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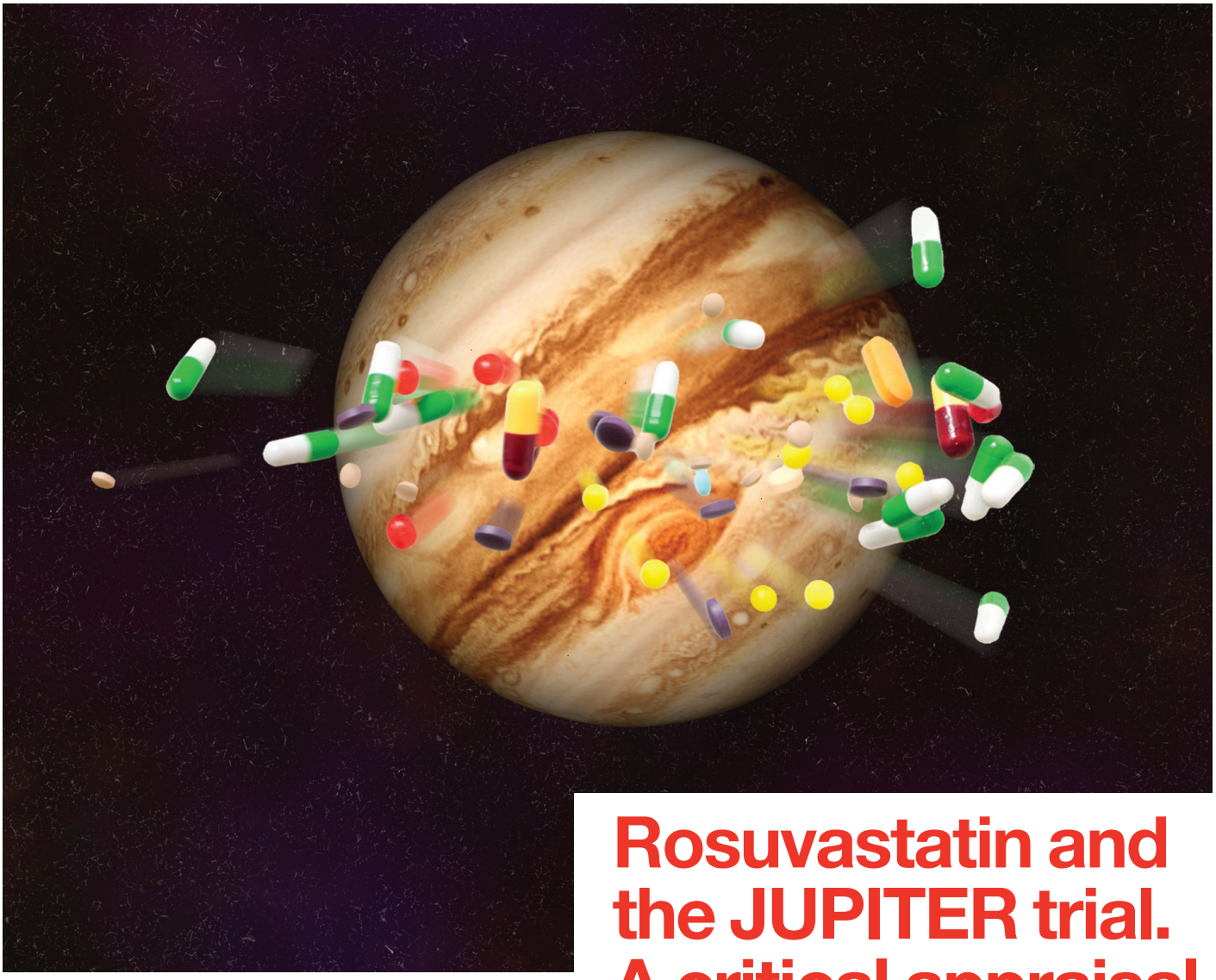

Rosuvastatin and the JUPITER trial. A critical appraisal

A lifeless planet in the galaxy of primary prevention

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abstract

Objective: to evaluate the relevance, design, results and conclusions of the study. The main regulatory agencies have approved the indication of rosuvastatin in the prevention of major cardiovascular events in patients who are at high risk of having a first cardiovascular event. High risk patients are defined as having a SCORE risk ≥ 5% or Framingham Risk >20%. **Material and methods:** critical appraisal of the trial. **Results and conclusions:** the role of hs-CRP in the pathogenesis of atherosclerosis still remains unclear. It should not be used as a cardiovascular risk marker due to its poor predictive value. The early stopping of the JUPITER study exaggerates the benefits. There were no significant differences in cardiovascular mortality and the causes of overall mortality are not clearly described in the trial. The long-term projection of total mortality is not significant and undermines the validity of the data offered in the study. There was a small significant increase in patients who developed diabetes. Substantial conflicts of interest of the main author adds to the high risk of bias of this study. The results of this study should not modify our practice in primary prevention.

In November 2008, the JUPITER trial was published[1]. A few months earlier, in March of the same year, during the congress of the American College of Cardiology, it was announced that the study would be interrupted given the fabulous results registered. These included a reduction of 50% in LDL-c levels, a 37% reduction in C-reactive protein and a 50% reduction in cardiovascular complications.

The objective of this bulletin is to evaluate in depth the relevance, design, results and conclusions of the study. The main regulatory agencies have approved the indication of rosuvastatin in primary prevention of vascular events and some other parties are proposing to modify the current clinical guidelines on the grounds of this trial's results.

Justification and research query of the Jupiter trial

Nearly half of the cardiovascular events occur in patients with normal or even low LDL-c levels. There is moreover controversy regarding whether the benefits obtained from statins go beyond the expected reductions in cholesterol levels[2]. For instance, statins modestly reduce the incidence of stroke and yet cholesterol levels are not a risk factor for stroke. On the other hand, according to other studies, the highly sensitive C-reactive protein (hs-CRP) could prove to be an independent biomarker or predictor of future vascular events[3]. These studies suggest that CRP as a biomarker of inflammation could identify those patients with atherothrombotic disease which involves an inflammatory process[4].

The CRP could participate in initial arteriosclerotic lesions and in the conversion of the stable plaque into an unstable form[5]. Therefore, high levels of CRP could indicate a high risk of myocardial infarction, stroke, peripheral arterial disease, or sudden death.

In the AFCAPS/TexCAPS trial[6] which studied the benefits of lovastatin in patients with different LDL-c levels and low HDL-c levels, it was seen that when stratifying results in relation to the basal concentrations of hs-CRP, lovastatin was most effective in those patients with high LDL-c levels, but also in patients with low LDL-c levels and high hs-CRP concentrations[7].

As a result of this analysis a panel of experts from the *Centers for Disease Control and Prevention* and the American Heart Association issued the first guidelines on biomarkers of inflammation in clinical practice in January 2003, and they assigned a role to the measurement and stratification of risk in relation to hs-CRP levels[8].

Design[9]

The Jupiter trial is a multicenter, randomized trial which compares 20 mg daily rosuvastatin with placebo. The sample size was estimated with a power of 90% to detect a reduction of 25% in the risk of a major cardiovascular event. According to the study 514 episodes were necessary. Estimation of a mean follow-up period of 3.5 years would require a sample size of 12,000 patients. The promoters of the study however estimated the size to

Table 1. Adapted from Ridker et al. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. N Engl J Med 2001;344: 1959-1965.

SUBGROUP	LOVASTATIN	PLACEBO	RR	NNT
	RATE OF EVENTS	RATE OF EVENTS		
LDL-c< median, CRP< median	0.025	0.022	1.08 (0.56-2.08)	
LDL-c < median, CRP >median	0.029	0.051	0.58 (0.34-0.98)	48
LDL-c > median, CRP < median	0.020	0.050	0.38 (0.21-0.70)	33
LDL-c > median, CRP >median	0.038	0.055	0.68 (0.42-1.10)	58

Median hs-CRP levels = 0.16 mg/dL. Median LDL-c = 149.1 mg/dL (3.86 mmol/L)

Table 2. Baseline characteristics of individuals in the JUPITER trial.

BASELINE CHARACTERISTICS	ROSUVASTATIN	PLACEBO
Age - years	66 (60.0-71.0)	66 (60.0-71.0)
Women - No (%)	3,426 (38.5%)	3,375 (37.9%)
BMI	28.3 (25.3-32.0)	28.4 (25.3-32.0)
Systolic BP - mmHg	134 (124-145)	134 (124-145)
Current smoker - No (%)	15.7%	16.0%
Use of aspirin - No (%)	16.6%	16.6%
Metabolic syndrome - No (%)	3,652 (41.0%)	3,723 (41.8%)
LDL-c - mg/dL	108 (94-119)	108 (94-119)
hs-CRP – mg/L	4.2 (2.8-7.1)	4.3 (2.8-7.2)

15,000 patients foreseeing a low incidence of events in the placebo group and withdrawals from the study.

Population under study

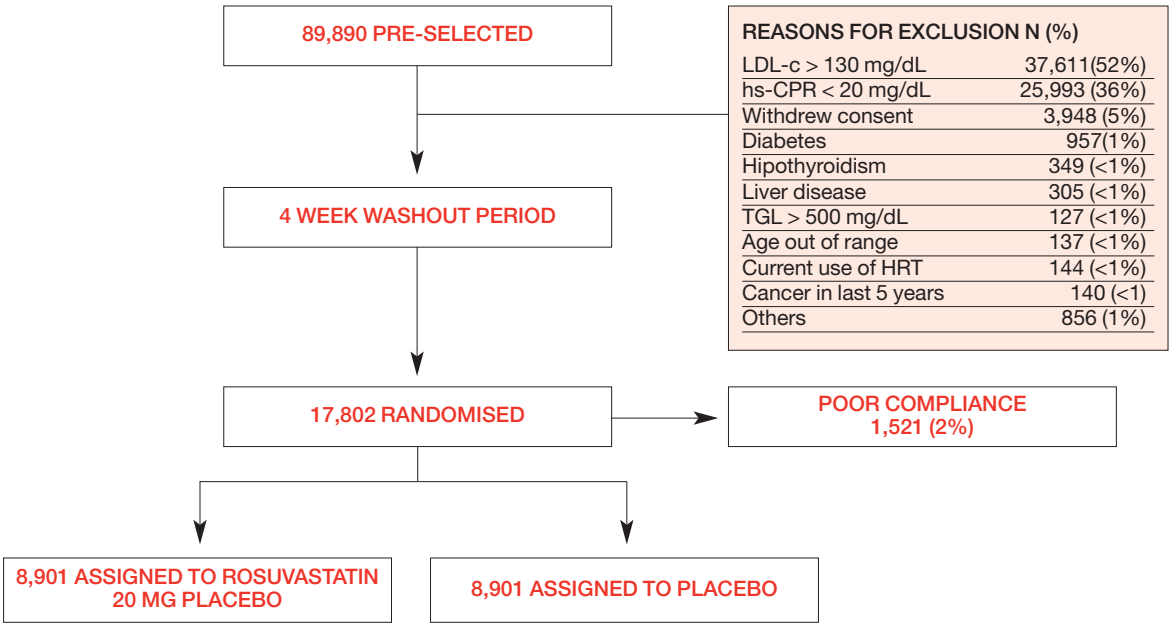
The trial recruited 17,802 patients, healthy men ≥ 50 years of age and women ≥ 60 years of age with hs-CRP levels > 2 mg/L and LDL-c levels < 3.4 mmol/L (130 mg/dL) and triglycerides < 5.6 mmol/L (500 mg/dL). This population had no previous medical history of myocardial infarction, stroke, revascularization or coronary risk equivalents (table 2). Other exclusion criteria included:

· current treatment with statins or other cholesterol lowering agents.

· use of hormone replacement therapy, diabetes, transaminase elevation, uncontrolled hypertension, history of cancer in the last years, disease with chronic inflammatory characteristics, and "severe medical or mental conditions that could compromise successful participation in the study". The study was carried out for 4 weeks in a pre-randomization phase to guarantee compliance with treatment of at least 80%.

Out of the 89,890 pre-selected patients, 72,088 (80%) were not included in the trial. 52.2% of the excluded individuals had LDL-c levels > 130 mg/dL (3.36 mmol/mL) and 36.1% had hs-CRP levels < 2.0 mg/L.

Figure 1. Reasons for exclusion.



Settings

Countries with the highest participations of patients included the USA (4,201), United Kingdom (2,873) South Africa (2,497) and Canada (2,020). The rest of the patients came from Western and Eastern Europe and Central and South America. There were no Asian patients included.

Objectives of the study[7]

To determine to what extent rosuvastatin 20 mg daily delays the first cardiovascular event (composite endpoint including cardiovascular death, stroke, myocardial infarction (MI), admission to hospital for unstable angina or revascularization). Other variables of the study included an evaluation of the long term safety profile of rosuvastatin in terms of total mortality, death of non-cardiovascular origin, and adverse effects. An evaluation of the reduction in the incidence of type 2 diabetes with the employment of rosuvastatin was also made. According to the authors this objective would bring to light the fact that hs-CRP also predicts the onset of diabetes and that inflammation appears to establish a close link between diabetes and atherothrombosis. Finally this study also predicted an association between rosuvastatin and the prevention of fractures and venous thrombotic events.

Results

The study was discontinued early after 1.9 years, despite the pre-established follow up period of 3.5 years. The early stopping was due to a reduction in the incidence of the primary endpoint in the group receiving rosuvastatin.

Conclusion of the authors

This trial shows that in apparently healthy men and women, with no hyperlipidemia, but with elevated hs-CRP levels, rosuvastatin significantly reduces the rate of a first major cardiovascular event and total mortality when compared to placebo.

Role of the sponsors

The sponsor of the trial was Astra Zeneca, owner of rosuvastatin. The sponsor was in charge of the collection of data from the study and monitored and supervised the settings where the trial was performed. The company declared that it was not involved in the analysis of the data and the preparation of the published manuscript. In addition the company declared not having any access to the unblinded information from the trial until the manuscript was sent for publication.

Declaration of conflicts of interest

Various authors of the trial declared conflicts of interest with different pharmaceutical companies and especially with the sponsor. But the principal conflict of interest rests with the main author who is the co-inventor of and holds the patent for the hs-CRP test. In addition, the license for rosuvastatin belongs to Astra Zeneca.

Table 3. Results of the JUPITER trial.

ENDPOINT	ROSUVASTATIN (8,901)		PLACEBO (8,901)		HR (95% CI)	p value
	No	Rate per 100 per/yr	No	Rate per 100 per/yr		
Primary endpoint	142	0.77	251	1.36	0.56 (0.46-0.69)	<0.00001
Nonfatal myocardial infarction	22	0.12	62	0.33	0.35 (0.22-0.58)	<0.00001
Any myocardial infarction	31	0.17	68	0.37	0.46 (0.30-0.70)	0.0002
Nonfatal stroke	30	0.16	58	0.31	0.52 (0.33-0.80)	0.003
Any stroke	33	0.18	64	0.34	0.52 (0.34-0.79)	0.002
Arterial revascularization	71	0.38	131	0.71	0.54 (0.41-0.72)	<0.0001
Hospitalization for unstable angina	16	0.09	27	0.14	0.59 (0.32-1.10)	0.09
Arterial revascularization or hospitalization for unstable angina	76	0.41	143	0.77	0.53 (0.40-0.70)	<0.00001
Myocardial infarction, stroke, or confirmed death from cardiovascular causes	83	0.45	157	0.85	0.53 (0.40-0.69)	<0.00001
Death on known date	190	0.96	235	1.19	0.81 (0.67-0.98)	0.03
Any death	198	1.00	247	1.25	0.80 (0.67-0.97)	0.02

A critical appraisal of the trial

External validity

The trial was well designed and included a large number of participants, and correct methodology and intention to treat analysis was applied. Individuals were required to take placebo for 4 weeks initially and only those with good compliance were randomized. A large number of people who were initially screened were excluded (81%). This fact significantly reduces the external validity of the study. There were no patients of Asian origin in the study, most probably because the information leaflet of rosuvastatin indicates that in these patients a modification in the drug's kinetics may occur leading to higher plasma concentrations of the drug by at least two fold[10].

It is worth mentioning that JUPITER included a subgroup of high risk patients, whose presence could explain part of the results: among the participants, 25% had a BMI > 32, 16% were smokers and another 25% had HDL-c levels < 1.03 mmol/L (40 mg/dL).

Primary endpoint

An important first critique of the study regards the primary endpoint. It is a composite endpoint which includes a variety of individual endpoints ranging from admission to hospital for a revascularization procedure to cardiovascular death. On many previous occasions we have commented that composite endpoints that include such a diverse variety of individual components can lead to erroneous interpretations and make it difficult to draw adequate conclusions[11]. Admission to hospital for a revascularization procedure and death do not have the same clinical implication for the patient.

Early stopping

Early stopping of the trial confers an important bias. Studies that end prematurely due to a demonstrated benefit significantly exaggerate the magnitude of the benefit independently of whether the statistical conditions affirming the benefits were reached[11]. For example, interventions that have a treatment effect of RR = 0.80 in completed trials, if stopped early show an average overestimated treatment effect of approximately RR = 0.57[12]. Because of this, it has been suggested that stopping trials early for benefit is unethical[13].

Committees that supervise trials should wait for a substantial number of accumulated events before suggesting an early end to the trial. Even more so, they should consider that the dangers of interrupting a trial are not trivial (risks include false positives, overestimation of benefits, less convincing results or a lost opportunity to obtain essential data on the adverse effects of the drug)[14].

The authors never justified the inclusion of 17,000 patients in total in spite of the sample size calculated being 15,000 individuals, including foreseen dropouts.

The strategy of stopping studies prematurely and presenting the effects in relative and not absolute terms is a common trend adopted by the pharmaceutical industry. The benefits of this strategy to the industry include making the results available quickly and favourably, plus minimizing the cost of research[15].

Is the research question relevant?

Is rosuvastatin more effective than placebo in reducing cardiovascular morbidity and mortality in patients with low LDL-c levels and high hs-CRP concentrations seems a relevant question. However, another question is whether new strategies of cardiovascular disease prevention can be recommended from the results obtained, when the effect of rosuvastatin in people with low hs-CRP is not known.

High sensitivity C- Reactive Protein (hs-CRP)

In the justification presented for the study it was seen that some authors claim hs-CRP could represent a causal factor in the pathogenesis of atherosclerosis. However it is also true that others consider hs-CRP is not implicated in this process, and is simply a marker that could lead to confusion, especially in a context where multiple risk factors play a role: tobacco, hypertension, obesity, sedentarism, etc.

An attempt to elucidate whether hs-CRP is a marker indicating an atherosclerotic process or a causal factor of the same process was made in a study involving a population with specific genetic polymorphism and therefore high hs-CRP levels. This study did not show any association between high hs-CRP and an increase in ischemic vascular disease[16]. This finding implied that hs-CRP is not a causal factor implicated in the pathogenesis of atherosclerosis and therefore a drug to reduce hs-CRP in plasma is not rational[17]. However, to confirm this hypothesis a clinical trial would be required with a drug that acted exclusively on hs-CRP.

In a later publication[18], the authors offered some of the results in relation to baseline hs-CRP concentrations. However, the data provided does not prove the concept. In fact, the data raises doubts on the biological plausibility of the association of a reduction in hs-CRP and the expected cardiovascular benefits because patients with the lower third hs-CRP levels showed the greatest risk reduction.

Furthermore the positive predictive value of hs-CRP in the JUPITER trial was only 1.35% (251 episodes in 8,901 patients in the placebo group). Moreover, even if the association between hs-CRP and cardiovascular events was great, it would require a group of patients with low levels of LDL-c and hs-CRP to prove the relationship, or as we have commented earlier, to test agents capable of reducing hs-CRP with no action on LDL-c. Paradoxically, the JUPITER trial cannot shed light on the importance or not of lowering hs-CRP levels, and whether this proves useful in reducing cardiovascular events. The authors actually recognized this flaw in the design of the study[7].

In a recent *post-hoc* analysis of the ASCOT trial[19], the significant decrease in the hs-CRP levels was not associated with a reduction in the incidence of cardiovascular events. In this study no evidence of the theoretical advantage of decreasing hs-CRP levels in absolute terms was observed, nor if compared to baseline hs-CRP levels. The results of this trial suggest that hs-CRP testing provides no added value to the main cardiovascular risk factors, namely smoking, hypertension, high BMI, and HDL-c and LDL-c levels. In fact, the authors challenge the appropriateness of the FDA's indication granted to rosuvastatin for the treatment of patients with high levels of hs-CRP (> 2 mg/L).

Are the results relevant?

The results of the JUPITER trial have been marketed as extraordinary, and we shall attempt to analyse them in detail. As can be seen in the table presented from the JUPITER trial, the absolute risk reduction of the primary endpoint was 1.22% (2.81 versus 1.59). Is that substantial? When the crude data is presented in a table of this type and one focuses for instance on the results regarding myocardial infarction, stroke, or cardiovascular death, the differences appear important (157 vs 83) and in many places this study has been publicized as one in which an indisputable reduction of cardiovascular mortality has been shown. An illustration of this data is shown below.

Nowhere in the publication of the trial or in the discussion of the authors is cardiovascular mortality mentioned. Curiously, data obtained from the FDA website[20] offers information on cardiovascular mortality (0.4% vs 0.5%), HR = 0.80 (0.51-1.24), n.s. Therefore, there is NO SIGNIFICANT DIFFERENCE in cardiovascular mortality between patients treated with rosuvastatin as compared to placebo. The fact that there are no significant differences in mortality due to cardiovascular causes, makes one question the early stopping of the trial even more so.

Some authors have calculated cardiovascular mortality indirectly from the outcomes on myocardial infarction, stroke and cardiovascular death, by deducting non fatal stroke, myocardial infarction. The result is 31 for rosuvastatin and 37 for placebo which are obviously not significantly different. Another indirect form of appreciating cardiovascular death is by deducting fatal myocardial infarctions and stroke from the tables, resulting in

Table 4. Incidence of cardiovascular events in male individuals in the JUPITER trial according to hs-CRP levels.

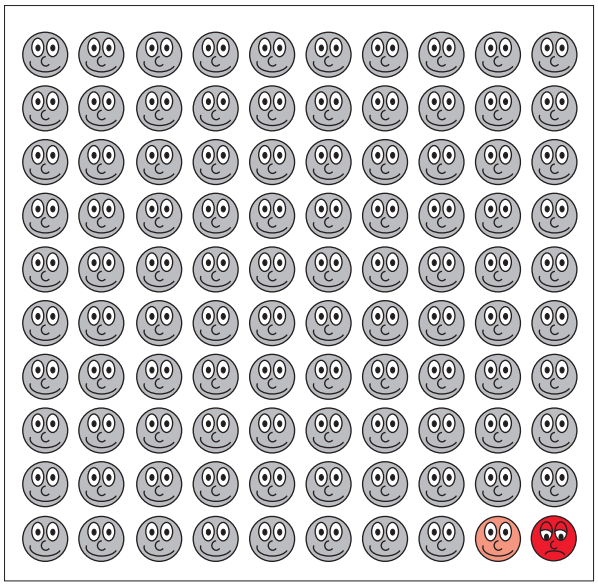
TERTILE	hs-CRP (mg/L)	PATIENTS (n)	INCIDENCE RATE PER 100 PERSON/YEARS			RR	95% CI	p value	ARR
			Total cohort	Rosuvastatin	Placebo				
PRIMARY END POINT									
Highest	>54	3,741	1.42	1.09	1.73	0.63	0.43-0.93	0.02	0.64
Middle	3.1-5.4	3,601	1.24	0.98	1.49	0.66	0.44-1.00	0.048	0.51
Lowest	2.0-3.1	3,659	0.99	0.59	1.39	0.43	0.26-0.69	0.0003	0.80
p for trend	0.023	0.042	0.20						
PRIMARY END POINT PLUS ALL-CAUSE MORTALITY									
Highest	>5,4	3,741	3.05	2.65	3.44	0.77	0.60-1.00	0.045	
Middle	3.1-5.4	3,601	2.03	1.59	2.46	0.65	0.47-0.89	0.0007	
Lowest	2.0-3.1	3.659	1.61	1.24	1.99	0.62	0.44-0.89	0.008	
p for trend	<0.0001	0.0001	0.0001						
PRIMARY END POINT PLUS VENOUS THROMBOSIS PLUS ALL-CAUSE MORTALITY									
Highest	>5.4	3,741	3.29	2.84	3.72	0.76	0.59-0.98	0.03	
Middle	3.1-5.4	3,601	2.18	1.65	2.70	0.61	0.45-0.84	0.002	
Lowest	2.0-3.1	3,659	1.84	1.44	2.25	0.64	0.46-0.89	0.007	
p for trend	0.0001	0.0001	0.0001						

ARR = absolute risk reduction.

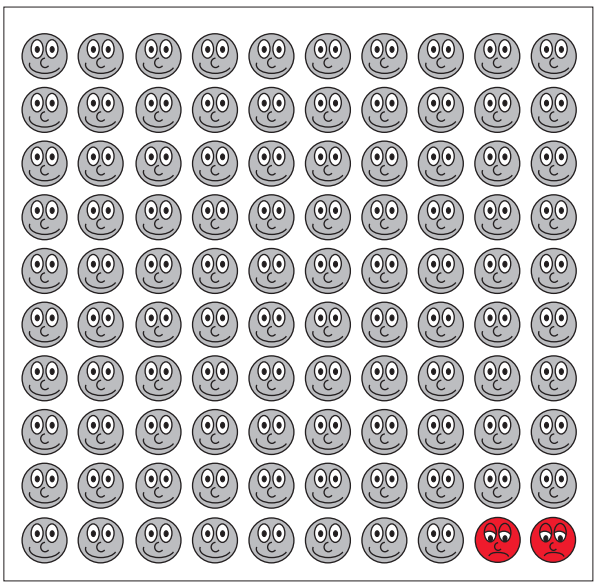
9 fatal infarctions with rosuvastatin and 6 fatal infarctions with placebo. According to the table there would be 3 fatal strokes in the rosuvastatin group compared to 6 among the placebo group.

Therefore, mortality exclusively due to myocardial infarctions and strokes would be identical in both groups, 12 versus 12. But if there were 12 deaths due to stroke or myocardial infarction in both

Rosuvastatin 20 mg



Placebo



Endpoint: MI, stroke, or cardiovascular mortality. Follow-up, 1.9 years. Probability of not benefiting from treatment in this outcome is approximately 99%.

Table 5. Results of the JUPITER trial in absolute terms.

	HR	ARR	NNT
Primary endpoint	0.56 (0.46-0.69)	1.22% (0.85%-1,5%)	83 (67-118)
Nonfatal myocardial infarction	0.35 (0.22-0.58)	0.45% (0.29%-0.55%)	221 (184-342)
Any myocardial infarction	0.46 (0.30-0.70)	0.41% (0.23%-0.53%)	245 (189-441)
Nonfatal stroke	0.52 (0.33-0.80)	0.31% (0.13%-0.43%	322 (231-774)
Any stroke	0.52 (0.34-0.79)	0.34% (0.15%-0.47%)	291 (211-666)
Arterial revascularization	0.54 (0.41-0.72)	0.67% (0.41%-0.86%)	150 (117-246)
Hospitalization for unstable angina	0.59 (0.32-1.10)	0.12% (-0.03%-0.2%)	815 (491-3345)
Arterial revascularization or hospitalization for unstable angina	0.53 (0.40-0.70)	0.75% (0.47%-0.95%)	135 (105-211)
Myocardial infarction, stroke, or confirmed death from cardiovascular causes	0.53 (0.40-0.69)	0.82% (0.54%-1.05%)	123 (96-186)
Death on known date	0.81 (0.67-0.98)	0.49% (0.05%-0.86%)	204 (117-1945)
Any death	0.80 (0.67-0.97)	0.49% (0.08%-0.86%)	204 (117-1296)

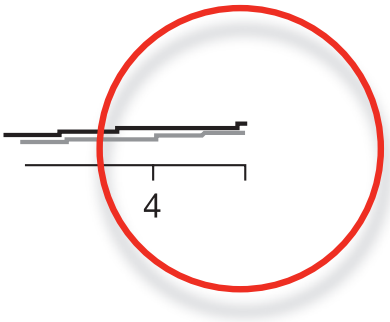
groups, then what did the other 19 and 25 patients respectively die of? This information is not provided in the publication and has been the cause of controversy and a number of exchanged letters[21,22].

Total mortality has been presented as significantly different however when the survival curves are studied more closely this is not as clear as it may seem (see Figure below).

Are the results plausible? Are they clear?

Does it make sense that a drug, which reduces cardiovascular events and total mortality and yet does not reduce cardiovascular mortality? As De Lorgergill[19] correctly comments in his article, the rate of mortality due to myocardial infarction is incredibly low (9/22 and 6/62), especially in the placebo group. According to the MONICA[23] study, 50% of the patients with infarction died 3-4 weeks

Graph 1

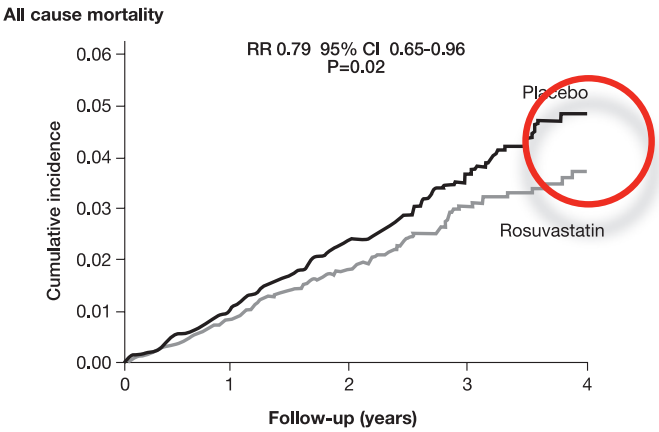


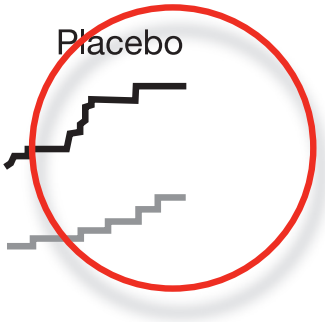
Graph 1 shows the original table, as it should be presented and in which it is difficult to see any benefit. *N Engl J Med 2008;359:2195-207.*

Graph 2

Graph 2 is the previous presentation but magnified 10 times, in order to perceive any differences. *N Engl J Med 2008; 359:2195-207.*

Graph 3





Graph 3 is the same as the above, but with differences: the "y" axis has been shortened to offer a greater sensation of difference between the curves and the duration has been limited in the "x" axis to 4 years, in search of the moment of maximum amplitude between the curves. *Cir Cardiovasc Qual Outcomes 2009;2:279-285.*

after the event. Even in low risk populations, such as in the Mediterranean area or Japan, mortality after the first myocardial infarction approximated 40%. In the JUPITER trial mortality among the patients with infarction is 8.8% in the placebo group while in the rosuvastatin group mortality is 29%. This data is questionably plausible[15].

Total mortality was reduced by rosuvastatin, HR = 0.80 (0.67-0.97) with an absolute risk reduction of 0.6% (0.1%-0.9%). However if we look at Graph 2, we can observe, as mentioned also by the FDA, that the curves tend to converge at the end, when the analysis is made after 4.4 years (which is the duration of the graph in the original study and re-

ported by the FDA). In this case the absolute risk reduction is 0.7% (-0.4 to 1.8%). Therefore it is not clear that rosuvastatin 20 mg/d offers any advantage over placebo in total mortality[24].

There is more information that calls into doubt the validity of the results of the JUPITER trial. Before the trial took place, rosuvastatin was not proven to reduce cardiovascular events in three large studies: CORONA[25] (patients with heart failure and in which 60% had suffered a myocardial infarction), the GISSI-HF[26] (patients with heart failure) and AURORA[27] (patients receiving hemodialysis in which 40% had cardiovascular disease). This is despite the fact that many of the patients included in these studies had previously had a myocardial infarction.

The 20 mg dose

It is rather curious, that a dose 4 times higher than the standard dose of statins does not cause more adverse effects than placebo. Recently the SEARCH[28] trial that compared intensive therapy (simvastatin 80 mg/d) with standard therapy (simvastatin 20 mg/d) in patients with a history of MI, showed an increased risk of myopathy with high dose simvastatin. It is important to recall that one of the most controversial issues regarding rosuvastatin since its commercialization has been its safety profile. In June 2004, Astra Zeneca Canada Inc and Health Canada warned of the association between rosuvastatin and rhadomyolysis. In November 2004 another alert was issued after an increase in the rate of rhabdomyolysis was documented with the use of rosuvastatin 40 mg/d[29]. At the same time the FDA published an alert on rosuvastatin and the risk of rhabdomyolysis which appeared to be greater than previously thought[30].

Later on in March 2005, the FDA regarded rosuvastatin as having the same risk as other statins and emphasized safety recommendations especially with the 40 mg tablet and in patients of Asian origin[31].

Other endpoints

In a later publication, an analysis of the results on thromboembolic events was offered. In the rosuvastatin group, 34 (0.38%) cases occurred while in the placebo group 60 (0.67%) [HR = 0.57 (0.37-0.86)]. The absolute difference in risk was 0.29% and the NNT was 349 (238-1073).

With respect to the incidence of new cases of diabetes, the authors had planned to determine how rosuvastatin prevented this incidence in the design of the study. However, the results were contrary to that expected, where 270 new cases of diabetes appeared among the rosuvastatin group compared to 216 among placebo (p=0.01). Recently in February of this year a meta-analysis was published[32] involving different trials with statins in which a mild, but significant increase in new cases of diabetes was observed in patients receiving statin therapy [OR= 1.09 (1.02-1.17)]. From this same paper it was deduced that there is greater risk of developing diabetes in older patients than younger populations.

It can be concluded from this that if we treat 1,000 patients with the same characteristics employed in the JUPITER trial for a 2 year period, a myocardial infarction or a stroke would be prevented in 8 patients, while 6 patients would develop diabetes.

Should these results be taken into account? Should the guidelines be modified?

An author (with important conflicts of interest) has proposed a modification in the guidelines on primary prevention, such that patients with c-LDL < 3.4 mmol/L (130 mg/dL) and a hs-CRP > 2 mg/L, would be treated with a statin[33]. This moreover would involve testing millions of people for hs-CRP concentrations.

Taking into account the arguments we have presented up to now: doubts on the causal or predictive value of hs-CRP for cardiovascular disease, bias´ in the premature ending of the JUPITER trial, results with little relevance in absolute terms, absence of statistical significance on cardiovascular mortality, doubts on the plausibility of the data, absence of clear data on the different outcomes employed, important conflicts of interest of the main author, it makes sense that we ignore the results when deciding on management of primary prevention patients with statins, or more precisely, rosuvastatin.

Curiously a few months ago the European regulatory agencies awarded rosuvastatin the indication for primary prevention of cardiovascular events in high risk patients as a result of a *post hoc* analysis in which patients with cardiovascular risk in the Framingham scale > 20% showed a significant reduction (8.8 per 1,000 patients-year) in MI, stroke or cardiovascular death (p=0.076). A reduction was also observed in patients with a SCORE > 5% in the same endpoint (5.1 per 1,000 patients-year)[34]. Total mortality did not change significantly in this risk group (p=0.076). It is no doubt surprising that this indication was awarded based on a *post hoc* analysis of secondary endpoints. However, the indication makes no mention of basal hs-CRP studies, which very much disturbed

the main author of the JUPITER trial, who is the owner of the patent for the detection of hs-CRP[35].

Primary prevention of cardiovascular disease with statins, as published in other issues of the DTB-Navarre, produces benefits in very few people and within this group there are few elderly people or women present. Recently a new meta-analysis[36] including the results of the JUPITER trial and more than 65,000 patients has been published. The conclusions of this meta-analysis are that total mortality does not change with statin therapy employed in primary prevention in high cardiovascular risk patients.

Recently a review published examining the different meta-analyses regarding this issue showed that when clinical trials of low risk of bias are selected, no clear efficacy is found from the evidence. The benefit that some meta-analyses show on mortality with statin therapy in primary prevention is more likely due to bias than a real effect[37]. There is a decrease in coronary events but no reduction in the total number of serious adverse events. Statins have not demonstrated any net health benefit in primary prevention patients and when employed widely in this indication they represent a poor use of health care resources.

Conclusions

The role of hs-CRP in the pathogenesis of atherosclerosis still remains unclear. It should not be used as a cardiovascular risk marker due to its poor predictive value.

The early stopping of the JUPITER study exaggerates the benefits.

Rosuvastatin did not significantly reduce cardiovascular mortality and the causes of overall mortality are not clearly described in the trial.

The long-term projection of total mortality is not significant and undermines the validity of the data offered in the study.

Rosuvastatin significantly increased the number of patients who developed diabetes.

Substantial conflicts of interest of the main author adds to the high risk of bias of this study.

The results of this study should not modify our approach to primary prevention.

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