

# **SUPPLEMENTAL MATERIAL**

Supplemental Table 1. Characteristics of participants by number of BP lowering drug classes at baseline

	Zero or one (N=1007)	Two (N=1363)	Three or more (N=2031)
Age, years, mean(SD)	61.0(9.6)	62.5(9.3)	64.1(8.7)
Sex, No.(%)			
Male	647(64.3)	903(66.3)	1357(66.8)
Female	360(35.7)	460(33.7)	674(33.2)
Race, No.(%)			
White	655(65.0)	852(62.5)	1424(70.1)
Black or African American	22(2.2)	60(4.4)	142(7.0)
Asian	232(23.0)	339(24.9)	306(15.1)
Native Hawaiian or other Pacific Islander	7(0.7)	8(0.6)	10(0.5)
American Indian or Alaska Native	26(2.6)	25(1.8)	27(1.3)
Multiple	17(1.7)	18(1.3)	29(1.4)
Other*	48(4.8)	61(4.5)	93(4.6)
Region, No.(%)			
North America	276(23.4)	352(29.8)	554(46.8)
Central/South America	288(30.6)	281(29.9)	372(39.5)
Europe	78(9.0)	202(23.4)	584(67.6)
Rest of the world	365(25.8)	528(37.3)	521(36.9)
Current smoker, No.(%)	151(15.0)	223(16.4)	265(13.1)
History of heart failure, No.(%)	83(8.2)	180(13.2)	389(19.2)
Duration of diabetes, years, mean(SD)	14.8(8.5)	15.5(8.5)	16.4(8.7)
BP lowering drug therapy, No.(%)			
RAS inhibitor	1002(99.5)	1363(100.0)	2030(>99.9)
Beta blocker	0(0.0)	345(25.3)	1425(70.2)
Calcium channel blocker	0(0.0)	550(40.4)	1579(77.7)
Diuretic	0(0.0)	451(33.1)	1606(79.1)
Peripherally acting antiadrenergic agents	0(0.0)	10(0.7)	292(14.4)
Centrally acting antiadrenergic agents	0(0.0)	5(0.4)	243(12.0)
Vasodilator	0(0.0)	2(0.2)	80(3.9)

Atherosclerotic vascular disease history, No.(%) †			
Coronary	127(12.6)	380(27.9)	806(39.7)
Cerebrovascular	110(10.9)	217(15.9)	373(18.4)
Peripheral	213(21.2)	315(23.1)	518(25.5)
CV disease history, No.(%)	370(36.7)	667(48.9)	1183(58.3)
Microvascular disease history, No.(%)			
Retinopathy	410(40.7)	602(44.2)	870(42.8)
Neuropathy	467(46.4)	678(49.7)	1002(49.3)
History of amputation, No.(%)	56(5.6)	70(5.1)	108(5.3)
Body mass index, Kg/m <sup>2</sup> , mean(SD)	29.2(5.3)	30.7(6.0)	32.8(6.3)
Systolic BP, mmHg, mean(SD)	135.5(14.7)	139.2(15.0)	142.8(15.9)
Diastolic BP, mmHg, mean(SD)	78.8(8.7)	78.6(9.2)	77.9(9.8)
HbA1c, %, mean(SD)	8.4(1.4)	8.3(1.3)	8.2(1.2)
eGFR, ml/min/1.73m <sup>2</sup> , mean(SD)	61.2(18.6)	56.9(18.2)	53.2(17.5)
UACR, mg/g, median(IQR)	902.0(434.0, 1848.0)	909.0(483.0, 1778.0)	943.0(471.0, 1889.0)

BP indicates blood pressure; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; DPP-4, dipeptidyl peptidase-4; HbA1c, glycohemoglobin; IQR, interquartile range; RAS, renin angiotensin system; SD, standard deviation; and UACR, urinary albumin/creatinine ratio.

\* Includes other, unknown, and not reported.

† Some participants had ≥1 type of atherosclerotic disease.

Supplemental Table 2. Characteristics of patients with or without resistant hypertension at baseline

	Resistant hypertension (N=962)	No resistant hypertension (N=3439)
Age, years, mean (SD)	64.2(8.9)	62.5(9.2)
Sex, No.(%)		
Male	640(66.5)	2267(65.9)
Female	322(33.5)	1172(34.1)
Race, No.(%)		
White	691(71.8)	2240(65.1)
Black or African American	63(6.6)	161(4.7)
Asian	124(12.9)	753(21.9)
Native Hawaiian or other Pacific Islander	3(0.3)	22(0.6)
American Indian or Alaska Native	13(1.4)	65(1.9)
Multiple	20(2.1)	44(1.3)
Other*	48(5.0)	154(4.5)
Region, No.(%)		
North America	241(25.1)	941(27.4)
Central/South America	195(20.3)	746(21.7)
Europe	307(31.9)	557(16.2)
Rest of the world	219(22.8)	1195(34.8)
Current smoker, No.(%)	115(12.0)	524(15.2)
History of heart failure, No.(%)	179(21.9)	473(13.8)
Duration of diabetes, years, mean (SD)	16.4(8.5)	15.6(8.7)
BP lowering drug therapy, No.(%)		
RAS inhibitor	961(99.9)	3434(99.9)
Beta blocker	602(62.6)	1168(34.0)
Calcium channel blocker	732(76.1)	1397(40.6)
Diuretic	962(100.0)	1095(31.8)
Peripherally acting antiadrenergic agents	136(14.1)	166(4.8)
Centrally acting antiadrenergic agents	120(12.5)	128(3.7)
Vasodilator	37(3.9)	45(1.3)
Atherosclerotic vascular disease history, No.(%) <sup>†</sup>		
Coronary	354(36.8)	959(27.9)
Cerebrovascular	182(18.9)	518(15.1)
Peripheral	248(25.8)	798(23.2)
CV disease history, No.(%)	545(56.7)	1675(48.7)
Microvascular disease history, No.(%)		
Retinopathy	428(44.5)	1454(42.3)
Neuropathy	462(48.0)	1685(49.0)
History of amputation, No.(%)	57(5.9)	177(5.2)
Body mass index, Kg/m <sup>2</sup> , mean (SD)	33.0(6.4)	30.9(6.0)
Systolic BP, mmHg, mean (SD)	152.8(11.1)	136.4(14.8)
Diastolic BP, mmHg, mean (SD)	80.7(9.5)	77.6(9.2)
HbA1c, %, mean (SD)	8.2(1.2)	8.3(1.3)
eGFR, ml/min/1.73m <sup>2</sup> , mean(SD)	53.2(17.4)	57.0(18.4)
UACR, mg/g, median (IQR)	1015.0(519.0, 2058.0)	883.0(452.0, 1778.0)

BP: blood pressure; CV: cardiovascular; eGFR: estimated glomerular filtration rate; GLP-1: glucagon-like peptide-1; DPP-4: dipeptidyl peptidase-4; HbA1c: glycated hemoglobin; IQR, interquartile range; RAS: renin angiotensin system; SD: standard deviation; UACR: urinary albumin/creatinine ratio.

\* Includes other, unknown, and not reported.

† Some participants had  $\geq 1$  type of atherosclerotic disease.

Supplemental Table 3. Baseline use and new initiation of BP lowering drug therapy

	Canagliflozin (n = 2202)	Placebo (n = 2199)	Total (n = 4401)
Baseline use			
RAS blockade	2201(>99.9)	2194(99.8)	4395(99.9)
Beta blocker	883(40.1)	887(40.3)	1770(40.2)
Calcium channel blocker	1051(47.7)	1078(49.0)	2129(48.4)
Diuretic	1026(46.6)	1031(46.9)	2057(46.7)
Peripherally acting antiadrenergic agents	140(6.4)	162(7.4)	302(6.9)
Centrally acting antiadrenergic agents	121(5.5)	127(5.8)	248(5.6)
Direct acting vasodilators	41(1.9)	41(1.9)	82(1.9)
New initiation			
RAS blockade	131(6.0)	160(7.3)	291(6.6)
Beta blocker	150(6.8)	207(9.4)	357(8.1)
Calcium channel blocker	195(8.9)	248(11.3)	443(10.1)
Diuretic	320(14.5)	474(21.6)	794(18.0)
Peripherally acting antiadrenergic agents	65(3.0)	85(3.9)	150(3.4)
Centrally acting antiadrenergic agents	33(1.5)	65(3.0)	98(2.2)
Direct acting vasodilators	34(1.5)	68(3.1)	102(2.3)

RAS: renin angiotensin system.

Supplemental Table 4. The least-squares mean change ( $\pm$ SE) in systolic BP and mean difference (95% CI) between canagliflozin and placebo by subgroups

	Baseline to week 3				Overall duration of the trial			
	Canagliflozin	Placebo	Difference	P-interaction	Canagliflozin	Placebo	Difference	P-interaction
Total population	-3.27(0.28)	0.20(0.28)	-3.48(-4.25, -2.70)		-2.82(0.22)	0.48(0.23)	-3.30(-3.87, -2.73)	
Age (years)				0.99				0.84
<55	-3.25(0.66)	0.40(0.67)	-3.65(-5.48, -1.83)		-1.83(0.52)	1.47(0.54)	-3.30(-4.62, -1.98)	
55-<65	-2.85(0.45)	0.51(0.46)	-3.36(-4.62, -2.10)		-2.11(0.37)	1.45(0.38)	-3.57(-4.51, -2.62)	
65-<75	-3.52(0.48)	-0.05(0.48)	-3.47(-4.80, -2.13)		-3.46(0.37)	-0.40(0.37)	-3.06(-4.02, -2.09)	
$\geq$ 75	-3.81(0.89)	-0.43(0.85)	-3.38(-5.79, -0.97)		-4.57(0.75)	-1.53(0.72)	-3.04(-4.89, -1.18)	
Sex				0.10				0.34
Male	-3.54(0.34)	0.41(0.34)	-3.95(-4.89, -3.01)		-3.18(0.27)	0.30(0.27)	-3.49(-4.18, -2.79)	
Female	-2.77(0.49)	-0.19(0.50)	-2.58(-3.94, -1.21)		-2.03(0.40)	0.90(0.41)	-2.93(-3.94, -1.92)	
Race*				0.40				0.74
White	-3.08(0.34)	0.16(0.34)	-3.24(-4.18, -2.30)		-2.49(0.26)	0.61(0.26)	-3.11(-3.79, -2.42)	
Black or African American	-2.80(1.38)	1.46(1.40)	-4.26(-8.12, -0.39)		-0.51(1.23)	2.64(1.23)	-3.15(-6.37, 0.07)	
Asian	-3.92(0.60)	-0.33(0.58)	-3.59(-5.21, -1.96)		-3.58(0.45)	-0.00(0.44)	-3.58(-4.76, -2.40)	
Native Hawaiian or other Pacific Islander	-7.09(4.61)	-0.15(3.43)	-6.94(-18.73, 4.84)		-6.03(2.31)	-1.39(2.05)	-4.64(-8.44, -0.84)	
American Indian or Alaska Native	-4.62(2.66)	-3.71(2.24)	-0.91(-7.80, 5.99)		-4.91(1.91)	-2.15(1.67)	-2.76(-7.61, 2.09)	
Multiple	-1.29(3.25)	2.73(3.19)	-4.02(-13.52, 5.49)		0.58(2.29)	3.82(2.18)	-3.24(-9.34, 2.87)	
Other†	-3.99(1.53)	2.53(1.52)	-6.52(-10.75, -2.29)		-2.86(1.19)	2.62(1.19)	-5.49(-8.72, -2.26)	
Baseline systolic BP (mmHg)				0.57				0.26
<130	5.05(0.59)	8.49(0.59)	-3.43(-5.06, -1.81)		7.87(0.46)	11.39(0.47)	-3.52(-4.73, -2.31)	
130-<140	-2.06(0.48)	1.77(0.48)	-3.83(-5.16, -2.50)		-0.71(0.40)	3.00(0.40)	-3.71(-4.69, -2.72)	
140-<150	-4.38(0.56)	-1.84(0.56)	-2.54(-4.10, -0.99)		-4.82(0.43)	-2.54(0.44)	-2.27(-3.39, -1.16)	
$\geq$ 150	-10.93(0.62)	-7.04(0.60)	-3.89(-5.57, -2.20)		-12.97(0.49)	-9.37(0.48)	-3.60(-4.84, -2.36)	
Number of BP lowering drug classes				0.45				0.08
None or one	-3.64(0.56)	0.71(0.55)	-4.35(-5.85, -2.85)		-2.76(0.46)	1.78(0.45)	-4.54(-5.61, -3.46)	
Two	-2.73(0.49)	0.19(0.52)	-2.93(-4.32, -1.53)		-2.22(0.40)	0.52(0.42)	-2.74(-3.78, -1.70)	
Three or more	-3.54(0.43)	-0.09(0.42)	-3.46(-4.64, -2.28)		-3.31(0.34)	-0.15(0.33)	-3.15(-4.01, -2.30)	

Resistant hypertension				0.92				0.62
Yes	-7.81(0.65)	-4.31(0.63)	-3.50(-5.28, -1.72)		-8.82(0.49)	-5.79(0.47)	-3.04(-4.29, -1.78)	
No	-1.97(0.31)	1.49(0.31)	-3.45(-4.31, -2.59)		-1.15(0.25)	2.23(0.26)	-3.37(-4.02, -2.73)	
Screening eGFR (ml/min/1.73m <sup>2</sup> )				0.57				0.34
30-<45	-3.43(0.55)	0.53(0.55)	-3.96(-5.49, -2.43)		-2.55(0.45)	1.14(0.45)	-3.69(-4.81, -2.57)	
45-<60	-3.32(0.54)	0.33(0.54)	-3.65(-5.15, -2.14)		-2.92(0.41)	0.56(0.42)	-3.48(-4.56, -2.39)	
60-<90	-3.33(0.40)	-0.35(0.40)	-2.98(-4.08, -1.88)		-3.13(0.32)	-0.25(0.32)	-2.88(-3.71, -2.06)	
Screening UACR (mg/g)				0.14				0.16
≤1000	-3.71(0.38)	0.35(0.38)	-4.06(-5.12, -3.00)		-3.22(0.31)	0.44(0.31)	-3.66(-4.45, -2.86)	
>1000	-2.91(0.41)	-0.04(0.41)	-2.88(-4.01, -1.74)		-2.45(0.32)	0.47(0.33)	-2.92(-3.74, -2.10)	
Baseline HbA1c (%)				0.53				0.30
<7	-3.37(0.72)	0.30(0.71)	-3.67(-5.65, -1.69)		-3.41(0.56)	0.65(0.56)	-4.05(-5.51, -2.59)	
7-<8	-3.16(0.50)	0.41(0.50)	-3.57(-4.95, -2.20)		-2.76(0.39)	0.31(0.40)	-3.06(-4.08, -2.05)	
8-<9	-2.77(0.56)	-0.30(0.55)	-2.48(-4.01, -0.94)		-3.14(0.43)	-0.56(0.43)	-2.58(-3.68, -1.49)	
≥9	-3.84(0.54)	0.19(0.55)	-4.03(-5.53, -2.53)		-2.24(0.44)	1.57(0.45)	-3.82(-4.93, -2.71)	

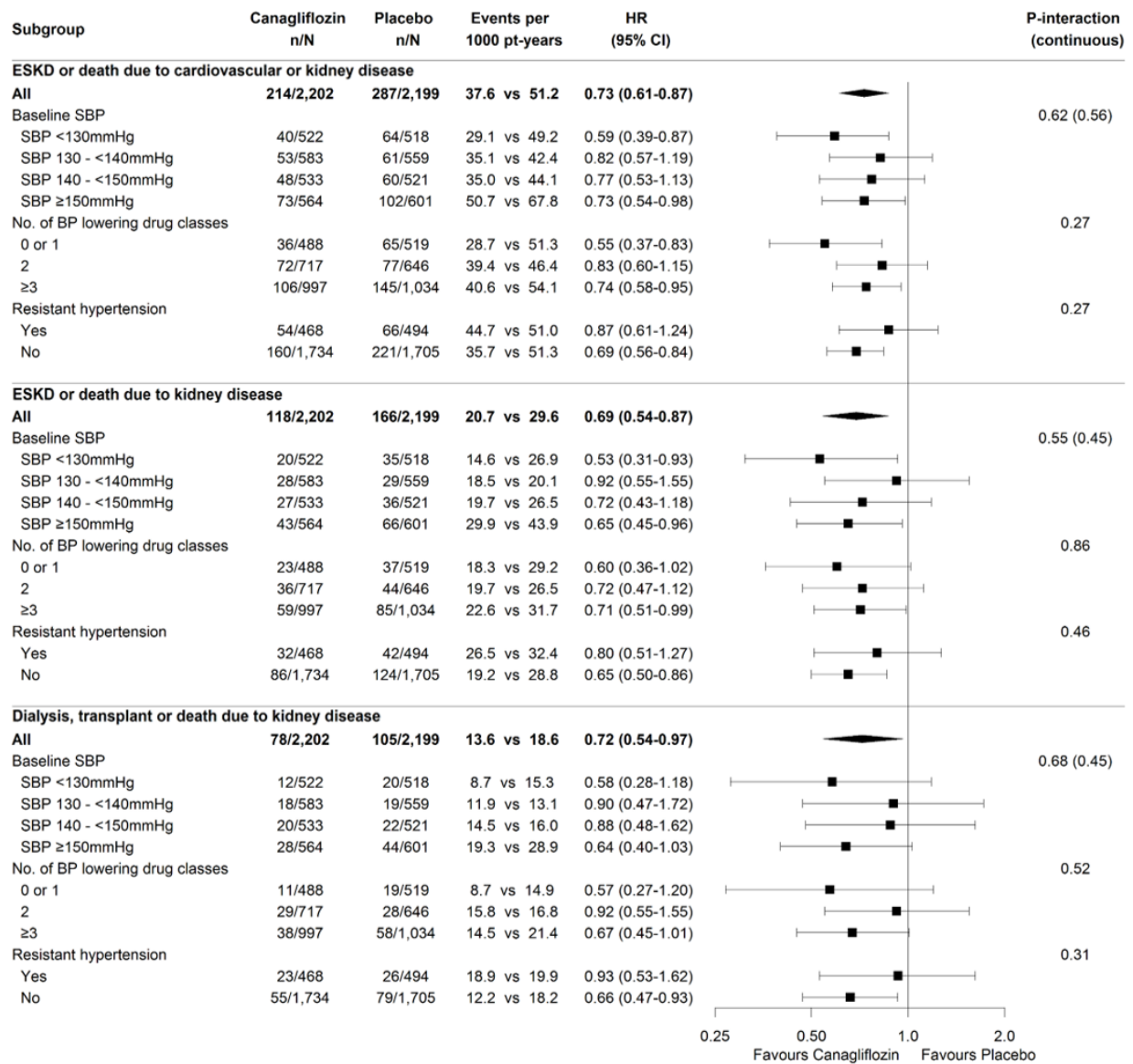
BP indicates blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycohemoglobin; UACR, urinary albumin/creatinine ratio.

\* Represents the mean difference in change between canagliflozin and placebo from baseline to week 130, while other variables represent the mean difference from baseline to week 182

† Includes other, unknown, and not reported

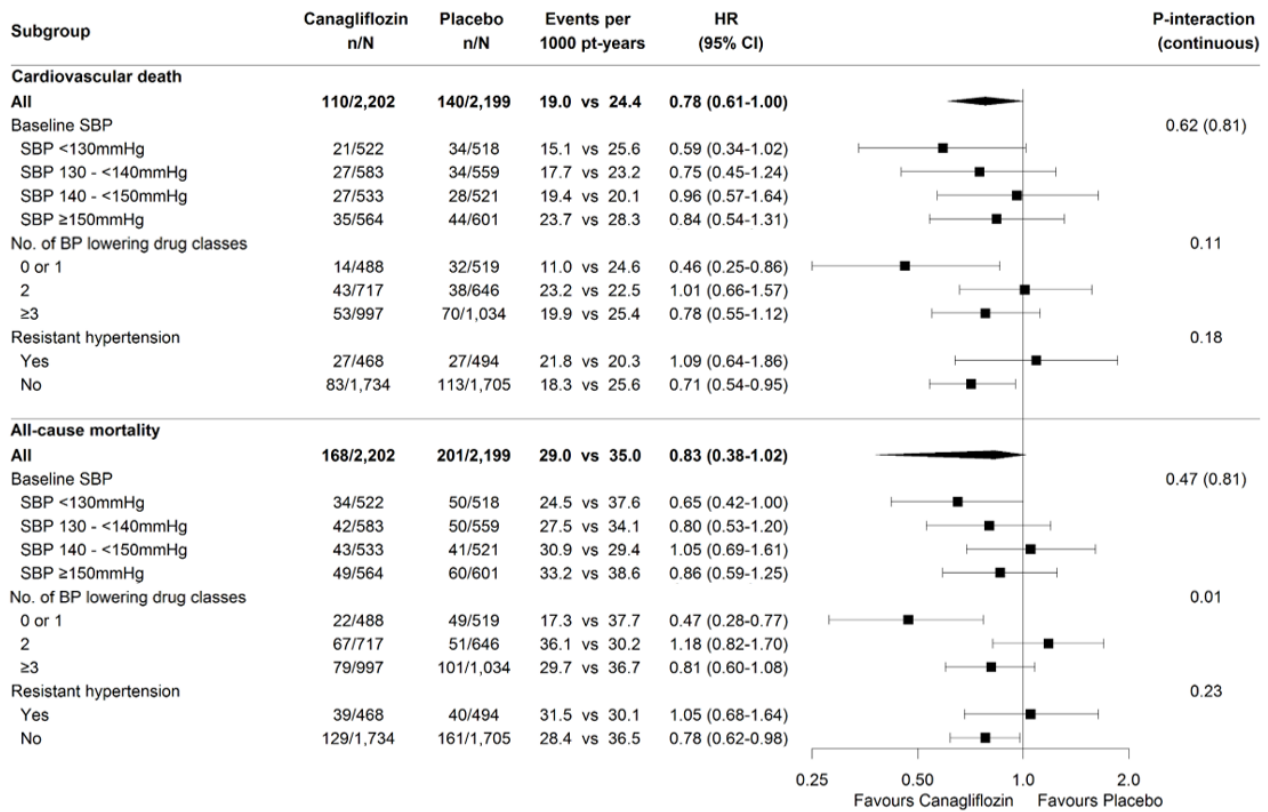


Supplemental Figure 1. Effect of canagliflozin on other kidney outcomes by baseline systolic blood pressure, number of blood pressure lowering drug classes, and history of resistant hypertension.



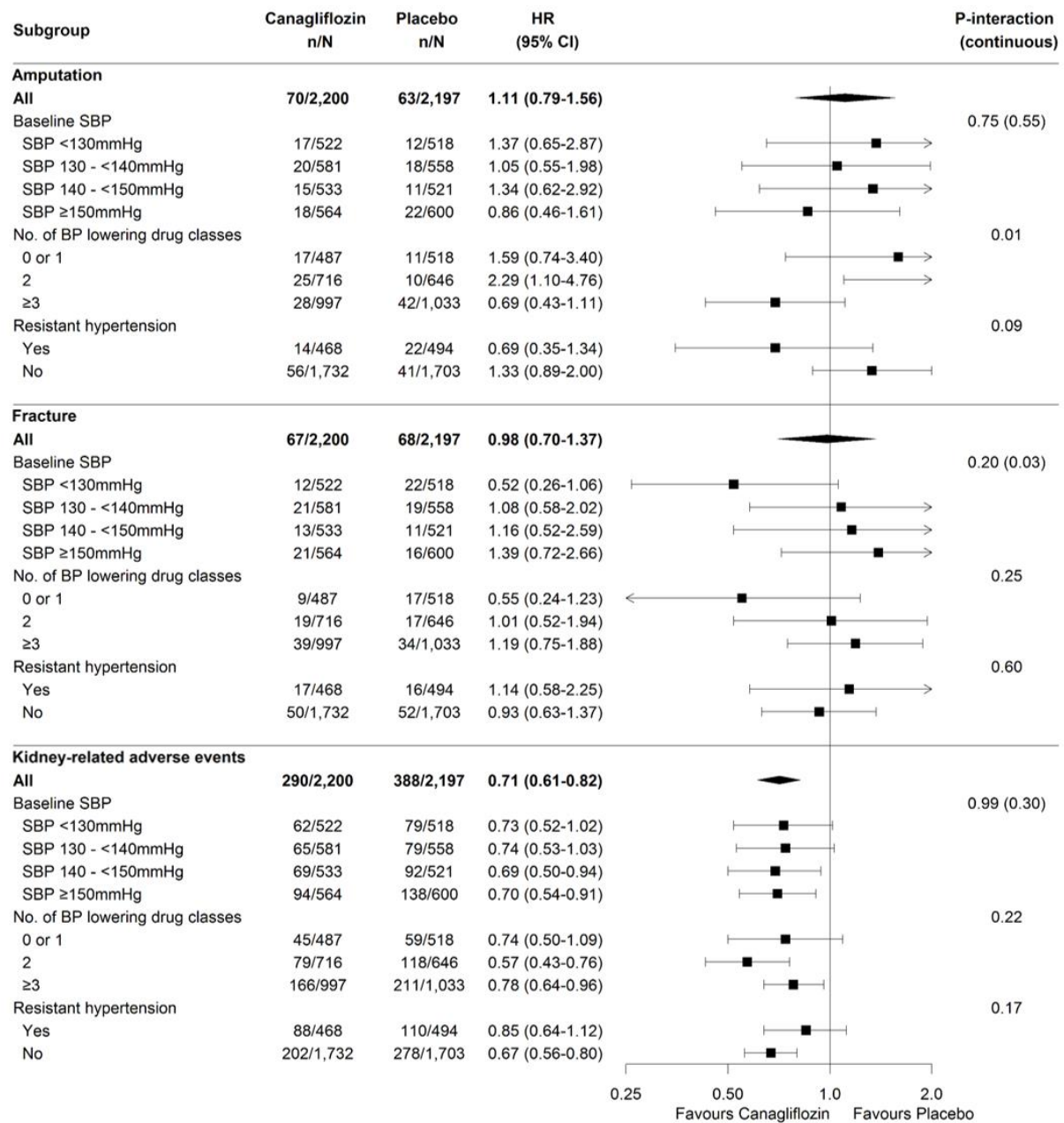
SBP: systolic blood pressure.

Supplemental Figure 2. Effect of canagliflozin on cardiovascular and all-cause mortality by baseline systolic blood pressure, number of blood pressure lowering drug classes, and history of resistant hypertension.



SBP: systolic blood pressure.

Supplemental Figure 3. Effect of canagliflozin on amputation, fracture, and kidney related adverse events by baseline systolic blood pressure, number of blood pressure lowering drug classes, and history of resistant hypertension.



SBP: systolic blood pressure.