

**Supplementary Online Content**

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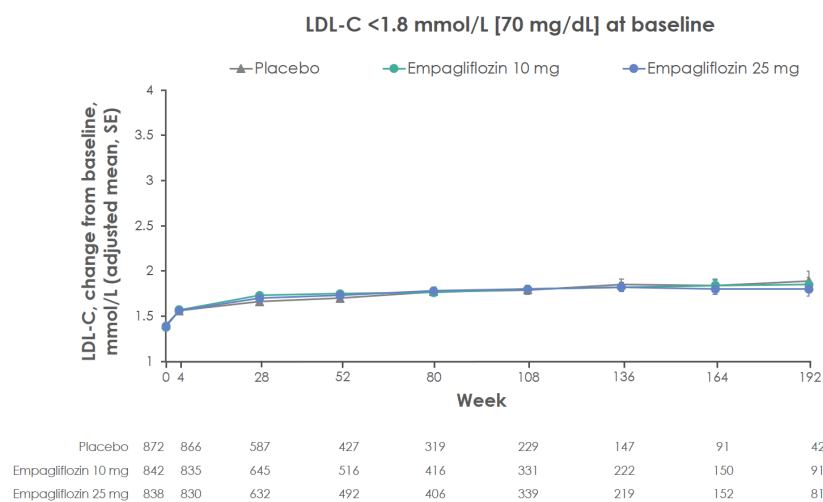
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## Empagliflozin efficacy by baseline LDL-C levels

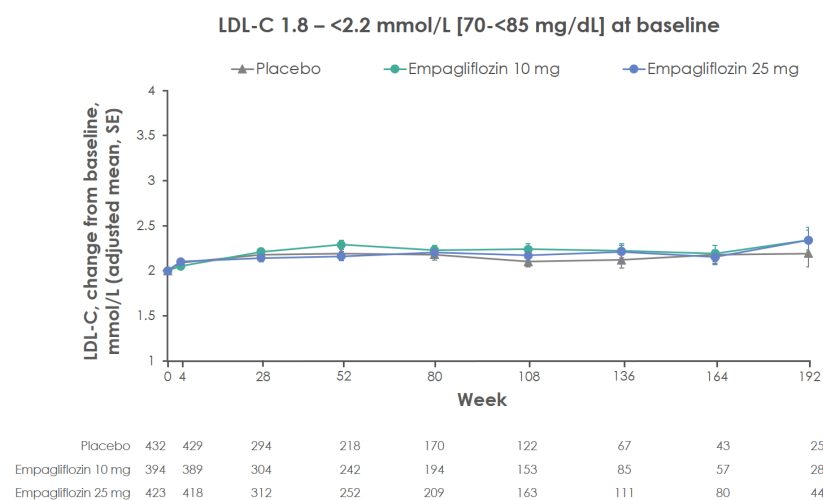
**Figure S1.** LDL cholesterol over time by empagliflozin and placebo treatment groups, and LDL cholesterol at baseline. Data are adjusted mean  $\pm$  standard error in the treated set.

The model includes baseline HbA1c as linear covariate(s) and baseline eGFR category, baseline BMI category, geographical region, week reachable lipid parameter, treatment, visit, baseline LDL category (mg/dL), treatment by visit interaction, visit by baseline LDL category (mg/dL) interaction, treatment by baseline LDL category (mg/dL) interaction, treatment by visit by baseline LDL category (mg/dL) interaction, baseline HbA1c by visit interaction as fixed effect(s).

### A. LDL-C <1.8 mmol/L [70 mg/dL] at baseline

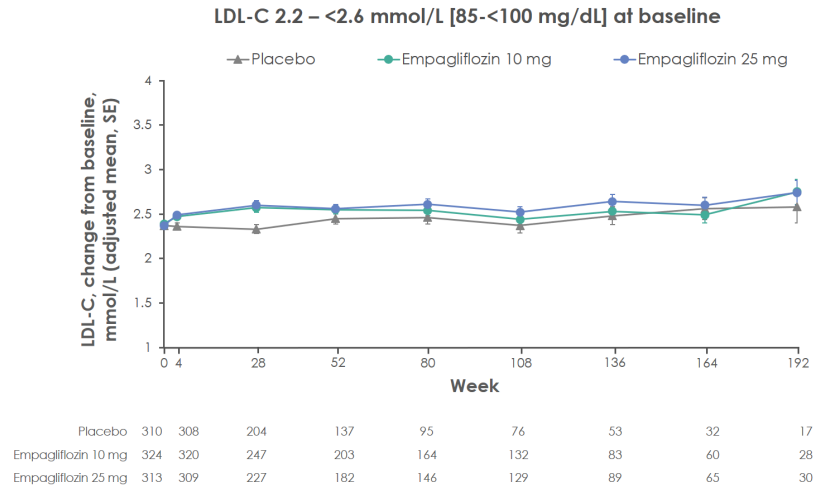


### B. LDL-C 1.8 – <2.2 mmol/L [70-<85 mg/dL] at baseline

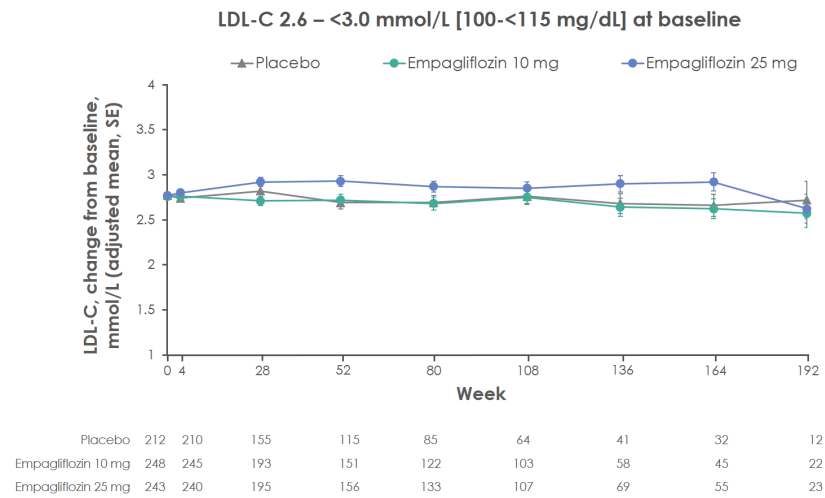


# Empagliflozin efficacy by baseline LDL-C levels

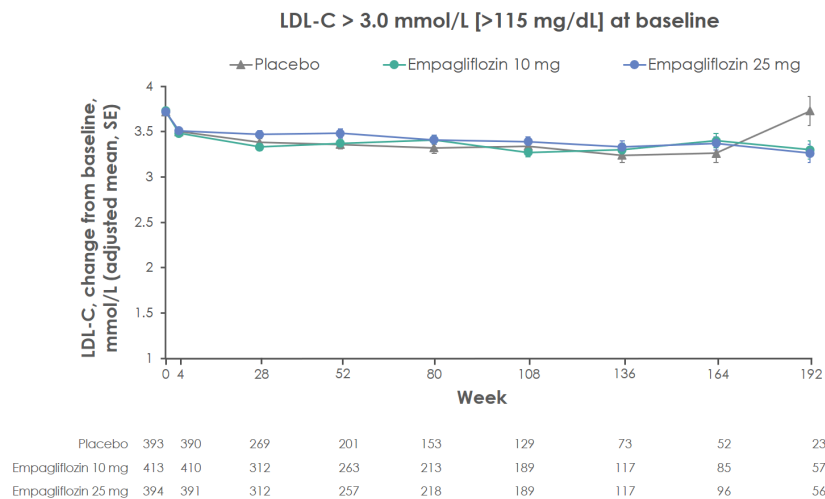
## C. LDL-C 2.2 – <2.6 mmol/L [85-<100 mg/dL] at baseline



## D. LDL-C 2.6 – <3.0 mmol/L [100-<115 mg/dL] at baseline



## E. LDL-C > 3.0 mmol/L [>115 mg/dL] at baseline



Empagliflozin efficacy by baseline LDL-C levels

**Table S1.** Baseline characteristics in subgroups by LDL cholesterol at baseline. Data are n (%) or mean  $\pm$  SD in patients treated with  $\geq 1$  dose of study drug.

	All patients (N=7020)	LDL cholesterol at baseline*				
		<1.8 mmol/L	1.8 to <2.2 mmol/L	2.2 to <2.6 mmol/L	2.6 to 3.0 mmol/L	>3.0 mmol/L
		<70 mg/dL (N=2669)	70 to <85 mg/dL (N=1294)	85 to <100 mg/dL (N=986)	100 to 115 mg/dL (N=736)	>115 mg/dL (N=1247)
Male	5016 (71.5)	2082 (78.0)	957 (74.0)	709 (71.9)	486 (66.0)	723 (58.0)
Age, years	63.1 $\pm$ 8.6	63.7 $\pm$ 8.6	63.8 $\pm$ 8.4	62.6 $\pm$ 8.5	62.6 $\pm$ 8.8	62.0 $\pm$ 8.8
Body Mass Index, kg/m <sup>2</sup>	30.6 $\pm$ 5.3	30.7 $\pm$ 5.2	30.7 $\pm$ 5.2	30.7 $\pm$ 5.4	30.6 $\pm$ 5.2	30.2 $\pm$ 5.2
LDL cholesterol, mmol/L	2.22 $\pm$ 0.92	1.39 $\pm$ 0.31	2.00 $\pm$ 0.10	2.38 $\pm$ 0.11	2.77 $\pm$ 0.11	3.74 $\pm$ 0.72
LDL cholesterol, mg/dL	85.6 $\pm$ 35.7	53.8 $\pm$ 11.9	77.4 $\pm$ 4.0	91.9 $\pm$ 4.4	107.0 $\pm$ 4.2	144.3 $\pm$ 27.8
SBP <140 mmHg and DBP <90 mmHg	4306 (61.3)	1715 (64.3)	811 (62.7)	581 (58.9)	436 (59.2)	710 (56.9)
eGFR (MDRD), mL/min/1.73m <sup>2</sup>	74.0 $\pm$ 21.4	73.3 $\pm$ 21.0	74.4 $\pm$ 21.2	74.0 $\pm$ 20.9	74.7 $\pm$ 22.2	74.9 $\pm$ 22.6
UACR (mg/g)						
Normal (< 30)	4171 (59.4)	1645 (61.6)	791 (61.1)	584 (59.2)	437 (59.4)	661 (53.0)
Microalbum. (30-300)	2013 (28.7)	751 (28.1)	357 (27.6)	286 (29.0)	212 (28.8)	382 (30.6)
Macroalbum. (> 300)	769 (11.0)	251 (9.4)	131 (10.1)	109 (11.1)	81 (11.0)	193 (15.5)
HbA1c**, %	8.07 $\pm$ 0.85	8.02 $\pm$ 0.82	8.04 $\pm$ 0.83	8.09 $\pm$ 0.87	8.11 $\pm$ 0.88	8.17 $\pm$ 0.89
Time since diagnosis of type 2 diabetes, years						
$\leq 1$	180 (2.6)	60 (2.2)	28 (2.2)	28 (2.8)	16 (2.2)	45 (3.6)
>1 to 5	1083 (15.4)	340 (12.7)	181 (14.0)	165 (16.7)	138 (18.8)	243 (19.5)
>5 to 10	1746 (24.9)	664 (24.9)	306 (23.6)	229 (23.2)	186 (25.3)	340 (27.3)
>10	4011 (57.1)	1605 (60.1)	779 (60.2)	564 (57.2)	396 (53.8)	619 (49.6)

\*Baseline LDL cholesterol information was not available for 88 patients. \*\* Data were not available for 2 patients. Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease formula, UACR, Urine albumin-to-creatinine ratio, album; albuminuria.

**Table S2.** Baseline CV risk factors and CV medications in subgroups by LDL cholesterol at baseline. Data are n (%) or mean  $\pm$  SD in patients treated with  $\geq 1$  dose of study drug.

	All patients (N=7020)	LDL cholesterol at baseline*				
		<1.8 mmol/L	1.8 to <2.2 mmol/L	2.2 to <2.6 mmol/L	2.6 to 3.0 mmol/L	>3.0 mmol/L
		<70 mg/dL (N=2669)	70 to <85 mg/dL (N=1294)	85 to <100 mg/dL (N=986)	100 to 115 mg/dL (N=736)	>115 mg/dL (N=1247)
Any CV risk factor	6964 (99.2)	2652 (99.4)	1283 (99.1)	977 (99.1)	731 (99.3)	1235 (99.0)
CAD	5308 (75.6)	2215 (83.0)	1035 (80.0)	745 (75.6)	502 (68.2)	747 (59.9)
Multi-vessel CAD	3279 (46.7)	1410 (52.8)	665 (51.4)	467 (47.4)	289 (39.3)	409 (32.8)
History of MI	3273 (46.6)	1351 (50.6)	607 (46.9)	454 (46.0)	314 (42.7)	514 (41.2)
Coronary artery bypass graft	1738 (24.8)	736 (27.6)	362 (28.0)	228 (23.1)	159 (21.6)	231 (18.5)
History of stroke**	1637 (23.3)	531 (19.9)	248 (19.2)	213 (21.6)	215 (29.2)	409 (32.8)
Peripheral artery disease	1461 (20.8)	511 (19.1)	248 (19.2)	212 (21.5)	149 (20.2)	316 (25.3)
Single vessel CAD*	736 (10.5)	326 (12.2)	147 (11.4)	111 (11.3)	64 (8.7)	81 (6.5)
Cardiac failure <sup>†</sup>	706 (10.1)	250 (9.4)	119 (9.2)	90 (9.1)	84 (11.4)	154 (12.3)
Anti-hypertensive therapy	6667 (95.0)	2582 (96.7)	1245 (96.2)	934 (94.7)	691 (93.9)	1132 (90.8)
ACE inhibitors/ARBs	5666 (80.7)	2208 (82.7)	1071 (82.8)	792 (80.3)	566 (76.9)	954 (76.5)
Statins	5403 (77.0)	2353 (88.2)	1090 (84.2)	768 (77.9)	488 (66.3)	635 (50.9)
Acetylsalicylic acid	5803 (82.7)	2306 (86.4)	1111 (85.9)	826 (83.8)	572 (77.7)	915 (73.4)

\*Baseline LDL cholesterol information was not available for 88 patients. \*\* Information was not available for 1

patient. <sup>†</sup>Based on the narrow standard MedDRA query 'cardiac failure'. Abbreviations: ACE, angiotensin-

converting enzyme; ARB, angiotensin receptor blocker; CAD, coronary artery disease; MI, myocardial infarction.

Empagliflozin efficacy by baseline LDL-C levels

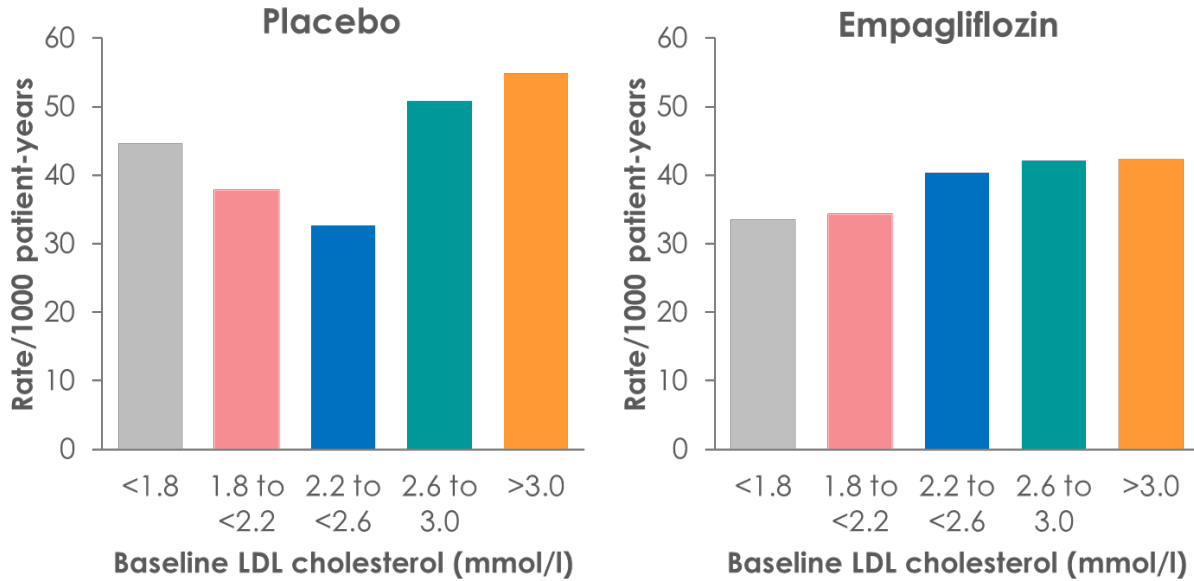
**Table S3.** Lipid-lowering therapy introduced post-baseline. Data are n (%) in patients treated with  $\geq 1$  dose of study drug.

	LDL cholesterol at baseline*									
	<1.8 mmol/L		1.8 to <2.2 mmol/L		2.2 to <2.6 mmol/L		2.6 to 3.0 mmol/L		>3.0 mmol/L	
	<70 mg/dL		70 to <85 mg/dL		85 to <100 mg/dL		100 to 115 mg/dL		>115 mg/dL	
	Placebo (N=908)	Empa (N=1761)	Placebo (N=449)	Empa (N=845)	Placebo (N=326)	Empa (N=660)	Placebo (N=221)	Empa (N=515)	Placebo (N=405)	Empa (N=842)
Lipid-lowering therapy	223 (24.6)	424 (24.1)	121 (26.9)	224 (26.5)	107 (32.8)	201 (30.5)	78 (35.3)	158 (30.7)	184 (45.4)	338 (40.1)
Statins	183 (20.2)	334 (19.0)	98 (21.8)	183 (21.7)	83 (25.5)	169 (25.6)	63 (28.5)	129 (25.0)	169 (41.7)	311 (36.9)
Fibrates	36 (4.0)	83 (4.7)	20 (4.5)	37 (4.4)	29 (8.9)	34 (5.2)	11 (5.0)	21 (4.1)	32 (7.9)	33 (3.9)
Ezetimibe	12 (1.3)	24 (1.4)	8 (1.8)	21 (2.5)	14 (4.3)	13 (2.0)	5 (2.3)	13 (2.5)	9 (2.2)	21 (2.5)
Niacin	6 (0.7)	6 (0.3)	4 (0.9)	5 (0.6)	1 (0.3)	2 (0.3)	1 (0.5)	4 (0.8)	3 (0.7)	3 (0.4)
Other**	29 (3.2)	41 (2.3)	11 (2.4)	26 (3.1)	8 (2.5)	8 (1.2)	10 (4.5)	15 (2.9)	13 (3.2)	18 (2.1)

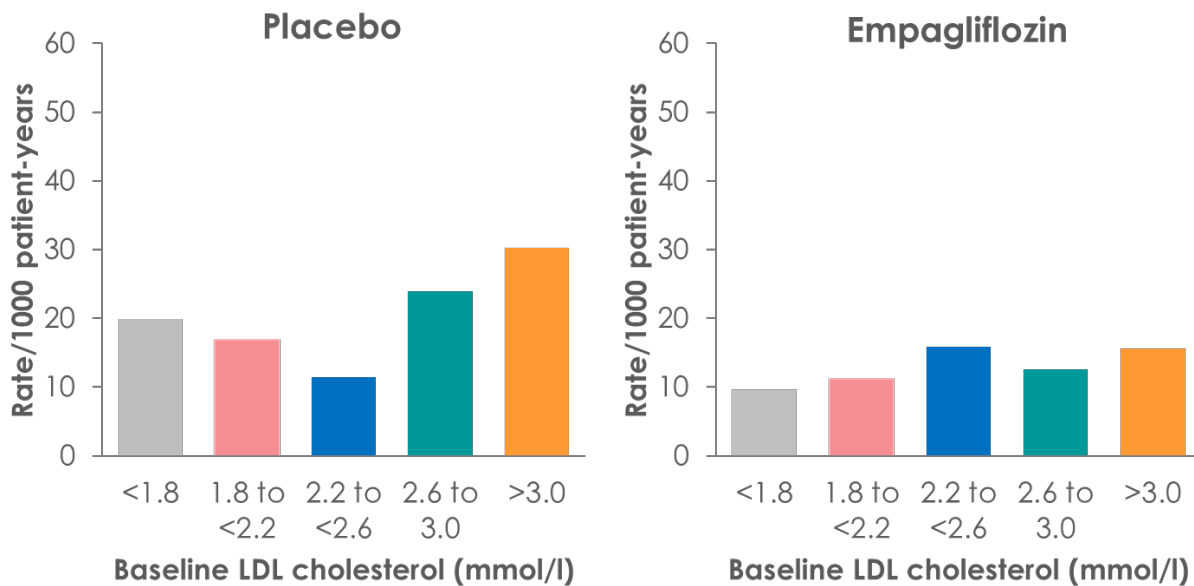
\*Baseline LDL cholesterol information was not available for 24 patients in the placebo group and 64 patients in the empagliflozin group.\*\*Includes omega-3 fatty acids and bile acid sequestrants.

Empagliflozin efficacy by baseline LDL-C levels

**Figure S2.** 3-point MACE event rates by LDL-cholesterol levels at baseline in EMPA-REG OUTCOME.

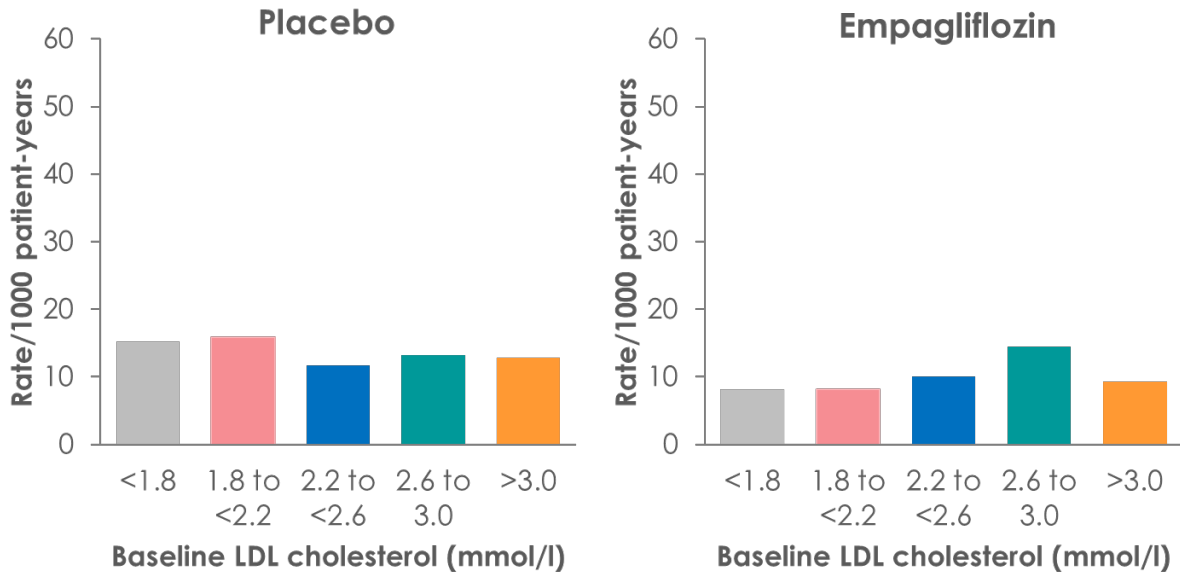


**Figure S3.** CV death event rates by LDL-cholesterol levels at baseline in EMPA-REG OUTCOME

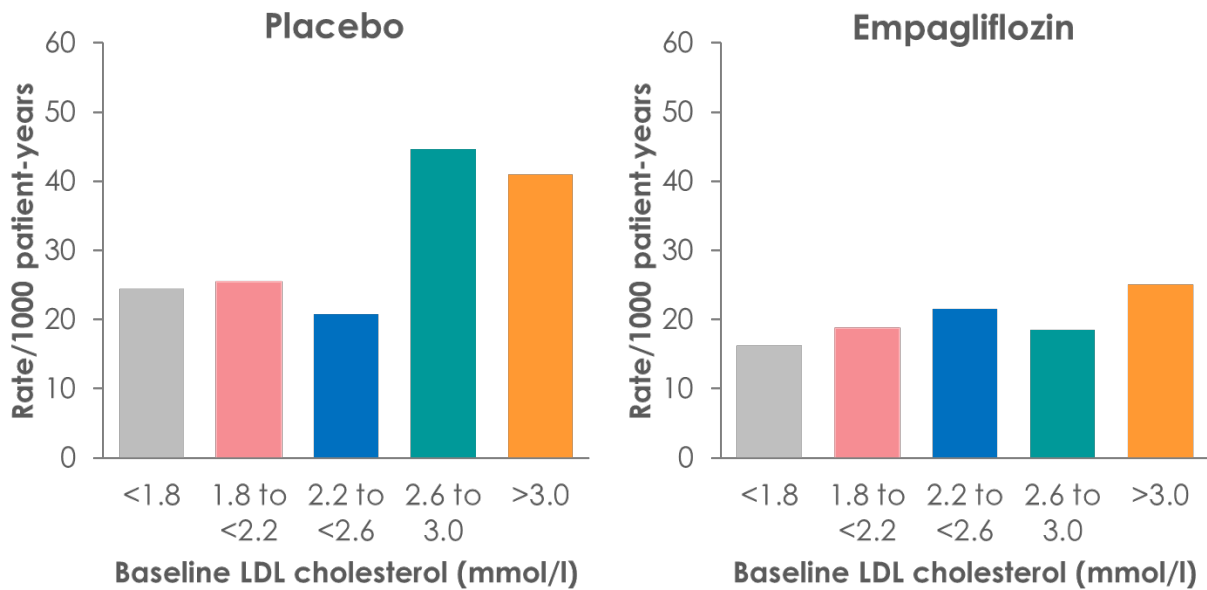


Empagliflozin efficacy by baseline LDL-C levels

**Figure S4.** Hospitalization for heart failure event rates by LDL-cholesterol levels at baseline in EMPA-REG OUTCOME



**Figure S5.** All-cause mortality event rates by LDL-cholesterol levels at baseline in EMPA-REG OUTCOME





Empagliflozin efficacy by baseline LDL-C levels

**Table S4** Adverse events occurring until 7 days after treatment discontinuation in participants in EMPA-REG OUTCOME by treatment group and by LDL-cholesterol levels at baseline.

	LDL cholesterol at baseline*									
	<1.8 mmol/L		1.8 to <2.2 mmol/L		2.2 to <2.6 mmol/L		2.6 to 3.0 mmol/L		>3.0 mmol/L	
	<70 mg/dL		70 to <85 mg/dL		85 to <100 mg/dL		100 to 115 mg/dL		>115 mg/dL	
	Placebo (N=908)	Empa (N=1761)	Placebo (N=449)	Empa (N=845)	Placebo (N=326)	Empa (N=660)	Placebo (N=221)	Empa (N=515)	Placebo (N=405)	Empa (N=842)
One or more AEs	838 (92.3)	1612 (91.5)	411 (91.5)	779 (92.2)	306 (93.9)	586 (88.8)	192 (86.9)	458 (88.9)	371 (91.6)	733 (87.1)
One or more serious AEs	400 (44.1)	686 (39.0)	189 (42.1)	332 (39.3)	130 (39.9)	257 (38.9)	97 (43.9)	193 (37.5)	164 (40.5)	295 (35.0)
One or more AEs leading to discontinuation of trial drug	176 (19.4)	305 (17.3)	74 (16.5)	157 (18.6)	62 (19.0)	121 (18.3)	41 (18.6)	83 (16.1)	94 (23.2)	138 (16.4)
Confirmed hypoglycaemic AEs**	292 (32.2)	509 (28.9)	107 (23.8)	272 (32.2)	103 (31.6)	183 (27.7)	52 (23.5)	135 (26.2)	90 (22.2)	183 (21.7)
Hypoglycaemia requiring assistance	19 (2.1)	21 (1.2)	5 (1.1)	13 (1.5)	7 (2.1)	10 (1.5)	3 (1.4)	10 (1.9)	2 (0.5)	8 (1.0)
Event consistent with UTI***	148 (16.3)	294 (16.7)	62 (13.8)	137 (16.2)	62 (19.0)	121 (18.3)	45 (20.4)	102 (19.8)	98 (24.2)	176 (20.9)
Event consistent with genital infection†	20 (2.2)	114 (6.5)	7 (1.6)	64 (7.6)	2 (0.6)	46 (7.0)	6 (2.7)	31 (6.0)	6 (1.5)	43 (5.1)
Event consistent with volume depletion‡	55 (6.1)	102 (5.8)	27 (6.0)	41 (4.9)	15 (4.6)	33 (5.0)	12 (5.4)	26 (5.0)	5 (1.2)	35 (4.2)
Acute renal failure§	69 (7.6)	95 (5.4)	28 (6.2)	48 (5.7)	21 (6.4)	33 (5.0)	11 (5.0)	26 (5.0)	26 (6.4)	43 (5.1)
Thromboembolic event¶	4 (0.4)	12 (0.7)	5 (1.1)	4 (0.5)	4 (1.2)	4 (0.6)	1 (0.5)	4 (0.8)	5 (1.2)	6 (0.7)
Bone fracture‡	31 (3.4)	69 (3.9)	20 (4.5)	35 (4.1)	13 (4.0)	20 (3.0)	8 (3.6)	19 (3.7)	18 (4.4)	31 (3.7)

n (%) of patients treated with  $\geq 1$  dose of study drug, based on events that occurred during treatment or  $\leq 7$  days after last intake of study drug. \*Baseline LDL cholesterol information was not available for 24 patients in the placebo group and 64 patients in the empagliflozin group. \*\*Plasma glucose  $\leq 3.9$  mmol/l and/or requiring assistance. \*\*\*Based on 79 MedDRA preferred terms. †Based on 88 MedDRA preferred terms. ‡Based on 8 MedDRA preferred terms. §Based on narrow standardised MedDRA query “acute renal failure”. ¶Based on narrow standardised MedDRA query “embolic and thrombotic events”. †Based on 62 MedDRA preferred terms. MedDRA, Medical Dictionary for Regulatory Activities. Empa – Empagliflozin. AE – adverse events.