# Atherosclerosis: Epidemiology

**Uptodate**

**Presented by Professor Geoffrey Rose, Department of Epidemiology, St Mary's Hospital.**

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**Black-and-white**
**Duration: 00:40:06:23**

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**<Opening titles>**

<**Opening film of commuters walking along crowded London streets, including men wearing bowler hats, interspersed with scenes of traffic. Brief close-up scenes in sequence of: exhaust fumes; mouth smoking cigarette; sausages, egg and bacon frying in pan; callipers measuring thickness of skin fat; blood pressure gauge; rotating molecular diagram**>

**<Rose to camera>**

Atherosclerotic disease has provided a very happy hunting ground for epidemiologists and it's kept a lot of us busy and, incidentally, taken us to very pleasant parts of the world to do our work. And as a result a great many papers have been published and there is a lot of evidence, and all I shall be able to do is to select and try and present a summary of the present state of that evidence on the main points. And I shall finish up with just one or two new thoughts and then later on in the series other speakers will be taking up the epidemiological evidence and relating it their own special topics.

In the first talk in the series, Dr Lewis spoke of the size of the problem of atherosclerotic disease and particularly of coronary heart disease. And I'll take up the story at that point and develop it a little further. And as an illustration let's look at the course of events in a group of, let's say, a thousand young men […]

**<Rose narrates over series of charts and tables, interspersed with talk to camera>**

[…] in the prime of life at the age of 30, looking forward to years of work and later retirement. But by the age of 65, when they are due to retire, in fact, only 750 of those 1000 are still alive and 250 have died. And among these 250 pre-retirement deaths, approximately 75, at present rates, are due to coronary heart disease. And that's the nub of our problem: the high mortality in men, in the middle life, in the productive and family years.

<*To camera*> Now, of course, there's also a problem for women and there's also a problem for old men, but as we're talking largely about the problem in middle aged men, it's where most concern has centred and it's where most of the evidence has been accumulated. I'll summarise it by saying that 1 man in 13 in Britain today dies of coronary heart disease before retirement, a big problem. Let's put it in its international context to see how we stand compared with other countries.

<*Next chart*> Now here we've got a chart which shows the mortality from coronary heart disease along this axis <*indicates x-axis*> for a few selected countries. And the point that emerges most strikingly of all is the enormous variation. Even between two developed countries like Japan and Finland, a tenfold difference. Tremendous variation, and some of this we can account for: rather more than 50 % of this international variation can be accounted for in terms of the differences in the mean levels of the known main risk factors. <*To camera*> And particularly important in these international differences is the difference in blood cholesterol level which in turn correlates, of course, very closely with differences in the dietary content of saturated fat. The international differences in mortality tie up pretty closely with

differences in the severity of atherosclerosis revealed at post-mortem. And it seems that this can account for most of our problem of international variation.

But we don't only have a problem of international variation, less often considered but also very striking are the regional variations within one country. And let's take a closer look at the United Kingdom and consider the regional variations within the UK <*previous chart*>. And I've just taken two examples here: Scotland, which heads the UK list, a very high rate almost up to the American rate; South East England, favoured in this as in so many characteristics, very much lower.

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Now, why should there be these big differences even within Britain? <*To camera*> To a large extent the answer is: we don't know. But we do know some of the explanation and quite a large part of the regional variation can be correlated with regional variations in the water supply. This is a story which when it first got spoken of some years ago was so extraordinary that nobody believed it. But pretty consistently in most of the studies that have looked at this factor, it's found that where the water supply is soft, mortality from many conditions, but particularly from cardiovascular disease is high; where the water supply is hard, the mortality is substantially lower. It is not certain that there is a causally important water factor. It may be some other factor associated with geographical characteristics. Nor do we know even the answer to the very important question: should people in soft water areas drink less because it's poisonous, or should people in hard water areas drink because it's protective? There's a lot to be found out but it is of very great interest and importance because one could imagine that it would be very much easier to alter the water supply to the population than it would be to try and change their personal habits of life. So, as a means of prevention, the water story is of great importance and we shall look forward to further research results with a lot of interest.

Now, we've looked at some of the international and regional differences at the present time; a word about the time trend. The epidemic of coronary heart disease started at different times in different countries. In the Netherlands, for example, it

didn't really get going until the 1950s and then it advanced very rapidly indeed. In Britain and in the United States of America, it started well before the last war. Let's take a look at the time trend in Britain in a recent period of 10 years <*next chart*>. And we have up here <*indicates y-axis*> standardised mortality ratio from coronary disease in men in England and Wales over a recent period of 10 years. Now, what you can see here is that, well, maybe there is a very slight upwards trend but it's arguable. And for practical purposes, the real point is that in this country the mortality from coronary heart disease is near or at a plateau <*to camera*>. In the United States, which is perhaps a little ahead of us in these matters, there's a definite suggestion that in the last 3 or 4 years they may even be off the plateau and experiencing some fall in rates.

Even the appearance of a levelling off in Britain is a little deceptive, an oversimplification. Different sections of the community have experienced different time trends. Once upon a time, coronary heart disease was the disease of the favoured upper classes; in recent years, mortality has been declining among professional people, particularly amongst doctors – which is very nice for us. But it's been increasing among working class people and the social class gradient has, in fact, completely reversed so that in Britain today coronary heart disease is predominantly a working-class disease, a very impressive and intriguing change, and on the whole one that we can't explain.

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Now, so much for the mortality pattern, but what about the problem for non-fatal disease in a community? There have been a lot of surveys and I just want to extract from a lot of information, three or four points of particular interest. The first is the high prevalence of non-fatal disease. If we go out and do a survey of middle-aged working men in Britain today, and if we take a standardised history to identify angina and a resting electrocardiogram, we're likely to find that something like 10 % of people at work have evidence suggesting myocardial ischaemia. That's the first point: the high prevalence, mostly not disabling them, mostly not diagnosed, but there if you look for it. And the next point to emphasise is that if you go back and re-examine these men

a year later, there is a remarkable degree of flux, of coming and going of disease. We find that something like 50 % of those who today have evidence of mild angina or minor ECG changes, if we examine them in a year's time will be apparently quite normal at that time. A great amount of flux.

The next point that's emerged, that I find very interesting, is that if you examine men repeatedly in this way, you find after a few years of examinations that very few of the major catastrophes, the myocardial infarctions and the sudden deaths, occur without some early warning. I think that nearly all of these major events which bring people to clinical attention have, in fact, been preceded by some evidence, often very transient and often very insignificant, of myocardial ischaemia in the previous few years.

And the last and perhaps most important point to emerge from the surveys of coronary heart disease to emerge in the community is concerning the natural history of sudden death. Let's go back to those 75 in every 1000 men who, at present rates, are going to die of coronary heart disease before they reach the age of retirement. <*Next diagram*> And let's see how those 75 are made up. And this is what we have learned from a number of coronary heart disease community registers that something like two thirds, 45 out of 75, of all coronary heart disease deaths are medically unattended; they occur so quickly that the doctor has not yet arrived on the scene. Something like 20 occur in hospital but, of course, we know that the majority of these deaths are, what you might say, inevitable, that is to say the myocardium is already so injured by the time the patient comes under medical care that there's precious little that can be done to improve the prognosis.

<*To camera*> And the moral from these striking figures is, of course, that prevention is our only substantial hope of controlling the community problem of coronary heart disease. If we want to prevent then we have to know about aetiology, about causes, and let's come on now to looking at some of the risk factors for coronary heart disease which have provided us with such helpful clues to aetiological factors. And by a risk factor I mean something very simple. I define a risk factor as a personal characteristic associated with an increased risk of disease. I think it's useful to keep the term in this simple sense not to imply necessarily that a risk factor is a cause, it's

a predictor of risk and it may or it may not be causally related to the occurrence of disease.

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Now, let's look first at the two, as it were, oldest established of the risk factors for coronary heart disease: age and sex. <*Next chart*> And what we have here is, on the vertical scale, coronary mortality expressed logarithmically against age here, for men and for women. You can see that the gap between the two sexes gets progressively narrower, and by the time old age is reached really there's very little in it. Another point you can see is that if we look at the rates in women, over the greater part of life, expressed logarithmically, it's very close to a straight line. In other words, the proportionate rate of increase is constant. Now, this is rather unexpected because we might have thought that around the menopause, around this age, the line might have taken a steeper curve upwards but it doesn't. <*To camera*> And I think this is very suggestive that at least a large part of the favourable experience of women from this disease is not hormonal; it may be related to differences in way of life, for example; at least until recently women have smoked a great deal less than men. Their physical activity patterns are different and so on.

But there is a hormonal influence and a very recently reported study compared women around the age of 50 who had experienced the menopause with those who had not yet reached it. And it reported that the incidence of coronary heart disease in women at the age of 50 was something like 3 times greater in those who had already reached the menopause. It does look as though there is a protective influence of female sex hormones, but it's by no means the whole explanation of their relatively favoured position in CHD mortality.

Now, let's come on to some of the risk factors that we have a hope of changing and the most important of these for coronary heart disease is blood pressure. And for this and for some of the other examples we'll be looking at, I've extracted the information from the Framingham Massachusetts Prospective Survey of Coronary Heart Disease. It's got the longest period of follow-up and it's got the best documented

results. And let's look at the Framingham data on blood pressure as a risk factor for subsequent development that manifests coronary heart disease.

<*Next graph*> And what we're going to look at is the incidence of coronary heart disease according to the initial systolic blood pressure, the blood pressure recorded when the subject first entered the study, came in and sat down and had his blood pressure taken. And these incidence rates are averaged over a period of the 16 years follow-up that has been reported. And let's see how it worked out. Here we've got the results according to age at entry to study: 35-year-olds, 45-year-olds, 55 to 64 at entry to study. There are two or three very important points to note here. The first is that the lower the blood pressure, the lower the risk. The line comes down all the way. There is no evident threshold, no level of hypertension above which for the first time CHD risk increases. The lower the pressure, the lower the risk.

The next point is that the slope of these lines increases as age increases and what that is saying is that for any given increase in blood pressure, the increase in coronary risk is greatest for the older man. Now, that's rather contrary to what we might have thought clinically. A systolic blood pressure of 160 is very common indeed in old men, and because it's common, we tend to think it's not very important. For coronary heart disease, a blood pressure of 160 is more risky in a man of 55 to 64 than it is for a man of 35 to 44.

Now, let's look next at the upper part of the range here, the clinical hypertension part of the range. And when we see the relation to coronary heart disease here, we can see how it takes a sharp upturn. It's been something not far away from a straight line until we reach this point of around 180 systolic when, in each age group, it turns up much more sharply.

And the last point on which I want to comment on this graph, or as a background to this graph, is the very remarkable thing that the best single predictor of the risk of coronary heart disease over the next 16 years in the Framingham study was the initial systolic blood pressure. Systolic, a slightly better predictor than diastolic; initial pressure, a slightly better predictor than the average of several measurements. I

think it's possible that it predicts so well because it gives us an indication not only of the subject's mean pressure but also it has a component due to the subject's lability, and it may well be that lability of blood pressure is damaging to arteries as well as mean pressure.

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Now, let's take a look at blood cholesterol as a risk factor and we'll look at a very similar layout of the data from Framingham. <*Next chart*> CHD risk against levels of initial serum cholesterol at entry to study in three age groups as before. And really, it's a very similar picture. Again, slope slightly increasing at each successive age. Again, no level, no threshold below which risk is no longer related to cholesterol; the lower the cholesterol, the lower the risk so far as these data tell us. Again, at the high range a distinct upturn in risk.

<*To camera*> Now, I'll be coming back to say a little bit more about cholesterol later on and I know that other speakers in this series will have a lot more to say about cholesterol, but let's leave it there just for the moment and let me say a little about other measurements of blood lipids: triglycerides, fasting plasma triglyceride levels. Considered as a single risk factor in isolation those with higher triglyceride levels have a higher coronary risk. As a single factor it's not as good a predictor as cholesterol but it does predict. The question is: is it an independent risk factor, or does it predict the risk simply because it keeps bad company? Because triglyceride levels are certainly correlated with a number of other potentially important coronary risk factors. There's a strong correlation with cholesterol level – we do have some evidence that at any given level of cholesterol, high triglycerides probably are associated with a somewhat higher coronary risk. There's also a correlation with, for example, obesity and with impairment of glucose tolerance, and here, unfortunately at the moment, we do not have any evidence to tell us whether the effect of triglycerides as a risk factor is or is not independent of these other risk factors.

What about lipoprotein typing about which there's been so much talk and research in recent years? Considered as a risk factor, we have at present no evidence that if you

know a subject's cholesterol and triglyceride levels that you can make any better prediction of his CHD risk if you also know the lipoprotein type. And that's all as an epidemiologist I'm going to say about this important subject. One can at least conclude that if you are examining subjects to predict their CHD risk, you could spare yourself the trouble of lipoprotein typing. It won't help you in that respect.

I'm not going to say anything in this talk about obesity or about diabetes as risk factors because they are going to be dealt with especially later on the series, but I do want to say something about cigarette smoking. We know that myocardial infarction rarely occurs in men under the age of 40 except in cigarette smokers. And let's go back to the Framingham data to see how this works out more quantitatively <*next chart*>. And we've got just the same layout as before, CHD incidence versus number of cigarettes smoked at entry to study for our three age groups. And again, a rather similar finding: the gradients of risk perhaps a little flatter than for cholesterol and distinctly flatter than for blood pressure. Another difference perhaps that – consider heavy smoking more than 20 a day – the relative risk, the height for the heavy smoker relative to the height for the non-smoker is perhaps, what, 3 or 4 to 1 for the young men, perhaps 1½ to 1 for the older man, a distinct fall-off in the relative risk associated with cigarette smoking as age advances.

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<*To camera*> These differences in CHD risk according to amount smoked correlate very well with what has been found from post-mortem epidemiology. At post-mortem the history of cigarette smoking, as recorded in the patient's records, correlates very strikingly with the severity and extent of atherosclerosis. And I think this means that probably the main mechanism by which smoking aggravates coronary heart disease is by an acceleration of the atherosclerotic process. We're not sure, of course, how this happens. We've known for a long time that for a given number of cigarettes smoked the man who inhales has a higher risk of coronary heart disease than the man who doesn't inhale. And we have been able to make much more sense of this recently with the work that has been done on the possible key role of carbon monoxide, and I think there is a lot to suggest that carbon monoxide retention in

inhaling smokers, particularly cigarette smokers, sometimes also inhaling cigar smokers, is of major importance in the acceleration of atherosclerosis. We would like to be able to say something about the role of nicotine which we know to have, of course, major acute cardiovascular effects, but the epidemiologists here, I'm afraid, have not yet come up with any very relevant evidence. We do not know whether nicotine is or is not an important contributory factor to the risk of coronary heart disease. It's a pity but there it is.

Now, we've been looking at factors one at a time; it's important that we should look at their interaction. Let's look at the interaction between smoking and serum cholesterol level. Again, the Framingham data <*next chart*>. And, first of all, we've got on a graph as the same layout as before, the risk of CHD here for non-smokers. And now let's contrast that with the risk according to serum cholesterol level in the men who smoke cigarettes. You can see that at every level of cholesterol, the smokers have risks something like, what, 50 % greater than the non-smokers. But there's a more important point: the height of this line <*indicates smokers*> above that line is a measure of the extra risk of being a smoker for a given level of serum cholesterol. And down here at a low cholesterol level, it's a smaller increment in risk than it is here at a high cholesterol level. The effect of smoking on risk is not a constant for all people, the risk is much greater for the person who is also at risk on other factors. And this is of great clinical and preventive importance. It means that whenever we see someone who is high risk for CHD on the basis of lipid levels, blood pressure, diabetes, that we have there an individual for whom smoking is particularly hazardous.

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Next, let's take a look at physical activity and here we're in trouble because of the problems of quantitation, the problems of making measurements. We've known for a long time that there tend to be fairly substantial benefits to CHD risk to men whose occupations are physically active. They are less likely to get a first attack; they are less likely to die in the attack. Recently, we've had some evidence on the possible importance of leisure time activity. Professor Morris has reported, in his study of civil

servants, a follow-up of men whose leisure time physical activity he assessed some years ago, and he has related the incidence of CHD in the follow-up period to whether or not these men took part in vigorous exercise in the weekend in which they were originally questioned. Let's see what he found.

<*Next chart*> The men are divided up here into three groups: those who took no vigorous exercise, the moderates and the really energetic types here. And the relative risk of CHD is, well, only about one third in the really vigorous exercisers what it was in the people who took no vigorous exercise at all. <*To camera*> Now, this is in civil servants, that is to say men who spend most of their time sitting doing nothing physically, and it may or may not apply to the benefits of leisure time activity in those whose jobs are physically more active, but it's interesting.

Now, let's try and synthesise what we've been seeing for the separate risk factors and consider how good a prediction of CHD risk can we make when we consider factors not one at a time or in pairs but all together. Some years ago, the group at the London School of Hygiene and Tropical Medicine, with which I collaborate, carried out a risk factor screening examination of something like 20 000 civil servants in London. And from these risk factor measurements, we calculated for each man a multivariate risk factor score, a measure of our best estimate of each man's future risk considering his levels for each of the various risk factors we measured. And we've been able to see how well this multivariate risk score performed in predicting 5 year mortality. And in outline here's what we found.

<*Next chart*> Here is a curve of the accumulative risk of total mortality according to level of this multivariate risk score. And what it's saying is that we can really nowadays make extremely powerful predictions of the future. Consider those people who fell in the top 20 % of the risk scoring, and these top 20 % included almost 60 % of all the deaths; a really very remarkably powerful prediction.

<*To camera*> Now, let's look at how this overall prediction is accounted for by contributions from the individual risk factors. Let's look at the three key risk factors, which are smoking and blood pressure and blood cholesterol. <*Next table*> Let's see

how they rank relative to each other, in their ability to produce the same high level of CHD risk, a fourfold increase in a 50-year-old man. Now, if that level of risk is going to be achieved by cholesterol alone in a non-smoker with a low blood pressure, the cholesterol's got to be very high indeed: 400. If it's going to be achieved by blood pressure alone in a non-smoker with a low cholesterol, the blood pressure's got to be very high indeed: systolic 250. But, supposing the same level of risk is going to be achieved not on one factor alone but on a combination of the three: cigarette smoking – systolic only 140, cholesterol only 260 will produce just the same high level of risk as the two earlier examples.

<*To camera*> The point is this: if you meet those first two customers, you will recognise them instantly as being unusual, you will identify them as high risk, but the last man is inconspicuous because he's common and yet his risk is just the same. And from the community point of view, it's that last customer who is more important just because there are so many of him, so many like that. It's the contrast between the importance of risk factors in identifying high risk individuals and the importance of risk factors to community risk – the incidence of the disease in the whole community. And this last factor depends very much on the prevalence of different levels and different combinations of the risk factors.

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If we think through the logic of community risk, it leads us to some interesting and important and perhaps unexpected conclusions, and I'd like to go back again to the Framingham data to try to work this one out for a particular example and we'll take the example of serum cholesterol. We could have just as well have taken any of the other main risk factors. Now, the point is, we're going to combine what we know about risk in individuals with what we know about the prevalence of different levels at the risk factor. Combine those two sources of information. Let's look first at the prevalence distribution of serum cholesterol in men entering the Framingham study.

<*Next chart*> And here we have a scale of the percentage of men with each successively higher level of serum cholesterol at entry to the study. The frequency

distribution with a high tail but not many men in this very high clinically interesting level. Now, we'll pick up the theme of the mortality from coronary heart disease related to cholesterol level that we've looked at already and here's the line linking CHD deaths with cholesterol level. We've seen this one already. And at any particular level of cholesterol, the height of this line above the sort of rock bottom minimum for the low cholesterol man represents the addition to risk associated with having a cholesterol at that particular level; the attributable risk we call it. Let's relate the attributable risk at various levels of cholesterol to the prevalence of those different levels, putting the last two charts together. These are the last two charts superposed, and all we have to do now to work out how the deaths from coronary heart disease, attributable to the cholesterol risk, relate to different levels is to multiply attributable risk, the height of the risk line above the basal level, to the number of men at each particular level. And what it works out at showing with a little simple arithmetic is that in a group of 1000 men in Framingham at this age, the number of deaths attributable to the cholesterol risk is likely to be about 2 per year. When we come one step up the cholesterol risk, 5 deaths a year in this group because they are both numerous and they have a slightly higher risk than the one before. <*Indicates successive cholesterol risk steps*> 3 deaths there where the risk is higher but there aren't so many people at risk, 3 again there, and this perhaps is the surprise – just 1 death per group of 1000 per year in the really high cholesterol range.

Now, what that is saying is that in each year in a group of a thousand, 2 plus 5 etc. – 14 CHD deaths can be blamed on the cholesterol risk, but out of those 14 attributable deaths, half – 2 and 5 – are attributable to elevations of less than 250, and only 1 attributable to the kind of level that we would get clinically excited about.

<*To camera*> And the conclusion from that is that from the community risk point of view, a lot of people with a slightly increased risk contribute a great deal more to the problem than a few people with a high risk and so, in conclusion, I think the main point of the epidemiological message is really this: atherosclerosis is first and foremost a problem not just for a few individuals with very high risk but for the whole community. And we must look at the whole distribution of risk factors, particularly

blood pressure and blood cholesterol, and not just at the clinically interesting but few individuals who lie at the extreme.

**<End credits>**