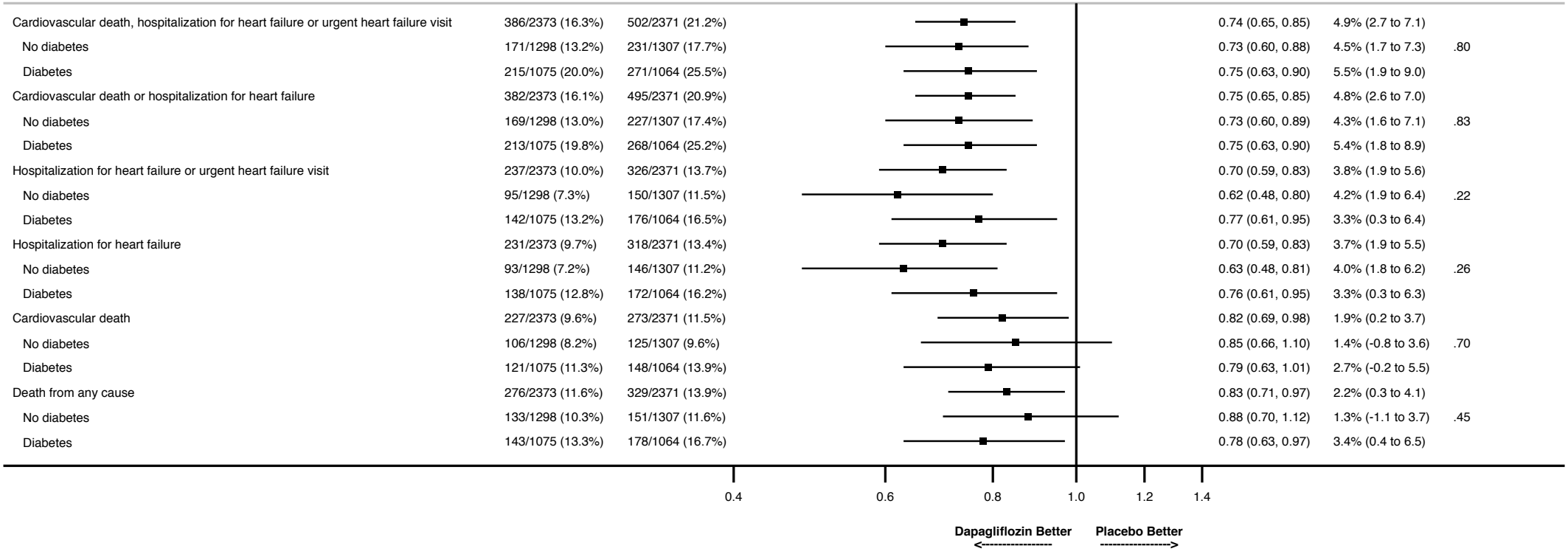
Supplementary Online Content

Petrie MC, Verma S, Docherty KF, et al. Effect of dapagliflozin on worsening heart failure and cardiovascular death in patients with heart failure with and without diabetes. *JAMA*. Published online March 27, 2020. doi:10.1001/jama.2020.1906

This supplementary material has been provided by the authors to give readers additional information about their work.

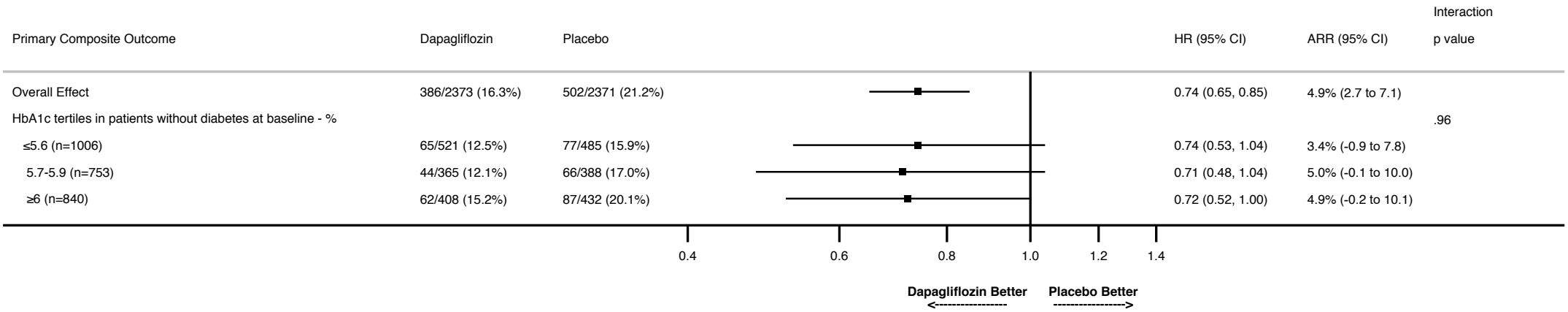
eFigure 1. Primary and secondary cardiovascular endpoints in the overall population and according to diabetes status

Outcome	Dapagliflozin	Placebo	HR (95% CI)	ARR (95% CI)	Interaction p value
Cardiovascular death, hospitalization for heart failure or urgent heart failure visit	386/2373 (16.3%)	502/2371 (21.2%)	0.74 (0.65, 0.85)	4.9% (2.7 to 7.1)	
No diabetes	171/1298 (13.2%)	231/1307 (17.7%)	0.73 (0.60, 0.88)	4.5% (1.7 to 7.3)	.80
Diabetes	215/1075 (20.0%)	271/1064 (25.5%)	0.75 (0.63, 0.90)	5.5% (1.9 to 9.0)	
Cardiovascular death or hospitalization for heart failure	382/2373 (16.1%)	495/2371 (20.9%)	0.75 (0.65, 0.85)	4.8% (2.6 to 7.0)	
No diabetes	169/1298 (13.0%)	227/1307 (17.4%)	0.73 (0.60, 0.89)	4.3% (1.6 to 7.1)	.83
Diabetes	213/1075 (19.8%)	268/1064 (25.2%)	0.75 (0.63, 0.90)	5.4% (1.8 to 8.9)	
Hospitalization for heart failure or urgent heart failure visit	237/2373 (10.0%)	326/2371 (13.7%)	0.70 (0.59, 0.83)	3.8% (1.9 to 5.6)	
No diabetes	95/1298 (7.3%)	150/1307 (11.5%)	0.62 (0.48, 0.80)	4.2% (1.9 to 6.4)	.22
Diabetes	142/1075 (13.2%)	176/1064 (16.5%)	0.77 (0.61, 0.95)	3.3% (0.3 to 6.4)	
Hospitalization for heart failure	231/2373 (9.7%)	318/2371 (13.4%)	0.70 (0.59, 0.83)	3.7% (1.9 to 5.5)	
No diabetes	93/1298 (7.2%)	146/1307 (11.2%)	0.63 (0.48, 0.81)	4.0% (1.8 to 6.2)	.26
Diabetes	138/1075 (12.8%)	172/1064 (16.2%)	0.76 (0.61, 0.95)	3.3% (0.3 to 6.3)	
Cardiovascular death	227/2373 (9.6%)	273/2371 (11.5%)	0.82 (0.69, 0.98)	1.9% (0.2 to 3.7)	
No diabetes	106/1298 (8.2%)	125/1307 (9.6%)	0.85 (0.66, 1.10)	1.4% (-0.8 to 3.6)	.70
Diabetes	121/1075 (11.3%)	148/1064 (13.9%)	0.79 (0.63, 1.01)	2.7% (-0.2 to 5.5)	
Death from any cause	276/2373 (11.6%)	329/2371 (13.9%)	0.83 (0.71, 0.97)	2.2% (0.3 to 4.1)	
No diabetes	133/1298 (10.3%)	151/1307 (11.6%)	0.88 (0.70, 1.12)	1.3% (-1.1 to 3.7)	.45
Diabetes	143/1075 (13.3%)	178/1064 (16.7%)	0.78 (0.63, 0.97)	3.4% (0.4 to 6.5)	

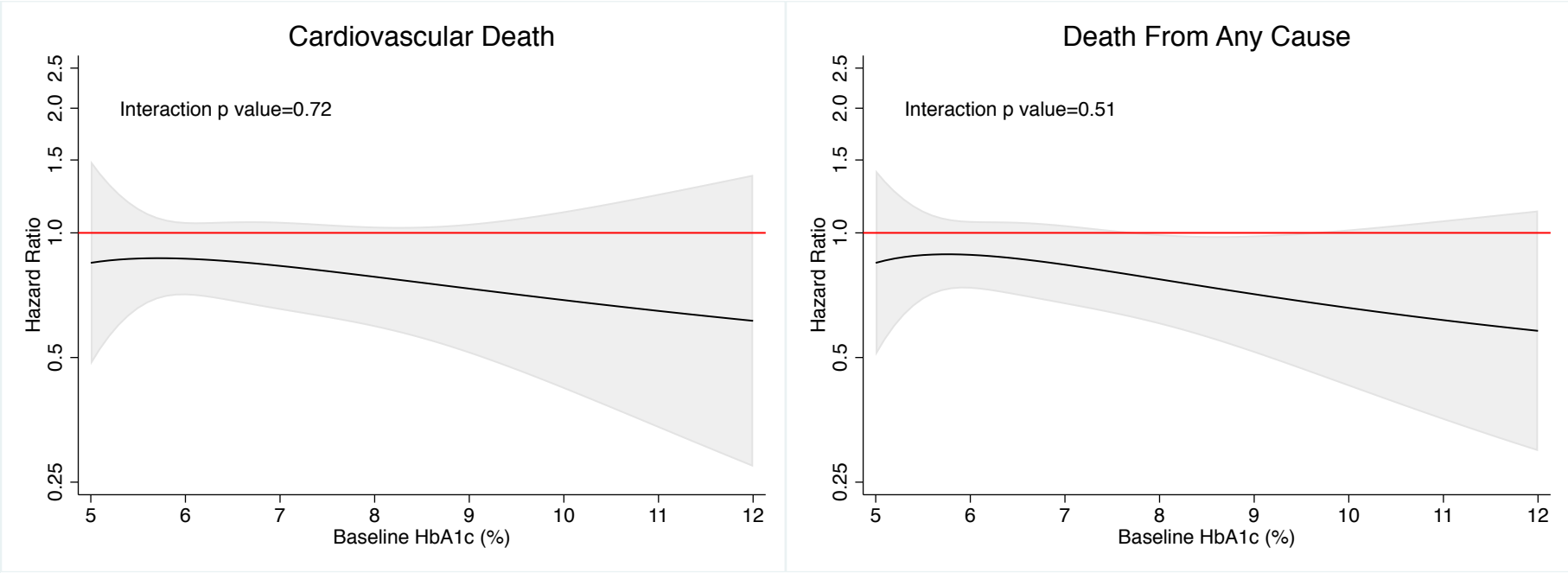


ARR, absolute risk reduction; CI, confidence intervals; HR, hazard ratio.

eFigure 2. Exploratory analysis of the primary composite outcome by tertile of glycated haemoglobin in those without diabetes at baseline

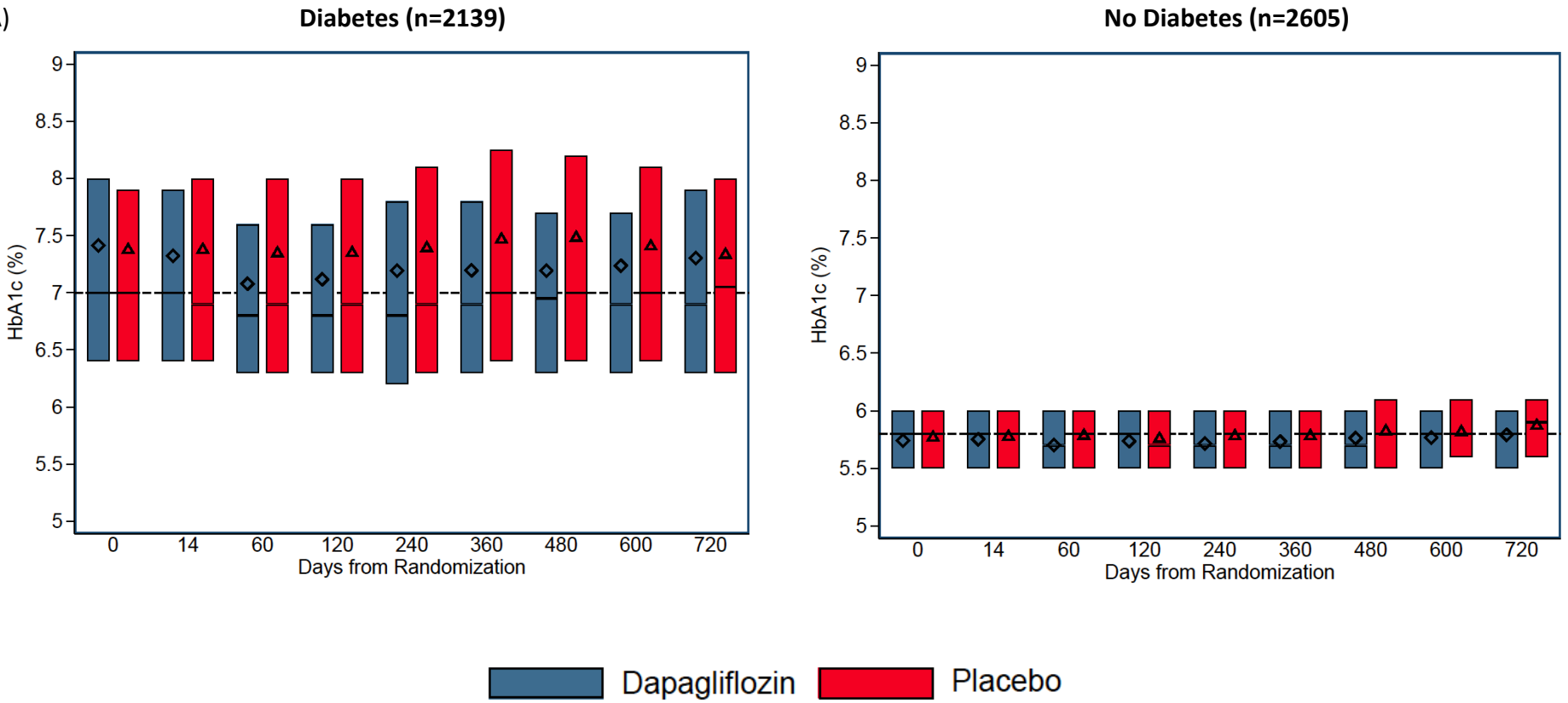


eFigure 3. Effect of dapagliflozin, compared with placebo on cardiovascular death and death from any cause according to baseline glycated haemoglobin as a continuous variable.

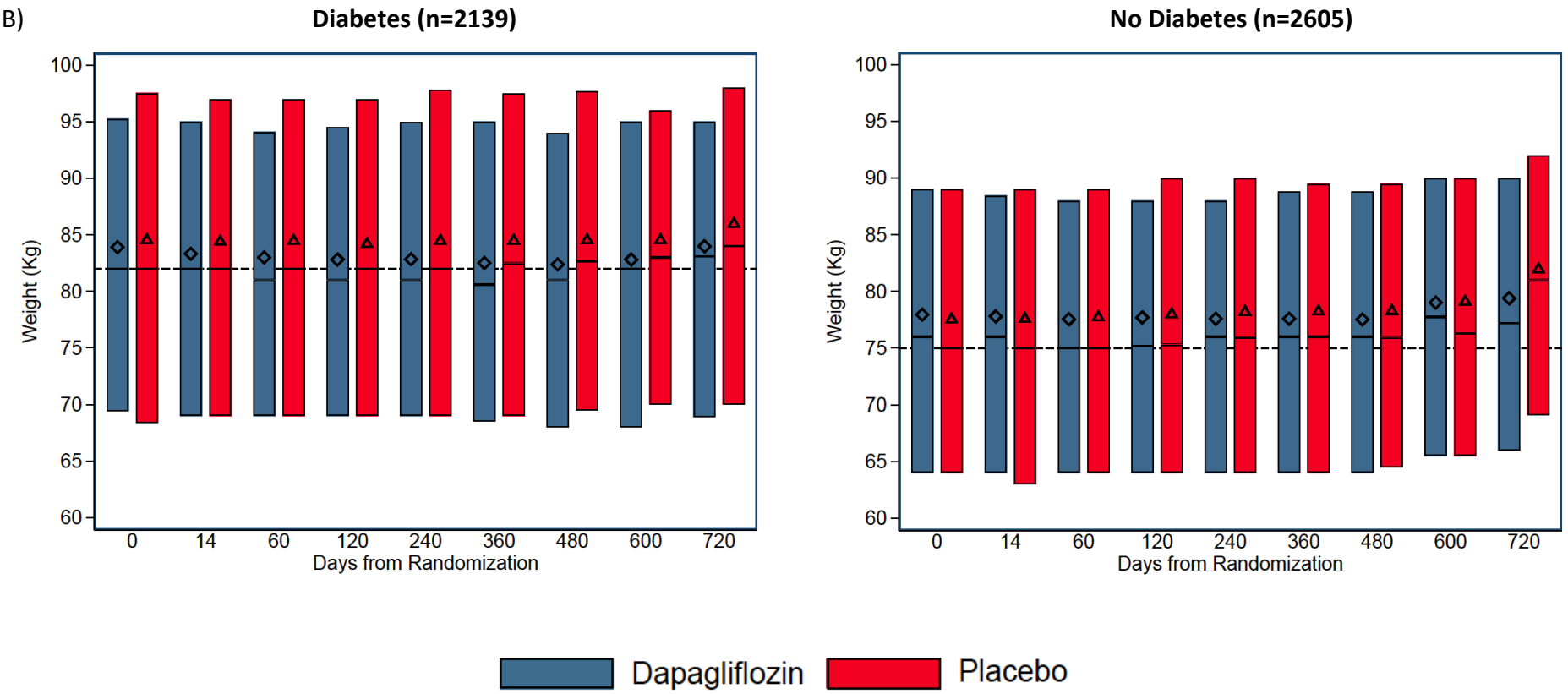


eFigure 4: Boxplot of laboratory measurements and vital signs by diabetes status over time

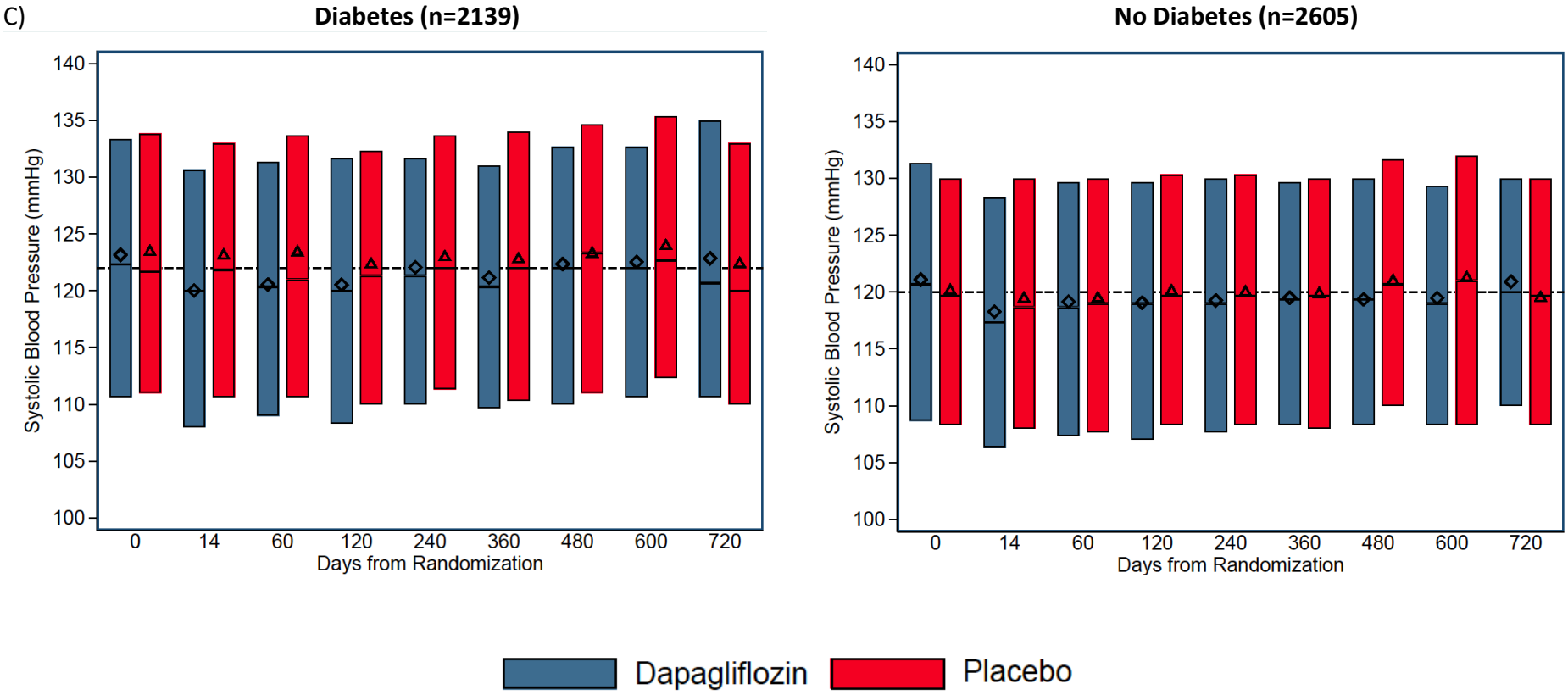
Panel A) Glycated haemoglobin; B) Weight; C) Systolic blood pressure; D) Estimated glomerular filtration rate; E) Hematocrit.
The diamonds and triangles indicate the unadjusted mean, the solid lines indicate the median (Q1, Q3), and the dashed lines indicate the median value at baseline.



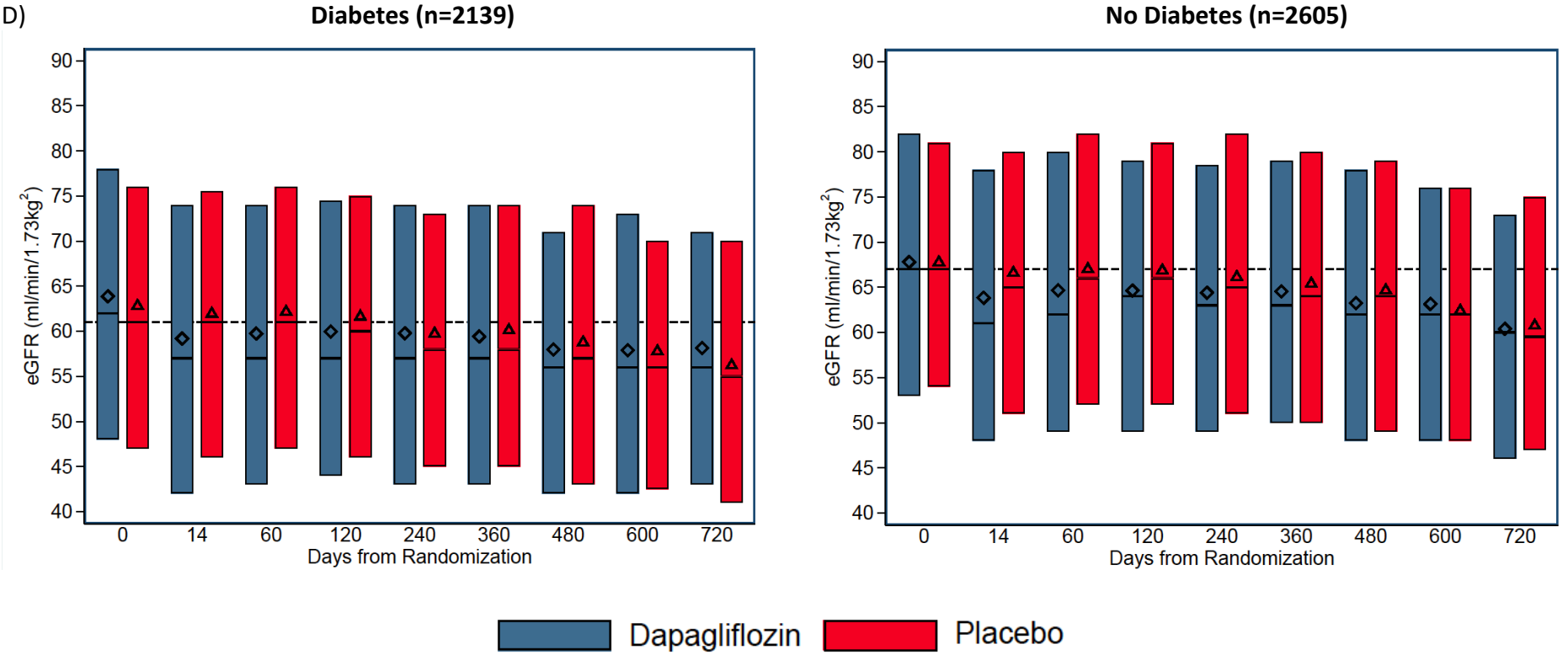
B)



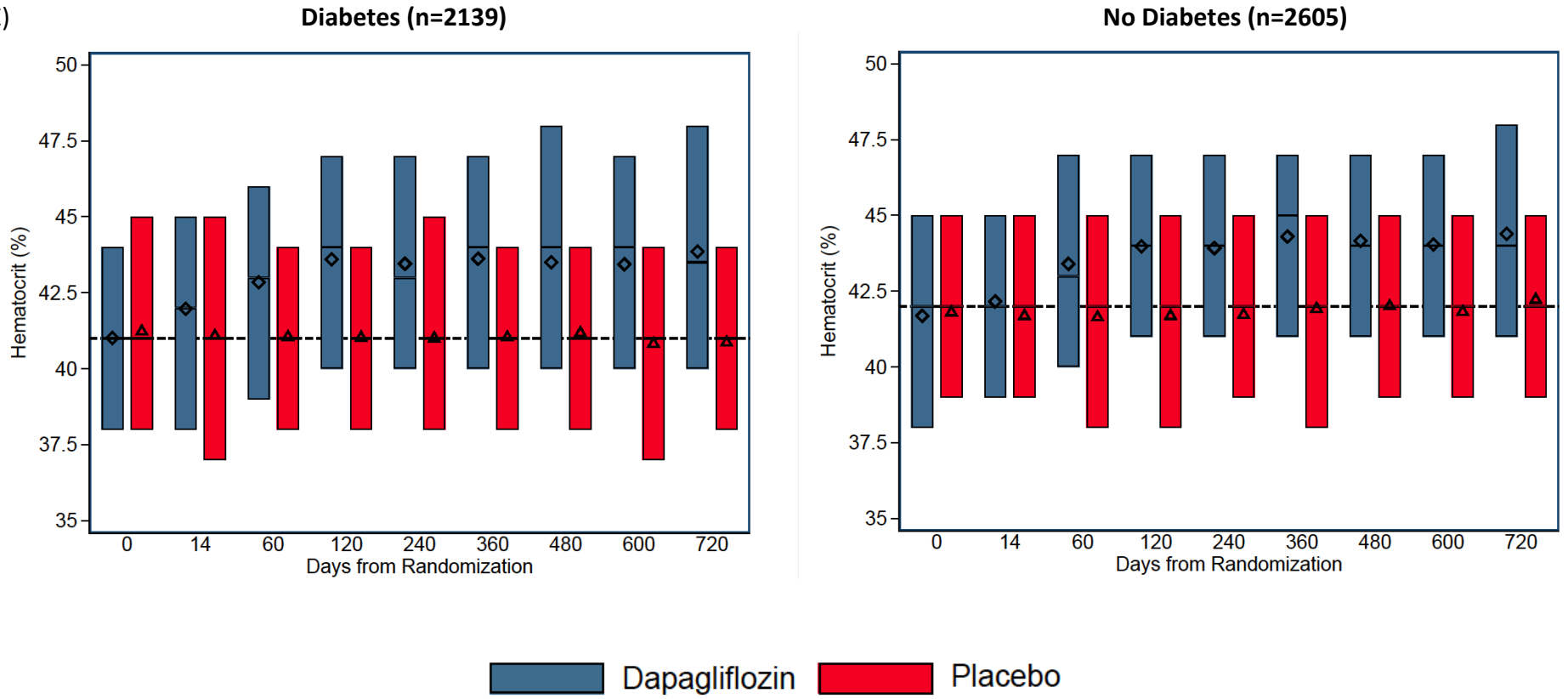
C)



D)



E)



eTable 1: Treatment effect of dapagliflozin versus placebo in patients with and without diabetes at baseline – sensitivity analysis accounting for trial site

Outcome	Hazard ratio (95% CI)	Interaction P Value
Efficacy Outcomes		
Cardiovascular death, hospitalization for heart failure or an urgent heart failure visit*		
No diabetes (n=2605)	0.72 (0.58 to 0.90); p=.004	.96
Diabetes (n=2139)	0.76 (0.62 to 0.92); p=.006	
Hospitalization for heart failure or an urgent heart failure visit		
No diabetes (n=2605)	0.56 (0.42 to 0.75); p<.001	1.0
Diabetes (n=2139)	0.76 (0.60 to 0.98); p=.034	
Hospitalization for heart failure		
No diabetes (n=2605)	0.57 (0.43 to 0.77); p<.001	1.0
Diabetes (n=2139)	0.77 (0.60 to 0.98); p=.036	
Urgent heart failure visit		
No diabetes (n=2605)	0.11 (0.02 to 0.55); p=.007	1.0
Diabetes (n=2139)	0.40 (0.14 to 1.15); p=.088	
Cardiovascular Death		
No diabetes (n=2605)	0.88 (0.66 to 1.17); p=.38	.64
Diabetes (n=2139)	0.80 (0.61 to 1.04); p=.09	
Secondary Outcomes		
Cardiovascular death or hospitalization for heart failure		
No diabetes (n=2605)	0.74 (0.59 to 0.92); p=.007	.98
Diabetes (n=2139)	0.76 (0.62 to 0.93); p=.007	
Death from any cause		
No diabetes (n=2605)	0.92 (0.71 to 1.19); p=.52	.41
Diabetes (n=2139)	0.78 (0.61 to 0.99); p=.043	
Worsening kidney function†		
No diabetes (n=2605)	0.89 (0.34 to 2.36); p=.82	.1.0
Diabetes (n=2139)	0.72 (0.37 to 1.40); p=.33	

C.I. = confidence interval.
*Analyzed as time-to-first occurrence of any of these events; an urgent visit was one in which intravenous therapy for heart failure was administered.
Hazard ratios and 95% confidence intervals were estimated with the use of Cox regression models, with a history of hospitalization for heart failure, treatment-group assignment and trial site as explanatory variables.
†Worsening renal function – composite outcome analyzed as time-to-first occurrence of 50% or greater reduction in eGFR sustained for at least 28 days, endstage renal disease (ESRD) or death from renal causes. ESRD consisted of eGFR below 15 ml/min/1.73m^2 sustained for at least 28 days, chronic dialysis treatment (sustained for at least 28 days) or kidney transplantation.