Effects of empagliflozin on progression of chronic kidney disease: results from the EMPA-KIDNEY trial

The EMPA-KIDNEY Collaborative Group

Supplementary Appendix

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Supplementary Statistical Methods

Shared parameter models for analyses of estimated GFR over time

Mean annual rates of change in estimated GFR from baseline to the final follow-up visit ("total slopes"), and from 2 months to the final follow-up visit ("chronic slopes") by treatment allocation were estimated using shared parameter models[1] adjusted for age, sex, prior diabetes, urinary ACR, and region (all in the categories used in the minimization process). Models estimating chronic slope were additionally adjusted for baseline estimated GFR (as a continuous variable) and the interaction between baseline estimated GFR and follow-up time. This approach jointly models: (a) the annual rate of change in estimated GFR using a linear mixed model (with random effects for each patient's slope and intercept); and (b) the time to event for end-stage kidney disease (ESKD) or death (using a Weibull survival model in which the scale parameter is assumed to be linearly related to the random effects from the linear mixed model).

Specifically, the linear mixed model component is

$$Y_{ij} = (\beta_0 + u_{0i}) + \beta_1 X_i + (\beta_2 + u_{1i})t_{ij} + \beta_3 X_i t_{ij} + e_{ij}$$

and the Weibull model for time to ESKD or death has hazard function

$$h(t_{ij}) = \gamma \exp(\varphi + \eta_0 u_{0i} + \eta_1 u_{1i} + \alpha X_i)^{\gamma} t_{ij}^{\gamma-1}$$

where t_{ij} is the time (in years) of visit *j* for patient *i*, Y_{ij} is the observed value of estimated GFR at visit *j* for patient *i*, X_i is the treatment allocation for patient *i*, β_0 is the mean estimated GFR at baseline in the placebo arm, β_1 is the mean difference in baseline estimated GFR between treatment allocations, β_2 is the mean estimated GFR slope in the placebo arm, and β_3 is the mean difference in estimated GFR slopes between treatment allocations. u_{1i} and u_{0i} are the random effects for each patient's slope and intercept respectively, which are assumed to be independent multivariate normal random vectors with mean 0 and an unstructured covariance matrix. e_{ij} is the random error at time t_{ij}, which are assumed to be independent and normally distributed with mean zero and constant variance.

Analyses used all available central laboratory estimated GFR measurements prior to the development of ESKD. The advantage of the above modelling approach (over a standard linear mixed model) is that it additionally allows for the dependence between the annual rate of change in estimated GFR and the time to ESKD or death (which is important because those with faster rates of change in estimated GFR will generally have a shorter time to ESKD or death). The mean slopes provided by the shared parameter model (total or chronic) may be thought of as the average of the patient-specific slopes, conditional on the baseline covariates in the model, and in the hypothetical scenario where estimated GFR had continued to be measured beyond the time of ESKD or death. As with other methods, the estimates they provide merely reflect averages over the follow-up period of interest (and hence, in the context of a drug which has an initial acute effect, the "total slope" requires careful interpretation).

Mixed model for repeated measures (MMRM)

Linear mixed models for repeated measures (MMRM) analyses were used to estimate effects of empagliflozin on study-average urinary ACR. These models were adjusted for baseline log-transformed urinary ACR (as a continuous variable), age, sex, prior diabetes, estimated GFR,

[1] Vonesh EF, Greene T, Schluchter MD. Shared parameter models for the joint analysis of longitudinal data and event times. Statistics in Medicine 2006; **25**(1): 143-63.

and region (all in the same categories used in the minimization process), treatment allocation, follow-up time point and the interaction between baseline log-transformed urinary ACR and follow-up time point. A further interaction term between treatment allocation and follow-up time point was then included in order to enable separate estimation of mean log-transformed urinary ACR at each follow-up time point for each treatment arm, conditional on the other factors in the model. The within-person error correlations were assumed to be unstructured. These models assume that any missing urinary ACR values can be predicted by the non-missing urinary ACR data for other individuals together with the other covariates in the model (i.e. that they are ‘missing at random’).

A weighted average of these baseline-adjusted mean follow-up values is then used (with weights proportional to the amount of time between visits) to calculate the study average log-transformed uACR in each treatment arm. These values are then back transformed to give geometric means of study average urinary ACR along with the relative differences in the geometric means.

Supplementary Tables

Webtable 1: Baseline characteristics by expanded eGFR and uACR categories

	eGFR (mL/min/1.73m²)				uACR (mg/g)				
	<20 (n=254)	≥20 to <30 (n=2028)	≥30 to <45 (n=2928)	≥45 (n=1399)	<30 (n=1328)	≥30 to <300 (n=1864)	≥300 to <1000 (n=1664)	≥1000 to <2000 (n=953)	≥2000 (n=800)
Demographics									
Age at randomization (years)	64 (14)	65 (13)	64 (13)	58 (15)	71 (9)	66 (13)	59 (14)	58 (15)	59 (14)
Sex									
Men	162 (64%)	1371 (68%)	1937 (66%)	947 (68%)	725 (55%)	1268 (68%)	1184 (71%)	681 (71%)	559 (70%)
Women	92 (36%)	657 (32%)	991 (34%)	452 (32%)	603 (45%)	596 (32%)	480 (29%)	272 (29%)	241 (30%)
Race									
White	148 (58%)	1292 (64%)	1833 (63%)	586 (42%)	1069 (80%)	1189 (64%)	788 (47%)	466 (49%)	347 (43%)
Black	9 (4%)	89 (4%)	119 (4%)	45 (3%)	71 (5%)	89 (5%)	56 (3%)	26 (3%)	20 (3%)
Asian	93 (37%)	614 (30%)	930 (32%)	756 (54%)	173 (13%)	562 (30%)	790 (47%)	449 (47%)	419 (52%)
Mixed	0 (0%)	6 (0%)	13 (0%)	2 (0%)	2 (0%)	6 (0%)	8 (0%)	2 (0%)	3 (0%)
Other	4 (2%)	27 (1%)	33 (1%)	10 (1%)	13 (1%)	18 (1%)	22 (1%)	10 (1%)	11 (1%)
Prior disease									
Prior diabetes*	136 (54%)	1015 (50%)	1371 (47%)	518 (37%)	647 (49%)	943 (51%)	616 (37%)	378 (40%)	456 (57%)
Prior diabetes type									
Type 1	6 (2%)	25 (1%)	28 (1%)	9 (1%)	11 (1%)	20 (1%)	18 (1%)	11 (1%)	8 (1%)
Type 2	128 (50%)	978 (48%)	1333 (46%)	497 (36%)	633 (48%)	916 (49%)	586 (35%)	362 (38%)	439 (55%)
Other/unknown	2 (1%)	12 (1%)	10 (0%)	12 (1%)	3 (0%)	7 (0%)	12 (1%)	5 (1%)	9 (1%)
History of cardiovascular disease§	81 (32%)	637 (31%)	828 (28%)	219 (16%)	484 (36%)	579 (31%)	332 (20%)	176 (18%)	194 (24%)
Clinical measurements									
Systolic blood pressure (mmHg)	138.2 (19.2)	137.5 (18.6)	136.0 (18.2)	135.9 (17.8)	130.8 (18.0)	134.3 (17.7)	136.6 (17.1)	140.3 (18.0)	146.3 (18.0)
Diastolic blood pressure (mmHg)	76.6 (12.2)	76.5 (11.8)	77.9 (11.7)	80.9 (11.6)	73.5 (10.7)	75.8 (11.6)	79.9 (11.0)	81.7 (11.8)	82.6 (11.9)
Body mass index (kg/m²)	29.7 (6.8)	30.1 (6.6)	30.1 (6.9)	28.5 (6.5)	31.5 (7.1)	29.9 (6.6)	28.7 (6.6)	29.0 (6.6)	29.5 (6.7)
Laboratory measurements									
eGFR (mL/min/1.73m²)†									
Mean (SD)	18.0 (1.8)	25.4 (2.8)	36.8 (4.2)	59.3 (13.5)	35.1 (8.2)	36.3 (12.8)	40.4 (17.2)	38.3 (16.9)	35.7 (15.6)
<30	254 (100%)	2028 (100%)	0 (0%)	0 (0%)	386 (29%)	639 (34%)	522 (31%)	373 (39%)	362 (45%)
≥30 to <45	0 (0%)	0 (0%)	2928 (100%)	0 (0%)	789 (59%)	896 (48%)	651 (39%)	324 (34%)	268 (34%)
≥45	0 (0%)	0 (0%)	0 (0%)	1399 (100%)	153 (12%)	329 (18%)	491 (30%)	256 (27%)	170 (21%)
uACR (mg/g)†									
Median (Q1,Q3)	916 (190-2144)	375 (55-1279)	187 (26-781)	515 (214-1199)	7 (6-18)	117 (59-202)	566 (413-770)	1384 (1168-1650)	3106 (2396-4177)
<30	27 (11%)	359 (18%)	789 (27%)	153 (11%)	1328 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
≥30 to ≤300	48 (19%)	591 (29%)	896 (31%)	329 (24%)	0 (0%)	1864 (100%)	0 (0%)	0 (0%)	0 (0%)
>300	179 (70%)	1078 (53%)	1243 (42%)	917 (66%)	0 (0%)	0 (0%)	1664 (100%)	953 (100%)	800 (100%)
NT-proBNP (ng/L)	1013 (2834)	675 (1469)	470 (1091)	211 (476)	506 (930)	535 (1220)	361 (824)	444 (1076)	756 (2302)
Glycated haemoglobin (mmol/mol)	44.3 (12.9)	45.7 (13.8)	45.5 (13.7)	43.1 (13.1)	45.5 (12.1)	45.8 (13.4)	43.0 (13.3)	42.9 (12.3)	48.8 (17.0)
Glycated haemoglobin (%)	6.2 (1.2)	6.3 (1.3)	6.3 (1.3)	6.1 (1.2)	6.3 (1.1)	6.3 (1.2)	6.1 (1.2)	6.1 (1.1)	6.6 (1.6)
Concomitant medication use									
RAS inhibitor	199 (78%)	1673 (82%)	2487 (85%)	1269 (91%)	1073 (81%)	1545 (83%)	1483 (89%)	843 (88%)	684 (86%)
Any diuretic	125 (49%)	1026 (51%)	1271 (43%)	393 (28%)	777 (59%)	868 (47%)	525 (32%)	333 (35%)	312 (39%)
Any lipid-lowering medication	181 (71%)	1476 (73%)	1955 (67%)	766 (55%)	992 (75%)	1274 (68%)	959 (58%)	595 (62%)	558 (70%)
Cause of kidney disease									
Diabetic kidney disease	99 (39%)	702 (35%)	901 (31%)	355 (25%)	376 (28%)	623 (33%)	431 (26%)	273 (29%)	354 (44%)
Hypertensive/renovascular disease	49 (19%)	484 (24%)	699 (24%)	213 (15%)	469 (35%)	444 (24%)	278 (17%)	151 (16%)	103 (13%)
Glomerular disease	61 (24%)	391 (19%)	636 (22%)	581 (42%)	66 (5%)	344 (18%)	649 (39%)	364 (38%)	246 (31%)
Other/unknown	45 (18%)	451 (22%)	692 (24%)	250 (18%)	417 (31%)	453 (24%)	306 (18%)	165 (17%)	97 (12%)

Figures are n (%), mean (SD) or median (Q1, Q3). NT-proBNP=N-terminal pro B-type natriuretic peptide. eGFR=estimated glomerular filtration rate. uACR=urinary albumin-to-creatinine ratio. RAS=renin-angiotensin system. *Prior diabetes mellitus defined as diabetes at randomization is defined as participant-reported history of diabetes of any type, use of glucose-lowering medication or baseline HbA1c ≥48 mmol/mol at Randomization visit. §Defined as self-reported history of myocardial infarction, heart failure, stroke, transient ischemic attack, or peripheral arterial disease. †Uses central measurement taken at the randomization visit, or more recent local laboratory result before randomization.

Webtable 2: Change in eGFR at 4 weeks after final follow-up

	Mean eGFR (mL/min/1.73m²)		Absolute difference
	Empagliflozin	Placebo	
All participants with a visit 4 weeks after final follow-up			
Number of participants	398	364	
Randomization	33.66 (0.58)	33.43 (0.62)	-
Final follow-up	28.99 (0.62)	28.73 (0.62)	-
4 weeks post final follow-up	29.89 (0.23)	27.98 (0.24)	1.91 (1.26, 2.56)
Restricted to participants on treatment at final follow-up visit			
Number of participants	268	229	
Randomization	33.66 (0.58)	33.43 (0.62)	-
Final follow-up	29.01 (0.70)	29.14 (0.73)	-
4 weeks post final follow-up	30.24 (0.24)	28.39 (0.26)	1.85 (1.16, 2.53)

Pre-specified exploratory analyses.

Webtable 3: Change in eGFR at 4 weeks after final follow-up, by level of baseline eGFR and uACR

	Mean eGFR (mL/min/1.73m²)		Absolute difference
	Empagliflozin	Placebo	
Baseline eGFR <30			
Number of participants	175	170	
Randomization	24.74 (0.24)	24.92 (0.27)	-
Final follow-up	21.41 (0.60)	21.30 (0.50)	-
4 weeks post final follow-up	22.50 (0.35)	20.61 (0.35)	1.90 (0.93, 2.86)
Baseline eGFR ≥30 to <45			
Number of participants	175	152	
Randomization	36.34 (0.33)	36.39 (0.36)	-
Final follow-up	30.94 (0.57)	32.00 (0.66)	-
4 weeks post final follow-up	32.73 (0.35)	30.73 (0.37)	2.00 (1.00, 2.99)
Baseline eGFR ≥45			
Number of participants	48	42	
Randomization	56.42 (1.82)	57.22 (2.26)	-
Final follow-up	49.48 (1.96)	47.02 (2.12)	-
4 weeks post final follow-up	47.89 (0.67)	46.45 (0.71)	1.44 (-0.48, 3.35)
Baseline uACR <30			
Number of participants	68	78	
Randomization	30.86 (0.77)	32.52 (0.82)	-
Final follow-up	28.06 (1.02)	32.70 (0.94)	-
4 weeks post final follow-up	32.25 (0.57)	29.60 (0.54)	2.66 (1.12, 4.19)
Baseline uACR ≥30 to ≤300			
Number of participants	113	92	
Randomization	33.24 (1.00)	31.46 (0.79)	-
Final follow-up	30.00 (1.12)	28.29 (0.92)	-
4 weeks post final follow-up	30.43 (0.43)	28.22 (0.48)	2.21 (0.95, 3.47)
Baseline uACR >300			
Number of participants	217	194	
Randomization	34.76 (0.88)	34.74 (1.05)	-
Final follow-up	28.75 (0.92)	27.35 (0.98)	-
4 weeks post final follow-up	28.97 (0.32)	27.45 (0.34)	1.51 (0.61, 2.42)

Post-hoc exploratory analyses using pre-specified subgroup definitions including all participants with a visit 4 weeks after final follow-up.

Webtable 4: Effect of allocation to empagliflozin on study average uACR, by key and other subgroups

	Median (IQR) uACR at randomisation	Geometric mean (approx SE) study average uACR (mg/g)		Relative difference in study average uACR
		Empagliflozin	Placebo	
Key subgroups				
Diabetes				
Present	263 (40-1158)	181 (5)	250 (7)	-28% (-33%, -22%)
Absent	380 (60-1034)	223 (6)	251 (6)	-11% (-17%, -5%)
Estimated glomerular filtration rate (mL/min/1.73m²)				
<30	410 (59-1373)	274 (9)	363 (12)	-25% (-31%, -18%)
≥30 to <45	187 (26-781)	136 (4)	163 (5)	-17% (-23%, -10%)
≥45	515 (214-1199)	291 (11)	343 (14)	-15% (-24%, -5%)
Urinary albumin-to-creatinine ratio (mg/g)				
<30	7 (6-18)	19 (1)	20 (1)	-5% (-15%, 6%)
≥30 to ≤300	117 (59-202)	110 (4)	133 (5)	-17% (-25%, -9%)
>300	1033 (575-1910)	708 (19)	951 (25)	-26% (-31%, -20%)
Demographics				
Age at randomization (years)				
<60	677 (276-1507)	461 (15)	522 (17)	-12% (-19%, -4%)
≥60 to <70	305 (44-1096)	183 (7)	252 (9)	-27% (-34%, -20%)
≥70	109 (20-564)	107 (3)	134 (4)	-20% (-26%, -13%)
Sex				
Male	382 (72-1134)	220 (24)	273 (30)	-19% (-24%, -14%)
Female	222 (25-940)	171 (38)	214 (48)	-20% (-27%, -12%)
Race				
White	173 (25-810)	132 (4)	164 (6)	-20% (-25%, -14%)
Black	151 (26-631)	128 (12)	173 (18)	-26% (-43%, -3%)
Asian	646 (237-1474)	419 (20)	512 (24)	-18% (-25%, -11%)
Other	354 (130-1166)	276 (46)	294 (45)	-6% (-40%, 46%)
Prior disease				
History of cardiovascular disease				
Yes	148 (25-789)	144 (5)	170 (6)	-16% (-24%, -7%)
No	403 (73-1147)	230 (5)	290 (6)	-21% (-25%, -16%)
Clinical measurements				
Systolic blood presure (mmHg)				
<130	196 (26-669)	147 (4)	176 (5)	-17% (-23%, -9%)
≥130 to <145	350 (55-1069)	218 (7)	250 (8)	-13% (-20%, -5%)
≥145	600 (109-1671)	275 (9)	388 (13)	-29% (-35%, -22%)
Diastolic blood presure (mmHg)				
<75	147 (22-660)	136 (4)	171 (5)	-20% (-27%, -14%)
≥75 to <85	363 (62-1067)	213 (7)	268 (9)	-21% (-28%, -13%)
≥85	632 (194-1566)	323 (11)	392 (13)	-18% (-25%, -9%)
Body mass index (kg/m²)				
<25	487 (136-1193)	304 (12)	357 (14)	-15% (-23%, -6%)
≥25 to <30	319 (51-1044)	204 (6)	247 (8)	-18% (-24%, -10%)
≥30	243 (29-1019)	159 (5)	208 (6)	-24% (-30%, -17%)
Laboratory measurements				
Glycated haemoglobin (mmol/mol)				
<39	438 (98-1096)	253 (8)	284 (9)	-11% (-18%, -3%)
≥39 to <48	244 (31-945)	167 (6)	203 (7)	-18% (-25%, -9%)
≥48	254 (39-1163)	182 (7)	259 (9)	-30% (-36%, -23%)
NT-proBNP (ng/L)				
<110	402 (92-1018)	232 (7)	291 (9)	-20% (-27%, -13%)
≥110 to <330	291 (41-1076)	194 (6)	241 (8)	-20% (-26%, -12%)
≥330	245 (33-1197)	179 (6)	219 (8)	-18% (-26%, -10%)
Concomitant medication use				
RAS inhibitor				
Yes	360 (55-1100)	213 (4)	270 (5)	-21% (-25%, -17%)
No	186 (29-886)	153 (8)	166 (8)	-8% (-20%, 5%)
Diuretic				
Yes	168 (25-896)	141 (4)	176 (5)	-20% (-26%, -13%)
No	446 (107-1166)	265 (6)	328 (8)	-19% (-24%, -13%)
Lipid lowering medication				
Yes	266 (36-1070)	181 (4)	233 (5)	-22% (-27%, -17%)
No	416 (107-1069)	252 (8)	293 (10)	-14% (-21%, -6%)
Risk of progression				
5 year risk of renal failure (%)				
<5	62 (10-413)	76 (2)	91 (3)	-17% (-23%, -9%)
≥5 to <20	212 (54-674)	173 (6)	215 (7)	-19% (-26%, -12%)
≥20	1060 (448-2055)	694 (24)	895 (31)	-22% (-29%, -15%)
All participants	329 (49-1069)	202 (4)	250 (5)	-19% (-23%, -15%)

Analyses use central laboratory measurements at follow-up time points 2, 18, 24 and 30 months, with similar findings in a sensitivity analysis including a baseline quadratic term to assess the effect of the violation of the assumption of linearity for quantitative predictors.

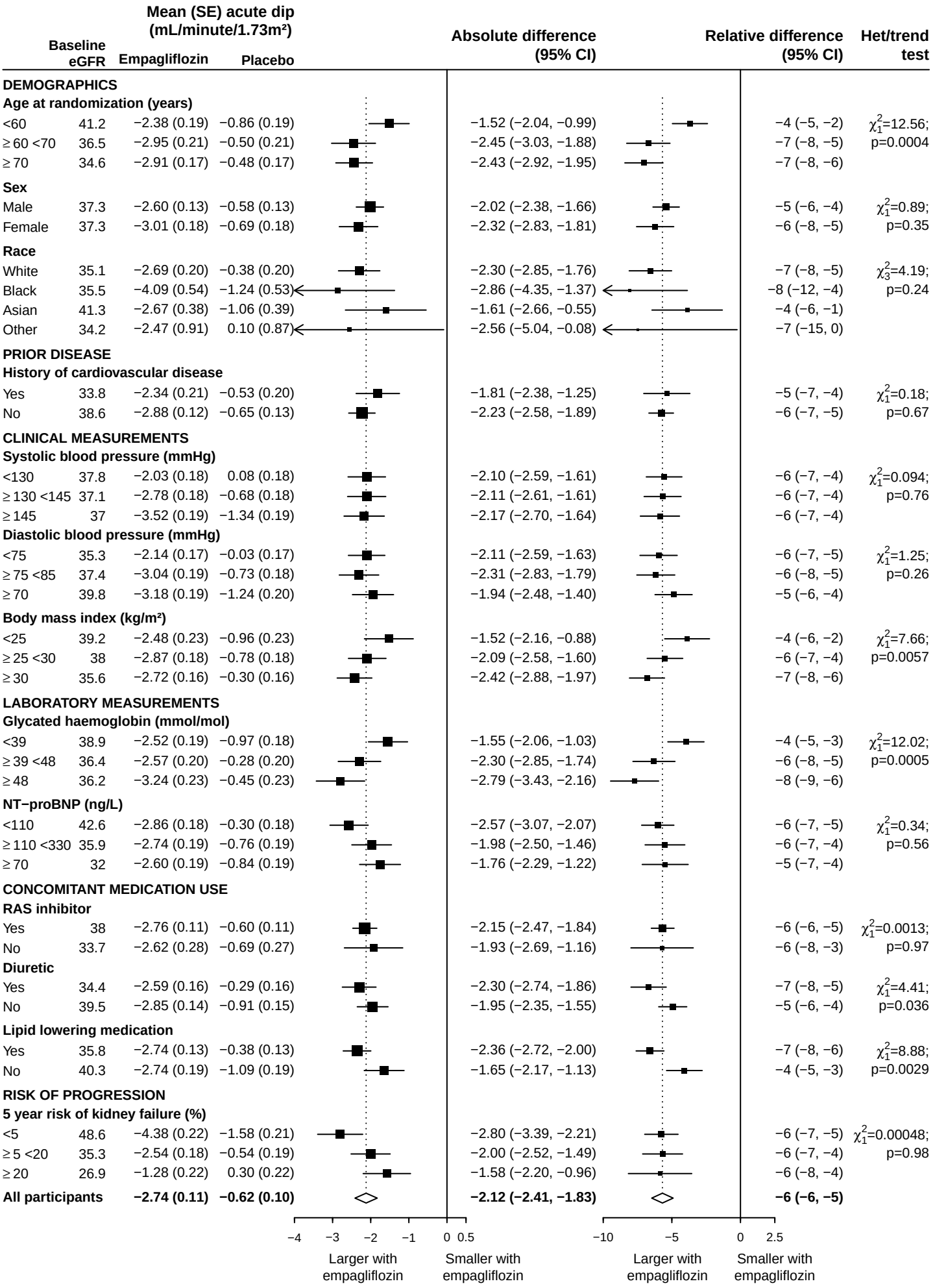
Webtable 5: Proportion of treatment effect for chronic slope explained by 2 month biomarkers

Biomarkers	Absolute difference in chronic slope for empagliflozin vs placebo*	Wald χ^2	% reduction in χ^2	Proportion of treatment effect explained (95% CI)
None	1.43 (1.11, 1.75)	78.4	0	-
uACR	1.10 (0.79, 1.41)	49.3	37	23% (17% to 32%)
SBP	1.32 (1.00, 1.63)	66.5	15	8% (5% to 12%)
DBP	1.39 (1.07, 1.70)	73.9	6	3% (1% to 6%)
HbA1c	1.44 (1.12, 1.76)	79.5	-1	-1% (-3% to 1%)
uACR, SBP, DBP and HbA1c	1.06 (0.76, 1.37)	46.2	41	26% (19% to 35%)

Analyses restricted to 5222 participants with measurements of uACR, SBP, DBP and HbA1c at 2 months and a minimum of 2 eGFR measurements between 2 months and the final follow-up visit. Chronic slopes calculated for each individual participant using linear regression. The proportion of the treatment effect explained by on-study biomarkers is estimated using the landmark method, adjusting a linear regression model with chronic slope as the dependent variable for 2 month values of the biomarkers. *After adjustment for biomarkers at 2 months. All analyses additionally adjusted for baseline variables specified in the minimisation algorithm (age, sex, prior diabetes, eGFR, uACR and region).

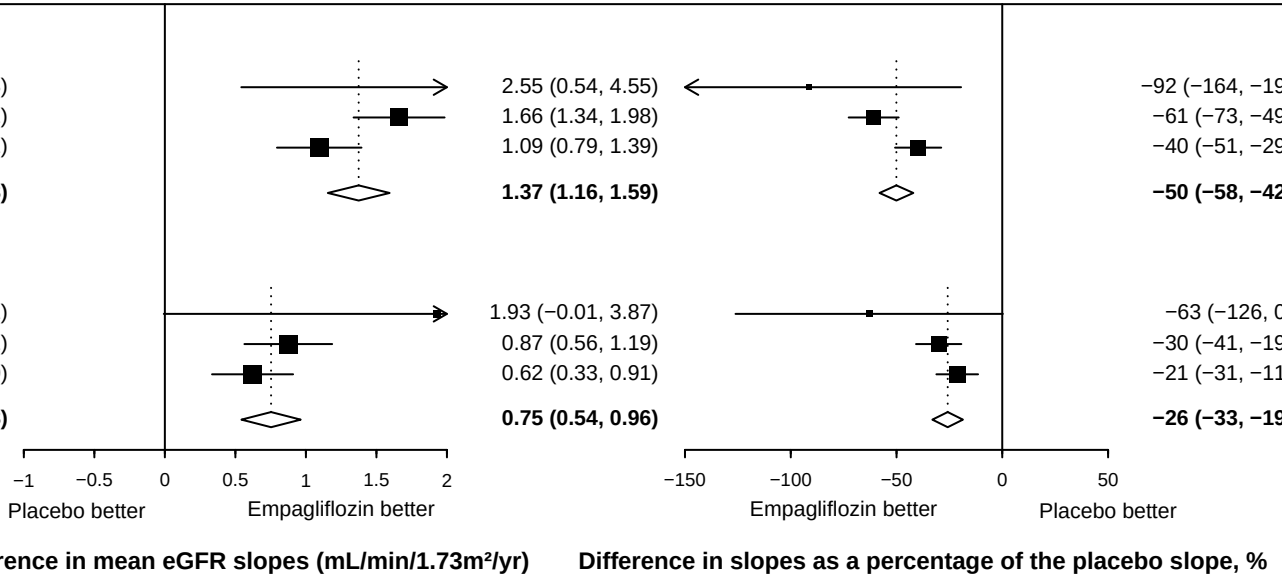
Supplementary Figures

Webfigure 1: Effect of allocation to empagliflozin on acute changes in estimated glomerular filtration rate, by other subgroups



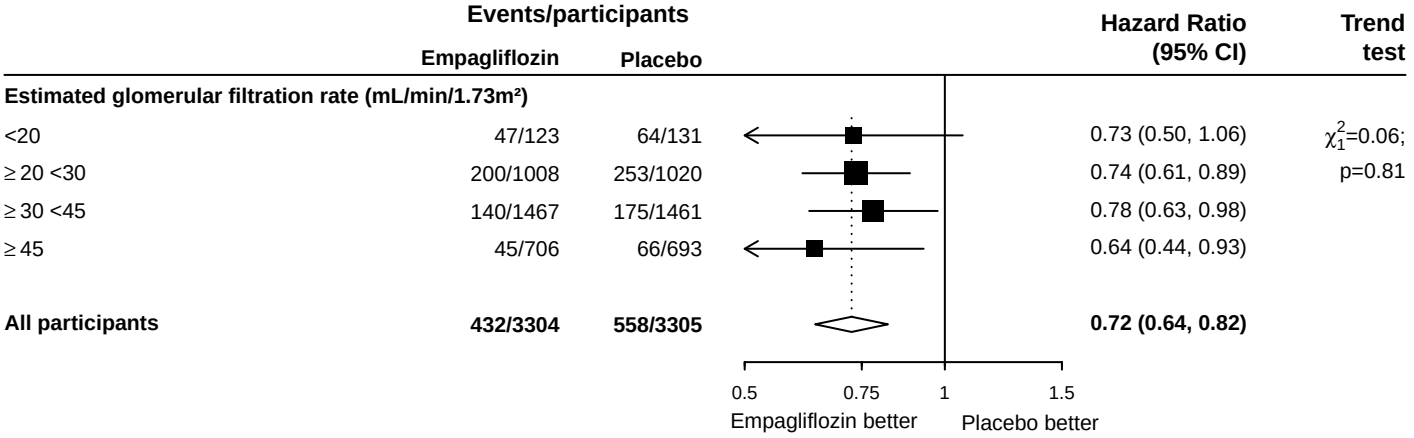
Webfigure 2: Absolute and relative effects of allocation to empagliflozin on 'total slopes' and 'chronic slopes', by diabetes status

	Study average reduction in uACR (%)	Mean (SE) slope (mL/min/1.73m²/yr) Empagliflozin	Placebo	Absolute difference (95% CI)	Relative difference, % (95% CI)	Het/trend test for relative difference
CHRONIC SLOPE						
Diabetes mellitus						
Type 1 diabetes	−11%	−0.23 (0.72)	−2.78 (0.73)	2.55 (0.54, 4.55)	−92 (−164, −19)	χ^2_2=7.87;
Type 2 diabetes	−47%	−1.07 (0.12)	−2.73 (0.12)	1.66 (1.34, 1.98)	−61 (−73, −49)	p=0.020
No diabetes	−27%	−1.66 (0.11)	−2.75 (0.11)	1.09 (0.79, 1.39)	−40 (−51, −29)	
All participants	**−19%**	**−1.37 (0.08)**	**−2.75 (0.08)**	**1.37 (1.16, 1.59)**	**−50 (−58, −42)**	
TOTAL SLOPE						
Diabetes mellitus						
Type 1 diabetes	−11%	−1.14 (0.69)	−3.07 (0.71)	1.93 (−0.01, 3.87)	−63 (−126, 0)	χ^2_2=2.74;
Type 2 diabetes	−47%	−2.03 (0.11)	−2.91 (0.11)	0.87 (0.56, 1.19)	−30 (−41, −19)	p=0.25
No diabetes	−27%	−2.30 (0.10)	−2.92 (0.10)	0.62 (0.33, 0.91)	−21 (−31, −11)	
All participants	**−19%**	**−2.16 (0.08)**	**−2.92 (0.08)**	**0.75 (0.54, 0.96)**	**−26 (−33, −19)**	



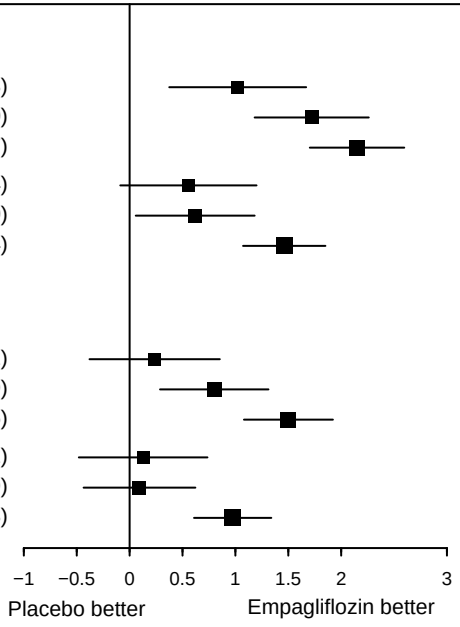
P values for tests of heterogeneity between absolute differences in chronic and total slopes by diabetes status 0.021 and 0.25 respectively.

Webfigure 3: Effect of allocation to empagliflozin on kidney disease progression or death from cardiovascular causes, by expanded eGFR categories

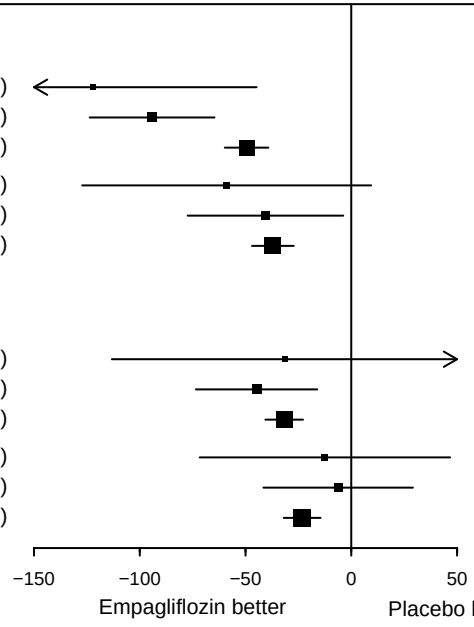


Webfigure 4: Effect of allocation to empagliflozin on 'total slopes' and 'chronic slopes', by diabetes status and uACR

		Mean (SE) slope (mL/min/1.73m²/yr)		Absolute difference (95% CI)	Relative difference, % (95% CI)	Trend test for relative difference
		Empagliflozin	Placebo			
CHRONIC SLOPE						
Diabetes	**uACR**					
Yes	<30	0.19 (0.24)	−0.84 (0.23)	1.02 (0.37, 1.67)	−122 (−199, −45)	χ^2_1=10.64;
Yes	≥ 30 ≤ 300	−0.11 (0.20)	−1.83 (0.20)	1.72 (1.18, 2.26)	−94 (−124, −65)	p=0.0011
Yes	>300	−2.19 (0.16)	−4.34 (0.17)	2.15 (1.70, 2.60)	−50 (−60, −39)	
No	<30	−0.39 (0.23)	−0.94 (0.24)	0.56 (−0.09, 1.20)	−59 (−127, 9)	χ^2_1=0.33;
No	≥ 30 ≤ 300	−0.91 (0.20)	−1.53 (0.20)	0.62 (0.06, 1.18)	−41 (−77, −4)	p=0.57
No	>300	−2.48 (0.14)	−3.94 (0.14)	1.46 (1.07, 1.85)	−37 (−47, −27)	
TOTAL SLOPE						
Diabetes	**uACR**					
Yes	<30	−0.52 (0.23)	−0.75 (0.22)	0.24 (−0.38, 0.85)	−31 (−113, 50)	χ^2_1=0.46;
Yes	≥ 30 ≤ 300	−0.99 (0.18)	−1.79 (0.19)	0.80 (0.29, 1.31)	−45 (−73, −16)	p=0.50
Yes	>300	−3.23 (0.15)	−4.73 (0.16)	1.50 (1.08, 1.92)	−32 (−41, −23)	
No	<30	−0.90 (0.22)	−1.03 (0.22)	0.13 (−0.48, 0.74)	−12 (−72, 47)	χ^2_1=0.70;
No	≥ 30 ≤ 300	−1.40 (0.19)	−1.49 (0.19)	0.09 (−0.44, 0.62)	−6 (−42, 29)	p=0.40
No	>300	−3.22 (0.13)	−4.19 (0.13)	0.97 (0.61, 1.34)	−23 (−32, −15)	



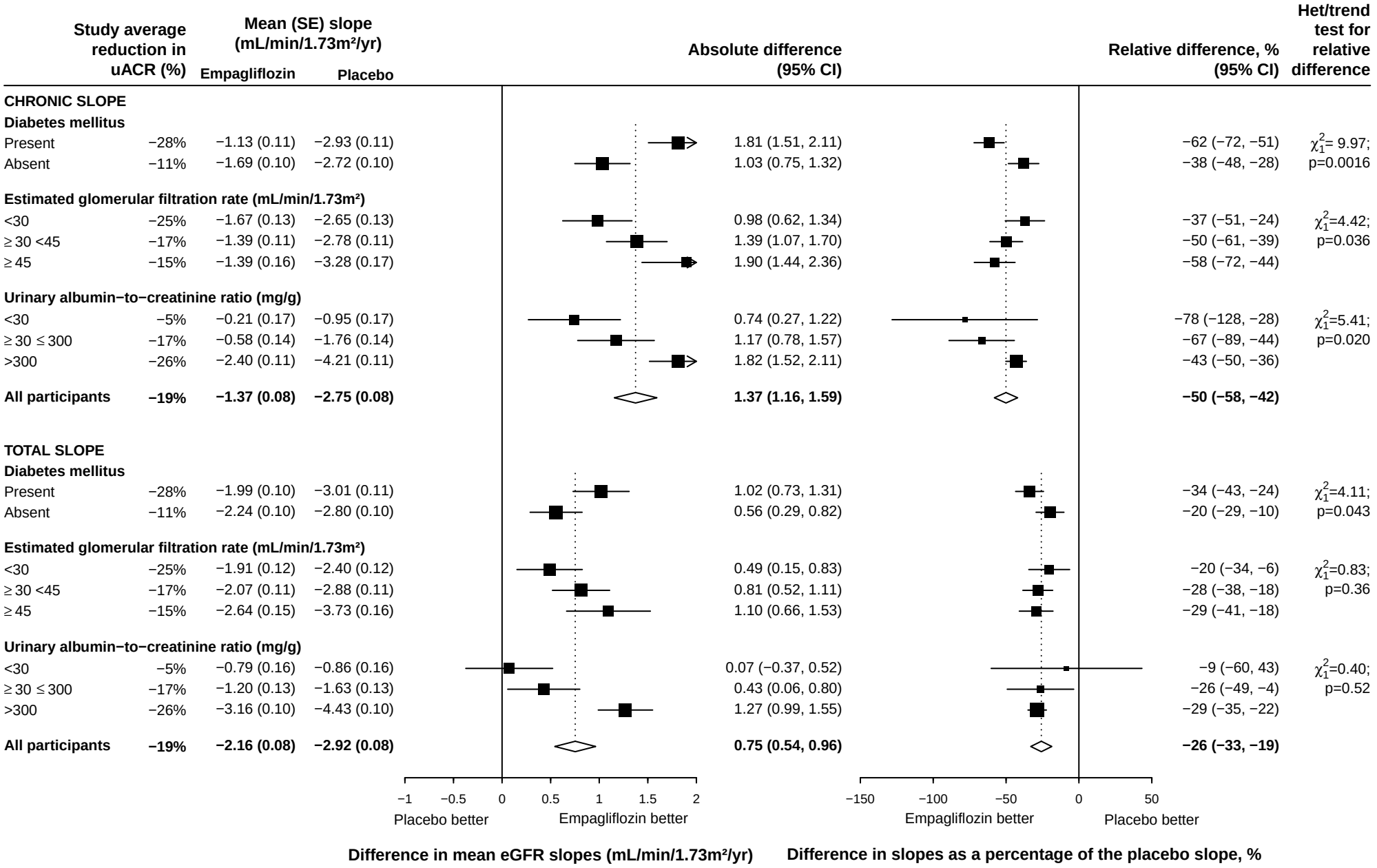
Difference in mean eGFR slopes (mL/min/1.73m²/yr)



Difference in slopes as a percentage of the placebo slope, %

P values for tests for trend in absolute differences in chronic slope across uACR categories among patients with and without diabetes are 0.0053 and 0.0060 respectively. P values for tests for trend in absolute differences in total slope across uACR categories among patients with and without diabetes are 0.0006 and 0.0050 respectively.

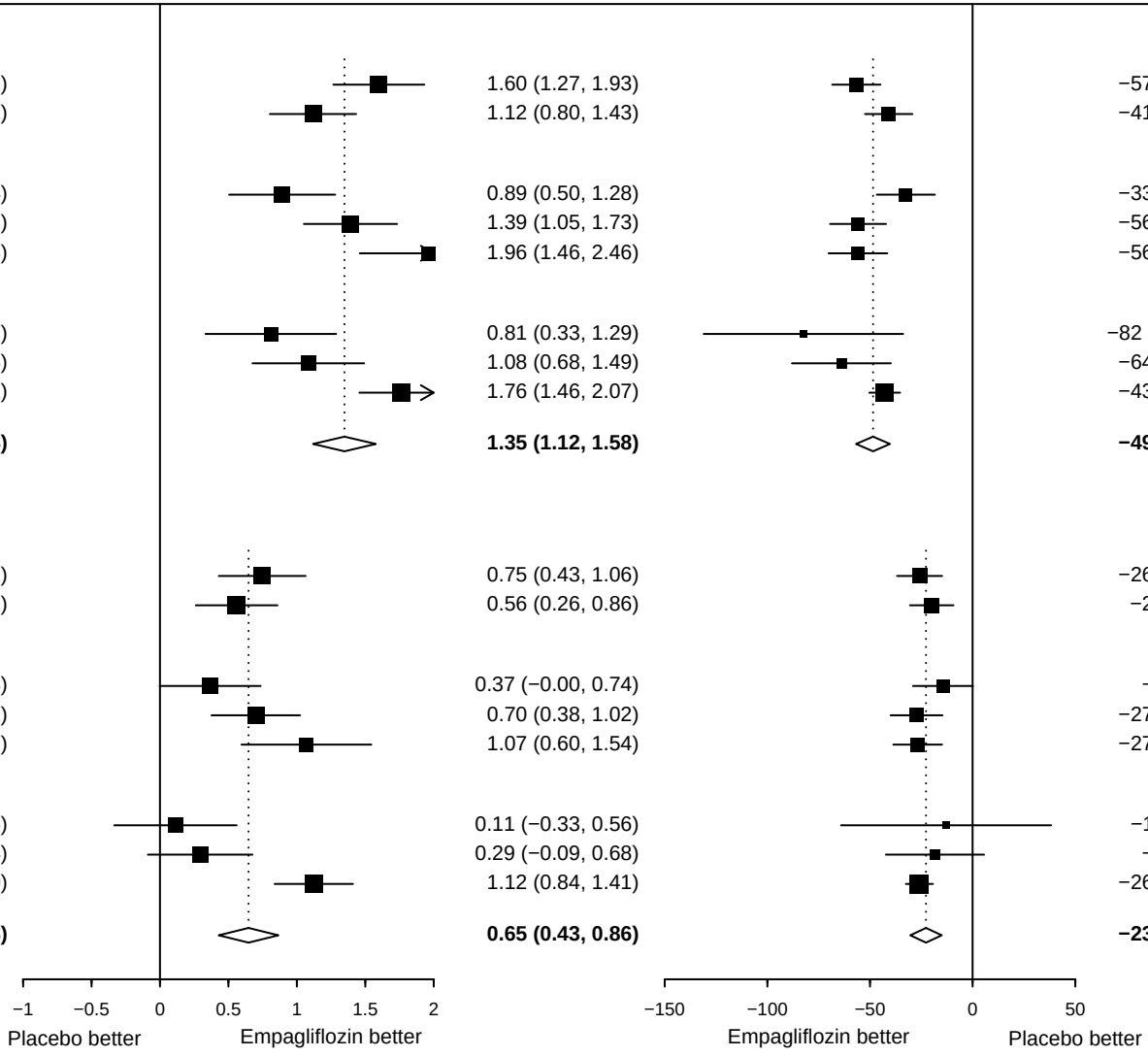
Webfigure 5: Absolute and relative effects of allocation to empagliflozin on 'total slopes' and 'chronic slopes', by key subgroups after including interactions with other key subgroups



P values for test of heterogeneity between absolute differences in chronic slopes for patients with and without diabetes and tests for trend in absolute differences in chronic slope across eGFR and uACR categories are 0.0003, 0.0019 and <0.0001 respectively. P values for test of heterogeneity between absolute differences in total slopes for patients with and without diabetes and tests for trend in absolute differences in total slope across eGFR and uACR categories are 0.021, 0.027 and <0.0001 respectively.

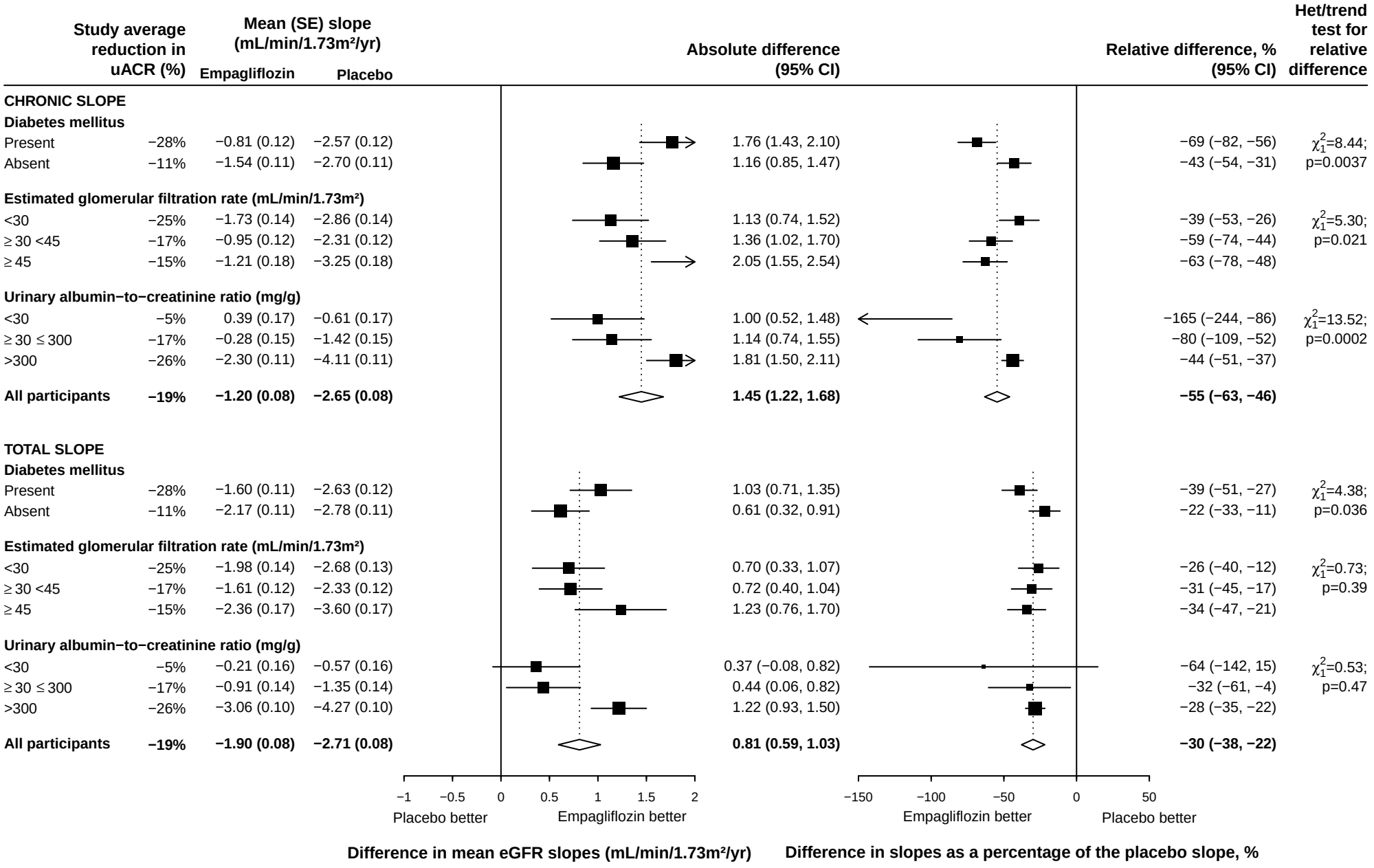
Webfigure 6: Absolute and relative effects of allocation to empagliflozin on 'total slopes' and 'chronic slopes', by key subgroups using on treatment eGFR measurements

	Study average reduction in uACR (%)	Mean (SE) slope (mL/min/1.73m²/yr) Empagliflozin	Placebo	Absolute difference (95% CI)	Relative difference, % (95% CI)	Het/trend test for relative difference
CHRONIC SLOPE						
Diabetes mellitus						
Present	−28%	−1.22 (0.12)	−2.82 (0.12)	1.60 (1.27, 1.93)	−57 (−68, −45)	χ^2_1=3.52;
Absent	−11%	−1.62 (0.11)	−2.73 (0.11)	1.12 (0.80, 1.43)	−41 (−52, −29)	p=0.061
Estimated glomerular filtration rate (mL/min/1.73m²)						
<30	−25%	−1.85 (0.14)	−2.74 (0.14)	0.89 (0.50, 1.28)	−33 (−47, −18)	χ^2_1=5.22;
≥ 30 <45	−17%	−1.10 (0.12)	−2.49 (0.12)	1.39 (1.05, 1.73)	−56 (−69, −42)	p=0.022
≥ 45	−15%	−1.55 (0.18)	−3.51 (0.18)	1.96 (1.46, 2.46)	−56 (−70, −42)	
Urinary albumin−to−creatinine ratio (mg/g)						
<30	−5%	−0.17 (0.17)	−0.98 (0.17)	0.81 (0.33, 1.29)	−82 (−131, −34)	χ^2_1=4.95;
≥ 30 ≤ 300	−17%	−0.61 (0.15)	−1.69 (0.15)	1.08 (0.68, 1.49)	−64 (−88, −40)	p=0.026
>300	−26%	−2.35 (0.11)	−4.12 (0.11)	1.76 (1.46, 2.07)	−43 (−50, −35)	
All participants	**−19%**	**−1.43 (0.08)**	**−2.78 (0.08)**	**1.35 (1.12, 1.58)**	**−49 (−57, −40)**	
TOTAL SLOPE						
Diabetes mellitus						
Present	−28%	−2.14 (0.11)	−2.89 (0.12)	0.75 (0.43, 1.06)	−26 (−37, −15)	χ^2_1=0.59;
Absent	−11%	−2.25 (0.11)	−2.81 (0.11)	0.56 (0.26, 0.86)	−20 (−30, −9)	p=0.44
Estimated glomerular filtration rate (mL/min/1.73m²)						
<30	−25%	−2.16 (0.13)	−2.53 (0.13)	0.37 (−0.00, 0.74)	−14 (−29, 0)	χ^2_1=1.41;
≥ 30 <45	−17%	−1.86 (0.12)	−2.56 (0.12)	0.70 (0.38, 1.02)	−27 (−40, −15)	p=0.24
≥ 45	−15%	−2.93 (0.17)	−4.00 (0.17)	1.07 (0.60, 1.54)	−27 (−39, −15)	
Urinary albumin−to−creatinine ratio (mg/g)						
<30	−5%	−0.76 (0.16)	−0.87 (0.16)	0.11 (−0.33, 0.56)	−13 (−64, 38)	χ^2_1=0.58;
≥ 30 ≤ 300	−17%	−1.30 (0.14)	−1.60 (0.14)	0.29 (−0.09, 0.68)	−18 (−42, 6)	p=0.45
>300	−26%	−3.21 (0.10)	−4.34 (0.10)	1.12 (0.84, 1.41)	−26 (−33, −19)	
All participants	**−19%**	**−2.20 (0.08)**	**−2.85 (0.08)**	**0.65 (0.43, 0.86)**	**−23 (−30, −15)**	



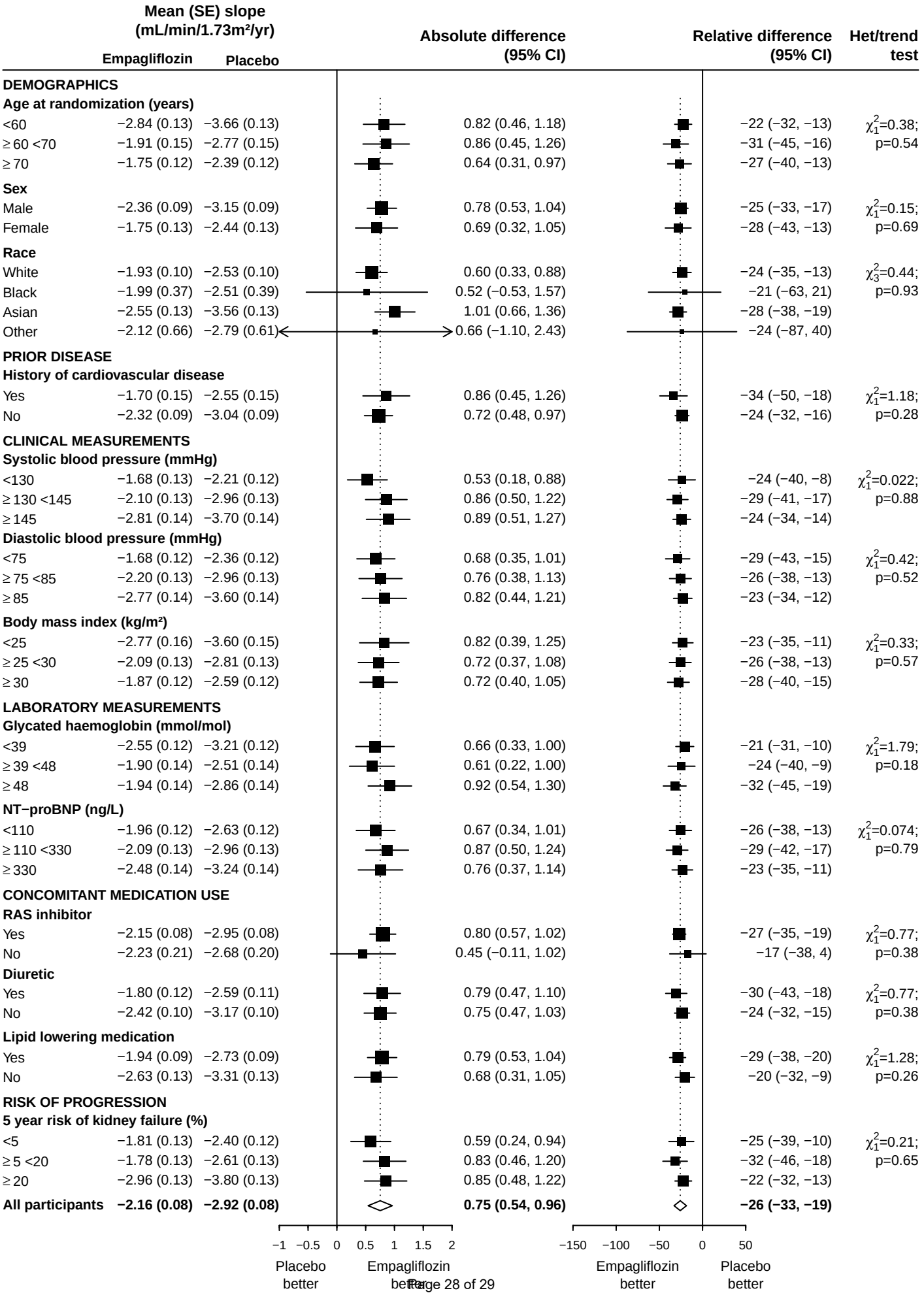
P values for test of heterogeneity between absolute differences in chronic slopes for patients with and without diabetes and tests for trend in absolute differences in chronic slope across eGFR and uACR categories are 0.039, 0.0009 and 0.0003 respectively. P values for test of heterogeneity between absolute differences in total slopes for patients with and without diabetes and tests for trend in absolute differences in total slope across eGFR and uACR categories are 0.40, 0.021 and <0.0001 respectively.

Webfigure 7: Absolute and relative effects of allocation to empagliflozin on 'total slopes' and 'chronic slopes' , by key subgroups using local creatinine values

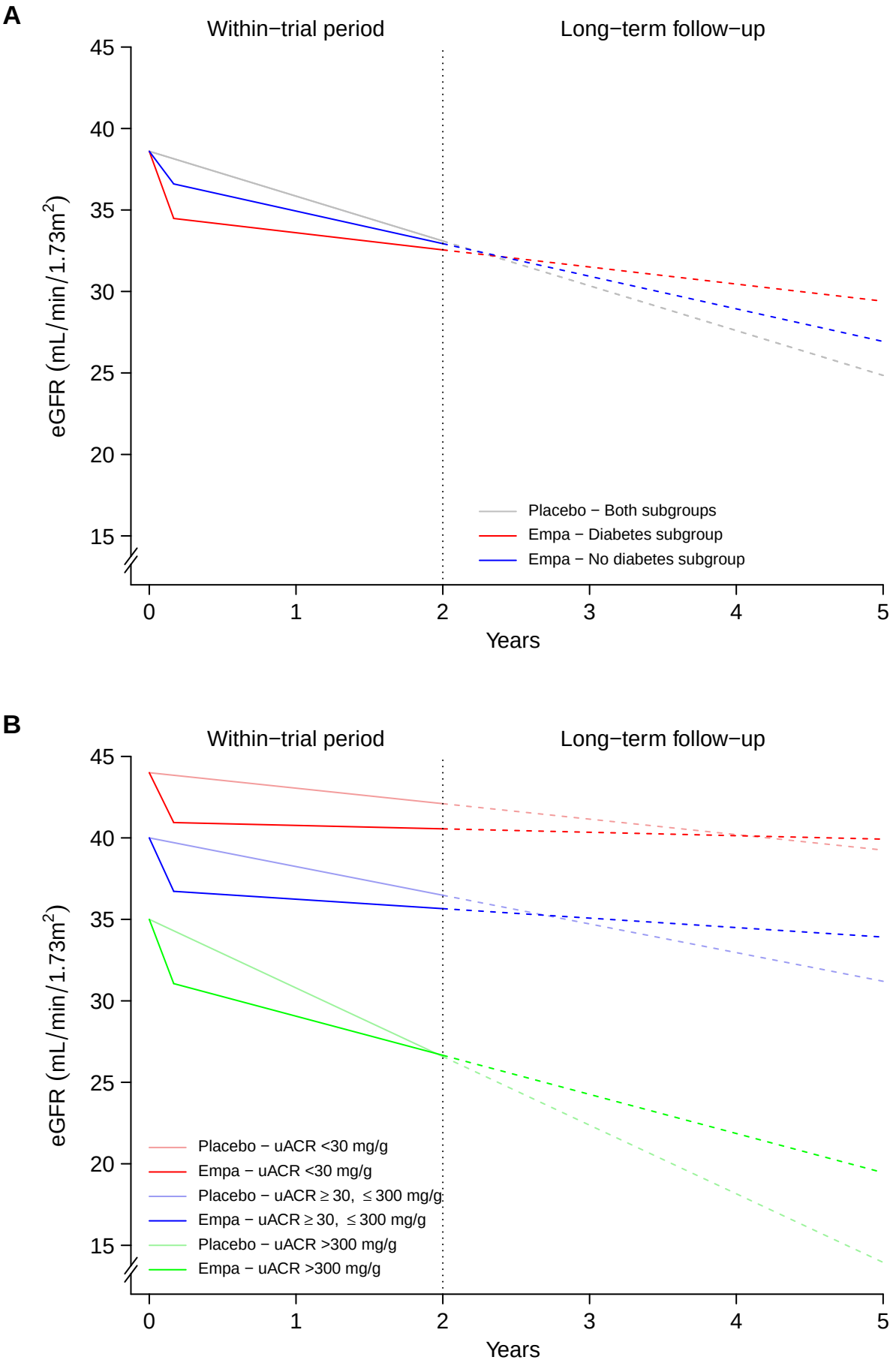


P values for test of heterogeneity between absolute differences in chronic slopes for patients with and without diabetes and tests for trend in absolute differences in chronic slope across eGFR and uACR categories are 0.0093, 0.0064 and 0.0017 respectively. P values for test of heterogeneity between absolute differences in total slopes for patients with and without diabetes and tests for trend in absolute differences in total slope across eGFR and uACR categories are 0.059, 0.11 and 0.0003 respectively.

Webfigure 8: Effect of allocation to empagliflozin on 'total slopes', by other subgroups



Webfigure 9: Scenarios illustrating the benefits of focussing on chronic slopes in subgroups



In panel A, the magnitude of the acute dip correlates with the relative reduction in chronic slope (which is plausible as they share causal mechanisms such as reduced intraglomerular pressure), which compresses variation in total slope when measured over 2−3 years. Chronic slopes estimated for the within−trial period are more informative about long term differences in progression rates, which only become apparent for total slope with longer follow−up. Panel B shows the time taken for benefits of treatment to emerge within uACR subgroups progressing at different rates. Note that values used in this figure are for illustrative purposes and so do not match values observed in the trial.