Targeting Patients for Statin Therapy for the Primary Prevention of Vascular Events: What is the Best Approach?

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The optimal strategy for targeting patients for interventions for the primary prevention of cardiovascular events could be considered a central objective of personalized medicine, and the consideration of cost-effectiveness in the process of identifying the best screening strategy is a cornerstone of efficient and responsible health policy in the current era. Starting with the introduction of lovastatin in the mid 1980s, several large clinical trials have demonstrated the efficacy of statins with respect to the prevention of coronary events in patients with established vascular disease or at moderate to high risk of cardiovascular events, while also demonstrating a favorable safety profile. Indeed, statins are one of the most highly studied and prescribed medications. More recently, attention has turned to the primary prevention setting, with recognition of the fact that nearly half of all coronary events occur in patients without overt hyperlipidemia. Results from key studies, including the Heart Protection Study and meta analyses, suggest that the threshold for initiation of statin therapy should be lowered, and the optimal strategy for identifying patients for whom there is an expected net benefit with statin therapy is now actively debated.

Results from the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial brought this issue to the fore; the highly significant and large magnitude of effect of rosuvastatin on the primary end point of vascular events patients with normal low-density lipoprotein cholesterol but elevated high-sensitivity C-reactive protein (hs-CRP) suggest a potential role for hs-CRP screening in moderate- to low-risk patients who would not otherwise meet criteria for statins according to Adult Treatment Panel III (ATP-III) guidelines. Studies have shown that elevated hs-CRP is associated with an increased risk of future vascular risk, even among patients with low to normal lipid levels, and statin therapy has been shown to lower hs-CRP independent of low-density lipoprotein. Therefore, a strategy of lipid + hs-CRP screening has intuitive appeal. However JUPITER was a trial of statin therapy, and provides only limited, indirect information about the potential for hs-CRP testing to serve as an effective and efficient strategy for the identification of patients for whom statin therapy should be targeted for primary prevention.

Prior reports have suggested that statins may be cost-effective for lower-risk patients than those currently considered appropriate for this therapy according to ATP-III guidelines. These reports describe how cost-effectiveness varies according to patient characteristics, especially age, and according to overall baseline risk over the short term (5 to 10 years) of experiencing a major vascular event. In general, subgroups tend to have more prominence in the evaluation of cost-effectiveness than clinical efficacy, as the absolute impact of an intervention on both effectiveness and cost indices has an influence. The consideration of heterogeneity and subgroup effects in health policy decision making offers the potential to maximize health gains by targeting interventions to patients for whom the expected health gain is greater than the health gains forgone from other programs competing for the same limited pool of resources. Because cost-effectiveness is a function of the absolute (as opposed to relative) difference in effectiveness between two strategies, therapeutic strategies that are associated with a fixed relative effect across patients with different levels of background risk will confer a greater absolute effect, and thus be more cost-effective (holding all else constant), when applied to higher versus lower-risk patients. The impact of increasing age on cost-effectiveness estimates can be complex, owing to the possibility of two opposing effects. While older patients tend to be at higher risk of vascular events in general, and therefore have greater absolute gains with respect to the prevention of events, the actual gain, in terms of life years or quality-adjusted life years, from a treatment that reduces mortality (or nonfatal events that impact mortality) will, holding other things constant, be greater in younger than older patients. This factor has been pointed out in studies that examine strategies involving Framingham risk-based targeting of patients for statin therapy, whereby for patients deemed “high risk” but for whom the only risk factor is advanced age, initiating therapy may not be an efficient use of resources.

In this issue of Circulation, Lee et al present results from a decision analytic model-based evaluation of the relative cost-effectiveness of three different strategies for targeting low- to intermediate-risk patients for statin therapy for the prevention of cardiovascular events. Their analysis was centered around the evaluation of the cost-effectiveness of hs-CRP testing as a tool for targeting patients for statin therapy who do not otherwise meet criteria for statin therapy based on the ATP-III guidelines. The strategy of testing for hs-CRP ≥2.0 mg per liter in these patients was compared to...
the (more conservative) “status quo” of full adherence to ATP-III guidelines, as well as a third (less conservative) “risk based treatment without CRP-testing” strategy, for which all individuals at or above specific predicted risk thresholds estimated by the 10-year Framingham risk score for coronary events would start receiving statins. Their model evaluated the influence of a variety of key factors on the optimal strategy, including a differential versus constant effect of statins on the relative risk (RR) of vascular events, differential compliance with statin therapy according to hs-CRP status, varying effects of major and minor side effects and differential compliance with statin therapy based on side effect profile, and varying cost of therapy (assumed, in the base case, to be that for 80 mg of generic simvastatin at $1.10/d).

Results from the model were particularly sensitive to the assumed RR reduction with statins for the high versus low hs-CRP groups. Under the assumption of equal RR reduction with statins across patients with hs-CRP levels above and below the cutoff point, (RR of 0.77, 0.83, and 0.83 for myocardial infarction, stroke, and cardiovascular death, respectively), while hs-CRP was found to be cost-effective compared to ATP-III guidelines-based management, risk-based treatment with statins, without CRP-testing, was found to be the optimal strategy across most patient subgroups, and for a range of willingness-to-pay thresholds between $50 000 to $100 000/quality-adjusted life year. Alternatively, when the RR reduction with statins was assumed to be favorable (using estimates from JUPITER) only for patients with elevated hs-CRP, the model showed that CRP testing was the most optimal of the three strategies across most patient subgroups and for willingness-to-pay thresholds. Threshold analysis suggested that the magnitude of treatment effect modification assumed in this “differential effects” analysis was approximately what was required for hs-CRP testing to be the optimal therapy. The 54% estimate of the RR reduction with statins for high hs-CRP patients from JUPITER, however, is greater than that obtained from the pooling of other studies12 and may be artificially inflated as a result of the early stopping of the trial.13 Data suggesting that hs-CRP level modifies the treatment effect of statins come from two prior studies14,15 that showed an interaction between hs-CRP level and the risk of coronary events of borderline significance (0.06). No significant interaction between hs-CRP level and treatment with statins was found in the JUPITER trail (P=0.15), however, and Lee et al rightly point out the value of further evaluating this issue through the use of stored serum samples from other statin trials.

Results from the model were also particularly sensitive to the long-term safety of statins, with greater potential harm from therapy rendering more conservative use of statins optimal. Early stopping of the JUPITER trial eliminated the somewhat unique opportunity of gaining important insight into the potential long-term harm from statin therapy in the primary prevention patient population. More precise knowledge of these parameters could contribute considerably to health gains resulting from a more optimal targeting of patients.

This study by Lee et al effectively extends a previous model-based analysis by Hayward et al,7 which compared ATP-III-based management to risk-based management, the results of which suggested that a relatively simple “tailored” strategy involving no low-density lipoprotein measurements, in which all patients with a 5% to 15% Framingham-based coronary artery disease risk over 5 years received a moderate potency statin (simvastatin 40 mg), and those with risk greater than 15% received a high potency statin (atorvastatin 40 mg), was optimal compared to a “treat-to-target” strategy based on AT-III guidelines. These results were demonstrated under assumptions highly favorable to the “treat-to-target” approach, and the authors of that study point out that a shortcoming of the treat-to-target approach is that it places too much weight on a single risk factor at the expense of other risk factors that contribute to the potential treatment benefit.

There has been heated debate regarding the optimality of hs-CRP testing for the identification of patients suitable for primary prevention with statin therapy. With no randomized trial data available to directly address cost-effectiveness, well balanced and properly informed model-based evaluations such as that presented by Lee et al provide valuable insight into the potential cost effectiveness of different treatment strategies, while also highlighting areas in which there remains a critical evidence gap which, if filled, would contribute significantly to improved decision making.

In addition to gaining certainty surrounding the potential statin by hs-CRP interaction, and better understanding of the risks associated with long-term statin use, future studies aimed at identifying the optimal approach to targeting patients for statin therapy for primary prevention should include consideration of other approaches (eg, imaging and genotyping) that have been put forth as alternatives. The use of estimates of lifetime risk in patients with low short- to intermediate-term risk (eg, 10 year risk from Framingham) has also been advocated as a potentially effective way of distinguishing a subset of higher-risk patients (due to greater subclinical atherosclerotic burden) among those deemed low risk by ATP-III guidelines.10,16,17 Advocates of this approach cite the importance of recognizing the time-varying nature of the effects of an “early” reduction of cholesterol on the risk of coronary events downstream—that is, the possibility that benefits increase with more prolonged treatment.18

With the proliferation of approaches being proposed for the targeting of patients for statin therapy as primary prevention and the slim likelihood of clinical trials data becoming available to provide empirical evidence of the relative merits of different approaches in the foreseeable future, identification of the optimal strategy will arguably continue to be one of the more vexing issues in the field of primary prevention. The approaches to primary prevention being considered have the potential to impact a large segment of the US population, and the concomitant health care budget impact could be considerable. Further evaluations using well-informed decision analytic models such that presented by Lee et al will help inform health policy decision making relating to the primary prevention of cardiovascular disease in a manner that is consistent with the societal goal of rational and judicious use of limited healthcare resources.
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References


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