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Efficacy and Safety of Dapagliflozin according to Baseline Blood Pressure
Observations From DECLARE-TIMI 58 Trial

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An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

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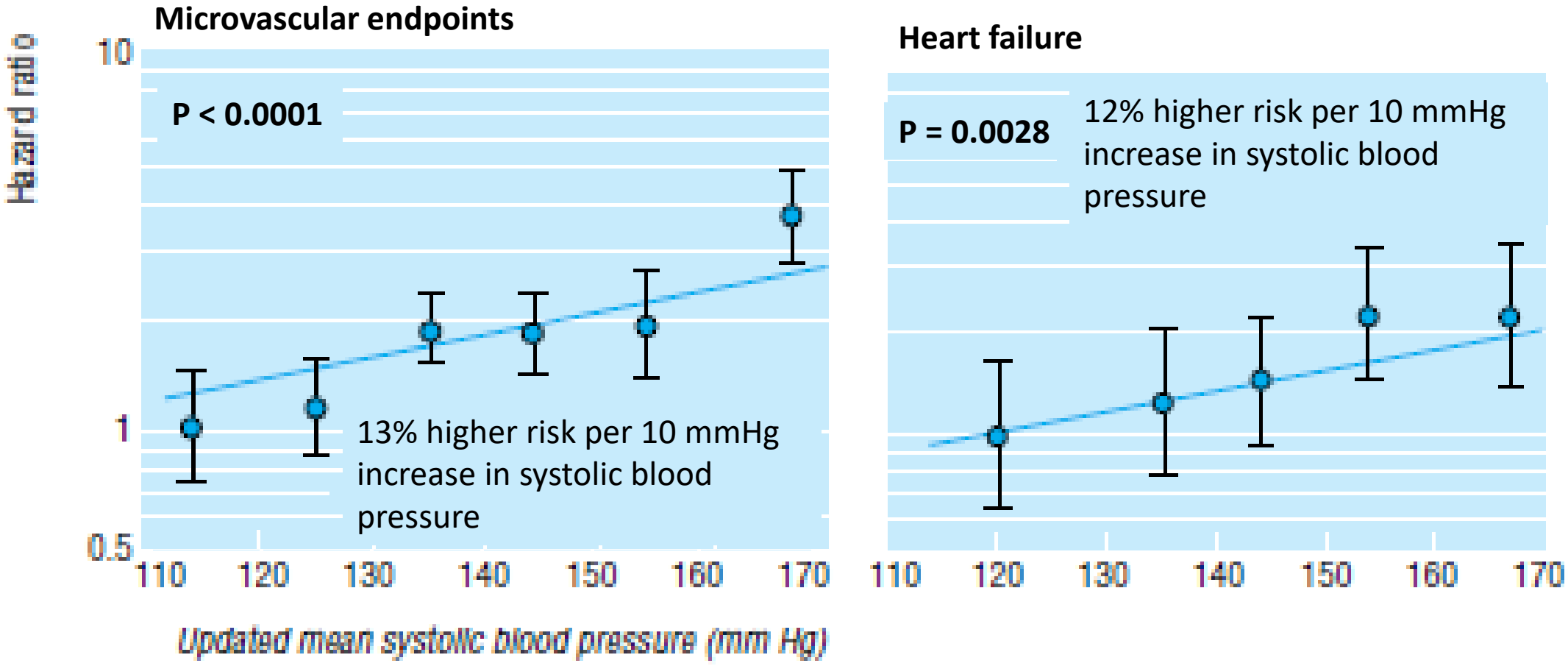
Declaration of Interest

- Dr. Furtado reports grants (received from his institution) from AstraZeneca, during the conduct of the study; research grants and personal fees from AstraZeneca; personal fees from Servier; research grants from DalCor, Behring, Jansen, Novartis , Novo Nordisk, Pfizer, and EMS, outside the presented work.
- The DECLARE-TIMI 58 study was sponsored by AstraZeneca, including research grants to the TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital

Background

Association between SBP and outcomes in patients with T2DM in UKPDS

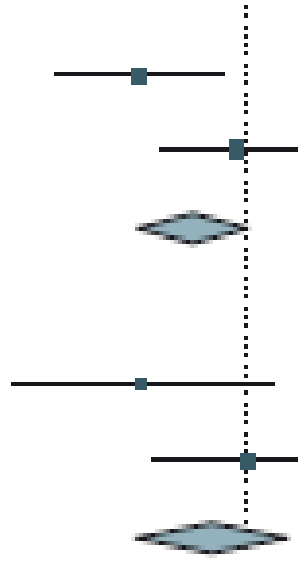


Adler et al. BMJ 2000; 321: 412

Background

Standardized associations between 10-mmHg lower SBP and HF and renal outcomes among patients with diabetes stratified according to baseline SBP in M-A of 44 trials of BP lowering

Outcome	Relative Risk (95% CI)	Favors BP Lowering	Favors Control	*P* for Interaction
Heart failure, mm Hg				
≥140[16, 18, 29, 30, 35, 39-41, 46, 47, 64, 65]	0.75 (0.59-0.94)			
<140[31, 42, 43, 58-60, 80, 81]	0.97 (0.79-1.19)			*P* = .09
Overall	0.86 (0.74-1.00)			
Renal failure, mm Hg				
≥140[16, 18, 29, 30, 35, 40, 41, 64, 65]	0.75 (0.52-1.08)			
<140[31, 58-60]	1.00 (0.77-1.29)			*P* = .21
Overall	0.91 (0.74-1.12)			

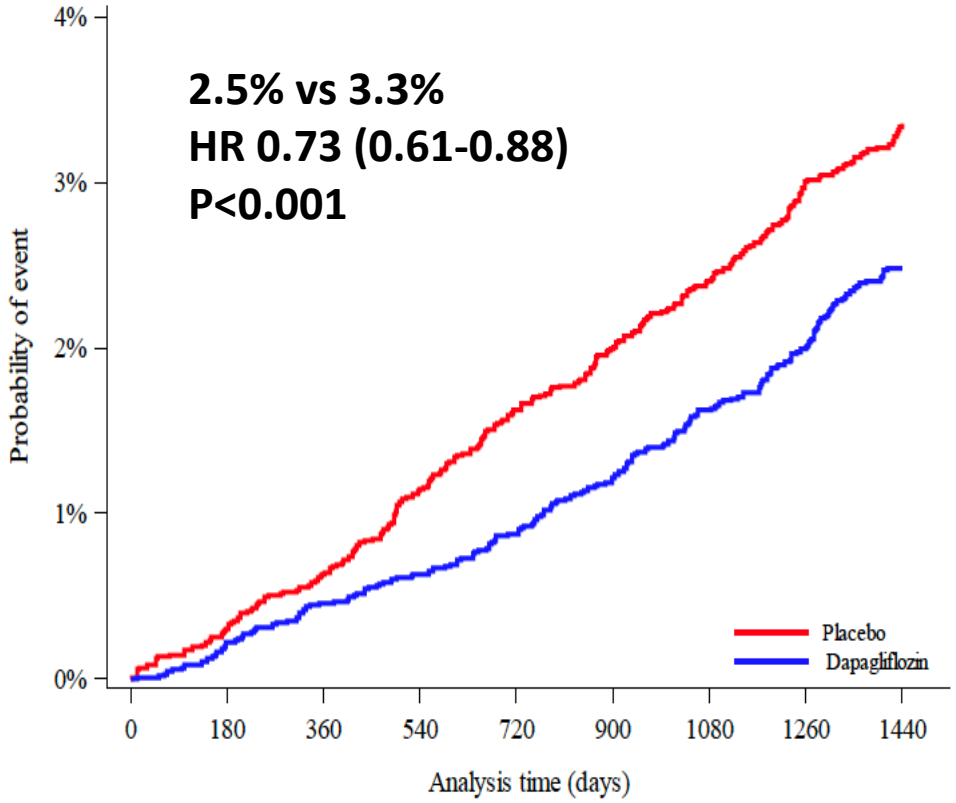


Emdin et al. JAMA 2015; 313: 603

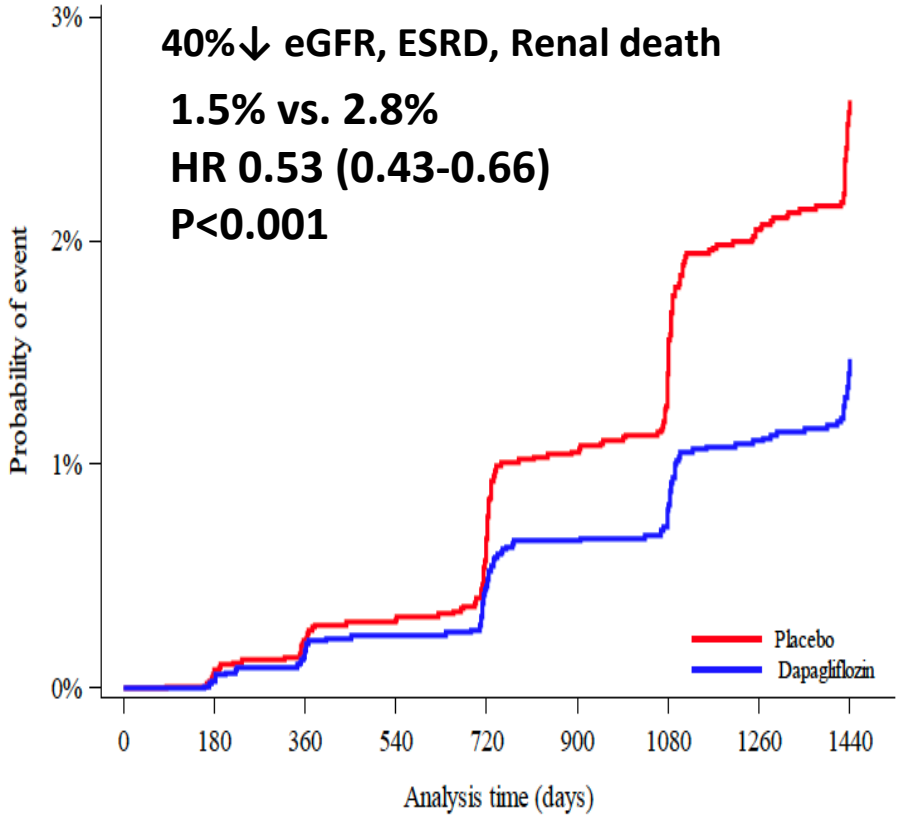
Background

In DECLARE TIMI 58, dapagliflozin reduced hospitalization for heart failure and renal outcomes in a broad range of patients with type 2 DM (60% w/o CV disease; 90% w/ hyp)

Hospitalization for HF



Renal Composite EP



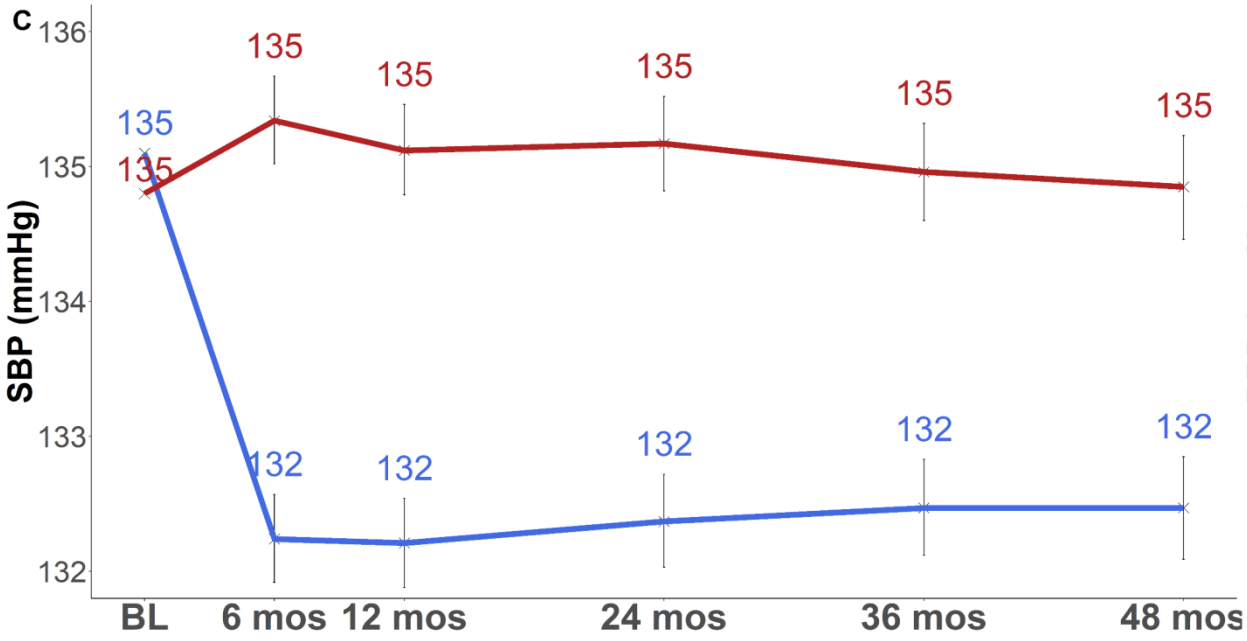
Wiviott et al. N Eng J Med 2019; 380: 347

Background

However, changes in BP with dapagliflozin and other SGLT2i have been only modest

SBP

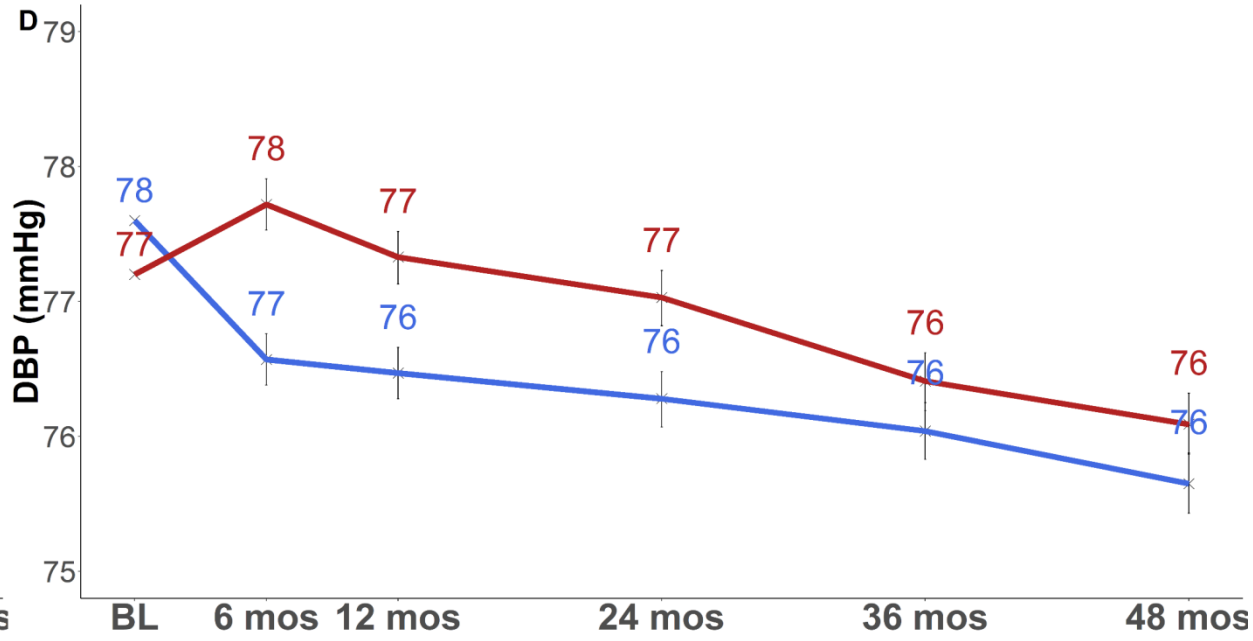
LSM Difference 2.7 mmHg (95% CI 2.4-3.0)



All P-values (except BL) <0.001

DBP

LSM Difference 0.7 mmHg (95% CI 0.6-0.9)



All P-values (except BL) <0.001

LSM = Least Square Mean

1- Wiviott et al. N Eng J Med 2019; 380: 347

Methods

- In this pre-specified analysis from DECLARE – TIMI 58, we sought to assess: 1) whether dapagliflozin consistently reduced heart failure and renal events across all levels of baseline systolic blood pressure, and 2) whether BP-lowering related adverse events (volume depletion, amputation and acute kidney injury) would be increased at any level of baseline SBP.
- Patients were categorized based on SBP into: optimal (SBP < 120 mmHg), normal (120-129), high normal (130-139), grade 1 hypertension (140-159), and grade 2-3 or severe hypertension (≥ 160 mmHg); according to current guidelines[1]

1- Williams et al. Eur Heart J 2018; 39: 3021

Statistical Analysis

- Within the placebo arm, efficacy outcomes were assessed according to the categories of SBP, with a Multivariable Cox proportional hazards models used in order to adjust for baseline co-variates;
- Furthermore, adjusted spline models were used in order to assess the association between continuous SBP and the outcomes of interest;
- Efficacy and safety of dapagliflozin versus placebo were analyzed stratified according to the aforementioned categories of SBP

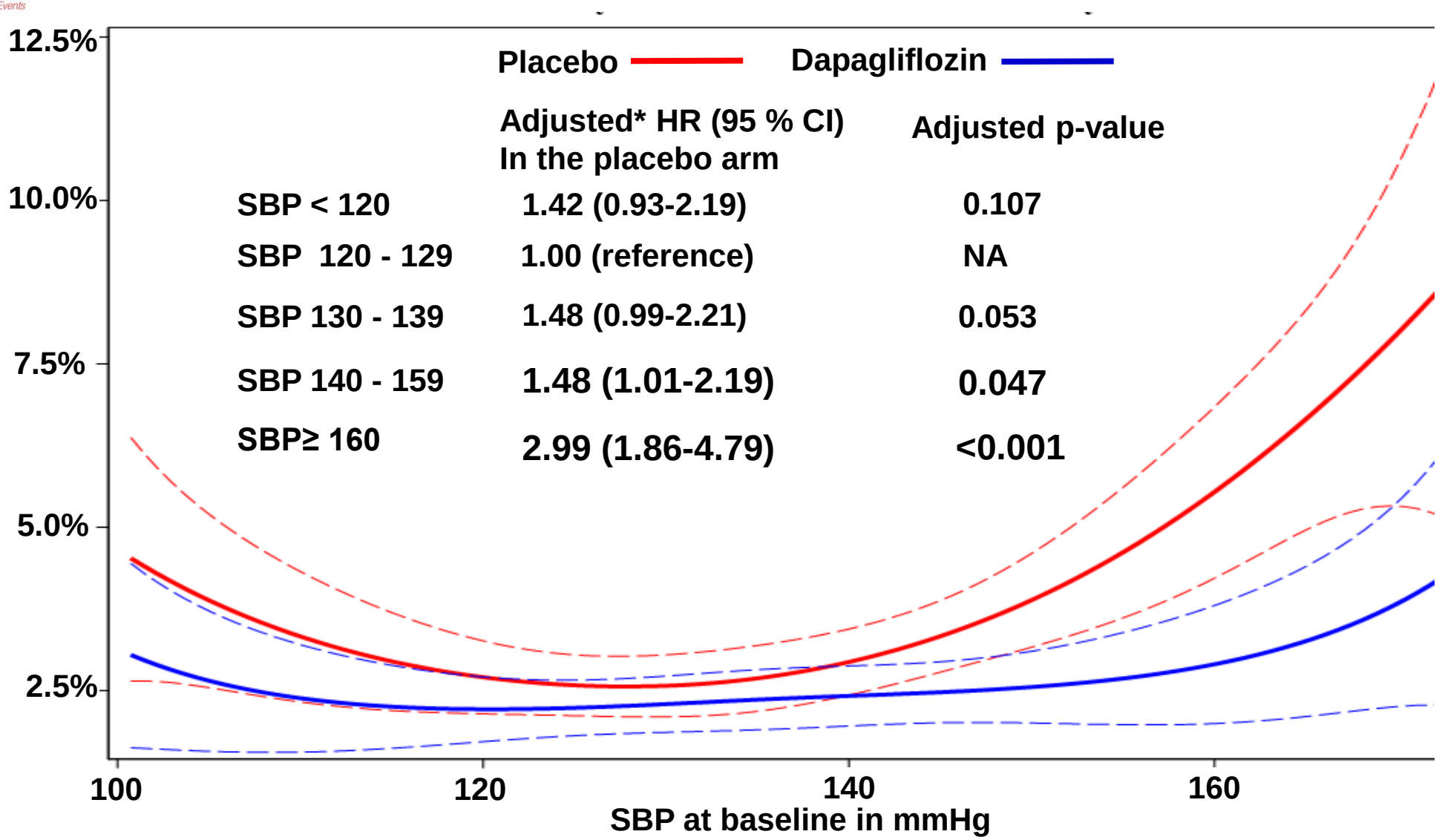
Results

Key Baseline characteristics according to SBP

	SBP < 120 (N= 2557)	SBP 120 – 129 (N = 3686)	SBP 130-139 (N = 4385)	SBP 140-159 (N = 5501)	≥ 160 (N = 1031)	p-value
ASCVD, (%)	**46.4**	**41.8**	**39.5**	**38.6**	**38.3**	**< 0.0001**
Age, median (IQR)	**63 (59, 68)**	**63 (59, 68)**	**64 (60, 68)**	**64 (60, 69)**	**65 (61, 70)**	**< 0.0001**
Female, (%)	**37.9**	**37.2**	**36.7**	**37.7**	**38.5**	**0.72**
White, (%)	**71.6**	**77.8**	**81.6**	**82.4**	**81.9**	**< 0.0001**
eGFR < 60 ml/min/1.73 m^2, (%)	**9.5**	**7.1**	**7.3**	**6.6**	**7.4**	**0.0002**
Prior HF, (%)	**10.7**	**9.6**	**10.8**	**9.7**	**8.4**	**0.074**
UACR > 300 mg/g, (%)	**3.2**	**4.4**	**5.8**	**9.2**	**17.9**	**< 0.0001**

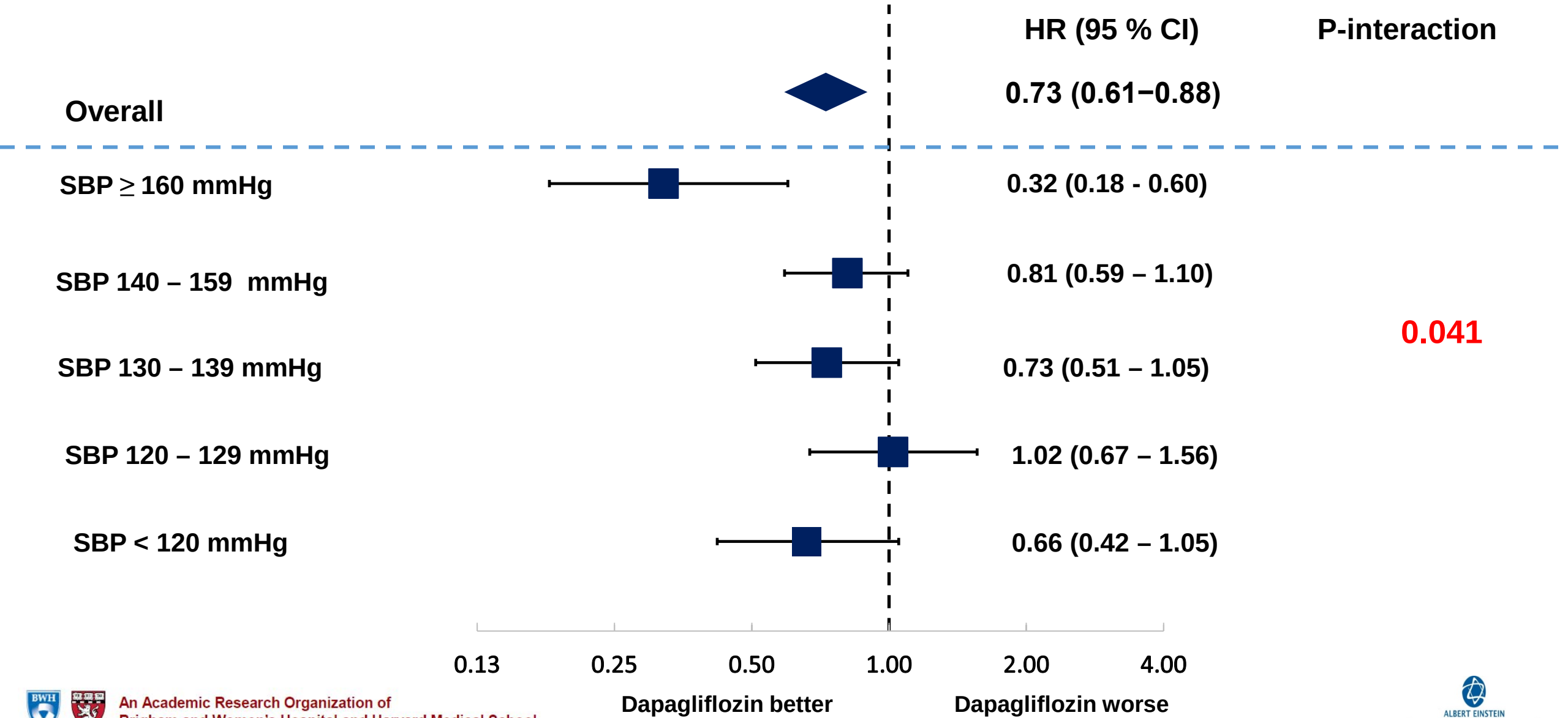
ASCVD = atherosclerotic cardiovascular disease; eGFR = estimated glomerular filtration rate; UACR = urinary albumin:creatinin ratio

Results: Event probability for Hospitalization for HF



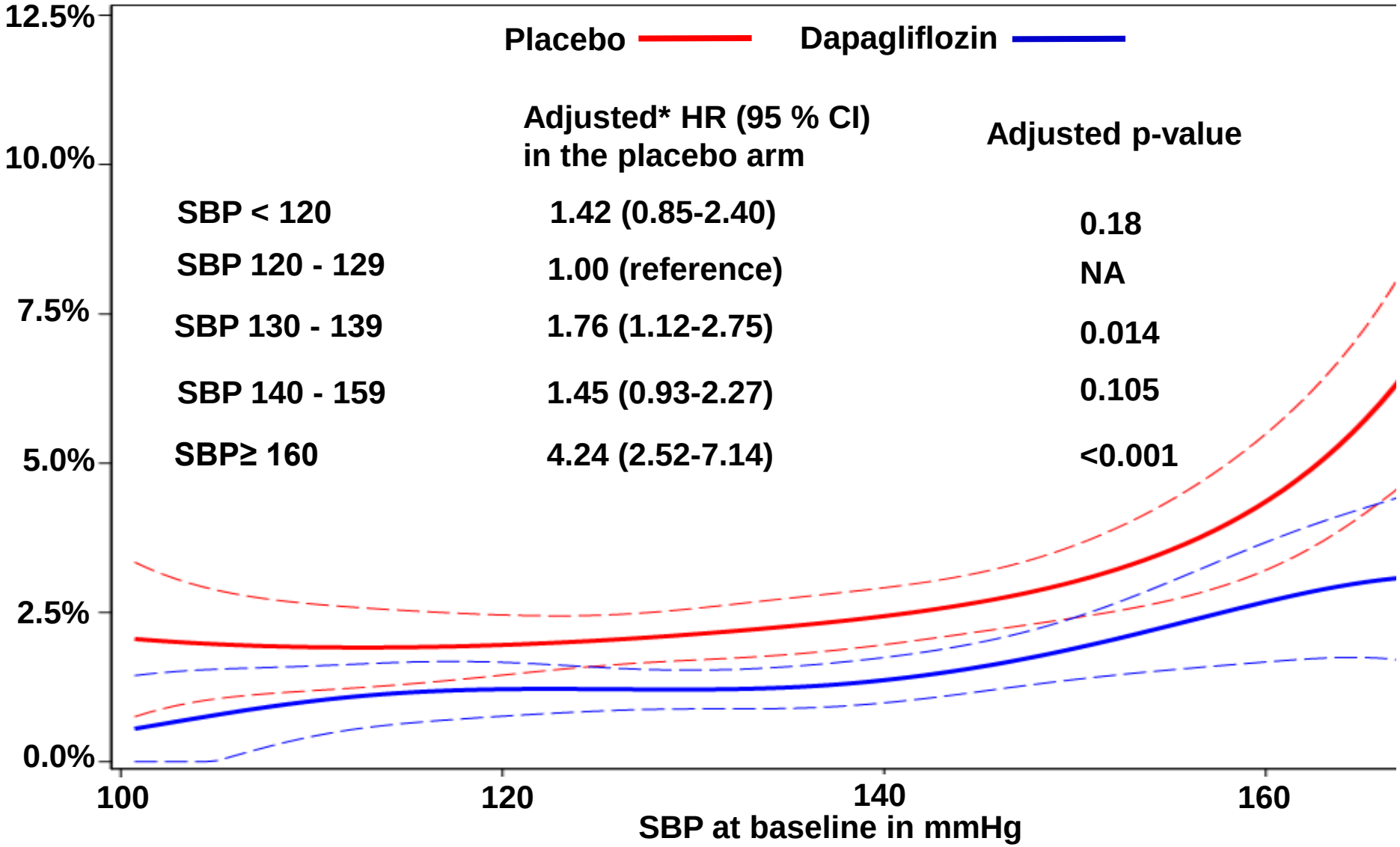
* Adjusted fordiastolic blood pressure, prior coronary artery disease, prior stroke, peripheral artery disease, dyslipidemia, history of hypertension, prior HF, glomerular filtration rate <60 ml/min/1.73 m2, urinary albumin to creatinin ratio >300 mg/g, age, race, body mass index, DM duration and region.

Hospitalization for HF with dapagliflozin by baseline SBP



Results: Event probability for the Renal Endpoint[1]

1- Decrease in GFR by 40% or more, ESRD, or renal death

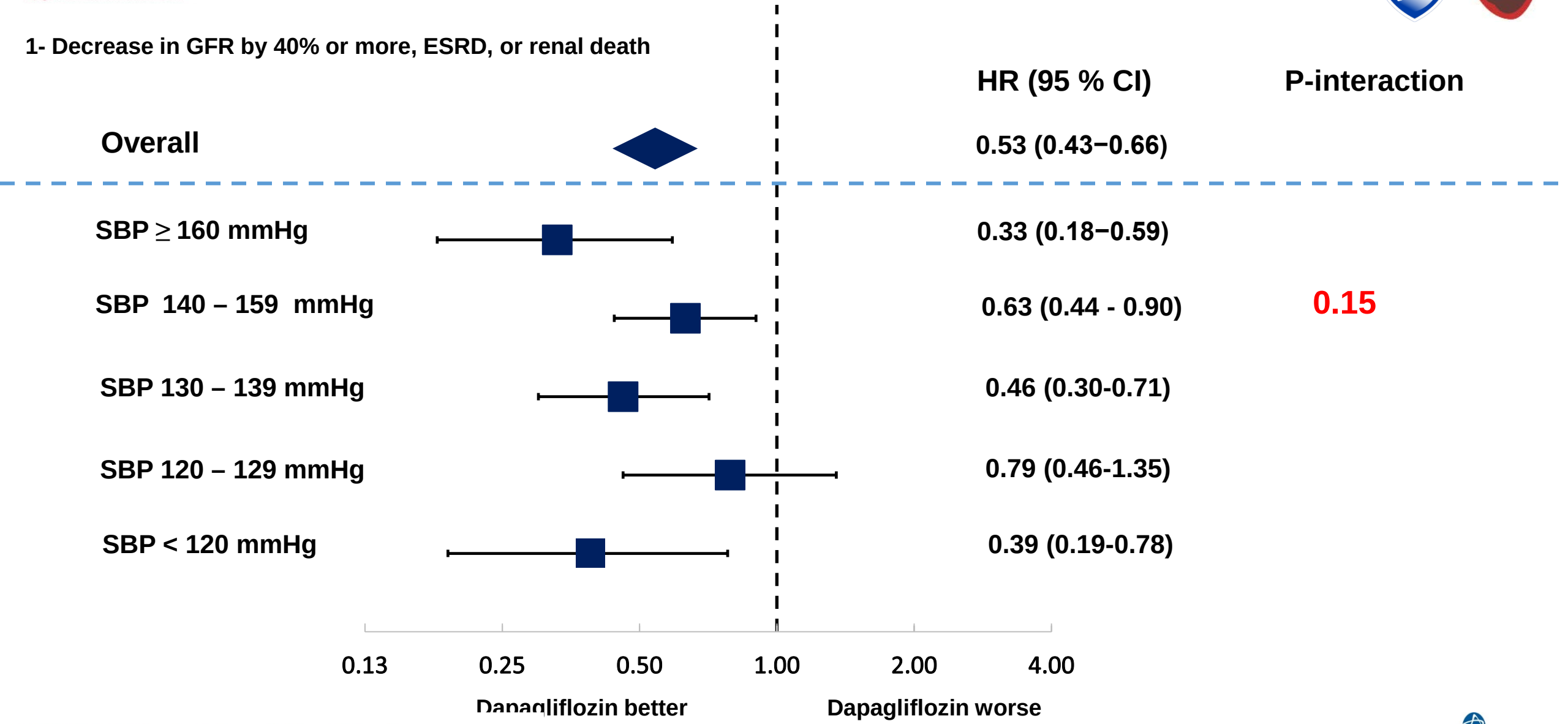


	Adjusted* HR (95 % CI) in the placebo arm	Adjusted p-value
SBP < 120	1.42 (0.85-2.40)	0.18
SBP 120 - 129	1.00 (reference)	NA
SBP 130 - 139	1.76 (1.12-2.75)	0.014
SBP 140 - 159	1.45 (0.93-2.27)	0.105
SBP≥ 160	4.24 (2.52-7.14)	<0.001

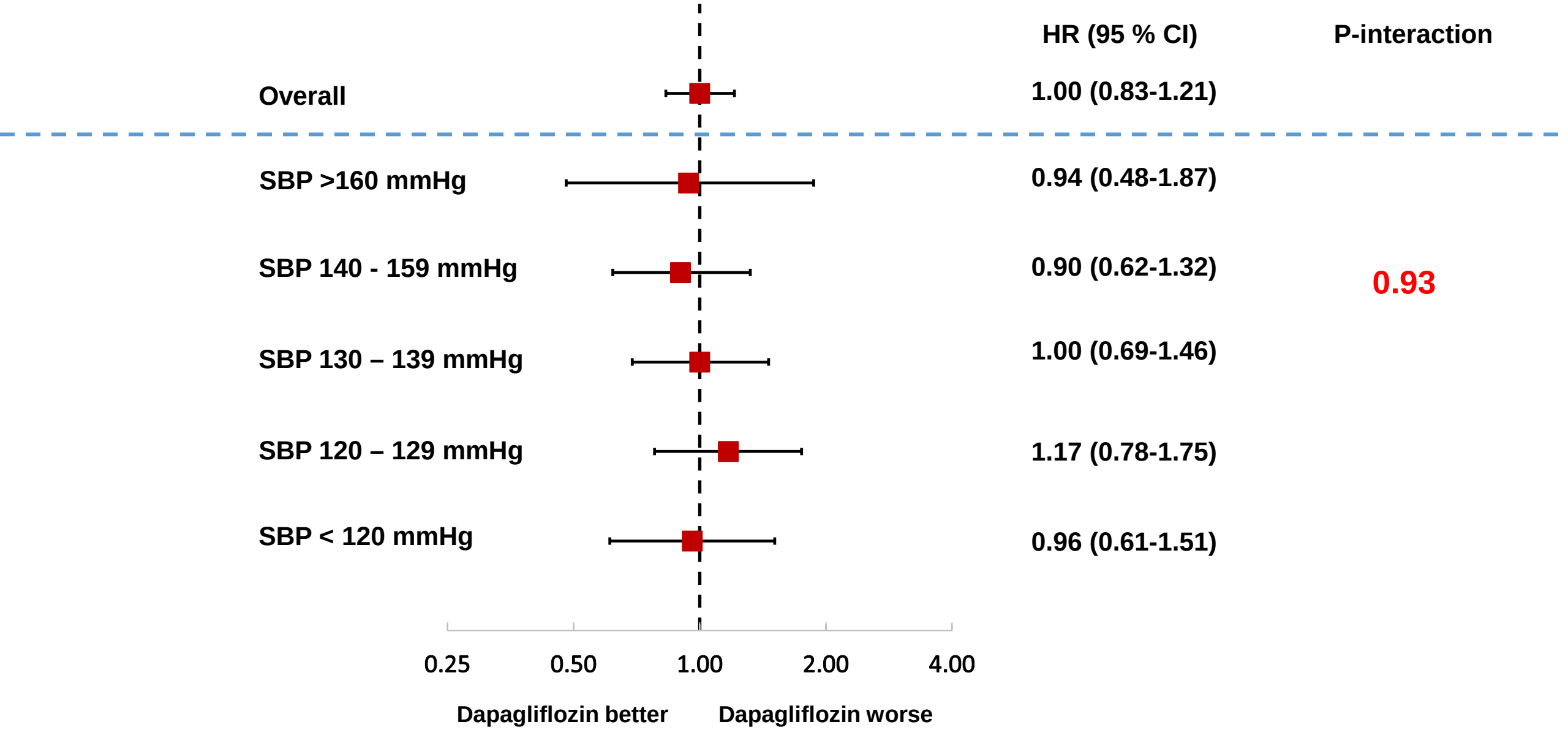
* Adjusted fordiastolic blood pressure, prior coronary artery disease, prior stroke, peripheral artery disease, dyslipidemia, history of hypertension, prior HF, glomerular filtration rate <60 ml/min/1.73 m2, urinary albumin to creatinin ratio >300 mg/g, age, race, body mass index, DM duration and region.

Renal Endpoint[1] with dapagliflozin by baseline SBP

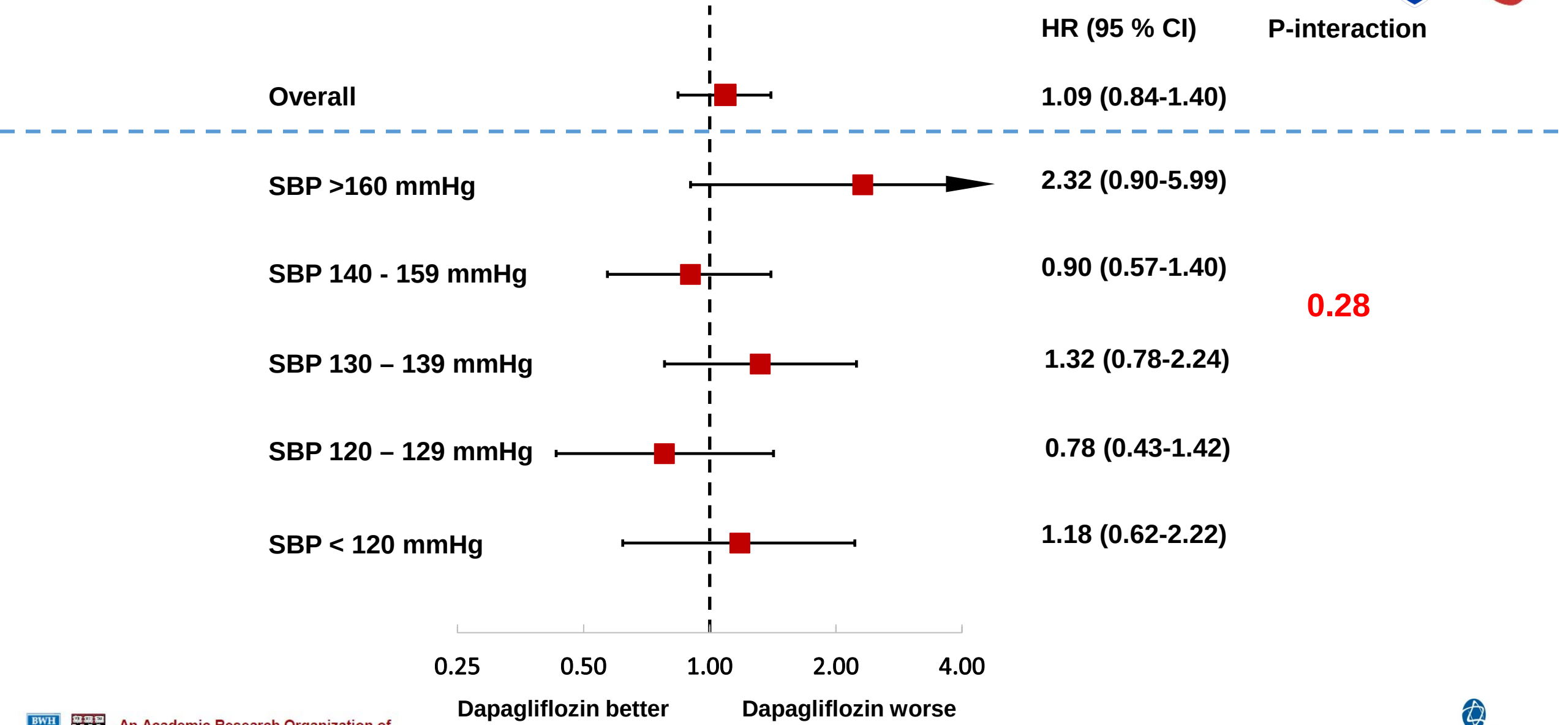
1- Decrease in GFR by 40% or more, ESRD, or renal death



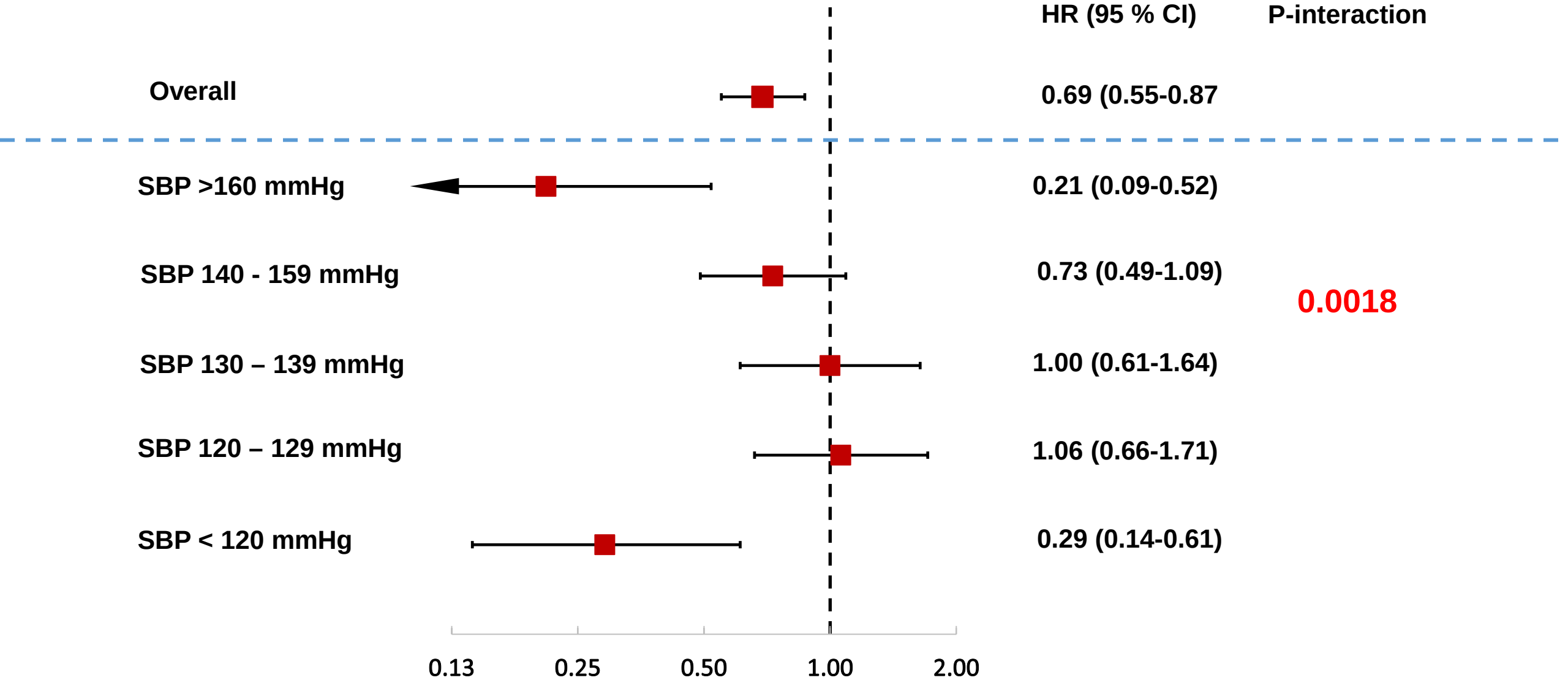
Volume depletion with dapagliflozin by baseline SBP



Amputation with dapagliflozin by baseline SBP



Acute kidney injury with dapagliflozin by baseline SBP



Conclusion

- In patients with type 2 diabetes, clinical benefit of dapagliflozin for cardio-renal outcomes was not affected by baseline blood pressure.
- Patients with type 2 diabetes and severe hypertension are at very-high risk of cardio-renal complications and may derive more benefit from dapagliflozin.
- Those results may help clinicians in the selection of treatments for patients with type 2 diabetes mellitus and prior CV disease or multiple risk factors.