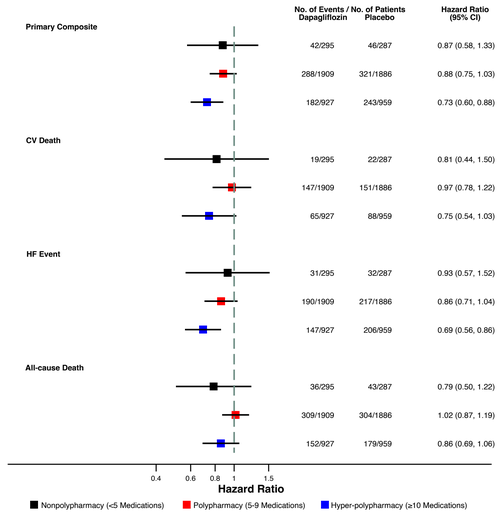


Figure 3. Effect of Dapagliflozin on the Occurrence of Key Outcomes according to Number of Total Medications

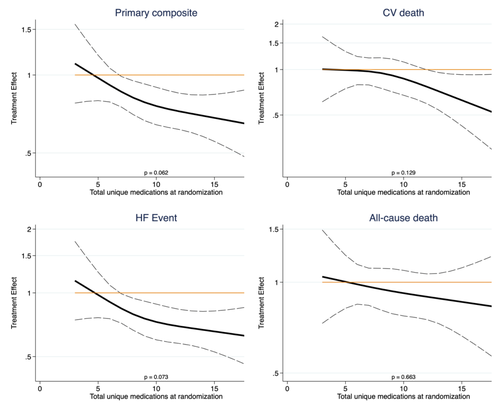
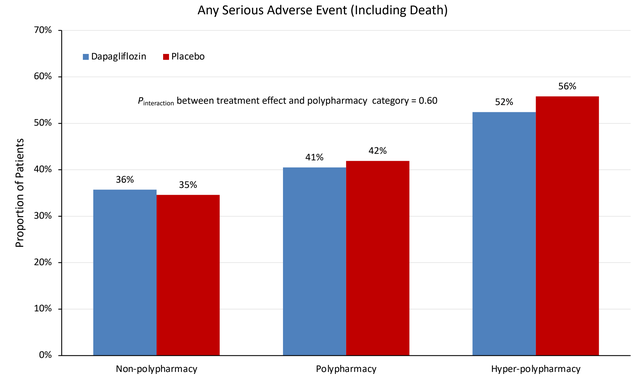


Figure 4. Occurrence of Adverse Events According to Total Number of Medications



CONCLUSION

- In DELIVER, polypharmacy was common, closely correlated with multimorbidity, and associated with increased risk of clinical events.
- Dapagliflozin consistently and safely reduced worsening HF events or cardiovascular death across the spectrum of medication burden, including among individuals with polypharmacy and hyper-polypharmacy.
- These findings further support the use of dapagliflozin as a safe and effective treatment option for patients with HF with mildly reduced or preserved EF, even among those already on multiple medications.

DISCLOSURE INFORMATION

The DELIVER trial was funded by AstraZeneca. Dr Peikert receives a research grant from the German Research Foundation. Dr Goyal has received consulting fees from Sensorum Health. 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 Boehringer Ingelheim. Dr Kosiborod has received research grant support from AstraZeneca and Boehringer Ingelheim; has served as a consultant or on an advisory board for Alnylam, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Esperion Therapeutics, Janssen, Lexicon, Merck (Diabetes and Cardiovascular), Novo Nordisk, Sanofi, Pharmacosmos, and Vifor Pharma; has received other research support from AstraZeneca; and has received honoraria from AstraZeneca, Boehringer Ingelheim, and Novo Nordisk. Dr Desai reports institutional research grants from Abbott, AstraZeneca, Alnylam, Bayer, Novartis, and Pfizer, as well as personal consulting fees from Abbott, AstraZeneca, Alnylam, Axidity, Axon Therapeutics, Bayer, Biofourmis, GlaxoSmithKline, Medpace, Merck, Novartis, Pareekh, Regeneron, RiverZhenai, Vershot, Verily, and Zydus. Dr Jhund reports speakers' fees from AstraZeneca, Novartis, Alkem Metabolics, ProAdWise Communications, Sun Pharmaceuticals; advisory board fees from AstraZeneca, Boehringer Ingelheim, Novartis; research funding from AstraZeneca, Boehringer Ingelheim, Analog Devices Inc; and serves as director of Global Clinical Trial Partners (GCTP). Dr Jhund's 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, Allysta Pharma, Amgen, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Cytokinetics, Darma Inc., Echolous Inc, Eli Lilly, Impulse Dynamics, Ionis Pharmaceutical, Janssen Research & Development LLC, Medscape/WebMD Global LLC, Merck, Novartis, Novo Nordisk, Prosciento Inc, Radcliffe Group Ltd., Roche Diagnostics, Sanofi, Siemens Healthcare Diagnostics and Us2.ai; and serves as co-founder & non-executive director of Us2.ai. Dr Inzucchi has served on clinical trial committees or as a consultant to AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Merck, Pfizer, vTv Therapeutics, Abbott, and Esperion; 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, Novartis, 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 (U54 HL160273, R01 HL132028, R01 HL140731, 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, Esai, Imara, Impulse Dynamics, GSK, Intellia, Ionis, Ironwood, Lilly, Merck, MyoKardia, Novartis, Novo Nordisk, Pfizer, Prothena, Regeneron, Rivus, Sanofi, Sardocor, Shifamed, Tenax, Tenaya, and United Therapeutics. Dr McMurray has received funding to his institution, Glasgow University, for his work on clinical trials, consulting, and other activities from Alnylam, Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Cardurion, Cytokinetics, GlaxoSmithKline, Novartis, Pfizer, and Theracos; and has received personal lecture fees from the Corpus, Abbott, Hickma, Sun Pharmaceuticals, and Medscp. Dr Solomon has received research grants from Actelion, Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, Bristol Myers Squibb, Celladon, Cytokinetics, Eidos, Gilead, GlaxoSmithKline, Ionis, Lilly, MesoblastMyoKardia, National Institutes of Health/NHLBI, Neurotronik, 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, Lilly, Merck, Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Cardurion, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellProThera, Moderna, American Regent, and Sarepta.