Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial

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Summary

Background In view of evidence that statin therapy increases risk of diabetes, the balance of benefit and risk of these drugs in primary prevention has become controversial. We undertook an analysis of participants from the JUPITER trial to address the balance of vascular benefits and diabetes hazard of statin use.

Methods In the randomised, double-blind JUPITER trial, 17 603 men and women without previous cardiovascular disease or diabetes were randomly assigned to rosuvastatin 20 mg or placebo and followed up for up to 5 years for the primary endpoint (myocardial infarction, stroke, admission to hospital for unstable angina, arterial revascularisation, or cardiovascular death) and the protocol-prespecified secondary endpoints of venous thromboembolism, all-cause mortality, and incident physician-reported diabetes. In this analysis, participants were stratified on the basis of having none or at least one of four major risk factors for developing diabetes: metabolic syndrome, impaired fasting glucose, body-mass index 30 kg/m² or higher, or glycated haemoglobin A_{1c} greater than 6%. The trial is registered at ClinicalTrials.gov, NCT00239681.

Findings Trial participants with one or more major diabetes risk factor (n=11 508) were at higher risk of developing diabetes than were those without a major risk factor (n=6095). In individuals with one or more risk factors, statin allocation was associated with a 39% reduction in the primary endpoint (hazard ratio [HR] 0·61, 95% CI 0·47–0·79, p=0·0001), a 36% reduction in venous thromboembolism (0·64, 0·39–1·06, p=0·08), a 17% reduction in total mortality (0·83, 0·64–1·07, p=0·15), and a 28% increase in diabetes (1·28, 1·07–1·54, p=0·01). Thus, for those with diabetes risk factors, a total of 134 vascular events or deaths were avoided for every 54 new cases of diabetes diagnosed. For trial participants with no major diabetes risk factors, statin allocation was associated with a 52% reduction in the primary endpoint (HR 0·48, 95% CI 0·33–0·68, p=0·0001), a 53% reduction in venous thromboembolism (0·47, 0·21–1·03, p=0·05), a 22% reduction in total mortality (0·78, 0·59–1·03, p=0·08), and no increase in diabetes (0·99, 0·45–2·21, p=0·99). For such individuals, a total of 86 vascular events or deaths were avoided with no new cases of diabetes diagnosed. In analysis limited to the 486 participants who developed diabetes during follow-up (270 on rosuvastatin *vs* 216 on placebo; HR 1·25, 95% CI 1·05–1·49, p=0·01), the point estimate of cardiovascular risk reduction associated with statin therapy (HR 0·63, 95% CI 0·25–1·60) was consistent with that for the trial as a whole (0·56, 0·46–0·69). By comparison with placebo, statins accelerated the average time to diagnosis of diabetes by 5·4 weeks (84·3 [SD 47·8] weeks on rosuvastatin *vs* 89·7 [50·4] weeks on placebo).

Interpretation In the JUPITER primary prevention trial, the cardiovascular and mortality benefits of statin therapy exceed the diabetes hazard, including in participants at high risk of developing diabetes.

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Introduction

Statin therapy effectively reduces cardiovascular events. Yet, trial data[1] and meta-analyses[2–4] suggest that statins also confer increased risk of development of diabetes. In particular, recent overviews show that all statin agents are associated with a small increase in risk of incident type 2 diabetes (hazard ratio [HR] 1·09, 95% CI 1·02–1·17),[3] and that intensive doses might be associated with higher risk than are lower doses (HR 1·12, 95% CI 1·04–1·22).[4] For these reasons, on March 1, 2012, the US Food and Drug Administration added a warning about diabetes risk to the labels of all statin agents,[5] and similar concern has been raised by European drug authorities. These regulatory changes have engendered controversy in the lay and medical press as to whether the cardiovascular benefit of treatment with statins exceeds the diabetes risk, particularly in primary prevention, a setting in which these agents have seen increasing use. The JUPITER (Justification for Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin)[1] trial provided a contemporary opportunity to address this issue directly.

Methods

Participants and procedures

JUPITER was a randomised, double-blind, placebo-controlled trial designed to investigate whether rosuvastatin 20 mg daily compared with placebo would decrease the rate of first-ever cardiovascular events in 17 802 apparently healthy men and women with LDL cholesterol lower than 3·37 mmol/L (130 mg/dL) and high-sensitivity C-reactive protein (hsCRP) 2 mg/L or

higher.[1,6] An important prespecified secondary aim of the trial was to address the effects of rosuvastatin on incident type 2 diabetes; as such, a history of diabetes was an exclusion criterion for the trial. However, many participants in the JUPITER trial had major risk factors for diabetes at study entry including metabolic syndrome, impaired fasting glucose, body-mass index (BMI) 30 kg/m² or higher, or glycated haemoglobin A_{1c} (HbA_{1c}) greater than 6% at entry; these diabetes risk factors were selected post hoc on the basis of literature review and to be consistent with previous publications. For all JUPITER analyses, metabolic syndrome was defined according to American Heart Association and National Heart Lung and Blood Institute 2005 consensus criteria,[7] and impaired fasting glucose was defined as a fasting glucose concentration greater than 5·55 mmol/L (100 mg/dL), but less than 6·99 mmol/L (126 mg/dL). For this analysis, trial participants were divided into those with none or at least one of these major diabetes risk factors.

	Major risk factors for diabetes		p value
	None (n=6095)	One or more (n=11 508)	
Age (years)	66 (60–72)	66 (60–71)	0·37
Women	1963 (32%)	4771 (41%)	<0·0001
Ethnic origin			
White	4544 (75%)	8010 (70%)	<0·0001
Black	772 (13%)	1439 (13%)	..
Hispanic	549 (9%)	1663 (14%)	..
Other/unknown	230 (4%)	396 (3%)	..
BMI (kg/m²)	25·4 (23·2–27·5)	30·7 (27·5–34·0)	<0·0001
Hypertension	2757 (45%)	7338 (64%)	<0·0001
Current smoking	1318 (22%)	1475 (13%)	<0·00001
hsCRP (mg/L)			
Men	3·9 (2·6–6·7)	4·2 (2·8–6·7)	<0·0001
Women	3·8 (2·7–6·2)	5·0 (3·3–8·3)	<0·0001
LDL cholesterol (mmol/L)	2·80 (2·41–3·08)	2·82 (2·46–3·08)	0·001
HDL cholesterol (mmol/L)	1·40 (1·17–1·71)	1·19 (0·98–1·45)	<0·0001
Triglycerides (mmol/L)	1·10 (0·82–1·45)	1·51 (1·08–2·17)	<0·0001
Total cholesterol (mmol/L)	4·77 (4·33–5·15)	4·82 (4·38–5·18)	0·001
Apolipoprotein A (g/L)	1·70 (1·51–1·93)	1·58 (1·41–1·79)	<0·0001
Apolipoprotein B (g/L)	1·04 (0·91–1·16)	1·12 (0·98–1·25)	<0·0001
Glucose (mmol/L)	4·94 (4·67–5·22)	5·49 (5·05–5·88)	<0·0001
HbA_{1c} (%)	5·6% (5·4–5·7)	5·8% (5·5–6·1)	0·001

Data are median (IQR), n (%), or p value. For high-sensitivity C-reactive protein (hsCRP), values are based on the average of the screening and randomisation visits. *Metabolic syndrome, impaired fasting glucose, glycated haemoglobin A_{1c} (HbA_{1c}) greater than 6%, or body-mass index (BMI) 30 kg/m² or higher.

Table 1: **Baseline characteristics of participants in the JUPITER trial with none or at least one major risk factor for diabetes***

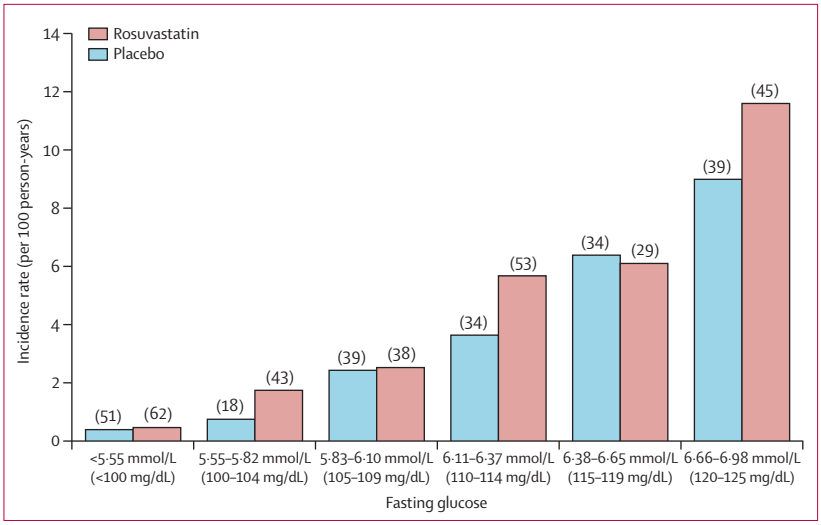

Figure 1: **Incidence rates of physician-diagnosed diabetes in the JUPITER trial, by baseline fasting glucose concentration**
Data are shown separately for participants allocated placebo and those allocated rosuvastatin. Numbers in parentheses are the absolute number of individuals who developed diabetes in each group.

For up to 5 years, all trial participants underwent prospective follow-up for incident vascular events, incident diabetes, and other adverse events. The prespecified JUPITER trial endpoint included first events of myocardial infarction, stroke, admission to hospital for unstable angina, arterial revascularisation, or cardiovascular death. Protocol-prespecified secondary endpoints designed to be used in analyses of net clinical benefit included venous thromboembolism, physician-reported diabetes, and all-cause mortality.

Consistent with previous reports from the JUPITER trial and as specified in the protocol, cardiovascular events included those occurring at any time between randomisation and March 30, 2008, the date of unmasking of the trial. Since physician-reported diabetes was regarded as an adverse event, reports of this disease were included if they occurred any time between randomisation and the last study visit for each individual participant, a process that continued until August, 2008. All components of the JUPITER primary endpoint were adjudicated by an endpoints committee unaware of randomisation status using prespecified endpoint criteria. Incident events of diabetes and total mortality was based on filed reports.

Statistical analysis

To address the net cardiovascular and mortality benefit and diabetes hazard associated with rosuvastatin, we used Cox proportional hazard regression models to calculate HRs and 95% CIs for first major cardiovascular events or death and for incident diabetes comparing participants on active therapy with those on placebo. Absolute numbers of vascular events or deaths prevented and diabetes cases diagnosed were also calculated for each study group. In addition to the total number of vascular events or deaths prevented, we did an additional analysis to be as conservative as possible in assessing net clinical benefit in which we allowed only the first vascular event to be counted for any trial participant; thus, in this additional analysis, a trial participant with non-fatal myocardial infarction, venous thromboembolism, non-fatal stroke, and death was counted as having one rather than four

events. So as not to underestimate potential hazards, we conservatively elected to include all physician-reported cases of diabetes irrespective of whether there was formal biochemical confirmation. Individual participants were allowed to contribute both to the cardiovascular and diabetes endpoints if each of these events occurred for that participant during the trial follow-up. All p values reported are two-sided and all confidence intervals computed at the 95% level. SAS (version 9.1) was used for all analyses.

This trial is registered at ClinicalTrials.gov, NCT00239681.

Role of the funding source

The JUPITER trial protocol was designed and written by the study chair (PMR) and approved by the local institutional review board at each participating centre. The trial data were analysed by the study chair, the academic study statistician (RJG), and the academic programmer (JM), who vouch for the accuracy and completeness of the data and the analyses. The sponsor collected the trial data and monitored the study sites, but played no part in the conduct of these analyses, in the drafting of this report, or in the decision to submit these analyses for publication. The corresponding author (PMR) had full access to all data in the study and had final responsibility to submit for publication.

Results

Of 17 802 JUPITER trial participants, 121 (1%) were missing data for at least one risk factor for diabetes and 78 (<1%) were found at randomisation to have fasting glucose 6·99 mmol/L or greater or clinical diabetes. The remaining 17 603 trial participants (99%) had complete data and were included in this analysis. By comparison with trial participants with no major diabetes risk factors (n=6095), those with one or more major diabetes risk factor (n=11 508) were more likely to be female, have higher baseline blood pressure, HbA_{1c}, glucose, and triglycerides and lower baseline HDL cholesterol. Smoking was more prevalent in participants with no major diabetes risk factors. In sex-specific analyses, hsCRP was higher in participants with one or more major diabetes risk factor (table 1). As expected, trial participants with one or more major diabetes risk factor had an increased risk of developing diabetes during trial follow-up (incidence rate 1·88 *vs* 0·18 per 100 person–years; HR 10·5, 95% CI 7·0–15·8, p=0·001). Tabular data stratifying these groups by randomised treatment assignment are shown in the appendix.

See Online for appendix

Overall, incident diabetes occurred more frequently in the rosuvastatin group (270 reports of diabetes *vs* 216 in the placebo group; HR 1·25, 95% CI 1·05–1·49, p=0·01). The average time from randomisation to diagnosis of diabetes was 84·3 (SD 47·8) weeks in the rosuvastatin group and 89·7 (50·4) weeks in the placebo group, an acceleration of 5·4 weeks. As shown in figure 1, almost all the excess risk of diabetes associated with rosuvastatin occurred in participants with baseline evidence of impaired fasting glucose.

Table 2 presents incidence rates for cardiovascular events, total mortality, and diabetes in participants with and without at least one major diabetes risk factor, according to statin or placebo allocation. For trial participants with at least one major diabetes risk factor, random allocation to rosuvastatin was associated with a 39% reduction in the primary endpoint (HR 0·61, 95% CI 0·47–0·79, p=0·0001), a 36% reduction in venous thromboembolism (0·64, 0·39–1·06, p=0·08), a 17% reduction in total mortality (0·83, 0·64–1·07, p=0·15), and a 28% increase in diabetes (1·28, 1·07–1·54, p=0·01). In absolute terms for those with diabetes risk factors, 134 total cardiovascular events or deaths were avoided for every 54 new cases of diabetes diagnosed. In analyses limited to first events only, the number of major cardiovascular events or deaths avoided in participants with one or more diabetes risk factors was 93.

For trial participants with no major diabetes risk factor, random allocation to rosuvastatin yielded a 52% reduction in the primary endpoint (HR 0·48, 95% CI 0·33–0·68, p=0·0001), a 53% reduction in venous thromboembolism (0·47, 0·21–1·03, p=0·05), a 22% reduction in total

	No major diabetes risk factors (n=6095)					One or more major diabetes risk factors (n=11 508)				
	Rosuvastatin	Placebo	Δ	HR (95% CI)	p value	Rosuvastatin	Placebo	Δ	HR (95% CI)	p value
Primary endpoint	44 (0·69)	91 (1·45)	−47	0·48 (0·33–0·68)	0·0001	96 (0·80)	157 (1·31)	−61	0·61 (0·47–0·79)	0·0001
Primary endpoint, any death	118 (1·85)	174 (2·77)	−56	0·67 (0·53–0·85)	0·0007	175 (1·46)	262 (2·18)	−87	0·67 (0·55–0·81)	0·0001
Primary endpoint, VTE, any death	122 (1·92)	187 (2·99)	−65	0·64 (0·51–0·81)	0·0001	196 (1·64)	289 (2·41)	−93	0·68 (0·57–0·81)	0·0001
MI, stroke, any death	99 (1·55)	147 (2·33)	−48	0·67 (0·52–0·86)	0·002	139 (1·15)	202 (1·67)	−63	0·69 (0·56–0·86)	0·0006
Any death	89 (1·32)	113 (1·69)	−24	0·78 (0·59–1·03)	0·08	109 (0·85)	132 (1·02)	−23	0·83 (0·64–1·07)	0·15
Diabetes	12 (0·18)	12 (0·18)	0	0·99 (0·45–2·21)	0·99	258 (2·12)	204 (1·65)	54	1·28 (1·07–1·54)	0·01

Data for rosuvastatin and placebo are absolute number of events (incidence rate per 100 person-years). The primary endpoint was a composite of non-fatal myocardial infarction, non-fatal stroke, unstable angina or revascularisation, and cardiovascular death. Analyses are limited to first events only. VTE=venous thromboembolism. MI=myocardial infarction. Δ=absolute difference in events between rosuvastatin and placebo.

Table 2: **Absolute number of events, incidence rates, and hazard ratios (HRs) for cardiovascular endpoints, death, and diabetes in the JUPITER trial in participants with or without major diabetes risk factors, according to random allocation to rosuvastatin or placebo**

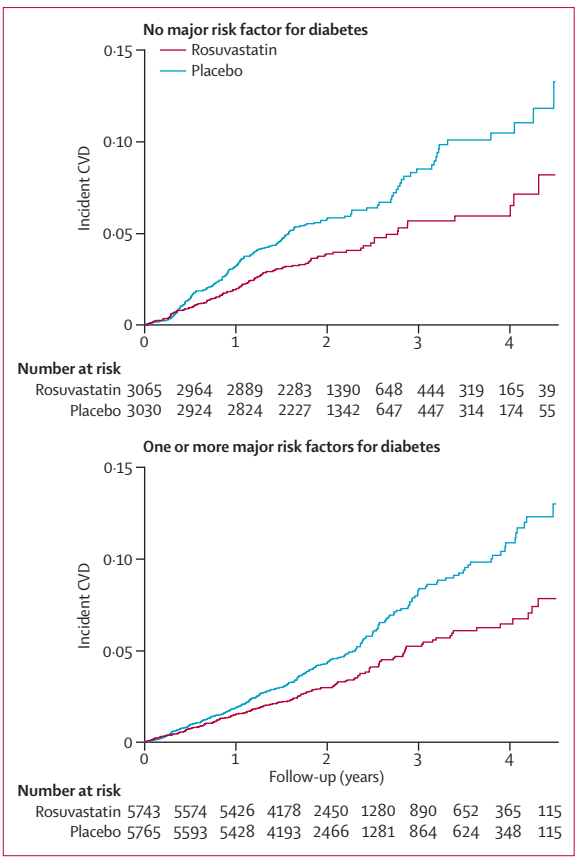

Figure 2: **Cumulative incidence of cardiovascular events and total mortality in participants with and without major risk factors for diabetes**
CVD=cardiovascular disease.

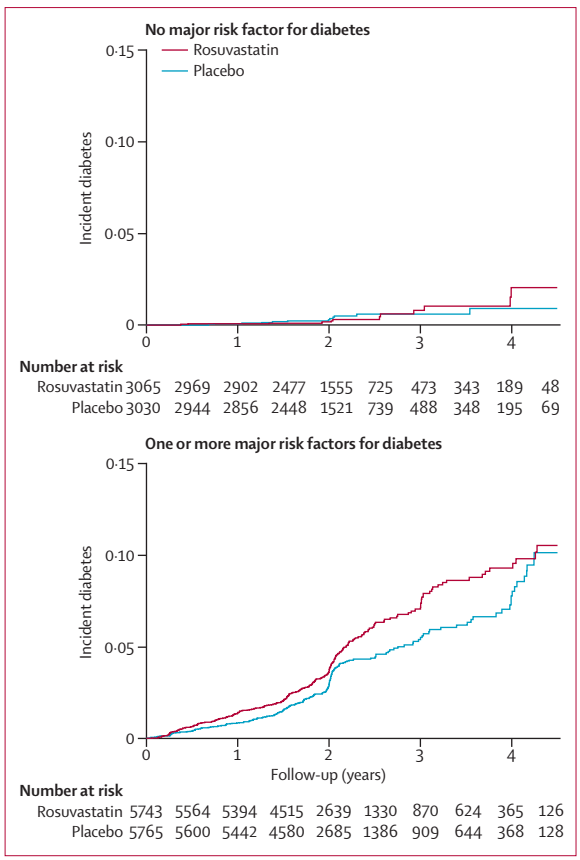

Figure 3: **Cumulative incidence of diabetes in participants with and without major risk factors for diabetes**

mortality (0·78, 0·59–1·03, p=0·08), and no increase in diabetes (0·99, 0·45–2·21, p=0·99). In absolute terms for those without a major diabetes risk factor, 86 total cardiovascular events or deaths were avoided with no excess new cases of diabetes diagnosed. In analyses limited to first events only, the number of major cardiovascular events or deaths avoided in participants with no major diabetes risk factor was 65.

Figure 2 shows the cumulative incidence of cardiovascular events or death and figure 3 the cumulative incidence of diabetes in participants with and without major diabetes risk factors. There were no significant violations of the proportional hazards assumptions for the data contained in these figures. As expected with respect to the primary cardiovascular endpoint, the relative treatment benefits attributable to rosuvastatin were similar in participants with and without diabetes risk factors (p value for interaction, 0·28).

Risks of diabetes associated with rosuvastatin allocation did not change substantially as the number of major diabetes risk factors increased. HRs for physician-diagnosed diabetes associated with rosuvastatin were 1·2 (95% CI 0·65–2·1) for participants with one risk factor, 1·2 (0·82–1·9) for two risk factors, 1·4 (1·1–1·9) for three risk factors, and 1·4 (1·0–2·0) for four risk factors; none of these HRs differed significantly from the HR for the study as a whole.

As shown in figure 4, the relative benefits and risks of rosuvastatin were generally consistent for all components of the JUPITER primary and secondary endpoints and in all subgroups evaluated, including in participants with or without metabolic syndrome, with or without impaired fasting glucose, with or without BMI 30 kg/m² or greater, or with or without HbA_{1c} greater than 6%. In no instance were tests for interaction significantly different from that noted in the main analyses of participants with none or at least one of these major diabetes risk factors.

Table 3 provides data for rates of adverse events (other than incident diabetes) and measured laboratory values in the JUPITER trial comparing rosuvastatin with placebo in participants with and without one or more major diabetes risk factor. Participants with and without diabetes risk factors had similar non-diabetes adverse event rates attributable to rosuvastatin. Furthermore, in those with and without diabetes risk factors, measured HbA_{1c} at 24 months increased by 0·1% in those allocated rosuvastatin (both p values 0·001). Of interest, measured fasting glucose concentrations were not significantly

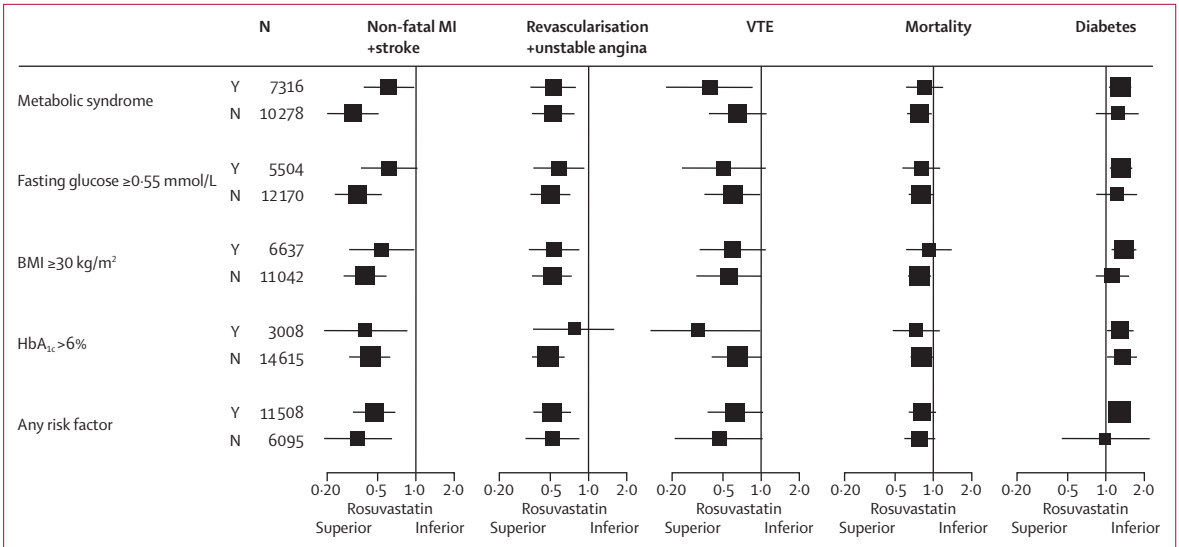

Figure 4: **Hazard ratios and 95% CIs for specific vascular events, total mortality, and diabetes in subgroup analyses in participants with and without major risk factors for diabetes**
BMI=body-mass index. HbA_{1c}=glycated haemoglobin A_{1c}.

	No major diabetes risk factors			One or more major diabetes risk factors		
	Rosuvastatin	Placebo	p value	Rosuvastatin	Placebo	p value
Rate of adverse events						
Muscular weakness, stiffness, or pain	8·72	8·53	0·76	8·20	7·75	0·28
Myopathy	0·06	0·06	0·98	0·05	0·04	0·75
Rhabdomyolysis	0·02*	0·0	..	0·0	0·0	..
Cancer	1·98	1·70	0·24	1·38	1·61	0·14
Renal disorders	3·10	2·65	0·14	2·77	2·52	0·24
Bleeding	1·32	1·52	0·34	1·41	1·42	0·90
Hepatic disorders	1·12	1·08	0·84	1·14	0·93	0·10
Haemorrhagic stroke	0·03	0·03	1·00	0·02	0·05	0·32
Laboratory values at 24 months						
HbA_{1c} (%)	5·8% (5·6–6·0)	5·7% (5·5–5·9)	0·001	6·0% (5·7–6·2)	5·9% (5·6–6·2)	0·001
Fasting glucose (mmol/L)	5·22 (4·83–5·55)	5·16 (4·83–5·49)	0·20	5·61 (5·22–6·11)	5·61 (5·16–6·11)	0·19

Data are rates per 100 person-years, median (IQR), or p value. HbA_{1c}=glycated haemoglobin A_{1c}. *Occurred after trial completion.

Table 3: **Adverse events and measured laboratory values for fasting glucose and HbA_{1c} during follow-up in participants with and without major diabetes risk factors**

different in the rosuvastatin and placebo groups; thus, as expected, had we relied on biochemical determination of diabetes rather than physician diagnosis, we could have systematically underestimated true effects.

In an analysis limited to participants who developed diabetes during the JUPITER trial (n=270 on rosuvastatin, 216 on placebo), 18 primary cardiovascular endpoints occurred. Of these, eight were on rosuvastatin (incidence rate 1·10 per 100 person-years) and ten were on placebo (1·73 per 100 person-years). Thus, among the 486 JUPITER trial participants who developed diabetes during follow-up, the cardiovascular risk reduction associated with rosuvastatin (HR 0·63, 95% CI 0·25–1·60) was consistent with that for the trial as a whole (0·56, 0·46–0·69).

In sensitivity analyses, we found no substantive change for any of these findings when alternative definitions of metabolic syndrome or alternative thresholds for BMI or HbA_{1c} were used. In analyses stratified by age, the HR for incident diabetes associated with rosuvastatin as compared with control was 1·26 (95% CI 1·02–1·56) for participants aged 50–69 years and 1·25 (0·90–1·74) for those aged 70 years and older.[8]

Discussion

Although JUPITER was the first placebo-controlled statin trial to formally report an increased risk of developing diabetes,[1] post-hoc evaluations of previously completed trials showed that this small increase in risk is present

Panel: Research in context

Systematic review

Three meta-analyses published between 2009 and 2011[2–4] suggested that all statins are associated with a small increase in the risk of incident type 2 diabetes (hazard ratio [HR] 1·09, 95% CI 1·02–1·17),[3] and that intensive-dose statin therapy is associated with higher risk than is lower dose therapy (HR 1·12, 95% CI 1·04–1·22).[4] In absolute terms, however, these risks are low compared with the absolute benefit of statin therapy in the setting of secondary prevention, from which most data are derived. We were unable to find any data directly addressing the cardiovascular benefits and diabetes risks in the setting of primary prevention, an issue that has caused much controversy in both the medical and lay press. Further, we were unable to find any data addressing whether the risks and benefits of statin therapy in primary prevention differ between people with and without risk factors for diabetes.

Interpretation

In the randomised, placebo-controlled JUPITER trial of rosuvastatin 20 mg, done in the setting of primary prevention, we noted that the small risk of developing diabetes on statin therapy was limited to participants who had biochemical evidence of impaired fasting glucose or multiple components of metabolic syndrome—groups already at high risk of developing diabetes. Further, both in participants with and without diabetes risk factors, the absolute benefit of statin therapy on vascular events was greater than the hazard of developing new onset diabetes. These data should provide reassurance for patients and physicians about the use of lipid lowering as an adjunct to diet, exercise, and smoking cessation in the primary prevention of myocardial infarction, stroke, and cardiovascular death.

for all statins and might relate to drug potency (panel).[2–4] In secondary prevention in high-risk patients with established coronary artery disease, the diabetes risk associated with statin therapy is low in absolute terms when compared with the reduction in cardiovascular events. However, in primary prevention in low-risk patients, for whom statin therapy is increasingly used for vascular prevention, there has been controversy in the lay and medical press as to whether the absolute benefit of treatment outweighs the diabetes risk.

This analysis from a contemporary primary prevention trial suggests that the risk of development of diabetes on statin therapy seems limited to people with baseline evidence of impaired fasting glucose, metabolic syndrome, severe obesity, or raised HbA_{1c}—a group of patients already at high risk of developing diabetes.[9,10] Of equal importance, within the JUPITER trial, the cardiovascular and mortality benefits of statin therapy exceeded the diabetes hazard in the trial population as a whole as well as in participants at increased risk of developing diabetes. Further, in analyses limited to the 486 participants who developed diabetes, the point estimate for the relative risk reduction for cardiovascular events was consistent with that for the trial as a whole. These cardiovascular benefits, however, came with the hazard of diagnosis of new-onset diabetes 5–6 weeks earlier in participants allocated rosuvastatin as compared with placebo. Whether this finding has clinical relevance is uncertain because most patients with diabetes are treated with statin therapy. For these data, we noted no effect modification by age.

Strengths of our analysis include its sample size, random allocation of statin therapy, and masked ascertainment of incident events. Our analysis plan was also highly conservative in several respects, an approach we took on an a-priori basis so as not to underestimate potential hazards of treatment. For example, we used the observed HR for diabetes within JUPITER of 1·25 rather than the smaller HRs reported in the most comprehensive recent meta-analysis of 1·18 for rosuvastatin and 1·09 for all statins.[3] We also elected to conservatively include all incident cases of physician-reported diabetes that occurred during the trial (including those reported between the time of study completion and the last patient closeout visit) as well as cases that lacked biochemical confirmation; both of these approaches further reduce the risk of systematic under-reporting of incident diabetes. Further, although we believe most physicians and patients would regard myocardial infarction, stroke, and death to be more severe outcomes than new-onset diabetes (which in some cases was merely a biochemical change in glucose concentration from lower than 6·99 mmol/L [126 mg/dL] to higher than this threshold), we elected not to introduce subjective bias into our analysis by weighting these events differently in our analysis plan. Finally, in addition to our primary analysis of total vascular events prevented, we undertook an additional analysis in which we limited each individual participant to a maximum of one vascular event. Even in this highly constrained analysis we found that statin therapy was associated with 65 fewer vascular events or deaths at no risk of diabetes in participants with no major diabetes risk factors, and with 93 fewer vascular events or deaths at a cost of 54 new diagnoses of diabetes in those with major diabetes risk factors.

Limitations of our analysis include the fact that all study participants had raised hsCRP, an independent risk marker for both incident type 2 diabetes and incident cardiovascular events.[11,12] Thus, care should be used when considering these primary prevention data for those with hsCRP less than 2 mg/L. Further, although all statins increase diabetes risk,[2–4] our data are limited to rosuvastatin at one dose (20 mg daily). Last, although we had more than 1000 participants followed up for 4–5 years, median follow-up within JUPITER was 2 years and thus long-term data for benefits and risks cannot be gleaned from this study. This limitation might be particularly relevant if an increased risk of diabetes results in microvascular as well as macrovascular disease that might not manifest for several years. However, as shown here, almost all individuals who had an increased risk of diabetes while taking statin therapy already had underlying evidence of impaired fasting glucose. These are the very individuals most likely to develop diabetes in the near future and who thus would typically be treated with a statin as part of their routine care.

We believe the present data have clinical relevance for several reasons. First, we hope the benefit and risk data presented here in a primary prevention setting will inform physician debate about the net usefulness of statin therapy, an issue that has recently become controversial particularly in the lay press. Second, as the increase in risk of diabetes associated with statin therapy seems limited to patients with major risk factors for diabetes, monitoring of glucose concentrations when starting statin therapy might not be needed in those who have normal pre-treatment glucose concentrations or who do not have multiple characteristics of metabolic syndrome.

Third, we expect that these and related data will spur research into the as yet unknown mechanisms by which statin therapy increases diabetes risk. Our findings that statins slightly accelerate the time to diabetes diagnosis and that risk is largely limited to patients with impaired fasting glucose suggest directions for such mechanistic work. To this end, ongoing work will evaluate change in biochemical markers showing β-cell function, insulin resistance and endothelial injury, adipokines, and other metabolic markers at the start of statin treatment and as predictors of incident diabetes in the trial.

Finally, for our patients, we hope these data ease concern about risks associated with statin therapy when these drugs are appropriately prescribed for cardiovascular risk reduction as an adjunct to dietary discretion, increased exercise, and smoking cessation.

Contributors

PMR designed the study and its analysis plan, contributed to the collection of data and its analysis and interpretation, provided study logistics, wrote the report, and gave final approval of the report. AP and PL contributed to the collection of data and its interpretation and reviewed the report. JGM did the primary data analyses, constructed tables and figures, and reviewed the report. RJG contributed to the study design and analysis plan, oversaw all statistical analyses, contributed to data interpretation and data analysis, and gave approval of the report.

Conflicts of interest

The JUPITER trial was an investigator-initiated project funded by AstraZeneca. PMR is the principal investigator of the trial and received grant support from AstraZeneca for its conduct. He has served as a consultant to Merck, ISIS, Vascular Biogenics, Boerhinger, Abbott, and Genzyme; receives additional research grant support from Novartis; and is listed as a co-inventor on patents held by the Brigham and Women's Hospital related to inflammatory biomarkers in cardiovascular disease and diabetes that have been licensed to Siemens and AstraZeneca. RJG is the independent academic trial statistician for JUPITER and has received grant support from AstraZeneca for its conduct. PL is an unpaid consultant or involved in clinical trials for AstraZeneca, GlaxoSmithKline, Merck, Novartis, Pfizer, ProNova, and Sigma-Tau and is a member of the scientific advisory boards for Athera Biotechnolgies, Carolus Therapeutics, Interleukin Genetics, and BIND Biosciences. AP and JGM declare that they have no conflicts of interest.

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