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Review Article

Statins and Changing Number Needed to Treat (NNT)

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Abstract

The absolute and proportionate benefits of statins for the primary prevention of deaths from coronary heart disease (CHD) are well-established. However its utility and cost-benefit depend on the prevalence of CHD and the incidence of deaths from it. At a time of very significant decline of deaths from CHD, the utility of statin medications for primary prevention of death must be continually reviewed. The number needed to treat (NNT) to delay one death will exponentially increase towards infinity and the time will be reached when statins for primary prevention will no longer be justi-fied. We might have reached this point as at present. The current NNT for death is about 1000 for men and 5000 for women aged less than 50 years, corresponding to prices of £200 000, $300 000 and £1million, $1.5 million respectively. We must remember that the major decline of deaths from CHD occurred before the introduction of statins.

Keywords: Cholesterol; Statin; NNT

Introduction

About seven million people in the UK take statin medications. In the west midlands of the UK statins are taken by 25% of people aged 70 years and by 10% at the age of 50 [1]. It is suggested by the National Institute for Health and Care Excellence (NICE) that this is not sufficient and that the use of statins for the primary prevention of deaths from coronary heart disease (CHD) should be extended to those with a lower risk than at present [2]. This has been challenged [3] and followed by debate and review within the British Medical Journal (BMJ) [4,5]. There is controversy concerning the balance between benefit and side-effects, the former being clear but the latter being uncertain [6]. Both need to be quantified.

Cardiovascular disease (CVD) risk calculators in use at present indicate the risk of heart attack or stroke for individuals without defining the implications of these [7]. A heart event can be chest pain with normal ECG and minimal elevation of high-sensitivity troponin, a condition with little risk that up to just a few years ago would have led to a low-implication diagnosis of "chest pain ?cause" [8]. The most important and reliable endpoint is death, of which CHD has been the major cause during recent decades. This has been the main endpoint of the various statin trials and it is the "saving of lives" that quite rightly receives the most widespread publicity. It has been stated by a critic of the BMJ articles that as a result of questioning the use of statins *"the damage that has been caused…. perhaps resulting in large numbers of unnecessary deaths"* [9]. The CVD calculators define a ten-year event risk, and if a linear relationship over this time-scale, this can be halved to give a five-year risk that conforms to the statin trials. When dealing with primary prevention of CHD that is in people not known to have CHD there is no evidence that statins will influence the occurrence of stroke [10]. We are thus dealing just with CHD prevention. Death is the major endpoint and unlike "myocardial infarction" its definition has remained unchanged.

Number Needed to Treat (NNT)

The effectiveness of any treatment within the population is judged by the number of people needed to be treated (NNT) to achieve one endpoint. The initial definitive statin primary prevention trial was the West of Scotland Coronary Prevention Study (WOSCOPS) [11] and the main endpoint was death. The data was presented clearly and it provides a good example for further assessment. The mortality reduction was from 4.2% in the control group to 3.1% in the treated group after five years. There was thus an absolute reduction of deaths by 1.1% (4.2-3.1) and this is the way in which people can most easily understand the effectiveness of the medication. However it sounds more dramatic if it is presented as a proportionate reduction of 26%, ((4.2-3.1)/4.2) x100. This is the result of the dubious process of taking percentages of percentages. 26% does not apply to the study groups directly but it is 26% of the *mortality* rate in the control group, and this usually not made clear.

In this study, for 100 men treated for five years 1.1 men did not die. The NNT was thus (100/1.1) = 91, meaning that 91 high risk men in the west of Scotland, aged between 55 and 65 years with serum cholesterol greater than 6.5 mmol/L, needed to be treated (with pravastatin) for five years to prevent one death. The men were recruited in about 1980 and they had what was about the world's highest incidence of CHD deaths, a peak of 960 per 100 000 per annum in 1970. [12] The prospect of treating 91 such men for five years to prevent, or delay, one death has been judged to be reasonable. In clinical practice the age range, the serum cholesterol limits, and the geography of residence have been extended considerably. At the time of the study only propriety pravastatin was available and the cost of one death delayed was £166 075 (91x365x5x£1), $249 000, at current prices of proprietary pravastatin (£1, $1.5 per day) [13].

The NNT is a function of two variables: the percentage proportionate reduction of events and the incidence of events in the control group or background population. The percentage reduction of events becomes a constant based on the experience of placebo-controlled studies, replicated over a prolonged period of time for validation. A recent meta-analysis reports a 20% proportionate reduction of deaths with statins given for primary prevention [14], similar to the 25% reduction in WOSCOPS. However the incidence of coronary deaths in the control groups, that is the local or national

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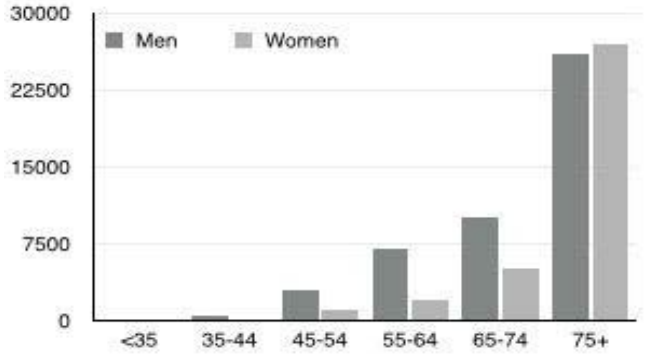

Figure 1: Deaths from CHD in the UK in 2010.

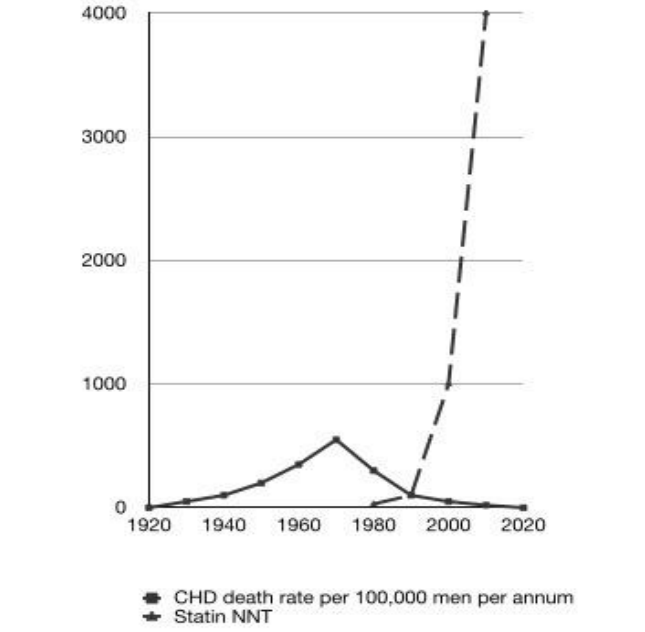

Figure 2: Changing NNT with decreasing CHD deaths.

incidence, is not a constant: in respect of CHD deaths it has changed greatly during the past forty-five years.

Changing mortality rates of CHD

In Scotland, when the annual mortality rate for CHD was 960 per 100 000 for men aged 55–64 years, that for men aged 45–54 years was 730 per 100 000 [12]. For men aged 35–44 years the annual death rate was much lower at 80 per 100 000 (0.4% at five years), giving a 5-year mortality NNT of 1000 in this age-group (100/0.1, given 25% death rate reduction). In England and Wales this age group had an annual mortality rate of 60 per 100,000 and the NNT would have been 1333, and in women of this age group in England and Wales with a lower mortality rate the NNT would have been 2000. This has never been explicit and the NNT of statin therapy does not appear in the current UK NICE guideline [15], but the recommendation is for the use of generic atorvastatin 20mg daily the UK price of which is £0.06, $0.1 [13]. Although NNT of 2000 amounts to £1 679 000, $2 518 500, for one death postponed with the use of proprietary atorvastatin, it would be less at £219 000, $328 500, with present day generic atorvastatin.

The mortality NNT will change as the national or local death rates change. CHD emerged as a major cause of death in about 1924 [16,17], increasing exponentially to a peak in 1970 [12]. Thereafter the reduction of death rate was similarly exponential, before the introduction of statins and other effective interventions. The pattern has been that of an epidemic, the cause of which is not clear [18]. The decline was slightly earlier in the USA than in the UK and it was so unexpected that it provoked a Bethesda conference in 1978 [19]. As a result of the conference the MONICA project was initiated [20] and its ultimate conclusion was that the decline was mainly the result of a reduction of coronary events rather than improved survival from events, but the reason remained unclear [21].

Reliable reports of age-related CHD deaths in 2010 of men in England and Wales indicate a fall to 20 per 100 000 population per annum [22, 23], and this would give a statin NNT of 4000. In women the corresponding death rate was just 7 per 100 000, indicating an NNT of more than 11 000. With generic statins this indicates approximately £2M, $3M, per death delayed.

Targeting statin therapy

The large reduction of age-related deaths is the main factor responsible for the rapid increase in the number of very elderly, and it is in this group that most deaths from CHD will occur. This is shown clearly in (Figure 1), deaths from CHD in the UK in 2010, data from the British Heart Foundation [24]. It is interesting to note that above the age of 75 years the deaths are in equal numbers for men and women, in part representing more women than men in this age-group.

Total population mortality rates are of little value if we wish to target treatments at those with the highest risk, especially with regard to NNT and its financial implications. Defined age ranges are necessary and these are shown in (Table 1). For each of these we can identify the NNT and from this the cost of one death delayed. A 20% reduction of mortality rate is used to calculate the NNT. The price of generic atorvastatin is taken as £0.06, $0.1, per day for five years.

Public policy

In defining a policy for primary prevention of CHD it is important to base it on up-to-date data of risk, the main feature of which is current mortality rates defined for age-groups. The suggestion has been to give statins for all by the age of 50 years [24], but this suggestion was made without any reference to NNT. Clearly we will be expecting at this age-group NNTs of about 1000 in men and about 5000 in women. Whether such numbers of fit and healthy people should take a statin for five years to delay one death is a matter of judgment, and this should be made by the recipients of statins as well as by policy makers. The costs of about £200 000, $300 000, and £1M, $1.5M, respectively to delay one death for an uncertain time is similarly a matter of judgment, bearing in mind that in the UK NICE has regarded £30 000, $45 000, per annum the maximum cost to be reasonable in cancer treatment [25] (this was increased in 2008 to £80 000, $120 000, by the health minister of the time Alan Johnson [26]). Obviously there will be savings in respect of reduction of non-fatal coronary events but they should not detract from the major objective of mortality reduction as these are quite small marginal costs in the UK, whereas pharmaceutical spending is all marginal.

Table 1: Death rate from CHD men and women in the UK in 2010, And NNT calculation (atorvastatin 20mg = £0.06, $0.1, per day).

Men	35-44	45-54	55-64	65-74
Annual death rate per 100 000	15	62	165	396
Annual death rate %	0.015	0.062	0.165	0.396
5 year death rate %	0.075	0.31	0.825	1.98
20% statin effect reduction	0.015	0.062	0.165	0.396
NNT = 100/20% statin effect reduction	6667	1613	606	253
Cost death delayed £	730,037	176,624	66,357	27,704
Cost per death delayed $	1,113,080	269,297	101,174	42,240
Women				
Annual death rate per 100 000	4	14	40	148
Annual death rate %	0.004	0.014	0.04	0.148
5 year death rate %	0.02	0.07	0.2	0.74
20% statin effect reduction	0.004	0.014	0.04	0.148
NNT - 100/20% statin effect reduction	25,000	7143	2500	676
Cost death delayed £	2,737,500	782,159	273,750	74.022
Cost per death delayed $	4,173,839	1,192,550	417,284	112,860

As the mortality rate within the population falls, there is an exponential increase of the NNT for death delayed by statin therapy (Figure 2). In the future, as perhaps the mortality risk approaches zero, the NNT will inevitably increase towards infinity. It is clear that at some stage primary prevention with statin therapy will be judged to be irrelevant, and this will be based on the current NNT. It could be considered that this point has now been reached. With the CHD mortality rate being now so low in those less than 75 years, there are very few below this age being at high risk.

The UK CVD calculator indicates that the event risk is almost twice as high in those with type 2 diabetes, 22% versus 12% for a 65 year-old man at ten years. Twice the mortality rate equates to half the NNT and half the cost of one death delayed. These calculations could easily be added to the standard risk calculator so as to give a more informed assessment of the value of prescribing a statin.

The seriously flawed diet-cholesterol-heart hypothesis of CHD underpins the current approach to CHD prevention. It is engrained in society, not only in medicine but also in the pharmaceutical industry, the food industry, political pressures, and in popular belief. There are many vested interests. The first advice (also in NICE) is to eat low fat foods, whereas a low fat diet has no consistent effect on mortality [27-29]. The proposition that CHD is a dietary disease is unsustainable. The second approach is pharmacological, aimed at lowering blood cholesterol levels. There is no doubt that statins lower blood levels of cholesterol and reduce deaths but whether or not the former is responsible for the latter is far from clear. Ezetimibe is also used for its effect of reducing blood levels of cholesterol, but it has had no demonstrable effect on coronary events or deaths [30]. The effectiveness of statins proves the effectiveness of statin therapy and does not "prove" the cholesterol-heart hypothesis (the meaning of "proof" requires clarification beyond the scope of this paper). However the absolute effectiveness of statins must be viewed in the context of current CHD mortality risk so as to determine the usefulness.

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