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Proprotein convertase subtilisin/kexin 9 inhibitors in reducing cardiovascular outcomes

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FIGURE LEGENDS

Figure 1. Flow diagram for study identification and inclusion (PRISMA Flow Diagram).

* These 47 citations included 55 randomized trials.

Figure 2. Effect of PCSK9 inhibitors on MACE

Abbreviations: CI, confidence interval; MACE, major adverse cardiovascular events; RR, relative ratio; PCSK9, proprotein convertase subtilisin/kexin type 9; M-H, Mantel-Haenszel.

Figure 3. Subgroup analyses based on the drug type

Abbreviations: CI, confidence interval; PCSK9, proprotein convertase subtilisin/kexin type 9.

Figure 4. Subgroup analyses based on the follow-up duration.

Abbreviations: CI, confidence interval; PCSK9, proprotein convertase subtilisin/kexin type 9.

Figure 5. Subgroup analyses based on the prevention type.

Abbreviations: CI, confidence interval; PCSK9, proprotein convertase subtilisin/kexin type 9.

Figure 6. Subgroup analyses based on the control type.

Abbreviations: CI, confidence interval; PCSK9, proprotein convertase subtilisin/kexin type 9.

TABLE LEGEND

Table 1. GRADE quality assessment

^a Indirectness of populations which varied across trials and were generally sparsely defined

^b The baseline risk in a 10-year time frame was estimated using the pooled event rates in the control group

^c The cutoff between the intermediate and high risk of CVD in FGR

^d The cutoff between the low and intermediate risk of CVD in FGR

^e Cumulative Z line crossed futility boundary in the trial sequential analysis

^f Cumulative Z curve did not cross futility boundary, trial sequential monitoring boundary, traditional boundary

Abbreviations: CI: confidence interval; CVD: cardiovascular disease; FGR: Framingham Globe Risk; GRADE: Grading of Recommendation Assessment, Development, and Evaluation; MACE: major adverse cardiovascular events; PCSK9: proprotein convertase subtilisin/kexin 9; RR: relative risk.

1 **Table 1. GRADE quality assessment**

Quality assessment							No of patients		Relative effect (95% CI)	Anticipated absolute effects (10-year time frame)		Quality
No of participants (studies)	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCSK9 inhibitors	Control		Baseline risk of CVD	Risk difference with PCSK9 inhibitors ¹ (95% CI)	
MACE (follow-up 12-145.6 weeks)												
92,736 (32)	Randomized trials	No serious risk of bias	No serious inconsistency	Serious ^a	No serious imprecision	None	2,188/48,518 (4.5%)	2,551/44,218 (5.8%)	RR 0.84 (0.79 to 0.89)	Risk in the control ^b		MODERATE
										286 per 1,000	47 fewer per 1,000 (32 to 59 fewer)	
										Intermediate to high risk in FGR ^c		
										200 per 1,000	32 fewer per 1,000 (22 to 42 fewer)	
										Low to intermediate risk in FGR ^d		
										100 per 1,000	16 fewer per 1,000 (11 to 21 fewer)	
Cardiovascular Death (follow-up 12-145.6 weeks)												
96,709 (51)	Randomized trials	No serious risk of bias	No serious inconsistency	Serious ^a	Serious ^e	None	585/50,914 (1.1%)	600/45,795 (1.3%)	RR 0.95 (0.85 to 1.07)	65 per 1,000 ²	3 fewer per 1,000 (10 fewer to 4 more)	LOW
Nonfatal Myocardial Infarction (follow-up 12-145.6 weeks)												
90,605 (38)	Randomized trials	No serious risk of bias	No serious inconsistency	Serious ^a	No serious imprecision	None	1,341/47,031 (2.9%)	1,602/43,574 (3.7%)	RR 0.83 (0.74 to 0.93)	207 per 1,000 ²	35 fewer per 1,000 (15 to 53 fewer)	MODERATE
Unstable Angina (follow-up 12-145.6 weeks)												
93,344 (36)	Randomized trials	No serious risk of bias	No serious inconsistency	Serious ^a	Serious ^f	None	371/48,877 (0.8%)	400/44,467 (0.9%)	RR 0.9 (0.78 to 1.04)	54 per 1,000 ²	5 fewer per 1,000 (12 fewer to 2 more)	LOW
Heart Failure (follow-up 12-145.6 weeks)												
92995 (34)	Randomized trials	No serious risk of bias	No serious inconsistency	Serious ^a	Serious ^e	None	388/48,673 (0.8%)	395/44,322 (0.9%)	RR 0.96 (0.83 to 1.10)	43 per 1,000 ²	2 fewer per 1,000 (7 fewer to 4 more)	LOW
Any Stroke (follow-up 12-145.6 weeks)												
94,408 (35)	Randomized trials	No serious risk of bias	No serious inconsistency	Serious ^a	No serious imprecision	None	393/49,537 (0.8%)	512/44,871 (1.1%)	RR 0.75 (0.65 to 0.85)	61 per 1,000 ²	16 fewer per 1,000 (9 to 21 fewer)	MODERATE
All-cause Mortality (follow-up 12-145.6 weeks)												
96,427 (51)	Randomized trials	No serious risk of bias	No serious inconsistency	Serious ^a	Serious ^e	None	941/50,888 (1.8%)	980/45,539 (2.1%)	RR 0.93 (0.84 to 1.03)	113 per 1,000 ²	8 fewer per 1,000 (19 fewer to 3 more)	LOW

2 a Indirectness of populations which varied across trials and were generally sparsely defined

3 b The baseline risk in a 10-year time frame was estimated using the pooled event rates in the control group

- 4 c The cutoff between the intermediate and high risk of CVD in FGR
- 5 d The cutoff between the low and intermediate risk of CVD in FGR
- 6 e Cumulative Z line crossed futility boundary in the trial sequential analysis
- 7 f Cumulative Z curve did not cross futility boundary, trial sequential monitoring boundary, traditional boundary
- 8 Abbreviations: CI: confidence interval; CVD: cardiovascular disease; FGR: Framingham Global Risk; GRADE: Grading of Recommendation
- 9 Assessment, Development, and Evaluation; MACE: major adverse cardiovascular events; PCSK9: proprotein convertase subtilisin/kexin 9; RR:
- 10 relative risk