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SCIENTIFIC EDITORIAL

Statins in the elderly: What evidence of their benefit in prevention?

Les statines chez les personnes âgées : quelle preuve de leur bénéfice dans le cadre de la prévention ?

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Statins are very potent at lowering low-density lipoprotein (LDL) cholesterol. In patients with established coronary artery disease, this reduction has been associated with consistent clinical benefit across the many large randomized trials conducted. In selected patients without established disease but at high risk, particularly those with elevated plasma concentrations of cholesterol, prolonged statin therapy has also been associated with impressive clinical benefits. However, most of the studies conducted in these populations have enrolled middle-aged patients, with few patients aged above 75 years. Therefore, it is valid to question whether the benefits achieved with statins in trials that enrolled mostly relatively young patients can be extended to truly elderly patients.

Cholesterol is a strong risk factor for cardiovascular death and cardiovascular disease; however, the relationship between cholesterol in the blood and cardiovascular mortality is much stronger in younger than in older patients [1]. A joint analysis of the primary prevention studies, entitled the Prospective Studies Collaboration, demonstrated that the association between total cholesterol and the risk of ischaemic heart disease mortality is age specific (Fig. 1). As expected, therefore, the impact of reducing cholesterol on the risk of cardiovascular death is also age specific: with every 1-mmol/L reduction in total

Abbreviations: JUPITER, Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL, low-density lipoprotein; NNT, number needed to treat; PROSPER, PROspective Study of Pravastatin in the Elderly at Risk; 4S, Scandinavian Simvastatin Survival Study.

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cholesterol among patients aged 40–49 years, ischaemic heart disease mortality is more than halved. In contrast, the same reduction in those aged 80 years and older yields a reduction of only 15%. Because of this lower benefit of statins in the elderly, questions have been asked about whether the clinical benefits observed with statins in young and middle-aged patients enrolled in randomized clinical trials really extend to the elderly patients encountered in routine clinical practice [2].

There is no question that statins are highly beneficial in preventing cardiovascular events and reducing cardiovascular mortality in secondary prevention in patients with established cardiovascular disease, particularly coronary artery disease. This benefit has been established consistently by a host of randomized clinical trials, starting with the Scandinavian Simvastatin Survival Study (4S) in the early 1990s and followed subsequently by similar trials performed in primary prevention in patients without established cardiovascular disease but with elevated cholesterol [3–8]. More recently, the benefit of a marked reduction in cholesterol, even in patients with 'normal' cholesterol concentrations, was also seen in patients with high cardiovascular risk but no established disease in Justification for the Use of statins in Prevention: an Intervention Trial Evalu-

ating Rosuvastatin (JUPITER) [9]. Again, the question arises of how this benefit observed in secondary prevention and in selected individuals in primary prevention is translated into the elderly patient population seen in routine clinical practice. In secondary prevention, a pooled analysis of patients enrolled in randomized clinical trials with statins and aged above 65 years, published by Afilalo et al. [10], reported a 22% reduction in 5-year mortality with statin use. However, among these studies, only one (PROspective Study of Pravastatin in the Elderly at Risk [PROSPER]) was designed specifically to examine the role of a statin (pravastatin) in the elderly, and that trial did fulfil its primary goal, which was to demonstrate a reduction in the composite endpoint of cardiovascular death, myocardial infarction and stroke in elderly patients [11]. It is interesting, however, to note that pravastatin had no direct effect on stroke in that trial. In addition, when the population from PROSPER was broken down as a function of prior risk, there was a very substantial group of patients who were in secondary prevention and who derived clear benefit from treatment, but the primary prevention cohort (a little more than 60% of the overall cohort) derived no apparent benefit from treatment (Fig. 2). More recently, a meta-analysis of randomized controlled trials indicated benefits of statins in

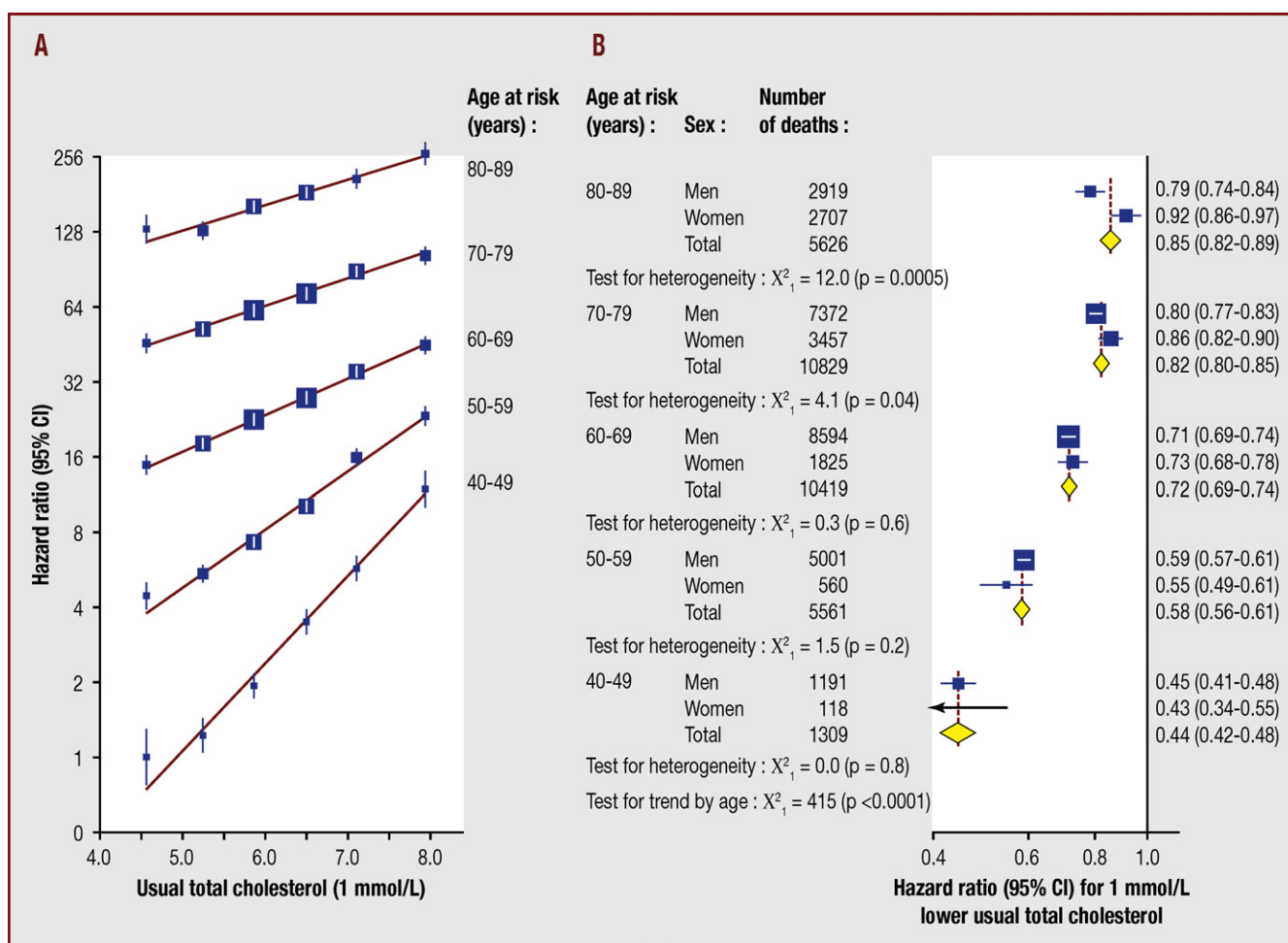


Figure 1. Ischaemic heart disease mortality versus usual total cholesterol. Reprinted from [1], copyright (2007), with permission from Elsevier. CHD: coronary heart disease; MI: myocardial infarction; TIA: transient ischaemic attack.

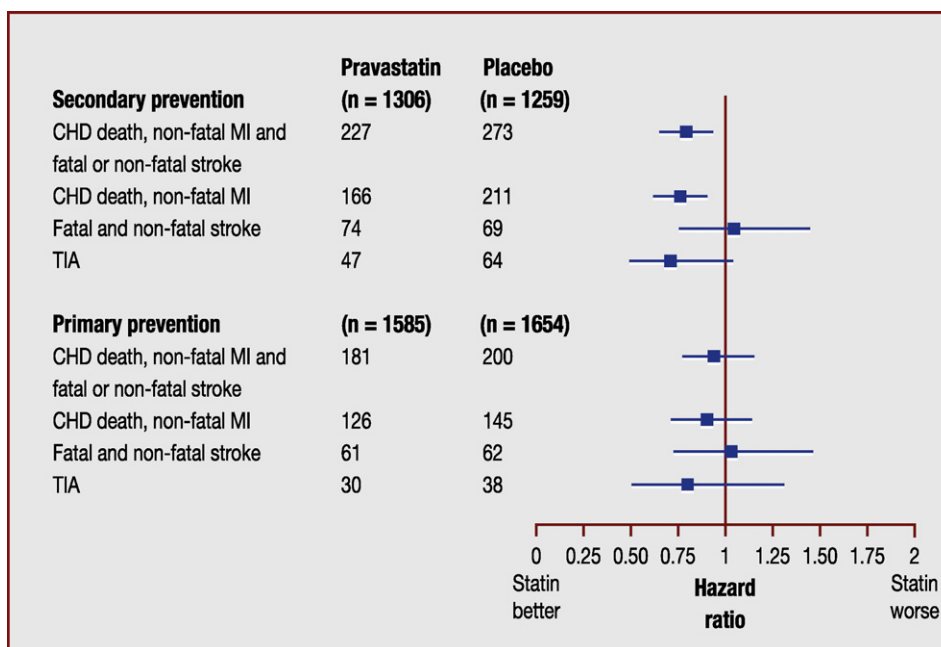


Figure 2. Effect of pravastatin according to primary or secondary prevention status in PROSPER. Reprinted from [11], copyright (2002), with permission from Elsevier. CHD: coronary heart disease; MI: myocardial infarction; TIA: transient ischaemic attack.

people without established cardiovascular disease but with cardiovascular risk factors, by showing a 30% reduction in major coronary events and a 12% reduction in all-cause mortality [12]. Moreover, the magnitude of cardiovascular risk reduction (i.e., acute myocardial infarction, percutaneous transluminal angioplasty or coronary artery bypass graft) was proportional to the magnitude of LDL cholesterol reduction, even in elderly patients at high cardiovascular risk [13].

It is established, therefore, that statins are beneficial in primary and secondary prevention in most patients with elevated cholesterol, but whether these benefits extend to the very elderly, particularly in primary prevention, is still not entirely clear. In addition, there seems to be some disparity between the effects that statins have on stroke, and on cardiovascular death and myocardial infarction in the elderly [11]. The recent presentation of JUPITER results in the elderly gives us an opportunity to revisit the evidence for the benefits of statins in the elderly [9]. Indeed, JUPITER did enrol a large fraction of patients aged above 75 years, and a prespecified analysis of the elderly has been conducted and was presented at the latest European Society of Cardiology meeting in Barcelona. What did JUPITER tell us with respect to statins and the elderly? First, the relative risk reduction from treatment with rosuvastatin in JUPITER was smaller in older than in younger patients, both for the primary endpoint (a composite of cardiovascular death, myocardial infarction, stroke and other events) and for the triple composite endpoint of death, myocardial infarction and stroke. However, because the risk is greater in older than in younger patients, the absolute risk reduction was also greater in older than in younger patients, regardless of the endpoints examined. For instance, the reduction in cardiovascular death, myocardial infarction and stroke per 100 patient-years was 0.34 for patients aged less than 70 years and 0.54 for patients aged 70 years and above. This

greater absolute benefit translates into a smaller number of patients needed to treat (NNT) for older compared with younger patients. For 5 years of therapy, in order to avoid one component of the primary endpoint, the NNT was 19 for the elderly compared with 29 for younger patients. To avoid one cardiovascular death, myocardial infarction or stroke, the NNT was 29 for patients aged above 70 years and 55 for younger patients. These data are important. They are derived from a large, contemporary, international, double-blind, randomized study, and they provide evidence for the clinical benefit of statins in primary prevention in the elderly with a large group of patients aged above 75 years. From this study, we can see that the benefit seen from rosuvastatin in the overall trial is also seen in the elderly subgroup, and, interestingly, includes a reduction in stroke. While the relative reduction may be smaller with older than with younger patients (Fig. 3), the absolute benefit is actually *higher* among the elderly (Fig. 4). Importantly, there was no evidence for a clear increase in risk of side effects with age, which therefore provides strong evidence for not depriving elderly patients of the benefits of statins. This is important because all registries and surveys concur in demonstrating that there is underuse of statins in elderly patients in both secondary and primary prevention [14,15].

There remain a number of caveats, however, as JUPITER pertained to a very special population of high cardiovascular risk patients with rather low LDL cholesterol values but selected on the basis of an elevated high-sensitivity C-reactive protein concentration; this therefore begs the question of whether we can extend the results to patients with elevated LDL cholesterol. It is indeed paradoxical to think that we now have much stronger evidence for using statins in primary prevention in elderly patients with low LDL cholesterol than we have for a similar type of population with elevated LDL cholesterol. There is no reason to

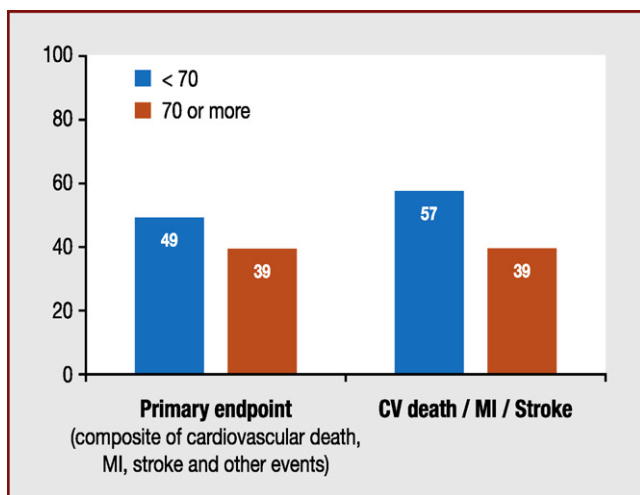


Figure 3. Relative risk reduction (as a percentage) from treatment with rosuvastatin compared with placebo in younger patients vs. older patients in JUPITER. Primary endpoint: composite of cardiovascular (CV) death, myocardial infarction (MI), stroke and other events. Unpublished data presented at the European Society of Cardiology Congress 2009

expect that there would be less benefit in patients with high LDL cholesterol, but this population simply has not been studied in adequately powered trials. A second important caveat is that the average age of the elderly patient population enrolled in JUPITER was 'only' 74 years with an interquartile range of 72–78 years and, therefore, the relevance of these results to very elderly patients aged above 80 years is still uncertain. In addition, it is well-known that a very elderly patient population encounters quite different problems related to polypharmacy and a high level of comorbidities, which may, in part, negate the benefits of

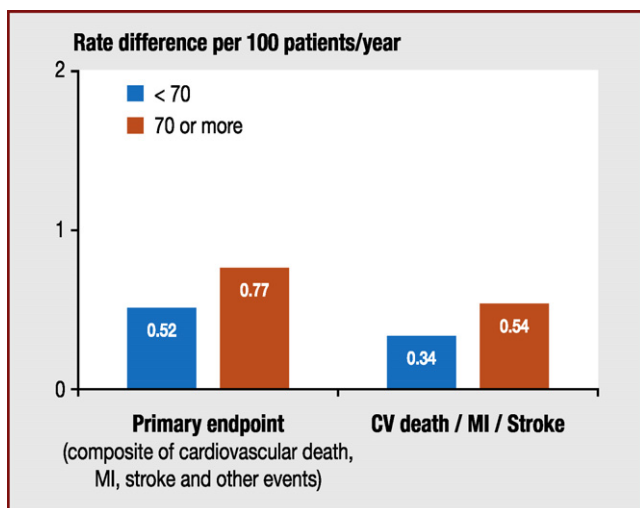


Figure 4. Absolute risk reduction from treatment with rosuvastatin in younger patients vs. older patients in JUPITER. Primary endpoint: composite of cardiovascular (CV) death, myocardial infarction (MI), stroke and other events. Unpublished data presented at the European Society of Cardiology Congress 2009.

statins. Clearly, further studies are needed to clarify the role of statins in the very elderly patient population.

In conclusion, there is no reason to deprive elderly patients at high cardiovascular risk and with elevated cholesterol from the benefits conferred by statin therapy. While the relative reduction in event rates achieved in older patients may be lower than in younger patients, the absolute benefit (and, therefore, the number of events avoided) is greater because the absolute risk is higher. Whether these findings apply to very elderly patients aged above 80 years is still uncertain, given the problems related to preventive polypharmacy in this specific patient subset.

Conflict of interest

None.

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