

Outcomes of JUPITER Trial will Change Primary Prevention Strategies in Daily Practice

Agonist

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The outcomes of the JUPITER trial (1) will increase the therapeutic use of statins. This statement is based on three viewpoints: shortcomings of the ATP III risk score based on the Framingham scoring, the increasing importance of C-reactive protein (CRP) in the prediction of cardiovascular risk (CVR) and, finally, the results of the JUPITER trial. All these issues are important to reassert the conclusions of JUPITER trial.

Most of the experts have accepted that the use of the Framingham risk score (FRS) has widely spread in clinical practice. However, the FRS has some shortcomings in women, in elderly people and in patients with family history of early coronary artery disease. For this reason, some studies have been carried out in order to improve the performance of the FRS.

For example, in the Women's Health Study (WHS), Ridker demonstrated an improvement in risk prediction estimated with lipid levels among women. The prediction was even better with low cholesterol levels and high CRP (Figure 1). (2)

Ridker also found that CRP significantly added prognostic information to the FRS and was better than the other risk factors previously studied. The Reynolds risk score was then created based on the relation of these results with family history of early coronary artery disease. The Reynolds risk score uses information from CRP and family history of coronary artery disease, two risk factors that were not considered by the FRS.

A subsequent study evaluated the relationship of CRP with the components of the metabolic syndrome (MS) among 14 719 women out of 28 263 participating in the Women's Health Study (WHS), and concluded that high CRP levels add prognostic information of clinical relevance concerning future vascular risk.

Most of the methods available for the assessment of sub-clinical atherosclerosis or inflammation have worse performance in patients with high and low cardiovascular risk. The usefulness of CRP was assessed in studies performed in patients with moderate or intermediate cardiovascular risk, and in this group of patients current methods for detecting sub-clinical atherosclerosis have the best performance.

Recently the authors of the Copenhagen City Heart Study have made some objections regarding the use of CRP. They concluded that there is an inverse causality between cardiovascular disease and CRP and thus it may be a good marker as it is genetically determined. Subsequently, several comments have objected the mendelian randomization used in the Copenhagen City Heart Study.

The JUPITER trial was designed to assess the effects of treatment with statins compared to placebo in intermediate risk patients. The difference of this trial with previous studies lies in the inclusion criteria used: age > 60 years in women and 50 years in men, LDL-cholesterol levels < 130 mg and C-reactive protein 2 mg/L. In this way, the outcomes of this

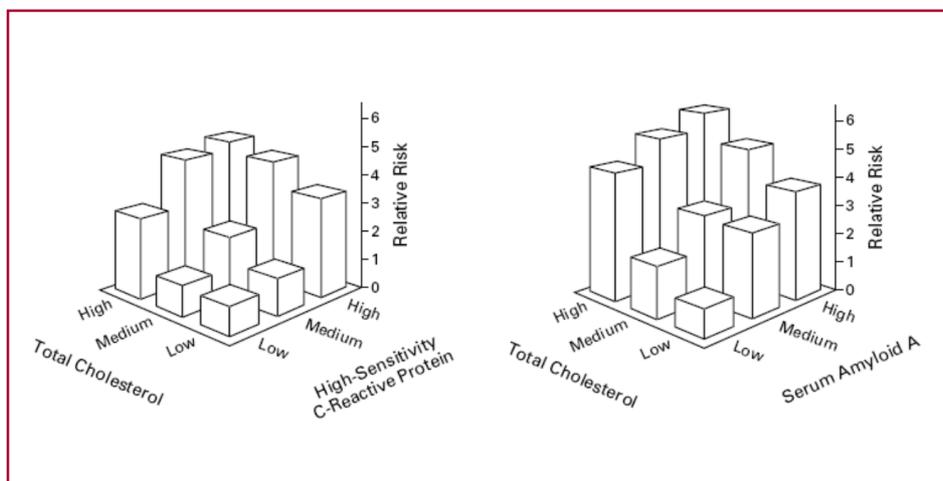


Fig. 1. Markers of inflammation in the prediction of cardiovascular disease in women

study are only applied to patients with the same characteristics.

Using data from the population of the National Health and Nutrition Examination Survey, the investigators from the University of Yale compared the results of the JUPITER trial in patients with similar characteristics (Figure 2). (3)

The authors concluded that the JUPITER findings are likely to have a profound impact on treatment recommendations for approximately 20% of middle-aged to elderly adults, thus increasing the proportion of this segment of the population with an indication for statin therapy.

They also pointed out that new patients with an indication for statin therapy are more likely to be female, to be older, and to have obesity, hypertension, and the metabolic syndrome.

Then the authors calculated the number of subjects from the population of USA with similar characteristics with LDL between 130 and 160 mg/dL which they called the “extended” JUPITER group, and concluded that may become newly eligible for statin therapy.

In general, the applicability of the results of clinical trials to clinical practice depends on several factors: the sources of evidence come from well-conducted randomized trials that have similar results and from experts’ opinions.

Since the recent publication of the JUPITER trial, most experts’ opinions have been favorable. In consequence its results may be rapidly applied

to the great number of subjects with intermediate risk and increased CRP who might benefit from therapy.

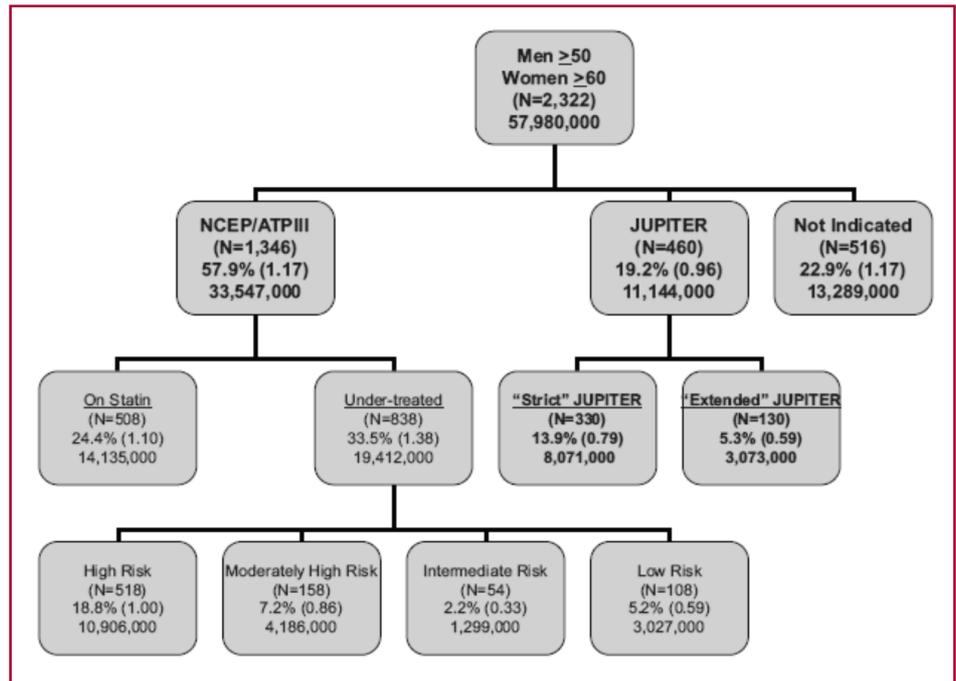
The JUPITER trial produced the the greatest risk reduction ever seen in a large placebo-controlled statin outcomes study in LDL levels with a dose of 20 mg/day. The JUPITER clinical trial was stopped more than two years early due to a significant reduction in morbidity and mortality among patients in the treatment arm of the study (Figure 3). (1)

The absence of rhabdomyolysis is promising as only one non fatal case was reported after closure of the trial in a participant with febrile influenza. There were no significant differences between the two study groups with regard to muscular weakness, stiffness or pain. Nineteen myopathic events were reported (in 10 subjects receiving rosuvastatin and 9 receiving placebo), defined as persistent increase in CK levels.

The is no other clinical study in primary prevention that has ever showed the magnitude of the effect of the JUPITER trial The onset of the benefits achieved in this trial is also uncommon, with the exception of studies carried out in patients with acute coronary syndromes. This group of patients is quite different from patients with absence of high risk included in primary prevention studies with statins. The results of the JUPITER trial are focused on these patients.

Costs of therapy with statins should be considered before transferring the benefits of the JUPITER trial

Fig. 2. population estimates for statin eligibility among men aged ≥50 years and women aged ≥60 years, based on data from the 1999-2004 NHANES



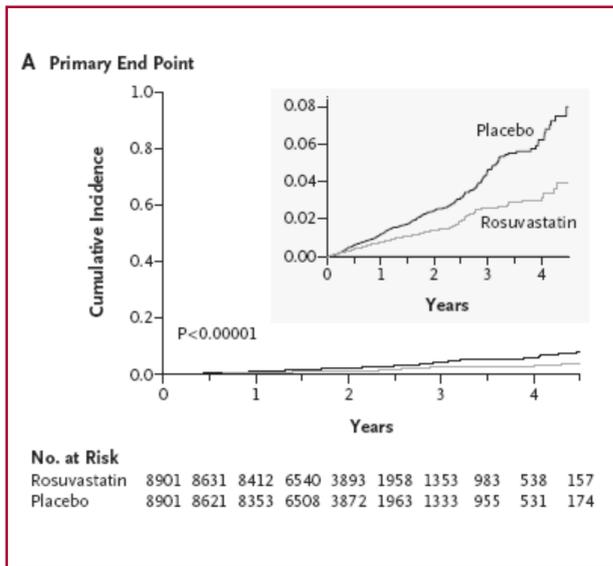


Fig. 3. Evolución acumulada del punto final primario comparando placebo con Rosuvastatina en el estudio Jupiter (1)

Antagonist

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The conclusions of the authors of the recently published JUPITER trial (1) was the following: “In this trial of apparently healthy persons without hyperlipemia but with elevated high-sensitivity C-reactive protein levels, rosuvastatin significantly reduced the incidence of major cardiovascular events”.

The trial included almost 18 000 patients (with a projected follow-up of 4 years but stopped after a median follow-up of 1.9 years), the incidence of major cardiovascular events with rosuvastatin decreased from 1.36 to 0.77 per 100 person-years of follow-up in the rosuvastatin group (hazard ratio, 0.56; 95% confidence interval [CI], 0.46 to 0.69) The rosuvastatin group did not have a significant increase in myopathy, hepatic injury or cancer.

The applicability of the aforementioned conclusion implies that high-sensitivity C-reactive protein (hsCRP) levels should be measured in every patient with no previous history of cardiovascular disease (primary prevention) and LDL cholesterol levels < 130 mg/L; treatment with rosuvastatin, 20 mg/day should be started if hsCRP levels are > 2 mg/L.

Guidelines for primary prevention should be modified in two main points: 1) treatment with statins should start with lower levels of LDL cholesterol with absence of inferior limits, and, 2) CRP with statins are considered a prognostic and therapeutic strategy.

to subjects with similar characteristics of the study group. In other countries these cost are minimized with the use of generic drugs; however in Argentina this will be a difficult instance due to economic issues. Immediately after the presentation of these results, new copies of rosuvastatin appeared with similar sale prizes.

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The generalization of this approach might have implications related to its applicability not only in the single patient but also in the whole health care system as a population strategy.

WHAT DID WE KNOW BEFORE THE JUPITER TRIAL?

1. Statins reduce the incidence of major vascular events due to decrease in the levels of LDL cholesterol. Relative risk reduction is 0.26 (CI 0.18-0.33) per 1 mmol/L (39 mg/dL) reduction in LDL cholesterol after 2 years of treatment. This relation derives from analyzing all patients with and without history of cardiovascular disease (53% in primary prevention). (2)
2. The “quantitative clinical effect” (number of patients needed to treat to prevent an event) depends on the global cardiovascular risk irrespective of the level of LDL cholesterol before starting with the treatment (Figures 1 and 2; Table 1).
3. The proportional reductions in major vascular events per 1 mmol/L (39 mg/dl) of LDL reduction is 25% in all the sub-groups analyzed.
4. The authors of the Cholesterol Treatment Trialists’ Collaborators (2) meta analysis reported that “there were significant reductions in major coronary events in other subgroups of interest, including

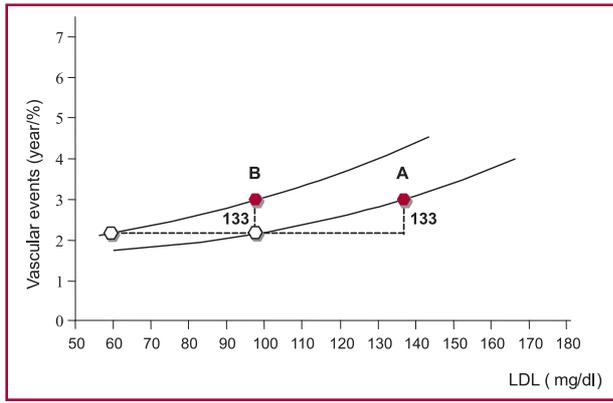


Fig. 1. Relationship between the clinical benefit of therapy with statins and the risk and the reduction of LDL cholesterol level. Two populations (A and B) with different baseline levels of LDL cholesterol have a similar risk due to the effect of other prognostic variables. The reduction of 40 mg/dl of LDL cholesterol induces a similar clinical benefit, expressed by the number needed to treat. In the example, it is necessary to treat 133 subjects to prevent a major vascular event. Both curves have the same slope: a decrease of 39 mg in LDL cholesterol reduces the risk by 25%.

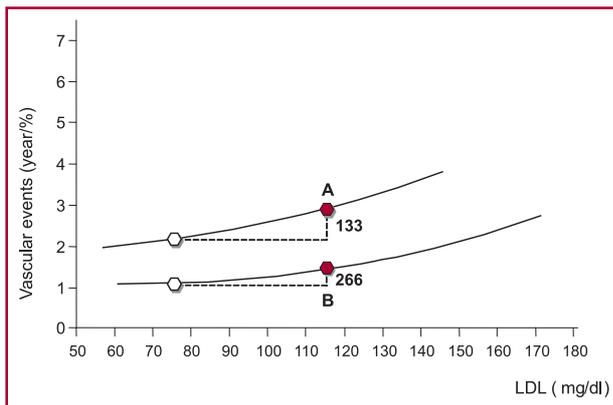


Fig. 2. In this case, two populations (A and B) with the same baseline level of LDL cholesterol have different risk. The clinical level achieved with a reduction of 39 mg/dl in LDL level is expressed by the number of patients necessary to treat: 133 subjects in the population A and 266 in B. The slope of both curves is identical to the curves of Figure 1.

Tabla 1. Effects of statin therapy on major vascular events (myocardial infarction, stroke, revascularization and mortality).

% per year	RRR/%	AR	NNT
3.0	25	0.75	133
2.5	25	0.63	160
2.0	25	0.50	200
1.5	25	0.36	266
1.0	25	0.25	400

% per year: annual rate of events in the control group. RRR: Relative risk reduction. AR: Absolute risk NNT: number of subjects needed to treat to prevent a major vascular event per year of treatment.

individuals with pretreatment LDL cholesterol of 2.6 mmol/L (100 mg/dl) or less (200 [6.0%] statin vs 247 [7.4%] control; RR 0.75, 99% CI 0.56—1.01; $p=0.01$)". (2)

WHAT DO WE KNOW AFTER THE JUPITER TRIAL?

1. Therapy with rosuvastatin 20 mg/d produced a 44% reduction in the number of major vascular events (myocardial infarction, stroke, revascularization, hospitalization for unstable angina, or cardiovascular death).
2. At the time of study termination (median follow-up, 1.9 years), therapy with rosuvastatin reduced LDL cholesterol levels by 50%, with a value of approximately 55 mg/dl and absence of significant adverse events.
3. The 46% reduction in the incidence of major vascular events was greater than would have been expected as the trial was designed to detect a 25% reduction in the rate of the primary endpoint. This might be due to a double mechanism: an important reduction in LDL cholesterol levels due to high doses of rosuvastatin and a greater clinical effect per unit of LDL reduction.
4. The results of this large randomized, double blind clinical trial confirmed the hypothesis of the effects of therapy with statins in apparently healthy patients with LDL cholesterol levels below 2.6 mmol/L (100 mg/dl). The level of evidence increased from grade B (meta analysis) to grade A (randomized clinical trial).

WHICH SHOULD NOT BE OUR CONCLUSIONS AFTER THE JUPITER TRIAL?

1. It is wrong to believe that the JUPITER trial included a population of low risk patients (1% per year or less) according to the Framingham risk score and that CRP allowed the selection of a subgroup of patients with intermediate risk. There are two reasons to exclude this possibility: firstly, the prognostic value of CRP has a reduced relative risk (3) and a limited capacity of discrimination (4), and secondly, 41% of patients had metabolic syndrome, 25% had a body mass index greater than 32, triglycerides were greater than 169 mg/dl and glucose blood level greater than 102 mg/dl; all these clinical situations, which are not considered in the Framingham risk score, are associated with vascular risk. (1)
2. In subjects with no previous history of vascular disease and LDL cholesterol level < 130 mg/L, the effect of rosuvastatin is limited to those with high levels of CRP as the effect of therapy with statins in patients with normal CRP levels is unknown. The design of the JUPITER trial should have been other to arrive at this conclusion: patients should

have been randomized to a CPR-guided strategy versus a habitual clinical strategy.

3. The absence of adverse events offers an adequate risk-benefit ratio due to the fact that a follow-up period of 1.9 years is particularly brief, specially in primary prevention. In fact, there was a higher incidence of physician-reported diabetes (0.6%) in the treatment group.

It is crucial to know the clinical implications of keeping LDL cholesterol levels in 55 mg/dl for 10 or 15 years under therapy with statins.

WHICH IS THE CHALLENGING, THOUGH NOT CONSISTENT FINDING?

1. The slope of the relationship between reductions in vascular events per unit of LDL reduction was steeper than what has been previously reported. A reduction of LDL cholesterol levels of 55 mg per deciliter implies a risk reduction from 44% to 35% if we consider the slope estimated in the meta analysis (a risk reduction of 25% for each 39 mg/dl of LDL reduction).

Interestingly, we may conclude that there is a correlation between increased CRP as an expression of inflammation or subclinical atherosclerotic disease and the pronounced reduction of clinical events related to therapy with statins. However, this is only inferred comparing the results of the JUPITER trial with bibliographic information. As we have previously pointed out, and to conclude with this issue, the trial should have included subjects with and without increased CRP.

DECISION -MAKING AFTER THE JUPITER TRIAL

In a primary prevention scenario, therapy with statins in patients with LDL cholesterol levels below 130 mg per deciliter according to CRP level might exclude patients who could benefit from treatment. It is wrong to conclude that population with normal CRP, considered at low risk or with absence of inflammatory activity, will not benefit from this therapy.

The decision to treat should be based on the global risk estimated by the Framingham scoring adjusted by other prognostic variables that are not considered in the score, such as family history, glycemia, obesity, waist diameter, metabolic syndrome, imaging of subclinical atherosclerosis, etc. Several studies have demonstrated that risk assessment based on the Framingham score may not be accurate in some cases.

The evidence regarding therapy with statins in intermediate risk patients has moved to level A after the JUPITER trial, due to the statistically and clinically significant findings: 172 individuals need to take 20 mg of rosuvastatin for 1 year for 1 person to avoid a major cardiovascular event (myocardial infarction,

stroke, revascularization or cardiovascular mortality, excluding hospitalization due to unstable angina).

The individual criterion on the number of patients we are determined to treat to avoid a vascular event is critical at the moment of decision making. Personally, I believe that this trial has demonstrated that this number justifies the intervention in patients with moderate to high risk as it does not exceed the number recommended in the guidelines.

Finally, we expect that the incidence of adverse will not surpass the risk benefit ratio in the long-term. This issue will probably be clarified by a prospective and observational registry.

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ANSWER FROM THE AGONIST

It is important to share points of coincidence with a sharp antagonist as Dr. Cagide.

In the first point of the section: what did we know before the JUPITER trial?, Dr. Cagide mentions that 53% of patients in the Cholesterol Treatment Trialists' (CTT) meta analysis were in primary prevention. This is correct. However, when Dr. Cagide asks: which should not be our conclusions?, I would like to highlight that the difference between the JUPITER trial and the CTT is that patients included in the former study had metabolic syndrome, obesity, hyperlipemia and impaired glucose tolerance. In consequence, these patients present greater risk and are more likely to benefit from therapy with statins than patients without these characteristics.

This category of patients of intermediate risk is not taken into account by the Framingham risk score (FRS). I shall not describe the shortcomings of such a useful tool as the FRS; however, I shall mention that the Reynolds risk score adds to the FRS information from CRP and family history.

I would like to comment Dr. Cagide's question regarding safety at long-term follow-up. Lovastatin has been used since 1987 and is currently available as a

generic drug, and pharmacoepidemiological studies have not reported any problems with this medication. Simvastatin is sold over the counter in two countries in Europe. The higher incidence of physician-reported diabetes has also been observed in several studies with different statins.

As an answer to the question: what do we know after the JUPITER trial?, Dr. Cagide mentions that rosuvastatin produces a greater clinical effect per unit of LDL reduction. The current evidence available shows that the addition of ezetimibe is a valid option with lower risk.

Dr. Alfredo Lozada

ANSWER FROM THE ANTAGONIST

According to the results of the JUPITER trial, the use of statins in primary prevention in patients with LDL cholesterol lower than 130 mg/dl depends strictly on the levels of CRP regardless of the global risk estimated. There are two reasons for questioning this conclusion.

1. When the subgroups are analyzed, the relative risk reduction is similar in subjects with a Framingham risk score of 1% per year or less (8.882) or greater than 1% per year (8.895) (RRR 0.56, similar to the entire group). However, in the subgroup of low risk patients, the confidence interval is greater according to the lower rate of events.

Considering a risk of 0.80-0.90 % per year (probably 50% of the population of the JUPITER trial is within this range) it is necessary to treat 267 subjects to prevent a major vascular event. This

number may not be cost-effective, especially for an unlimited time-related strategy with unknown collateral effects in the long-term.

2. My colleague quotes the study "From here to Jupiter" that analyzes three populations under primary prevention: individuals who were currently taking a statin or indicated for statin therapy based on NCEP/ATP III guidelines, individuals who would be indicated for statin therapy based on JUPITER's findings, and those without any NCEP/ATPIII or JUPITER indication for statin therapy

In the latter group with average LDL cholesterol levels of 114 mg/dl and CRP lower than 2 mg/L, 27% of subjects have a Framingham risk score of 1-2 per 100 events per year and in 13% is greater than 2 per 100 events per year, 43% have impaired glucose tolerance or diabetes, 37% hypertension and 34% metabolic syndrome. This group of high risk individuals would be excluded from therapy with statins despite they have a clear indication to start therapy due to CRP levels lower than 2 mg/L.

Finally, a CRP-guided strategy has less shortcomings (it is not used for treating high-risk patients) and more shortcomings (when treating individuals for whom the cost-risk/benefit relation is questionable) compared to a risk-guided strategy.

The JUPITER trial adds information but does not modify completely the concept that the effect of statins depends on the global cardiovascular risk estimated by the Framingham risk score "adjusted" to variables that are not considered in that score.

Dr. Arturo Cagide