

# Clinical and public health assessment of benefits and risks of statins in primary prevention of coronary events: Resolved and unresolved issues

Yola Moride PhD FISPE<sup>1,2</sup>, Robert A Hegele MD FRCPC FACP FAHA<sup>3</sup>, Anatoly Langer MD MSc FRCPC FACC<sup>4,5</sup>, Ruth McPherson MD PhD FRCPC<sup>6</sup>, David B Miller MD FRCPC<sup>7</sup>, Stéphane Rinfret MD MSc FRCPC<sup>8</sup>

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Peer-reviewed, evidence-based recommendations for statin use in primary prevention of cardiovascular events are limited. A narrative review of published randomized controlled trials and meta-analyses was conducted to critically appraise the benefits and risks of statins in primary prevention. Statins effectively reduce plasma concentrations of low-density lipoprotein cholesterol, and reduce the risk of cardiovascular events and death. The greatest benefits are observed in high-risk subjects, such as patients with diabetes or hypertension. Serious cardiovascular events should not be included among serious adverse events because they are efficacy outcomes and are dependent on the baseline risk of patients. Rates of specific serious adverse events, such as cancer and rhabdomyolysis, seem to be similar between the statin and control arms of the clinical trials examined. Thus, the benefits of statins in primary prevention outweigh the risks, particularly among high-risk patients. However, the benefit-risk ratio would likely be optimized through interventions designed to increase persistence and adherence in a real-life setting.

**Key Words:** *Clinical trials; Coronary artery disease; Drugs; Health outcomes; Hypercholesterolemia; Prevention*

In Canada, cardiovascular diseases (CVDs) account for 37% of all deaths and remain the principal cause of death (1). Recent recommendations (2) emphasize the importance of prevention to reduce economic burden and improve the health of the population. Considering the modifiable and nonmodifiable risk factors, it has been estimated that 83.8% of the Canadian population in 1992 is at low risk, 6.5% at moderate risk and 9.7% at high risk (3).

Among modifiable coronary artery disease (CAD) risk factors, dyslipidemia is one of the most prevalent. According to the Canadian Heart Health Survey (1985 to 1991) (4), 45% and 43% of men and women, respectively, had a plasma total cholesterol (TC) concentration higher than 5.2 mmol/L. Numerous observational studies have demonstrated a direct relationship between CAD risk and plasma low-density lipoprotein cholesterol (LDL-C) concentration (5,6). The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor class of drugs (statins) reduce plasma TC by more than 20% over the long term (7).

Statins also increase survival and reduce the incidence of adverse cardiovascular events in both secondary and primary CAD prevention (8-12). According to a recent meta-analysis of 14 randomized trials

## L'évaluation clinique et de santé publique des bienfaits et des risques des statines dans la prévention primaire des événements coronariens : Problèmes résolus et non résolus

Les recommandations probantes et révisées par des pairs relativement à l'utilisation des statines dans la prévention primaire des événements cardiovasculaires sont limitées. Les auteurs ont procédé à une analyse narrative des essais aléatoires et contrôlés et des méta-analyses publiés pour parvenir à une évaluation critique des bienfaits et des risques des statines pour la prévention primaire. Les statines réduisent avec efficacité les concentrations plasmatiques de cholestérol à lipoprotéines de basse densité, de même que le risque d'événements cardiovasculaires et de décès. On en constate les principaux bienfaits chez les sujets très vulnérables, tels que les patients diabétiques ou hypertendus. Il ne faut pas inclure les événements cardiovasculaires graves dans les réactions indésirables graves, car il s'agit d'issues d'efficacité qui dépendent du risque des patients en début d'étude. Les taux de réactions indésirables graves précises, comme le cancer et la rhabdomyolyse, semblent être semblables entre les statines et le volet témoin des essais cliniques évalués. Ainsi, les bienfaits des statines sont supérieurs à leurs risques en prévention primaire, notamment chez les patients très vulnérables. Cependant, le ratio bienfait-risque serait sûrement optimisé par des interventions conçues pour accroître la persistance et l'adhésion en situation réelle.

(13), a 12% relative risk (RR) reduction in all-cause mortality is achieved per 1 mmol/L reduction in LDL-C. This corresponds to a 19% RR reduction for CAD mortality, which translates into four fewer deaths per 1000 primary prevention patients (95% CI 1 to 7). The overall incidence of major coronary events is reduced by approximately 25% per 1 mmol/L reduction in LDL-C in primary prevention, which translates into the avoidance of 25 major cardiovascular events, which translates into 18 major coronary events, 12 coronary revascularizations and five strokes per 1000 patients. While the biochemical benefits of statins are evident within the first year of treatment, the clinical benefits increase in subsequent years, when the coronary risk is higher (12). However, safety issues are of particular concern in the setting of primary prevention because these patients have not yet experienced any adverse events or symptoms related to CVDs. Because the baseline risk of CVDs is lower in this population than in secondary prevention patients, larger numbers of individuals must be treated to observe measurable treatment effects, such as prevented CAD events. Proper quantification of adverse events is therefore crucial when assessing the benefit-risk profile of statins in primary prevention. Depending on the definition of 'adverse event', the reporting

<sup>1</sup>Faculty of Pharmacy, Université de Montréal; <sup>2</sup>Centre for Clinical Epidemiology, Sir Mortimer B Davis Jewish General Hospital, Montreal, Quebec;

<sup>3</sup>Schulich School of Medicine and Dentistry, University of Western Ontario, London; <sup>4</sup>Division of Cardiology, University of Toronto; <sup>5</sup>St Michael's Hospital, Canadian Heart Research Centre, Toronto; <sup>6</sup>Lipid Research Laboratory, University of Ottawa Heart Institute, Ottawa, Ontario; <sup>7</sup>Division of Endocrinology, Vancouver Island Health Authority, Vancouver, British Columbia; <sup>8</sup>Centre Hospitalier de l'Université de Montréal Research Centre; Montreal, Quebec

Correspondence: Dr Yola Moride, Faculty of Pharmacy, Université de Montréal, CP 6128, succ. Centre-ville, Montreal, Quebec H3C 3J7.

Telephone 514-343-6111 ext 3011, fax 514-343-5691, e-mail yola.moride@umontreal.ca

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can potentially combine CVD events (hence, efficacy outcomes) with non-CVD events, as well as relatively trivial side effects, such as headaches, fatigue or asthenia. Indeed, post hoc analyses of primary prevention trials that elected to use an inclusive and nonspecific definition of adverse events were interpreted as indicating that statins had little benefit (14). But the validity of combining efficacy and toxicity outcomes into an aggregate measure, while giving equal weight to serious and nonserious adverse events, is questionable; it likely overestimates the rates of clinically significant adverse events (15).

Developing policies or recommendations for intervention in any disorder requires evidence beyond simple demonstration of efficacy from literature reviews (16). It can also require careful weighing of benefits and harms, together with factors such as the role of lifestyle changes (17), acceptability to patients, cost-effectiveness and budgetary impact of the health care strategy. In secondary prevention, statins are clearly cost-effective in most patients because of the high absolute baseline CAD risk (18). Primary prevention, however, is more appropriately approached from a public health and economic perspective, because it involves treating a large proportion of the population who have a heterogeneous absolute baseline CAD risk (19). While some clinicians recommend treating all at-risk patients, not just those with dyslipidemia (20), clinical evaluative scientists have argued for more restricted use of statins, largely due to cost considerations and constraints (3). Indeed, studies that modelled the economical impact of statins in primary prevention showed that the incremental cost-effectiveness ratios are highly dependent on the baseline CVD risk. For instance, the incremental cost-effectiveness of atorvastatin in primary prevention varies between \$3,846 and almost \$20,000 per year of life saved for high-risk and low-risk patients, respectively (21).

The purpose of the present review was to synthesize the evidence for statin use in primary CAD prevention and to provide a framework for carefully weighing the benefits and harms, especially with respect to serious adverse events (SAEs), using an approach that may be helpful to policy makers (22).

## METHODS

A scoping review of the published trials on statins in primary prevention was conducted. To be included in the review, trials must have been conducted in the primary prevention setting only or have included a primary prevention component as a prespecified subgroup of patients. Data on the trial design, population, treatments, end points, lipid profiles, changes in lipid profiles (when available), and safety and efficacy measures were extracted. Benefits were determined from the efficacy data reported in these trials for the various populations studied based on both the primary end point and on total cardiovascular events to better capture the public health perspective. Risk was assessed based on the occurrence of total adverse events and SAEs reported in the trials.

To make trial-specific efficacy information more relevant to decision makers, the number needed to treat (NNT) was used as an estimate of the expected number of patients for whom treatment would help to avoid one adverse outcome. The crude NNT is the reciprocal of the absolute reduction in risk of the event due to the treatment ( $1/[R_1-R_0]$ ) (23,24). The NNTs for each trial were computed for statistically significant RR or hazard ratio (HR) of the effect of statin treatment on a given outcome measure. Because it is clear from the trials that the baseline risk, or hazard, is not constant over time, the duration of follow-up was not standardized (25). The NNT metric is not without its limitations, which include the inability to account for differences in trial variables, such as differences in dose, length of follow-up, comparators (eg, placebo or usual care) and reference event rates. In the case of statin trials, one may also add the failure to account for varying baseline plasma lipoprotein levels as another limitation. Thus, the NNT should be used carefully when comparing different trials.

No quantitative quality assessment was conducted, but study strengths and limitations were determined during the synthesis

process and are discussed herein. Differences across trials in baseline rates and population demographics were also addressed qualitatively. Consistent with a policy or management context, the questions and conclusions have been developed at the outset of the review process, taking into account the views of clinicians and epidemiologists on the review panel (16).

## RESULTS

A total of eight publications on statins in the primary prevention of CVD were found in the literature, corresponding to seven independent clinical trials (9,12,26-31). The proportion of patients treated for primary prevention was more than 85% in these trials, except for the Heart Protection Study (HPS) (28) and the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) (31), which included 49% and 56% of primary prevention patients, respectively. Both of these studies separately reported at least the primary outcome for the primary prevention subpopulation. Information from a separate meta-analysis conducted by the Cholesterol Treatment Trialists' (CTT) Collaborators (13) that analyzed individual data of more than 90,000 patients participating in 14 randomized controlled trials, including the seven trials mentioned above, was used to supplement individual trial information reported here.

### Benefits of treatment

The effects of statins on plasma lipoproteins and CAD rates, including NNTs, are summarized in Table 1. The aggregate of data shows that statins effectively reduce LDL-C and TC in primary prevention with relatively low doses (lovastatin 40 mg or less, pravastatin 40 mg, simvastatin 40 mg or atorvastatin 10 mg). The differential mean change after one year of treatment (ie, mean change from baseline in control arm minus mean change from baseline in statin arm) ranged between  $-1.1$  mmol/L (12) and  $-1.5$  mmol/L (29) for TC, and between  $-1.08$  mmol/L (12) and  $-1.26$  mmol/L (29) for LDL-C.

### Primary end points

The composition of primary end points varied substantially across studies from specific composite end points such as nonfatal myocardial infarction (MI) or death from CAD (West Of Scotland COronary Prevention Study [WOSCOPS] [9]), to general end points, such as all-cause mortality (Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial – Lipid-Lowering Therapy [ALLHAT-LLT] [30]). In addition, the study populations differed widely with respect to baseline plasma lipoprotein profile and cardiovascular risk. Despite these differences, statins showed robust significant benefits in primary end points in five of seven clinical trials, with ALLHAT-LLT (30) and PROSPER (31) trials being the exceptions.

In the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid-Lowering Arm (ASCOT-LLA) (27), atorvastatin 10 mg reduced the risk of nonfatal MI or fatal CAD in patients with hypertension who had three or more CVD risk factors over a median of 3.3 years of treatment. In the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) (12), patients with average LDL-C levels, low high-density lipoprotein cholesterol and no clinical evidence of CVD who were treated with lovastatin 20 mg to 40 mg for an average of 5.2 years experienced significant reductions in rates of major coronary events, defined as fatal or nonfatal MI, unstable angina or sudden cardiac death. In WOSCOPS (9), the primary outcome, namely, nonfatal MI or death from CAD, was significantly reduced among middle-aged men with hypercholesterolemia who were treated with pravastatin 40 mg for a mean of 4.9 years; this reduction was mainly due to reduced rates of nonfatal MI.

Three studies enrolled substantial numbers of patients with diabetes, namely, ASCOT-LLA – diabetes (27), HPS (28) and Collaborative Atorvastatin Diabetes Study (CARDS) (29). Given the higher baseline absolute risk of CVD events in this subgroup compared with the overall primary prevention sample, benefits were

**TABLE 1**  
**Review of the trials on the efficacy of statins in primary prevention of cardiovascular disease**

Trial (reference)	Design	Population (% primary prevention*)	Treatment	End points	Baseline lipid profile (mmol/L)	Differential mean change† in lipid profile (mmol/L)	Reference event rate in control arm (%)	NNT
ASCOT-LLA (26)	RCT 2×2 factorial Median follow-up: 3.3 yrs	n=10,304 (86%); 19% women With HT, ≥3 CVD risk factors, and TC ≤6.5 mmol/L Age: 40–79 yrs	Atorvastatin 10 mg/day Placebo	<i>Primary:</i> Nonfatal MI or fatal CAD <i>Secondary:</i> Total CV events and procedures Total coronary events All-cause mortality CV mortality Stroke	TC: 5.5 LDL: 3.4 HDL: 1.3 TG: 1.7	At 1 year: TC: Δ -1.3 LDL: Δ -1.2 HDL: Δ +0.02 TG: Δ -0.29	<i>Primary:</i> Nonfatal MI or fatal CAD: 3.0 <i>Secondary:</i> Total CV events and procedures: 9.5 Total coronary events: 4.8 All-cause mortality: 4.1 CV mortality: 1.6 Stroke: 2.4	<i>Primary:</i> Nonfatal MI or fatal CAD: 91 <i>Secondary:</i> Total CV events and procedures: 50 Total coronary events: 71 All-cause mortality: NS CV mortality: NS Stroke: 143
ASCOT-LLA (27)	RCT 2×2 factorial Median follow-up: 3.3 yrs	n=2532; 24% women With type 2 diabetes and as above	Atorvastatin 10 mg/day Placebo	<i>Primary:</i> Total CV events and procedures <i>Secondary:</i> Nonfatal MI + fatal CAD Fatal + nonfatal stroke	TC: 5.3 LDL: 3.3 HDL: 1.2 TG: 1.9	At 1 year: TC: Δ -1.3 LDL: Δ -1.2 HDL: Δ 0 TG: Δ -0.3 At end of follow-up: TC: Δ -0.9 LDL: Δ -0.9 HDL: Δ 0 TG: Δ -0.2	<i>Primary:</i> Total CV events and procedures: 11.9 <i>Secondary:</i> Nonfatal MI + fatal CAD: 3.6 Fatal + nonfatal stroke: 3.2	<i>Primary:</i> Total CV events and procedures: 37 <i>Secondary:</i> Nonfatal MI + fatal CAD: NS Fatal + nonfatal stroke: NS
MRC/BHF HPS (28)	RCT Mean follow-up: 4.8 yrs	n=5963 (49%); 30% women With type 1 or 2 diabetes, fasting TC ≥3.5 mmol/L Age: 40–80 yrs	Simvastatin 40 mg/day Placebo	<i>Primary:</i> First major vascular event (nonfatal MI, coronary death, stroke or TRV) First major coronary event (nonfatal MI or coronary death) <i>Secondary:</i> Nonfatal MI Coronary death Stroke TRV	TC: 5.7 LDL: 3.2 HDL: 1.1 TG: 2.3	Average during follow-up: TC: Δ -1.1 LDL: Δ -0.9 HDL: Δ +0.01 TG: Δ -0.3	<i>Primary:</i> First major vascular event: 13.5%† First major coronary event: 12.6% <i>Secondary:</i> Nonfatal MI: 5.5% Coronary death: 8.0% Stroke: 6.5% TRV: 10.4%	<i>Primary:</i> First major vascular event: 24† First major coronary event: 31 <i>Secondary:</i> Nonfatal MI: 50 Coronary death: 67 Stroke: 67 TRV: 59
CARDS (29)	RCT 4 yrs follow-up (median 3.9 yrs)	n=2838 (96%); 32% women With type 2 diabetes, LDL ≤4.14 mmol/L, and TG ≤6.78 mmol/L Age: 40–75 yrs	Atorvastatin 10 mg/day Placebo	<i>Primary:</i> Acute CAD event, CRV or stroke (combined and specific) <i>Secondary:</i> All-cause mortality event Any acute CVD	TC: 5.4 LDL: 3.0 HDL: 1.4 TG: 1.4	At 1 year: TC: Δ -1.5 LDL: Δ -1.3 HDL: Δ +0.03 TG: Δ -0.4 At 4 years: TC: Δ -1.2 LDL: Δ -1.0 HDL: Δ +0.06 TG: Δ -0.3	<i>Primary:</i> Acute CAD: 5.5 CRV: 2.4 Stroke: 2.8 Combined: 9.0 <i>Secondary:</i> All-cause mortality: 5.8 Any acute CVD event: 13.4	<i>Primary:</i> Acute CAD: 53 CRV: NS Stroke: 77 Combined: 31 <i>Secondary:</i> All-cause mortality: NS Any acute CVD event: 25
ALLHAT-LLT (30)	Nonblinded RCT Mean follow-up: 4.8 yrs; maximum: 8 yrs	n=10,355 (86%); 49% women With stage 1 or 2 HT plus 1 additional CAD risk factor; fasting LDL: 3.2–5.0 mmol/L without CAD or 2.6–3.4 mmol/L with CAD Age: ≥55 yrs	Pravastatin 40 mg/day Usual care	<i>Primary:</i> All-cause mortality <i>Secondary:</i> Nonfatal MI or fatal CAD CVD mortality Non-CVD mortality Cancer	TC: 5.3 LDL: 3.8 HDL: 1.2 TG: 1.7	At 6 yrs: TC: Δ -0.48 LDL: Δ -0.45 HDL: Δ +0.09 TG: Δ 0	<i>Primary:</i> All-cause mortality: 15.3 <i>Secondary:</i> Nonfatal MI or fatal CAD: 10.4 CVD deaths: 7.1 Non-CVD mortality: 7.8 Cancer: 9.3	<i>Primary:</i> All-cause mortality: NS <i>Secondary:</i> Nonfatal MI or fatal CAD: NS CVD deaths: NS Non-CVD mortality: NS Cancer: NS

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**TABLE 1 – CONTINUED**  
**Review of the trials on the efficacy of statins in primary prevention of cardiovascular disease**

Trial (reference)	Design	Population (% primary prevention*)	Treatment	End points	Baseline lipid profile (mmol/L)	Differential mean change† in lipid profile (mmol/L)	Reference event rate in control arm (%)	NNT
PROSPER (31)	RCT Mean follow-up: 3.2 yrs	n=5804 (56%); 52% women With raised CV risk (smoking, HT or diabetes), TC 4.0–9.0 mmol/L and TG <6.0 mmol/L Age: 70–82 yrs	Pravastatin 40 mg/day Placebo	<i>Primary:</i> CAD death, non-fatal MI, fatal or nonfatal stroke <i>Secondary:</i> CAD death or nonfatal MI Fatal or nonfatal stroke TIA	TC: 5.7 LDL: 3.8 HDL: 1.3 TG: 1.5	Mean difference between pravastatin and placebo arms at 3 months TC: NR LDL: Δ -32% HDL: Δ +5% TG: Δ -12%	<i>Primary:</i> CAD death, nonfatal MI, and fatal or nonfatal stroke: 12.1‡ <i>Secondary:</i> CAD death or nonfatal MI: 8.8‡ Fatal and nonfatal stroke: 3.7‡ TIA: 2.3‡	<i>Primary:</i> CAD death, nonfatal MI, and fatal or nonfatal stroke: NS‡ <i>Secondary:</i> CAD death or nonfatal MI: NS‡ Fatal and nonfatal stroke: NS‡ TIA: NS‡
AFCAPS/ TexCAPS (12)	RCT Mean follow-up: 5.2 yrs	n=6605 (97%); 15% post-menopausal women Exclusion criteria: uncontrolled HT, secondary hyperlipidemia, diabetes, obesity Age: 45–73 yrs (men), 55–73 yrs (women)	Lovastatin 20–40 mg/day Placebo	<i>Primary:</i> Fatal or nonfatal MI, unstable angina, or sudden cardiac death <i>Secondary:</i> Fatal or nonfatal CRV Unstable angina Fatal or nonfatal CVD events Fatal or nonfatal coronary events CVD mortality CAD mortality	TC: 5.7 LDL: 3.9 HDL: 0.94 (men) 1.03 (women) TG: 1.8	At 1 year: TC: Δ -1.15 LDL: Δ -1.08 HDL: Δ +0.05 TG: Δ -0.23	<i>Primary:</i> Fatal or nonfatal MI, unstable angina, or sudden cardiac death: 10.9 <i>Secondary:</i> Fatal or nonfatal CRV: 9.3 Unstable angina: 5.1 Fatal or nonfatal MI: 5.6 Fatal and nonfatal CVD events: 15.3 Fatal and nonfatal coronary events: 12.8	<i>Primary:</i> Fatal or nonfatal MI, unstable angina or sudden cardiac death: 49 <i>Secondary:</i> Fatal or nonfatal CRV: 65 Unstable angina: 122 Fatal or nonfatal MI: 87 Fatal or nonfatal CVD events: 54 Fatal or nonfatal coronary events: 63
WOSCOPS (9)	RCT Mean follow-up: 4.9 yrs	n=6595 (92%); all men With fasting LDL 4.5–6.0 mmol/L Age: 45–64 yrs	Pravastatin 40 mg/day Placebo	<i>Primary:</i> Nonfatal MI or death from CAD <i>Secondary:</i> Nonfatal MI Death from CAD Death from CVD All-cause mortality	TC: 7.0 LDL: 5.1 HDL: 1.2 TG: 1.9	No data to calculate change in lipid levels	<i>Primary:</i> Nonfatal MI or death from CAD: 7.9 <i>Secondary:</i> Nonfatal MI: 6.5 Death from CAD: 1.7 Death from CVD: 2.3 All-cause mortality: 4.1	<i>Primary:</i> Nonfatal MI or death from CAD: 41 <i>Secondary:</i> Nonfatal MI: 50 Death from CAD: NS Death from CVD: 135 All-cause mortality: NS

\*If not clearly stated in the original publication, the percentage of participants in primary prevention was taken from the Cholesterol Treatment Trialists' Collaborators meta-analysis (13); †Mean change from baseline in control group minus mean change from baseline in statin group; ‡For primary prevention subgroup only, AFCAPS/TexCAPS Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial – Lipid-Lowering Therapy; ASCOT-LLA Anglo-Scandinavian Cardiac Outcomes Trial – Lipid-Lowering Arm; CARDS Collaborative Atorvastatin Diabetes Study; MRC/BHF HPS Medical Research Council/British Heart Foundation Heart Protection Study; PROSPER PROspective Study of Pravastatin in the Elderly at Risk; WOSCOPS West Of Scotland Coronary Prevention Study; CAD Coronary artery disease; CRV Coronary revascularization; CVD Cardiovascular disease; HDL High-density lipoprotein cholesterol; HT Hypertension; LDL Low-density lipoprotein cholesterol; MI Myocardial infarction; NNT Number needed to treat; NR Not reported; NS Not significant; RCT Randomized controlled trial; TC Total cholesterol; TG Total triglycerides; TIA Transient ischemic attack; TRV Total revascularization procedures (coronary and noncoronary); yrs Years

observed in all trials regardless of agent (atorvastatin or simvastatin), dosage and primary outcome definitions.

#### Total cardiovascular disease events

In the atorvastatin arm of ASCOT-LLA (27) and in AFCAPS/TexCAPS (lovastatin) (12), the secondary outcome (total cardiovascular events and procedures) was significantly reduced in all patients and in those with diabetes, respectively. In CARDS (29), the rate of any acute CVD event was significantly lower in patients with diabetes randomly assigned to atorvastatin 10 mg than to placebo.

CVD mortality was investigated as a secondary end point in four studies. In WOSCOPS (9), a significant RR reduction in cardiovascular death was observed in the pravastatin arm after a mean follow-up of 4.9 years. In HPS (28), the NNT to prevent one CAD death among patients with diabetes was 67. However, in ASCOT-LLA (27), the absolute reference event rate of CVD mortality was lower than that observed in the other trials, and no significant protection related to atorvastatin treatment was found. In AFCAPS/TexCAPS (12), the absolute rate of fatal CVD events appeared lower in the lovastatin arm than in the placebo arm (1.0% versus 1.4%), but there were too few

events to perform survival analysis based on the prespecified criteria (12). Both ASCOT-LLA (26) and AFCAPS/TexCAPS (12) were terminated prematurely because of highly significant risk reductions in the primary outcome among patients randomly assigned to statins.

### Neutral trials

In PROSPER (31), pravastatin was found to have no statistically significant effects, despite a substantial reduction (32%) in LDL-C in the primary prevention subpopulation, which comprised 56% of the total elderly study sample, as indicated by nonsignificant HR for the primary end point of CAD death, nonfatal MI, and fatal or nonfatal stroke. However, the primary and secondary end points, CAD death or nonfatal MI, were significantly reduced in the entire study population, which included both primary and secondary prevention patients.

In patients with hypertension and moderate hypercholesterolemia in ALLHAT-LLT (30), the primary outcome, all-cause mortality, and the key secondary outcome, combined nonfatal MI and fatal CAD, were not significantly affected by pravastatin treatment. This may have been due to several factors (32). For instance, by the sixth year of follow-up, almost one-third of participants randomly assigned to usual care were taking lipid-lowering drugs (mostly statins), while only 70.3% of patients in the pravastatin group were still taking the study drug. The low adherence and substantial cross-over was reflected in small differences in LDL-C and TC reduction between the active treatment and control arms, which were only approximately one-half of those achieved in other trials (Table 1). The power of this study was also limited for the end point of mortality, in part due to enrolment of only approximately 50% of the originally planned 20,000 participants.

### CTT meta-analysis

Beneficial effects of statin treatment have been observed for primary end points in most trials. However, because primary end points can be composed of varying individual end points (eg, nonfatal MI or fatal CAD), it is difficult to synthesize benefits into a single figure without access to individual patient data from each study. In addition, some trials lack statistical power with respect to certain secondary end points (eg, CVD mortality) because the trials were not sufficiently powered to investigate these end points or were prematurely terminated. These problems were, in part, resolved through the recent meta-analysis conducted by the CTT Collaborators (13).

The CTT meta-analysis found that, averaged over five years of treatment, statins reduced the incidence of major vascular events – defined as the combined outcome of major coronary event, coronary revascularization, and fatal or nonfatal stroke – by approximately one-fifth per 1 mmol/L reduction in LDL-C in all prespecified subgroups, including primary prevention study participants with no history of CAD or MI (13). The RR of major CVD events in this subgroup was 0.72 (95% CI 0.66 to 0.80). This translates into 18 major CAD events, 12 coronary revascularization procedures and five strokes avoided per 1000 individuals treated with statins for primary prevention. In addition, pooling all patient data showed that statin treatment significantly reduced all-cause mortality by 12% per 1 mmol/L LDL-C reduction (RR 0.88; 95% CI 0.84 to 0.91), which was mainly attributable to a 19% reduction in CAD mortality (RR 0.81; 95% CI 0.76 to 0.85). The benefits of statins did not appear to be influenced by baseline cholesterol levels (13). The reduction in major coronary events per 1 mmol/L LDL-C reduction appeared to be smaller for female than male patients, but was still statistically significant.

Due to large differences across trials in patient populations, baseline event rates, dosage and the relative lack of head-to-head trials, it is not possible to directly compare individual statins.

### Potential harms

Non-CVD mortality, cancer and rhabdomyolysis are the SAEs of concern when assessing the potential harmful effects of statin therapy for primary prevention. Although it is well established that statins reduce

CVD mortality, their impact on non-CVD mortality is less clear. Because of the large number of patients exposed, any proposed intervention for primary prevention must be assessed with respect to its potential effect on the incidence of non-CVD important adverse events, such as cancer. Moreover, rhabdomyolysis is a rare but serious condition that has been specifically linked to statin therapy.

### Total SAEs

Most trials compared overall absolute adverse event rates between treatment and control arms; such reporting does not allow differentiation between the occurrence of SAEs and nonserious side effects. PROSPER, AFCAPS/TexCAPS and CARDS reported SAE rates separately and found similar rates between statin and control arms; however, their figures included CVD events, which confounds the true incidence and clinical significance of non-CVD SAEs in each group. True safety outcomes most often involve idiosyncratic reactions that have unknown etiologies as opposed to CVD events. Also, a single patient who experienced both a non-CVD and a CVD SAE – which is, in fact, an efficacy end point – would only be counted as having experienced a SAE. Consequently, to properly assess SAEs in primary prevention, it is necessary to specify non-CVD SAE rates.

ASCOT-LLA (26) reported SAEs separately from CVD end points and found no statistical difference between treatment and control arms after a median follow-up of 3.3 years. Although the actual SAE incidence was not published, an economic analysis of ASCOT-LLA, which was based on patient level data, reported that the mean number of non-end point-related hospitalization days was 2.7 per patient for atorvastatin versus 3.2 for placebo. These results suggest that treatment with a statin does not pose a higher risk of experiencing SAEs (23). In addition, CARDS reported SAEs that were possibly related to the study drug, with 1.1% of patients in the atorvastatin and the placebo arms experiencing such events (29). Because individual trials might have been insufficiently powered to detect small differences in SAE rates, a meta-analysis pooling the results from all trials would be very useful. Unfortunately, the CTT Collaborators did not undertake such an analysis for nonfatal and non-end point SAEs. Given the low overall absolute risk of these SAEs, very large sample sizes would be required to detect a clinically and statistically significant difference between statin and control groups. Consequently, a small difference in absolute risk may not be clinically relevant in the context of the overall benefit of statin treatment, provided that the seriousness of the event is taken into account in the qualitative assessment of overall benefits and risks.

### Non-CVD mortality

Non-CVD death is the most relevant outcome from a safety point of view. The comparison of point estimates for non-CVD death rates across studies does not yield a consistent pattern (Table 2); also, the recent CTT meta-analysis (13) reported no significant effect of statins on nonvascular mortality (RR=0.95; 95% CI 0.90 to 1.01).

In ASCOT-LLA (26), atorvastatin did not significantly affect all-cause mortality. Similarly, pravastatin did not affect all-cause mortality in either ALLHAT-LLT (30) or WOSCOPS (9). Among diabetic patients, only CARDS examined all-cause mortality as an outcome, and found no statistically significant difference in the treated group; however, CARDS (29) was stopped early, resulting in shorter follow-up time. In AFCAPS/TexCAPS (12), there was no significant difference between the lovastatin and placebo arms with respect to overall absolute mortality rates (4.6 and 4.2 per 1000 patient-years, respectively). However, while the above trials lacked the statistical power to detect differences in overall mortality, the CTT meta-analysis showed that the effect of statins on noncardiac mortality is highly unlikely.

### Cancer

Among the major trials reviewed, only PROSPER (31) showed a signal (a potential safety concern) for increased cancer rates among patients on statin therapy. While HR point estimates indicated a

**TABLE 2**  
**Absolute mortality rate differences (as percentage of patients) between statin and control arms (by cause) and cancer rates across primary prevention studies**

Study (reference)	CVD death	Non-CVD death	All-cause death	Cancer cases (deaths, where reported)
ASCOT-LLA – general (26)	-0.2	-0.3	-0.5	-0.1 (deaths)
MRC/HBF HPS – diabetes (28)	NR	NR	NR	NR
CARDS (29)	-0.9	-0.7	-1.5	-0.7 (deaths)
ALLHAT-LLT (30)	-0.2	-0.1	-0.4	+0.3
PROSPER (31)	-0.7	+0.5	-0.2	+1.6*
AFCAPS/TexCAPS (12)	-0.2	+0.3	+0.1	-0.2
WOSCOPS (9)	-0.7	-0.2	-0.9	+0.3

– indicates less with statin; + indicates more with statin; AFCAPS/TexCAPS Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial – Lipid-Lowering Therapy; ASCOT-LLA Anglo-Scandinavian Cardiac Outcomes Trial – Lipid-Lowering Arm; CARDS Collaborative Atorvastatin Diabetes Study; CVD Cardiovascular disease; MRC/HBF HPS Medical Research Council/British Heart Foundation Heart Protection Study; NR Not reported; PROSPER PROspective Study of Pravastatin in the Elderly at Risk; WOSCOPS West Of Scotland Coronary Prevention Study. \* $P < 0.05$

possible increase in the risk of breast, gastrointestinal, respiratory and other cancers, only total cancer risk reached statistical significance (HR=1.25; 95% CI 1.04 to 1.51) (32). While the ratio is low, if it is true, it can translate into a large absolute number of cancers at the population level. However, a meta-analysis (31) of the cancer risk in eight large statin trials including approximately 60,000 patients found no increased risk, suggesting that PROSPER might have been an outlier and the finding due to chance. In contrast to the other trials included in the meta-analysis, PROSPER was conducted exclusively in elderly subjects (mean age 74 years, range 70 to 82), who perhaps had a greater baseline cancer risk than patients in other trials, suggesting a possible interaction between age and statin use for this adverse outcome.

Furthermore, the CTT meta-analysis (13) also did not find an association between LDL-C lowering by 1 mmol/L with statin treatment and the overall (RR=1.00 95% CI 0.95 to 1.06) or site-specific risk of cancer. In addition, there was no trend to increased cancer risk with increasing duration of statin therapy. Another recent meta-analysis (34), which focused exclusively on the risk of cancer in an overall patient population of 86,000, found no link between the incidence of cancer and statin use.

### Rhabdomyolysis

Only four cases of rhabdomyolysis were reported in the seven clinical trials that were included in this review: one patient among 5158 hypertensive patients receiving atorvastatin in the ASCOT-LLA (26), one patient among 3304 patients randomly assigned to lovastatin in AFCAPS/TexCAPS and two patients in the placebo arm of AFCAPS/TexCAPS (12). In CARDS, one case of myopathy was reported in each of the atorvastatin and the placebo arms (29). In the CTT meta-analysis (13), the absolute risk of rhabdomyolysis ascertained in slightly less than 40,000 patients treated with statins was very low (0.023%), and the five-year excess risk compared with placebo was small and not significant (absolute excess risk 0.01%).

### Benefit-risk assessment

Because of heterogeneity in efficacy end points and adverse events, risks and benefits from all trials cannot easily be pooled into aggregate measures. In addition, because harm includes different types of adverse events, these should be more appropriately weighed according to patient preference (utility) or according to their consequence (ie, morbidity, hospitalization, use of health services, and scheduled and unscheduled medical visits).

In the CTT meta-analysis (13), benefits were expressed as the reduction in mortality per 1 mmol/L reduction in LDL-C. However, the benefit-risk profile of statins in a real-life setting may differ from that derived from clinical trials because of differences in drug adherence and discontinuation, as well as follow-up care, especially in primary prevention for asymptomatic conditions such as hypercholesterolemia. Although intent-to-treat analysis and discontinuation rates have sometimes been considered in clinical trials, these may not reflect patterns of use in a real-life setting. For instance, AFCAPS/TexCAPS (12) reported no significant difference between treatment arms in the absolute rate of adverse events leading to discontinuation (13.6% versus 13.8%), and WOSCOPS (9) reported similar withdrawal rates at five years (30.8% versus 29.6%) for pravastatin and placebo, respectively. Two studies on the rate of statin discontinuation in Quebec (35,36) used administrative prescription databases. Among new users of statins in either primary or secondary prevention, persistence after 24 months of treatment was 83%, but the proportion of patients with greater than 80% adherence was only 60% (35). More specifically, in primary prevention among patients 50 to 64 years of age, persistence was 65% after six months of treatment and only 35% after three years (36). Because the greatest benefits can be expected with long-term treatment, population-based interventions aimed at improving adherence should be envisaged to maximize the benefit-risk ratio of statins in primary prevention.

Delaying CAD onset and preventing associated mortality results in major societal benefits, given that people will spend a longer time in the workforce. A recent study by Unal et al (37) conducted in England and Wales showed that primary prevention by modifying major risk factors effectively reduced CAD mortality. Furthermore, the absolute number of avoided deaths was four times greater in primary prevention than in secondary prevention. The greatest impact was achieved through population-wide tobacco control and diet modification. When prevention by statins was analyzed separately, in a total population of 35.5 million, 2135 fewer deaths attributable to statins were observed. However, in contrast to nonstatin interventions, most of the avoided deaths were in secondary prevention; specifically, 1990 deaths in CAD patients compared with 145 in people without CAD. Until the recent National Institute of Health and Clinical Excellence was published (38), statins were only recommended for secondary prevention in the United Kingdom.

## DISCUSSION

Clearly, for all medical interventions, benefits should outweigh risks. Clinically, statins reduce LDL-C and reduce the rate of CVD events both in primary and secondary prevention. In primary prevention, the most favourable NNTs are achieved in populations in which baseline risk is relatively large, such as patients with diabetes and hypertension. However, all CVD risk factors should be considered jointly because they have a synergetic effect on the patient's absolute risk (20). Given that the benefits of statins appear to be independent of baseline cholesterol levels and extend to patients who are not considered to be dyslipidemic, statins have been recommended in all at-risk patients, based on the global CVD risk profile (13).

Our review shows that the benefits of statins translate into a reduction in CVD mortality even in primary prevention. In the studies that reported overall SAEs, namely PROSPER, AFCAPS/TexCAPS, CARDS and ASCOT-LLA (non-end point-related), there was no increase in SAEs associated with the use of statins. With respect to specific SAEs, there is no evidence of an increase in the incidence of rhabdomyolysis or cancer. An exception was PROSPER, which enrolled elderly subjects and showed a higher rate of cancer in the group treated with statins than with placebo. However, the CTT meta-analysis, which included the PROSPER trial, found no difference in cancer risk. It should be recognized that clinical trials are not optimal for detecting very rare but serious and harmful SAEs such as rhabdomyolysis and cancer. Even meta-analyses may not detect very rare SAEs if they are very infrequent and have a long delay of onset.

This is because the patient selection process will likely exclude patients who are at higher risk of known SAEs. In addition, participants in clinical trials are much more closely monitored than in clinical practice, and this can result in early discontinuation of treatment when early warning symptoms of SAEs appear. In contrast, in a real-life setting, individuals who are at higher risk for such SAEs can continue to receive treatment past the point of mild warning symptoms, because monitoring of adverse effects is usually less intensive than in clinical trials. Absence of adequate evidence to show excess risk of such adverse effects in clinical trials does not mean no excess risk if the SAEs are rare.

A general limitation of a more precise assessment of risks and benefits is the lack of individual patient data. Some individual patients could have contributed to more than one study outcome, making it difficult to precisely appraise statin benefits from the trials reported here. We recommend that this issue be addressed using original trial data, similar to the approach used by the CTT (13). While some have argued that in primary prevention, statins reduce the risk of CVD mortality but not overall mortality, perhaps due to a higher incidence of death due to non-CVD mortality (14), our review suggests that this conclusion is not warranted. Only ALLHAT-LLT considered all-cause mortality as a primary outcome, and the treatment effect was non-significant. However, there were several study limitations, such as low adherence and a high crossover rate between treatment arms, which contributed to a relatively low LDL-C and TC difference. Other trials investigated overall mortality either as an outcome included in a composite measure of primary outcome or as a specific secondary outcome, but all had insufficient statistical power to show a difference within the context of the experimental design. However, there is no evidence that statins increase the risk of non-CVD death, based on estimates from individual trials and the CTT meta-analysis of data collected over hundreds of thousands of patient-years. Even with an overall sample size of approximately 45,000 patients per treatment arm in the CTT meta-analysis, the study only had a 34% statistical power to detect a risk difference of 5% in overall mortality. To investigate specifically whether statins increase the risk of nonvascular mortality,

as previously hypothesized, would require access to primary data such as those used by the CTT.

Finally, pooling all adverse events, without weighting by utility or clinical consequence, gives little clinically relevant information about the potential harm of any intervention. The appropriateness of pooling CVD and non-CVD adverse events is methodologically questionable (15). In addition, most trials included some mixture of primary and secondary prevention patients. Access to the original trial data would help to stratify adverse events according to primary and secondary prevention, and to appraise the long-term consequences of adverse events, which must be supported by properly designed research on patient utility or preference. Furthermore, all SAEs within the clinical trial setting are reported to regulatory authorities. Based on the large number of patients exposed to statins in clinical trials over the last 20 years, no patterns in noncardiovascular SAEs have been observed by regulatory authorities. However, it should be recognized that clinical trial patients exclude those who are at higher risk for SAEs. In a real-life setting, patients who are at higher risk for such SAEs can still be treated, and generally, monitoring of adverse effects may not be as intensive as in clinical trials.

## CONCLUSION

Based on the present review of the evidence, we recommend that statins are appropriate in the primary prevention of CVD events, especially among patients whose risk profiles reflect those of patients in clinical trials, particularly high-risk patients with diabetes, hypertension and multiple risk factors. Due to the limited number of head-to-head studies published thus far, there is insufficient evidence to draw conclusions about the superiority of specific statins in primary prevention. The fact that the cardioprotective effect increases with the magnitude of the reduction in LDL-C should also be taken into account in the selection of a statin.

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