

DECLARE – TIMI 58

Efficacy and safety of dapagliflozin in the elderly population

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55th Annual Meeting

European Association for the Study of Diabetes
Barcelona, 2019.



Background

- Type 2 Diabetes Mellitus (T2DM) is a prevalent disorder in the elderly with approximately one quarter of people age >65 with diabetes
- Limited therapeutic experience and insufficient long-term safety data in very elderly patients, age ≥ 75 years, led some authorities not to recommend initiation of SGLT2i therapy at this age.
- The DECLARE TIMI-58 study included 7907 elderly patients (age ≥ 65) of whom 1096 were very elderly (≥ 75 years).
- We studied the efficacy and safety of dapagliflozin in elderly and very elderly patients with diabetes

Baseline characteristics

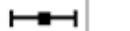
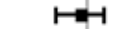
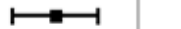
Characteristic	Age < 65	Age ≥65-<75	Age ≥75	P-Trend
	(N = 9253)	(N = 6811)	(N = 1096)	
Duration of diabetes (years), Median (IQR)	10.0/9251 (5.0, 15.0)	12.0 (7.0, 18.0)	14.0 (8.0, 20.0)	<.0001
Male Sex, N (%)	6203 (67.0)	3873 (56.9)	662 (60.4)	<.0001
White, N (%)	7052 (76.2)	5639 (82.8)	962 (87.8)	<.0001
Black, N (%)	351 (3.8)	222 (3.3)	30 (2.7)	0.0203
Asian, N (%)	1493 (16.1)	727 (10.7)	83 (7.6)	<.0001
BMI, Median (IQR)	31.6/9249 (28.0, 35.9)	31.1/6807 (27.8, 35.0)	30.2/1095 (27.4, 33.9)	<.0001
Established ASCVD N (%)	3973 (42.9)	2519 (37.0)	482 (44.0)	<.0001
History of HF, N (%)	886 (9.6)	682 (10.0)	156 (14.2)	0.0002
eGFR, Median (IQR)	94.0/9252 (81.0, 100.0)	84.0 (70.0, 92.0)	75.0 (64.0, 84.0)	<.0001
HbA1c, Median (IQR)	8.2/9251 (7.5, 9.3)	7.9/6809 (7.3, 8.7)	7.8/1094 (7.2, 8.5)	<.0001

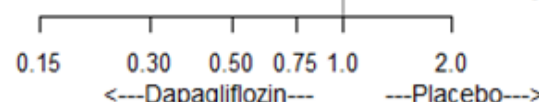
Baseline characteristics

Characteristic	Age < 65	Age ≥65-<75	Age ≥75	P-Trend
	(N = 9253)	(N = 6811)	(N = 1096)	
Metformin, N (%)	7702 (83.2)	5572 (81.8)	794 (72.4)	<.0001
SU, N (%)	3962 (42.8)	2882 (42.3)	478 (43.6)	0.9301
Insulin, N (%)	3779 (40.8)	2805 (41.2)	429 (39.1)	0.6789
Statin, N (%)	6772 (73.2)	5164 (75.8)	823 (75.1)	0.001
ACE Inhibitor/ARB, N (%)	7404 (80.0)	5629 (82.6)	917 (83.7)	<.0001
Any diuretics, N (%)	3453 (37.3)	3000 (44.0)	514 (46.9)	<.0001
Diuretics - loops, N (%)	832 (9.0)	791 (11.6)	183 (16.7)	<.0001
Antiplatelet Therapy, N (%)	5605 (60.6)	4171 (61.2)	711 (64.9)	0.0203
Beta Blockers, N (%)	4854 (52.5)	3570 (52.4)	606 (55.3)	0.2689

Cardiovascular and renal efficacy

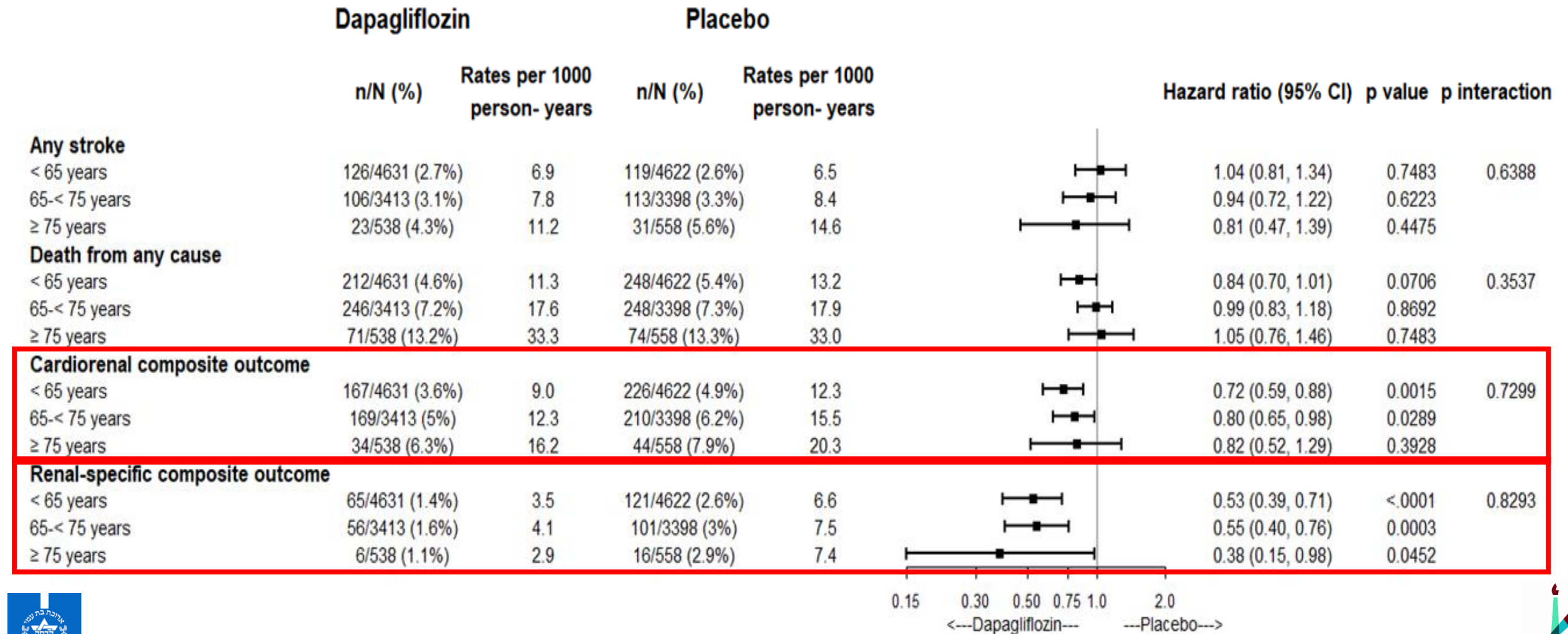
Efficacy outcomes

	Dapagliflozin		Placebo			Hazard ratio (95% CI) p value p interaction		
	n/N (%)	Rates per 1000 person- years	n/N (%)	Rates per 1000 person- years				
CVD / HHF								
< 65 years	189/4631 (4.1%)	10.2	211/4622 (4.6%)	11.6		0.88 (0.72, 1.07)	0.1902	0.5277
65-< 75 years	176/3413 (5.2%)	12.8	225/3398 (6.6%)	16.7		0.77 (0.63, 0.94)	0.0099	
≥ 75 years	52/538 (9.7%)	25.2	60/558 (10.8%)	28.2		0.94 (0.65, 1.36)	0.7330	
MACE								
< 65 years	366/4631 (7.9%)	20.3	385/4622 (8.3%)	21.5		0.93 (0.81, 1.08)	0.3478	0.7352
65-< 75 years	323/3413 (9.5%)	24.2	332/3398 (9.8%)	25.2		0.97 (0.83, 1.13)	0.6509	
≥ 75 years	67/538 (12.5%)	33.2	86/558 (15.4%)	41.4		0.84 (0.61, 1.15)	0.2722	
CVD								
< 65 years	102/4631 (2.2%)	5.4	109/4622 (2.4%)	5.8		0.92 (0.70, 1.21)	0.5460	0.7953
65-< 75 years	115/3413 (3.4%)	8.2	111/3398 (3.3%)	8.0		1.03 (0.79, 1.34)	0.8238	
≥ 75 years	28/538 (5.2%)	13.1	29/558 (5.2%)	12.9		1.06 (0.63, 1.78)	0.8315	
HHF								
< 65 years	102/4631 (2.2%)	5.5	113/4622 (2.4%)	6.2		0.88 (0.68, 1.15)	0.3624	0.1402
65-< 75 years	81/3413 (2.4%)	5.9	133/3398 (3.9%)	9.9		0.60 (0.46, 0.79)	0.0003	
≥ 75 years	29/538 (5.4%)	14.1	40/558 (7.2%)	18.8		0.81 (0.50, 1.30)	0.3768	
Myocardial infarction								
< 65 years	199/4631 (4.3%)	11.0	227/4622 (4.9%)	12.6		0.86 (0.71, 1.04)	0.1205	0.8621
65-< 75 years	162/3413 (4.7%)	12.0	173/3398 (5.1%)	13.0		0.93 (0.75, 1.15)	0.5139	
≥ 75 years	32/538 (5.9%)	15.7	41/558 (7.3%)	19.3		0.85 (0.54, 1.36)	0.5020	



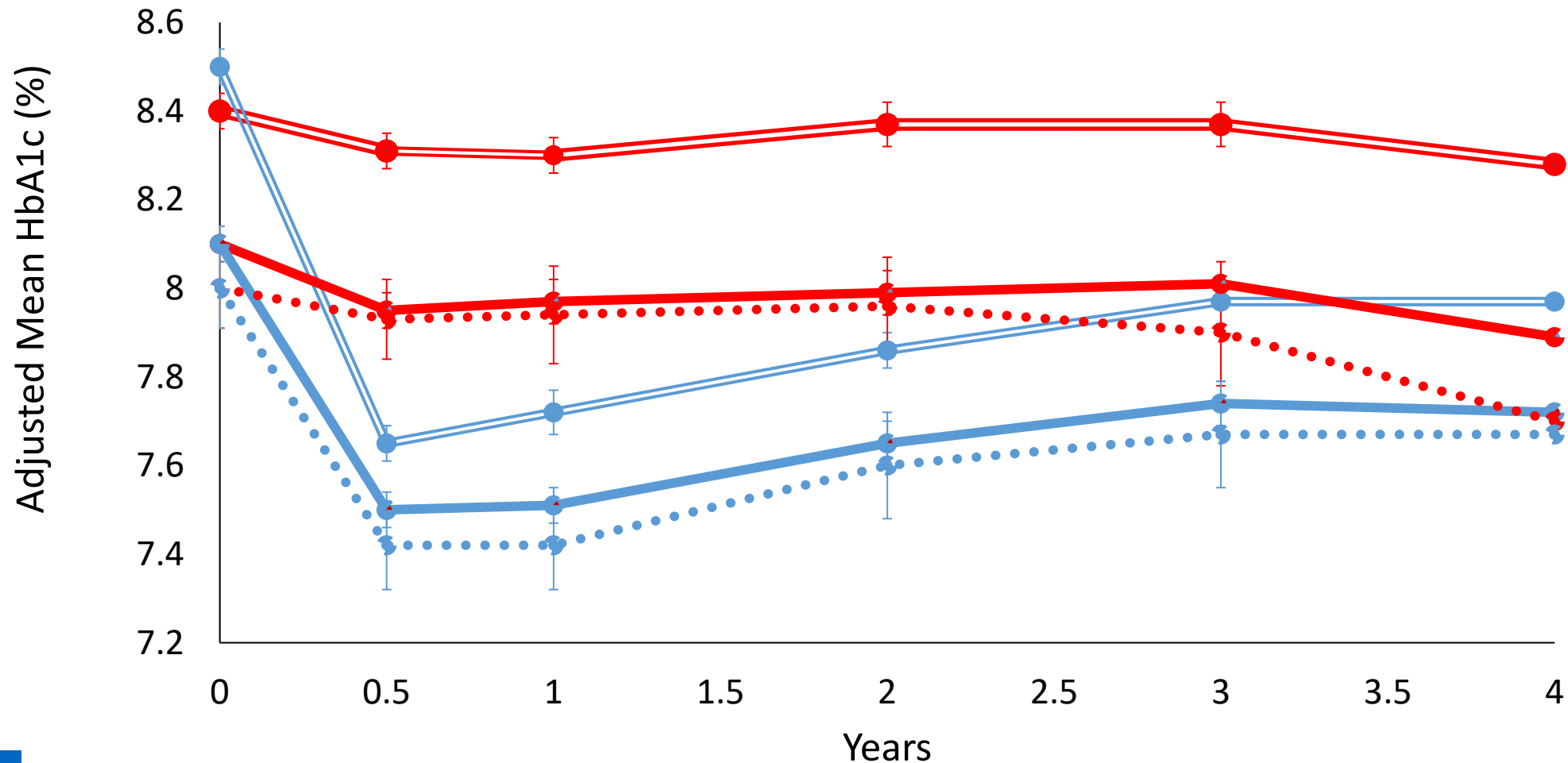
0.15 0.30 0.50 0.75 1.0 2.0
---Dapagliflozin--- ---Placebo---

Efficacy outcomes

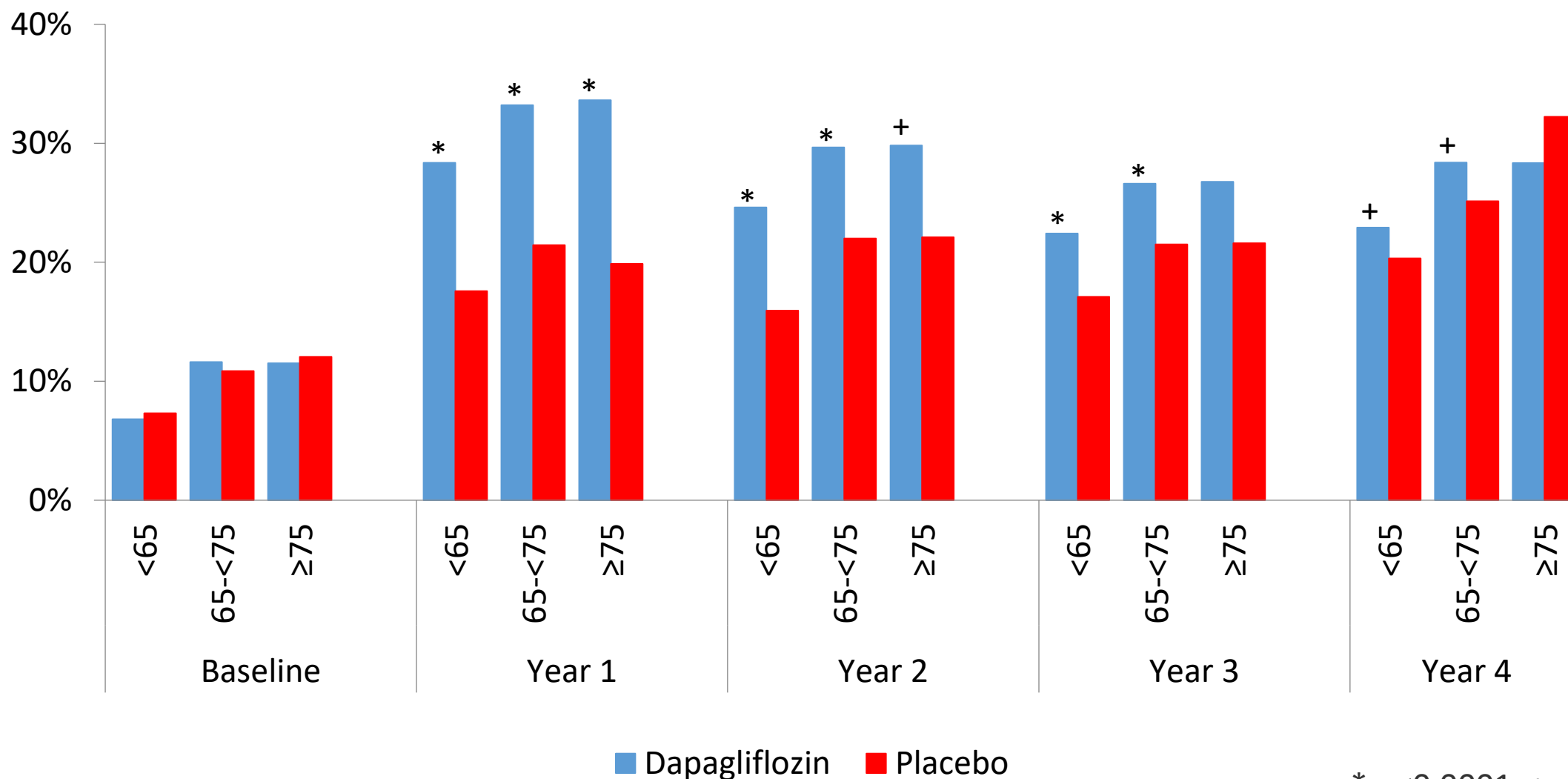


Metabolic efficacy

HbA1c changes in the age groups

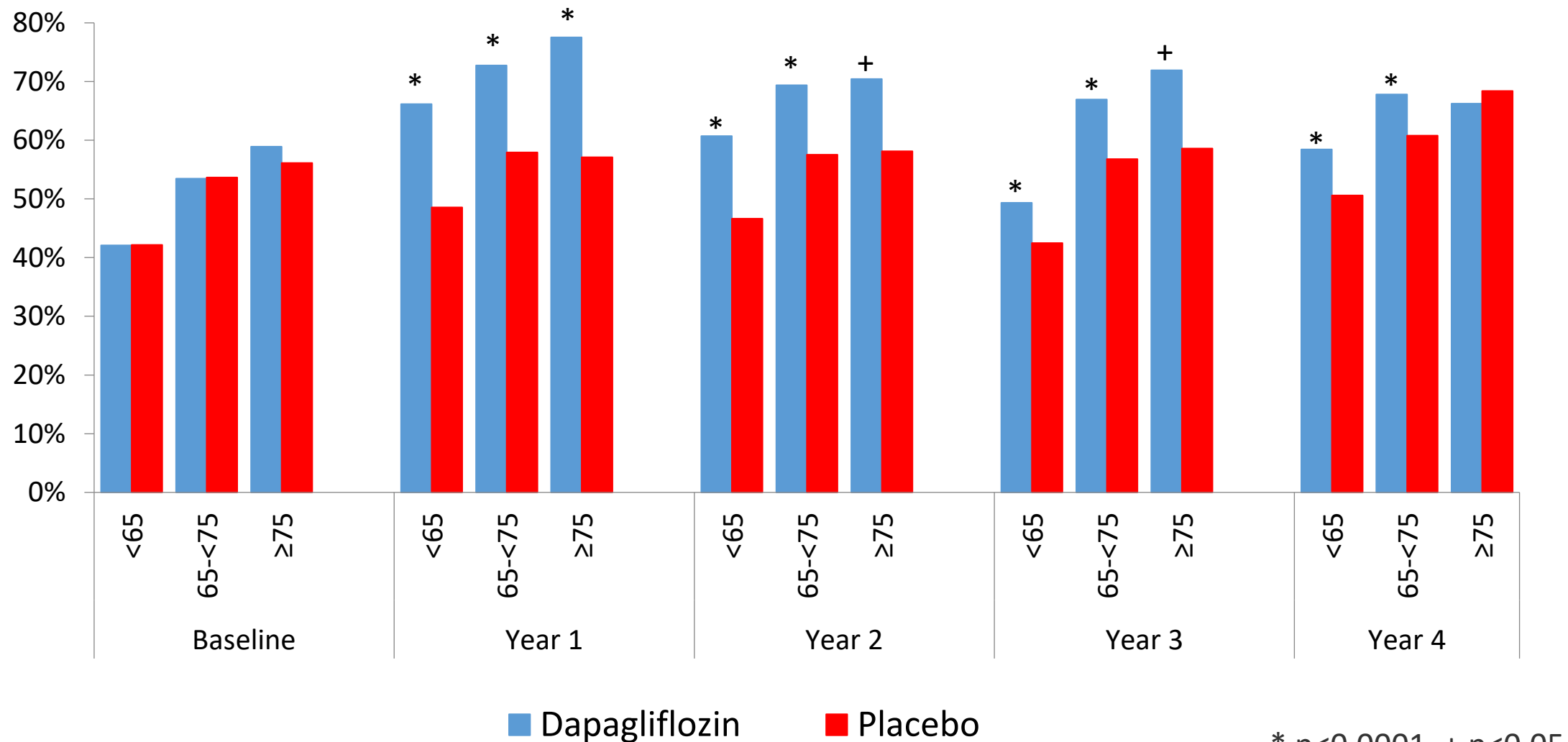


HbA1c <7% with dapagliflozin vs. placebo

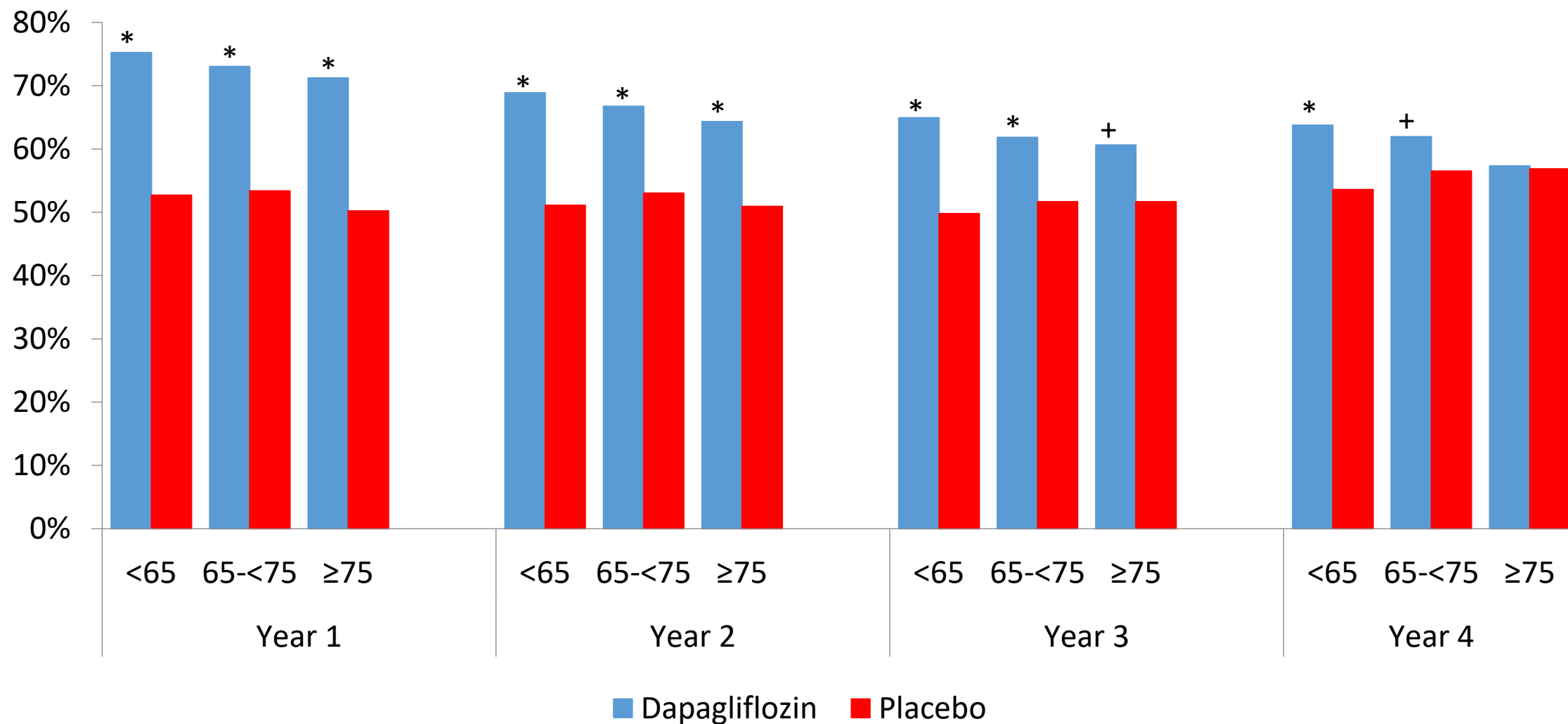


* p<0.0001, + p<0.05

HbA1c <8% with dapagliflozin vs. placebo

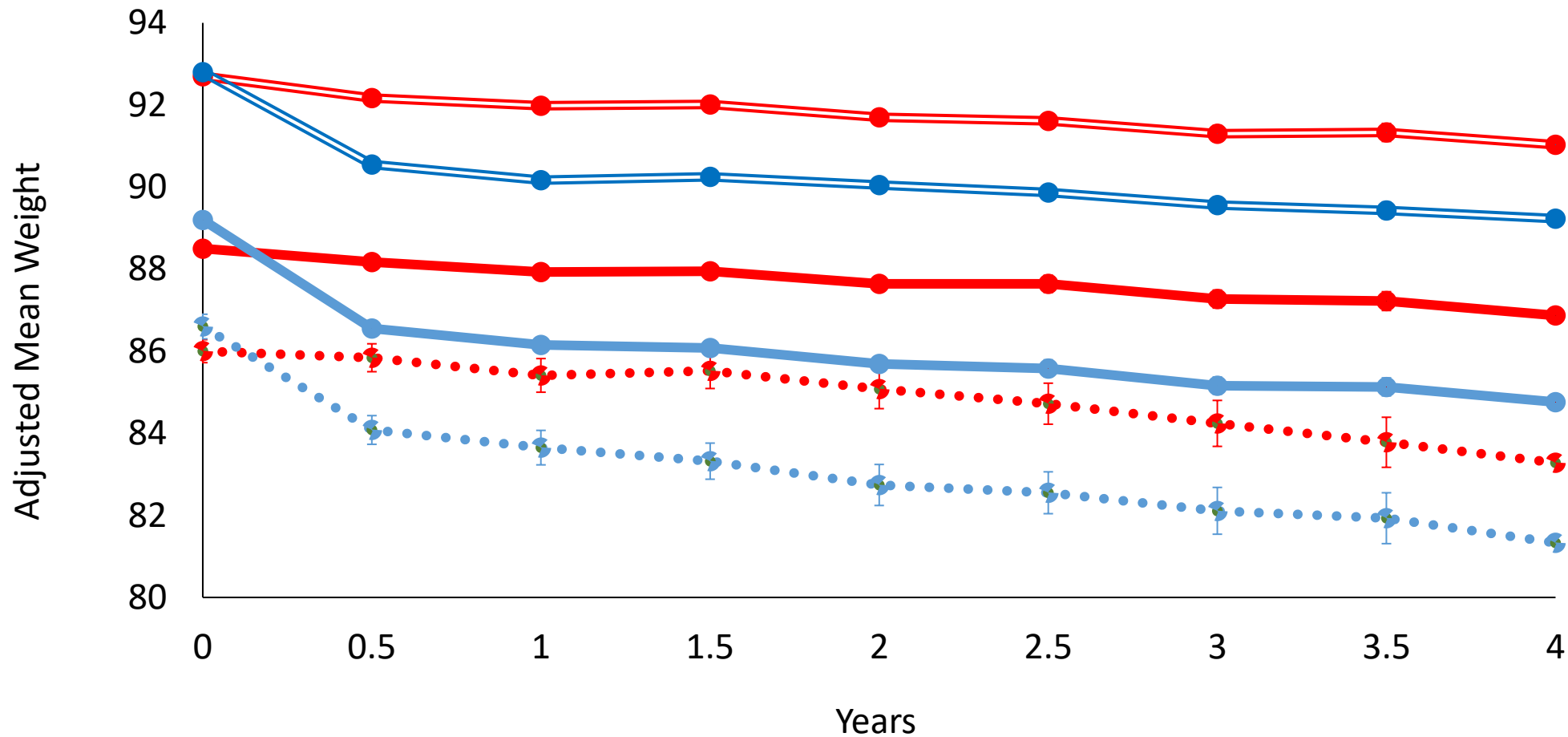


Decline of <0.5% in HbA1c

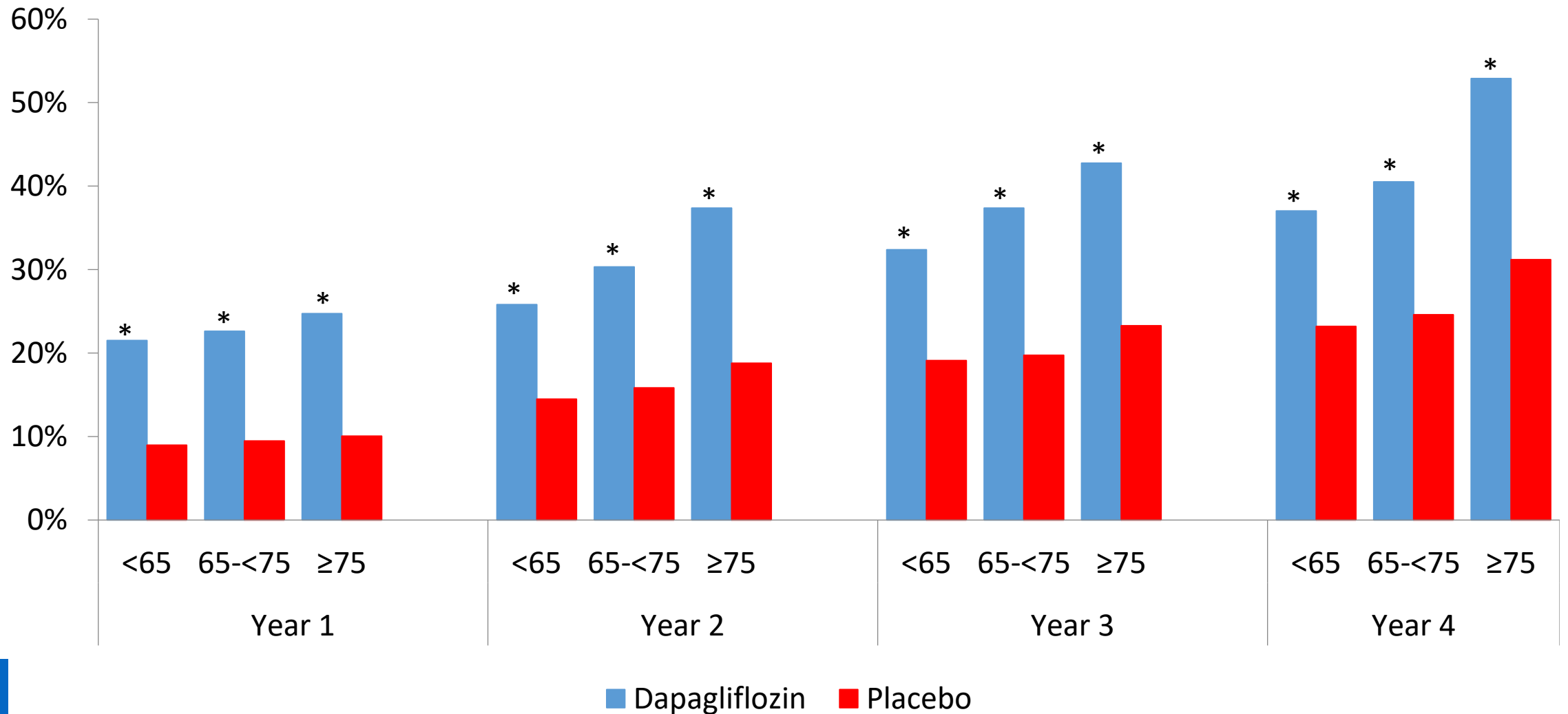


* p<0.0001, + p<0.05

Weight changes in the age groups

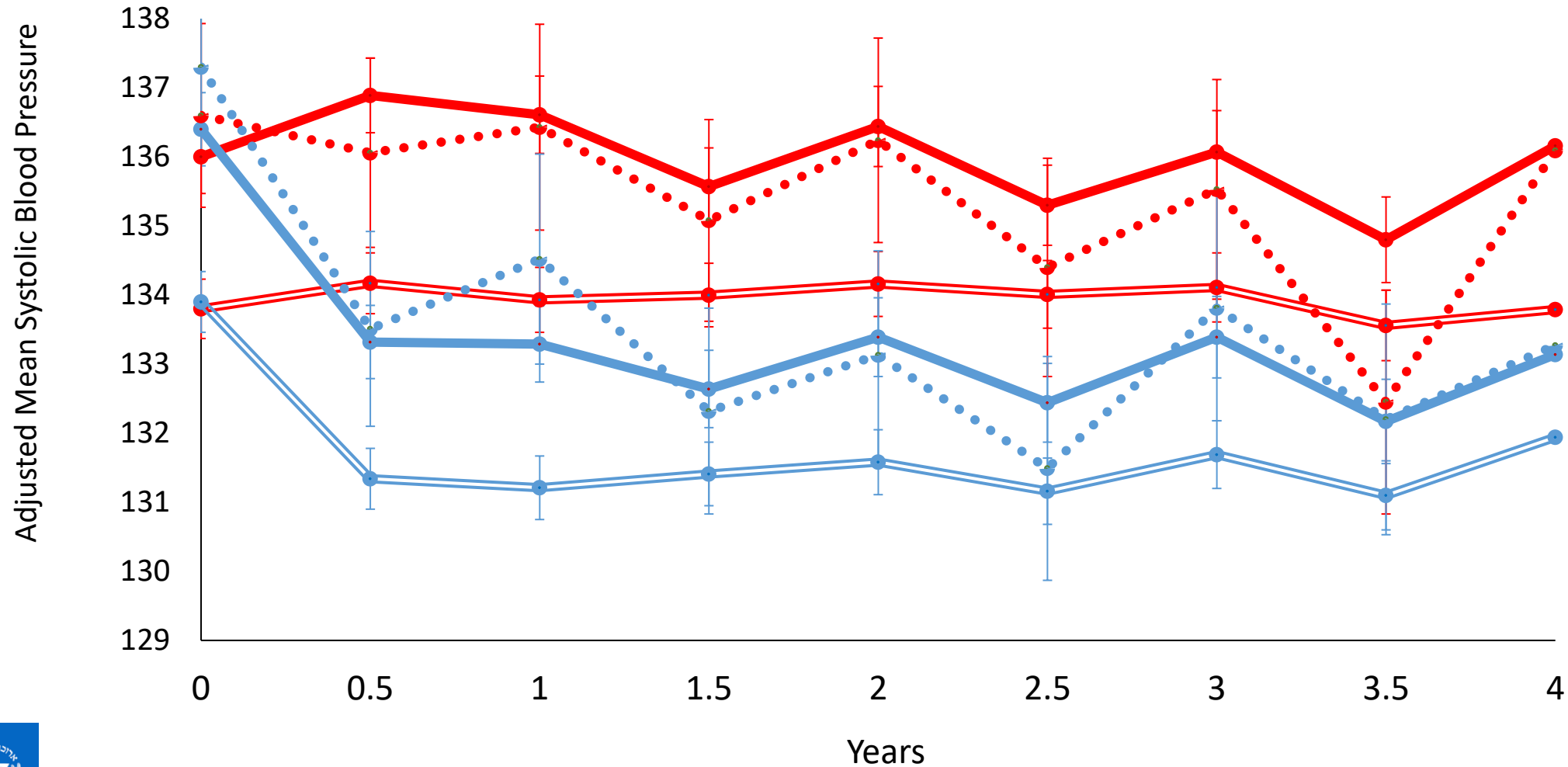


5% weight loss

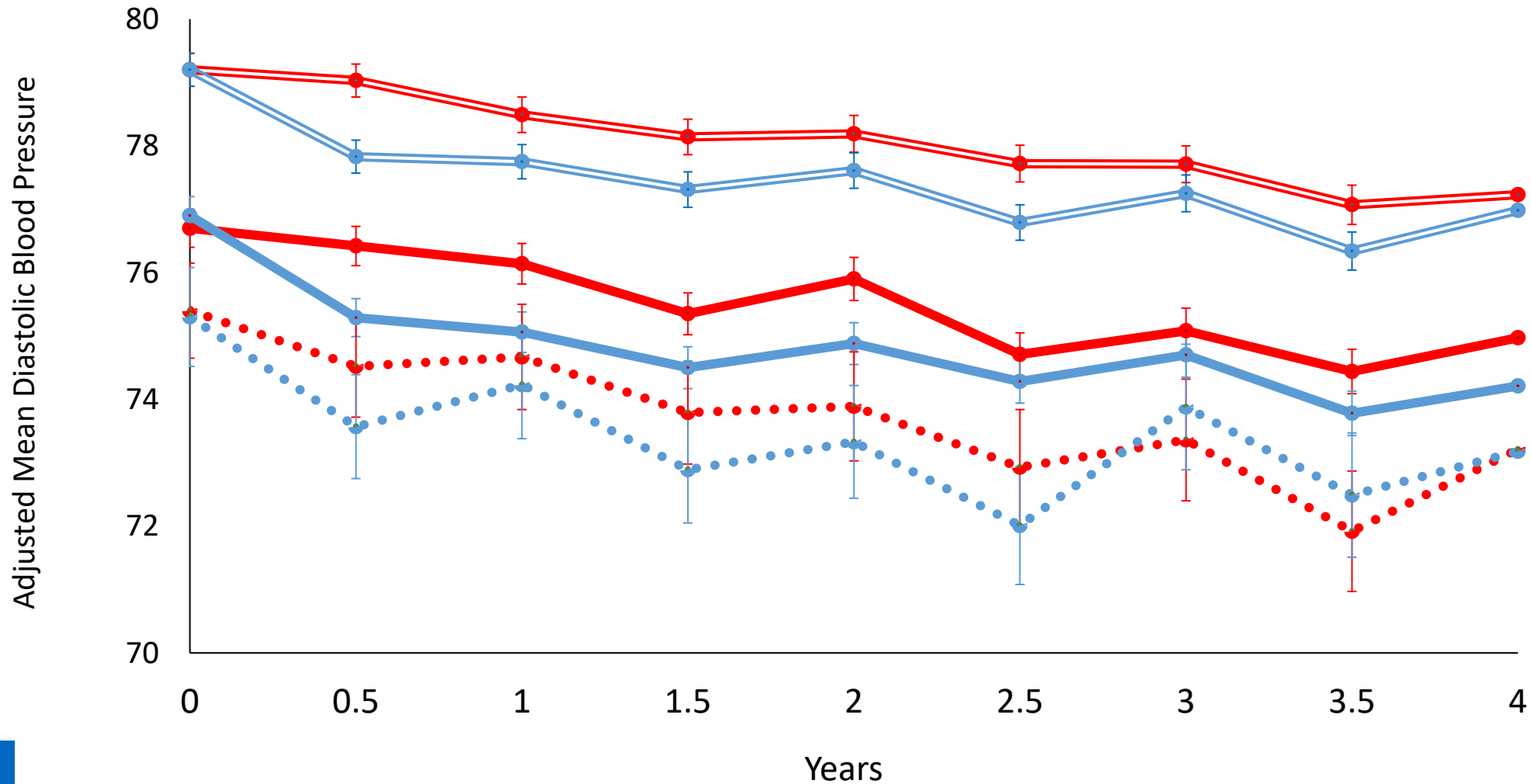


* p<0.0001, + p<0.05

Systolic BP in the age groups



Diastolic BP in the age groups

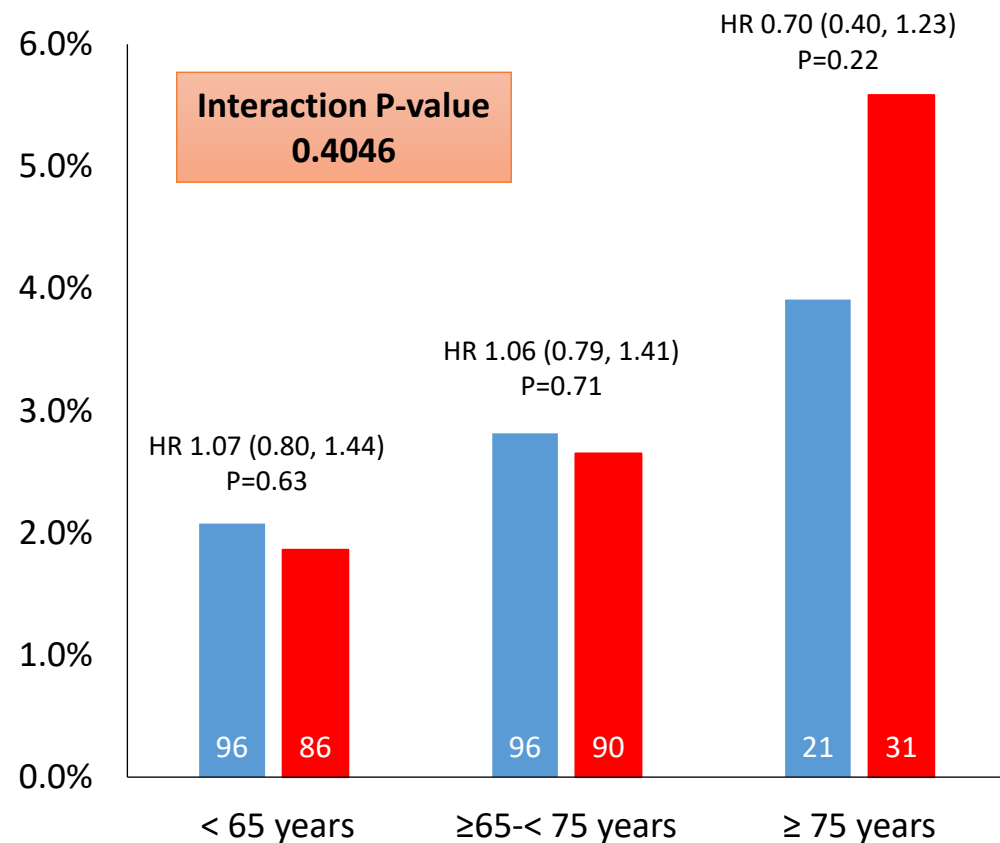


Safety outcomes

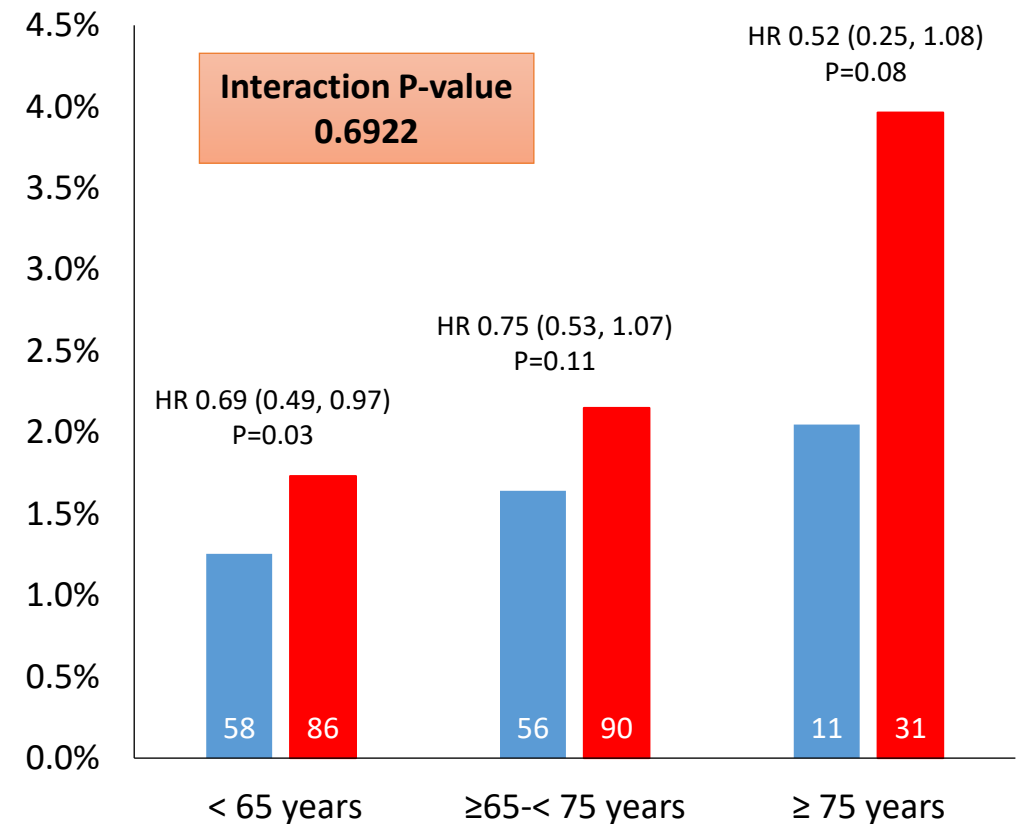
- The incidence of serious adverse events was lower with dapagliflozin vs. placebo in the overall study population with no age based treatment interaction.
- HR (95% CI):
 - 0.93 (0.86, 1.00) in age <65
 - 0.88 (0.81, 0.95) in age ≥65-<75
 - 1.02 (0.85, 1.21) in age ≥75Interaction p value 0.2667
- No heterogeneity across age groups was observed for any of the outcomes assessed, although the number of events in the very elderly was often quite small yielding wide confidence intervals in this age category.

Safety outcomes

Volume depletion



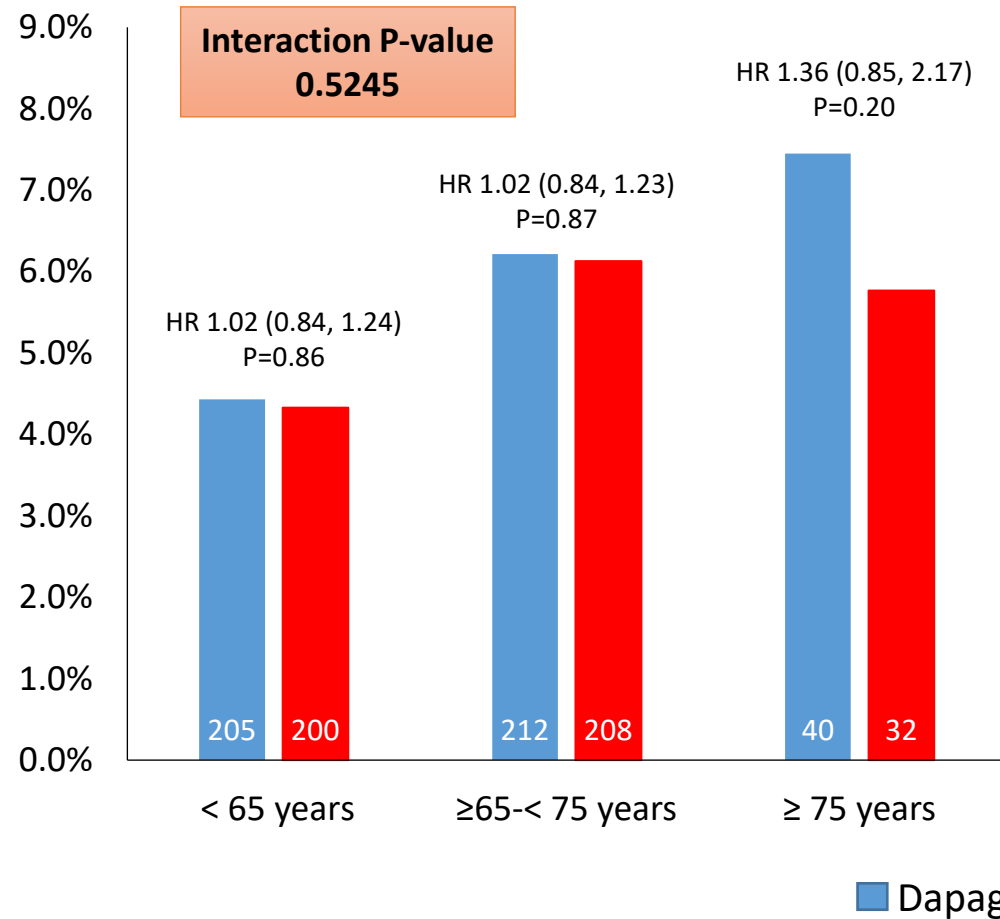
Acute kidney injury



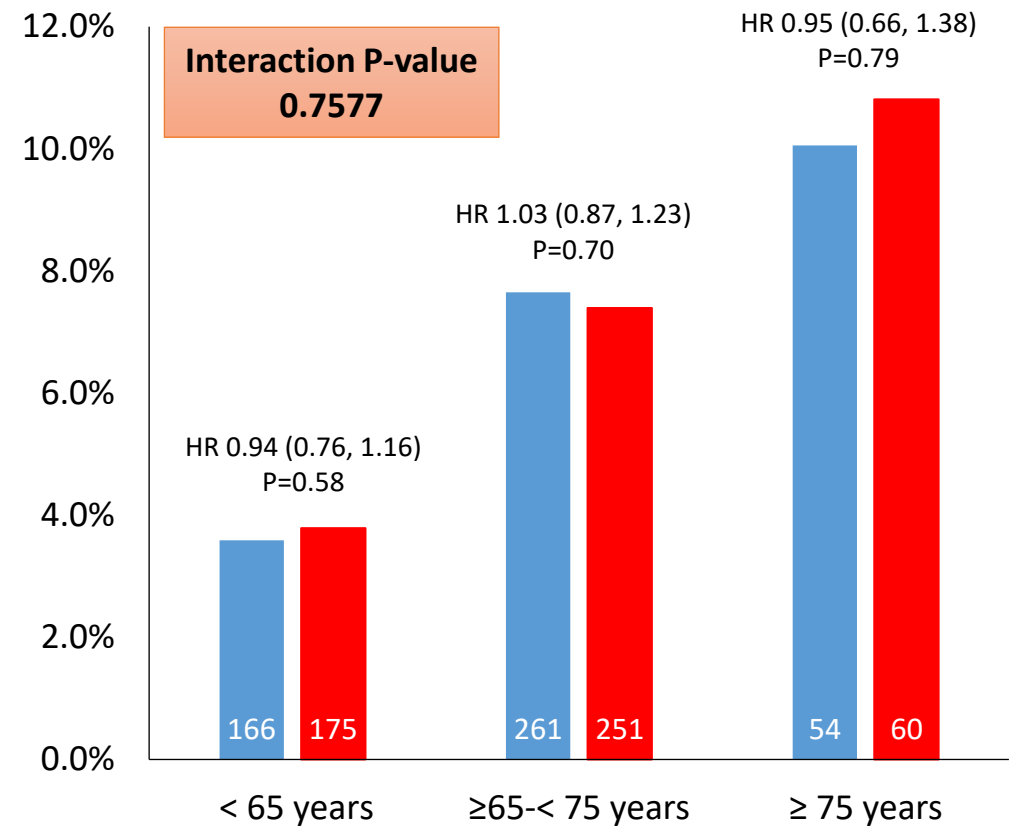
■ Dapagliflozin ■ Placebo

Safety outcomes

Fractures

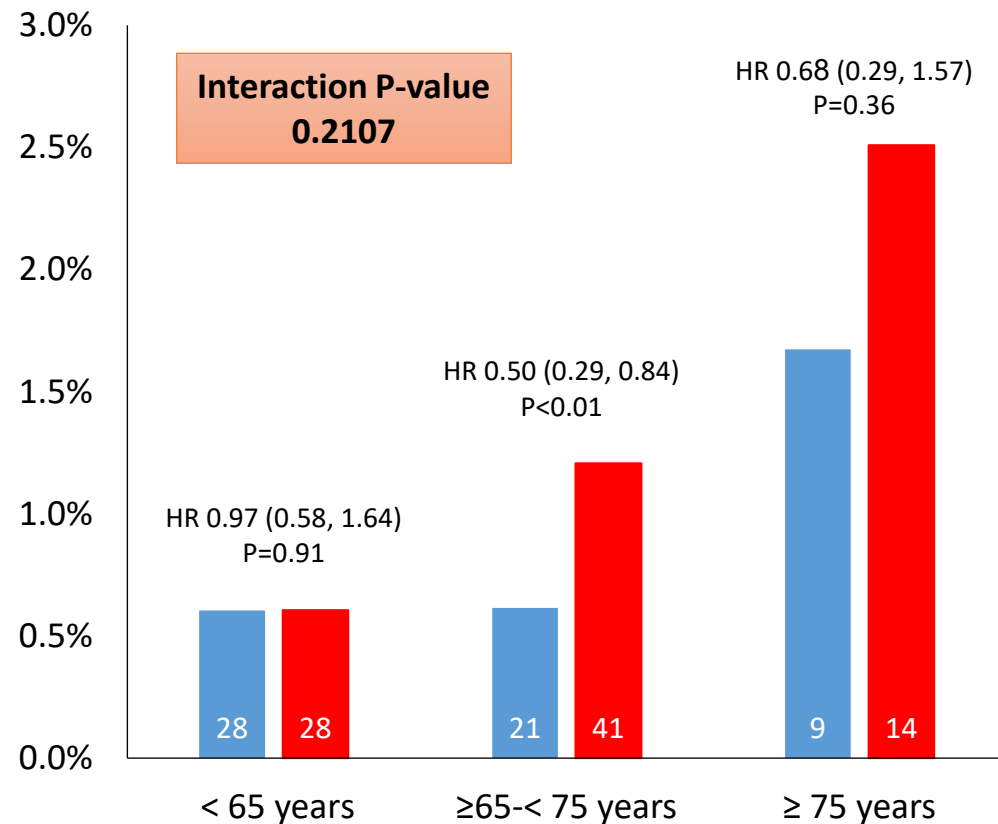


Malignancies

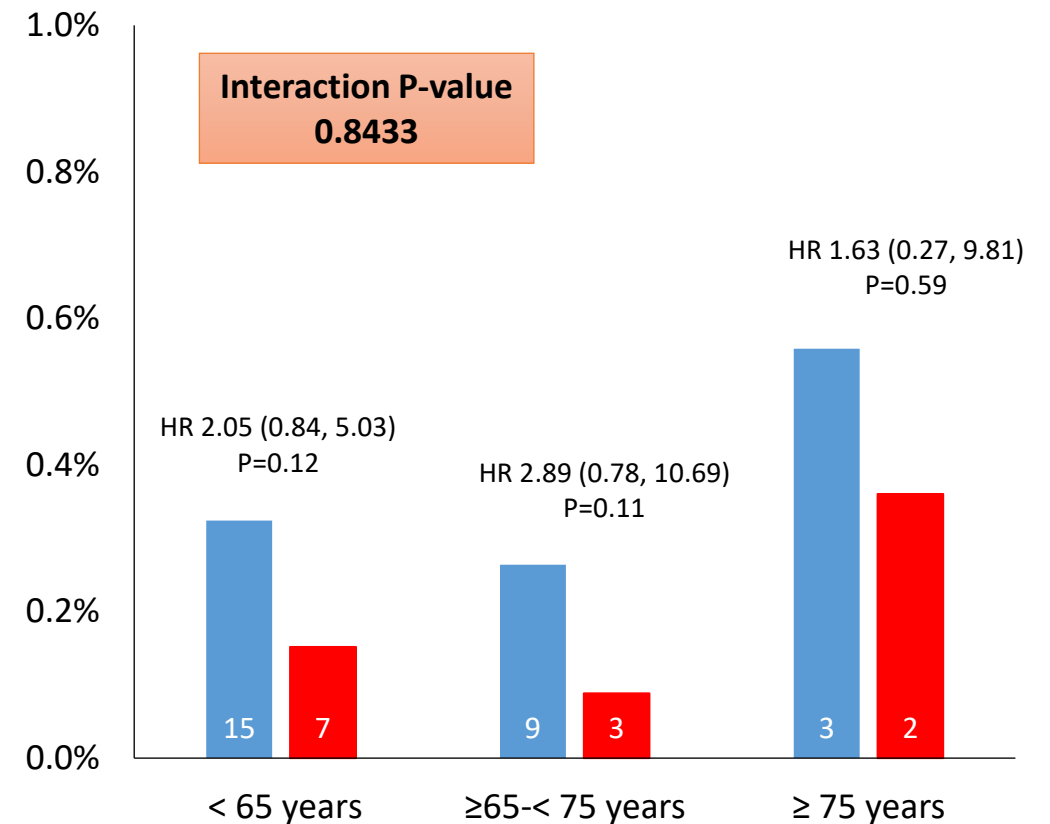


Safety outcomes

Major hypoglycemia



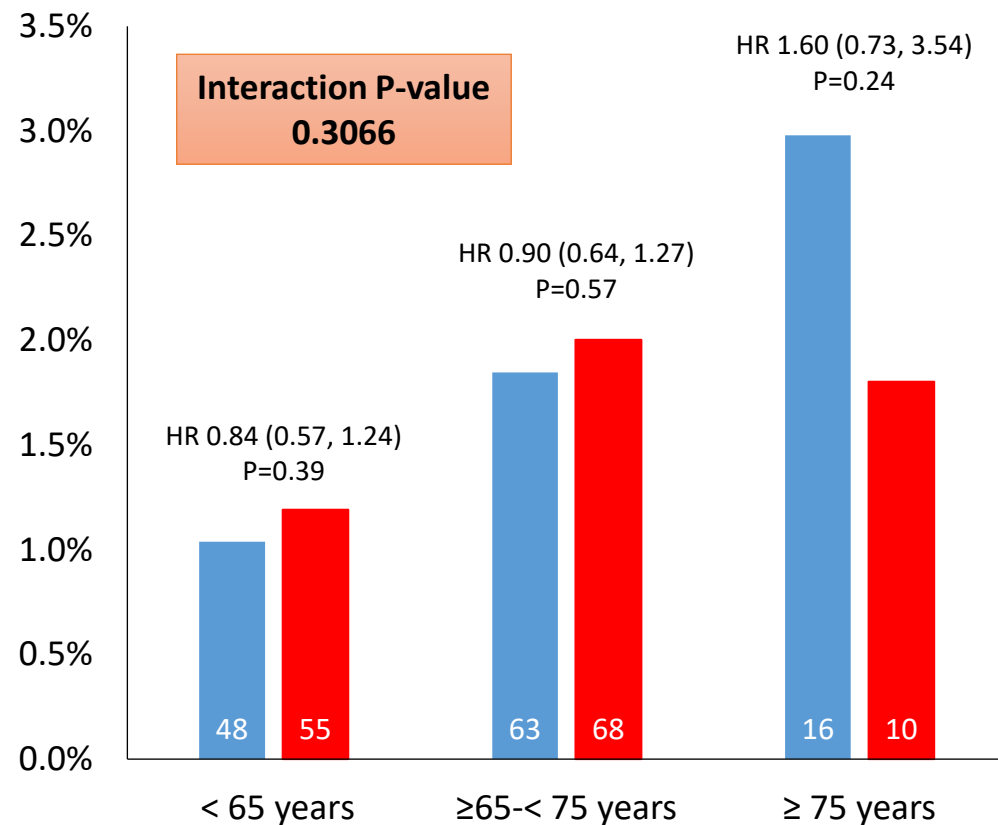
Diabetic ketoacidosis



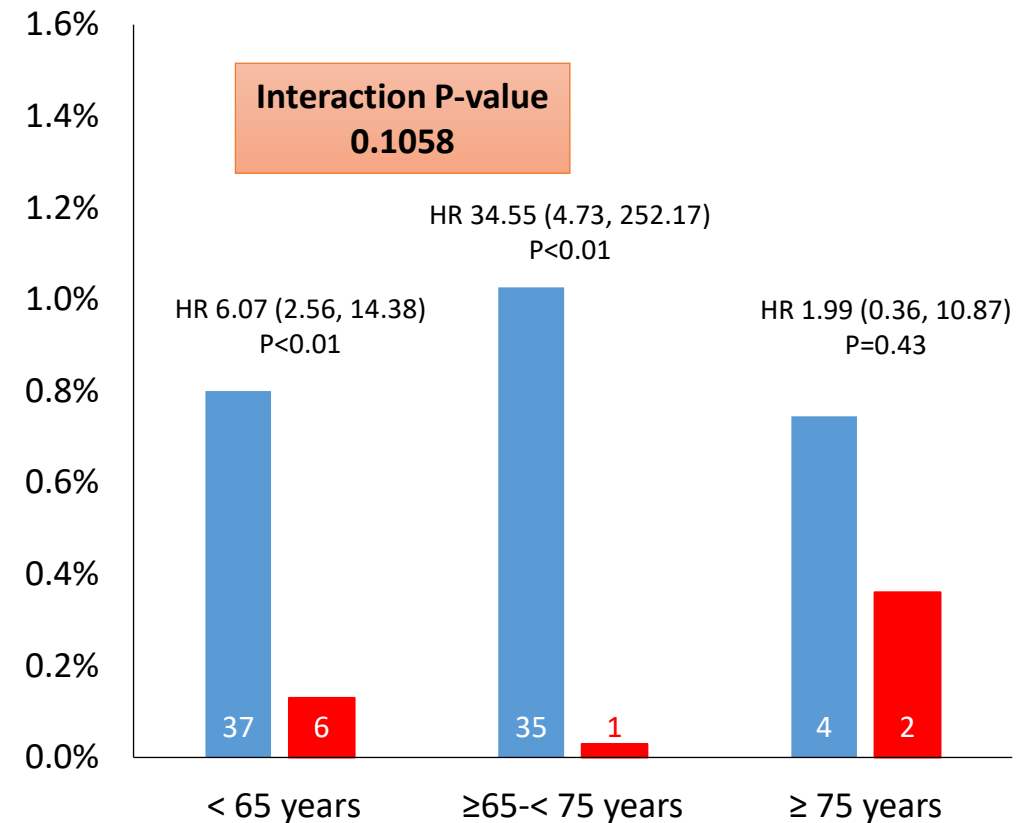
■ Dapagliflozin ■ Placebo

Safety outcomes

Urinary tract infections



Genital infections



■ Dapagliflozin ■ Placebo

Conclusions

- The DECLARE TIMI 58 study establishes the cardiovascular and renal benefits of dapagliflozin in the elderly and very elderly.
- The overall efficacy and safety of dapagliflozin was consistent regardless of age.
- This drug may be considered a valuable glucose lowering agent regardless of age.