Blood Pressure, Dapagliflozin, and Cardiovascular Outcomes In Heart Failure With Mildly Reduced or Preserved Ejection Fraction: DELIVER

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on behalf of the DELIVER Committees, Investigators, Sponsor, and Participants

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Background and Rationale

- Hypertension is *very* common in HFpEF
  - Consequences:
    - LVH
    - Diastolic dysfunction
    - Abnormal ventricular arterial coupling
    - Coronary microvascular dysfunction
    - End organ damage

- Optimizing BP remains *sole* class I recommendation in HFpEF
  - Extrapolation from SPRINT

7.7.1. HF With Preserved Ejection Fraction

Recommendations for HF With Preserved Ejection Fraction* Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
1	C-LD	1. Patients with HFpEF and hypertension should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity.[1–3]
2a	B-R	2. In patients with HFpEF, SGLT2i can be beneficial in decreasing HF hospitalizations and cardiovascular mortality.[4]
2a	C-EO	3. In patients with HFpEF, management of AF can be useful to improve symptoms.
2b	B-R	4. In selected patients with HFpEF, MRAs may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[5–7]
2b	B-R	5. In selected patients with HFpEF, the use of ARB may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[8,9]
2b	B-R	6. In selected patients with HFpEF, ARNi may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[10,11]
3: No-Benefit	B-R	7. In patients with HFpEF, routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QOL is ineffective.[12,13]

Heidenreich et al., ACC/AHA/HFSA HF Guidelines, 2022

Objectives

- Understand the prognostic influence of baseline and mean-achieved SBP on clinical outcomes
- Analyze the impact of dapagliflozin on SBP
- Evaluate the beneficial treatment effects of dapagliflozin on clinical outcomes in relation to baseline SBP
- Assess whether the SBP lowering effect of dapagliflozin accounted for its treatment effects.

Study Population

- International, randomized, double-blind, event-driven trial of dapagliflozin vs. placebo
- Inclusion criteria: >40 years, NYHA class II–IV, LVEF>40%, elevated NT-proBNP, and evidence of structural heart disease
- Exclusion criteria: eGFR < 25 mL/min/1.73 m^2, recent CV event, and SBP <95 or ≥160 mm Hg (if not on treatment with ≥3 agents) or ≥180 mmHg (irrespective of treatments)
- Primary outcome: composite of cardiovascular death or worsening HF event
- Final N=6263 for analysis (entire DELIVER study population)
- Statistical analysis:
  - Participants described in SBP clinical categories, using restricted cubic splines analysis
    - Baseline and time-updated (mean achieved) SBP variables employed
  - Mediation analysis: Cox models between treatment assignment and outcomes adjusting for baseline/change in SBP, landmarked at 1 month visit

Solomon et al., EJHF, 2021; Solomon et al., NEJM, 2022

Baseline Characteristics by SBP Group

	SBP < 120 N=1809	SBP 120-129 N=1535	SBP 130-139 N=1514	SBP ≥ 140 N=1405	P-value
SBP (mmHg)	110 ± 7	125 ± 3	134 ± 3	149 ± 8	
DBP (mmHg)	68 ± 9	73 ± 9	76 ± 9	80 ± 11	<0.001
Age	71 ± 10	72 ± 10	72 ± 9	72 ± 9	0.043
Men	58%	56%	58%	52%	0.001
Atrial Fib/Flutter	62%	57%	56%	51%	<0.001
Type 2 DM	39%	44%	47%	51%	<0.001
BMI	29 ± 6	30 ± 6	30 ± 6	31 ± 6	<0.001
LVEF(%)	54 ± 9	54 ± 9	54 ± 9	55 ± 9	<0.001
NT-proBNP (ng/L)	1097 [668, 1884]	1015 [626, 1747]	1024 [621, 1743]	907 [562, 1596]	<0.001
ARNI	9%	4%	3%	2%	<0.001
Beta Blocker	85%	82%	83%	80%	0.017
MRA	53%	43%	42%	32%	<0.001
Loop diuretics	80%	77%	75%	75%	0.006

Adverse Events by Baseline SBP

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	SBP < 120 N=1809	SBP 120-129 N=1535	SBP 130-139 N=1514	SBP ≥ 140 N=1405	P-value
Any AE leading to IP discontinuation	6.5 %	5.0 %	6.4 %	5.3 %	0.17
Any AE leading to interruption of IP	15.4%	14.2%	14.9%	15.0%	0.81
Any amputation	0.3 %	0.5 %	1.0 %	1.2 %	0.005
Any definite or probable diabetic ketoacidosis	0.0 %	0.0 %	0.1 %	0.0 %	0.10
Any MI	1.5 %	2.6 %	2.2 %	2.8 %	0.06
Any Stroke	2.8 %	2.9 %	3.1 %	4.6 %	0.017
Any SAE or DAE suggestive of volume depletion	1.5 %	1.1 %	1.0 %	1.1 %	0.54
Any renal SAE or DAE	2.8 %	1.8 %	2.3 %	2.8 %	0.22

Adverse Events by Treatment Arm in Patients with SBP<120 mmHg

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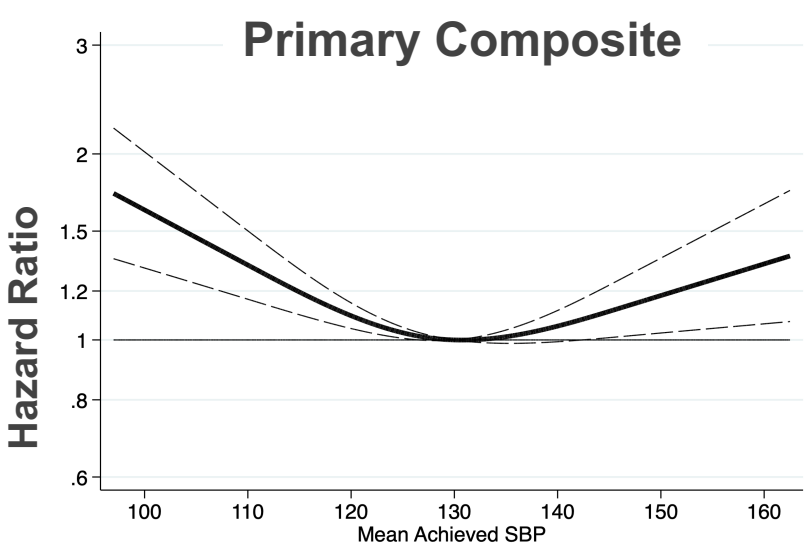
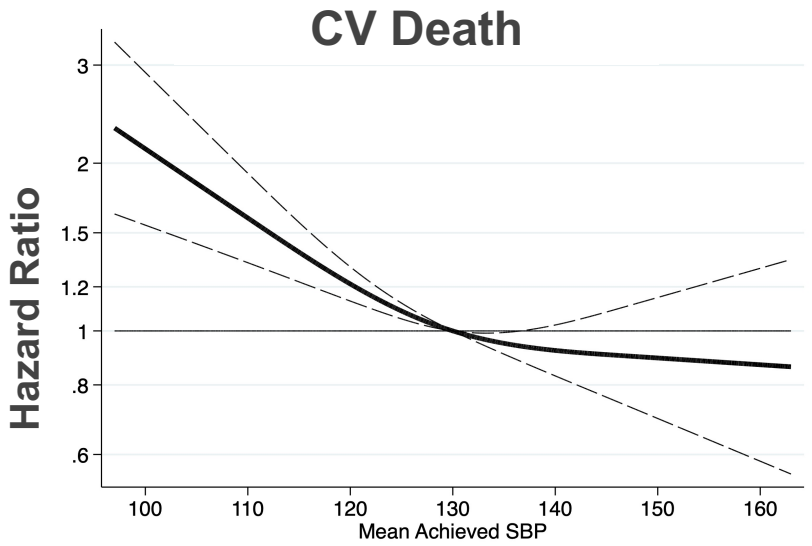
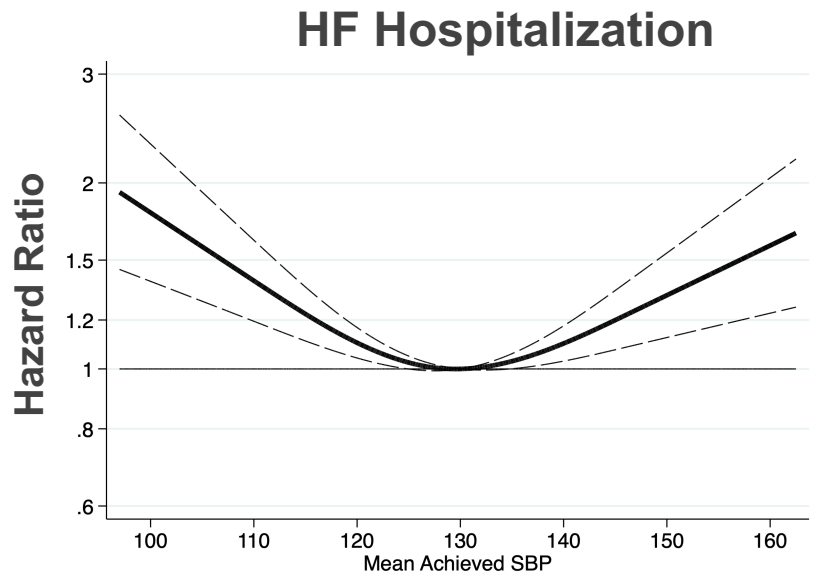
	Placebo N=902	Dapagliflozin N=907	P-value
Any SAE (including outcome = death)	399 (44.2%)	408 (45.0%)	0.73
Any AE leading to discontinuation of treatment	58 (6.4 %)	59 (6.5 %)	0.94
Any amputation	4 (0.4 %)	1 (0.1 %)	0.18
Any potential risk factor AE for amputation affecting lower limbs	59 (6.5 %)	55 (6.1 %)	0.68
Any definite or probable DKA	0 (0.0 %)	0 (0.0 %)	
Any MI	11 (1.2 %)	16 (1.8 %)	0.34
Any Stroke	22 (2.4 %)	29 (3.2 %)	0.33
Any major hypoglycemic event	2 (0.2 %)	3 (0.3 %)	0.66
Any SAE or DAE suggestive of volume depletion	11 (1.2 %)	16 (1.8 %)	0.34
Any renal SAE or DAE	33 (3.7 %)	18 (2.0 %)	0.032

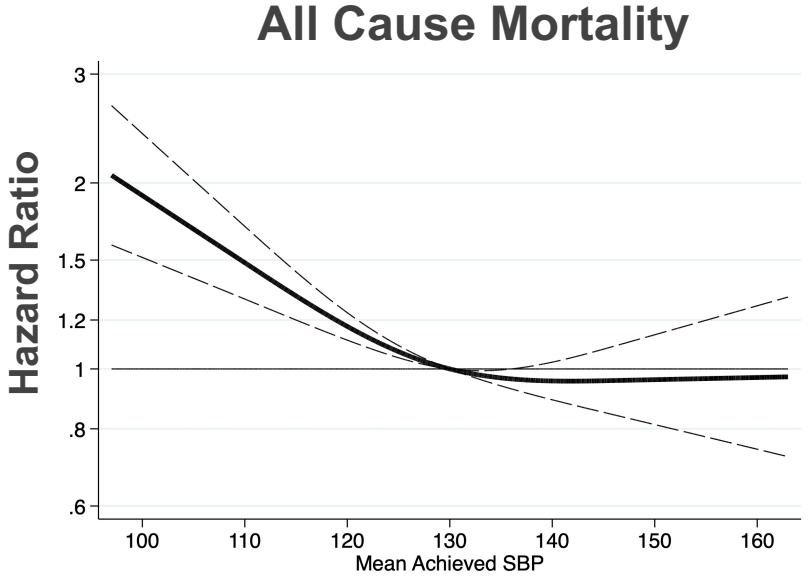
Similar AEs by Treatment Arm in Other SBP Categories

Mean-achieved SBP and Events



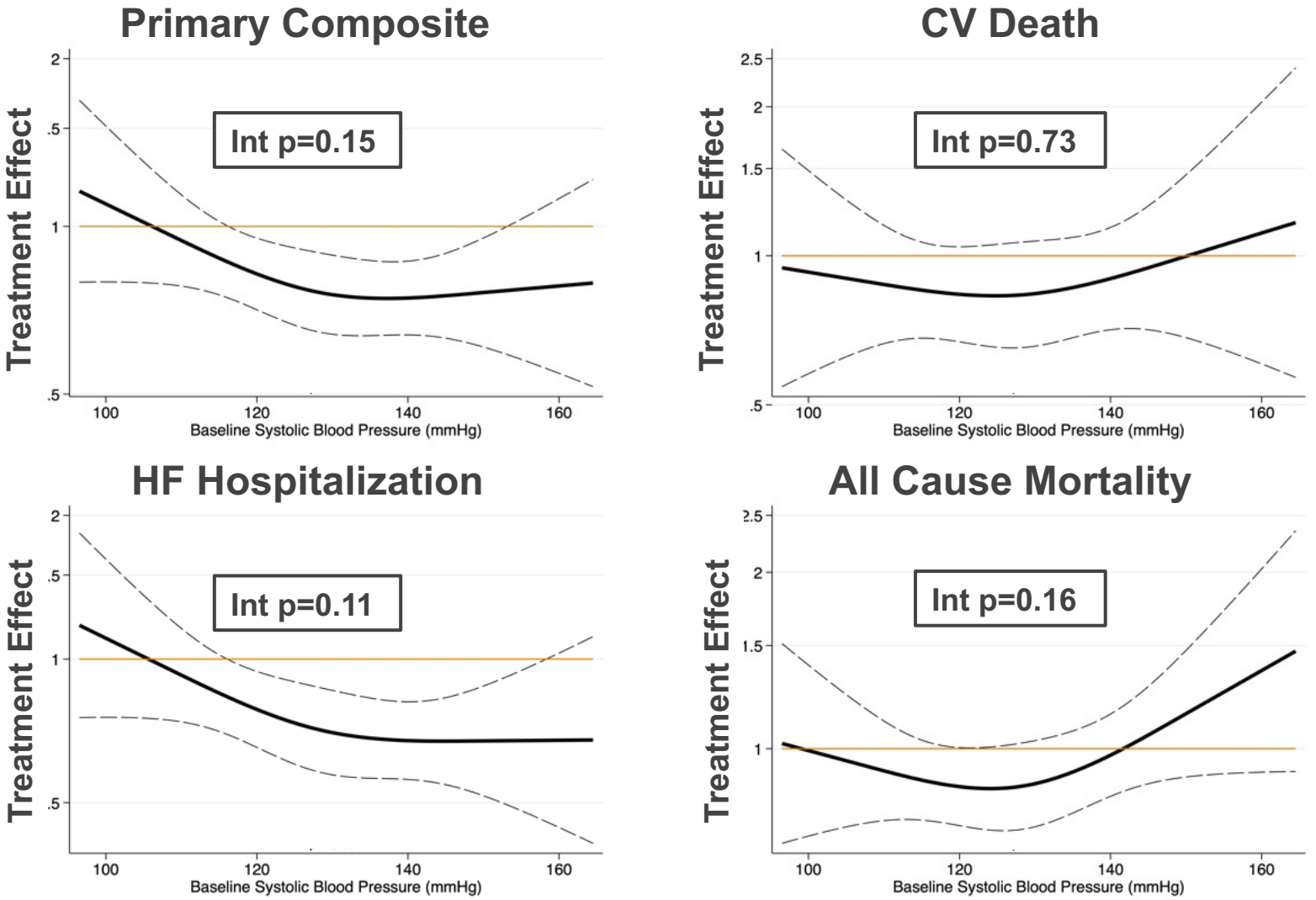




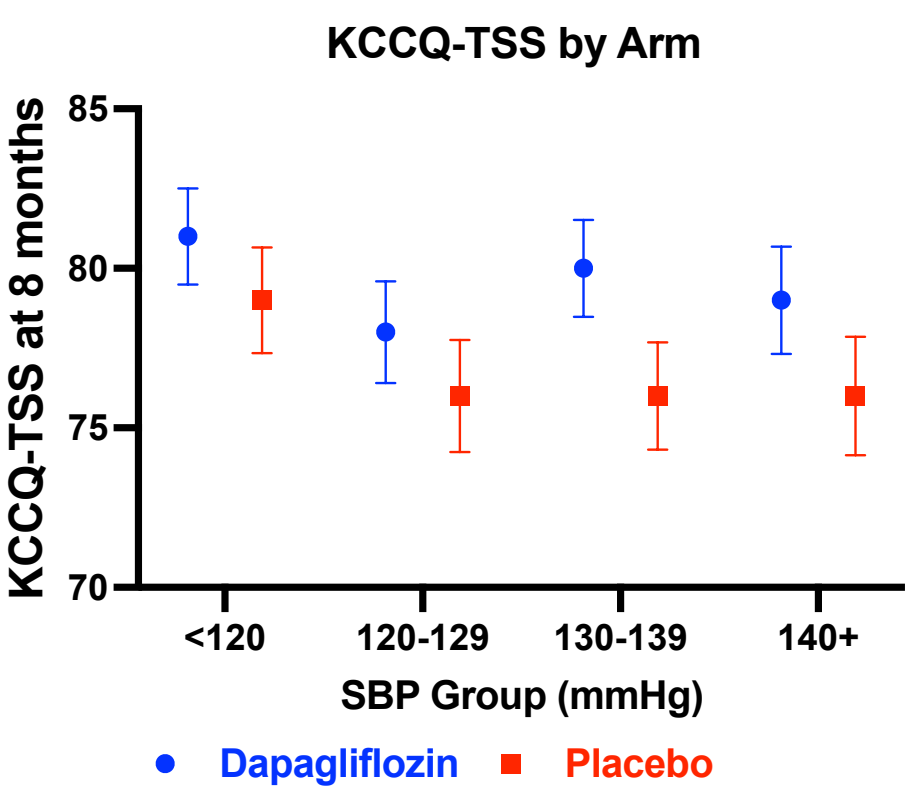


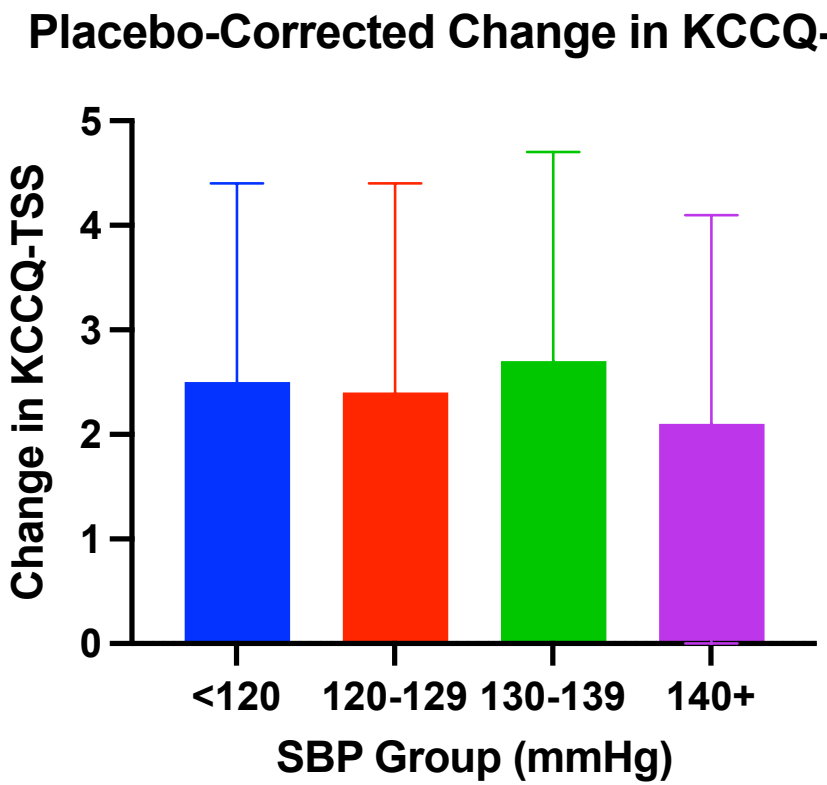
Adjusted for region, AF, creatinine, DM, NYHA class, heart rate, sex, age, race, smoking status, ejection fraction, and treatment group.

Treatment Effect of Dapagliflozin across Baseline SBP



Effect of Dapagliflozin on KCCQ-TSS across Baseline SBP



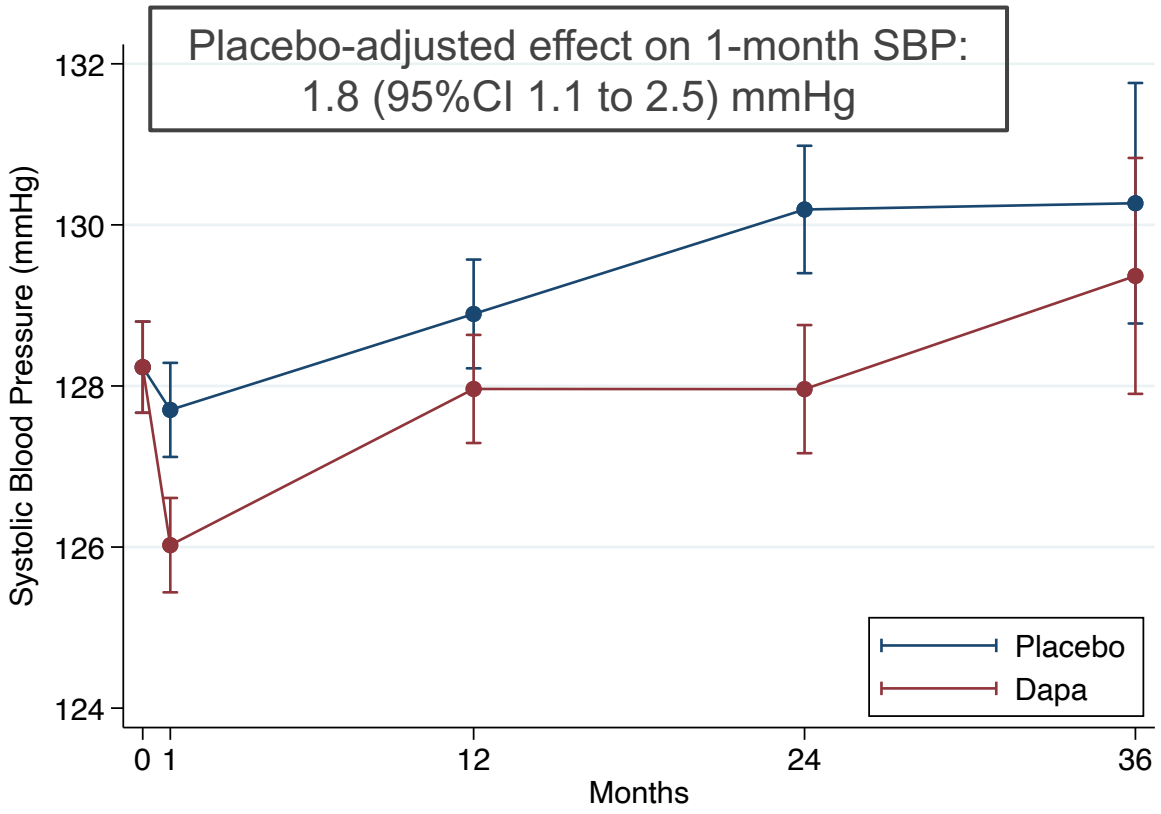


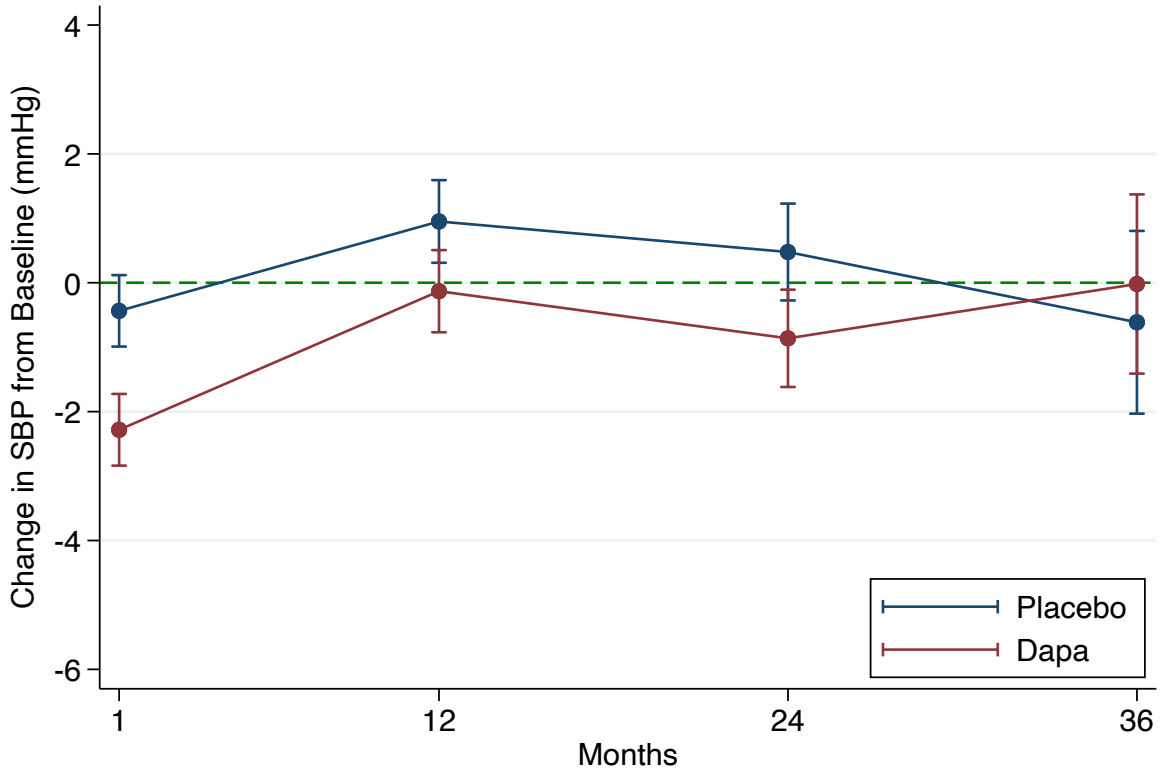
Mean and 95% CI shown

*Adjusted for baseline KCCQ-TSS scores

Treatment * SBP baseline category p-interaction=0.98

Effect of Dapagliflozin on SBP





Treatment * SBP baseline category p-interaction=0.16

Effect of Change in SBP on Treatment Effect of Dapagliflozin

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	Unadjusted HR Dapagliflozin vs. Placebo (95% CI)	Adjusted HR Dapagliflozin vs. Placebo (95% CI)*
Primary composite	0.82 (0.73, 0.92)	0.85 (0.75, 0.96)
HF hospitalization	0.77 (0.67, 0.89)	0.80 (0.68, 0.93)

*Adjusted for baseline SBP and 1-month SBP.
Analyses were landmarked at the 1-month visit.

Conclusions

- SBP<120 mmHg and >140 mmHg identified patients at the highest risk for HF events and/or vascular events
  - Need RCT data to delineate optimal BP goals
- Dapagliflozin provided consistent treatment benefits with respect to cardiovascular events and HF-related health status across baseline SBP
  - Well tolerated and safe across baseline SBP
- Dapagliflozin reduced SBP by ~2 mmHg, vs. placebo, by 1-month visit, and consistently across baseline SBP
- Treatment effect was minimally related to changes in BP

Thank you

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