Ulster Medical Society

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'*Blood Pressure: Relevance in 2010*'
Professor Gordon T McInnes
Western Infirmary Glasgow

Professor Brew Atkinson:

Good evening, ladies and gentlemen, and welcome to the meeting. Our speaker tonight is Professor Gordon McInnes, whom I've known for a long time. When I was working in Glasgow during the middle of that time, Gordon came back up to Glasgow. He's from Glasgow originally, and he came back from the Hammersmith to Glasgow, and he's had a very distinguished career in Glasgow, mainly interested in blood pressure, clinical pharmacology and vascular risk. And you'll notice I'm being very careful talking about 'blood pressure', and I think he's probably going to talk along the Glasgow theme that's been there for a long time, that some people have got extremes of high blood pressure, and there really is no dividing point where hypertension is. So at least I think we're going to be agreeing on that tonight, and maybe a little bit more. So it's a great pleasure for us to have Gordon here tonight. He's a professor of clinical pharmacology in the division of cardiovascular and medical science in the University of Glasgow, and he's a consultant physician in the Western Infirmary in Glasgow. He's just finished a very successful stint as president of the British Hypertension Society, and he's very involved in vascular risk assessment, and those of you who are family doctors, also in hospital practice, know that these are very important to us, as we gauge where patients are in terms of risk, and he's going to be telling us about that tonight. Among other things as well, Gordon is the classic non-partisan Glaswegian. He's a supporter of the Jags. Now, the question is, does anybody here, apart from me and Gordon, know who the Jags are?

Audience member:

Partick Thistle.

Professor Atkinson:

Partick Thistle!—but I did hear it once from Dennis Johnson, who has had too many dinners with Gordon over the years, and that's how I know about Partick Thistle, so it's a great pleasure to have Gordon, and I know it's going to be a very informative and probably a very interesting talk as well, so you're very welcome to the Ulster Medical Society.

Professor McInnes:

Thank you. Thanks very much, Professor Atkinson, Brew, it's been many years since we worked together in Glasgow, and it's a great pleasure for me to be here tonight, and it's a great pleasure to see so many of my old friends in the audience who will recognise the slides right away!—because nothing changes very much. Partick Thistle?—sometimes known, of course, as 'Partick Thistle—nil', but doing well this year, so we're optimistic that maybe this will be one of their better seasons.

So we're going to talk a bit about blood pressure tonight, and it's a sort of rambling account where we'll see where we get to. You'll see I took my watch off, because I've been told how long I have to speak for, so hopefully we'll get through it all. So the title is, "Blood Pressure: Relevance in 2010", so relevance next year, and of course I come from Glasgow, and Glasgow is, as you may know, the city of the damned! It's the city of the damned because of its very high rate of death from myocardial infarction. Those of you with sharp eyesight will see that it's not just Glasgow, but if you read the text there, it's Belfast as well, so it's a very appropriate slide for this audience, it makes us feel close together! We are terrible, we are top of the league when it comes to myocardial infarction, and I know how Belfast is doing now. You'll see this is a few years ago, but Glasgow continues to shine, and it tops the death list. It's always number one in the UK, and it's always worst for life expectancy, and living in Glasgow is said to be equivalent to involuntary euthanasia. So there's a lot of it about, we die a lot in Glasgow and you die a lot in Belfast, and we die from vascular disease, but vascular disease is not limited to the Celtic fringe, because if you look at this picture here, none of these guys coming from either Glasgow or Belfast, all dying from vascular disease, and in the case of Roosevelt, Stalin and Churchill, dying from strokes, from cerebral vascular disease, but they might equally have died of other types of vascular disease. This is quite a good clinical teaching slide, because in the middle of this picture, Franklin D Roosevelt. When this picture was taken in the Yalta Conference in 1944, he had malignant hypertension, and he died a few weeks later from a cerebral haemorrhage, so this is what someone with untreated malignant hypertension looks like. So they had vascular disease, and they had vascular disease because of high blood pressure, because of hypertension, which was uncontrolled. There was no treatment for high blood pressure at that time, so that's where we're coming from. We've learnt a lot about high blood pressure over the intervening years, and one of the things we've learnt is indeed what our Chairman told us, is that hypertension is an artificial construct. This is the relationship between blood pressure and the risk of dying from ischaemic heart disease—lots of important information on this slide. The left-hand panel is systolic blood pressure, the right-hand panel is diastolic blood pressure, and the first thing you see is that it doesn't matter. You hear people saying, oh, systolic blood pressure is much more important than diastolic blood pressure—it doesn't matter, they both have roughly the same predictive power in telling you whether or not someone's going to have a vascular event. A continuous relationship—no threshold—so

high blood pressure, hypertension, diabetes, hypercholesterol, these are all conditions made up by doctors, because doctors can't count beyond two, and they have to have normal or abnormal. In fact, as our chairman said, it's a continuous relationship, and that's what we should be thinking of when we're dealing with blood pressure-related problems. It's here in all ages, it doesn't matter whether you're young, or relatively young, or old—the same sort of relationship exists, so there's no excuse about not treating older people, at least from an epidemiological perspective, and this is good epidemiology, this is the pooling project, almost one million people, mainly from North America and Europe, so it's a sort of Caucasian-type population, but there'll be a fair number of black Americans in this as well, and so the relationship is pretty powerful, pretty strong, right down to 115 mm systolic down to 75 mm diastolic, a continuous relationship, and probably beyond that, but there's just not enough people with really low levels of blood pressure to produce reliable data.

You'll notice that the vertical axis is not a linear scale, it's a doubling or logarithmic scale, so this is a log-linear relationship, and those of you who are general practitioners might think, why the hell's he telling us that?—that sounds very technical, but in fact it's very important, because what that tells us is that we would anticipate any change in blood pressure in millimetres of mercury, say 5 mm of mercury, should have the same proportional impact on outcome, whether or not you start with a high blood pressure or low blood pressure, so that's the relationship between blood pressure and the risk of dying from a stroke, and if we look at myocardial infarction, it's exactly the same—slopes are slightly different, but otherwise exactly the same, and it's the same for all cardiovascular complications, this continuous relationship with blood pressure. So at last year's meeting of the British Hypertension Society, we spent a huge amount of money in bringing one of the world's leading authorities to Cambridge to address the Society, the Sir George Pickering lecture, and what did he tell us?—he said, you could change the name of the society, because hypertension doesn't exist. There's no justification for the term hypertension, and I think that is probably correct, although we have resisted the change in the name of the Society, and we probably will do for the foreseeable future, so that's really why the title is the way it is. We're now not talking so much about hypertension, but blood pressure.

We know that lowering blood pressure, while we know that increasing blood pressure is bad for you, we also know that lowering blood pressure is a good thing to do, and this is, sorry, before we go onto that, this is just to show you how important blood pressure is, and we're now talking not about hypertension, but sub-optimal blood pressure, anything above 115 systolic over about 75 diastolic, and you see that it's responsible each year for more deaths than anything else. It is about seven million deaths per year are attributable to high blood pressure, and the small print tells us a lot here down the bottom left-hand corner, so that represents about 13% of all deaths. 62% of stroke events, and 49% ischaemic heart disease events can be attributed to sub-optimal blood pressure control, so this is an important public health problem, and as I said a moment ago, we know that reducing blood pressure is a good thing to do, and this is the evidence base for that. Up until the mid-1990s, it was ethical to do placebo-controlled trials, trials in which you gave no active therapy to people with high blood pressure, to see the effects of treatment. Beyond that, it became increasingly difficult, from an ethical perspective, to do trials like that, so really the evidence base closed in the mid-1990s, when this very good meta-analysis was done.

As you'll see, as we go on tonight, the meta-analyses, some of them are good and some of them are not so good, but this is a good meta-analysis, this is looking at the 17 uncompounded prospective randomised trials of blood pressure lowering due to drug therapy, that was available at that time, and you know the results in general terms—stroke reduced by about 40%, coronary heart disease by 15—20%, all vascular mortality reduced by 20—25%, and since non-vascular mortality, that's the columns at the right, are not affected, all-cause mortality is reduced by around 12, 13%. Not shown on this slide, but all of these differences are highly statistically significant. Now, our chatting before the meeting about the need for long-term studies, and many of you will look at these and think, this is long-term data, but in fact it's not, because if you look at the figures in parentheses, you'll see we're looking here at studies which had an average duration of five years. Now, in clinical trials, people don't do the decent thing and wait until the last day of the trial to drop dead. They start having events on the first day of the trial, and events are evenly spaced across the trial, so this is, the average time to an event in these studies is two-and-a-half years, so what this is showing you is the short-term effects of blood pressure lowering within two or three years of initiating therapy, and you'll see also in parentheses that the change in blood pressure was very modest, so very small reductions in blood pressure, for hardly any time at all, having big proportional impacts on events, and these trials were conducted in an era when we didn't have the drugs we have nowadays. They were mainly using thiazide-type diuretics, at doses that Dennis would get very upset about. I think in these trials, the usual dose of bendroflumethiazide equivalent would be 10 mg, so this is using industrial doses of diuretics without any consideration of metabolic consequences, and you see these huge beneficial effects.

So the evidence base for reducing blood pressure is good. There was one gap which was filled only very recently, and that was what should we do in the very elderly? The epidemiology said yes, these people will benefit, but many of us were a bit sceptical about

that, but now the HYVET study has published, and showed quite clearly beneficial effects across the board. As with many of these trials, the primary end point didn't quite make its statistical significance, but the study was stopped prematurely because there was a clear reduction of mortality in this elderly group. The design of this slide is typical of what you might see later, the vertical line is the line of identity. Each of these points is a point estimate for a relative risk reduction, and the horizontal lines are 95% confidence intervals, and I think it's always reassuring when everything goes in the same direction, so there's clearly evidence of benefit, so people over the age of 80, we have no excuse for not treating them now. There was a vogue for stopping treatment when people reached the age of 80. If anything, that's what this study showed most clearly, the wisdom of continuing treatment, because two-thirds of the people on this trial had already been treated before they went into the study, so it was a placebo-controlled trial, so essentially you could say that it was a study of stopping treatment in very old people, and clearly that was not a good thing to do, because those that continued treatment did better, but I'm assured that in the one-third who had never been treated, the results were just the same. So I think we have pretty good evidence now that treatment should extend into older age, and it should probably be limited not by chronological age, but by biological age, because these people in this trial were the free-range elderly, they were fit and well and out and about.

So lowering blood pressure is clearly something that's worth doing. How low should we go? Well, not all that many years ago, in fact before this study was published, this is data from the MRC blood pressure unit in Glasgow, and the Glasgow blood pressure clinic, people believed that it was the blood pressure that you arrived with when you were diagnosed which determined what was going to happen to you, but this study, this observational study, suggested that was not the case, because on the left-hand panel, we're looking at outcome mortality in relation to the blood pressure that these people started with, their initial diastolic blood pressure, and you can see that there is a slight increase with age, but different levels of blood pressure didn't really discriminate between individuals in terms of outcome.

If you look at the right-hand panel, this is the achieved blood pressure, and now you see a clear separation of the lines. So what this is telling us is, it's not the starting blood pressure that matters, but what you achieve during treatment that matters. So I think that's now been accepted that it's the on-treatment blood pressure which really determines how someone is going to do after you start treatment. As practice has changed in this country, and very few people now do not have high blood pressure picked up at an early stage, then I think this is increasingly relevant. But how low should we go? What does the evidence tell us is the best level of blood pressure? Well, there's been a lot of effort expended on this, and we don't yet have a good understanding. The biggest trial, and probably the best trial to date, was the Hypertension Optimal Treatment Study, which looked at different targets for diastolic blood pressure. This was a study that was invented before systolic hypertension came along, so they had diastolic targets in 90 or less, 85 or less or 80 or less. People were randomised to get to these targets, and the study just did not produce enough events, because I think treatment was so good in all of the groups, that there were very few events, so they kept on being extended, kept on being extended. Eventually they gave up, and they looked retrospectively at the data, and this is what they found. They found that the best outcomes came at a systolic blood pressure between 130 and 140, and a diastolic between 80 and 85, so you can see how this field trial has been hugely influential in determining what we do in the management of high blood pressure.

Now, as I say, there's been a lot of work in this area. Not many of the studies have been as well-designed as that study, but the results generally suggest that more intensive blood pressure lowering is better than less intensive blood pressure lowering. This is another meta-analysis from the Blood Pressure Lowering Treatment Trialists' Collaboration, and you see that for stroke and for major cardiovascular events, there's a significant advantage of more intensive blood pressure lowering, and there's a trend across the board, but it's not quite as striking as you might hope it would be, But remember that, in this analysis, the difference in blood pressure between intensive and less intensive is only 4 over 2 millimetres of mercury, so it wasn't a huge difference, but it suggests that the lower the better.

Now, some of you will be older chaps, will remember the old J-shaped curve, and think, reducing blood pressure, that might not always be a good thing to do. We might kill people by reducing blood pressure. They've already got occluded coronary arteries, and I would agree that there must be a J-shaped or U-shaped relationship between the blood pressure and risk of dying, for the simple reason that if your blood pressure is zero, you've got a 100% chance of being dead, as you can see from this slide. What we don't know is where this point of inflection lies, the level of blood pressure associated with the lowest level of risk, and there's lots of controversy in the literature about that at the moment, and some of the more silly guidelines, I think, are going to change on the basis of, I believe, inappropriate analysis of outcome data.

So this is a hot topic, but the bottom line is, we don't really know what the best level of blood pressure is, but I would suggest to you that it's probably, although I don't know, but it's probably below any level that we ever achieve in clinical practice, unless we achieve it very rapidly, and that might be bad for some people. But I think we now know that there are some people in whom there is great benefit from rig-

orous control of blood pressure, and in the HOT Study of the group which got the clearest benefit were those with Type 2 diabetes. In the HOT Study, which had a total of nearly 20,000 patients in it, there were 1,501 who had Type 2 diabetes at randomisation, and this is what happened in these people, the step-wide reduction in risk with more rigorous blood pressure control, and if you look at this carefully, you'll see that the reduction in risk between 90 or less and 80 or less was 51%, a 50% reduction in risk, by going from good control to very good control. And it was actually more impressive than that, because remember I suggested to you that it's their achieved blood pressure that matters. The achieved blood pressure in this arm here, 90 or less, was 85 millimetres of mercury, and in the right-hand column, it was 81 millimetres of mercury, so 4 millimetres of mercury, a difference that you couldn't reliably measure in your office, in population terms, in a high-risk population, halves the risk of cardiovascular outcome. Now, that may be an exaggeration, but I think the message is nonetheless clear, and that's why we recommend that you try very hard to control blood pressure rigorously in people with diabetes, and there were other populations also where we should try to reduce blood pressure very carefully. One group that we now know should have their blood pressure controlled carefully are people who have survived from strokes, and the best data from that comes from the PROGRESS study, where a modest reduction, 12 over 5 millimetres of mercury, reduced the risk of subsequent stroke, and indeed other vascular events, by a considerable amount, and you see that it didn't matter whether the people had this arbitrary definition of hypertension, or whether they had normotension—they all got benefit. Now, I showed you an example of one American president who died from a stroke. In fact, eleven American presidents have died from a stroke, the most recent of which was Richard Nixon, so the worrying thing is that tighter control of blood pressure might yet save George Bush, which might not be a great thing to do!

So, tight control in patients with stroke, I work in the stroke unit as well as in general medicine, and anyone who's had an ischaemic stroke already, I mean it doesn't matter what kind of stroke they've had, I will aim to send them out on more intensive blood pressure lowering treatment than they had when they arrived, even if their blood pressure is reasonably normal in the stroke unit. So what I will do is, if they're on no treatments, I'll add in a single drug; if they're on treatment already, I'll add in another drug, and I think that is evidence-based practice. Another group where there's a clear benefit from reducing blood pressure is people with renal impairment. I don't need to tell you that, but perhaps the most important thing you can do in someone with renal impairment, to preserve what renal function they have, is to rigorously control their blood pressure, perhaps to really very low levels. This slide's suggesting levels way below the current targets would be beneficial, down to a mean arterial pressure of well under 100. So undoubtedly there are groups in whom we should be very rigorous, but the evidence overall for rigorous control is perhaps not as good as we would like it to be. At the end of the day, and this is another meta-analysis, again the Blood Pressure Lowering Treatment Trialists' Collaboration, it appears that it's blood pressure that matters, so if you look at trials which have looked at one drug against another, or one treatment against placebo, or more intensive therapy against less intensive therapy, you see very clearly this sort of relationship, that individual studies, plus they're around the regression line between blood pressure and change in outcome, here it's the change in stroke outcome, so in other words, it's blood pressure that matters. What you use to reduce blood pressure is much less important. It may have some influence, but it's the blood pressure lowering which matters, rather than how you get there, and perhaps surprisingly to some people, the same is true for coronary heart disease, so the two main vascular outcomes, it's the blood pressure which really matters in reducing risk. So I think we could sum up what we've learnt about anti-hypertensive drug trials in this slide: benefits, it doesn't matter what the level is to start with, you see benefits, the proportional benefits are constant across the blood pressure range. We see benefits in any age of patient, we see benefits if you treat systolic or diastolic hypertension, the benefits are there at all levels of risk, but the bigger the risk, the bigger the benefit is likely to be, and I think that is a reasonable summary of where we're at, and we'll come back to some more recent evidence which I think supports that later on, but in the meantime, let's look at those who argue that maybe it's the type of drug we use that matters, and the drugs which always come up as being suggested as having beneficial effects which go beyond blood pressure are the drugs that block the renin-angiotensin system, and particularly ACE inhibitors, and this is the study which caused all the trouble, this is the HOPE study. It wasn't a study in hypertension, but half the people in the HOPE study had hypertension, high blood pressure, which had been treated. About 40% had diabetes. All of them had evidence of cardiovascular disease, so it was a very high-risk population, and what they did was, they randomised them to placebo or to take ramipril in addition to whatever else they were taking, and they got this result.

Now, it didn't really surprise me very much, that ramipril was better than doing nothing at all in this group of patients, but it astonished the authors, because ramipril was such a useless anti-hypertensive agent, and only reduced blood pressure by 4 over 3 millimetres of mercury, and I remember Dennis writing a very good letter to the journals following the publication of this, in which he pointed out that, in this study, ramipril had effectively done less well than it even did in normal volunteers, was that right, Dennis? So for some reason or other, the blood pressure

effect was very modest, and that was taken as being the reason why this had to be something other than blood pressure. So the experts looked at the data carefully, so here we see one arm studying the HOPE data very carefully, get it under the microscope, and what does he see?—he says, wow, I see the magic of ramipril!—so we have the magic of ACE inhibitors, and they do something special which other blood pressure-lowering drugs don't do really.

Well, on the next slide, I'm going to try and persuade you that that's not necessarily true. I'm going to show you the HOPE data, and alongside it the EUROPA data, which was a copycat study using perindopril instead of ramipril, and then two studies that didn't use ACE inhibitors, but in a high-risk population, in diabetic populations, the HOT data you've seen already, and also the Syst-Eur diabetic population, and I've chosen them to get the risk up to the same sort of high level risk in the HOPE study, and this is what we found.

If we put them all side-by-side, the two ACE inhibitor studies and the two other studies, which happen to use calcium channel blockers as first-line therapy, but that doesn't matter; now you see that there's a bit of a difference in starting blood pressure, and the apologists for HOPE will say, well that's it, you see, they didn't have high blood pressure, but we know that hypertension's an artificial construct. We also know that the proportional reduction in risk doesn't matter, at the starting level of blood pressure, and it's important to know that. The cardiovascular risk reduction, you can see in all of these studies, 20% or so in the ACE inhibitor, 68% in Syst-Eur, and you've seen the 51% in the HOT study. Changes in blood pressure—none of these studies showed big changes in blood pressure, and the bottom line tells you the answer, that cardiovascular risk reduction per millimetre of change in blood pressure, and you can see it's not particularly impressive for the ACE inhibitors, so I think that there must be some doubt as to whether this study showed us the magic of ACE inhibitors, or whether it simply showed us that lowering blood pressure, remembering, as our chairman told us at the beginning, that hypertension doesn't exist and this is a continuous relationship, and you would expect these sort of changes, and there's further evidence in support of this from a very small sub-study within the HOPE study, and here you see the differences that were found in the clinic, 4 over 3, or 3 over 2 millimetres, whatever it was. When do you ambulatory blood pressure monitoring, the differences are much greater, and the other interesting thing in this study is, for reasons which I don't understand, they gave ramipril at night. If you look at the night-time blood pressure, now one of your colleagues, Harry Potter's auntie or granny, told me beforehand, it's night-time blood pressure that matters, and she might be right. We certainly have done an analysis from data from the ASCOT study suggesting that night-time blood pressure was very important—look at that, we looked at the night-time blood pressure differences, which you would expect with a short-acting drug like ramipril, given at night-time. So I would suggest to you that there is a considerable amount of doubt about whether or not ACE inhibitors have any beneficial effects which are beyond blood pressure, and perhaps the authors need to have a lesson on clinical trial methodology, because they're reading from a book of fairy tales here, which is where the HOPE study should have been published.

But I've also been involved in fairy tales, because another fairy tale that reached the Daily Mail a few years later was the fairy tale of the ASCOT study—remember the ASCOT study? You did the ASCOT study in Belfast, didn't you?—and I was an author in this wonderful study, and it was a belter—look at this. Again we've got the line of identity, a dotted line here, we're looking at hazard ratios, point estimates, 95% confidence intervals, contemporary treatment, that's amlodipine with perindopril, against conventional, which is beta-blockers and diuretics, and you see everything's going the right way. We'll just ignore the failure of the primary end point to reach statistical significance, we'll not worry about that, but if we just look at the overall data, the picture is of benefit; so in other words, amlodipine is almost as magical as ramipril But again I think we have to look at blood pressure, and here the blood pressure does not look impressive, because you see, what they've done here is, they've presented this figure to make it look as though there's no difference in blood pressure between the treatments at all. In actual fact, the differences in blood pressure here are almost exactly the same as the differences that we saw between ramipril and placebo in the HOPE study. Early on, differences of 5 or 6 millimetres of mercury systolic in favour of amlodipine, and remember that events occur early in trials, they don't occur at the end of the trial, they occur throughout the trial, so the amlodipine arm had a big benefit in terms of blood pressure control, which might explain the results. Now, you don't need to take my word for it—there is a very, very intelligent man, a small man but with a brain the size of a minor planet, who's a Belgian, so he's not the most exciting man you'll ever meet, but by Jove, he knows his numbers, and he predicted, he said, I will tell you what the results of the ASCOT study will be, depending on the differences in blood pressure between the treatment arms. You don't need to do the study, I'll tell you what the results will be, and here is what he found. Here's Jan Staessen's analysis. His predicted beneficial effects on the left for a 3 millimetre difference in blood pressure, systolic blood pressure, and what was observed for the difference which was 2.7 millimetres of mercury, and you see it's exactly what he predicted for blood pressure differences. So to misquote a famous American president, it's the blood pressure, stupid—it's nothing to do with amlodipine, it's nothing to do with ramipril, it's the blood pressure that gives you the benefit. So don't be taken in by these city

slickers who try and tell you all this stuff about new drugs being better than old drugs. You have to be very, very sceptical about what they're telling you. This study, a terrible slide, but this study, I think, has again come back to this message quite recently, this was in the BMJ earlier this year, this is Law *et al*, a big, big meta-analysis of lots and lots of studies, and basically what they're showing is that for a reduction in blood pressure, in this case 10 over 5 millimetres of mercury, you see benefits across the board, regardless of whether the individual's had a previous vascular event, regardless of whether he's had a heart attack, regardless of whether he's had a stroke, the same benefit is seen for the same proportional reduction, for a given absolute reduction in blood pressure. This sort of confirms what we expected from the epidemiology. Out of this has come a number of interesting discussion points, shall we say. First of all, they suggested that, based on this analysis, it didn't matter what drug, which is what I've been telling you, there was no material pleiotropic effects of drugs, and benefits were regardless. It didn't matter what sort of patient you were dealing with, it didn't matter what the level of blood pressure was, everybody was going to get the same proportional benefit. But of course, as you heard, I was till recently present at the British Hypertension Society, and the British Hypertension Society has said, beta-blockers might not be too good for you, so how does that fit in with this analysis which suggests it does not matter what you give them?—and of course, the beta-blockers story boils down to this meta-analysis, and similar meta-analyses. Now, I told you at the beginning, meta-analyses can be good, and they can be bad, and they can be ugly, and this is an ugly meta-analysis. It doesn't matter where it's published—look at that, it's published in some journal which I think has got an impact factor, but don't just be persuaded because it's in a so-called good journal, that it's believable. This is a very poor meta-analysis. There's lots of technical problems with it, but the main thing I would point out to you is that this analysis which suggests that other drugs are better than beta-blockers in terms of stroke prevention, is driven by this study here, and that's the ASCOT study. And it's also driven to a certain extent by the LIFE study, and it may be that angiotensin receptor blockers are a bit better than other drugs in stroke prevention, so that might be correct, but this is driven largely by the results of the ASCOT study, and Law *et al* recognise this, because they said, the lesser effect of beta-blockers in stroke prevention is entirely dependent on trials of beta-blockers versus calcium channel blockers, which are, calcium channel blockers have greater preventative effects than all other classes, so there's a minor, it works out at about 8%, hardly worth talking about, advantage for calcium channel blockers and stroke prevention. Generally when we set up a big clinical trial, the first question you have to ask is, how big a difference is it important for us to detect?—and it's usually 10 to 15%, so 8% is not worth knowing about, but there is that advantage which makes the calcium channel blockers a wee bit better than beta-blockers, and so it was not because beta-blockers were bad, but because calcium channel blockers weren't good, so that analysis was a bit dodgy, but is that the only reason?—and sadly it isn't the only reason. Of course, there's also this that we have to take into consideration, and this is new onset diabetes. This is probably, when you see the word network in front of a meta-analysis, generally speaking throw it in the bin, but this is actually quite a good network meta-analysis, and this has been re-analysed in a Bayesian method, and don't ask me to talk about the Reverend Bayes and his statistical ... Dennis will tell you about that later, but basically what this is telling us is that overall, diuretics are most likely to cause diabetes. Beta-blockers are also likely to cause diabetes. Calcium channel blockers are neutral on it, and drugs that block the angiotensin system might be having favourable effects. And so that was really the reason, because when NICE and the British Hypertension Society looked at the beta-blocker data, it didn't look good for beta-blockers, but it's when you put in the cost of having diabetes, they just wipe them off the map.

They wanted to write diuretics off as well, but we said no, Dennis would never speak to us again, so we managed to keep diuretics in the picture, but beta-blockers went, I'm afraid, and it didn't go just because of these dreadful meta-analyses, they went because of the diabetes, but does it matter?, and this is where I'm going to ask Brew to tell me whether it matters. We looked at the VALUE study, I was also involved in the VALUE study, and we looked at the VALUE study in terms of diabetes, and what we're showing you in this slide is not one drug and another drug, but all of the patients in the VALUE study, and we divided them into three groups, depending on how likely they were to develop diabetes. Don't worry about any of that, that doesn't matter, but that's how the figure was constructed.

What you need to look at is the chi-squared value, which is this column here, and this tells you the power of the association, and you can see that by far and away the most powerful predictor whether somebody developed diabetes was what their blood sugar was to start with, and the next most important was their weight, so my contention is, and Brew could correct me if I'm wrong here, and he may have a different view, is that there's arbitrary line in the sand beyond which you'll get diabetes, and here you don't have diabetes, so I can be right up at the line there, and I'm fine, I'm healthy, I've got normal blood sugar, but they give me a beta-blocker and I go over the line with that, and suddenly, you've got diabetes, it's a disaster. So this new onset diabetes business, I think we still don't know what it means. It may simply be identifying people who are at a very high risk of cardiovascular disease, so it might be a sort of metabolic stress test, and so it might be a good thing to give

them a beta-blocker, and if they get diabetes, then they are people you really need to work hard on. But we don't actually know the answers to that, but that was really why beta-blockers disappeared.

So getting back to Law *et al*, I think there were much more important and interesting things which came out of their meta-analysis, so here it is again, and they said that the relative benefits of blood pressure reduction were independent of starting blood pressure, and that's exactly what the epidemiology tells us it should be. You don't need to measure blood pressure any more—just treat anyone over the age of 50, so you don't need to measure blood pressure any more. If you read the paper carefully, it then starts procrastinating, and what they say is that whether you treat should be based on absolute risk, and I would suggest to them that you can't estimate absolute risk without measuring blood pressure, so I think it's a circuitous argument, and remember that these guys have the patent on the polypill, which they want to give to everybody, so you have to maybe be a bit careful about how you interpret their data. But I think this is right, I think it fits in with what we're talking about tonight, that we need to get away from hypertension and talk about risk and the management of risk, rather than the management of hypertension, so it brings us into this area, the principles of risk factor management, relative risk reduction, and it doesn't matter whether it's blood pressure or any other intervention, the benefit you get is proportional to the reduction in the risk factor. Absolute risk is what determines the absolute benefit, and then what we do about that depends on what we as a society decide we can afford and what we're willing to do, and I think society's not yet ready to throw away the sphygmomanometer. I think we probably need to continue to measure blood pressure, at least for the time being, but we need to take risk into consideration.

So I'm going to finish off by just running through, over the next 10/15 minutes, about how we go about managing high blood pressure, and some of the issues which I think we should be addressing in the near future.

So we need to continue measuring blood pressure. Here's how not to measure blood pressure, and I know you have many patients in whom this would be an ideal way to measure their blood pressure, but you'll notice the cuff is too small, it's above the level of the heart, and so it's going to give you a very wrong impression of what the blood pressure is. When I speak to GPs, they're obsessed by measuring blood pressure out of the office. I think they're trying to find reasons not to treat people, so let's not talk about how you measure it, just have it done accurately by a nurse who knows what she's doing.

Then you feed the information into a formula which tells you when to treat, and this looks terribly complex, but in fact the older members of the audience, like Dr Riddle, will recognise this as being not much different from even when he was a lad, so in other words, anyone whose systolic blood pressure's 160 systolic or higher, or diastolic is 100 or higher, we suggest you treat them, because they've got quite a high risk of having a stroke. At the other end, anyone with a systolic less than 140 or a diastolic less than 90, we, in this country at least, don't think they're worth treating. The big change in recent years has been in this grade one, type one hypertension, these people with systolics between 140 and 159 and diastolic between 90 and 99, where we suggest you might treat these people, depending on risk. So we already have adopted this risk assessment approach to management, and we decide to treat, in this group of stage one hypertension, depending on whether they've got target organ damage, cardiovascular complications or diabetes, and I'm not sure whether the modern definition of diabetes should get these people automatically into this category, but again, Brew might tell us. They don't have any of these things, they have to have at least a 20% ten-year risk, and if they don't have these things, we suggest you don't treat their blood pressure. So that's the general simple, I think it's quite a simple strategy for deciding about these people in this intermediate hypertension range, but below that you don't treat at all, and above that, you treat everyone. What do we aim for?—well, as I said to you earlier, the evidence base for targets is not strong, but we have divided targets into those with just bog-standard hypertension as compared to those at high risk, and the targets depend on the risk, so in anyone, you're aiming to get down to less than 140/85, and in those with high risk, where tight control of blood pressure appears to be particularly useful, we aim at 130 over 80, less than. But of course, we made a mistake, and I think it might have been the version that you appended your name to, was it Dennis, where we made the mistake of suggesting that it was quite difficult to get to target, and we should have a sort of fallback position, a sort of audit standard, and of course this is literally what they went for in the [COFFS?] which you get paid for. So I'm not going to bore you about targets, that's what the guidelines tell you. We're not very good at it, as you'll see later, but that's what they tell us we should be doing, and we do it. GPs now get to target all the time. This is them getting to target, and it's a much more painful way of getting to target, and of course the horn of the dilemma would be in the back pockets of the GP, rather than inserted just where it is. I'm not allowed to show this, if anyone in the audience is from the United States, so anyone from the United States, turn around, look away, close your eyes immediately—you may become offended by this slide.

So, we can get to targets, you're very good at it, we're much better than we ever were before, but still, what other things should we be doing?—well, here is another version of the factors, the correctable factors for mortality, not quite the same data that I showed you earlier, but very similar, and of course this is all conditions of civilisation. The famous struggler

against British rule has been on the television recently, Ghandi was once asked, what did he think of western civilisation, and Ghandi, of course, was a very thoughtful man, and he went away and thought about it, and he came back after a while and said, "I think it would be a very good idea", and that's the problem—we think we're very civilised, but in fact we're not really very civilised. We think that cardiovascular disease is largely a genetic problem, and yet when we look around we see this sort of group of characters, so each one identifying the cardiovascular cliff there quite nicely, so this is a real problem that we face, and of course in Glasgow, as you can see from what I showed you earlier, we are working very hard to reduce the risk of vascular disease, and of course, we have reduced our dependency on red meat. We now have much more of a vegetarian type of diet, and Glasgow's an example of the Glasgow vegetarian diet services—it's known as the Glasgow salad, which I suspect is similar to the Belfast salad. So we're working hard all the time to get risk down, and the message here is that lifestyle modification can be useful, and so it's not just drugs, when we're trying to reduce blood pressure and reduce cardiovascular risk. In this slide on the left-hand column, there are things that we know will reduce blood pressure, and on the right, things which will not reduce blood pressure, but which will reduce cardiovascular risk, and I'm not going to recite all these to you, I'm sure you know them already. The reason I show you this slide is that I had to write this section in that edition of the guidelines, so I'm reasonably confident that the data is accurate. I don't think there's been many changes since. So lifestyle is important, but here is an example again, getting back to what we were talking about earlier, short-termism. You can demonstrate short term effects of lifestyle changes on blood pressure, but there have never been any controlled outcome trials, and even the DASH diet in the United States, if you look at longer term follow up, the benefit is lost, so it's very difficult to have long term effects on lifestyle, but it doesn't mean to say we shouldn't try.

So we try very hard to control blood pressure, to control cardiovascular risk, but we often don't succeed. "The greatest danger to a man with high blood pressure lies in its discovery, because then some fool tries to reduce it." Now, when that was written, that was probably a reasonable statement because we didn't have any treatments available, but still we don't do as well as we should. Although you make lots of money from reaching government targets, you don't actually do as well as you should be doing. Something stops us getting better, doing better, and the thing that I want to focus upon tonight is, our reluctance to use multiple drugs.

There's no doubt about it, that if you're going to get rigorous control of blood pressure, you aren't going to achieve it by monotherapy, and I think that message has now been learned, but I don't think you've learnt it well enough. This is a number of studies where tight control of blood pressure was achieved, and you can see that anything between two and four drugs in combination are being used, so any nonsense about which drug we should be using, it's quantity that matters. And just how important combination therapy is, I think is, I hope going to be clear to you if we look at the next two slides. This is just showing you that, regardless of whether you start with a thiazide, a beta-blocker, an ACE inhibitor or a calcium channel blocker, the effect is the same as any other drug, so none of the drugs have any magical effect on blood pressure, but the key message from this slide is, if you look at the right-hand column in each of these corners, you see that you get approximately an additive effect of combining drugs, so there's no magical combinations, they're all additive, so that's important—drugs given together are additive. But how much better are they, or worse are they, than going with one drug and pushing it to the limit?—and that's where I think you see the benefits of combination. Here, in the dark columns, is pushing a single drug to the limit; the white columns are the blood pressure reductions that you get by combining drugs. You get five times more effect by combining two drugs in low doses than you get by pushing up a drug to the top end of the dose range on monotherapy, so the message is strong, that we should be using combination therapy to achieve targets, and of course monotherapy at high doses often is associated with more side-effects, so that's an additional benefit of using combinations.

So the British Hypertension Society in its guideline suggests using combinations. It has two important, well three important messages from this slide. First of all, it's a slide which is, it's the British Hypertension Society NICE algorithm, but it's not an algorithm for everyone with hypertension, it's an algorithm for those people with uncomplicated hypertension. This is telling you nothing about diabetic hypertensive people, angina, this is just ordinary hypertension, where there's no compelling indication of contra-indications for any therapy, that's the first point.

The second point, we are using age as a surrogate for renin. Some people say that measuring renin is just an expensive way of asking somebody how old he is, so people who are young tend to have high renin, people who are old tend to have low renin, so if you start with a drug that blocks the renin angiotensin system in a young person, you'll get more blood pressure reduction with that drug than with another drug, because in old people, there's no point in doing that, use a diuretic or a calcium channel blocker, but then start combining A plus C or A plus D, and then A plus C plus D, and so on, and so forth. Uncomplicated hypertension, age is a surrogate for renin, and combination therapy—these are the messages that we want to get over here.

Now, when we get down to step four, we move into an evidence-free area. We have no idea what to do, and we suggest you send all your patients to Den-

nis who will sort them all out for you. So we have a real problem in stage four, because about 20% of treated hypertensive patients end up there. They've had three drugs, in combination often, but sometimes unable to tolerate one or more of the drug classes, and they get to the step where they need a fourth drug, and we have no idea what to do. One possibility is to base their ... but before we get onto drug treatment, we have to make absolutely certain that there are no other reasons why they have apparent resistant or refractory hypertension, and there's a whole list of things that we need to think about. Is blood pressure being measured properly? Do they have white coat hypertension? Are they already on an optimal treatment for them? Are they taking their treatment? Are there other drugs which are interfering with the blood pressure lowering?—or occasionally they might have a secondary form of hypertension. Generally speaking, it's none of these things, and we have to move on to intensify treatment, and here we, as I say, we have no real idea what we should do, but one possibility is that we might select drugs based on renin, and that in these difficult patients, if they've got a low renin, we might increase the thiazide diuretic, we might add in a loop diuretic or spironolactone. There's quite a lot of evidence that certainly spironolactone can have a very big effect in these people. If their renin is fairly average, then we might use an alpha-blocker, and in those people with high renin, we might use a beta-blocker, or we might use one of the direct renin inhibitors, but there's only one available at the moment, but there will be more in the future. So that's one possibility, one possible approach to the management of refractory hypertension. As I say, we have a bit of an evidence-free zone, and it's very difficult to know what best to do.

Another area that's become important recently has been this notion of failure to catch up. Here is data from the VALUE study, a study which most of you will be familiar with, a comparison of treatment based on amlodipine and treatment based on valsartan, and you can see, in terms of blood pressure lowering, amlodipine was better, but remember in these studies, drugs are added and added in all the time to get to a target, and you'll notice that, despite that, the people in the valsartan arm never achieved the same level of control as those in the amlodipine arm, and although more difficult to see, you've seen this slide already, the same thing was apparent in the ASCOT study, so there's this problem of, never catch up. So the British Hypertension Society has just received quite a substantial grant from the British Heart Foundation to look at this, amongst other things, so these are the areas which we think are quite important at the present time. This is the PATHWAY programme of studies. The first one is to look at this issue of never catch up—is it better to start with two drugs, rather than with one drug, in the hope that we will achieve better long term control of blood pressure?—and that's been suggested in a number of guidelines nowadays. In those people who require a fourth level, a fourth step drug, what is the best one?—and that's likely not to be the same for everyone, so a complicated rotational study is being conducted in these people, and then finally, how can we prevent people getting diabetes? Is it down to potassium, can we do something about it by controlling potassium levels? So three important issues being addressed in this important group of studies, and we should know in a year or two, but we won't know all the answers, and I think we have to think about what we can do in the meantime, and blood pressure management, as well as being a strategy based now on risk rather than blood pressure levels, is an integrated strategy where we should be looking at other risk factors as well. I don't have time to go into these now, in detail, but clearly lipid lowering is going to be important; blood sugar control in those people with diabetes, whatever that is, and anti-thrombotic therapy, which might be an anti-platelet agent or, in people with arterial fibrillation, it might be warfarin or one of the new anti-thrombin drugs. Here you need to do a risk assessment, because otherwise you do more harm than good, and then other things that you might try, anti-oxidants, well they certainly do more harm than good, so I wouldn't recommend that you give your patients vitamins. Numerous studies now have suggested no benefit, and indeed possible harm.

We don't know the answers, and we can fall back on the poetry of Donald Rumsfeld, to reassure us that answers are not always easy to find. The unknown, as we know, there are no knowns, the things we know, we know. We also know there are no unknowns, that's to say we know there are some things we do not know. There are also unknown unknowns, the ones we don't know we don't know. I think the more you read that, the more profound that statement is, and I guess that will keep us going in high blood pressure research for some time, so I suppose that my summation of what I've tried to say this evening is that high blood pressure is important. There's a strong evidence base for reducing it. We need to assess risk, we need to reduce blood pressure rigorously. To do that, we need to use lots of drugs, and we need to focus on strategies which control blood pressure, rather than individual drugs, and not just blood pressure but other risk factors. So hopefully I've enthused the Ulster Medical Society to take high blood pressure seriously, even in the coming decade, but I don't want you to get too excited and come to any harm on the way home tonight, just by reminding you of R J Harwell, who was born in 1914, and gave up smoking in 1959, gave up the booze in 1973, gave up red meat in 1983, and he died anyway in 1991. This is just to remind you that, so far, we can't prevent death. Thank you very much.

Professor Atkinson:

Well, I think I said at the start that we'd have a marvellous talk, and I think we've had a marvellous

talk. Will you take some questions?

Professor McInnes:
Oh, I'm happy to.

Professor Atkinson:
Happy to, who's going to start?—John?

Dr John Craig:
You presented a very convincing argument, or series of arguments, for the efficacy of treatment, and the need to be aggressive in treatment. You didn't say much about tolerability and the [drop out?] rate, in an otherwise largely well population? Is that where the differences in the drugs lies?

Professor McInnes:
I think that is an important point, and of course, I did think, I had originally a section on compliance in this talk tonight, but I realised that I had far too much, and so I had to drop something, but you're quite right. If you look at high blood pressure management, and you look at continuation with drugs in population studies out there in the real world, you find that only about 50% of people are still on any particular drug at the end of the one-year period, and that's not unique to high blood pressure, it's the same for any chronic disease, but it may be more important in a condition which is essentially asymptomatic. So why is that happening? Well, I think that in the past, you're right that a lot of the drugs had side-effects, and they were the reason why people wouldn't take them, but the drugs that we use now are by and large well tolerated. You could debate that, but they are pretty well tolerated. Angiotensin receptor blockers probably have no real symptomatic side-effects, you could debate that, but they come out against placebo as being clean. ACE inhibitors cause a dry cough in about 15% of people, otherwise they're clean. Even calcium channel blockers like amlodipine, which causes a lot of ankle swelling, about 80% of people will not get ankle swelling, so in about 80% of people, there's no problem. You've got a range of really pretty well tolerated drugs. Beta-blockers are better tolerated than most people think they are, and diuretics are extremely well tolerated; thiazide at low doses, very well tolerated, so I don't think we can just say that it's tolerability that the problem is, although some people will not tolerate many drugs, and those of us in secondary care, we see these people all the time, they seem to have side-effects on every drug.

I think the reason why people don't take their therapy is not because the drugs are bad, but because the doctors are bad. I think it's professional non-compliance. We don't sit down with people and enter into a contract with them, about their long-term cardiovascular health before we start them on treatment. I obviously see people in a secondary care setting which is therefore not readily transferable to what happens in primary care, but my feeling is that those people who really want to get their blood pressure under control, they take their tablets and they generally get there. A lot of people are not convinced that they need to be on treatment, and they just drift away. I think that when it comes to compliance, the people who are not compliant are the doctors, is my final answer, and not the patients, but that's my own personal view.

Professor Atkinson:
Yes, Patrick?

Dr Patrick Bell:
Can I ask you a rather personal question?—I realise you may not want to, a particular agent, would you like to give us two or three of your favourite anti-hypertensive drugs?

Professor McInnes:
My favourite anti-hypertensive drugs?—I have to say that I have in recent years followed what's called the ACD algorithm, partly because of being vice-president and then president of the Society, and if I didn't, it wouldn't look too good, and I must say that I think that works quite well. I think that angiotensin receptor blockers are very well tolerated drugs, which are quite effective, and I don't think they're any less effective than any other drugs, now that we use them at appropriate doses, of course. They started off being used at quite the wrong dose, and that meant that they were pretty weak, but at the appropriate doses, I think they're okay, so I use ARBs. I'm not allowed to use ARBs very much where I come from, so I have to use ACE inhibitors because they're cheap, and we even have therapeutic substitution in Glasgow, so if I prescribe lisinopril, they'll be switched to ramipril, which I think is a particularly useless drug, but never mind, that seems to be the one that they all want us to use, so I use ACE inhibitors, I use ARBs, I use bendroflumethiazide, I find there are very few patients with difficult hypertension that I can control without using a thiazide. I use amlodipine. I actually recently increasingly have been using lercanidipine to try and get round the ankle swelling, so I think lercanidipine probably does cause less ankle swelling, I'm not entirely sure I know why, and I use lots of spironolactone. I did my MD thesis on spironolactone, and I'm a long term advocate of spironolactone, and we used to use 200 mg a day, and we used to use 200 mg of hydrochlorothiazide those days as well, so everything was used in big doses. I think spironolactone at low doses is often the difference between good control and not so good control. Then a final tip is, beetroot juice. I've got two or three old patients who are struggling on multiple drugs, and I saw this juice, you see that guy who presented at the British Hypertensive Society, there's some really interesting crossover studies of giving people beetroot juice, and big responses, and I gave one lady, I started her on beetroot juice, and her blood pressure's perfectly well con-

trolled. I've actually been able to stop the calcium channel blocker that was giving her ankle swelling, as it's still perfectly controlled, and I've got another couple in whom it seemed to have some beneficial effect, so we need to think about all these strategies. I don't really have particular favourites. I use a wide range of drugs, I have to use a wide range of drugs, and they all have their place, but I think it's getting into the habit of, I think that everybody needs a model to follow. Even so-called experts need a model to follow, which they adapt to individuals, and I think there are lots of very effective drugs out there nowadays, which are by and large quite well tolerated.

Professor Atkinson:

Ciaran Doherty.

Dr Ciaran Doherty:

You mentioned the controversy about the existence of a J-shaped curve, particularly in elderly patients, with regard to cardiac events. There's some worrying evidence emerging that there may be a J-shaped curve with regards to the effect on kidney function on progressive blood pressure lowering. Again selectively, the elderly patients, and particularly those on ACE inhibitors as part of their treatment, and there have been some dramatic improvements in renal function in that selected group until you withdraw ACE inhibitors, so I'll just mention it firstly for interest, and secondly because there's many people here I might have written to in recent years advocating ACE inhibitors, (?? 1:03:52) may absolutely, finding in that selected group, the elderly with advanced levels of chronic kidney disease, we may have to rethink our strategy for that particular group.

Professor McInnes:

I think you make two points there, which I entirely agree with. I think there is emerging evidence which makes me a little bit worried about this notion. If we had had this conversation two years ago, I would have said, it's the lower the better, but one or two studies have been, one or two analyses of studies have begun to suggest that maybe in coronary heart disease, you can go too low, as far as diastolic pressure's concerned, but unfortunately these studies are very difficult to interpret, because it could be reverse causality. It could just be that these people with low blood pressure are iller than those who have not, so there's a real problem there, and I think the same is perhaps true to a lesser extent about the renal problem, but you're right—we have advocated very rigorous control, 111 systolic targets for people with renal impairment, and that might be too low. There's evidence that you don't seem to get much benefit, going down as low as that, and also remember that ACE inhibitors are still, until recently at least, were the most common cause of emergency haemodialysis. If you don't watch ACE inhibitors, then you can run into problems, and the people who you get the biggest problems with are little old ladies with diabetes, who are taking non-steroidals and maybe a potassium-sparing diuretic, in other words, all of these old ladies that you are dealing with, so in old people, we monitor renal function very carefully, and there will be a number in whom you have to stop the ACE inhibitor. They're susceptible, I agree with you.

Professor Atkinson:

Would Professor Bell like to make any comment on the diabetes story, so somebody doesn't ask me, in terms of the beta-blockers and maybe Professor Johnson as well, in terms of the thiazide diuretics?

Professor Bell:

Well, I guess the issue, I think there are two points, I think the point that you make, that we need all the anti-hypertensive agents that we've got, is an absolutely critical one, so we don't want to go round being too negative. Having said that, I guess the diabetes prevalence issue with beta-blockers is a cause of concern, and I wouldn't disagree with the British Hypertension Society line that it's a little further down the list. I think it's not a top agent, but having said that, for the patients who have angina, they get a beta-blocker.

Professor Johnson:

Just the relationship between the drugs and the risk of diabetes. I wrote a letter on that, and it looked to me that it was the length of time it was on the market, and it was too [?] neat. The other thing was that the diabetic group probably were on quite high doses, and the beta-blockers too, so maybe it be a dose-related effect, and it was remarkably straight, and it was the time on the market.

Professor McInnes:

I do remember that letter that you wrote now, indeed, and in fact I have a slide of it, because I thought it was a good argument. I think that my view is that the diabetic story has been blown out of all proportion. I think there is no doubt about that, that diuretics will, you'd be more likely to get, and I think you would agree with that, Dennis, there'll be a trend towards diabetes in people who take diuretics, even at low doses, but certainly at higher doses, and I think I agree with you also that beta-blockers do. The question is, is the diabetes that you get, the same as naturally occurring diabetes?—because it seems to me that looking at the literature, that you find that the people who are just people who get pushed over this arbitrary line, they already have a high-ish blood sugar anyway, and whether or not they're at a significantly different risk by moving over the line, I'm not sure about that, and it's a very, very difficult thing to study. I thought we could study that using the Glasgow blood pressure clinic database, to try and get a feel for that, but it's not proving easy. But one thing I would say, that in the VALUE study, when we looked

at the people who got new-onset diabetes, they were all people who were at a very high risk, even before they had diabetes. It may just be a marker for very high risk.

Professor Johnston:

The other thing is, if we stopped the diuretic or stopped the beta-blocker, would they cease to be diabetic, or would they remain in the high range?

Professor McInnes:

Well, you know that there were studies done in the 1970s, and this is not new. We've known about beta-blockers and diuretics causing changes in blood sugar since then, and in these studies, it was reversible if you stopped the drug, but whether that changes the risk in these people, that's what I don't know. I think there probably isn't, they're still a higher risk group of people, and of course, the other thing is that recent evidence suggests that the biochemical changes occur very rapidly, within about, certainly within three months of initiating treatment, so that's why we're able to do this study that we're going to do, looking at the diabetes, because it seems to occur very, very rapidly. They very rapidly get abnormal glucose tolerance test.

Professor Atkinson:

I think the other thing that you said, among a lot of other things, that I'd like to emphasise, is that resistant hypertension is virtually impossible to control without a diuretic of some sort, and it's always the first thing, I bet, that Dennis looks at in his resistant hypertension clinic, or Dr Mullen and myself, in the one that we do, is the first thing, are the people on diuretics?—because if they're not, you can achieve so much.

Professor McInnes:

I think another message to people who might be in primary care, is that I see in Glasgow, whenever the diagnosis of diabetes is made, the diuretic is stopped, and I think that is a crazy thing to do, because I think diabetic patients are people who need diuretics, because they tend to be salt-retaining, and they need everything they can get to control their blood pressure, and I think that the cost of a little bit worsening blood sugar control is more than compensated by much better blood pressure control, I don't know whether you'd agree with that?

Professor Atkinson:

One last question from Dr Mullen.

Dr Mullen:

I just wondered what your view was on Rasilez?

Professor McInnes:

You're one of the few people that's heard of this drug. We took a vote, at the British Hypertension Society, we were talking about refractory hypertension, and we took a vote, it was GPs who had come to this, the British Hypertension Society blood pressure meeting, so these were interested GPs, and we asked them how many of them had tried Rasilez, and only a very few hands went up, so I then said to them, well how many of you have never heard of this drug?—and 90% of the audience put their hands up, so Rasilez is an option, it's a direct renin inhibitor. It's been very poorly promoted by the manufacturers, I don't know why, but it's, of course, expensive at a time when all drugs are generic, and I think that they recognise that they're never going to be able to sell this in the climate that we're in at the moment, and it's been promoted therefore as a fourth-line drug, and of course they have no fourth-line data, because drug companies don't like to test new drugs as fourth-line, they want the first line, you see, so that's a bit of the background. Having said all of that, aliskerin, which is its proper name, the trouble with these drugs is, they've been around for a long time, drugs of this class, but they've got very, very poor bioavailability, and this drug has got poor-ish bioavailability, but it's okay because it doesn't seem to have a lot of inter-individual variability. It's got a long half-life, and it's quite well tolerated up to a dose of 300 mg a day. Beyond that, a very high proportion of patients get diarrhoea, and so that restricts its dose range, and my feeling is that it might not be as effective within that dose range as other drugs might be, but in the context of refractory hypertension, you're really struggling to find drugs that you can use, I think it is, as somebody said earlier, we need all the help we can get. We can't just discount it. It will, I guess, find a place in these difficult patients, and who knows, if it turns out to be much better than I think it is, then people will start to use it more widely, but remember, and it's an important message for spironolactone users, when you get into people who are on fourth-line therapy, they're probably going to be on an A drug already, so you're now adding in another A drug, and so you need to be very vigilant about renal function and potassium. Most people will not have a problem, you just need to be aware of it.

Professor Atkinson:

Okay, I think we'll stop there. I think we could go on for a long time, but I think it's tea time.