Arterial Disease – Can We Improve Its Prediction?

The Scientific Basis of Medicine

Ultv

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<Opening titles>

<Meade to camera>

I'm going to talk about attempts to improve the prediction of arterial disease. In fact, I'm going to be speaking exclusively about ischaemic heart disease, but the principles that I shall be bringing forward are equally applicable to cerebrovascular disease or peripheral vascular disease.

Well now, why should we want to improve the prediction of arterial disease – ischaemic heart disease? Some people, including doctors, say that this isn't necessary. Myocardial infarction is a good way to die; we can't do much about it anyway at the moment, so why bother? This seems, to me, to be a plan for inaction and an argument that's not likely to cut much ice with the families of people who've died in their forties, fifties or sixties of coronary disease. I mention it, however, simply to get it out of the way. And as I hope to show, I think that it may be that we

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won't be able to produce really effective and acceptable preventive measures without indeed being able to improve the prediction of those who are at very high risk of this disease.

There are two reasons really why it's worthwhile trying to think about an improvement in the prediction of an individual's chance of getting ischaemic heart disease. First of all, an improvement in ability to predict, by whatever means, might lead to better motivation in those who are at very high risk to take up the kind of changes in lifestyle or to take long-term medical treatment if this is what they're recommended to do. And an improvement in prediction would also lessen the interference that we might make with those who are at very low risk and who really don't need to take any particular precautions. An advance of this sort, an advance in purely statistical terms, would be worthwhile even if we really didn't understand the mechanism by which it had been produced. For example, if we could predict the onset of coronary disease by the colour of a person's eyes, this would be an advance in itself, even though we wouldn't have any idea why eye colour should be related to later chances of the disease.

A second reason though for trying to improve our predictive capacity is that, depending on the variables we measure, we may get new information about causes, mechanisms and the pathogenesis of coronary disease which may indicate new preventive measures, for example – studies on water composition, trace elements, may indicate mechanisms in the development of ischaemic heart disease which suggest that modifications in domestic water supplies were indicated. Some people already believe this is so.

In what I'm going to be saying in the next few minutes, it's the process of thrombosis and measures based on the haemostatic system, where we're thinking about thrombus formation and also thrombus dissolution, that I have in mind as the mechanism that may be going to tell us more about the individual risks of coronary disease, and on which we might base preventive measures.

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Now if we had a perfect test for the prediction of coronary disease, we could represent the situation like this.

<Meade refers to diagram displayed beside him, using indicator stick, and then narrates over a series of diagrams>

This rectangle represents a hundred middle-aged men. This line here <*indicating x-axis*> represents the incidence; the height of this line above the base line represents the incidence in, let us say, a ten-year follow-up period of ischaemic heart disease in these one hundred people.

Now we can subdivide these hundred people according to some kind of predictor, some kind of test, which will distinguish those who are at very high risk, that's the people to the left of this vertical line here, from those who are at low risk, that's the people to the right of this vertical line here. And in this situation, all the people who are at high risk, 100% of them, develop ischaemic heart disease during our ten-year follow-up period. None of the people who are at low risk develop the disease. This test, this ideal or perfect test, is in fact very sensitive; all those who are at high risk, 100% of those at high risk, develop the disease, none of those at low risk develop the disease.

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<*Next diagram*> Now the situation, as it actually exists at the moment, is like this: here again we have our 100 men. In this case, we define high risk as a high level of blood pressure, or a high level of blood cholesterol, or both according to cut-off points which are now fairly generally agreed for these two variables here <*indicates BP and cholesterol*>, and we see that using these, about 42% of our population are said to be at risk of the disease because they have high values of one or other or both of these. But in this case, only 22% of those who are at high risk actually develop the disease during our ten-year follow-up period. And 7% of those who are at low risk, to the right of this line here, they also develop the disease. Now it's the relationship between this 22% and the 7% here or about 3 to 1 which is used to

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express the relative risk of developing coronary disease amongst those men who are said to be at high risk, but you can see that within the group of men who are said to be at high risk, only about a quarter actually develop the disease during our ten-year follow-up period. Three quarters of the men, the people represented by this green rectangle here, do not develop the disease. In other words, this combination <*indicates BP and cholestero*l> of tests here has a rather poor sensitivity.

Now if we were to reduce the follow-up period from ten years to five years in order to try and encourage a greater sense of immediacy or urgency, both in doctors and in members of the public who may be concerned about the prevention of the disease in themselves, then, in fact, this figure would go down and only about one in six or seven of those at high risk would actually develop the disease during the five-year follow-up period.

Now one approach to try to improve this situation <*next diagram*> is to measure multiple risk factors, instead of just concentrating on cholesterol and blood pressure; we can also measure cigarette smoking, early ECG changes, obesity and so on. And in this situation, we do get better sensitivity. Now 44% of those who are said to be at high risk actually develop the disease. 44% represented by this blue line here out of all those said to be at high risk. But this 44% occurs in really a very small proportion of the total population, only about 3%, maybe it's 5%, but generally not very many and certainly, I think, much less than the man in the street is often led to believe, actually are at high risk in these terms. And so we're really only being more precise about a small proportion of people and about a small proportion of the disease as a whole, because the disease as a whole is represented by that little blue rectangle there, and also by the blue part here amongst those who are said to be at low risk.

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<Meade to camera>

Now I've oversimplified a very complicated subject and it's certainly true that errors in the measurement of blood cholesterol and of blood pressure and of other variables,

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and indeed difficulties in the accurate diagnosis of the disease itself, probably mean that the true picture is not quite as gloomy as I've painted it so far. But, nevertheless, I think there is a need to improve our predictive capability. How should we go about this?

Well, first of all, I think we have to consider much more carefully than perhaps we have hitherto that the relationship between what I'll call the conventional risk factors – high blood pressure, cigarette smoking, high cholesterol values and so on – on the one hand, and the pathological and clinical manifestations of ischaemic heart disease on the other. Presumably variables such as high cholesterol levels and high blood pressures, cigarette smoking, obesity, lack of exercise lead to the chronic pathology underlying clinical ischaemic heart disease, namely atheroma. And it's true that virtually all those who develop clinical coronary disease, ischaemic heart disease, do have advanced atheroma. But it's not true that all those with advanced atheroma develop clinical ischaemic heart disease. And so the question is – is there some more rapid process responsible for the clinical onset of some of the manifestations of coronary disease at least, for example myocardial infarction or sudden death? If so, a thrombus formation is an obvious possibility. I'm assuming here incidentally that a thrombosis causes a myocardial infarct and not the other way round. There is controversy about this but I think the overwhelming weight of evidence suggests the former, namely that the thrombus causes the infarct and not vice versa.

<Meade narrates over diagram, using indicator stick>

We can summarise the situation like this: here are four men, all of whom have atheroma, but only one of them actually develops clinical heart disease. Here he is, here. And the question is what distinguishes him from these other three people here? And our hypothesis is that it is the formation of a thrombus. Now if thrombosis is also one of the causes of atheroma, which it is according to those who believe in the encrustation hypothesis for atheroma, then this is added reason for studying the thrombotic process. The other process, of course, is the lipid infiltration theory, and

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this is also likely to occur; these situations are very rarely either or, they're probably both involved.

<Meade to camera>

Now there's nothing very new about this, of course, except that so far there has been no direct epidemiological study of the variables in the haemostatic system which may be involved. And this is what we're trying to do in our prospective study which is being carried out in a number of industrial groups in North West London. It's very conventional in its design; people are recruited into the study, they are examined and then followed up. But, as I say, what we're trying to do is to measure aspects of the haemostatic system which may be involved in the production of thrombosis, of thrombi, as well as of conventional risk factors. And I can summarise it like this:

<Meade narrates over series of diagrams, using indicator stick>

I'm not giving you a detailed list of all the tests that we're doing, but we're testing platelet function, we're looking at clotting factor levels, these two systems being those that are involved in the production of thrombi, and we're also measuring fibrinolytic activity, the fibrinolytic system being one which many believe acts as a kind of counterbalance to this and dissolves thrombi as they tend to be formed by this system here *<indicates platelet function and clotting factor levels>*.

Now the results in a study of this sort come along in this sort of way *<next diagram>*. First of all, one has the opportunity of looking at cross associations between variables that one is interested in. One can look at the relationship between age and fibrinolytic activity or between the taking of oral contraceptives and factor VII levels and so on. Then we get the prevalence data: now these are data about people who have had the disease when they come into the study. There are two disadvantages though about prevalence data. First of all, it's not possible to deduce from these data, whether the disease causes the abnormal findings that one may come up with or whether it's the abnormal findings that cause the disease; there's a kind of chicken and egg situation.

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There's another rather special difficulty with prevalence data in the study of coronary disease and that is that almost by definition, prevalence data don't capture a very important segment of the disease – and that is those who die suddenly.

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We then will get the incidence data. These are data about people who were free of the disease when they were recruited into the study, but who then subsequently develop the disease. And the point here, of course, is that we do in these cases know the abnormal findings, if this is what they turn out to be, preceded the onset of the disease.

<Meade to camera, referring to chart beside him>

Well now, what I'm going to spend a few minutes talking about are these two types of data, mainly this one here <*indicates cross association*>. And I'm going to be looking at these two types of data with the background of the general question – are the results that are obtained so far those that would be expected if thrombosis were indeed involved in the onset of clinical ischaemic heart disease?

Well now, we can ask one simple but very important question – do these variables alter with age in the way that one might expect?

<Meade narrates over series of diagrams, using indicator stick>

Here we have the findings for fibrinogen, fibrinogen in milligrams percent up the vertical scale here, age along here <*x-axis*>. The findings for women in purple, the findings for men in white. These vertical lines are the 95% confidence intervals for the means in each age-specific group, and you can see that there is really a very considerable increase with age in fibrinogen in both; women and in men, it's much the same for the two sexes.

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<*Next diagram*> We have a look at the same sort of thing for fibrinolytic activity. Now we measure fibrinolytic activity as the reciprocal of the dilute blood clot lysis time in hours, the whole figure multiplied by a hundred, so that a high figure means good fibrinolytic activity, a low figure means poor fibrinolytic activity. Now we have a rather interesting difference here between the men and the women. In the case of the women of whom there are a smaller number in the study so far, there is, in fact, no significant change in fibrinolytic activity with age: it's about 30 at all ages. In the case of the men, however, there is a very significant decrease in fibrinolytic activity which is mainly between the age here of about 25 and the age of 55. By the age of 50, the decrease seems to have run out, and after that it's much the same at all ages in men. This may be due to some kind of survivor effect, the people with better fibrinolytic activity amongst the men having survived. But the important point is that there is this highly significant difference between the change in fibrinolytic activity with age, in men going down as they get older and no change at all in women.

<*Next diagram*> We can have a look, for example, also at the relationship between fibrinolytic activity and smoking. Now the results in many of the captions that I'm going to show you now have been adjusted to the age of 40 for the reasons that I've just indicated in the previous two captions, and that is that there are these age changes. Here we have the fibrinolytic activity in smokers which is significantly less than the fibrinolytic activity in the non-smokers. There have been hints of this sort of thing in previous publications, but the numbers that we're able to have in our study and base our findings on, really begin to show that this kind of difference exists and may be rather an important one.

<*Next diagram*> Now one of the problems that we want to bear in mind all the time is the extent to which all the conventional risk factors, things like blood pressure and cholesterol, are either dependent or independent of the newer variables that we're measuring, the haemostatic variables. And here, I've shown the relationship between fibrinolytic activity and blood pressure in men and women. And you can see that, by and large, there is no relationship between fibrinolytic activity and blood pressure except in the case of diastolic blood pressure in the men where there is a significant

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negative correlation, that is the lower the fibrinolytic activity, the higher the blood pressure.

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We can have a look <*next diagram*> at fibrinolytic activity and its relationship with lipids. And here you can see that there are significant negative correlations in the men between fibrinolytic activity on the one hand and both cholesterol and triglycerides, in the case of the women, there is only a relationship for triglycerides.

<*Next diagram*> We can have a look also at the relationship between fibrinolytic activity and a measure of obesity – supra iliac skin fold thickness. And here you can see that there is, in fact, a negative significant association in both the men and the women between fibrinolytic activity and supra iliac skin fold thickness.

Now, in all these three cases, we have to allow for the fact that these correlations, as shown here, are almost certainly lower than the true associations between these variables or the other pairs of variables that I've shown you, because of measurement areas and biological variability in both the measurement of this variable <*indicates fibrinolytic activity*> and this variable here < *indicates supra iliac skin fold thickness*>. And it may be that we can't really say whether the haemostatic system has, exemplified here by fibrinolytic activity and the other variables, are dependent or independent of one another until we get the incidence data.

Well now, we can also look, for example, at the relationship between fibrinolytic activity and clotting factors <*next diagram*>, cholesterol and blood pressure and so on, and the use of the oral contraceptive pill. And what we see here is that women who are on the pill have high levels of factor VII compared with those who are not on the pill; they have high fibrinogen levels, their cholesterol levels are higher than those not on the pill, and their blood pressures are also higher than those not on the pill. All these are changes which one might expect to be associated with an increased risk of thromboembolic episodes, which we know, of course, that women who are on the pill do run. But at the same time, their fibrinolytic activity is considerably and certainly

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significantly greater than it is in the women who are not on the pill. And it's interesting to speculate, I think it is a bit speculative at the moment, that the pill, at the same time as it produces these changes which are perhaps not very welcome ones, does produce this sort of change <*indicates fibrinolytic activity*> as a kind of counterbalance to this < *indicates fibrinogen*> and it may be that it's women who can't increase their fibrinolytic activity in the face of this sort of change, who do run risks of clinical thromboembolic episodes later on.

<*To camera*> Most of these findings here have already been reported, but the interesting thing in a number of studies now is the measurement of fibrinolytic activity and these other things in the same women at the same time.

<*Next diagram*> With Professor Keane at Guy's Hospital and Dr Pike at King's College Hospital, we've been carrying out our haemostatic tests in diabetic patients under their care, and here you can see the difference in factor VIII in diabetics and non-diabetics. Here are the male people studied; here are the females studied. These are the diabetic patients and these are the people in our own study for comparison with the diabetic patient. Here are the numbers in each group, and you can see that the factor VIII levels in the diabetic patients are very much higher than they are in those without diabetes. This is true for both the men and also the women.

<*Next diagram*> Here are the findings for fibrinogen and again you can see higher levels in the diabetics than in the non-diabetics, again for the men and for the women. <*Next diagram*> And here are the findings for fibrinolytic activity, and as one might by now rather expect, fibrinolytic activity is significantly poorer in the diabetics than in the non-diabetics. And again this is true for the women as well as for the men.

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<*To camera*> We're able to study blacks and whites in our prospective study. The blacks in our study being first generation immigrants from the West Indies. Now I haven't given all the results in detail, but they are summarised here <*next diagram*>. Here are the men, here are the women: the whites and the blacks amongst the men,

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the whites and the blacks amongst the women. And within each sex, plus means that the system is more active in the group shown by comparison with the people of the same sex of the other colour. So that, for example, the white men are more 'coagulable' if I can use this term to include a number of changes such as high cholesterol levels, high factor VII levels and so on than the black men are. As far as the women are concerned, the same is true: the white women seem to be more 'coagulable' than the black women.

When one looks at fibrinolytic activity, we find that the white men actually have poorer fibrinolytic activity than the black men. But, we find that the white women have better fibrinolytic activity than the black women. And it's interesting to note that the only group who are both 'coagulable' and have poor fibrinolytic activity, by comparison with those of the same sex but of the different colour, are the white men here – both 'coagulable' and have rather poor fibrinolytic activity comparatively speaking, and, of course, this is the group that it is at very high risk of coronary disease.

Well now, this is perhaps a little bit speculative to suggest that this change here <*indicates term 'coagulable'*> is responsible for the onset of the disease, but it fits in with the general pattern that seems to be emerging.

Now finally, here are our prevalence results or some very early prevalence results. <*Next diagram*> Remember that prevalence data are difficult to interpret because of the 'chicken and egg' situation. We don't know whether it's the changes that precede the disease or whether it's the disease that causes the changes. However, here we have the results in the first 10 men into the study who had had a definite myocardial infarction at some time before they came into the study.

Here are the variables that I want to mention. These are the values for these 10 men who have had myocardial infarcts. These are the values, the mean values in men over 40 for comparison, and you can see that the factor VII levels in those who have already had a myocardial infarct are higher than the levels in those who have not. And the same is true for factor VIII, where there really is quite a big difference. There

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is a very big difference in fibrinogen levels, and there is also an increase in platelet adhesiveness in these men compared with those who have not had the disease. And at the same time, and again as we're now really beginning to expect with results of this sort, those who have had myocardial infarcts in the past have significantly and really quite appreciably poorer fibrinolytic activity than those who haven't .

<Meade to camera>

So, I think the results we've got so far do fit in with the possibility that the direct study of thrombosis will improve our ability to predict the onset of arterial disease. Those I've indicated, only incidence data, where we can compare the value in prediction of the thrombotic tests and of the conventional risk factors will really tell us about this. I should here add a warning about the interpretation even of incidence data, simply because an abnormal finding precedes the onset of the disease, it doesn't mean to say that that abnormal finding causes the disease. Association is not causation, and incidence data of the sort that we will eventually have, have to be interpreted cautiously, and they have to be interpreted alongside data from other sources, laboratory experiments and so on.

Now, it is conceivable that the picture of thrombosis which I've tried to indicate to you is due to non-specific changes in the haemostatic system in clotting factor levels, platelet activity, fibrinolytic activity, other sort that occur, for example in pregnancy or after surgery. But, I think it's really rather difficult to accommodate all the findings – findings in the diabetics, the blacks and whites, findings in relation to age, in oral contraceptive use – in an explanation of this sort.

<End credits>

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