In the Name of God

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Effects of statin therapy on diagnoses of new-onset diabetes and worsening glycaemia in large-scale randomised blinded statin trials: an individual participant data meta-analysis

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Statins have few confirmed adverse effects, metaanalyses of summary data in published reports from large randomised controlled trials of statin therapy indicated that standard statin regimens **increased the risk of new-onset diabetes** by about **10%** compared with placebo or usual care. The more intensive statin regimens produced a further 10% relative increase in risk.

Assessment of the effects of statin therapy on the risk of developing new diabetes is incomplete. In particular, which types of people are at particularly high risk of developing diabetes due to a statin, the timing of any excess risk after commencing therapy, or the effects of statin therapy on glycaemic control in people with known diabetes.

Methods:

Search strategy and selection criteria Methods were described in the published **CTT (Cholesterol Treatment Trialists)** Collaboration protocol. Briefly, we conducted a meta-analysis of individual participant data from randomised controlled trials of statin therapy participating in the CTT Collaboration. Double-blind, randomized controlled trials of statin therapy were eligible for inclusion.

at least 1000 participants; and there was a mean follow-up of at least 2 years. We requested data related to all adverse events recorded during the scheduled period of treatment and follow-up. These data included the timing of such events, use of other medications (including glucose-lowering medications), physical measurements, any comorbidities, and laboratory results (including glucose and HbA1c values.

Data analysis:

Baseline diabetes was defined as a recorded history of diabetes, adverse event of diabetes on or before the date of participant assignment to a treatment group, use of glucose-lowering medication, FBS≥7·0 mmol/L (126 mg/dl) or random plasma glucose≥11·1 mmol/L (200 mg/dl), or HbA1c≥6·5%.

For participants without baseline diabetes, the outcome of new-onset diabetes was defined as the first record after participant assignment to a treatment group of an adverse event of diabetes, use of glucose-lowering medication, **at least two measurements** (not necessarily consecutive) of FBS≥(126 mg/dl) or random plasma glucose≥(200 mg/dl), or HbA1c≥6·5%.

In baseline diabetes participants , the worsening glycaemia was defined as a recording after participant assignment to a treatment group of an adverse event relating to **ketosis** or complications of glucose control, an **HbA1c increase (from baseline) of 0·5% or higher**, or escalation of glucose-lowering medication (ie, starting such medication for participants not on medication at baseline, starting insulin for those not on insulin therapy at baseline, or an increase in the number of non-insulin glucose-lowering medications).

In addition to the prespecified subgroup analyses, additional post-hoc analyses were done to further explore variation according to baseline levels of glycaemia by dividing participants into quartiles defined hierarchically on the basis of HbA1c, fasting glucose concentration (if HbA1c value was not available), or random glucose concentration.

Results are reported separately for low-intensity or moderate-intensity and high-intensity statin regimens. Only two trials allowed for direct assessments of high-intensity statin versus placebo.

To estimate the average absolute effect of statin therapy on the underlying rate of particular outcomes, we applied the RR (or its lower and upper 95% CIs). We used the summary RRs for all statin regimens in 16 trials of statin versus placebo to estimate the absolute excess annual rate of new-onset diabetes according to quartiles of baseline glycaemia and a risk score of new-onset diabetes, developed using a Poisson regression model.

	Year of publication of primary results	Number of participants	Treatment comparison	Median follow up, years	Mean LDL cholesterol concentration, mmol/L (SD)	Mean age, years (SD)	Mean BMI, kg/m² (SD)	Mean estimated GFR, mL/min per 1·73 m² (SD)	Women, n (%)	White participants, n (%)	Participants with a history of vascular disease, n (%)	Participants with diabetes at baseline, n (%)†
Statin *vs* placebo (19 trials)	..	123 940	..	4·3	3·5 (0·7)	63 (8)	27·2 (4·1)	69·5 (15·0)	34 533 (28%)	60 152 (81%)*	59 610 (48%)	25 701 (21%)
Low-intensity statin (one trial)	..	6605	..	5·0	3·9 (0·4)	58 (7)	26·9 (3·1)	65·4 (11·6)	997 (15%)	5860 (89%)	0	232 (4%)
AFCAPS/TexCAPS[20]	1998	6605	Lovastatin 20–40 mg/day *vs* placebo	5·0	3·9 (0·4)	58 (7)	26·9 (3·1)	65·4 (11·6)	997 (15%)	5860 (89%)	0	232 (4%)
Moderate-intensity statin (16 trials)	..	95 890	..	4·6	3·6 (0·8)	63 (8)	27·2 (4·2)	69·5 (15·3)	25 254 (26%)	49 877 (80%)*	54 879 (57%)	23 818 (25%)
4S[21]	1994	4444	Simvastatin 20–40 mg/day *vs* placebo	5·4	4·9 (0·7)	59 (7)	26·0 (3·3)	NA	827 (19%)	NA	4444 (100%)	202 (5%)
WOSCOPS[22]	1995	6595	Pravastatin 40 mg/day *vs* placebo	4·8	5·0 (0·5)	55 (6)	26·0 (3·2)	77·8 (12·4)	0	NA	1066 (16%)	143 (2%)
CARE[23]	1996	4159	Pravastatin 40 mg/day *vs* placebo	4·9	3·6 (0·4)	59 (9)	27·6 (4·4)	67·2 (15·7)	576 (14%)	3851 (93%)	4159 (100%)	667 (16%)
LIPID[27]	1998	9014	Pravastatin 40 mg/day *vs* placebo	5·9	3·9 (0·8)	61 (8)	26·8 (3·8)	70·6 (16·3)	1516 (17%)	NA	9014 (100%)	1077 (12%)
LIPS[33]	2002	1677	Fluvastatin 80 mg/day *vs* placebo	4·0	3·4 (0·8)	60 (10)	26·5 (3·3)	67·6 (15·5)	271 (16%)	1650 (98%)	1677 (100%)	204 (12%)
HPS[24]	2002	20 536	Simvastatin 40 mg/day *vs* placebo	5·2	3·4 (0·8)	64 (8)	27·6 (4·4)	72·2 (16·5)	5082 (25%)	19 901 (97%)	17 386 (85%)	5973 (29%)
PROSPER[28]	2002	5804	Pravastatin 40 mg/day *vs* placebo	3·3	3·8 (0·8)	75 (3)	26·8 (4·2)	56·7 (13·6)	3000 (52%)	NA	2565 (44%)	760 (13%)
ASCOT-LLA[29]	2003	10 240	Atorvastatin 10 mg/day *vs* placebo	3·3	3·4 (0·7)	63 (9)	28·6 (4·6)	68·4 (12·9)	1919 (19%)	9687 (95%)	1684 (16%)	2699 (26%)
ALERT[31]	2003	2102	Fluvastatin 40–80 mg/day *vs* placebo	5·5	4·1 (1·0)	50 (11)	25·8 (4·5)	49·6 (17·0)	715 (34%)	2039 (97%)	409 (19%)	430 (20%)
CARDS[26]	2004	2838	Atorvastatin 10 mg/day *vs* placebo	4·2	2·9 (0·8)	61 (8)	28·8 (3·6)	64·2 (11·3)	909 (32%)	2676 (94%)	106 (4%)	2838 (100%)
4D[25]	2005	1255	Atorvastatin 20 mg/day *vs* placebo	2·7	3·3 (0·8)	66 (8)	27·6 (4·8)	NA	578 (46%)	924 (74%)	1041 (83%)	1255 (100%)
ASPEN[34]	2006	2410	Atorvastatin 10 mg/day *vs* placebo	4·0	2·9 (0·7)	60 (8)	28·9 (3·8)	65·9 (12·8)	811 (34%)	2029 (84%)	747 (31%)	2410 (100%)
CORONA[30]	2007	4982	Rosuvastatin 10 mg/day *vs* placebo	2·7	3·6 (0·9)	72 (7)	26·4 (3·6)	55·4 (15·1)	1175 (24%)	NA	4982 (100%)	1481 (30%)
GISSI-HF[31]	2008	4574	Rosuvastatin 10 mg/day *vs* placebo	3·9	3·1 (0·9)	68 (11)	27·1 (4·5)	66·3 (20·4)	1032 (23%)	4574 (100%)	4574 (100%)	1771 (39%)
AURORA[32]	2009	2555	Rosuvastatin 10 mg/day *vs* placebo	3·9	2·6 (0·9)	64 (9)	24·8 (3·9)	NA	969 (38%)	NA	1025 (40%)	747 (29%)
HOPE-3[35]	2016	12 705	Rosuvastatin 10 mg/day *vs* placebo	5·5	3·3 (0·9)	66 (6)	27·1 (4·7)	79·6 (16·1)	5874 (46%)	2546 (20%)	0	1161 (9%)
High-intensity statin (two trials)	..	21 445	..	2·6	2·9 (0·5)	65 (9)	27·6 (4·0)	70·7 (14·6)	8282 (39%)	4415 (93%)*	4731 (22%)	1651 (8%)
SPARCL[36]	2006	4731	Atorvastatin 80 mg/day *vs* placebo	4·9	3·5 (0·6)	63 (11)	27·9 (5·2)	65·2 (13·8)	1908 (40%)	4415 (93%)	4731 (100%)	909 (19%)
JUPITER[37]	2008	16 714	Rosuvastatin 20 mg/day *vs* placebo	1·9	2·7 (0·5)	65 (8)	27·5 (3·6)	72·3 (14·8)	6374 (38%)	NA	0	742 (4%)
More intensive *vs* less intensive statin (double blind; four trials)	..	30 724	–	4·9	2·5 (0·6)	62 (9)	28·4 (5·1)	72·2 (15·6)	5965 (19%)	28 865 (94%)	30 724 (100%)	5340 (17%)

	Year of publication of primary results	Number of participants	Treatment comparison	Median follow up, years	Mean LDL cholesterol concentration, mmol/L (SD)	Mean age, years (SD)
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PROSPER[28]	2002	5804	Pravastatin 40 mg/day vs placebo	3·3	3·8 (0·8)	75 (3)
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More intensive vs less intensive statin (double blind; four trials)	--	30 724	--	4·9	2·5 (0·6)	62 (9)

	Mean BMI, kg/m² (SD)	Mean estimated GFR, mL/min per 1·73 m² (SD)	Women, n (%)	White participants, n (%)	Participants with a history of vascular disease, n (%)	Participants with diabetes at baseline, n (%)†
	27·2 (4·1)	69·5 (15·0)	34 533 (28%)	60 152 (81%)*	59 610 (48%)	25 701 (21%)
	26·9 (3·1)	65·4 (11·6)	997 (15%)	5860 (89%)	0	232 (4%)
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	27·2 (4·2)	69·5 (15·3)	25 254 (26%)	49 877 (80%)*	54 879 (57%)	23 818 (25%)
	26·0 (3·3)	NA	827 (19%)	NA	4444 (100%)	202 (5%)
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	27·6 (4·4)	67·2 (15·7)	576 (14%)	3851 (93%)	4159 (100%)	667 (16%)
	26·8 (3·8)	70·6 (16·3)	1516 (17%)	NA	9014 (100%)	1077 (12%)
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	25·8 (4·5)	49·6 (17·0)	715 (34%)	2039 (97%)	409 (19%)	430 (20%)
	28·8 (3·6)	64·2 (11·3)	909 (32%)	2676 (94%)	106 (4%)	2838 (100%)
	27·6 (4·8)	NA	578 (46%)	924 (74%)	1041 (83%)	1255 (100%)
	28·9 (3·8)	65·9 (12·8)	811 (34%)	2029 (84%)	747 (31%)	2410 (100%)
	26·4 (3·6)	55·4 (15·1)	1175 (24%)	NA	4982 (100%)	1481 (30%)
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	24·8 (3·9)	NA	969 (38%)	NA	1025 (40%)	747 (29%)
	27·1 (4·7)	79·6 (16·1)	5874 (46%)	2546 (20%)	0	1161 (9%)
	27·6 (4·0)	70·7 (14·6)	8282 (39%)	4415 (93%)*	4731 (22%)	1651 (8%)
)	27·9 (5·2)	65·2 (13·8)	1908 (40%)	4415 (93%)	4731 (100%)	909 (19%)
	27·5 (3·6)	72·3 (14·8)	6374 (38%)	NA	0	742 (4%)
	28·4 (5·1)	72·2 (15·6)	5965 (19%)	28 865 (94%)	30 724 (100%)	5340 (17%)

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	Year of publication of primary results	Number of participants	Treatment comparison	Median follow up, years	Mean HDL cholesterol concentration, mmol/L (SD)	Mean age, years (SD)	Mean BMI, kg/m² (SD)	Mean estimated GFR, mL/min per 1·73 m² (SD)	Women, n (%)	White participants, n (%)	Participants with a history of vascular disease, n (%)	Participants with diabetes at baseline, n (%)†
(Continued from previous page)												
Comparison of moderate-intensity regimens (two trials)	..	16 561	..	5·6	2·4 (0·6)	63 (9)	28·0 (4·3)	74·8 (16·8)	3152 (19%)	15 679 (95%)	16 561 (100%)	2339 (14%)
A to Z[37]	2004	4497	Simvastatin 40 mg/day then 80 mg/day vs placebo then simvastatin 20 mg/day	2·0	2·1 (0·5)	60 (11)	27·6 (4·8)	68·4 (16·0)	1100 (24%)	3825 (85%)	4497 (100%)	1059 (24%)
SEARCH[38]	2010	12 064	Simvastatin 80 mg/day vs 20 mg/day	7·0	2·5 (0·6)	64 (9)	28·1 (4·1)	77·2 (17·1)	2052 (17%)	11 854 (98%)	12 064 (100%)	1280 (11%)
Comparison of high-intensity vs moderate-intensity regimens (two trials)	..	14 163	..	4·1	2·5 (0·6)	60 (10)	29·0 (6·0)	69·1 (14·3)	2813 (20%)	13 186 (93%)	14 163 (100%)	3001 (21%)
PROVE-IT[39]	2004	4162	Atorvastatin 80 mg/day vs pravastatin 40 mg/day	2·1	2·6 (0·7)	58 (11)	29·5 (5·7)	78·8 (18·7)	911 (22%)	3776 (91%)	4162 (100%)	1034 (25%)
TNT[40]	2005	10 001	Atorvastatin 80 mg/day vs 10 mg/day	5·0	2·5 (0·5)	61 (9)	28·8 (6·1)	65·0 (12·4)	1902 (19%)	9410 (94%)	10 001 (100%)	1967 (20%)
All trials	..	154 664	..	4·4	3·3 (0·7)	63 (8)	27·5 (4·3)	70·1 (15·1)	40 498 (26%)	89 017 (85%)*	90 334 (58%)	31 041 (20%)

All trials randomised in a 1:1 allocation. Some participants in the AURORA (n=218), CORONA (n=27), and JUPITER (n=1088) trials withdrew consent for use of their data after the trial, and hence data from these participants is excluded. The ASCOT-LLA trial excludes 65 participants for whom data were not available due to protocol violations, and so are not included in the number of participants or percentages shown. 4D=Die Deutsche Diabetes Dialyse Studie. 4S=Scandinavian Simvastatin Survival Study. AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study. ALERT=Assessment of Lescol in Renal Transplantation. ASCOT-LLA=Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm. ASPEN=Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus. A to Z=Aggrastat to Zocor. AURORA=A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events. CARDS=Collaborative Atorvastatin Diabetes Study. CARE=Cholesterol And Recurrent Events. CORONA=Controlled Rosuvastatin Multinational Trial in Heart Failure. GISSI-HF=Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca. HOPE-3=Heart Outcomes Prevention Evaluation-3 trial. HPS=Heart Protection Study. JUPITER=Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin. LIPID=Long-term Intervention with Pravastatin in Ischaemic Disease. LIPS=Lescol Intervention Prevention Study. NA=not available. PROSPER=PROspective Study of Pravastatin in the Elderly at Risk. PROVE-IT=Pravastatin or Atorvastatin Evaluation and Infection Therapy. SEARCH=Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine. SPARCL=Stroke Prevention by Aggressive Reduction in Cholesterol Levels. TNT=Treating to New Targets. WOSCOPS=West of Scotland Coronary Prevention Study. *Percentages were calculated after excluding the seven trials where information on race and ethnicity was not provided (the relevant denominators are therefore 73 832 for all trials of statin vs placebo, 62 496 for trials of moderate-intensity statin therapy vs placebo, 4731 for trials of high-intensity statin therapy vs placebo, and 104 556 for all trials). †Baseline diabetes is defined as participants with a history of diabetes plus those retrospectively defined as having diabetes at baseline on the basis of adverse events, glucose-lowering medication, or glucose or HbA_{1c} measurements at the time of assignment to a treatment group.

Table: Characteristics of the participating trials

	Year of publication of primary results	Number of participants	Treatment comparison	Median follow up, years	Mean LDL cholesterol concentration, mmol/L (SD)	Mean age, years (SD)
(Continued from previous page)						
Comparison of moderate-intensity regimens (two trials)	..	16 561	..	5·6	2·4 (0·6)	63 (9)
A to Z[39]	2004	4497	Simvastatin 40 mg/day then 80 mg/day *vs* placebo then simvastatin 20 mg/day	2·0	2·1 (0·5)	60 (11)
SEARCH[40]	2010	12 064	Simvastatin 80 mg/day *vs* 20 mg/day	7·0	2·5 (0·6)	64 (9)
Comparison of high-intensity *vs* moderate-intensity regimens (two trials)	..	14 163	..	4·1	2·5 (0·6)	60 (10)
PROVE-IT[39]	2004	4162	Atorvastatin 80 mg/day *vs* pravastatin 40 mg/day	2·1	2·6 (0·7)	58 (11)
TNT[40]	2005	10 001	Atorvastatin 80 mg/day *vs* 10 mg/day	5·0	2·5 (0·5)	61 (9)
All trials	..	154 664	..	4·4	3·3 (0·7)	63 (8)

All trials randomised in a 1:1 allocation. Some participants in the AURORA (n=218), CORONA (n=27), and JUPITER (n=1088) trials withdr trial excludes 65 participants for whom data were not available due to protocol violations, and so are not included in the number of parti Study. AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study. ALERT=Assessment of Lescol in Renal Transplantat Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus. A to Z=Aggrastat to Zocor. AURORA=A Stu Cardiovascular Events. CARDS=Collaborative Atorvastatin Diabetes Study. CARE=Cholesterol And Recurrent Events. CORONA=Controlled nell'Insufficienza cardiaca. HOPE-3=Heart Outcomes Prevention Evaluation-3 trial. HPS=Heart Protection Study. JUPITER=Justification fo with Pravastatin in Ischaemic Disease. LIPS=Lescol Intervention Prevention Study. NA=not available. PROSPER=PROspective Study of Pra SEARCH=Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine. SPARCL=Stroke Prevention by Aggressive Study. *Percentages were calculated after excluding the seven trials where information on race and ethnicity was not provided (the relev statin therapy *vs* placebo, 4731 for trials of high-intensity statin therapy *vs* placebo, and 104 556 for all trials). †Baseline diabetes is defin basis of adverse events, glucose-lowering medication, or glucose or HbA_{1c} measurements at the time of assignment to a treatment group

Table: Characteristics of the participating trials

Mean BMI, kg/m² (SD)	Mean estimated GFR, mL/min per 1·73 m² (SD)	Women, n (%)	White participants, n (%)	Participants with a history of vascular disease, n (%)	Participants with diabetes at baseline, n (%)†
28·0 (4·3)	74·8 (16·8)	3152 (19%)	15679 (95%)	16561 (100%)	2339 (14%)
27·6 (4·8)	68·4 (16·0)	1100 (24%)	3825 (85%)	4497 (100%)	1059 (24%)
28·1 (4·1)	77·2 (17·1)	2052 (17%)	11854 (98%)	12064 (100%)	1280 (11%)
29·0 (6·0)	69·1 (14·3)	2813 (20%)	13186 (93%)	14163 (100%)	3001 (21%)
29·5 (5·7)	78·8 (18·7)	911 (22%)	3776 (91%)	4162 (100%)	1034 (25%)
28·8 (6·1)	65·0 (12·4)	1902 (19%)	9410 (94%)	10001 (100%)	1967 (20%)
27·5 (4·3)	70·1 (15·1)	40 498 (26%)	89 017 (85%)*	90334 (58%)	31 041 (20%)

drew consent for use of their data after the trial, and hence data from these participants is excluded. The ASCOT-LLA rticipants or percentages shown. 4D=Die Deutsche Diabetes Dialyse Studie. 4S=Scandinavian Simvastatin Survival ation. ASCOT-LLA=Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm. ASPEN=Atorvastatin Study for Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and ed Rosuvastatin Multinational Trial in Heart Failure. GISSI-HF=Gruppo Italiano per lo Studio della Sopravvivenza for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin. LIPID=Long-term Intervention ravastatin in the Elderly at Risk. PROVE-IT=Pravastatin or Atorvastatin Evaluation and Infection Therapy. ive Reduction in Cholesterol Levels. TNT=Treating to New Targets. WOSCOPS=West of Scotland Coronary Prevention evant denominators are therefore 73 832 for all trials of statin vs placebo, 62 496 for trials of moderate-intensity ned as participants with a history of diabetes plus those retrospectively defined as having diabetes at baseline on the up.

Results

Of the trials in the CTT Collaboration, individual participant data were available from 19 eligible doubleblind trials of any statin regimen versus placebo (123 940 participants; median follow-up of 4·3 years), of which 16 trials (117 437 participants) included participants with and without a history of diabetes, and three trials (6503 participants) recruited only participants with a history of diabetes.

In the 14 trials of **low-intensity or moderate-intensity** statin versus placebo that included participants without diabetes at baseline, allocation to statin therapy resulted in a **10% relative increase in new-onset diabetes** (2420 of 39 179 participants assigned to statin therapy[1·3% per year] vs 2214 of 39266 participants assigned to placebo [1·2% per year]; RR 1·10, 95% CI 1·04–1·16), which corresponded to a mean absolute excess of 0·12% (95% CI 0·04–0·20) during each year of treatment (figure 1).

The placebo event rate for new-onset diabetes was substantially higher in the two trials of high-intensity statin (905 of 9859 participants assigned to placebo [3·5% per year]) than in the 14 trials of low-intensity or moderate-intensity statins (1·2% per year), and this **difference was driven by biochemical diagnosis of diabetes** (788 of 9859 participants assigned to placebo [3·0% per year] for high-intensity statins vs 1369 of 39266 participants assigned to placebo [0·8% per year] for low-intensity or moderate-intensity statins; figure 1).

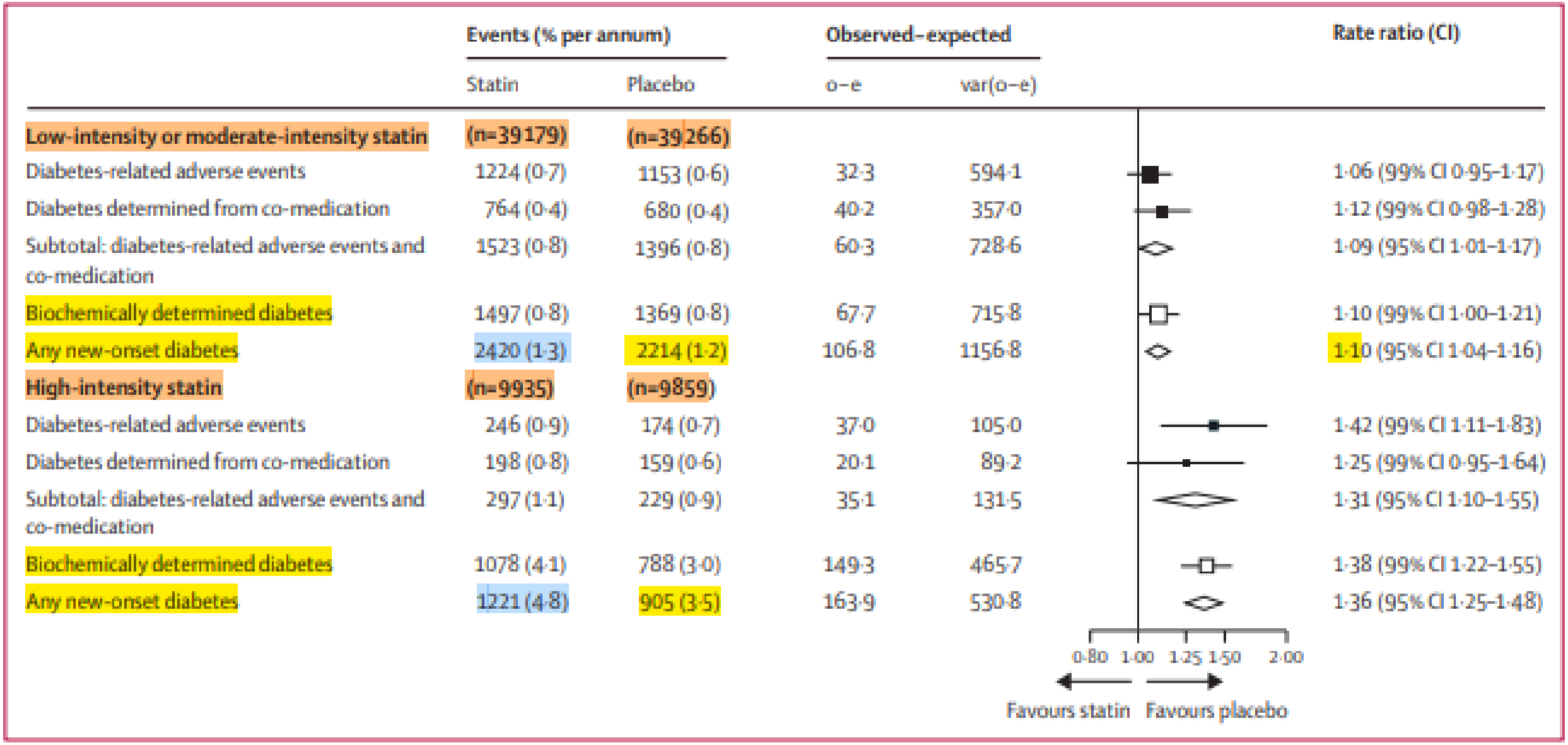

Figure 1: Effect of statin vs placebo on new-onset diabetes by statin intensity

In the two trials of high-intensity statin versus placebo that included participants without baseline diabetes, allocation to statin therapy resulted in a **36%** relative increase in **new-onset diabetes** (1221 of 9935 participants assigned to statin therapy [4·8% per year] vs 905 of 9859 participants assigned to placebo [3·5% per year]; RR 1·36, 95% CI 1·25–1·48; figure 1), representing an absolute annual excess of 1·27% (95% CI 0·88–1·69).

Although the absolute excess risk of new-onset diabetes varied depending on the method of diagnosis, the RRs were broadly similar.

from four trials of more versus less intensive statin therapy, more intensive statin therapy resulted in **a 10% proportional increase in new-onset diabetes** (RR 1·10, 95% CI 1·02–1·18), corresponding to an absolute annual excess of 0·22% (95% CI 0·05–0·41).

The RR for high-intensity statin derived **indirectly** by combining selected trials was 1·27 (95% CI 1·11–1·44; data not shown), which was similar to the estimate obtained in the direct comparison of high-intensity statin versus placebo (1·36, 1·25–1·48; figure 1).

Overall, at a given level of statin intensity, the relative effects on new-onset diabetes **did not vary much between types of participants** (eg, by age, sex, race or ethnicity, history of vascular disease, BMI, eGFR, quartiles of glycaemia, diabetes risk score, and lipid characteristics, between statins, or over time.

In particular, the RRs for new-onset diabetes were similar among quartiles of baseline glycaemia and quartiles of baseline-defined risk of new-onset diabetes.

Among people **without Diabetes** The mean increase in **glucose** concentration during the treatment period compared with participants assigned to receive placebo was **0·04 mmol/L** for **both low-intensity or moderateintensity** (95% CI 0·03–0·05) and high-intensity statin therapy (0·02–0·06), and the corresponding increases in **HbA1c** values were **0·06%** (0·00–0·12) for low-intensity or moderate-intensity and **0·08%** (0·07–0·09) for high-intensity statin therapy.

The annual rate of development of new-onset diabetes in the placebo group was substantially greater in higher versus lower quartiles of baseline glycaemia.

- Consequently, the majority (ie, approximately 62%) of excess cases of new-onset diabetes occurred among participants in the **highest quarter** of the baseline glycaemia distribution for both low-intensity or moderate-intensity and high-intensity statin therapy.
- The proportion of excess cases in the top quarter increased only slightly to approximately 67% when baseline age, sex, BMI, triglycerides, eGFR, and HDL cholesterol were added to glycaemia in a diabetes risk score (figure 2).

- Mean HbA1c for group 1 of glycaemia is 4·72%, for group 2, 5·51%, for group 3, 5·80%, and for group 4 is 6·17% for low-intensity or moderate-intensity therapy.
- Mean HbA1c for group 1 of glycaemia is 5·13%, for group 2 is 5·51%, for group 3 is 5·79%, and for group 4 is 6·14% for high-intensity therapy.
- Individuals were categorised into four equally sized groups of predicted 5-year risk of new-onset diabetes: <2·9% (group 1), 2·9% to <5·7% (group 2), 5·7% to <11·5% (group 3), and ≥11·5% (group 4).

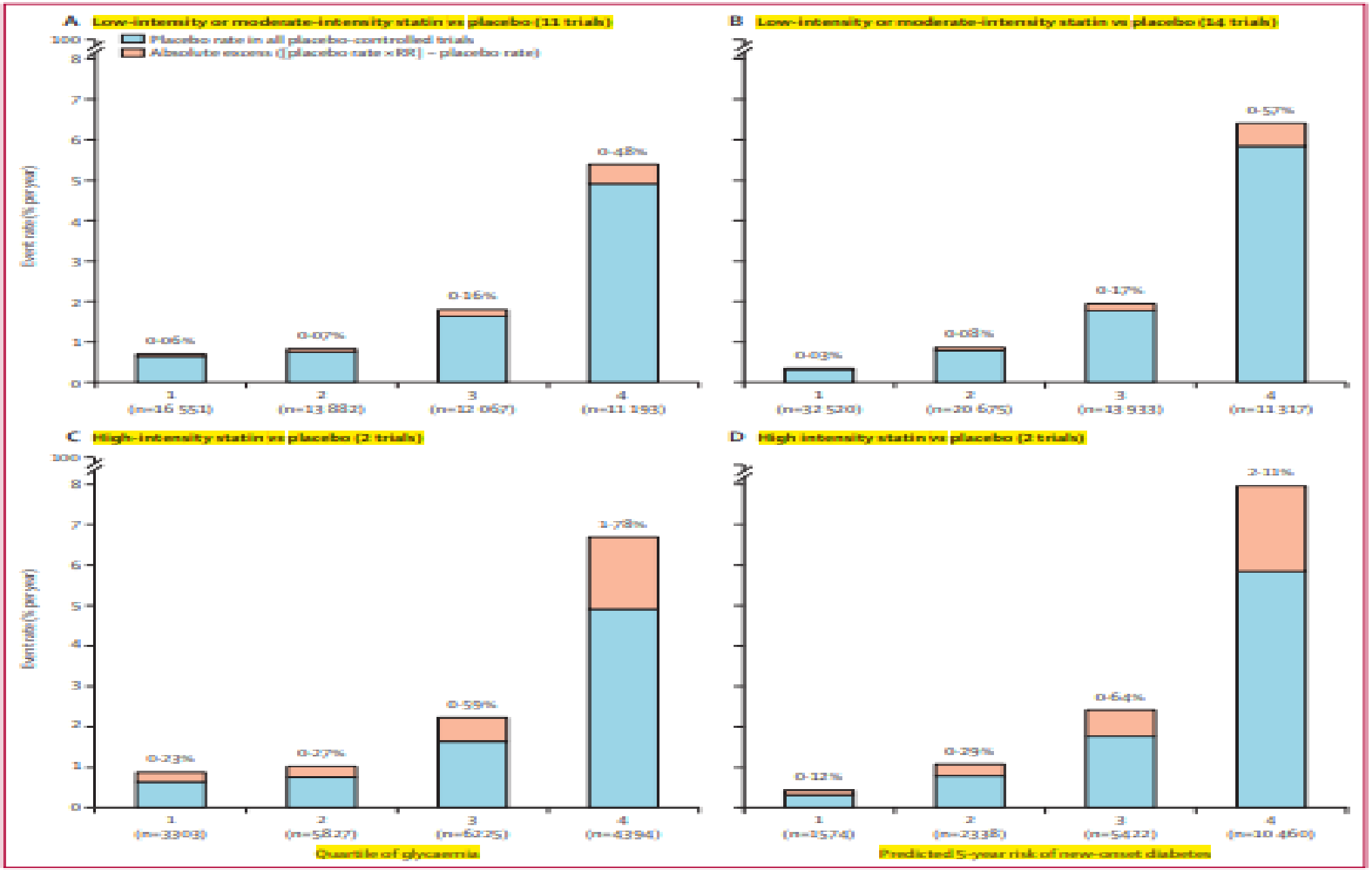

Figure 2: Absolute excess rates of new-onset diabetes in trials of statin versus placebo

In the trials of low-intensity or moderate-intensity statin versus placebo and the trials of more versus less intensive statin versus placebo, the relative effects on **worsening glycaemia were larger in the earlier than later years of follow-up**.

Among people **with Diabetes** The mean increase in glucose concentration during the treatment period compared with participants assigned to receive placebo was 0·12 mmol/L (95% CI 0·04 to 0·21) for low-intensity or moderate-intensity statin therapy and 0·22 mmol/L (–0·02 to 0·45) for high-intensity statin therapy, and the corresponding increases in HbA1c were 0·09% (0·05 to 0·14) for low-intensity or moderate-intensity statin therapy and 0·24% (0·09 to 0·38) for high-intensity statin therapy.

	Events (% per annum)		Observed–expected		Rate ratio (CI)
	Statin	Placebo	o–e	var(o–e)	
Low-intensity or moderate-intensity statin	**(n=12109)**	**(n=11941)**			
Ketosis or glucose control complications	308 (0·6)	299 (0·6)	2·2	151·7	1·01 (99% CI 0·82–1·25)
Worsening HbA_{1c}	2732 (6·4)	2484 (5·9)	181·8	1284·2	1·15 (99% CI 1·07–1·24)
Escalation of diabetes co-medication	4081 (9·3)	3924 (9·0)	100·9	1680·4	1·06 (99% CI 1·00–1·13)
Any worsening glycaemia	6224 (16·3)	5902 (15·4)	252·5	2737·5	1·10 (95% CI 1·06–1·14)
High-intensity statin	**(n=805)**	**(n=846)**			
Ketosis or glucose control complications	7 (0·3)	5 (0·2)	1·1	3·0	1·42 (99% CI 0·32–6·30)
Worsening HbA_{1c}	108 (3·9)	78 (2·7)	20·2	45·8	1·55 (99% CI 1·06–2·27)
Escalation of diabetes co-medication	254 (11·9)	231 (10·0)	20·5	120·8	1·18 (99% CI 0·94–1·50)
Any worsening glycaemia	338 (16·0)	295 (12·8)	33·3	157·2	1·24 (95% CI 1·06–1·44)

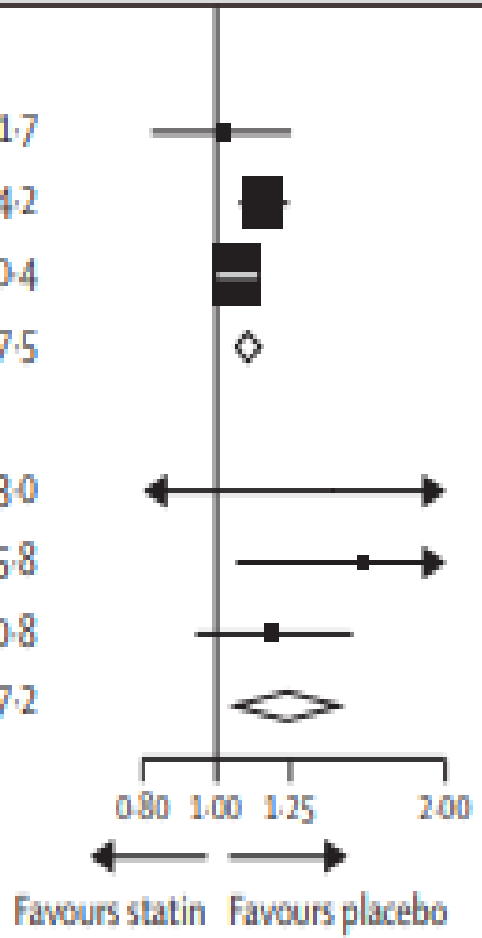

Figure 3: Effect of statin vs placebo on worsening glycaemia by statin intensity

12 placebo-controlled trials recorded at least one measure of bodyweight in participants **without diabetes** after assignment to a treatment group. In these participants, the mean baseline weight was 78·14 kg (SD 14·67), and allocation to statin therapy resulted in an **increase of 0·16 kg** (95% CI 0·08 to 0·24) at 1 year and 0·30 kg (0·22 to 0·37) at the final measurement compared with placebo.

11 placebo controlled trials recorded at least one measure of bodyweight in participants **with diabetes** after assignment to a treatment group. In these participants, the mean baseline weight was 81·27 kg (SD 14·61), and allocation to statin therapy resulted in an increase of **0·02 kg** (–0·10 to 0·14) at 1 year and 0·04 kg (–0·15 to 0·23) at the final measurement compared with placebo.

Discussion:

The JUPITER trial was the first large randomised trial of statin therapy to report a significant increase in the risk of incident diabetes (270 participants assigned to receive 20 mg rosuvastatin vs 216 participants assigned to receive placebo; p=0·01; corresponding to a 25% proportional increase in physician-diagnosed diabetes for participants in the rosuvastatin group).

More recently, the REPRIEVE trial reported a higher rate of incident diabetes in participants assigned to receive 4 mg pitavastatin daily compared with placebo (RR 1·35, 95% CI 1·09–1·66).

Atorvastatin has also been reported to induce a small increase in blood glycaemia within a few months of starting treatment, both in people without diabetes and in those with diabetes.

- Small population-wide shifts in blood glycaemia (of the magnitude seen in our analyses) can have a large relative effect on the proportion of a population exceeding a diagnostic threshold level near the tail of the distribution (figure 4).

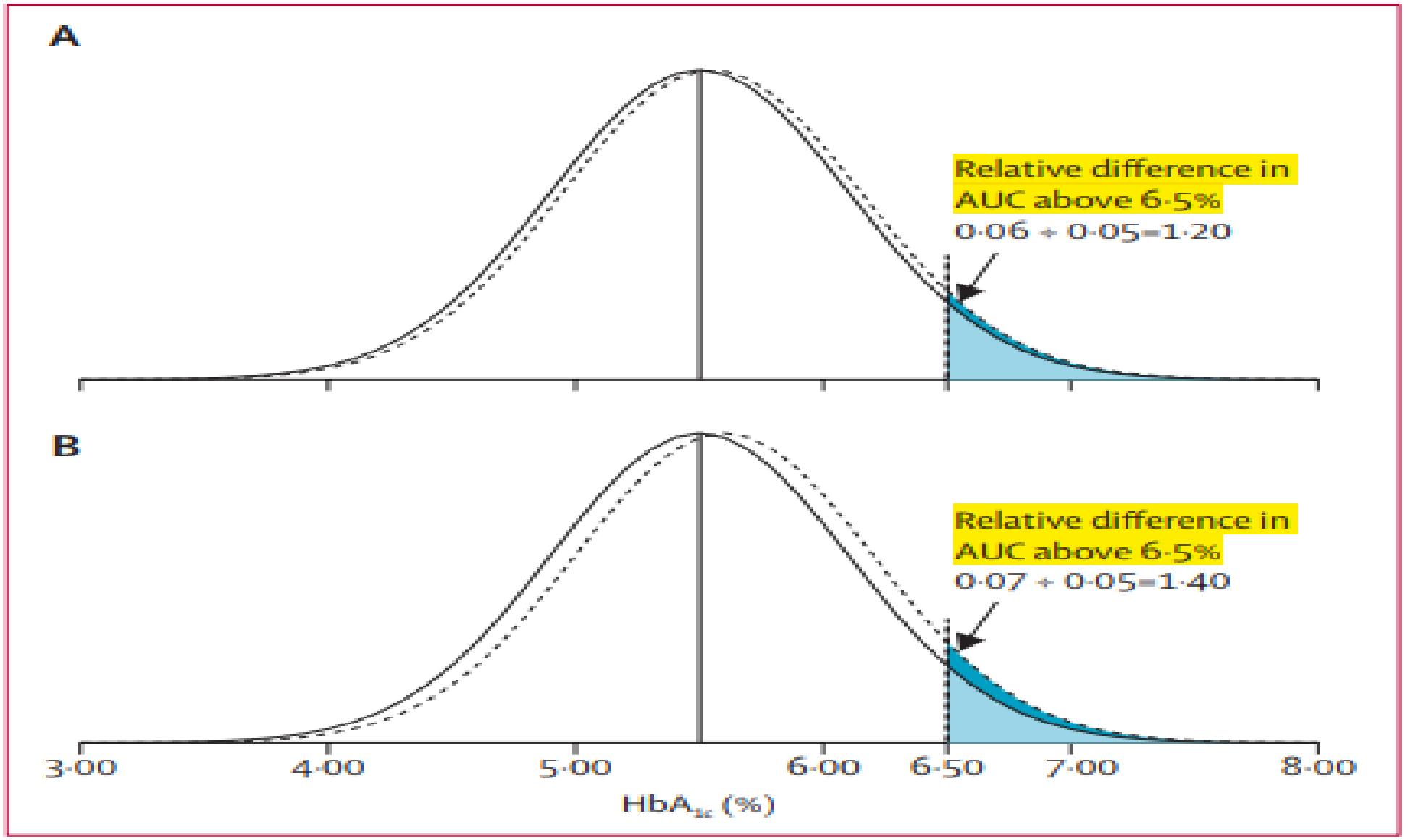

Figure 4: Examples of the effects of population-wide upwards shifts in mean HbA

Overall, there was little availability of data from postrandomisation glycaemic measures among people without known diabetes. This scarcity was particularly true for HbA1c, which was recorded systematically at baseline and at least once during follow up among all people without diabetes in only two trials of statin versus placebo (GISSI-HF trial of low-intensity or moderate-intensity statin therapy [mean baseline HbA1c 5·5%]; JUPITER trial of high-intensity statin therapy [mean baseline HbA1c 5·7%].

The paucity of HbA1c data is not surprising because HbA1c did not become a widely recognised **diabetes diagnostic marker until 2011**.

In the **high-intensity** statin trials, the event rate for the development of **new-onset diabetes** was substantially **higher** in both the intervention and placebo groups than that seen in the low-intensity or moderate-intensity statin trials.

This higher rate was driven by a **greater proportion of trial participants** in the high-intensity statin trials, particularly in the JUPITER trial, having at least one follow-up HbA1c measurement.

Biochemically determined diabetes rates were 3·0% per annum for high intensity trials and 0·8% for low-intensity or moderate intensity therapy trials in the placebo groups, whereas rates of diabetes determined by reports of diabetes-related adverse events and use of glucose-lowering medication in the placebo groups for the same groups of trials were similar (figure 1).

- This finding indicates that, although the relative excesses of new-onset diabetes observed for low intensity or moderate-intensity statin versus placebo and high-intensity statin versus placebo are likely to be robust and generalisable, the differences in absolute excesses of diagnoses of diabetes between these two groups of trials were determined predominantly by the proportion of trial participants for whom a biochemical diagnosis was made solely through an HbA1c measurement after randomisation. In practice, such measurements might **not be obtained routinely** in people without diabetes, but it is likely that the rate of diagnosis of diabetes would be higher than currently practice.

The RRs for new-onset diabetes did **not vary** significantly **over time**. We hypothesise that the reason for this finding is that, in each successive year of follow-up, a new group of people becomes at risk of exceeding the diagnostic threshold for diabetes because of an age-related increase in glycaemia, and those taking a statin will be slightly more likely to do so.

For high-intensity statin therapy, the absolute rates were observed to be greater for JUPITER compared with SPARCL, particularly when biochemical measurements of glycaemia were included as a diagnostic criterion.

By contrast, among people with a known diagnosis of diabetes at baseline, the early excess of worsening glycaemia with a statin **did not persist in the long term.**

Previous scientific literature has suggested that the increased risk of diabetes caused by statin therapy might be partly due to an **increase in bodyweight**, The observed increase in bodyweight due to statin therapy in participants without diabetes in our analyses (ie, 0·30 kg at final measurement; was much smaller than in these studies. It therefore seems implausible that such a small change in bodyweight would explain more than a small proportion of the observed increase in diagnoses of diabetes due to statin therapy.

Based on the results of the JUPITER trial previously concluded that the **cardiovascular benefits** of rosuvastatin greatly outweighed the risks of new-onset diabetes, despite this trial being conducted in a primary prevention setting among apparently healthy people (without hyperlipidaemia but with increased concentration of CRP on a high-sensitivity CRP test).

Notably, vascular benefits of statin therapy represent the net effect of the aggregate effects of statins on blood lipids and glycaemia, such that any theoretical adverse effects of statins on cardiovascular risk that might arise from small increases in glycaemia.

Our findings have several implications for clinical practice.

First, our findings make clear that the majority of new diagnoses of diabetes resulting from statin therapy will occur among people who are already close to the biochemical diagnostic threshold for diabetes. In our study, approximately 62% of cases of new-onset diabetes attributable to statin therapy occurred among individuals **in the top quarter of the glycaemia distribution**, and adding other risk factors to glycaemia resulted in only a modest increase (to approximately 67%) in the proportion of cases attributable to statin therapy than for glycaemia alone.

Our findings also imply that, since the effect of statin therapy on measures of glycaemia within an individual is small , there is likely to be little clinical benefit in measuring glucose concentrations and HbA1c values routinely after starting statin therapy.

Limitations

The most important of these limitations is that most of the included trials were **not principally designed** to test a hypothesis of the effects of statin therapy on diabetes.

Moreover, cases of diabetes in our analysis were constructed by use of trial data, and we were unable to assess **type of diabetes**, but we expect that the vast majority of cases in participants of the age included in the trials would have been type 2 diabetes.

Very occasionally, glucose-lowering medication might have been used for an **indication other than diabetes**, and although we were able to count initiation and escalation of diabetes treatment, we were not able to analyse any changes in doses of these medications.

The diabetes-related risks arising from the small changes in glycaemia resulting from statin therapy are greatly outweighed by the benefits of statins on major vascular events when the direct clinical consequences of these outcomes are taken into consideration.

THANKS FOR YOUR ATTENTION