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ANALYSIS

Statins for primary prevention of cardiovascular disease

Paula Byrne, **John Cullinan**, and **Susan Smith** explain the uncertainties about the benefits of statins, particularly in people at low risk of cardiovascular disease, and the need for better data to help shared decision making

Paula Byrne *health services researcher* [1], John Cullinan *senior lecturer* [1], Susan M Smith *professor* [2]

[1]JE Cairnes School of Business and Economics, National University of Ireland Galway, Galway, Ireland; [2]Royal College of Surgeons in Ireland—General Practice, Dublin, Ireland

Statins are now the most commonly used drug in the UK and one of the most commonly used medicines in the world.[1 2] Although prices have fallen since their patents expired, statins account for substantial drug expenditure in a context of often overstretched healthcare budgets, with estimated global sales approaching $1tn by 2020.[3] Use of statins in people with established cardiovascular disease is generally uncontroversial, but debate remains about their use for primary prevention for people without cardiovascular disease.[2] The controversy centres on uncertainty about whether the benefits of statins outweigh the harms and whether widespread statin use can be justified from a societal perspective.

Nevertheless, clinical guidelines have expanded the eligibility criteria over time, and in many countries the majority of people taking statins do so for primary prevention. For example, our study of a national cohort of people aged over 50 in Ireland found that nearly two thirds of those taking statins were in this category, with a higher proportion of women than men taking them for primary prevention (73% of women versus 57% of men).[4] Similar findings have been reported in other countries, including Denmark.[5]

The polarised debate on statins may have caused some confusion among patients and doctors. Greater awareness of the limitations of our current knowledge could facilitate communication to aid informed choices that are aligned with the patient's preferences and values. Indeed, shared decision making is particularly important in this context. We draw on the findings of our three recent peer reviewed papers on statins for primary prevention,[4 6 7] to outline the implications of changing clinical guidelines that have increased the number of healthy people who could be eligible for statins, highlight gaps in the evidence to support statins in primary prevention, and suggest ways in which clinicians and patients might think their way through the uncertainties.

How clinical guidelines support the rise of statins

We examined the effects of changes to European guidelines on cardiovascular disease prevention from 1987 to 2016[8-14] using data from a national cohort of older people in Ireland.[6] We found that the proportion of our sample of over 50s who would have been eligible for statins increased from 8% based on the 1987 guidelines to 61% with the 2016 guidelines. The broadening of the diagnostic criteria over this period meant that increasingly lower risk people became eligible for treatment and the number of people that would need to be treated (NNT) to prevent one major cardiovascular event also went up substantially: 40 people at the lowest risk in the 1987 guidelines compared with 400 of those at the lowest risk in the 2016 guidelines.[6]

Given the increased number of people taking statins and the dilution of benefit due to lower risk profiles of those being treated, we need to assess and understand the evidence underlying these trends.

Evidence for statins in primary prevention

Little information on the benefits of statins is based on data relating exclusively to primary prevention. For example, most published systematic reviews have reported on trials that included some participants with a history of cardiovascular disease. This is potentially problematic, since people taking the drugs for primary prevention, particularly those at low risk, have less to gain from statin use and this gain may not justify the risk of side effects.[15 16] We therefore undertook an overview of systematic reviews that examined the benefits of statins using only primary prevention data.[7] Only three reviews fully disaggregated primary prevention data from secondary data (we counted the two publications by the Cholesterol Treatment Trialists' (CTT) Collaboration as one review).[17-20] The reviews

Correspondence to: P Byrne p.byrne13@nuigalway.ie

included people taking statins for between one and five years and whose average age was between 62 and 69 years.

Overall, we found significant reductions among those taking statins in all-cause mortality (relative risk 0.91, 95% confidence interval 0.85 to 0.97), vascular deaths (0.85, 0.77 to 0.95), major coronary events (0.71, 0.65 to 0.77), and major vascular events (0.75, 0.70 to 0.80).[7] However, the net benefit or absolute risk reduction achieved with statins depends on a person's baseline risk of developing cardiovascular disease, which is based on factors such as age, sex, smoking status, cholesterol levels, and blood pressure. Therefore, outcomes stratified by baseline risk or by sex are most applicable to clinical decision making. The CTT review stratified participants by baseline risk and by sex,[19 20] and Mora and colleagues reported results for women only.[17] When stratified in this way, the estimated effects of statins on most outcomes were not statistically significant (table 1), raising uncertainty about the benefits of statins for primary prevention in some subgroups of patients. The reduced number of participants in each subgroup analysis may have reduced the power to detect an effect.

To further complicate matters, the systematic reviews report relative risk reductions—that is, the difference in event rates between those taking statins and those not taking statins in clinical trials. But the absolute risk reduction is more relevant to decision making for an individual patient. Sun and colleagues give a good example comparing two people who "represent the extremes of high and low-risk candidates for lipid-lowering therapy." [21] One is a 65 year old man who smokes, does not have heart disease, but who has high total cholesterol levels and raised blood pressure. The second is a 45 year old woman who does not smoke and has raised total cholesterol levels and slightly raised blood pressure. The man has an estimated 38% absolute risk of having a major coronary event in the next 10 years; the woman a 1.4% absolute risk. According to the risk reductions we reported,[7] statins would reduce the man's relative risk by 24% and the woman's by 41%. However, the man could expect an absolute risk reduction of about 9% (NNT=11) compared with just 0.6% (NNT=166) for the woman (fig 1). Indeed, our analysis suggested that none of those classified as low or moderate risk in primary prevention would reach the levels of risk reduction that patients say would justify taking a daily preventive medicine.[6]

Not only are the absolute benefits in primary prevention relatively small but, as noted above, there is a lack of certainty about these benefits. For someone in the lowest risk category (<5%) table 1 shows the relative risk of dying from vascular causes is 0.80 (95% confidence interval 0.43 to 1.47). This means that a person in this category could see a relative reduction of 20% in their risk of dying from vascular causes if they take a daily statin for five years but that there is some uncertainty around this point estimate. The confidence interval suggests that the true effect will be somewhere between a 57% reduction (based on the lower confidence limit) and a 47% increase (based on the upper limit). Although it is important not to overstate the implications of statistical significance or non-significance, doctors should "remember that all the values between the interval's limits are reasonably compatible with the data."[22] They can then consider how they would advise their patients if either the lower or upper bound represented the truth.[23]

Balancing benefits and harms of statins

Decisions to take or prescribe a medicine involve a trade-off between the perceived benefits and harms of that medicine for the individual, and it can be difficult to decide on valid demarcation lines. This trade-off is particularly salient for people choosing to take a statin for primary prevention, when the benefits may vary considerably. There are clear benefits for high risk groups, such as people with familial hypercholesterolaemia,[24] but for most patients the benefits may be marginal at best.

Some clinicians and patients may desire a reduction in risk of cardiovascular disease, regardless of whether the benefit is small.[25] For others, the impact of potential adverse effects heavily influences their decision making, and even modest estimates of harms caused by daily medication could negate the benefits of statins.[26] For example, one study reported that only 3% of community living older people would agree to a medication with adverse effects that affected their activities of daily living, while almost half would not agree if the medication was associated with mild fatigue or nausea.[27]

Studies have found that statin use can be associated with an increased risk of myopathy, rhabdomyolysis, diabetes, and haemorrhagic stroke.[28] Although these adverse effects are rare, the prevalence of milder non-specific side effects is still debated,[29] including whether these side effects are real or can be attributed to an expectation of harm—the nocebo effect.[30] However, it has also been argued that sources of bias within published studies may be widespread. For example, the characteristics of those participating in trials may not be representative of real world patients, while studies reporting results that are favourable to the pharmaceutical industry may be more likely to be published[31] and may under-report harms.[32]

For a complete picture on statins, we need objective data on harms as well as benefits. Despite calls to make access to full clinical trial data a legal, regulatory, or ethical requirement, and, in particular, for the publication of CTT's data from statin trials,[29 33] these remain unavailable for independent analysis. Thus doctors and patients cannot make fully informed decisions.

This is particularly relevant for another recent systematic review by CTT. The study reported statistically significant reductions in major vascular events in those aged between 55 and 70 years who had not previously had cardiovascular disease but non-significant effects among those older than 70 years.[34] Again, this raises the prospect that for some older people, statins might provide little or no benefit and may even cause them to have poorer outcomes than those not taking statins. Decision making with older patients is further complicated by the high prevalence of multimorbidity and related polypharmacy. Detailed data on trial participants is needed to determine generalisability to all older patients.

Towards more informed decisions

Although statins are commonly prescribed, serious questions remain about their benefit and acceptability for primary prevention, particularly in patients at low risk of cardiovascular disease. Statins, in this context, may be an example of low value care (having little benefit and potential to cause harm[35]) in these patients and, in some cases, represent a waste of healthcare resources. However, the boundaries between appropriate use, overuse, and low value care are difficult to delineate, as neither clinical outcomes in individuals nor patient preferences can be accurately predicted.

Lack of access to data on the potential harms of statins has hindered independent research. In addition, larger trials are needed that focus on low risk populations, including people over 70 and women. This would overcome potential problems of small sample sizes reducing statistical power and provide much needed clarity on the benefits of statins to individual

patients. In the meantime, we argue that the prescription, use, and reimbursement of statins in primary prevention warrants more careful consideration, incorporating patient preferences and NNTs. More generally, the evidence on statin use for primary prevention suggests that the concepts of overuse and low value care should become integral to policy making and resource allocation decisions.

Key messages

- Eligibility for statins has expanded over the past two decades
- Uncertainty remains about the benefits of their use for primary prevention
- Absolute risk reductions for low risk patients are small and patients may not consider that the absolute benefits justify taking a daily medication or the risk of adverse effects
- Better data on harms and low risk populations are needed to facilitate shared decision making

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Table

Table 1| Results for statin treatment in systematic reviews that disaggregated data on primary prevention[7]

Review	Relative risk (95% confidence interval)					
	All cause mortality	Any vascular death	Non-vascular death	Major coronary events	Major vascular events	Total
CTT 2012 and 2015[19 20]						
Overall	0.91 (0.85 to 0.97) P=0.007	0.85 (0.77 to 0.95) P=0.04	0.97 (0.88 to 1.07) P=0.6	0.71 (0.65 to 0.77) P=0.0001	0.75 (0.70 to 0.80) P=0.0001	—
Baseline risk profile:						
<5%	0.94 (0.71 to 1.26)	0.80 (0.43 to 1.47)	1.13 (0.76 to 1.69)	0.59 (0.37 to 0.96)	0.61 (0.45 to 0.81)	—
≥5% to <10%	0.83 (0.69 to 0.99)	0.75 (0.55 to 1.04)	0.87 (0.67 to 1.11)	0.58 (0.48 to 0.72)	0.66 (0.57 to 0.77)	—
≥10% to <20%	0.88 (0.76 to 1.02)	0.84 (0.67 to 1.05)	0.94 (0.76 to 1.15)	0.78 (0.65 to 0.93)	0.82 (0.72 to 0.93)	—
≥20% to <30%	1.06 (0.86 to 1.32)	0.97 (0.72 to 1.32)	1.13 (0.81 to 1.57)	0.80 (0.60 to 1.06)	0.81 (0.65 to 1.01)	—
≥30%	0.94 (0.70 to 1.25)	0.88 (0.59 to 1.33)	1.07 (0.68 to 1.69)	0.76 (0.50 to 1.17)	0.83 (0.58 to 1.18)	—
Sex:						
Men	—	—	—	—	0.72 (0.66 to 0.80)	—
Women	—	—	—	—	0.85 (0.72 to 1.00)	—
Mora 2010[17]						
Women only	0.78 (0.53 to 1.15)	—	—	—	—	0.63 (0.49 to 0.82)
Ray 2010[18]						
Including diabetes trials:						
Random effects model	0.91 (0.83 to 1.01)	—	—	—	—	—
Fixed effects model	0.93 (0.86 to 1.00)	—	—	—	—	—
Excluding diabetes trials:						
Random effects model	0.92 (0.84 to 1.02)	—	—	—	—	—
Fixed effects model	0.94 (0.86 to 1.01)	—	—	—	—	—

Figure

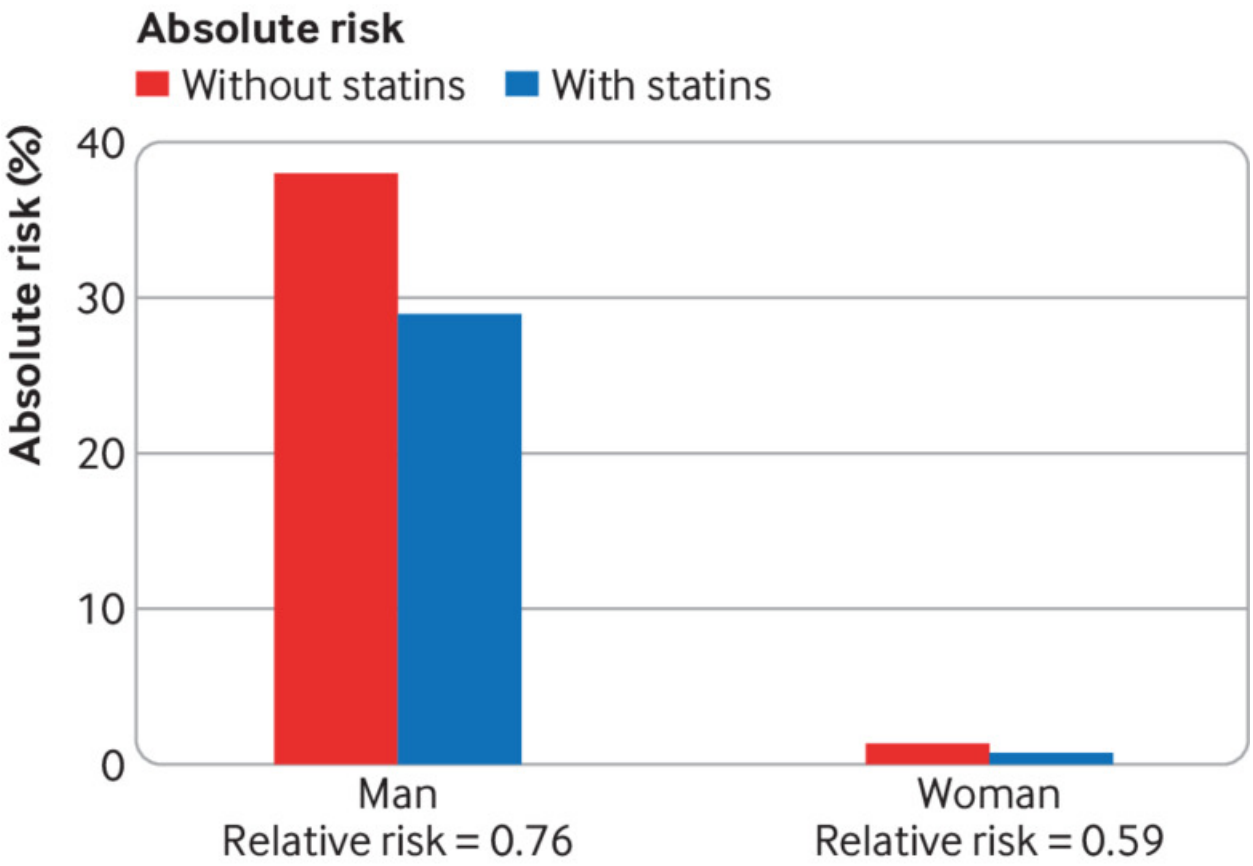

Fig 1 Reduction in absolute risk of major coronary event in next 10 years from taking statins for a hypothetical high risk man and low risk woman