

# Never too old for statin treatment?



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In 2005, in a participant-level meta-analysis of large randomised controlled trials, the Cholesterol Treatment Trialists' (CTT) Collaboration conclusively showed that for most patients HMG-CoA reductase inhibitors (statins) reduced major adverse cardiovascular events.<sup>1</sup> Since then, generic versions of commonly used statins have become available. An evidence-based life-saving class of drugs with minimal known side-effects is therefore available, and are largely affordable even in lower income countries and for national health services. A statin is a key ingredient in polypills for cardiovascular disease prevention. So why is there a need for another meta-analysis?

The first reason is a scientific one. There is a gap in the evidence for statins for primary prevention in people older than 75 years.<sup>2</sup> In the PROSPER trial of 5084 male and female elderly patients in Scotland, Ireland, and the Netherlands, the primary endpoint, a composite of coronary death, non-fatal myocardial infarction, and fatal and non-fatal stroke, was significantly reduced in the secondary but not in the primary prevention subgroup.<sup>3</sup> In the HOPE-3 trial, which randomised 12705 men and women with intermediate risk of cardiovascular disease from 21 countries to 10 mg rosuvastatin or placebo, statin therapy did not reduce risk in participants aged 70 years or older.<sup>4</sup> An ongoing trial (STAREE; NCT02099123) is investigating the benefits and risks of primary prevention in healthy participants aged 70 years and above in Australia. Initiation of statin therapy in older patients requires special considerations, including pharmacokinetics, drug-drug interactions, life expectancy, quality of life, frailty, cognitive function, comorbidities, and patient choice. Lipid lowering might prevent cardiovascular events but cannot reverse established severe atherosclerosis.

The second reason to update the CTT meta-analysis is to reinforce the message that statins should be considered for cardiovascular prevention in people at risk, even if they are older in age. Ongoing medical debate exists about whether the risks of statins have been under-recognised<sup>5</sup> or exaggerated.<sup>6</sup>

In *The Lancet*, the latest meta-analysis by the CTT Collaboration<sup>7</sup> focuses on the influence of advancing age on major endpoints in 28 statin trials. Overall,

statin therapy or a more intensive statin regimen produced a 21% (rate ratio [RR] 0.79, 95% CI 0.77–0.81) proportional reduction in major vascular events per mmol/L reduction in LDL cholesterol, but in participants older than 75 years, the relative risk reduction was slightly less (RR 0.87, 0.77–0.99), especially among those without previous vascular disease (0.92, 0.73–1.16). As statins have not been shown to reduce cardiovascular events in patients with cardiac or renal failure, inclusion of older participants with cardiac or renal dysfunction in the trials might be an explanation for this result, which was borne out by additional analyses excluding trials conducted in cardiac and renal failure patients.

Statin therapy is often discontinued in older patients for various reasons, such as concomitant diseases and perceptions of risk-benefit.<sup>8</sup> As clinical trials are analysed on an intention-to-treat basis, discontinuation or poor adherence can lead to a diminished drug effect. Furthermore, statins are not a treatment for hypertension, hypotension, cardiac arrhythmia, or ventricular dysfunction, all of which can cause heart attack, stroke, and death.

Even if the relative risk reduction in people older than 75 years is less than expected, statin therapy might still be justified by a high baseline cardiovascular risk, which is usually present in older people. Among trial participants older than 75 years, the absolute risk reduction in major vascular events was roughly



0.5% per year per mmol/L decrease in LDL cholesterol. This risk reduction would be expected to be higher in high-risk patients. The present meta-analysis<sup>7</sup> makes a case to reduce LDL cholesterol in people at risk of cardiovascular events regardless of age, provided that the benefits outweigh the risks and the patient accepts long-term treatment.

There are limitations in this meta-analysis.<sup>7</sup> First, patients in trials are highly selected, with fewer comorbidities, less drug intolerance, and better adherence than the general patient population. Second, the mean age of the trial participants was 63 years, and only 14 483 (8%) of 147 242 participants were older than 75 years. Third, the included clinical trials concentrated on efficacy endpoints—adverse events, especially if non-serious, were not as fully recorded and analysed, which limited the ability of this meta-analysis to develop insights into the risks of side-effects for older people with statins. Last, not all relevant trials could be included in the meta-analysis if they were not part of the collaboration, and the trials included, if done many years ago, might not reflect contemporary management. More research in older people is needed to enrich the evidence on the risks and benefits of statins.

No drug is completely harmless. When statins are used in people with low cardiovascular risk, the risks and benefits need to be weighed against each other. Statins have been associated with a slight increase in incidence of muscle pain, diabetes, and haemorrhagic stroke, but their benefits in prevention of major vascular events are shown to be much greater.<sup>6</sup> The

present meta-analysis that includes people older than standard trial populations echoes this conclusion.<sup>7</sup> The challenge for the health-care profession and the media is to convey risks and benefits in ways that patients can understand, enabling them to make an informed choice.

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## Evidence-based medicine and infertility treatment

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Intracytoplasmic sperm injection (ICSI) is a procedure that is used to help couples with fertility problems achieve parenthood. Initially developed for couples with severely diminished sperm counts,<sup>1</sup> it is increasingly used as the method of choice for couples with fertility problems who are undergoing in-vitro fertilisation (IVF) treatment, despite the available data suggesting that IVF is superior to ICSI in couples with normal sperm counts.<sup>2</sup> ICSI differs from IVF in that a single sperm is selected by a trained embryologist and directly injected into the oocyte, rather than letting

fertilisation take place unaided after adding a few thousand motile sperm to a single oocyte. Traditionally, sperm selection is done by visual inspection at about 200 times magnification; sperm that show progressive motility and normal morphology are selected for injection. An alternative method to select sperm for ICSI is the so-called physiological, hyaluronan-based selection (PICSI) method, in which processed semen is allowed to bind to hyaluronan, and sperm that bind to hyaluronan are selected for injection.<sup>3</sup> Hyaluronan is a biologically active molecule that is also a major