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What is the optimal age for starting lipid lowering treatment? A mathematical model

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Coronary heart disease is the major cause of morbidity and mortality in industrialised countries. The Framingham cohort study has identified the quantitative impact of different risk factors and their interactions,[1–3] and large intervention studies have confirmed that drug treatment to reduce risk factors decreases progression to heart attack and stroke.[4 5] However, with this increased understanding have come additional problems. The treatments to reduce cholesterol concentrations or blood pressure are often expensive, and the population that might benefit is vast. Indeed if every individual who might benefit was treated with a statin or fibrate, a large portion of the total drugs budget would be consumed.[6] Thus some form of rationing is inevitable, and various recommendations have emerged in an attempt to contain cost while targeting treatment at those who stand to gain the most. Current UK policy recommends treatment should be offered to anyone with an absolute annual risk of 3% or more.[7] Others, however, favour a 1.5%-2% absolute threshold before beginning treatment,[8 9] and some have argued that estimates of relative risk should form the basis for treatment guidelines.[10] Since age is the major determinant of absolute risk, treatment thresholds based on absolute risk will tend to postpone treatment to older age, whereas guidelines based on relative risk will tend to lead to treatment of younger people.

Whichever type of risk assessment is used, guidelines have tended to focus on who to treat, whereas in practice when to start treatment is another equally important and related issue. Faced with a 35 year old man with a total cholesterol concentration of 6.0 mmol/l, a high density lipoprotein cholesterol concentration of 1.1 mmol/l, and a blood pressure of 145/95 mm Hg, should a clinician delay treatment

Summary points

Lipid lowering drugs are expensive and the population that might benefit from treatment is potentially vast

Current guidelines recommend targeting treatment to those who will gain the most; gain being cardiovascular events avoided over a fixed period of 5 or 10 years

Modeling of lifetime risk of cardiovascular disease suggests that many individuals will have accumulated most of their risk before they become eligible for treatment

It is possible to predict an age at which starting treatment provides maximum benefit for each year for which treatment is given by using lifetime risk calculations and presenting benefits as event free life years gained

This approach may help with young individuals at risk whose absolute risk of cardiovascular events is low but whose relative risk of cardiovascular events is high

until the patient is aged 60 when the 2% threshold for annual risk is crossed, wait until he is aged 75 when the 3% threshold is crossed, or treat immediately on the grounds that he is already at twice the risk of an age and sex matched general population? If a policy of delayed treatment was adopted what would be the risk associated with the delay and how should this be communicated to the patient? We present different ways of modelling and assessing risk and attempt to identify whether there is an optimal age for treatment that meets clinical need while containing costs.

Calculating risk

With the aid of a computer program based on data from the Framingham study, which we have described in detail elsewhere,[11] we calculated the five year risk of coronary heart disease events for different risk factor profiles. Coronary heart disease events were defined as either fatal or non-fatal myocardial infarction, death from coronary heart disease, coronary insufficiency, or angina pectoris.[1 2] Cumulative risk of coronary heart disease, the number of first coronary heart disease events, and the number of survivors free of coronary heart disease events at each age from 15-95 years was calculated for cohorts of 100 hypothetical individuals with specific combinations of risk factors (see appendix 1). To adjust for competing causes of death, we repeated the same calculations after subtracting the number of expected deaths not attributed to coronary heart disease from every five year age block, as described previously.[12] Mortality adjusted for age was obtained from the *UK Mortality Statistics 1996*.[13] For simplicity we have used the same hypothetical example for many of the calculations—a man with a total cholesterol concentration of 7.0 mmol/l, a high density lipoprotein cholesterol concentration of 0.8 mmol/l, and a blood pressure of 160/90 mm Hg. This man may be considered a typical individual at moderately increased risk of coronary heart disease, but the calculations could equally apply to other risk profiles in men or women.

Calculating treatment effects

To estimate the influence of treatment we assumed that treatment with a statin would reduce total cholesterol concentration by 20% and increase the high density lipoprotein cholesterol concentration by 5%,[5 14–16] and that this would reduce risk to that of an otherwise equivalent individual whose baseline cholesterol concentration was the same as the new concentration after treatment. Such assumptions about reversibility of risk seem justified for reduction of cholesterol concentration[17 18] but tend to overestimate benefits of lowering blood pressure.[19] We calculated the cumulative risk of coronary heart disease, the number of coronary heart disease events, and the number of survivors free of coronary heart disease events at different ages for statin starting treatment, ranging from 25 to 70 years.

To assess life years gained that were free of events, the predicted number of survivors free of events with treatment was subtracted from the predicted number obtained without treatment. Summation of event free survivors for each five year age block gave the total number of life years gained that were free of coronary heart disease events (event free life years gained) either for treatment in general or for treatment started at any specific age (see appendix 2). To estimate the effectiveness of each treatment year, we divided the total number of event free life years gained by the number of years for which treatment would be given up to the age of 75. The resulting number is the predicted event free life years gained per year of drug treatment.

Five year risk assessment

Figure 1 shows the five year absolute risk of coronary heart disease and cumulative risk adjusted for other causes of death for three hypothetical groups of men: smokers with a total cholesterol concentration of 7.2 mmol/l, a high density lipoprotein cholesterol concentration of 0.8 mmol/l, and a blood pressure of 162/95 mm Hg; non-smokers with a total cholesterol concentration of 6.0 mmol/l, a high density lipoprotein cholesterol concentration of 1.1 mmol/l, and a blood pressure of 145/95 mm Hg; and non-smokers with a total cholesterol concentration of 4.5 mmol/l, a high density lipoprotein cholesterol concentration of 1.1 mmol/l, and a blood pressure of 120/85 mm Hg. The age at which the 3% threshold of coronary heart disease would be crossed in each group is shown in figure 1. Thus for individuals at low risk this threshold is never achieved, whereas for individuals at high risk it is reached at around 47 years of age. Unlike absolute risk, which shows an inexorable increase with age, cumulative risk estimates tend to show a sigmoid pattern.

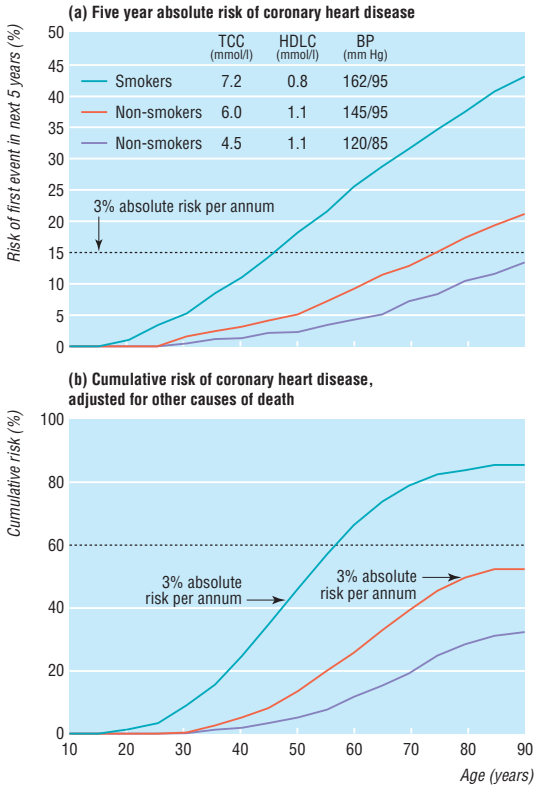

Fig 1 Predicted absolute risk of coronary heart disease for three different groups of men. TCC, total cholesterol concentration; HDLC, high density lipoprotein cholesterol concentration; BP, blood pressure

Lifetime risk and life years free of coronary heart disease events

Figure 2 shows the predicted effect of reducing cholesterol concentration at different ages. These calculations indicate that reducing cholesterol concentration is unlikely to decrease significantly the overall burden of ischaemic heart disease events or death in a population (fig 2a). Rather it would shift the relation with age so that events occurred later in life (fig 2b). Perhaps more important for the individual and society is the number of event free life years gained by treatment rather than the number of events avoided. Figures 2c and figure 3 show the curves for life years gained free of coronary heart disease events.

Treatment effects and life years free of events

Figure 3 shows the effects of cholesterol lowering treatment for a hypothetical group of men with a total cholesterol concentration of 7.0 mmol/l, a high density lipoprotein cholesterol concentration of 0.8 mmol/l, and a blood pressure of 160/90 mm Hg. The number of event free life years gained for every age at which treatment started from age 25-70 years in five year intervals are shown either as total event free life years gained (fig 3a) or as event free life years gained in each five year age block (fig 3b). The total number of event free life years gained per 100 men is similar (around 300 years for the whole cohort) for all ages at which treatment is started until age 40, but from then onwards the total number of event free life years gained declines steadily. Figure 3c shows the number of event free life years gained per treatment year, assuming treatment until age 75. This graph shows that the maximum benefit per treatment year is gained by starting treatment at age 40 in this particular group.

Comparison with policy guidelines

To investigate the influence of different treatment policies for drug treatments for reducing cholesterol concentration, we calculated coronary heart disease events and the event free life years gained by starting treatment at age 50 and 60 respectively (the ages at which 2% and 3% absolute risk per year are reached for this particular group of individuals). We also calculated coronary heart disease events and event free life years gained by starting treatment at age 40 (chosen as the age at which the total number of life years gained free of coronary heart disease events begins to decline (fig 3a) and the benefit per treatment year is the highest (fig 3c). Figure 2a shows the total number of coronary heart disease events for the different treatment policies, adjusted for other causes of death. This number is equivalent to the lifetime risk of coronary heart disease for each treatment policy. Figure 2b gives an indication of the ages at which these coronary heart disease events are likely to occur for each policy. The overall number of predicted coronary heart disease events at each age for starting treatment at ages until 40 years are equivalent (data not shown), whereas if treatment is started later more events are observed at younger ages, with fewer events occurring at older ages

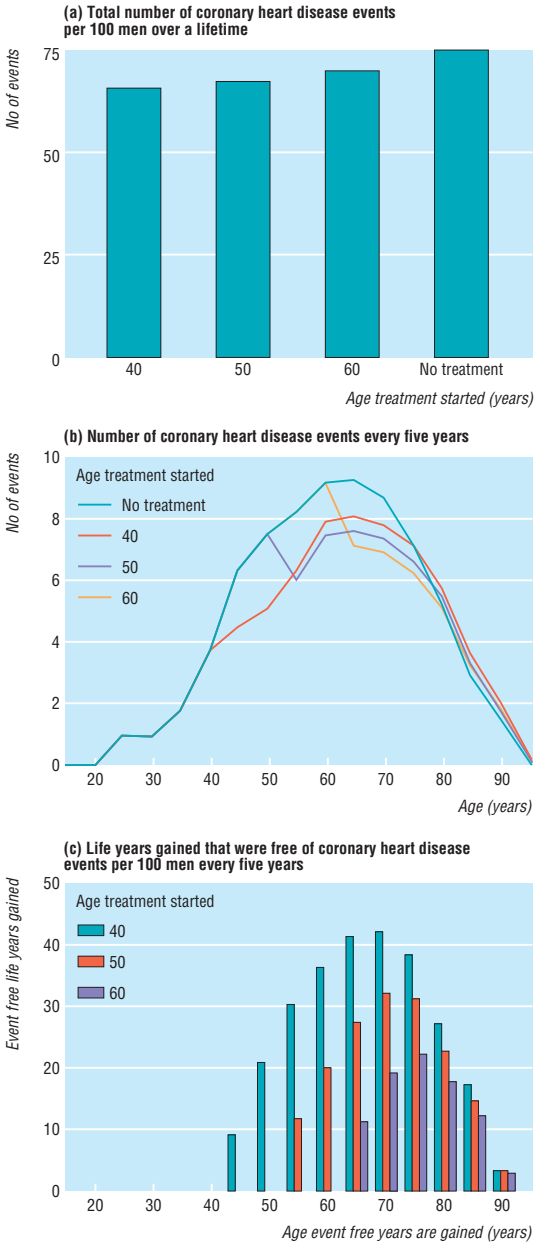

Fig 2 Risk of coronary heart disease and predicted treatment effects for cohort of 100 non-smoking individuals with total cholesterol concentrations of 7.0 mmol/l, concentrations of high density lipoprotein cholesterol of 0.8 mmol/l, and blood pressure of 160/90 mm Hg. (a) Calculated total lifetime risk of coronary heart disease if no treatment given or if treatment with statin is started at age 40, 50, or 60. (b) Predicted number of first coronary heart disease events every five years (once an event has occurred individual is removed from cohort). (c) Event free life years gained every five years per 100 men treated with a statin

(fig 2b). Figure 3a presents the total life years gained free of coronary heart diseases for each policy.

By lowering the treatment threshold for this group of individuals from 60 to 40 years, the cumulative risk of coronary heart disease for this period would be reduced by 7.4% (data not shown), which means that for every 100 men treated between the ages of 40 and 60, seven or eight coronary heart disease events would be avoided during this time. Assuming that all

guidelines would accept treating a 60 year old patient, at current drug prices for a statin the total extra drug cost would be in the order of £4000 per patient for starting at age 40 and £2000 per patient for starting at age 50.

Combining when to treat with whom to treat

To determine at which initial risk level individuals would profit from lowering the treatment threshold to an earlier age, we computed risks for a series of hypothetical individuals with different initial cholesterol concentrations, and we assessed the age at which they would reach the 3% threshold. We computed the number of event free life years gained, in total and per treatment year. To assess the "optimal" age for starting treatment we used the principles illustrated in figure 3b and c. The number of life years gained free of coronary heart disease events by lowering the treatment threshold from an absolute risk of 3% per year (UK policy) to the "optimal" point are shown in figure 4a. To calculate cost effectiveness the total number of event free life years gained was divided by the number of additional treatment years required (fig 4b). The results show that absolute and relative benefits of lowering the treatment threshold to our predicted "optimal" point are highest for individuals at moderate initial risk.

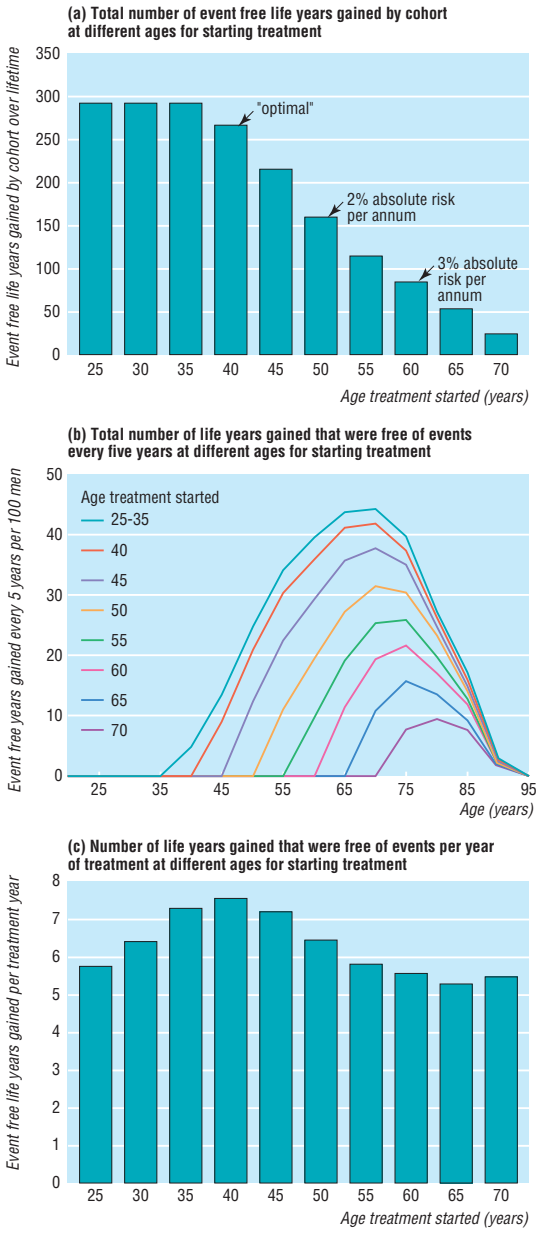

Fig 3 Effect of statin treatment on event free life years gained for cohort of 100 non-smoking individuals with total cholesterol concentration of 7.0 mmol/l, high density lipoprotein cholesterol concentration of 0.8 mmol/l, and blood pressure of 160/90 mm Hg

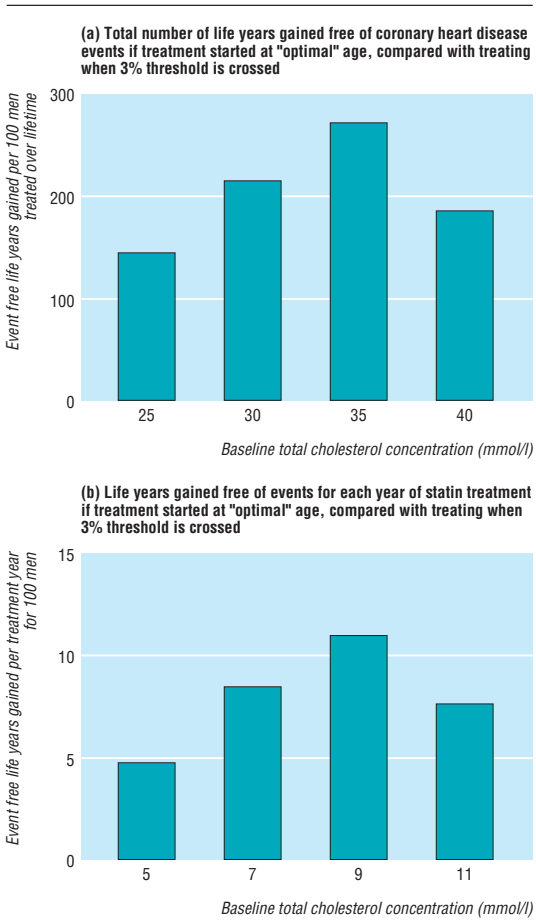

Fig 4 Predicted benefits of statin treatment for non-smoking men with blood pressure of 160/90 mm Hg, high density lipoprotein concentration of 0.8 mmol/l, and varying concentrations of total cholesterol

Discussion

Reducing cholesterol concentrations decreases the risk of heart attacks and strokes without increasing other causes of mortality or morbidity. Identification of individuals at high absolute risk is comparatively straightforward and can be undertaken accurately using charts or simple computer programs.[8 9 11 20] However, such calculations and treatment policies based on absolute risk tend to lead to treatment of older individuals. A dilemma facing practising clinicians is what advice to offer younger people who are at substantially increased risk compared with their age

group but who nevertheless remain below the defined absolute risk threshold for treatment. Of course all such individuals should be offered appropriate advice on lifestyle at the earliest opportunity, but we suggest that it is possible to calculate a predicted optimum age for drug treatment for each individual. Starting treatment at this age should offer the most cost effective use of statins or other lipid lowering agents for the individual, while minimising exposure to risk.

Modelling risk

We used the Framingham risk equations to model risk. These have been shown to predict absolute risk accurately for North American and northern European populations.[11 21–23] Plotting the five year absolute risk against age makes it possible to predict when an individual will cross the 2% or 3% threshold for absolute annual risk (fig 1a). When this is compared with curves for cumulative and lifetime risk (fig1b), it is clear that individuals at moderate to high initial risk of coronary heart disease are already in the steep part of their slope for lifetime risk at this stage. Indeed by the time many individuals reach an age at which "eligibility" for treatment is achieved according to current UK policy, half of their total lifetime risk has already accumulated.

Unlike the curves for absolute risk in any five year period, the curves for cumulative risk of coronary heart disease flatten towards old age. This reflects the shorter life expectancy and period at risk for older people and the increase in competing causes of death. The higher the initial risk, however, the earlier on this flattening of the curve starts.

Assessing benefits

We assumed that cholesterol lowering treatment would reduce the absolute risk of coronary heart disease immediately at the beginning of every five year age block. Various studies have shown that cholesterol lowering treatment produces near maximal reduction of cholesterol concentration within months and that this translates to risk reduction within 1-2 years. These studies also suggest that individuals tend to adopt the new level of risk predicted by their new cholesterol concentration. Therefore our assumption is justified although it may slightly overestimate the benefits of treatment.[4 5 17 18] Our results show that if lifetime risk is considered, the "benefits" of treatment can not be measured simply by summating the events avoided over a five year period, since events avoided in younger ages will let more people survive free of events to older ages, so that the treated cohort will eventually have a similar number of events as the non-treated group, although these will tend to occur at older ages (figure 2b).

An alternative approach is to assess the number of life years gained free of events by treatment. Patients and society value health and this seems to be a reasonable way of expressing the potential benefits of lifelong treatment. In our hypothetical example, the total number of event free life years gained remains more or less the same if treatment is started at any time up to the age of 40 but starts to decline steadily if treatment is delayed until later years (fig 3a). Furthermore, the number of event free life years gained per treatment year is optimal if treatment is started around age 40 (fig 3c). This calculation suggests that, for some individuals, the most cost effective use of statins is probably greatest when started earlier than current guidelines recommend. For individuals at high risk the 3% absolute risk threshold per year is crossed close to the calculated optimal point for starting treatment. However, individuals at moderate risk (the bulk of patients presenting difficult treatment dilemmas) seem to gain the most from lowering the treatment threshold towards the optimal point (fig 4). These calculations suggest that there exists for every risk factor combination an optimal age at which treatment should be started to achieve the maximum cost effectiveness. The challenge is to calculate this point simply and accurately within a consultation.

Treatment costs

Our method of measuring the number of event free life years gained per treatment year predicts the most cost effective age at which to start treatment for any given combination of risk factors. Furthermore, it allows the clinician to suggest clearly a treatment plan that includes a projected start date for treatment and calculates the risk associated with the delayed start date. However, with such a system some form of rationing would still be necessary, and it might be possible to base policies on the slope of the cumulative risk curve rather than on arbitrary absolute risk thresholds.[12] One implication of basing treatment on the calculated optimal age rather than a 3% threshold is that more life years free of events would be gained at younger ages. Thus, although it is inevitable that reducing the age at which treatment is started will increase the amount of money spent on drugs, the age at which events occur and the age at which event free life years were gained would need to be taken into account in more detailed calculations of economic costs and benefits to the individual, healthcare providers, and the nation. Such calculations are outside the scope of our article.

Limitations, assumptions, and uncertainty

One weakness of our approach is that we have assumed that the risk factor profile for coronary heart disease remains stable with age, whereas in reality blood pressure and cholesterol concentration are likely to increase with advancing age. Further modelling would need to be undertaken to determine the likely impact of age related changes in risk factors on the lifetime risk curves and event free curves for survivors we have generated, but it is interesting to note that the model predictions resemble closely observational datasets.[24] This may be because the increase in cholesterol concentration with age is probably only in the order of 0.04 mmol/l/year.[25] In practice it might be better to generate new lifetime risk curves for individuals as their risk profiles for coronary heart disease alter, rather than try to predict changes. This would also take into account changes due to lifestyle adjustments or drug treatment. Finally, it should be recognised that application of population data to the individual will lead to inaccurate estimates for some individuals.

Indeed, the percentage reduction in cholesterol concentration in response to treatment would be expected to vary between individuals, and the lifetime risk predictions show only the mean data rather than the range of possible responses. However, these limitations—the uncertainty associated with applying trial data to the individual—apply equally to other methods for determining treatment policies and are unlikely to be less of a problem when treatment decisions are based solely on "clinical judgment."

Using the model in practice

The appendices show the equations necessary to calculate the risk curves and optimum treatment points described. We have shown previously that simple graphical presentations of risk can be undertaken as part of consultation, with a desktop computer. If the concept of optimal age for treatment is considered valid and useful, it would be comparatively simple to include such data as part of any risk calculation, and this might be used also for targeting antihypertensive treatments.

ADH is the British Heart Foundation (Gerry Turner) intermediate fellow. JFM is British Heart Foundation professor of cardiovascular science.

Contributors: PV and ADH formulated the ideas on which the modelling was based. PV and SU developed the mathematical models. SU undertook the life table analyses with assistance from ADH. All authors took part in discussion of data and their intepretation. SU wrote the first draft of the paper, and all authors commented on this and contributed to the final text. PV will act as guarantor for the paper.

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Appendix 1

Life table method to estimate cumulative risk of coronary heart disease, coronary heart disease events, and event free survivors for any individual with specific baseline risk factor profile designated [z]

The table shows the life table for a cohort of 100 males with the following risk factor profile [z]: total cholesterol concentration 7.0 mmol/l, high density lipoprotein cholesterol concentration 0.8mmol/l, and blood pressure 160/95 mm Hg. The age for starting treatment is 15 years, and all calculations are done for five year age blocks (designated i) from age 15 until age 95, where i = 1 for the age block of 10-15 years, i = 2 for the age block of 15-20 years, and so on.

A different cohort of 100 individuals with a different risk factor profile for coronary heart disease [z_x] would have their own table [t_x], with x being 1, 2, 3 … for any different risk factor profile [z_x].

For each five year block i, the methods for deriving (c) the number of deaths not due to coronary heart disease, (d) the number of coronary heart disease events, (e) the number of survivors free of coronary heart disease events, and (f) the cumulative risk of coronary heart disease with (a) the five year absolute risk of coronary heart disease and (b) the death rate not due to coronary heart disease for the general population are:

(a) The five year absolute risk of coronary heart disease (a_i; in %) is calculated with a simple computer program based on the Framingham risk equation.

(b) The age specific death rate not due to coronary heart disease (b_i; in %) for the general population is obtained from the *UK Mortality Statistics 1996*.

(c) The deaths not due to coronary heart disease c_i are calculated from $c_i = (e_{i-1}/100) \times b_i$, where e_{i-1} is the number of survivors free of coronary heart disease events carried over from the immediately preceding age block i-1.

(d) The number of coronary heart disease events (d_i) in each age block i is calculated from $d_i = (e_{i-1}/100) \times a_i$.

(e) The survivors free of coronary heart disease events e_i at the end of each five year block i are calculated from $e_i = e_{i-1} - c_i - d_i$.

Life table method (see Appendix 1)

Age block (i)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Age (years) in five year blocks i	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89	90-94
(a) 5 year absolute risk of coronary heart disease(%)		0	1	1	2	4	7	9	11	14	17	20	23	25	28	31	33
(b) Age specific deaths rate for deaths not due to coronary heart disease (%)		0.352	0.352	0.455	0.455	0.626	0.626	1.168	1.168	3.085	3.085	9.138	9.138	24.69	24.69	66.01	66.01
(c) Deaths not due to coronary heart disease	0	0.352	0.351	0.447	0.440	0.591	0.564	0.972	0.874	2.026	1.68	3.977	2.818	5.168	2.6	3.288	0.098
(d) Coronary heart disease events	0	0	0.997	0.983	1.937	3.78	6.309	7.493	8.226	9.196	9.259	8.705	7.094	5.233	2.948	1.544	0.049
(e) Survivors free of coronary heart disease events	100	99.65	98.3	96.87	94.49	90.12	83.25	74.79	65.69	54.46	43.53	30.84	20.93	10.53	4.98	0.15	0.0
(f) Cumulative risk for coronary heart disease	0	0	0.997	1.98	3.92	7.7	14.0	21.5	29.72	38.92	48.18	56.88	63.98	69.21	72.16	73.7	73.75
Survivors free from coronary heart disease events$_i$ (x)	100	99.65	99.3	97.85	95.45	91.99	86.82	80.59	73.2	62.89	52.78	40.04	29.17	16.13	8.44	0.76	0.05
Survivors free from coronary heart disease events$_i$ (y)	100	99.65	98.3	96.87	94.49	90.12	83.25	74.79	65.69	54.46	43.53	30.84	20.93	10.53	4.98	0.15	0.0
Life years gained free of coronary heart disease events g_i (x, y)	0	0	5	5	5	10	20	30	40	40	45	45	40	30	15	5	0

(f) The cumulative risk for coronary heart disease (f_i) for the beginning of each five year block i is calculated from $f_i = f_{i-1} + d_i$.

Appendix 2

The life table method (table) is used either to calculate and compare coronary heart disease events, survivors free of coronary heart disease events, and cumulative risk of coronary heart disease in groups of individuals with different risk factor profiles or to examine the effect of risk factor profile changes due to treatment

We compared the profile $[z_x]$ to the profile $[z_y]$ and each variable calculated from the comparison of these two profiles is given the suffix (x,y).

Life years gained free of coronary heart disease events

(g) For each five year age block i, the life years gained free of coronary heart disease events over five years = $e_i(x) - e_i(y)$. The life years gained free of coronary heart disease events g_i (x,y) is thus 5 $[e_i(x) - e_i(y)]$.

(h) For each five year age block i, the total number of life years gained free of coronary heart disease events h (x,y) is calculated from h (x,y) = g_2 (x,y) + g_3 (x,y) and so on up to g_{17} (x,y).

Coronary heart disease events avoided

(j) The coronary heart disease events avoided j_i (x,y) are calculated from j_i (x,y) = d_i (y) – d_i (x).

(k) The total number of coronary heart disease events avoided k (x,y) is given by k (x,y) = j_2 (x,y) + j_3 (x,y) and so on up to j_{17} (x,y).

Life years gained free of coronary heart disease events and coronary heart disease events avoided per treatment year

(l) We denote the starting age for treatment of the risk factor profile $[z_x]$ for coronary heart disease by t_x. We define the number of treatment years l (x,y) by l (x,y) = $t_y - t_x$. For the profile [z] without treatment we set t = 95 or arbitrary as 75.

(m) The free life years gained free of coronary heart disease events per treatment year m (x,y) are calculated from m (x,y) = h(x,y)/l(x,y).

(n) The coronary heart disease events avoided per treatment year n (x,y) are calculated from n (x,y) = k(x,y)/l(x,y).

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One hundred years ago

Damages claimed for antenatal injuries

According to the New York *Medical Record,* the Supreme Court of Illinois has recently adjudicated in a remarkable case. An infant claimed damages for a deformity alleged to have resulted from injury to the mother before its birth. The mother, while pregnant, was injured in an elevator accident at St. Luke's Hospital, Chicago, her left leg being caught and crushed. When the child was born his left leg was deformed. The hospital authorities settled with the woman for her injuries, and then she brought suit in the child's name for 50,000 dollars damages for the deformity, which it was claimed was due to the same accident. The Court dismissed the suit on the ground that at the time of the accident the child could not be credited as a separate being capable of sustaining an action independent of the mother.

(*BMJ* 1900;i:659)