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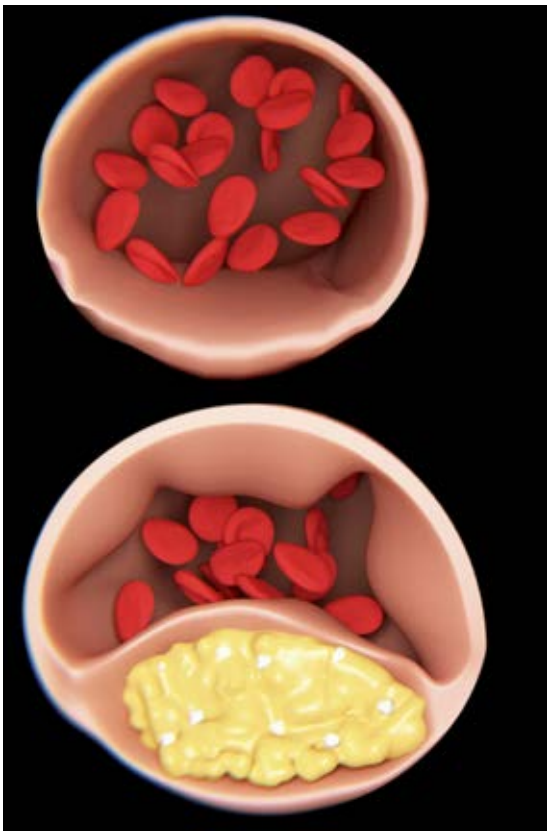
Taking a longer term view of cardiovascular risk: the causal exposure paradigm

Allan D Sniderman and colleagues argue that many people already have advanced arterial damage when they are identified at high risk of a cardiovascular event. A better approach might be to prevent the damage by earlier intervention against the treatable causes of cardiovascular disease



The decision to treat a healthy person with statins to prevent cardiovascular disease remains challenging. All the major cholesterol guidelines recommend that, except for people with diabetes and very high low density lipoprotein (LDL) cholesterol concentrations, the decision is principally based on the patient's risk of a cardiovascular event over the next 10 years.[1-4] However, the instruments they use to quantify this risk, the threshold of risk that activates statin treatment, and the emphasis they allocate to LDL cholesterol all differ.

Age is by far the strongest predictor of cardiovascular risk. This is not because age causes cardiovascular events but because progressive and incessant injury to the arterial wall over time from LDL cholesterol, blood pressure, and smoking cause the advanced, complex atherosclerotic lesions that are the precursors of cardiovascular events.[5] Since clinical risk cannot rise until advanced, extensive, intramural disease is present, many, or perhaps most, of those who become eligible for primary prevention with statins based on 10 year risk already have at least moderately advanced, diffuse atherosclerosis. It therefore makes sense to identify and treat the known causes of vascular disease earlier. The causal exposure paradigm aims to prevent advanced disease by assessing the treatable causes of vascular disease and projecting their clinical consequences over 20-30 years in order to identify those who would gain most from earlier pharmacological intervention.

Limitations of using 10 year risk

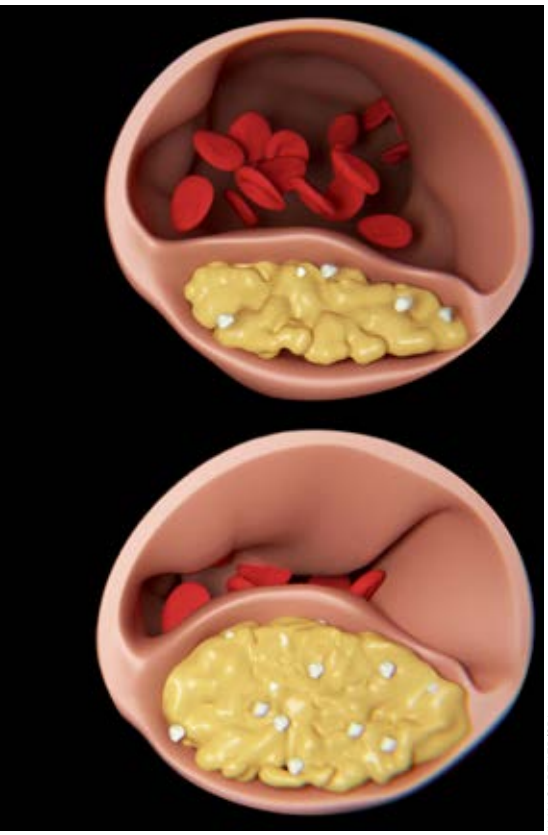
A 40 year old non-smoking American man with a LDL cholesterol level of 4.16 mmol/L (160 mg/dL, the 90th centile of the American population),[6] normal HDL cholesterol of 1.17 mmol/L (45 mg/dL), and raised systolic blood pressure of 145 mm Hg is at low risk (2%) of a cardiovascular event over the next 10 years[3] but faces a 30% chance of a coronary event before the age of 70[7] and a lifetime risk of a cardiovascular event of 45%.[3] Nevertheless, his 10 year risk would not reach a level at which statins are unequivocally recommended under the latest US guidelines until he was 53.[3]

Why the delay in a patient with appreciable hyperlipidaemia and hypertension? Because cardiovascular events are uncommon before the age of 60, risk cannot commonly be high until after 60. However, after 60, the incidence of cardiovascular events rises exponentially. Accordingly, if primary prevention is tied principally to risk over the next 10 years, statin therapy will not become common until later in life, at which point, suddenly, it may become close to universal. Thus, in the United States, we have shown that just under 90% of men and just over 50% of women older than 60 will be eligible for preventive statins based on the 7.5% threshold of 10 year risk in the American College of Cardiology and American Heart Association guidelines.[8] In the UK, even with the much higher threshold risk of a 20% chance of an event over a decade, statins are already recommended for about half of men.[4]

One approach suggested to improve selection of people at higher risk is to measure coronary calcification in those that algorithms identify as at intermediate risk. Although a positive result may be helpful in individual cases—particularly in younger people, in whom coronary calcification is not common [9]—coronary calcification points to advanced intramural disease[10] and is therefore late not early prevention. Moreover, although the data are limited, the only randomised trial of coronary calcification to determine statin treatment did not support its use to select individuals more likely to benefit from lipid lowering.[11] Furthermore, calcification screening makes primary prevention more expensive and exposes people to radiation. Finally, given the age dependence of the incidence of coronary calcification,[9]with the 7.5% risk thresholds in the United States most people over 60 will already qualify for preventive statins.[3]

Using causal exposure to assess risk

In the example above, our 40 year old man does not have the diffuse advanced atherosclerotic lesions that create high short term risk. However, over the next decade, because his arteries will remain exposed to sustained higher LDL cholesterol concentrations and systolic pressures than



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normal, the lesions that he does have are likely to become larger and more complex. So by the time he reaches 50 or 55 it is increasingly likely that he will have advanced lesions. Waiting until advanced arterial disease has developed when treatable causes of arterial disease were manifest much earlier does not seem to be the most prudent strategy to protect life. Moreover, once advanced lesions are present, risk remains substantial even with our best evidence based therapeutic strategies.

Both the US and the UK guidelines explicitly recognise this failing of the 10 year risk model and identify lifetime risk as a useful tool for discussion with patients.[3 4] The limitation of using lifetime risk of cardiovascular disease is that it is substantial in the great majority of the population[12] and so setting a threshold for intervention will be challenging. However, by starting earlier and focusing on a more extended period of time—say the 30 year risk of cardiovascular disease—and by taking into account all the major causes of vascular disease, the causal exposure paradigm would identify younger people who are at substantial cardiovascular risk not only during the next decade but also in the two that follow. Because the personal events of this period can be so concretely imagined—careers, growth and education of children, birth of grandchildren—they will help people to evaluate the advantages and disadvantages of earlier therapy when discussing whether to take preventive statins with their physician. Moreover, those who will benefit most from earlier intervention are those with the more extreme levels of the major causes of vascular disease, and this group will be easier to identify and will be smaller than the number who might benefit from later intervention.

On the other hand, earlier intervention translates into longer exposure to drugs with side effects—in particular in the case of statins, a small increase in risk of diabetes[13]—as well as greater expense to purchase them. There is also the reality that adherence to statin therapy diminishes sharply with time,[14] which is also a challenge for conventional models of prevention. However, just as patients have the right to choose to start treatment, they also have the right to stop. And if they wish, they can restart. In this, as in so much else, we must not let perfect be the enemy of the good.

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Limitations in the evidence

Although the causal exposure paradigm is intuitively attractive—preventing the advanced disease that produces the clinical events should be the most effective risk prevention strategy—it has not been investigated in randomised controlled trials, and given the length of time that would be required to demonstrate greater clinical benefit from earlier versus later intervention, such evidence will not be acquired any time soon, if ever. Multiple observational studies have established that risk relates exponentially to the level of the causal factors of vascular disease such as LDL cholesterol and blood pressure and the Cholesterol Treatment Trialists have shown that the reduction in events is roughly constant for each mmol/L decrease in LDL cholesterol with statins. Though not well appreciated, this also means that the absolute potential benefit from statins relates to the initial level of LDL cholesterol. A patient whose LDL cholesterol is 4 mmol/L can have more 1 mmol/L reductions than a patient whose LDL cholesterol is 2 mmol/L. Also, the same dose of the same statin will produce greater reduction of LDL cholesterol—and therefore greater benefit—at a higher than a lower LDL cholesterol level.[15]

This is consistent with the evidence from mendelian randomisation studies and functionally significant mutations, which show that a given difference in LDL cholesterol over a lifetime produces a much greater decrease in risk than a similar difference produced later in life by a statin. All of this evidence speaks strongly in favour of the validity of the causal exposure model.[16 17]

That said, the potential benefits of starting statins at age 30 or 40 are challenging to estimate. Greater benefit is likely, but how certain and how much? Law et al estimate that earlier intervention will result in much greater clinical benefit than later intervention,[15] and the Joint British Societies (JSB3) present accessible tools to estimate event-free years gained from earlier intervention.[4] Such estimates are of great interest and potentially informative but they may not be as definitive as many may think because once the artery is severely damaged, our therapies are probably only partially effective. Nevertheless, although benefit from earlier intervention can be estimated only imperfectly, the effects of high risk factors over more extended periods such as 30 years can be defined more concretely.[8] Accordingly, right now, patients and physicians may have to rely more on risk than benefit when deciding whether to take statins. Clinical reasoning and judgment will be essential to this process.[18] Testing of prevention strategies based on the causal exposure paradigm should provide more information about the thresholds at which treatment of the risk factors is beneficial.

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Competing interests: PPT has acted as a consultant Aegerion, Amgen, AstraZeneca, Kowa, and Merck and is in the speakers bureau for AstraZeneca, Genzyme, Kowa, Merck, and Novartis.

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References can be found on bmj.com

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