EDITORIAL COMMENT

The Cost-Effectiveness of Rosuvastatin Therapy

JUPITER (Justification for the Use of statins in Prevention: An Intervention Trial Evaluating Rosuvastatin)*

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The most appropriate use of statins in primary prevention of coronary artery disease has been difficult to establish. Clinical trials have been conducted in various segments of the population and suggest that statin treatment reduces the relative risk of coronary events over follow-up periods of 2 to 5 years [1,2]. But are the benefits of preventive treatment worth the costs of long-term drug prescription? The answer to this question depends on the balance between the absolute risk reduction attained, the frequency and severity of adverse events due to treatment, the cost of drug treatment, and the potential for downstream cost savings by preventing future coronary events. Cost-effectiveness analysis is a framework that gathers data on all these aspects of the treatment decision and weighs them to assess the value provided for the money spent.

JUPITER (Justification for the Use of statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) was a landmark randomized trial that compared rosuvastatin treatment with placebo among individuals who did not have coronary disease, but were at intermediate risk of developing it [3]. The 54% relative risk reduction in major cardiac events (from 2.8% to 1.6% over 1.9 years of follow-up) reported by JUPITER has elicited a great deal of commentary [4–6], in large part because there are millions of Americans who might become eligible for statin treatment [7]. JUPITER did not include a formal economic analysis, so the actual costs of the treatment strategies and their cost-effectiveness cannot be evaluated on the basis of primary data from that trial. In this issue of the *Journal*,

Choudhry et al. [8] report the results of an economic simulation based on published and unpublished data from the JUPITER trial.

The model of Choudhry et al. [8] projects the clinical outcomes and costs of JUPITER patients (men ≥50 years of age and women ≥60 years of age with low-density lipoprotein cholesterol levels <130 mg/dl, elevated high-sensitivity C-reactive protein [hs-CRP] [≥2.0 mg/l], and baseline characteristics of the JUPITER trial population) under 2 management strategies: 1) treatment with rosuvastatin; or 2) no treatment. They assumed the risk reductions reported by the JUPITER trial would continue for 15 years, then taper off over the subsequent 10 years. They also assumed that the cost of rosuvastatin would drop to $1 per day after 9 years of treatment, when generic versions should become available. On the basis of these and other assumptions, they project the average JUPITER patient will have $7,900 higher lifetime costs and accrue an additional 0.31 quality-adjusted life years (QALYs), yielding an incremental cost-effectiveness ratio of $25,200/QALY. By the standard benchmarks of economic evaluation, this is a reasonable return on the money spent on treatment.

The model of Choudhry et al. [8] does not really address the cost-effectiveness of hs-CRP testing, but instead examines whether to treat with rosuvastatin after hs-CRP testing has already been done. Although the strategies in their model are labeled "test and treat" and "no testing, no treatment," they did not examine the full array of options needed to evaluate an hs-CRP screening program, such as the frequency of testing, the yield in different segments of the population, or alternative methods to treat higher-risk subjects. Effectively, the model simply added the one-time cost of hs-CRP testing ($19 per test, or $37.77 per positive test), which is just 0.4% of the net treatment costs in the model, the bulk of which come from the cost of rosuvastatin treatment. A comprehensive analysis of hs-CRP screening is needed to inform policy decisions.

A key feature of any cost-effectiveness model is the systematic attempt to determine how much the results change when the model assumptions and parameters are varied over a "reasonable range." This key exercise (termed a sensitivity analysis) identifies whether the results change drastically or only slightly under alternative assumptions and thereby provide insight into the critical determinants of economic value. Not surprisingly, results of the model of the cost-effectiveness of rosuvastatin treatment in JUPITER were sensitive to several parameters in the model, particularly the degree of risk reduction from treatment, the potential for adverse events, and the cost of rosuvastatin.

Clearly, the degree of risk reduction from rosuvastatin ought to have a major effect on the cost-effectiveness of treatment: If a treatment did not reduce risk, it would not be worth paying for. The model of Choudhry et al. [8] was based only on the results of JUPITER, however, not the totality of evidence about the effectiveness of statin treat-

ment for primary prevention. Their sensitivity analysis tested only a narrow range of risk reduction, based only on the statistical confidence limits of the JUPITER trial. It has been widely noted that the early stopping of JUPITER may have biased the observed risk reduction toward lower levels (4,9), but the model did not account for this possibility. Even more important than the level of risk reduction is how long the risk reduction can be expected to last. Cost-effectiveness analysis takes a lifetime perspective, and so it matters whether a treatment will continue to work over the long term. The problem is that few if any clinical trials follow patients for more than a couple of years, so there are simply no reliable data on long-term treatment efficacy. Choudhry et al. (8) assumed that rosuvastatin would cut the risk of cardiac events by more than 50% for a full 15 years (and have some effect for up to 25 years), even though the average follow-up in JUPITER was only 1.9 years. When they ran the model under the alternative assumption that the effect of rosuvastatin would last only 5 years, the cost-effectiveness ratio almost tripled, rising to $62,100/QALY from its initial value of $25,200/QALY. The results of this sensitivity analysis show that the cost-effectiveness ratio from JUPITER is highly leveraged on the assumption of sustained, deep risk reductions, an assumption for which we have little data.

Choudhry et al. (8) also showed that the cost-effectiveness of rosuvastatin treatment depends on baseline risk of developing coronary disease. Among JUPITER-eligible individuals with a Framingham Risk Score ≥10%, the cost-effectiveness of treatment was $14,200/QALY, but for those with a Framingham Risk Score <10%, it was more than 4-fold higher ($55,000/QALY). This result is consistent with other models of statins for primary prevention (10,11). Simply put, the cost of drug treatment is the same for all patients, but the absolute benefits are much lower in low-risk individuals, so cost-effectiveness becomes much less favorable as baseline risk is lowered.

The results of this cost-effectiveness analysis were also highly sensitive to model assumptions about adverse effects. The base case assumed that all individuals would feel completely well while taking rosuvastatin, without any annoying side effects or qualms about taking the drug every day for the rest of their lives. If, however, patients taking rosuvastatin had just a 2% decrement in their well-being, the cost-effectiveness ratio soared to more than $62,600 per QALY. This result implies that even small levels of adverse effects from treating healthy individuals will greatly affect the cost-effectiveness of preventive drug treatment. This is because the benefits of treatment are small in absolute terms and occur years in the future and so can be offset by even small negative effects of treatment.

On the cost side, Choudhry et al. (8) made 2 assumptions that reduce the net cost impact of rosuvastatin treatment. First, they assumed the drug price would decrease from $3.63/day to off-patent levels ($1.00/day) after 8 years. My back-of-the-envelope calculation is that the cost-effectiveness ratio would be at least $45,000/QALY if this assumption weren't made. Second, they omitted the added medical costs from living longer as a result of statin treatment, even though it is conventional to include such costs. That is a smaller effect, but including these costs would also have made the cost-effectiveness ratio less favorable.

It is essential to remember that a cost-effective therapy actually costs more money, not less. Prevention rarely saves money, despite the wishes of some that it did. It has been estimated that between 6 million and 12 million patients might begin statin treatment based on JUPITER results (7). Choudhry et al. (8) estimate that such treatment would increase lifetime health care costs by $7,900 per person, even after factoring in generic rosuvastatin prices and later cost saving from preventing heart disease. Putting these figures together implies it would cost between $50 billion and $95 billion to extend rosuvastatin therapy to JUPITER-eligible patients in the U.S. Are we convinced this is the best use of these health care dollars?

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