

Jupiter Trial

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Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein (CRP) by Ridker et al, also known as JUPITER, investigated the use of rosuvastatin in a population that had elevated CRP but normal cholesterol levels. Elevated CRP is associated with increased cardiovascular events, and statin drugs have shown to reduce CRP level. The goal of the study was to determine if there were any benefits associated with statin therapy via reduction of

CRP levels. Jupiter was a randomized, double-blinded, placebo-controlled study consisting of 17,802 individuals with low-density lipoprotein (LDL) cholesterol levels of less than 130 mg per deciliter. It spanned 1,315 sites in 26 countries. The primary outcome included nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, arterial revascularization procedure, or confirmed death from cardiovascular events. Ridker et al found that rosuvastatin decreased cardiovascular events in patients with both

an elevated CRP and normal cholesterol levels (LDL <130), but who are otherwise healthy. The study was financially supported by Astra-Zeneca.

Median follow-up was 1.9 years. After the use of rosuvastatin, the authors found the rate of the primary end point per 100 person-years of rosuvastatin group to be 0.77 and the placebo group to be 1.36 person-year (P<0.00001). The authors also noted that the rosuvastatin group had higher incidence of physician-reported diabetes.

Table 1

Element	Criteria	Comments
Study Design Assessment	<p>Is the design appropriate to the research question? Is the research question useful?</p> <ul style="list-style-type: none"> For efficacy, use of experimental study design (meaning study subjects and others were not allowed choice in determining interventions) Clinically significant area for study (morbidity, mortality, symptom relief, functioning and health-related quality of life) and reasonable definitions for clinical outcome such as response, treatment success or failure If composite endpoints used, reasonable combination used and used for safety if used for efficacy 	<p>JUPITER was a double-blinded, randomized, placebo-controlled study. This is an appropriate study design in order to answer this question because it minimizes potential bias that could influence the interpretation of the results. Comparing against a placebo will ensure that any changes observed can be associated with the intervention, which is rosuvastatin in this case.</p> <p>THREAT: A limitation of a controlled study is the threat to external validity.</p>
Internal Validity Assessment	<p>Can bias, confounding or chance explain the study results?</p> <ul style="list-style-type: none"> Ensure prespecified and appropriate 1) research questions, 2) populations to analyze, 3) outcomes, 4) group assignment methods, 5) study conduct methods, 6) analysis methods, and 7) level for statistical significance 	<p>End points such as hospitalization for unstable angina and revascularization procedure.</p> <p>THREAT: The assumption that cardiovascular events were reduced due to the reduction of CRP by rosuvastatin is questionable. Other effects such as lowering of LDL may be a contributing factor to the reduction of cardiovascular events.</p>
Selection Bias	<ul style="list-style-type: none"> Groups are appropriate for study, of appropriate size, concurrent and similar in prognostic variables Methods for generating the group assignment sequence are truly random, sequencing avoids potential for anyone affecting assignment to a study arm and randomization remains intact Concealment of allocation strategies are employed to prevent anyone affecting assignment to a study arm 	<p>The authors state that randomization was assured through the use of interactive voice-response system and stratification according to center.</p> <p>THREAT: There was no mention of how the generation of the randomization sequence was accomplished. Voice-response systems are likely to be successful in concealing allocation to groups. However concealment of allocation was not explicitly mentioned.</p>
Performance Bias	<ul style="list-style-type: none"> Double-blinding methods employed (i.e., subject and all working with the subject or subject's data) and achieved Reasonable intervention and reasonable comparator used (e.g., placebo) No bias or difference, except for what is under study, between groups during course of study (e.g., intervention design and execution, co-interventions, concomitant medication use, adherence, inappropriate exposure or migration, cross-over threats, protocol deviations, measurement methods, study duration, etc.) 	<p>According to the authors, study participants were either given rosuvastatin 20 mg daily or a matching placebo.</p> <p>THREAT: Details about the blinding of the clinicians involved in the intervention are not mentioned.</p>

Although the authors claimed that JUPITER was a double-blinded, placebo-controlled, multi-center trial, several aspects of the design were unclear. The details about the blinding of the assessors and clinicians were not explained thoroughly. Also, the data of the drop-out patients was not analyzed and elaborated upon. This is important because without analysis, pertinent information such as whether the discontinuation of the medication was due to serious adverse effects that could cause harm to the patient were not discovered. The study population was highly selected and may not apply to the general population (external validity), especially the elderly who have the highest rate of cardiovascular events. With a relatively short study, NNT of 95 at approximately two years,

and taking into consideration the potential for further complications (eg diabetes), the benefits may not outweigh the risks of administering this medication to otherwise healthy adults. Therefore, the findings in this study may be somewhat useful to a specific population, which consequently will limit its applicability on a grand scale. Further study is required before rosuvastatin should be recommended as a part of the patient's regimen to reduce cardiovascular events. **Overall Grade: B-U**

Statin use for the primary prevention of cardiovascular events in patients with elevated C-reactive protein (CRP) without elevated lipid levels requires further study because of limitations of this single study and remaining uncertainty regarding the benefit/risk ratio of statin use in this population. It should also be pointed

out that when studies are stopped early for benefit, the statistically significant differences between outcome measures in the groups are very likely to be due to chance—even if stopping rules are employed.¹ Furthermore, when studies are stopped early, absolute differences between study groups are likely to be exaggerated. Taken together, clinicians may be well-advised to wait for confirmatory studies before routinely testing low-risk, healthy patients for CRP and routinely recommending statins for them. 📌

References

1. Bassler D, Montori VM, Briel M, Glasziou P, Guyatt G. "Early stopping of randomized clinical trials for overt efficacy is problematic." *J Clin Epidemiol.* 2008 61(3):241-6. PMID: 18226746

Attrition Bias	<ul style="list-style-type: none"> Zero or minimal missing data points or loss from randomization (e.g., approximately 5% with differential loss, or approximately 10% without differential loss) unless good ITT analysis (see ITT below) 	0.5% of patients from the rosuvastatin arm and 0.4% of the placebo arm dropped out of the study THREAT: The dropped-out patients were not well accounted for in the analysis (see Assessment Bias). Although the drop-out rate was comparatively low, the reasons behind the drop-outs were undisclosed, which begs the question of whether the drug was harmful to the patient.
Assessment Bias	<ul style="list-style-type: none"> Assessors are blinded Low likelihood of findings due to chance, false positive and false negative outcomes (judgment call on statistical significance, including confidence intervals) Non-significant findings are reported, but the confidence intervals include clinically meaningful differences Intention-to-Treat Analysis (ITT) performed (all people are analyzed as randomized + reasonable method for imputing missing values which puts the intervention through a challenging trial or reasonable sensitivity analysis) Use of modeling only with use of reasonable assumptions 	The primary end points were adjudicated by an independent committee that were uninformed of the assignments. The authors plotted a Kaplan-Maier curve showing the cumulative incidence of the primary and secondary end points. THREAT: No elaboration was provided for the missing data of the patients who dropped out of the study. The data points were also extrapolated to beyond four years, when the median follow-up period was only 1.9 years. This is misleading because it attempts to show a long term benefit from short term data.
Usefulness Assessment	<ul style="list-style-type: none"> Clinically significant area + sufficient benefit size = meaningful clinical benefit (consider efficacy vs effectiveness) 	At two years of statin therapy, the NNT to prevent a primary outcome was 95. THREAT: The NNT of 95 may be considered by some to be somewhat high.
External Validity	<p>How likely are research results to be realized in the real world considering population and circumstances for care?</p> <ul style="list-style-type: none"> Review n, inclusions, exclusions, baseline characteristics and intervention methods — this is a judgment call 	52% and 36% of the 89,890 people initially screened were excluded on the basis of their LDL-C >130 mg/dL and hsCRP >2.0 mg/L, respectively. THREAT: The vast majority of people would be excluded, and the results from this study are not as applicable.
Patient Perspective	<ul style="list-style-type: none"> Consider benefits, harms, risks, costs, uncertainties, alternatives, applicability to which patients, adherence issues, potential for abuse, dependency issues and patient satisfaction 	When taking any medications, one must always look at the risks and benefits. One of the risks associated with rosuvastatin, according to the author, is the development of DMII. This possibility must be weighed against a questionable reduction in CV outcomes.
Provider Perspective	<ul style="list-style-type: none"> Satisfaction, acceptability, likely appropriate application and actionability (e.g., FDA approval, affordability, external relevance, circumstances of care, able to apply, tools available) 	As a clinician, the worry that risks may outweigh the benefit is present. Providers may not be willing to prescribe medication to an otherwise healthy individual.

*Chart taken from the Delfini Group, LLC. Short Critical Appraisal Checklist: Updated 02/19/08

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