Dapagliflozin in Patients With Heart Failure With and Without Peripheral Artery Disease

A patient-level pooled meta-analysis of DAPA-HF and DELIVER

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On behalf of the DAPA-HF and DELIVER Committees and Investigators

Disclosures

- Advisory board honoraria: AstraZeneca; Bayer
- Consultant honoraria: AstraZeneca; Novartis
- Travel grants: AstraZeneca

Introduction: PAD and HF

- Patients with HF and PAD have worse clinical outcomes than those with HF and no PAD
- Since the CANVAS trials reported a higher rate of amputations with canagliflozin, there has been a concern about the safety of SGLT2 inhibitors in patients with PAD
- Although these findings have not been replicated with other SGLT2 inhibitors or in other populations, this concern remains, especially in individuals with HF
  - Diuretics, an integral part of HF management, have also been associated with an elevated risk of amputations

Objective

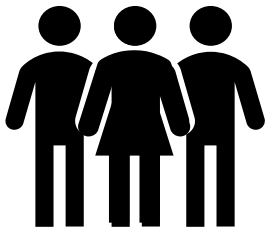
To examine the efficacy and safety of dapagliflozin, compared with placebo, in patients with and without PAD across the range of LVEF

DAPA-HF and DELIVER trial designs

DAPA-HF	DELIVER
LVEF ≤40%	LVEF >40%
NYHA II-IV	NYHA II-IV
Elevated NT-proBNP	Elevated NT-proBNP
Guideline-recommended therapy	Structural heart disease

N=11,007

Double-blind treatment period



Dapagliflozin 10 mg once daily

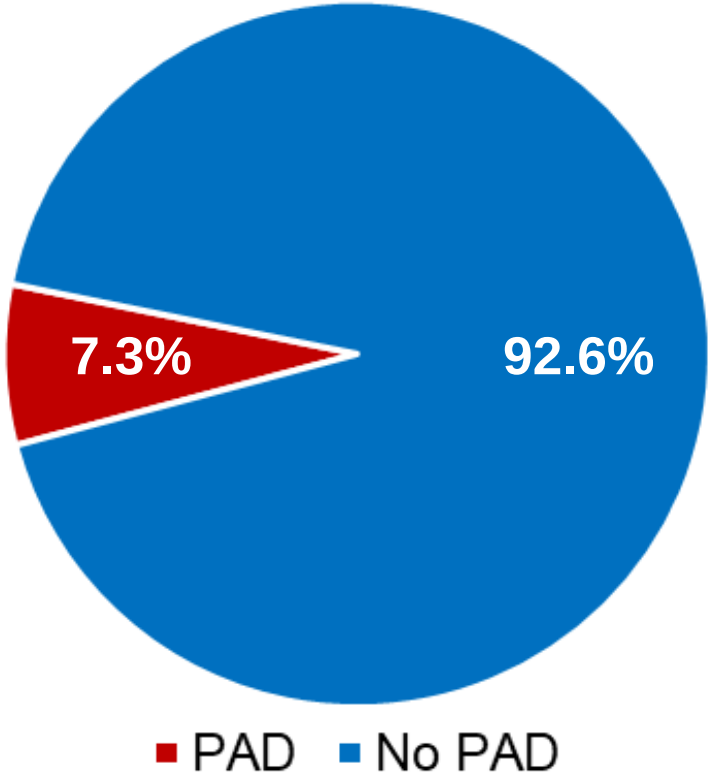
Placebo

Primary outcome: Worsening HF or cardiovascular death

PAD status at baseline

Investigator-reported history of:

- ***peripheral arterial occlusive disease***
- ***prior revascularization of a peripheral artery***
- ***prior stent insertion in a peripheral artery***



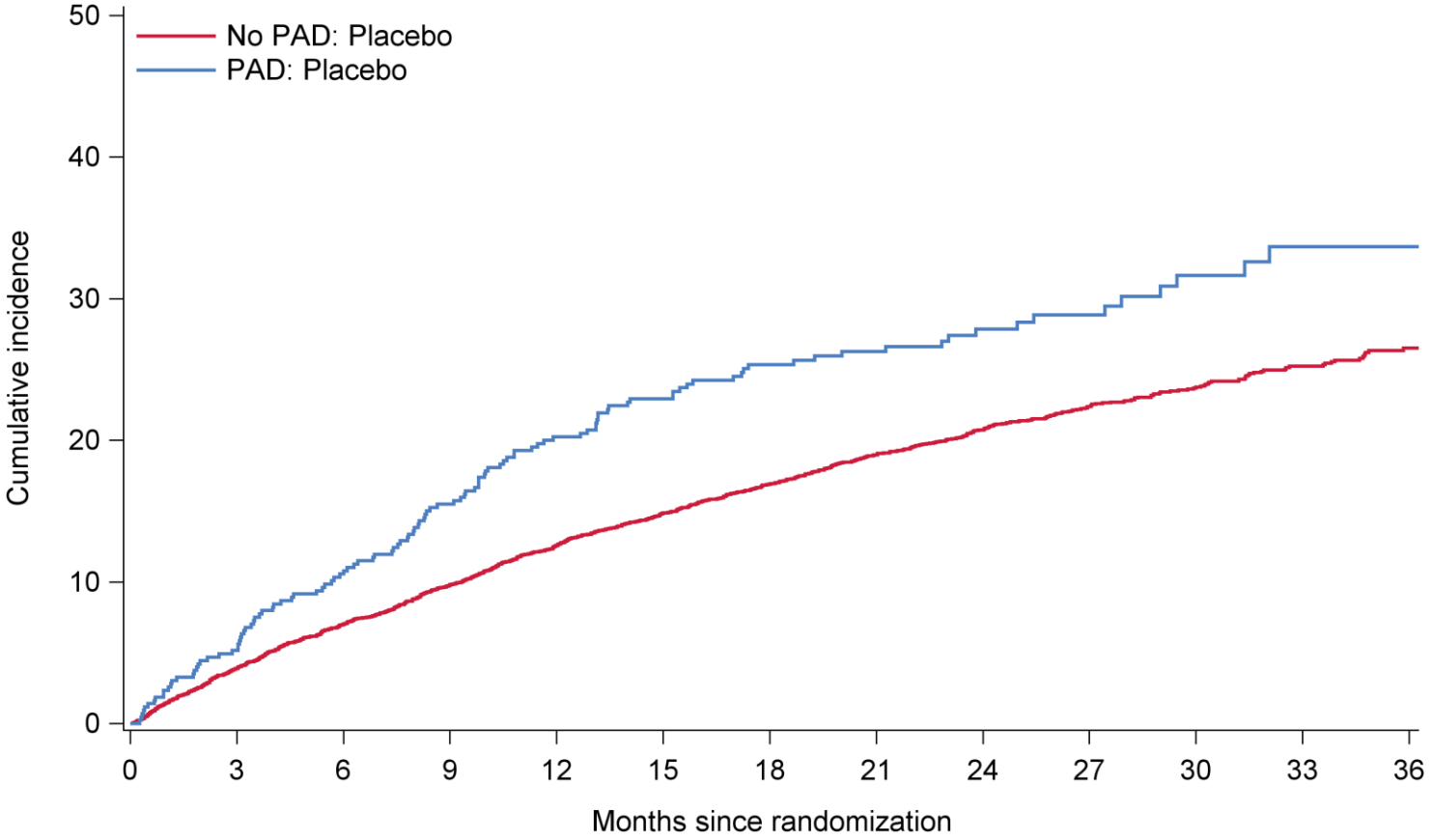
Selected baseline characteristics by PAD status

	No PAD N=10196	PAD N=809	P-value
Age (years), mean	69	71	<0.001
Female sex, %	36	24	<0.001
eGFR (mL/min/1.73m^2), mean	63	59	<0.001
NT-proBNP (pg/mL), median	1172	1269	0.12
Duration of HF >5 years, %	32	38	0.008
LVEF (%), mean	44	44	0.23
NYHA class III/IV, %	28	31	0.11
KCCQ-TSS, mean	72	69	<0.001

Selected baseline characteristics by PAD status

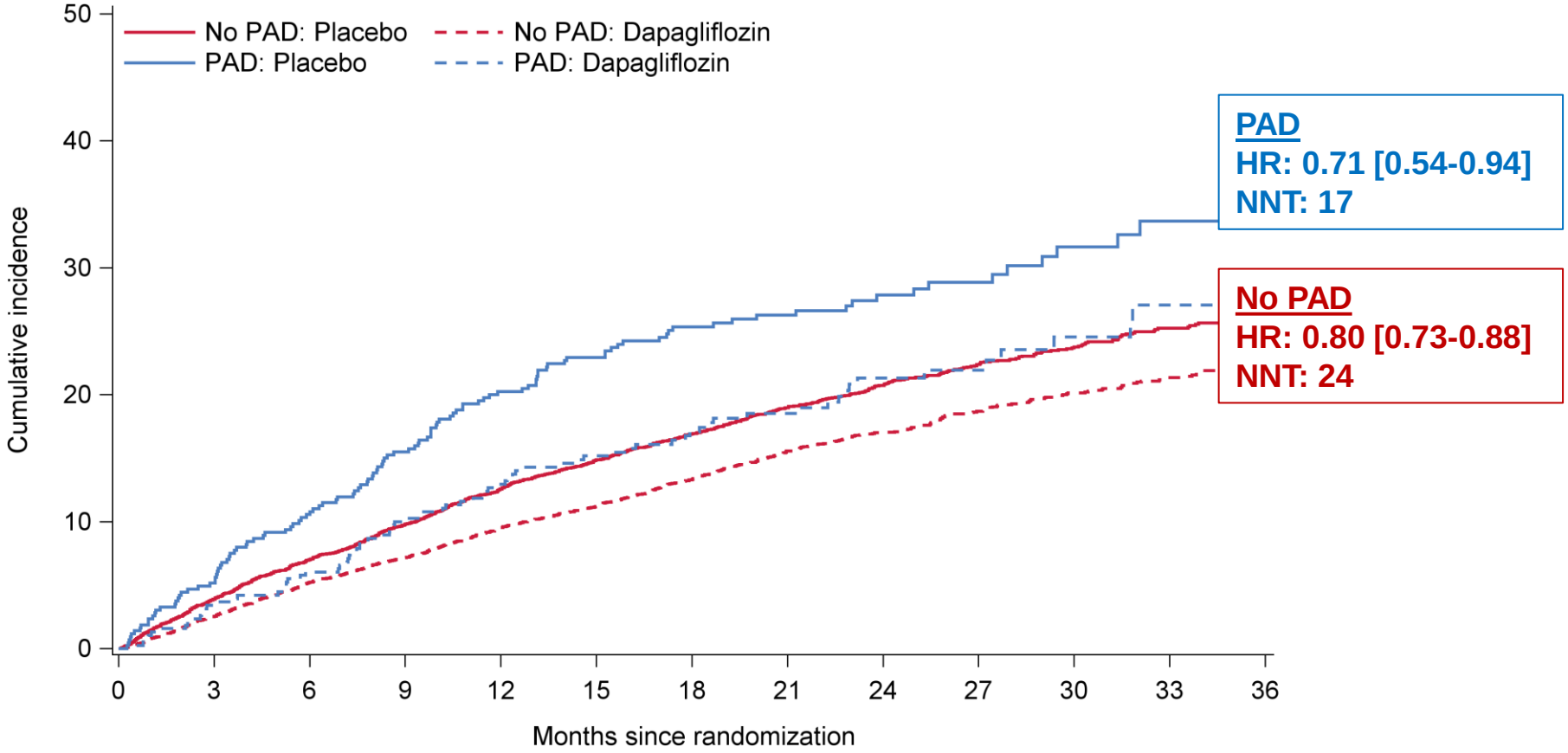
	No PAD N=10196	PAD N=809	P-value
Current/former smoking, %	49	68	<0.001
Hospitalization for HF, %	43	44	0.61
Atrial fibrillation, %	48	43	0.002
Hypertension, %	82	90	<0.001
Stroke, %	9	17	<0.001
MI or coronary revascularization, %	44	73	<0.001
Type 2 diabetes, %	43	55	<0.001

Treatment effect by PAD status: Primary outcome



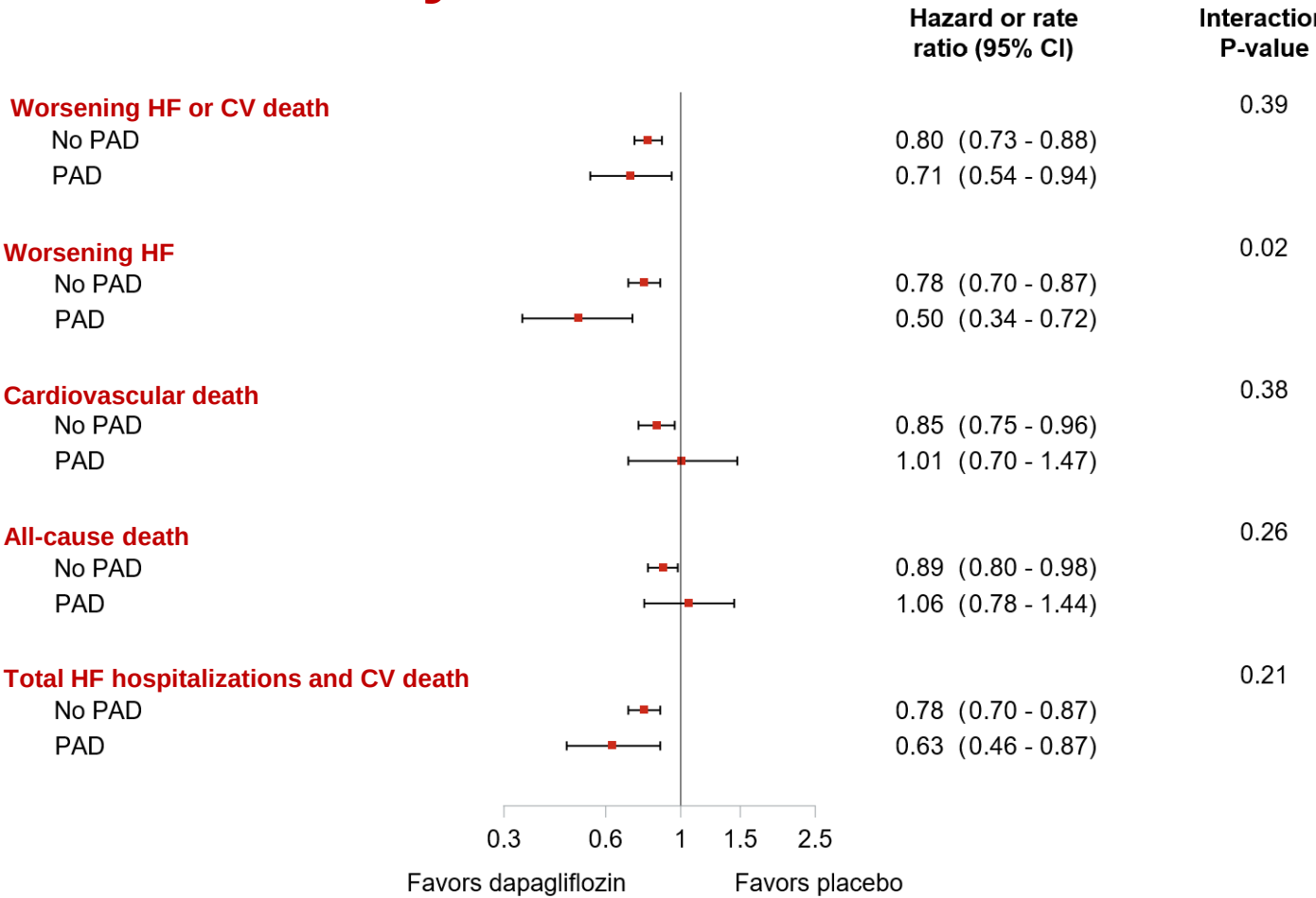
NNT: Number of patients needed to be treated with dapagliflozin to prevent one event over the median follow-up

Treatment effect by PAD status: Primary outcome



NNT: Number of patients needed to be treated with dapagliflozin to prevent one event over the median follow-up

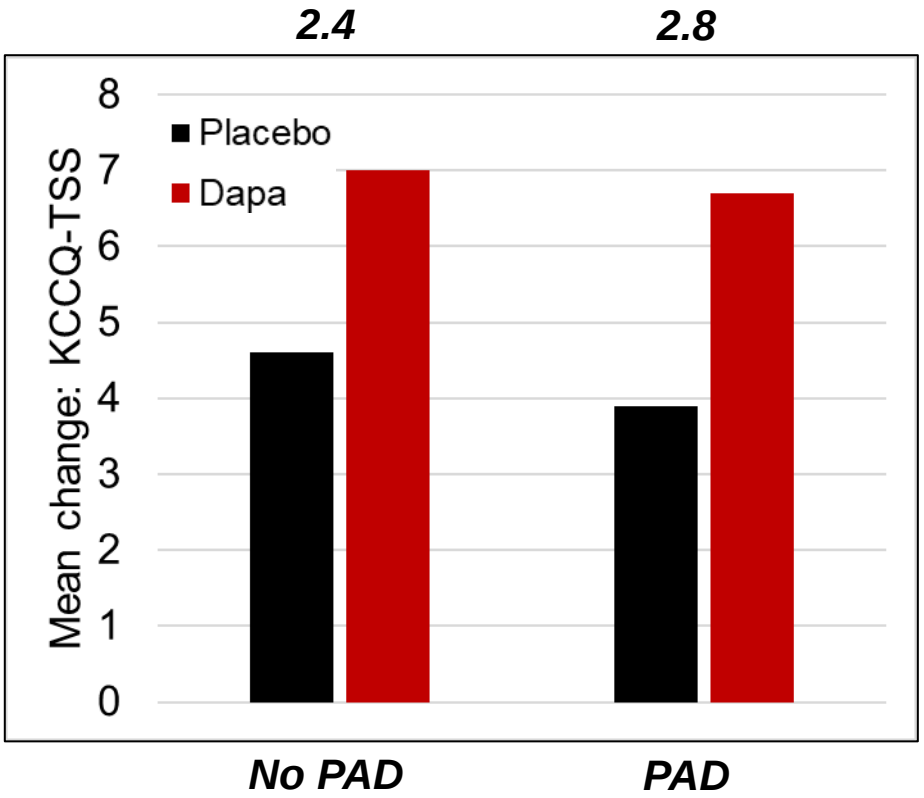
Treatment effect by PAD status: Clinical outcomes



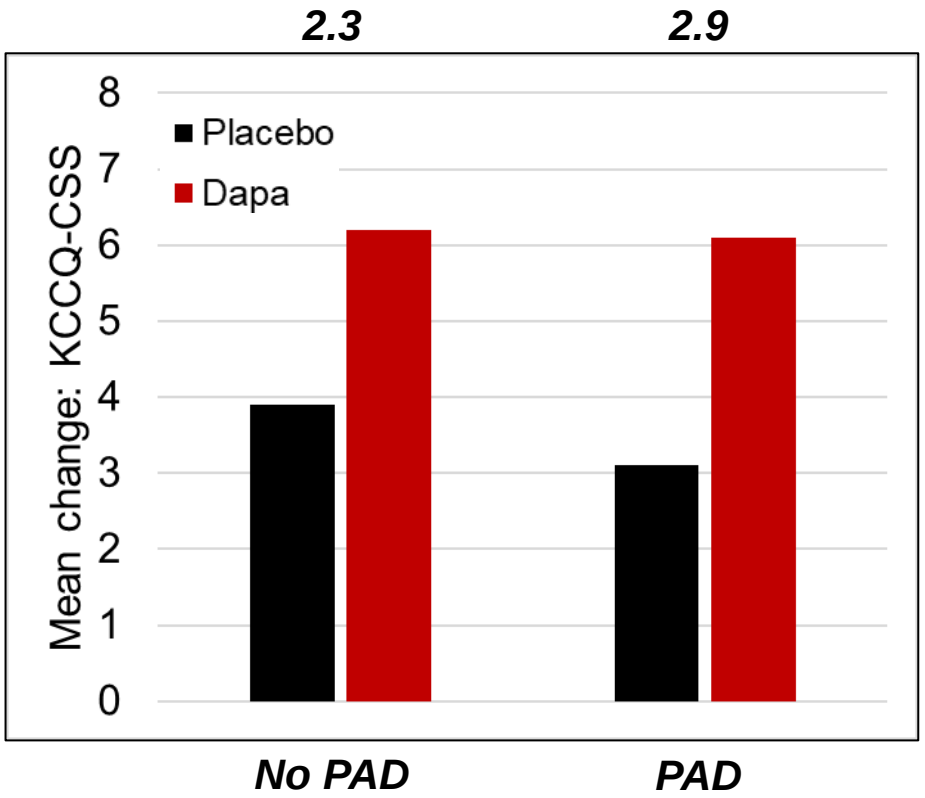
Undetermined causes of death were considered cardiovascular death; worsening HF was defined as an unplanned HF hospitalization or an urgent HF visit requiring intravenous diuretics.

Treatment effect by PAD status: Health status and symptoms

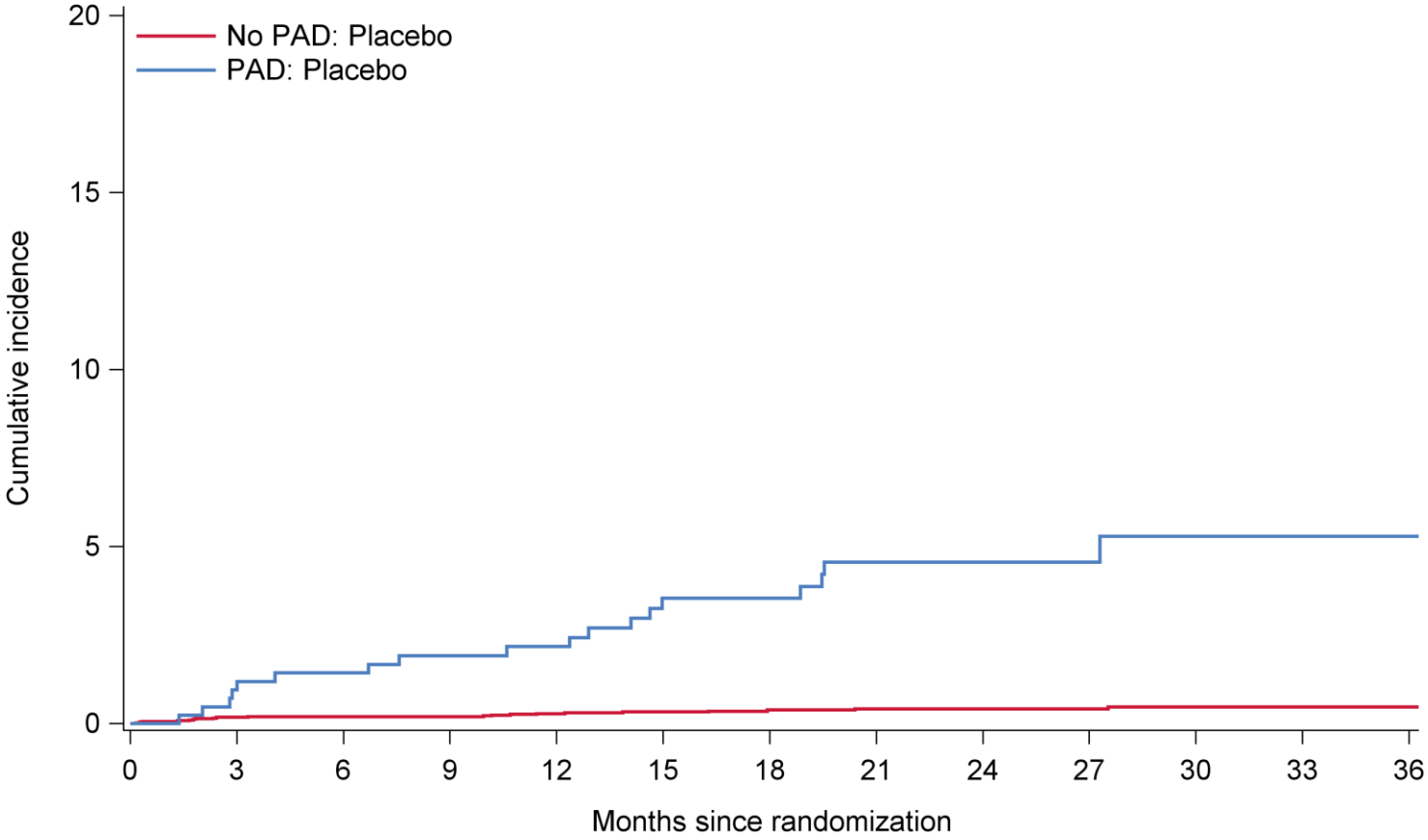
Mean change in KCCQ-TSS from randomization to 8 months (P_{int}=0.78)



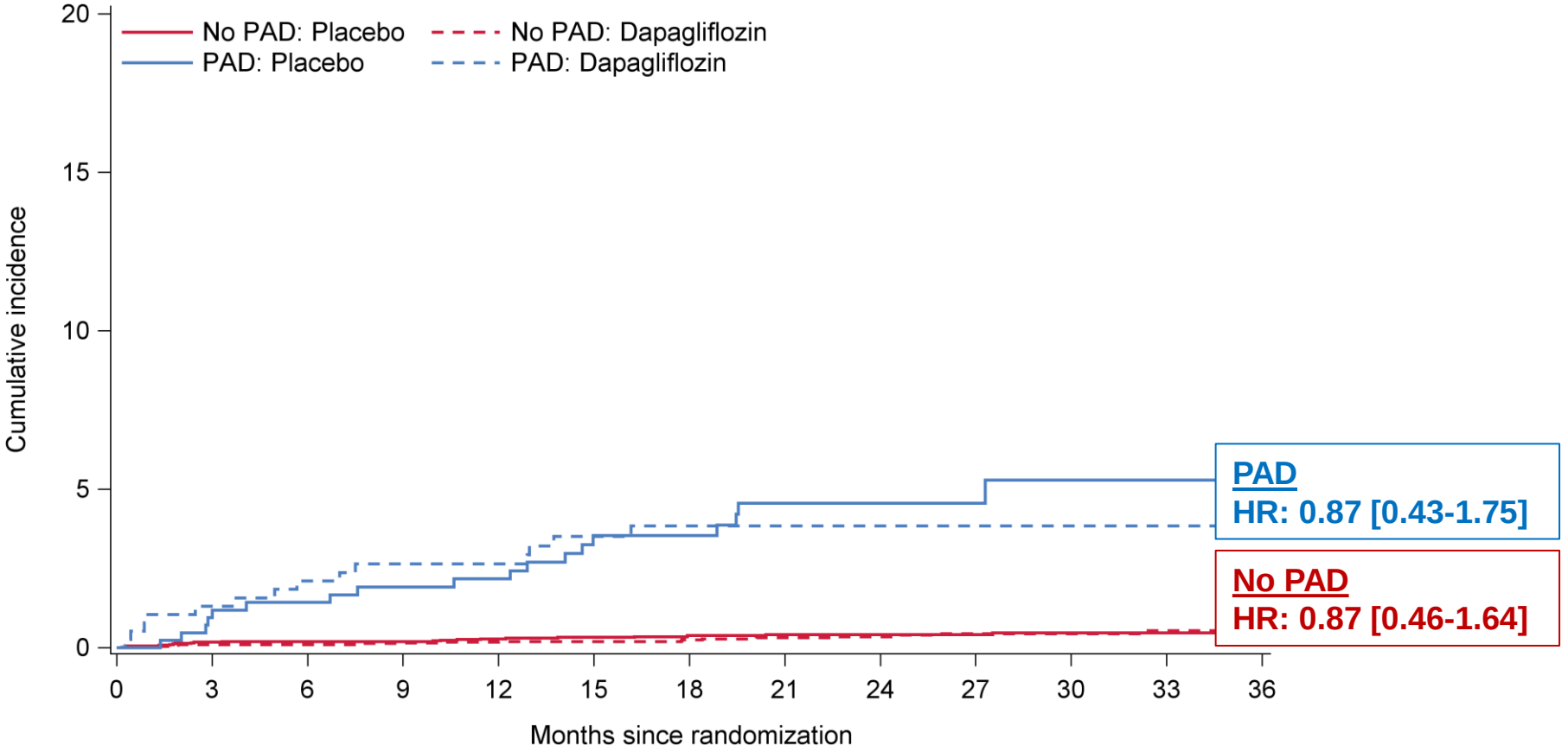
Mean change in KCCQ-CSS from randomization to 8 months (P_{int}=0.70)



Treatment effect by PAD status: Amputation



Treatment effect by PAD status: Amputation



Amputations and triggering conditions

	No PAD		PAD	
	Placebo N=5067	Dapa N=5112	Placebo N=427	Dapa N=381
Amputation, N	20	18	18	14
Conditions triggering amputation				
Infection, N	18	11	11	11
Acute limb ischaemia, N	2	2	4	2
Chronic limb ischaemia, N	1	6	6	4

Conditions triggering amputation were investigator-reported, and more than one category could be selected.

Treatment discontinuation and adverse events

% of patients	No PAD		PAD		P-value*
	Placebo N=5067	Dapa N=5112	Placebo N=427	Dapa N=381	
Discontinuation for any reason	12.3	12.3	17.8	16.8	0.72
Discontinuation due to adverse event	5.1	5.1	9.4	8.4	0.61
Volume depletion**	3.5	3.9	4.9	7.3	0.31
Renal adverse event**	4.5	4.0	8.2	9.2	0.35
Major hypoglycemia	0.2	0.2	0.5	0.0	N/A
Diabetic ketoacidosis	0.0	0.1	0.0	0.5	N/A

**P-value is for interaction between PAD status and treatment effect on the occurrence of adverse events.*
***Any serious adverse event or adverse event that led to discontinuation in DELIVER.*

Conclusions: Dapagliflozin in patients with HF with and without PAD

- Dapagliflozin reduced the risk of adverse clinical outcomes, across the range of LVEF, to a similar extent in patients with and without PAD
- Dapagliflozin improved symptoms and quality of life in both patients with and without PAD
- Dapagliflozin was safe and well-tolerated irrespective of PAD status
- Dapagliflozin did not increase the risk of amputation regardless of PAD status

ESC European Society of Cardiology

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FASTTRACK CLINICAL RESEARCH
Heart failure and cardiomyopathies

Heart failure, peripheral artery disease, and dapagliflozin: a patient-level meta-analysis of DAPA-HF and DELIVER

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