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JUPITER

A Few Words of Caution

Viola Vaccarino, MD, PhD; J. Douglas Bremner, MD; Mary E. Kelley, PhD

Since the JUPITER trial results were released in November 2008,¹ they have been applauded by various sources (the media, the medical literature, cardiology experts, and health authorities) and described as a breakthrough, heralding large public health benefit and potentially dictating change in clinical practice toward the expansion of the use of statins for primary prevention. Such comments include the concept that statins should be given to everyone, regardless of their lipid levels.^{2,3} Based on the results of JUPITER, an additional 19% of the United States older population (men ≥ 50 years and women ≥ 60 years), or more than 11 million people, may become eligible for statin therapy, bringing the proportion of older adults with indications for statin therapy to $\approx 80\%$.⁴

JUPITER, an acronym for Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin, tested the hypothesis that statin treatment may reduce vascular events in persons with elevated high-sensitivity C-reactive protein (CRP) but without hyperlipidemia. The study enrolled apparently healthy people with LDL cholesterol levels of < 130 mg/dL but with high-sensitivity CRP levels of ≥ 2.0 mg/L. Participants were randomly assigned to receive either rosuvastatin, 20 mg orally per day, or a placebo, and followed for cardiovascular events. The trial was planned to last 4 years, but it was stopped early for benefit by the data and safety monitoring board, after a median follow-up of 1.9 years.

Are the Claimed Benefits Large Enough to Advocate a Change in Clinical Practice?

The reason for the enthusiasm and early termination of JUPITER was a hazard ratio of 0.56 (95% CI, 0.46 to 0.69), translating into a 44% relative risk reduction for the primary outcome favoring statin treatment, with similar reductions in other cardiovascular end points. But as Dr Hlatky cautioned, in his editorial to the JUPITER trial,⁵ what really matters for dictating changes in clinical practice is the absolute risk reduction. This is because the absolute benefit of the treatment must be large enough to justify its potential risks and costs. Importantly, the threshold for tolerating risks and costs is particularly low when dealing with predominantly healthy

populations who have low event rates, such as the sample enrolled in JUPITER. The question therefore is: are the treatment benefits achieved in the JUPITER trial large enough to advocate an expansion in the clinical indications for statins?

JUPITER used a composite outcome as the primary outcome of this trial, a technique used to minimize the enrolled sample size and a subject of potential controversy in the medical literature, especially when including outcomes of markedly different clinical severity (eg, arterial revascularization versus mortality).⁶ The rate of the primary end point, a composite of 5 conditions (nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, arterial revascularization, or confirmed death from cardiovascular causes) was only 0.77% per year in the rosuvastatin arm and 1.36% in the placebo arm. These rates translate into an absolute risk reduction of about a half percentage point per year (0.59%), or 1.2% over the approximately 2-year total duration of the trial. This figure is obviously much less impressive to the casual reader than the relative risk reduction of 44%. If one considers the more important and customary outcome of major coronary events, including nonfatal or fatal myocardial infarction, the yearly rate in the two arms was 0.17% and 0.37%, respectively, yielding an absolute risk reduction of only 0.20% per year. However, the corresponding relative risk reduction remained an impressive 54%. When dealing with low event rates, even a small absolute difference in rates can appear dramatic when expressed in relative terms (eg, as a hazards ratio, or relative risk reduction).

A useful measure to assess effectiveness of health care interventions is the number needed to treat.⁷ This is the number of patients who need to be treated to prevent one additional adverse outcome, and is calculated as the inverse of the absolute risk reduction. Based on an absolute risk reduction of 0.59% per year for the primary end point, 169 persons need to be treated for 1 year to prevent 1 combination of clinical events measured in JUPITER. For more unambiguous major coronary events, including fatal or nonfatal myocardial infarction, 500 persons need to be treated for 1 year to prevent 1 event. These are large numbers, considering

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that the persons being treated were deemed to be healthy at the start of the study. Therefore, the safety and costs associated with treating such patients need to be carefully considered.

Although more formal cost-effectiveness studies are needed, a preliminary estimate of the economic impact of applying JUPITER in clinical practice can be approximated. Treatment with rosuvastatin costs approximately \$3.50 per day, translating into a potential cost of \$638 750 per year for each major coronary event averted. Using a generic statin, which costs approximately \$4 per month, this figure is lower, at \$24 000 per year, but still substantial. These estimates do not include the costs of screening patients and monitoring safety. In JUPITER, approximately 80% of the people who attended the screening visit eventually did not qualify for inclusion; it follows that many people would be screened for CRP and other tests who eventually would not be treated. Assuming a CRP screening test cost of \$25, an additional \$62 500 would have to be spent per year for each major coronary event averted. To these costs one would have to add the costs of initial testing and monitoring for liver function as recommended before and during statin therapy, and the costs of testing for plasma glucose and glycohemoglobin, as glycohemoglobin and diabetes incidence were elevated in JUPITER in the rosuvastatin group. Assuming that all these tests could be done for a total of \$30, this could bring the costs of screening and monitoring to >\$137 000 per year for each event averted.

As an alternative to screening and prescribing medications to eligible patients, potentially safer and less costly strategies could be considered for the primary prevention of cardiovascular diseases. For example, although less than 3% of health care expenditures are currently targeted toward the amelioration of behavioral risk factors such as smoking, poor diet, and physical inactivity, these factors are attributed as the principal etiology of almost 40% of deaths in the United States.⁸ Preventive strategies aimed at these risk factors are supported by good evidence of effectiveness⁹ and yield a high return on investment.¹⁰

Incidentally, a modest absolute risk reduction is not unique to JUPITER but is a characteristic of statin trials in general. In a meta-analysis including 90 056 patients with hypercholesterolemia of whom 47% had preexisting CHD,¹¹ there was a 23% relative risk reduction of nonfatal or fatal myocardial infarction, but only a 2.4% absolute risk reduction over a mean of 5 years, or approximately 0.48% per year (number needed to treat: 208). Thus, on average the absolute risk reduction was higher and the number needed to treat lower in previous statin trials than in JUPITER, which is expected because JUPITER enrolled lower-risk individuals. However, the relative risk reduction was higher in JUPITER (54% versus 23%, for major coronary events). This magnitude of the relative risk reduction in JUPITER raises the possibility that the effect of statin treatment was overestimated in JUPITER.

Issues Related to Early Trial Termination

Trials stopped early for benefit can overestimate treatment effects, especially when the expected number of events is

low.^{12,13} Compounding this issue is the fact that details of the reasons for stopping are often not reported, and effect estimates are rarely adjusted for the number of interim analyses and decreased sample size associated with stopping early.⁸ Despite these issues, this practice has escalated in recent years.¹³ The ethical rationale for stopping a trial early is to offer the beneficial intervention to the control arm and to disseminate the new findings as early as possible. However such motivation is often not justified. The rationale would hold if, once the information was made available, patients had a greater than 50% chance (ie, greater than their randomization probability) of receiving the intervention in clinical practice. However, this seems unlikely given known delays in dissemination and translation of new trial results into practice.¹⁴

Stopping trials early for benefit can also be ethically questionable because of reduced information on other outcomes and long-term risks that would otherwise accrue.¹⁵ Thus, ethical requirements for the risk-benefit ratio may be violated when trials are terminated early. These considerations would seem to apply to JUPITER which was stopped after only 1.9 years of the planned 4 years. In the case of JUPITER, for example, we will never know the long-term consequences of the higher glycohemoglobin levels and incidence of diabetes that were observed in the rosuvastatin group, or the long-term effects of lowering LDL cholesterol to levels below 60 mg/dL, which were never attained in previous randomized trials. Cholesterol is a physiological molecule required for many vital processes. Long-term safety is a concern especially because randomized trials carefully screen out subjects who have comorbidities or are otherwise at risk of experiencing side effects from the tested drug. This is less likely to occur in regular clinical practice. Of note, subjects with a history of diabetes, uncontrolled hypertension, renal dysfunction, cancer within 5 years, and many other comorbidities were excluded from JUPITER.

Potential Role of Industry

Because JUPITER was an industry-sponsored trial, readers should be cognizant of potential marketing interests when evaluating the trial results; interests may not necessarily align with public health goals.¹⁶ The strategy of stopping the trial early and the choice of presenting relative rather than absolute effect estimates are in line with the industry goals of disseminating the results quickly and in the most favorable way, therefore maximizing potential profits, while at the same time minimizing research costs. Promoting the use of drugs for healthy people, an enormous potential market, is a powerful business strategy for pharmaceutical corporations in need of showing sustained profit growth to their share holders and seeking to extend the life of their patents. Medical professionals should be aware of the commercial implications of industry-sponsored trials, which unfortunately represent the majority of contemporary drug trials. A bias related to industry sponsorship has been previously demonstrated in the presentation of trial results.^{17,18} Thus, it is imperative to carefully and critically evaluate the data generated by industry-sponsored trials, because these data remain the

cornerstone of evidence-based medicine and practice guidelines.

Conclusion

We believe that the treatment benefits achieved in the JUPITER trial are not large enough to advocate an expansion in the clinical indications for statins. The potential implications of this trial for a change in clinical practice are further limited by a lack of information on the long-term risks and benefits of statin therapy in predominantly healthy individuals. Unfortunately, it is unlikely that we will be able to gather these data in the future. Because sponsorship of major treatment trials is almost exclusively left to the pharmaceutical industry, it is doubtful that another trial will be carried out, with sufficient sample size and proper follow-up, to study the effects of statin treatment in such healthy individuals. Perhaps the most important lesson to be learned from this trial is that extreme caution should be placed in deciding to terminate early an industry-sponsored trial, such as JUPITER. At the current status of knowledge, behavioral prevention strategies remain the best investment for the prevention of cardiovascular disease and its risk factors in predominantly healthy individuals.

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