GRADE Tables

Bile Acid Sequestrants

Outcome	No. of RCTs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (range)	Median (IQR)	Certainty	Other Comments
Overall Outcomes											
MACE	3	Serious Discrepancies exist in what is presented in the Lipids Research Clinic Trial. The effect estimate presented in the paper used a 90% confidence interval, however in the original publication on design (1979) stated the use of an alpha=0.01 (99% confidence interval).	Serious All three RCTs have different effect sizes, ranging from 0.35-0.83 (none statistically significant)	Serious All three definitions of MACE vary, including CAD progression in one outcome.	Serious Confidence intervals are wide and contain both significant benefit as well as harm. Further, only 1/3 RCTs contribute >1000 patients.	Undetected Only 1 small trial was industry-funded (Watts, 1992)	53-3,806	RR 0.35-0.83	N/A	Very low This outcome had four serious **(-4)** therefore **downgrade by 4 to very low.**	
CV Mortality	2 (3 outcomes)	Serious Discrepancies exist in what is presented in the Lipids Research Clinic Trial. The effect estimate	Serious The effect estimates ranges from significant benefit to harm.	Serious The population is mainly in European men (largest trial).	Serious Confidence intervals are wide, including both important harms and	Undetected	2,278-3,806	RR 0.46-1.08		Very low This outcome had four serious **(-4)** therefore **downgrade**	

Outcome	No. of RCTs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (range)	Median (IQR)	Certainty	Other Comments
		presented in the paper used a 90% confidence interval, however in the original publication on design (1979) stated the use of an alpha=0.01 (99% confidence interval).			benefits, despite large sample sizes in 2/3 trials.					**by 4 to very low.**	
All-Cause Mortality	3 (4 outcomes)	Serious Discrepancies exist in what is presented in the Lipids Research Clinic Trial. The effect estimate presented in the paper used a 90% confidence interval, however in the original publication on design (1979) stated the use of an alpha=0.01 (99% confidence interval).	Serious The effect estimates varied greatly, with none being statistically significant.	Serious The population is mainly in European men (largest trial)	Serious Confidence intervals are wide, including both important harms and benefits, despite large sample sizes in 2/3 trials	Undetected	53-3,806	RR 0.35-0.95	N/A	Very low This outcome had four serious **(-4)** therefore **downgrade by 4 to very low.**	

Outcome	No. of RCTs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (range)	Median (IQR)	Certainty	Other Comments
MI (Non-Fatal)	2	Serious Discrepancies exist in what is presented in the Lipids Research Clinic Trial. The effect estimate presented in the paper used a 90% confidence interval, however in the original publication on design (1979) stated the use of an alpha=0.01 (99% confidence interval).	Serious One effect estimate shows benefit, and one shows harm.	Serious 100% men	Serious Confidence intervals are wide, including both important harms and benefits.	Undetected	53-3,806	RR 0.82-1.04	N/A	Very low This outcome had four serious **(-4)** therefore **downgrade by 4 to very low.**	
MI (Fatal)	1	Not serious	Not serious	Serious 100% men.	Very serious Very few events and large confidence intervals.	Undetected	1,094	RR 0.06 (95% CI 0.00, 1.01)	N/A	Very low This outcome had one serious **(-1)** and one very serious **(-2)** therefore **downgrade by 3 to very low.**	
Stroke (All)	2	Serious	Not serious	Serious	Very serious	Undetected	53-3,806	RR 1.04-1.21	RR 1.13	Very low	

Outcome	No. of RCTs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (range)	Median (IQR)	Certainty	Other Comments
		Discrepancies exist in what is presented in the Lipids Research Clinic Trial. The effect estimate presented in the paper used a 90% confidence interval, however in the original publication on design (1979) stated the use of an alpha=0.01 (99% confidence interval).		100% men.	Very large confidence intervals, containing both benefit and harms, including the largest trial.					This outcome had two serious **(-2)** and one very serious (**-2)** therefore **downgrade by 4 to very low.**	
Primary Prevention											
MACE	1	Serious Discrepancies exist in what is presented. The effect estimate presented in the paper used a 90% confidence interval, however in the original publication on design (1979) stated the use	Not serious	Serious 100% male population, majority European (96%). MACE definition is not congruent with traditional 3-point.	Serious Summary confidence intervals contains both important benefits and potential harms.	Undetected	3,806	RR 0.83 (95% CI 0.67-1.01)	N/A	Very low This outcome had three serious **(-3)** therefore **downgrade by 3 to very low.**	

Outcome	No. of RCTs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (range)	Median (IQR)	Certainty	Other Comments
		of an alpha=0.01 (99% confidence interval).									
CV Mortality	1	Serious Discrepancies exist in what is presented. The effect estimate presented in the paper used a 90% confidence interval, however in the original publication on design (1979) stated the use of an alpha=0.01 (99% confidence interval).	Not serious	Serious 100% male population, majority European (96%).	Serious Summary confidence intervals contains both important benefits and potential harms.	Undetected	3,806	RR 0.79 (95% CI 0.49-1.26)	N/A	Very low This outcome had three serious **(-3)** therefore **downgrade by 3 to very low.**	
All-Cause Mortality	1	Serious Discrepancies exist in what is presented. The effect estimate presented in the paper used a 90% confidence interval,	Not serious	Serious 100% male population, majority European (96%).	Serious Summary confidence intervals contains both important benefits and potential harms.	Undetected	3,806	RR 0.95 (95% CI 0.69-1.32)	N/A	Very low This outcome had three serious **(-3)** therefore **downgrade by 3 to very low.**	

Outcome	No. of RCTs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (range)	Median (IQR)	Certainty	Other Comments
		however in the original publication on design (1979) stated the use of an alpha=0.01 (99% confidence interval).									
MI (Non-Fatal)	1	Serious Discrepancies exist in what is presented. The effect estimate presented in the paper used a 90% confidence interval, however in the original publication on design (1979) stated the use of an alpha=0.01 (99% confidence interval).	Not serious	Serious 100% male population, majority European (96%).	Serious Summary confidence intervals contains both important benefits and potential harms.	Undetected	3,806	RR 0.82 (95% CI 0.66-1.03)	N/A	Very low This outcome had three serious **(-3)** therefore **downgrade by 3 to very low.**	
Stroke (All)	1	Serious Discrepancies exist in what is presented. The effect estimate presented in the paper used	Not serious	Serious 100% male population, majority European (96%).	Serious Summary confidence intervals contains both important	Undetected	3,806	RR 1.21 (95% CI 0.60-2.45)	N/A	Very low This outcome had three serious **(-3)** therefore **downgrade**	

Outcome	No. of RCTs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (range)	Median (IQR)	Certainty	Other Comments
		a 90% confidence interval, however in the original publication on design (1979) stated the use of an alpha=0.01 (99% confidence interval).			benefits and potential harms.					**by 3 to very low.**	
Secondary Prevention											
MACE	1	Not serious	Not serious	Serious Primarily male population (19% female); MACE definition is not congruent with traditional 3-point and includes CAD progression	Very serious The 95% CI contains both important benefits and harms; very small sample size (n=143)	Undetected	143	OR 0.60 (95% CI 0.30-1.21)	N/A	Very low This outcome had one serious **(-1)** and one very serious **(-2)** therefore **downgrade by 3 to very low.**	
Adverse Events (Overall)											
Overall AEs	1 SR	Not serious	Not serious	Very serious Diabetic population (not CVD) looking at	Not serious	Undetected	2,714	RR 1.09 (95% CI 1.02-1.17)	N/A	Low This outcome had one very	

Outcome	No. of RCTs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (range)	Median (IQR)	Certainty	Other Comments
				glycemic control. Only pulled harms data from this SR. Older RCTs did not report harms.						serious **(-2)** therefore **downgrade by 2 to low.**	
Serious AEs	1 SR	Not serious	Not serious	Very serious Diabetic population (not CVD) looking at glycemic control. Only pulled harms data from this SR. Older RCTs did not report harms.	Not serious	Undetected	2,484	RR 1.56 (95% CI 1.01-2.40)	N/A	Low This outcome had one very serious **(-2)** therefore **downgrade by 2 to low.**	
Withdrawals due to Adverse Events	1 SR	Not serious	Not serious	Very serious Diabetic population (not CVD) looking at glycemic control. Only pulled harms data from this SR. Older RCTs did not report harms.	Serious Confidence intervals contain both important benefits and harms.	Undetected	2,501	RR 1.48 (95% CI 0.91-2.42)	N/A	Very low This outcome had one serious **(-1)** and one very serious **(-2)** therefore **downgrade by 3 to very low.**	

Ezetimibe

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (range)	Median (IQR)	Certainty	Other Comments
Overall											
MACE	3	Not serious	Not serious	Serious One study (N= 18,144) contributed ≥85% data and was in a post-MI population. Definition of MACE included revascularization, could be very serious	Not serious	Undetected Only one (Cochrane) had more than 10 studies. No ne found publication bias	18,921-21,727	RR 0.93-0.94	RR 0.93 (0.93-0.94)	Moderate This outcome had one serious **(-1)** therefore **downgrade by 1 to moderate.**	
CV Mortality	2	Not serious	Not serious	Serious One study (N= 18,144) contributed ≥85% data and was in a post-MI population.	Not serious	Undetected	18,967-19,457	RR 1.00-1.00	RR 1.00	Moderate This outcome had one serious **(-1)** therefore **downgrade by 1 to moderate.**	
All-Cause Mortality	2	Not serious	Not serious Noted some inconsistency in point estimate but borderline and already	Serious One study (N= 18,144) contributed ≥85% data and was in a	Serious CI broad and could include important risk of harm or benefit.	Undetected	19,968-21,222	RR 0.89-0.98	RR 0.94	Low This outcome had two serious **(-2)** therefore **downgrade by 2 to low.**	

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (range)	Median (IQR)	Certainty	Other Comments
			penalized in imprecision.	post-MI population.							
MI (All)	1	Not serious	Not serious	Serious One study (N= 18,144) contributed ≥85% data and was in a post-MI population.	Not serious	Undetected		OR 0.86 (95% CI 0.79-0.95)	N/A	Moderate This outcome had one serious **(-1)** therefore **downgrade by 1 to moderate.**	CIs do not overlap
Stroke (All)	1	Not serious	Not serious	Serious One study (N= 18,144) contributed ≥85% data and was in a post-MI population.	Not serious	Undetected	20,585	OR 0.86 (95% CI 0.74-1.00)	N/A	Moderate This outcome had one serious **(-1)** therefore **downgrade by 1 to moderate.**	Toyota was only SR so reviewed the metagraphs of SR
Primary Prevention											
MACE	1 (1 RCT)	Not serious	Not serious	Very serious Trial in familial hypercholesterolemia and primary outcome was intimal thickness	Very serious Very small trial with 17 outcomes	Undetected	720	RR 1.45 (95% CI 0.56-3.77)	N/A	Very low This outcome had two very serious **(-4)** therefore **downgrade by 4 to very low.**	
All-Cause Mortality	2 trials	Not serious	Not serious	Very serious Larger trial in familial hypercholesterolemia and primary outcome was	Very serious Very small event numbers (4) and high CI	Undetected	879	RR 0.78 (95% CI 0.16-3.89)	N/A	Very low This outcome had two very serious **(-4)** therefore **downgrade by 4 to very low.**	

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (range)	Median (IQR)	Certainty	Other Comments
				intimal thickness. Ot her study compared fibrate not statin.							
Secondary Prevention											
MACE	1	Not serious	Not serious	Serious MACE outcome included re-vascularizati on	Not serious	Undetected	20,745	RR 0.94 (95% CI 0.90-0.98)	N/A	Moderate This outcome had one serious **(-1)** therefore **downgrade by 1 to moderate.**	
All-Cause Mortality	1	Not serious	Not serious	Not serious	Not serious	Undetected	20,343	RR 0.98 (95% CI 0.91-1.05)	N/A	High This outcome has no downgrades.	
Patients with Diabetes											
MACE	1	Not serious	Not serious	Very serious MACE definition includes revascularizа tion All from subgroups analysis and mostly in secondary prevention	Not serious	Undetected	5,195	RR 0.86 (95% CI 0.78-0.94)	N/A	Low This outcome had one very serious **(-2)** therefore **downgrade by 2 to low.**	
Adverse Events (Overall)											
Withdrawals	1	Not serious	Not serious	Not serious	Not serious	Undetected	21,746	RR 0.91 (95% CI 0.75-1.09)	N/A	High This outcome has no downgrades.	

Fibrates

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (range)	Median (IQR)	Certainty	Other Comments
Overall Outcomes											
MACE	2	Not serious However, 7/19 trials rated as high risk of bias in at least one domain by SR authors	Not serious I^2 = 0%, 45.25%	Not serious	Not serious	Strongly suspected Multiple outcomes suggest publication bias in one SR	16,064-16,135	RR 0.84-0.88	RR 0.86	Moderate This outcome had one serious **(-1)** therefore **downgrade by 1 to moderate.**	
CV Mortality	1	Not serious	Not serious I^2 = 11.34%	Not serious	Not serious	Undetected	13,653	RR 0.95 (95% CI 0.86-1.05)	N/A	High This outcome has no downgrades.	
All-Cause Mortality	3	Not serious	Not serious I^2 = 0%, 22.73% and 33%	Not serious	Not serious	Strongly suspected Multiple outcomes suggest publication bias in one SR	8,471-45,935	RR 0.98-1.01	RR 0.98 (0.98-1.01)	Moderate This outcome had one serious **(-1)** therefore **downgrade by 1 to moderate.**	
MI (All)	3	Not serious	Not serious All I^2<25%	Serious One SR did not combine fatal and non-fatal MI's)	Not serious	Strongly suspected Multiple outcomes suggest publication	13,942-45,445	RR 0.79-0.86	RR 0.80 (0.79-0.86)	Low This outcome had two serious **(-2)** therefore **downgrade by 2 to low.**	

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (range)	Median (IQR)	Certainty	Other Comments
						bias in one SR					
Stroke (All)	2	Not serious	Not serious All I^2<25%	Not serious	Not serious	Undetected	11,719-43,188	RR 1.01-1.03	RR 1.02	High This outcome has no downgrades.	
Primary Prevention											
MACE	1	Serious 3/6 included trials were rated as high risk of bias in at least one domain by the SR authors	Not serious I^2 = 0%	Serious 4/6 trials had only diabetic patients enrolled, 73.2% patients overall were diabetic	Not serious	Strongly suspected Multiple outcomes suggest publication bias	16,135	RR 0.84 (95% CI 0.74-0.96)	RR 0.84	Very low This outcome had three serious **(-3)** therefore **downgrade by 3 to very low.**	
All-Cause Mortality	1	Serious 3/6 included trials were rated as high risk of bias in at least one domain by the SR authors	Not serious I^2 = 0%	Serious 4/6 trials had only diabetic patients enrolled, 73.2% patients overall were diabetic	Not serious	Strongly suspected Multiple outcomes suggest publication bias	8,471	RR 1.01 (95% CI 0.81-1.26)	RR 1.01	Very low This outcome had three serious **(-3)** therefore **downgrade by 3 to very low.**	
MI (All)	1	Serious 3/6 included	Not serious I^2 = 0.24%	Serious 4/6 trials had only	Not serious	Strongly suspected	16,135	RR 0.79 (95% CI 0.68-0.92)	RR 0.79	Very low This outcome had three serious **(-3)**	

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (range)	Median (IQR)	Certainty	Other Comments
		trials were rated as high risk of bias in at least one domain by the SR authors		diabetic patients enrolled, 73.2% patients overall were diabetic		Multiple outcomes suggest publication bias				therefore **downgrade by 3 to very low.**	
Secondary Prevention											
MACE	1	Not serious	Not serious I^2 = 45.25%	Not serious	Not serious	Undetected	16,064	RR 0.88 (95% CI 0.81-0.97)	RR 0.88	High This outcome has no downgrades.	
CV Mortality	1	Not serious	Not serious I^2 = 11.34%	Not serious	Not serious	Undetected	13,653	RR 0.95 (95% CI 0.86-1.05)	RR 0.95	High This outcome has no downgrades.	
All-Cause Mortality	1	Not serious	Not serious I^2 = 22.73%	Not serious	Not serious	Undetected	13,653	RR 0.98 (95% CI 0.91-1.06)	RR 0.98	High This outcome has no downgrades.	
MI (All)	1	Not serious	Not serious I^2 = 23.62%	Not serious	Not serious	Undetected	13,942	RR 0.86 (95% CI 0.80-0.93)	RR 0.86	High This outcome has no downgrades.	
Stroke (All)	1	Not serious	Not serious I^2 = 11.44%	Not serious	Not serious	Undetected	11,719	RR 1.03 (95% CI 0.91-1.16	RR 1.03	High This outcome has no downgrades.	
Adverse Events (Overall)											

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (range)	Median (IQR)	Certainty	Other Comments
Withdrawals	1	Serious 3/6 included trials were rated as high risk of bias in at least one domain by the SR authors	Serious I^2 = 73.88%	Serious 4/6 trials had only diabetic patients enrolled, 73.2% patients overall were diabetic	Not serious	Strongly suspected Multiple outcomes suggest publication bias	4,805	RR 1.38 (95% CI 0.71-2.68)	RR 1.38	Very low This outcome had four serious **(-4)** therefore **downgrade by 4 to very low.**	

Niacin

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect estimate (range)	Median (IQR)	Certainty	Other Comments
Overall Outcomes											
MACE	2	Not serious	Not serious	Not serious	Not serious	Undetected	10,295-29,254	RR 0.88-0.97	RR 0.93	High This outcome has no downgrades.	Lots of COI, no RoB analysis in one of 2 SRs (Jenkins), but results consistent with higher-quality SR (D'Andrea)
CV Mortality	5	Not serious	Not serious	Not serious	Not serious	Undetected	3,581-35,652	RR 0.91-1.14	RR 0.99 (0.95-1.08)	High This outcome has no downgrades.	Multiple COIs with 2 SRs, though results consistent with others
All-Cause Mortality	4	Not serious	Not serious	Not serious	Not serious	Undetected	29,195-35,543	RR 0.99-1.05	RR 1.04 (1.00-1.05)	High This outcome has no downgrades.	Multiple COIs with 2 SRs, though results consistent with others

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect estimate (range)	Median (IQR)	Certainty	Other Comments
MI (All)	4	Not serious	Not serious	Not serious	Not serious	Undetected	30,196-35,643	RR 0.87-0.96	RR 0.91 (0.88-0.95)	High This outcome has no downgrades.	Multiple COIs with 2 SRs, though results consistent with others
Stroke (All)	5	Not serious	Not serious	Not serious	Not serious	Undetected	30,196-34,875	RR 0.89-1.01	RR 0.95 (0.91-0.98)	High This outcome has no downgrades.	Multiple COIs with 2 SRs, though results consistent with others

Omega-3 Fatty Acids

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (range)	Median (IQR)	Certainty	Other Comments
Overall Outcomes: EPA + DHA											
MACE	3	Not serious	Not serious	Serious Aung included revascularization, the other 2 SRs didn't define MACE	Not serious	Not detected	337-25,871	RR 0.97-0.99	RR 0.98 (0.97-0.99)	Moderate This outcome had one serious **(-1)** therefore **downgrade by 1 to moderate.**	
CV Mortality	5	Serious 2 of the SRs have a low Amstar score (3/7), 2 others have a	Not serious	Serious Uncertain what outcomes were included – for example, OMEGA	Not serious	Not detected	13-25,871	RR 0.93-0.94	RR 0.93 (0.93-0.94)	Low This outcome had two serious **(-2)** therefore **downgrade by 2 to low.**	

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (range)	Median (IQR)	Certainty	Other Comments
		medium score (5/7)		trial: 2/4 SR used sudden death; 2/4 used something else that was not defined but had more than double the events than sudden death							
All-Cause Mortality	2	Not serious	Not serious	Not serious	Not serious	Not detected	13-25,871	RR 0.97-0.98	RR 0.98	High This outcome has no downgrades.	
MI (Non-fatal)	1	Not serious	Not serious	Not serious	Serious Lots of heterogeneity, effect size from RCTs ranged from 0.24-1.23	Not detected	206-12,536	OR 0.88 (95% CI 0.74-1.04)	N/A	Moderate This outcome had one serious **(-1)** therefore **downgrade by 1 to moderate.**	
Stroke (All)	1	Not serious	Not serious	Serious Non-fatal strokes only	Serious Wide CI 1.0-1.34; 5/6 RCTs on the harm side of 1, 1/6 RR 0.53	Not detected	337-25,871	RR 1.16 (95% CI 1.00-1.34)	N/A	Low This outcome had two serious **(-2)** therefore **downgrade by 2 to low.**	Non-fatal, ischemic and hemorrhagic strokes reported, not all strokes. Reported results here refer to non-

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (range)	Median (IQR)	Certainty	Other Comments
											fatal strokes as statistically significant
Atrial Fibrillation	2	Not serious	Not serious	Not serious	Serious Wide CI: for 1 SR 0.88-1.46; for the other 1.02-1.49	Not detected	182-15,480	RR 1.14-1.23	RR 1.19	Moderate This outcome had one serious **(-1)** therefore **downgrade by 1 to moderate.**	
Overall Outcomes: EPA only											
MACE	1	Not serious	Not serious	Serious Did not define MACE	Not serious	Not detected	27,305	RR 0.78 (95% CI 0.71-0.85)	N/A	Moderate This outcome had one serious **(-1)** therefore **downgrade by 1 to moderate.**	
CV Mortality	2	Not serious	Not serious	Not serious	Not serious	Not detected	8,159-27,062	RR 0.82-0.82	RR 0.82	High This outcome has no downgrades.	
All-Cause Mortality	2	Not serious	Not serious	Not serious	Not serious	Not detected	26,804-27,062	RR 0.96-0.98	RR 0.97	High This outcome has no downgrades.	
MI (Non-fatal)	1	Not serious	Not serious	Not serious	Not serious	Not detected	27,062	RR 0.72 (95% CI 0.62-0.84)	N/A	High This outcome has no downgrades.	
Stroke (All)	1	Not serious	Not serious	Serious	Not serious	Not detected	8,417	RR 0.71	N/A	Moderate	

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (range)	Median (IQR)	Certainty	Other Comments
				Non-fatal strokes only						This outcome had one serious **(-1)** therefore **downgrade by 1 to moderate.**	
Atrial Fibrillation	1	Not serious	Not serious	Not serious	Not serious	Not detected	8,179	RR 1.35	N/A	High This outcome has no downgrades.	

PCSK9 Inhibitors

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (Range)	Median (IQR)	Certainty	Other Comments
Overall Outcomes											
MACE	16 (14 with usable data)	Not serious	Not serious	Serious 4/16 systematic reviews that report on MACE use the traditional 3-point composite; 2/16 do not report their definition and many provide a vague definition of "CV events"	Not serious	Undetected	24,803-92,736	RR 0.80-0.89	RR 0.84 (0.83-0.87)	Moderate This outcome had one serious **(-1)** therefore **downgrade by 1 to moderate.**	

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (Range)	Median (IQR)	Certainty	Other Comments
CV Mortality	16 (14 with usable data)	Not serious	Not serious	Not serious	Not serious	Undetected	20,570-96,709	RR 0.87-1.01	RR 0.95 (0.94-0.97)	High This outcome has no downgrades.	
All-Cause Mortality	16 (14 with usable data)	Not serious	Not serious	Not serious	Not serious	Undetected	1,234-96,427	RR 0.43-1.01	RR 0.93 (0.88, 0.95)	High This outcome has no downgrades.	
MI (All)	15 (14 with usable data)	Not serious	Not serious	Not serious	Not serious	Undetected	36,691-86,020	RR 0.56-0.83	RR 0.79 (0.77-0.80)	High This outcome has no downgrades.	
Stroke (All)	20 (19 with usable data)	Not serious	Not serious	Not serious	Not serious	Undetected	34,793-94,408	RR 0.74-0.81	RR 0.77 (0.75-0.78)	High This outcome has no downgrades.	
Primary Prevention											
MACE	1	Serious Only one SR contributed data for primary prevention. While the AMSTAR was low risk of bias, 52% of the individual trials included in the SR were rated as high risk of	Serious Only reported the overall results of their meta-analyses, however, did not include their forest plots, therefore unable to determine heterogeneity, confidence intervals or consistency	Serious Criteria to be included as a primary prevention study was containing 60% or more of primary prevention patients.	Serious Summary confidence intervals contains both important benefits and potential harms.	Undetected	7,660	RR 0.65 (95% CI 0.35-1.21)	N/A	Very low This outcome had four serious **(-4)** therefore **downgrade by 4 to very low.**	

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (Range)	Median (IQR)	Certainty	Other Comments
		bias due to incomplete outcome reporting	between point estimates.								
CV Mortality	1	Serious Only one SR contributed data for primary prevention. While the AMSTAR was low risk of bias, 52% of the individual trials included in the SR were rated as high risk of bias due to incomplete outcome reporting	Serious Only reported the overall results of their meta-analyses, however, did not include their forest plots, therefore unable to determine heterogeneity, confidence intervals or consistency between point estimates.	Serious Criteria to be included as a primary prevention study was containing 60% or more of primary prevention patients.	Serious Summary confidence intervals contains both important benefits and potential harms.	Undetected	10,225	RR 0.63 (95% CI 0.21-1.87)	N/A	Very low This outcome had four serious **(-4)** therefore **downgrade by 4 to very low.**	
All-Cause Mortality	1	Serious Only one SR contributed data for primary prevention. While the AMSTAR was low risk of bias, 52% of the individual trials included in the SR	Serious Only reported the overall results of their meta-analyses, however, did not include their forest plots, therefore unable to determine heterogeneity, confidence intervals or	Serious Criteria to be included as a primary prevention study was containing 60% or more of primary prevention patients.	Serious Summary confidence intervals contains both important benefits and potential harms.	Undetected	10,225	RR 0.42 (95 CI 0.16-1.12)	N/A	Very low This outcome had two serious **(-4)** therefore **downgrade by 4 to very low.**	

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (Range)	Median (IQR)	Certainty	Other Comments
		were rated as high risk of bias due to incomplete outcome reporting	consistency between point estimates.								
Stroke (All)	1	Serious Only one SR contributed data for primary prevention. While the AMSTAR was low risk of bias, 52% of the individual trials included in the SR were rated as high risk of bias due to incomplete outcome reporting	Serious Only reported the overall results of their meta-analyses, however, did not include their forest plots, therefore unable to determine heterogeneity, confidence intervals or consistency between point estimates.	Serious Criteria to be included as a primary prevention study was containing 60% or more of primary prevention patients.	Serious Summary confidence intervals contains both important benefits and potential harms.	Undetected	8,064	RR 0.52 (95% CI 0.19-1.45)	N/A	Very low This outcome had four serious **(-4)** therefore **downgrade by 4 to very low.**	
Secondary Prevention											
MACE	4	Not serious	Not serious	Serious All four of the included SRs that report on this outcome use a different definition (traditional 3-point MACE, traditional or	Not serious	Undetected	30,738-78,566	RR 0.80-0.89	RR 0.84 (0.81-0.88)	Moderate This outcome had one serious **(-1)** therefore **downgrade by 1 to moderate.**	

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (Range)	Median (IQR)	Certainty	Other Comments
				nearest equivalent, CV death, MI, stroke, or definitions from individual trials)							
CV Mortality	4	Not serious	Not serious	Not serious	Not serious	Undetected	5,337-79,003	RR 0.76-1.11	RR 0.95 (0.81-1.07)	High This outcome had no downgrades.	
All-Cause Mortality	3	Not serious	Not serious	Not serious	Not serious	Undetected	52,504-78,033	RR 0.86-0.94	RR 0.94 (0.86-0.94)	High This outcome had no downgrades.	
MI (All)	3	Not serious	Not serious	Not serious	Not serious	Undetected	5,337-54,002	RR 0.74-0.80	RR 0.75 (0.74-0.80)	High This outcome had no downgrades.	
Stroke (All)	5	Not serious	Serious 2/5 systematic reviews were not statistically significant, with one SR containing benefit but also potential harm	Not serious	Not serious	Undetected	6,281-78,566	RR 0.75-0.90	RR 0.77 (0.76-0.85)	Moderate This outcome had one serious **(-1)** therefore **downgrade by 1 to moderate.**	
Patients with Diabetes											
MACE	1	Serious Only one systematic	Not serious	Not serious	Not serious	Undetected	16,700	RR 0.84 (95% CI 0.76-0.92)	N/A	Moderate This outcome had one	

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (Range)	Median (IQR)	Certainty	Other Comments
		review reported data on this population and only searched MEDLINE. It is also unclear if they utilized dual title and full text screening. The risk of bias of the included trials was overall low.								serious **(-1)** therefore **downgrade by 1 to moderate.**	
All-Cause Mortality	1	Serious Only one systematic review reported data on this population and only searched MEDLINE. It is also unclear if they utilized dual title and full text screening. The risk of bias of the included trials was overall low.	Not serious	Not serious	Very serious For this outcome, <2000 participants contributed to the forest plot. The effect estimate was OR 0.53 95% CI 0.08-3.59, which is quite wide.	Undetected	739	RR 0.53 (95% CI 0.08-3.59)	N/A	Very low This outcome had one serious (**-1**) and one very serious **(-2)** therefore **downgrade by 3 to very low.**	
Adverse Events (Overall)											

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (Range)	Median (IQR)	Certainty	Other Comments
Overall AEs	5	Not serious	Not serious	Not serious	Not serious	Undetected	24,748-59,536	RR 0.99-1.01	RR 1.00 (0.99-1.01)	High This outcome had no downgrades.	
Serious AEs	8	Not serious	Not serious	Not serious	Not serious	Undetected	24,773-62,281	RR 0.94-0.99	RR 0.97 (0.96-0.99)	High This outcome had no downgrades.	
Withdrawals	4	Not serious	Not serious	Not serious	Not serious	Undetected	55,289-66,623	RR 0.99-1.08	RR 1.05 (1.00-1.08)	High This outcome had no downgrades.	

Statins

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (range)	Median (IQR)	Certainty	Other Comments
Overall Outcomes											
MACE	7 (6 used in calculations)	Not serious	Not serious	Not serious	Not serious	Undetected	23,805-88,876	RR 0.71-0.78	RR 0.74 (0.71-0.76)	High	Definitions varied but did not affect point estimate
CV Mortality	8 (7 used in calculations)	Not serious	Not serious	Not serious	Not serious	Undetected	34,012-134,059	RR 0.80-0.90	RR 0.85 (0.83-0.86)	High This outcome had no downgrades.	
All-Cause Mortality	9 (8 used in calculations)	Not serious	Not serious	Not serious	Not serious	Undetected	47,083-143,995	RR 0.87-0.93	RR 0.91 (0.88-0.92)	High This outcome	

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (range)	Median (IQR)	Certainty	Other Comments
										had no downgrades.	
MI (All)	4	Not serious	Not serious	Not serious	Not serious	Undetected	17,856-121,190	RR 0.56-0.73	RR 0.69 (0.59-0.73)	High This outcome had no downgrades.	
MI (Fatal)	3	Not serious	Not serious	Not serious	Serious Rationale: Li 2019 has wider CI (0.24-0.98)	Undetected	NR-10,975	RR 0.49-0.73	RR 0.72 (0.49-0.73)	Moderate This outcome had one serious **(-1)** therefore **downgrade by 1 to moderate.**	
MI (Non-fatal)	2	Not serious	Not serious	Not serious	Not serious	Undetected	NR-41,191	RR 0.60-0.62	RR 0.61	High This outcome had no downgrades.	
Stroke (All)	6	Not serious	Not serious	Not serious	Not serious	Undetected	35,622-131,086	RR 0.70-0.86	RR 0.79 (0.76-0.82)	High This outcome had no downgrades.	
Stroke (Fatal)	3	Not serious	Serious Variances in RR (0.63, 0.79, 1.11)	Not serious	Serious Wider CIs (e.g. 0.18-2.23)	Undetected	NR-27,238	RR 0.63-1.11	RR 0.79 (0.63-1.11)	Low This outcome had two serious **(-2)** therefore **downgrade by 2 to low.**	
Stroke (Non-fatal)	2	Not serious	Not serious	Not serious	Not serious	Undetected	NR-28,097	RR 0.69-0.84	RR 0.77	High	

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (range)	Median (IQR)	Certainty	Other Comments
										This outcome had no downgrades.	
Primary Prevention											
MACE	6	Not serious	Not serious	Serious Variation in definitions of MACE	Not serious	Undetected	12,820-88,876	RR 0.71-0.79	RR 0.75 (0.73-0.78)	Moderate This outcome had one serious **(-1)** therefore **downgrade by 1 to moderate.**	Definitions varied but did not affect point estimate
CV Mortality	7	Not serious	Serious 4 out of 7 SRs statistically significant; 2 SRs have wider CIs (Kim 2020: 0.66-1.01; Ponce 2019: 0.83-1.24); one outlier for point estimate (Ponce 2019 RR 1.01)	Not serious	Not serious Wider CIs already downgraded for inconsistency	Undetected	15,076-95,959	RR 0.80-1.01	RR 0.83 (0.81-0.90)	Moderate This outcome had one serious **(-1)** therefore **downgrade by 1 to moderate.**	If results of Ponce 2019 SR removed, the certainty in results would be higher.
All-Cause Mortality	8	Not serious	Not serious	Not serious	Not serious	Undetected	17,515-88,876	RR 0.87-0.95	RR 0.91 (0.87-0.93)	High This outcome had no downgrades.	Although statistical significance varied (i.e. 4 out of 8 were statistically significant)

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (range)	Median (IQR)	Certainty	Other Comments
											point estimates and CI all similar.
MI (All)	4	Not serious	Not serious	Not serious	Not serious	Undetected	8,240-95,148	RR 0.45-0.73	RR 0.59 (0.48-0.70)	High This outcome had no downgrades.	
MI (Fatal)	3	Not serious	Not serious	Not serious	Serious Wide CI (Li 2019: 0.24-0.98)	Undetected	NR-10,975	RR 0.49-0.72	RR 0.61 (0.49-0.72)	Moderate This outcome had one serious **(-1)** therefore **downgrade by 1 to moderate.**	
MI (Non-fatal)	2	Not serious	Not serious	Not serious	Not serious	Undetected	NR-41,191	RR 0.60-0.62	RR 0.61	High This outcome had no downgrades.	
Stroke (All)	5	Not serious	Not serious	Not serious	Not serious	Undetected	18,515-78,473	RR 0.76-0.80	RR 0.78 (0.77-0.79)	High This outcome had no downgrades.	
Stroke (Fatal)	3	Not serious	Serious CIs are inconsistent and heterogeneity present (e.g., I2=0%, 68% or 77%)	Not serious	Serious Wide CIs (e.g. Kim 2020: 0.08-8.21; Taylor 2013: 0.18-2.23)	Undetected	NR-27,238	RR 0.63-0.81	RR 0.79 (0.63-0.81)	Low This outcome had two serious **(-2)** therefore **downgrade by 2 to low.**	

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (range)	Median (IQR)	Certainty	Other Comments
Stroke (Non-fatal)	2	Not serious	Not serious	Not serious	Not serious	Undetected	NR-28,097	RR 0.69-0.84	RR 0.77	High This outcome had no downgrades.	
Secondary Prevention											
MACE	5	Not serious	Not serious	Not serious	Not serious	Undetected	2,080-52,874	RR 0.68-0.81	RR 0.80 (0.73-0.81)	High	
CV Mortality	4	Not serious	Not serious	Not serious	Serious Wide CIs for 2 SRs: Kim 2020: 0.20-1.45, Vale 2014: 0.28-1.09	Undetected	1,954-47,115	RR 0.55-0.78	RR 0.62 (0.55-0.76)	Moderate This outcome had one serious **(-1)** therefore **downgrade by 1 to moderate.**	
All-Cause Mortality	10	Not serious	Serious Wide variation in point estimates (0.68-1.47), CIs overlap but more variable; 3 out of 10 SRs are statistically significant.	Serious Different populations studied in some SRs (e.g., post-stroke (5 SRs)) and ACS (one SR)).	Serious Wide CIs indicating benefit and harm (eg. Fang 2017 0.60-2.35, Squizzato 2011 0.60-3.81, Vale 2014 0.39-1.20); 2 out of 10 SRs were under 500 patients	Undetected	239-57,354	RR 0.68-1.47	RR 0.92 (0.84-1.07)	Very low This outcome had three serious **(-3)** therefore **downgrade by 3 to very low.**	
All-Cause Mortality	4	Not serious	Not serious	Not serious	Not serious	Undetected	7,993-52,874	RR 0.80-0.95	RR 0.86	High	Post-hoc analysis;

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (range)	Median (IQR)	Certainty	Other Comments
									(0.81-0.93)	This outcome had no downgrades.	Post-stroke and ACS SRs removed
MI (All)	3	Not serious	Serious Heterogeneity due to Vale (point estimate and CI and NSS)	Serious Downgraded due to Vale (ACS patients)	Serious Vale's CI was wide and included no benefit	Undetected	1,954-26,922	RR 0.68-0.94	RR 0.73 (0.68-0.94)	Very low This outcome had three serious **(-3)** therefore **downgrade by 3 to very low.**	
MI (All)	2	Not serious	Not serious	Not serious	Not serious	Undetected	7,051-26,922	RR 0.68-0.73	RR 0.71	High This outcome had no downgrades.	Post-hoc analysis; ACS SR removed
MI (Fatal)	1	Not serious	Serious High heterogeneity (I2=59% moderate-substantial)	Not serious	Very serious Wide CI (0.08-7.18)	Undetected	NR	RR 0.75 (95% CI 0.08-7.18)	N/A	Very low This outcome had one serious **(-1)** and one very serious **(-2)** therefore **downgrade by 3 to very low.**	
Stroke (All)	7	Not serious	Serious Variance in point estimate (e.g. 0.38-1.05); 1 out of 7	Serious 4/7 are stroke population; 1/7 is ACS	Serious Vale is outlier and wide CI	Undetected	889-22,763	RR 0.38-1.05	RR 0.90 (0.88-0.93)	Very low This outcome had three serious **(-3)** therefore **downgrade**	

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (range)	Median (IQR)	Certainty	Other Comments
			statistically significance							**by 3 to very low.**	
Stroke (All)	2	Not serious	Not serious	Not serious	Not serious	Undetected	10,706-22,763	RR 0.90-0.93	RR 0.92	High This outcome had no downgrades.	Post-hoc analysis; Post-stroke, ACS SRs removed
Stroke (Fatal)	1	Not serious	Not serious	Not serious	Serious Wide CI (0.70-1.78)	Undetected	NR	RR 1.11 (95% CI 0.70-1.78)	N/A	Moderate This outcome had one serious **(-1)** therefore **downgrade by 1 to moderate.**	
Patients with Diabetes											
MACE	2	Not serious	Not serious	Not serious	Serious CIs are wide (e.g. Singh 2020: 0.19-1.04; Ponce 2019: 0.42-1.06)	Undetected	NR-1,129	RR 0.45-0.67	RR 0.56	Moderate This outcome had two serious **(-1)** therefore **downgrade by 1 to moderate.**	Primary prevention population
CV Mortality	2	Not serious	Not serious	Not serious	Serious Wide CIs (Ponce 2019: 0.30-1.33; Singh 2020: 0.36-1.15)	Undetected	NR-1,129	RR 0.63-0.65	RR 0.64	Moderate This outcome had one serious **(-1)** therefore **downgrade by 1 to moderate.**	Primary prevention population

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (range)	Median (IQR)	Certainty	Other Comments
All-Cause Mortality	2	Not serious	Not serious	Not serious	Serious Wide CIs for Ponce 2019 (0.51-1.18)	Undetected	NR-1,129	RR 0.70-0.78	RR 0.74	Moderate This outcome had one serious **(-1)** therefore **downgrade by 1 to moderate**	Primary prevention population
MI (All)	2	Not serious	Not serious	Not serious	Serious CIs are wide (Ponce 2019: 0.22-0.77, Singh 2020: 0.35-0.81) – calculation for OIS was attempted but CARDS study did not report sample size needed for the outcome of MI.	Undetected	NR-1,129	RR 0.41-0.53	RR 0.47	Moderate This outcome had one serious **(-1)** therefore **downgrade by 1 to moderate.**	Primary prevention population
Stroke (All)	2	Not serious	Not serious	Not serious	Serious Wide CIs (Ponce 2019: 0.27-1.03, Singh 2020: 0.39-0.89)	Undetected	NR-1,129	RR 0.53-0.59	RR 0.56	Moderate This outcome had one serious **(-1)** therefore **downgrade by 1 to moderate.**	Primary prevention population
Patients with Chronic Kidney Disease											

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (range)	Median (IQR)	Certainty	Other Comments
MACE	1	Not serious	Not serious	Not serious	Not serious	Undetected	36,033	RR 0.72 (95% CI 0.67-0.79)	N/A	High This outcome had no downgrades.	
CV Mortality	1	Not serious	Not serious	Not serious	Not serious	Undetected	19,059	RR 0.77 (95% CI 0.69-0.87)	N/A	High This outcome had no downgrades.	
All-Cause Mortality	1	Not serious	Not serious	Not serious	Not serious	Undetected	28,276	RR 0.79 (95% CI 0.69-0.91)	N/A	High This outcome had no downgrades.	
MI (All)	1	Not serious	Not serious	Not serious	Not serious	Undetected	9,018	RR 0.55 (95% CI 0.42-0.72)	N/A	High This outcome had no downgrades.	
Stroke (All)	1	Not serious	Serious High heterogeneity (I^2=53% moderate-substantial)	Not serious	Serious Wide CI (0.35-1.12)	Undetected	8,658	RR 0.63 (95% CI 0.35-1.12)	N/A	Low This outcome had two serious **(-2)** therefore **downgrade by 2 to low.**	
Adverse Events (Overall)											
Overall AEs	2	Not serious	Not serious	Not serious	Not serious	Undetected	3,254-40,716	RR 0.99-1.00	RR 1.00	High This outcome had no downgrades.	
Serious AEs	2	Not serious	Not serious	Not serious	Not serious	Undetected	15,947-42,952	RR 0.99-1.01	RR 1.00	High This outcome	

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (range)	Median (IQR)	Certainty	Other Comments
										had no downgrades.	
Withdrawals	6	Not serious	Not serious	Not serious	Not serious	Undetected	4,219-129,680	RR 0.87-1.16	RR 1.00 (0.90-1.08)	High This outcome had no downgrades.	
Any muscle symptoms	5	Not serious	Not serious	Not serious	Not serious	Undetected	16,633-94,635	RR 1.01-1.05	RR 1.03 (1.01-1.05)	High This outcome had no downgrades.	Wide spectrum of symptoms included in SR definitions: pain, weakness, cramps, tenderness, etc.
Myalgia	5	Not serious	Not serious	Not serious	Not serious	Undetected	22,533-62,214	RR 1.02-1.13	RR 1.03 (1.02-1.11)	High This outcome had no downgrades.	
Myopathy	7 (6 used in calculations)	Not serious	Serious Varying point estimates	Not Serious	Serious Wide CIs that include potential benefit to largely increased relative harm, Vale outlier (ACS patients)	Undetected	4,677-85,740	RR 0.88-4.69	RR 1.09 (1.02-2.16)	Low This outcome had two serious **(-2)** therefore **downgrade by 2 to low.**	Two SRs defined as muscle symptoms with CK>10 times ULN (Singh 2020, Vale 2014), two used trial definitions (Yebyo 2019, Cai 2021); Cai may have included

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (range)	Median (IQR)	Certainty	Other Comments
											rhabdomyolysis cases); 3 SRs did not provide definition (Li 2019, Zhou 2020, Riaz 2017)
Liver dysfunction	4 (3 used in calculations)	Not serious	Not serious	Serious Various definitions used in SRs	Not serious	Undetected	18,071-74,078	RR 1.15-1.33	RR 1.17 (1.15-1.33)	Moderate This outcome had one serious **(-1)** therefore **downgrade by 1 to moderate.**	Varied definitions: liver enzyme changes & liver disorders (Cai 2021); original trial definitions (Yebyo 2019); no definition (Li 2019, Liang 2018)
Elevated liver enzymes	6	Not serious	Serious Varying point estimates, I2 is moderate-substantial for some SRs (0%-73%)	Serious 4 SRs did not define; 2 defined as AST/ALT >2-3x ULN	Serious Wide CIs (Palmer 2014: 0.39-1.50; Li 2019: 1.00-5.60; Vale 2014: 1.16-5.32)	Undetected	7,991-123,051	RR 0.76-2.49	RR 1.32 (1.06-2.39)	Very low This outcome had three serious **(-3)** therefore **downgrade by 3 to very low.**	Varied definitions: degree of elevation not defined (Li 2019, Palmer 2014, Taylor 2013, Villani 2019); >2-3X ULN (Singh 2020, Vale 2014)
Incident diabetes mellitus	9	Not serious	Not serious	Serious	Not serious	Undetected	24,407-95,102	RR 1.01-1.21	RR 1.10 (1.07-1.14)	Moderate This outcome had one	Varied definitions: One SR defined

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (range)	Median (IQR)	Certainty	Other Comments
				Various definitions used in SRs						serious **(-1)** therefore **downgrade by 1 to moderate.**	inclusion as a clear report of newly diagnosed diabetes mellitus as adverse effect in RCT, or initiation of diabetic medications during trial, or two consecutive readings of fast blood glucose ≥ 7mmol/L during study (Khan 2019). The remaining SRs used trial definitions of diabetes (Cai 2021, Yebyo 2019) or did not describe diagnostic criteria (Li 2019, Domecq 2019, Engeda 2019, Wang 2017, Singh 2020, Taylor 2013)

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (range)	Median (IQR)	Certainty	Other Comments
Renal disorder	4	Not serious	Not serious	Serious 3 SRs did not define renal disorders beyond "renal dysfunction/ disorder"; one defined as proteinuria & non-specified renal disorders	Not serious	Undetected	27,804-32,001	RR 1.11-1.13	RR 1.12 (1.11-1.13)	Moderate This outcome had one serious **(-1)** therefore **downgrade by 1 to moderate.**	Variably described: "renal dysfunction" (Yebyo 2019, Taylor 2013), "renal disorder" (Li 2019), proteinuria & non-specified disorders (Cai 2021)
Rhabdomyolysis	8	Not serious	Serious Varying point estimates	Not serious	Very Serious Wide CIs for all SRs (e.g. Vale 2014: 0.36-133.47)	Undetected	4,497-76,507	RR 0.84-6.90	RR 1.15 (0.95-2.58)	Very low This outcome had one serious **(-1)** and one very serious **(-2)** therefore **downgrade by 3 to very low.**	Six SRs did not define rhabdomyolysis criteria (Li 2019, Singh 2020, Taylor 2013, Vale 2014, Zhou 2020, Palmer 2014) while Davis 2021 used trial definition.
CK elevation	4	Not serious	Serious Varying point estimates	Not serious	Very serious Wide CIs for all SRs (e.g. Davis 2021: 0.25-30.11;	Undetected	5,000-61,396	RR 0.88-2.73	RR 1.24 (0.95-2.38)	Very low This outcome had one serious **(-1)** and one very serious **(-2)**	Defined in 2 SRs as CK >10XULN (Davis 2021, Singh 2020); one SR did not define beyond "CK

Outcome	No. of SRs	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients (range)	Effect Estimate (range)	Median (IQR)	Certainty	Other Comments
					Li 2019: 0.14-12.22)					therefore **downgrade by 3 to very low.**	elevation**”** (Li 2019)

ACS= Acute Coronary Syndrome; CIs=Confidence Intervals; SR=Systematic Review; ULN= upper limit of normal; CK=creatine kinase