

The efficacy and cost-effectiveness of statins in low-risk patients

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See related research article by Tonelli and colleagues at www.cmaj.ca/lookup/doi/10.1503/cmaj.101280 and synopsis on page 1845, and related research article by Conly and colleagues at www.cmaj.ca/lookup/doi/10.1503/cmaj.101281 and synopsis on page 1846.

In this issue of the *CMAJ*, the results of two studies^{1,2} have important implications for clinical practice, as well as for health care policy-makers.

In their meta-analysis of 29 trials involving 80 711 participants, Tonelli and colleagues report that, among people at low cardiovascular risk, the use of statins significantly reduces cardiovascular morbidity and has important survival benefits compared with a placebo (relative risk 0.90, 95% confidence interval 0.84–0.97).¹ Using these results, Conly and colleagues conducted a cost-effectiveness study and reported that the lifetime use of statins among people at low cardiovascular risk is cost-effective under current international standards (i.e., willingness to pay, which is arbitrarily set at less than US\$50 000 per quality-adjusted life-year gained in the United States and Canada, and less than £30 000 in the United Kingdom).² These messages may potentially affect the decision-making of millions of Canadians and thus require careful consideration.

First, it is important to understand to whom the results of these studies apply. The purpose of the meta-analysis¹ was to evaluate whether statins are effective among patients at low cardiovascular risk (as defined in routine clinical practice). Thus, the authors included only those trials of primary preventions that showed a 10-year risk of less than 20% for nonfatal myocardial infarction or cardiovascular mortality in the placebo arm. However, this approach raises two questions: should the observed 10-year risks of cardiovascular events be used instead of 10-year estimations of cardiovascular risk in routine practice,³ and are the patients included in these trials representative of those who would be classified as having low risk in a routine practice setting? The likely answer to both questions is no for several reasons.

Studies have shown that risk scores, such as the Framingham risk score,³ consistently overestimate rates of events in trials. As such, the

actual risk seen in clinical trials may be substantially lower than the estimated risks based on predictions from baseline risk factors. Therefore, the cardiovascular risk of less than 20% that was seen in the placebo arm may have included trials with a substantial proportion of patients who would have been classified as high risk (> 20%) in routine practice. Indeed, this possibility is evident in the authors' report: the mean baseline characteristics of the included studies were used to estimate the corresponding 10-year cardiovascular risks, and 19 of the 29 included trials had estimated risks of 20% or more.¹

Another way to determine whether the results of the meta-analysis apply only to patients at low risk is to examine the inclusion criteria of the original trials. Most of the 80 711 patients were participants in large trials such as the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack trial, the Anglo-Scandinavian Cardiac Outcomes trial: Lipid Lowering Arm, and the West of Scotland Coronary Prevention study. Based on their inclusion criteria, such studies cannot be classified as solely involving low-risk populations.

These arguments suggest that the risks seen during clinical trials are not equivalent to clinically assigned risks in routine practice, and an observed risk of less than 20% may include trials with high proportions of patients who have an intermediate to high level of cardiovascular risk. For example, among the 36 608 participants in the placebo groups of the trials used to analyze

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KEY POINTS

- Statin therapy is associated with a significant reduction in cardiovascular morbidity and has survival benefits in primary prevention settings, particularly among patients with an intermediate and high baseline cardiovascular risk.
- Further research is needed to determine whether the benefits of statin therapy extend to patients at low cardiovascular risk.
- The use of high-potency statins in primary prevention settings is likely to be more cost-effective than other low-potency options.

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all-cause mortality, there were 1518 deaths during a median follow-up of two years (about 20.7 deaths per 1000 person-years),¹ which is quite high for a “low-risk” population. Thus, it is more likely that the results of the meta-analysis are applicable to patients with a wider range of risks, most of whom are between intermediate and high levels of risk.

Second, given that the use of statins is not completely harmless,^{4,5} it is important to evaluate the validity of the survival benefits they confer. The results of the meta-analysis¹ are similar to those of previous reports⁶⁻⁹ (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.111674/-/DC1). Although these studies found similar point estimates, some of the results were not statistically significant.^{6,8} For example, Ray and colleagues,⁶ found no significant survival benefits, whereas Tonelli and colleagues did.¹ The difference in the interpretation of the results of these two reports is probably due to the inclusion⁶ or exclusion¹ of the Prospective Study of Pravastatin in the Elderly at Risk trial,¹⁰ which included elderly patients with very high mortality. Notwithstanding these differences, the cumulative results of all five reports^{1,6-9} suggest that the use of statins is associated with a significant reduction in cardiovascular morbidity, and that statins have associated survival benefits in primary prevention settings.

Third, it is important to evaluate whether there are significant differences between the efficacies of high- and low-potency statins, since there are substantial differences in their costs. To date, there are no head-to-head comparisons between high- and low-potency statins in terms of cardiovascular outcomes or death. However, in a stratified analysis, Tonelli and colleagues¹ found that the relative risks of death and some cardiovascular outcomes, such as myocardial infarction, compared with placebo, were significantly lower for high-potency statins than for their low-potency counterparts. It is possible that these results are due to chance, as a test for interaction was not statistically significant. In short, the findings of Tonelli and colleagues¹ suggest that high-potency statins may have added cardiovascular and survival benefits (consistent with the evidence on lipid lowering), but doubts remain.

Finally, the results of the cost-effectiveness study by Conly and colleagues² should be re-evaluated in light of the concerns over the applicability of the results of the systematic review solely to people with low cardiovascular risk and the uncertainty as to whether high-potency statins are more efficacious than low-potency statins.

The number needed to treat to prevent one event will decrease as the baseline risk of a popu-

lation increases. As such, the estimates by Conly and colleagues² of the cost per quality-adjusted life-year gained will further reduce if the estimates are reapplied to populations with intermediate to high levels of risk rather than to populations with low risk. In addition, the authors' reasonable estimates of cost may further improve given the recent finding that statins may have prolonged survival benefits (> 10 yr), and that the survival benefits associated with the use of statins may persist even after treatment has ended.¹¹ These conditions would equally apply to high- and low-potency statins, suggesting that the use of either would be cost-effective for primary prevention as per current standards, regardless of differences in cost or efficacy. However, if the reported differences in efficacy between high- and low-potency statins do exist, high-potency statins will be the more cost-effective choice.

In summary, the following inferences can be made using the results of the cost-effectiveness study: (i) statin use (regardless of potency) in primary prevention is cost-effective, particularly among patients with intermediate to high levels of risk; (ii) the cost-effectiveness of generic high-potency statins is likely within current international standards. Indeed, the findings of Conly and colleagues refute concerns raised by a recent meta-analysis⁹ that queried the cost-effectiveness of statins in primary prevention.

In conclusion, the results of these two studies,^{1,2} in conjunction with those of other recent reports,^{1,6,7,12} reaffirm the important role of statins in primary prevention of cardiovascular events. The results of the cost-effectiveness analysis² also clearly show that generic versions of high-potency statins are likely cost-effective as per current international standards. However, it remains unclear as to the level of cardiovascular risk at which the use of statins ceases to be beneficial and/or cost-effective. Indeed, this controversy may persist because so few trials have included only patients with low risk. However, several trials have included patients who could be classified as having low risk. Thus, it is possible that evaluations of patient-level data derived from such trials may answer our remaining questions. Until such evaluations have been done, and given the potential harms associated with statin use (particularly new-onset diabetes and statin-induced myopathy),^{4,5} it is unwise to commence statin therapy for patients who are asymptomatic and have low cardiovascular risk.

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