

Dapagliflozin And Prevention of Adverse-outcomes in CKD (DAPA-CKD)

Analysis of patients with and without cardiovascular disease at baseline

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My employer, Glasgow University, has been paid by a number of pharmaceutical companies for my participation in clinical trial committees and other activities related to these trials/products

Relevant to this presentation: AstraZeneca

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DAPA-CKD: Background

- Chronic kidney disease (CKD) is an important cause of cardiovascular morbidity and mortality, including heart failure hospitalization.
- The hypothesis behind DAPA-CKD was that the sodium glucose cotransporter 2 (SGLT2) inhibitor dapagliflozin would improve kidney and cardiovascular outcomes in people with CKD, *independently of the presence of T2D*.
- In DAPA-CKD, dapagliflozin did reduce the risk of end-stage kidney disease, heart failure and all-cause mortality.
- In this prespecified analysis examined the effect of dapagliflozin in patients *with and without cardiovascular disease at baseline*.

DAPA-CKD: Trial design

Conducted 2 Feb. 2017 to 12 June 2020*; 21 countries, 386 sites, 4304 participants; median follow-up 2.4 years.

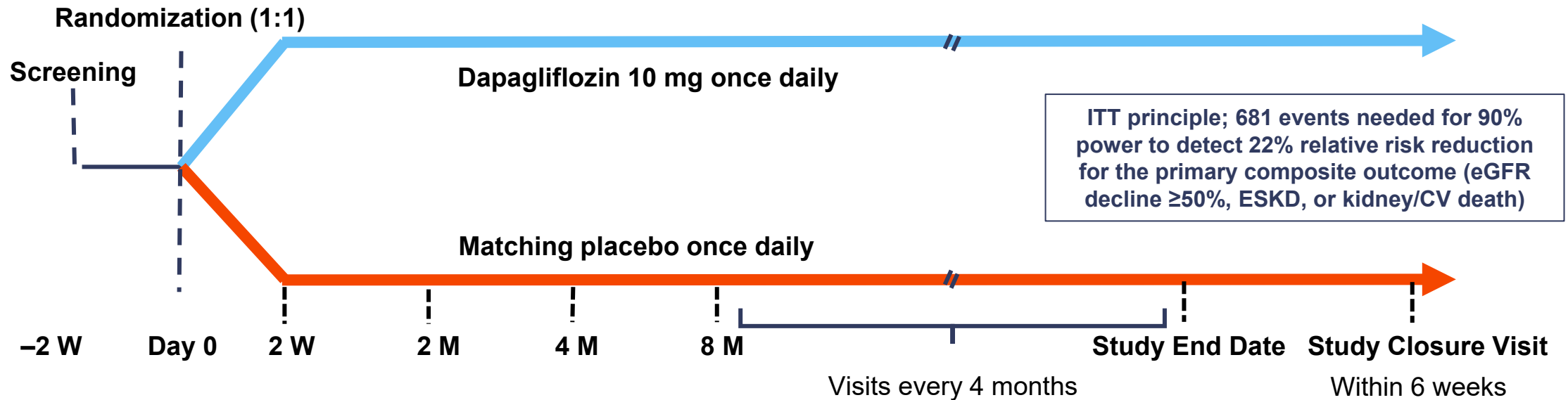
**DMC recommended stopping early for efficacy 26 March 2020*

Key inclusion criteria:

- ≥ 18 years of age
- eGFR 25 to 75 mL/min/1.73m²
- UACR 200 to 5000 mg/g (22.6 to 565 mg/mmol)
- Stable maximum tolerated labelled dose of ACEi or ARB for ≥ 4 weeks (if not contraindicated)

Key exclusion criteria:

- Type 1 diabetes
- Polycystic kidney disease, lupus nephritis, ANCA-associated vasculitis
- Immunosuppressive therapy within 6 months prior to enrollment



Outcome analyses based on Cox proportional hazard model stratified by type 2 diabetes and UACR and adjusted for eGFR

ANCA, anti-neutrophil cytoplasmic antibody; ITT, intention-to-treat; UACR, urinary albumin-to-creatinine ratio.

Heerspink HJL. et.al. Nephrol Dial Transplant. 2020 Feb 1;35(2):274-282; Wheeler DC. et.al. Nephrol Dial Transplant. 2020 DOI 10.1093/ndt/gfaa234.

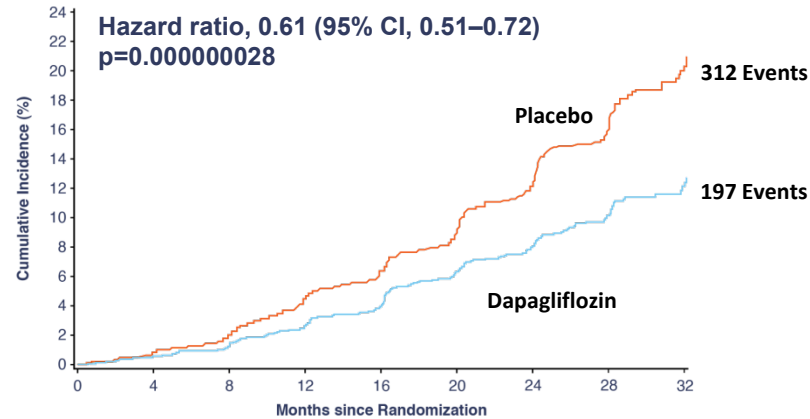
DAPA-CKD: Baseline characteristics

	Dapagliflozin (N=2152)	Placebo (N=2152)
Age, years, mean	62	62
Sex, female, %	33	33
Type 2 diabetes, %	68	67
Hypertension, %	96	96
Any cardiovascular disease, %	38	37
Myocardial infarction, %	8.6	9.6
Stroke, %	6.7	7.2
Atrial fibrillation/flutter, %	5.3	5.2
Heart failure, %	11	11
Systolic blood pressure, mmHg, mean	137	137
eGFR, mL/min/1.73m ² , mean	43	43
ACEi or ARB, %	97	97

**Overall results:
Primary and secondary outcomes**

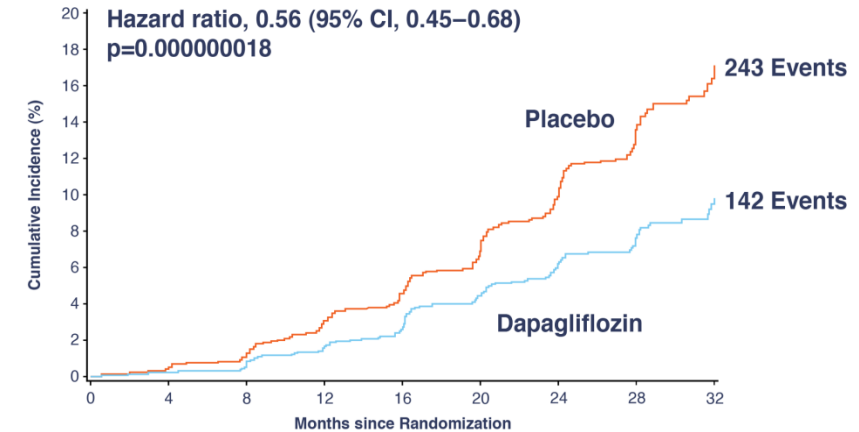
DAPA-CKD: Primary and secondary outcomes

Primary outcome: eGFR decline $\geq 50\%$, ESKD, or kidney/CV death



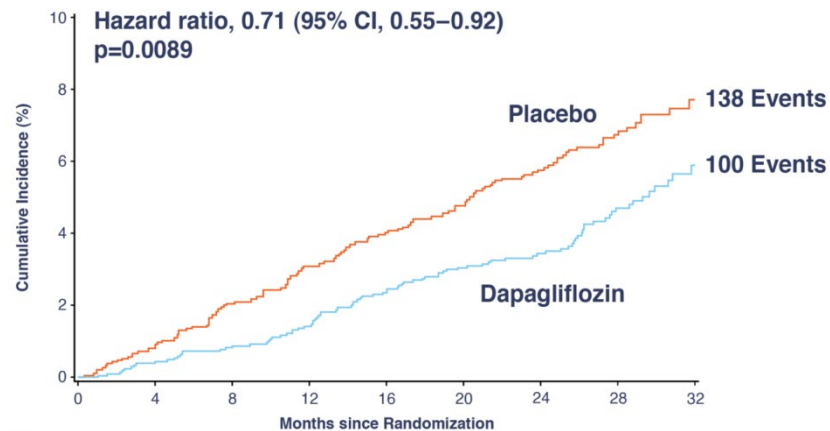
No. at Risk	0	4	8	12	16	20	24	28	32
Dapagliflozin	2152	2001	1955	1898	1841	1701	1288	831	309
Placebo	2152	1993	1936	1858	1791	1664	1232	774	270

Secondary outcome: eGFR decline $\geq 50\%$, ESKD, or kidney death



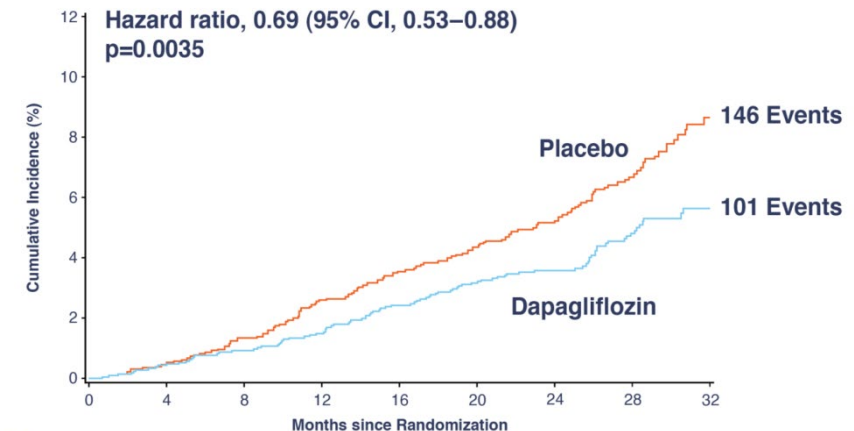
No. at Risk	0	4	8	12	16	20	24	28	32
Dapagliflozin	2152	2001	1955	1898	1841	1701	1288	831	309
Placebo	2152	1993	1936	1858	1791	1664	1232	774	270

Secondary outcome: CV death or HF hospitalization



No. at Risk	0	4	8	12	16	20	24	28	32
Dapagliflozin	2152	2035	2021	2003	1975	1895	1502	1003	384
Placebo	2152	2023	1989	1957	1927	1853	1451	976	360

Secondary outcome: All-cause mortality



No. at Risk	0	4	8	12	16	20	24	28	32
Dapagliflozin	2152	2039	2029	2017	1998	1925	1531	1028	398
Placebo	2152	2035	2018	1993	1972	1902	1502	1009	379

**Results by baseline CV disease status:
Primary and secondary outcomes**

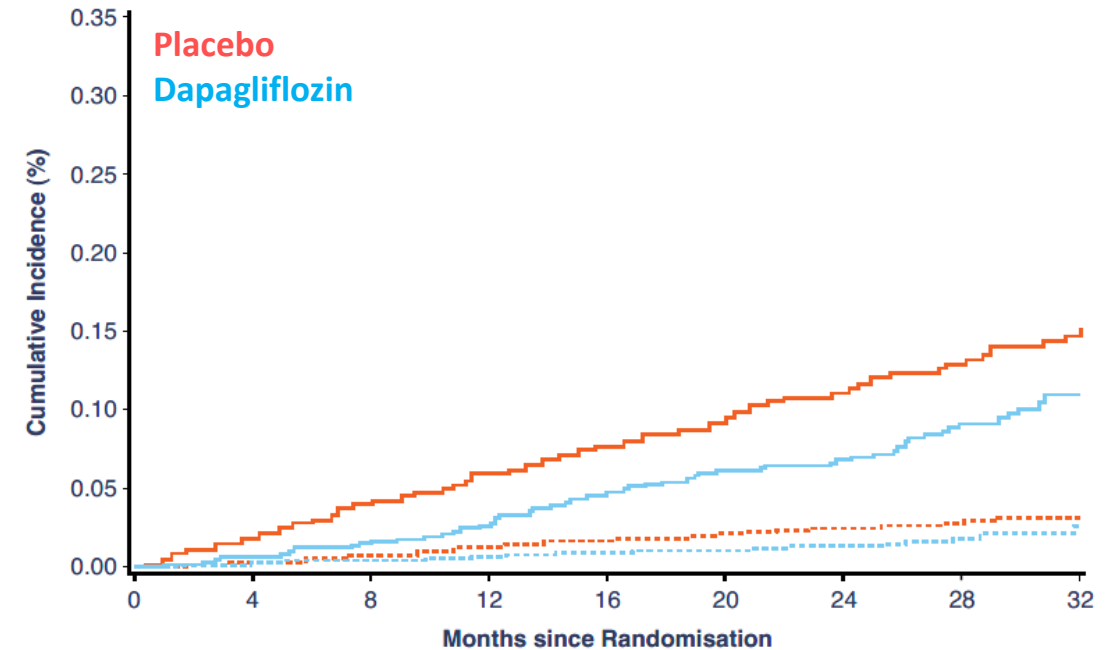
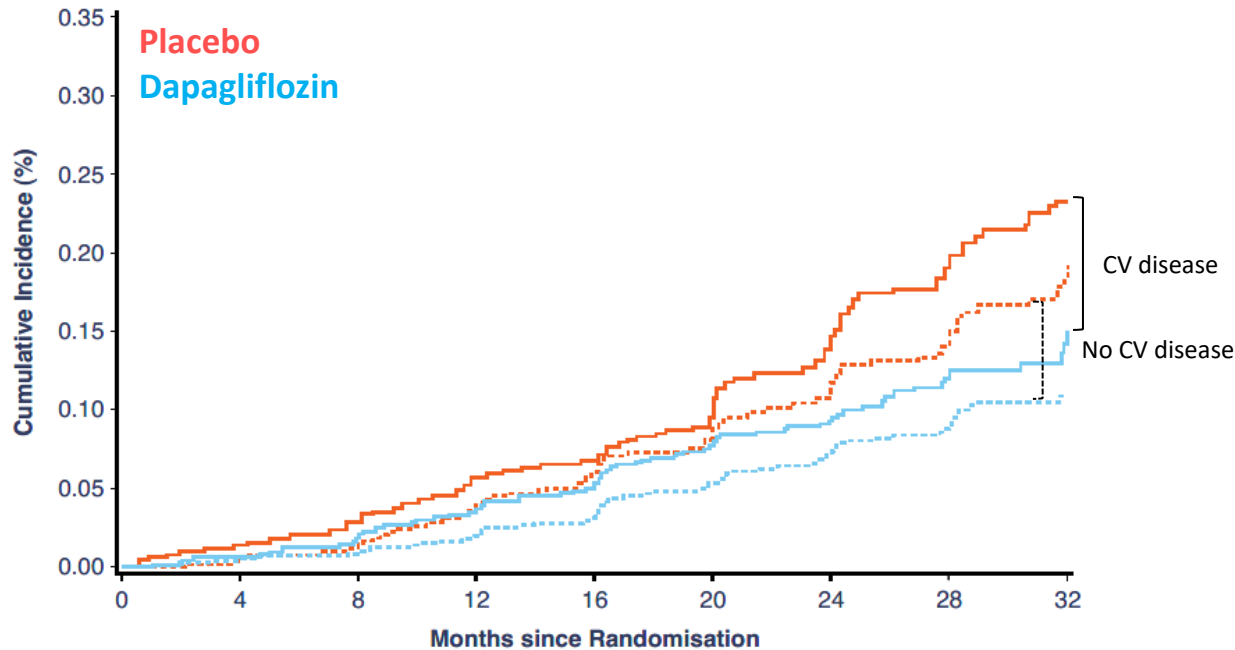
DAPA-CKD: Outcomes by baseline CV disease

Primary endpoint

eGFR decline $\geq 50\%$, ESKD, or kidney/CV death

Secondary endpoint

Heart failure hospitalization or CV death



No. at Risk	0	4	8	12	16	20	24	28	32
Dapa 10mg/CV	813	780	760	736	710	650	510	326	124
Dapa 10mg/No CV	1339	1221	1195	1162	1131	1051	778	505	185
Placebo/CV	797	757	734	703	677	626	470	289	94
Placebo/No CV	1355	1236	1202	1155	1114	1038	762	485	176

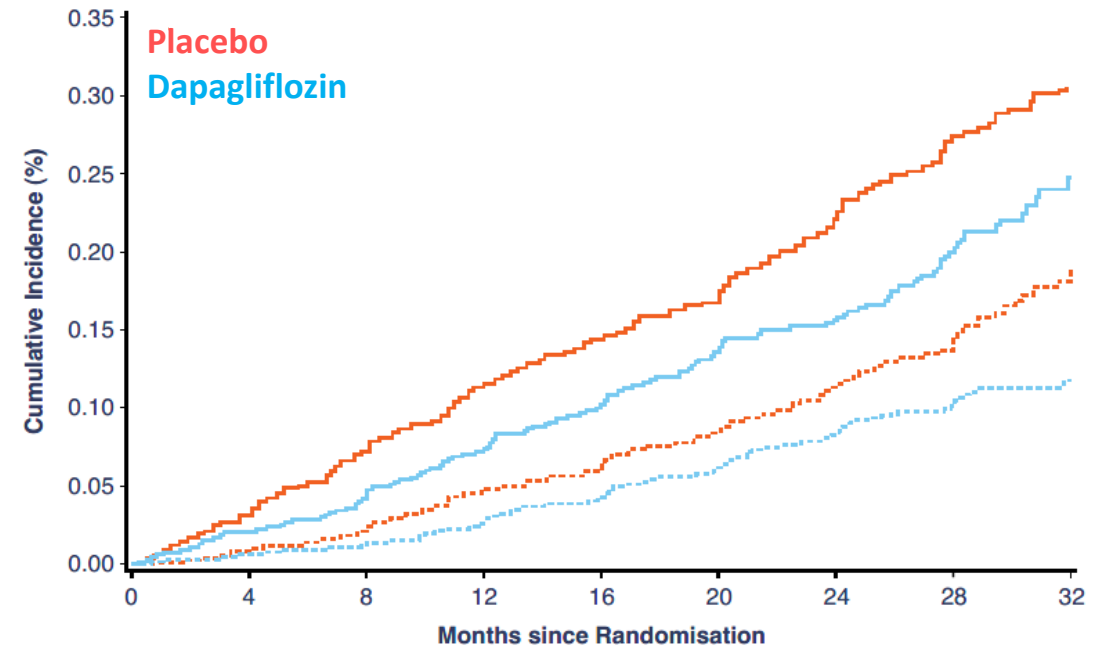
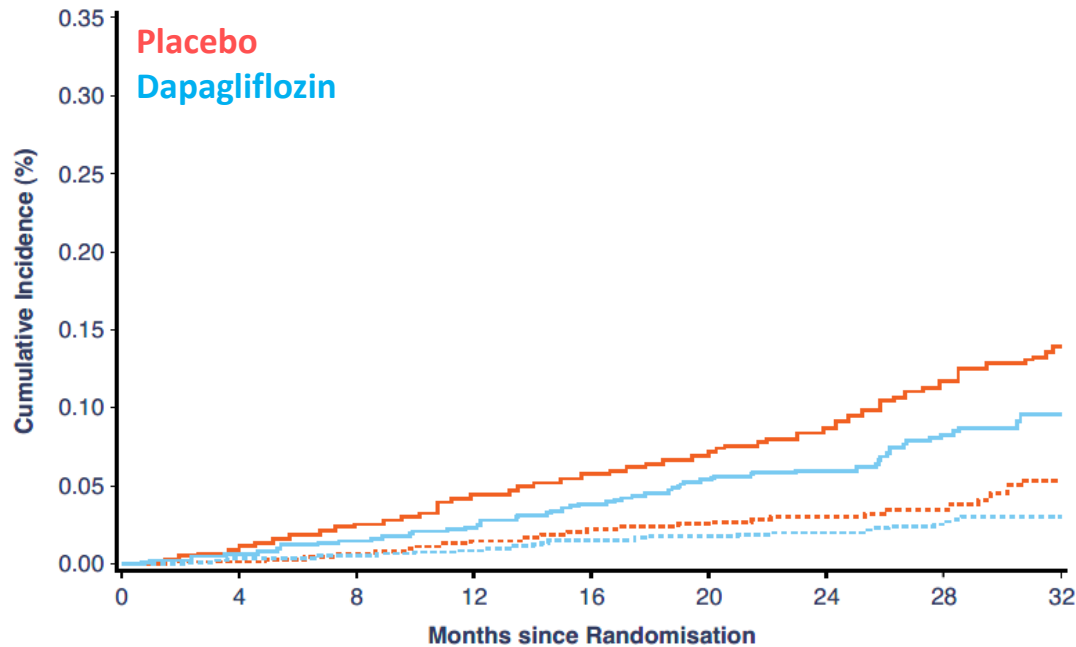
No. at Risk	0	4	8	12	16	20	24	28	32
Dapa 10mg/CV	813	787	779	767	747	712	581	384	150
Dapa 10mg/No CV	1339	1248	1242	1236	1228	1183	921	619	234
Placebo/CV	797	761	740	721	703	671	531	366	124
Placebo/No CV	1355	1262	1249	1236	1224	1182	920	610	236

No CV disease - - - - -
CV disease ————

DAPA-CKD: Outcomes by baseline CV disease

Secondary endpoint
All-cause mortality

Post hoc endpoint
MI, stroke, HF hospitalization, ESKD or death

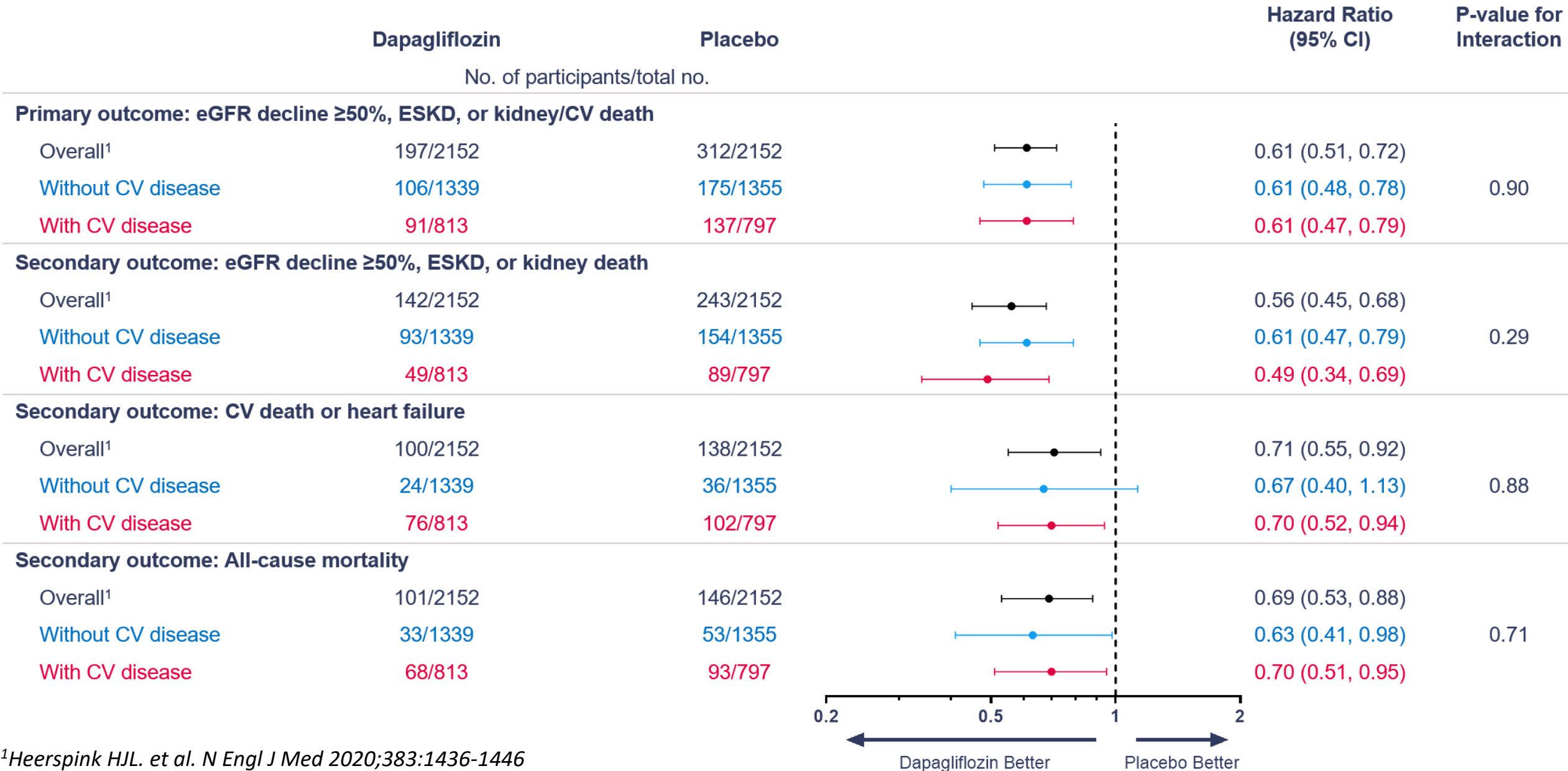


No. at Risk	0	4	8	12	16	20	24	28	32
Dapa 10mg/CV	813	790	783	776	764	731	600	403	160
Dapa 10mg/No CV	1339	1249	1246	1241	1234	1194	931	625	238
Placebo/CV	797	770	759	745	734	702	566	386	137
Placebo/No CV	1355	1265	1259	1248	1238	1200	936	623	242

No. at Risk	0	4	8	12	16	20	24	28	32
Dapa 10mg/CV	813	771	747	715	687	627	493	305	114
Dapa 10mg/No CV	1339	1219	1194	1158	1127	1050	776	504	187
Placebo/CV	797	743	706	669	637	595	448	276	84
Placebo/No CV	1355	1231	1195	1151	1119	1041	772	490	188

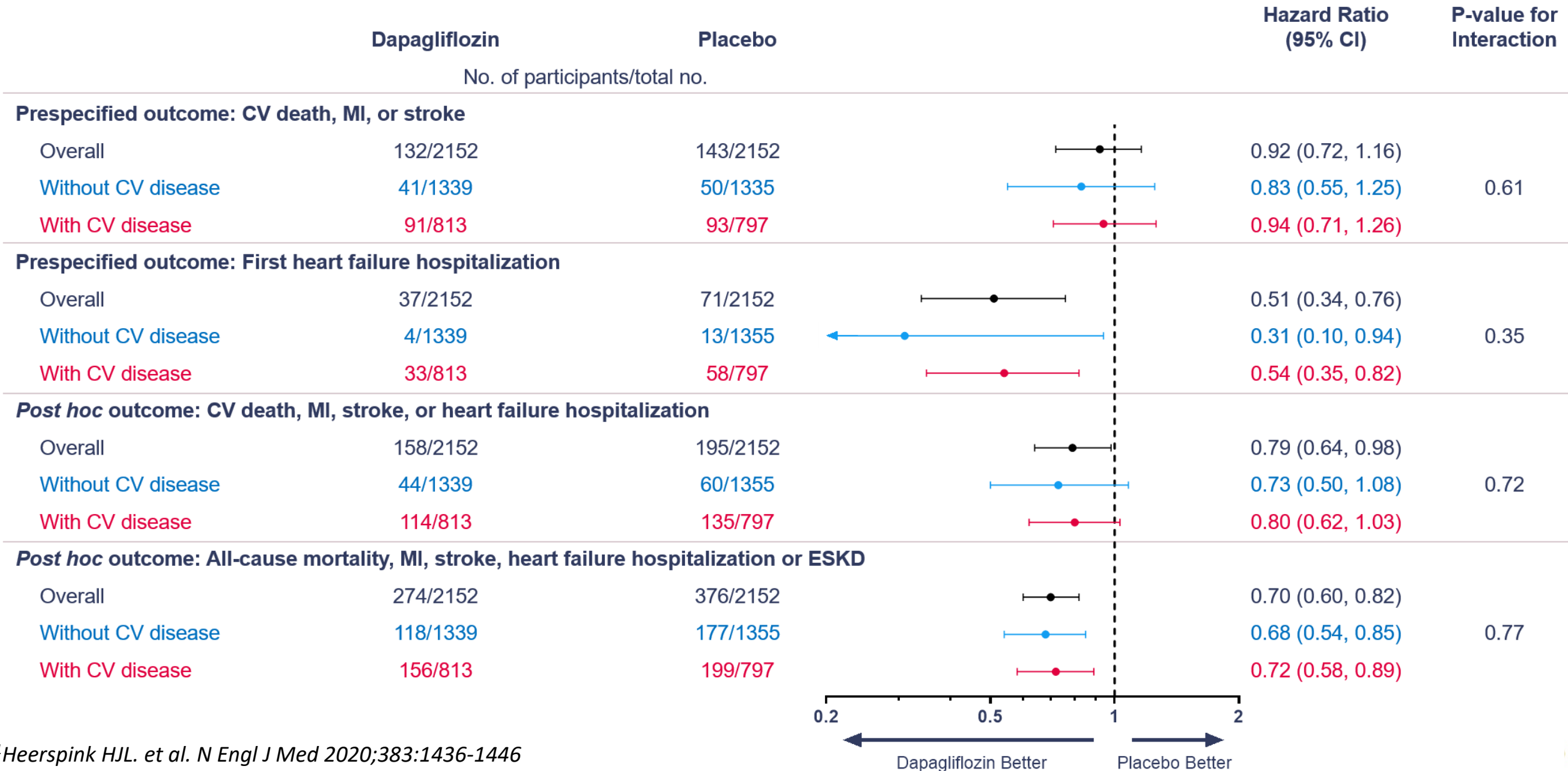
No CV disease - - - - -
CV disease —————

Primary and secondary outcomes by baseline CV disease



¹Heerspink HJL. et al. *N Engl J Med* 2020;383:1436-1446

Prespecified and *post hoc* exploratory outcomes by CV disease



¹Heerspink HJL. et al. N Engl J Med 2020;383:1436-1446

DAPA-CKD: Summary and conclusions

- In patients with CKD, with and without type 2 diabetes (T2D), dapagliflozin compared to placebo:
 - Reduced the risk of kidney failure
 - Reduced the risk of death from CV causes or hospitalization for HF
 - Prolonged survival
- **The benefits of dapagliflozin in CKD patients (with and without T2D) were consistent in those with and without cardiovascular disease**
- The results of DAPA-CKD are consistent with those of DAPA-HF
- In DAPA-CKD, dapagliflozin was well tolerated, in keeping with its established safety profile, with a similar picture to that observed in DAPA-HF