# HSF Patients' Day

Wednesday 18th May 2016

GOVERNORS' HALL, ST THOMAS' HOSPITAL, LONDON

## P R O G R A M M E

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|---|---|
| 1.30 pm | REGISTRATION |
| 1.55 pm | Charity introduction |
| 2.00 pm | Professor Graham Hughes<br>*Hughes syndrome in ten minutes* |
| 2.10 pm | Professor Anisur Rahman<br>*Testing for APS—who, why and how?* |
| 2.30 pm | Professor Beverley Hunt<br>*Anticoagulation Q&A session* |
| 2.50 pm | Dr Hannah Cohen<br>*Results of the Rivaroxaban in APS (RAPS) trial* |
| 3.10 pm | Drs Lindsay Bearne, Sofia Georgopoulou & Heidi Lempp<br>*"It's as if I've hit a wall" - the results of the APS and Fatigue study* |
| 3.20 pm | Questions from the audience |
| 3.30 pm | COMFORT BREAK WITH REFRESHMENTS |
| 3.50 pm | Bethan Thomas<br>*Dealing with a diagnosis: treating your mind and body in tandem* |
| 4.00 pm | Yvonne Wren<br>*Introducing INRTracker* |
| 4.10 pm | Cath Atkin<br>*How to Eat on Warfarin* |
| 4.20 pm | Dietitian Abigail Wilson<br>*Keeping a happier, healthier you* |
| 4.40 pm | Questions from the audience |
| 5.00 pm | CLOSE |

**APS Patient's Day 2016**

**Part 1**

**Lynne Kirwin**

Good afternoon everybody and welcome to our National Patients' Day. In fact I think it's our International Patients' Day because we have visitors here from the USA and Slovenia and the Netherlands.

I'm Lynne Kirwin, a trustee of the charity and very proud to be the voluntary Chief Executive. Before we start I wanted to say a very warm thank you to our very distinguished experts who have taken time out from their hectic schedules to speak this afternoon; also to the team of volunteers who have worked tirelessly with Kate and Yvonne to make the day possible.

Some brief charity news. It's been a really exciting and ground-breaking year for our charity. As those of you who read our members' newsletter, packed with useful information, will know we are about to start work with the Royal College of General Practitioners on developing an online educational programme for GPs. This will potentially reach 100,000 UK health professionals, and it is our biggest breakthrough yet in raising awareness of the condition in the medical community. We've listened to our members on this as one of if not the most frequent comments we get is that their GP is either unaware of APS or not sure about how it is treated. This of course is something with which we totally sympathise, and hardly surprising given the bewildering array of symptoms and the increasing pressure on GPs' time.

When we first approached the Royal College they immediately acknowledged, in their words, that there is, quote "an APS sized gap" in their educational programmes. We haven't been able to embark on this before because it's frankly rather expensive, although worth every penny. And indeed we are only able to do it now thanks to a very generous donation from a family who tragically lost a loved one to APS.

The other really significant breakthrough is that the charity has been instrumental in changing the national stroke guidelines, which for the first time will include testing for APS. I will leave it to our trustee, Professor Rahman, who put forward the proposal to

the inter-collegiate stroke working party to say more about this in his talk. But it is really, really exciting.

On the subject of our speakers could I just mention that Hannah Cohen will be talking about the RAPS trial, which is not in its final stages of publication, so please, what she says is embargoed and not to go beyond this room.

Thank you so much for coming today and for your extremely valuable support; without it we wouldn't exist or be able to continue our vital work on your behalf. I hope you enjoy the afternoon.

**Professor Graham Hughes**

Thank you very much indeed, Lynne, for all the work that you do for the charity. Well, I've got ten minutes and I know that some of you have not been here before so I'm going to give a very quick introduction to what we know before I bring my colleagues on.

I want to start with a set of twins, identical twins, and I'm going to come back to them at the end of this little talk. The second slide is another clinical study – some of you might recognise this drawing; I produced it in the paper I wrote on the 30th anniversary of Antiphospholipid syndrome. And this was sent to me by a patient and it tells – I think a lot of you will nod at this and say, "Yes, I recognise those things" – from joint pains to circulation. But I'd like to look at the top one there: fainting. This girl fainted at school, fainted a lot, collapsed, and the lesson from this I'll come back to as well.

So, back to 1983. This is where we wrote the first papers on the syndrome. I, as my colleagues will know, there's a thing called the Hebadon Society, which is a British rheumatology society, and in those days you invited patients along and discussed with the patients what they had. And all these girls had various forms of Lupus, but three of them had Antiphospholipid syndrome: one with low platelets and a stroke, no DNA antibodies, no Lupus and so on. And this was the very first public presentation at the Hammersmith Hospital. The next year in the British Medical Journal we published two big papers on thrombosis, abortion, cerebral disease and the lupus. And I'm rather proud of it because both the first papers on this were in British journals. And some of you in the front row will know The Lancet; it took a year

and a half to get this accepted, there was lots of toing and froing. But this was the first paper on the antibody assay, which Anisur Rahman is going to be talking about what the tests are and what they mean. And we were so excited by this, November 26th, which is my birthday. So, we actually all went for a pizza down at Hammersmith in this thing to celebrate what we knew actually was a very important day.

A year later we had the first world symposium – I like the world, because I think there were 47 attendees at that meeting, and since then every two years there have been international meetings.

Well, that's the background to our side of it. And now, as you know, doctors throughout the world are collaborating in research. So, for those who have not been to this meeting just a few slides on what the symptoms are:

Perhaps the commonest of all is memory loss. Often the patients don't talk about it until you ask them, "Oh, I'm the joke of the family. I have to write everything down. It's quite severe and it's a big worry. Have I got Alzheimer's?" I notice on the radio and on television the last week there's been a lot on memory loss, and this is one of the causes which, fantastically, is treatable.

Second commonest perhaps in my clinical practice is migraine. "Did you have migraine as a teenager?" "Yes doctor, every week severe. Often missed school or college. Went away for a few years and then it came back and it's been quite severe recently".

But the brain has other ways of being angry. And a number of patients are labelled at some stage as, 'query, multiple sclerosis'. And on your seats there's a questionnaire for those who have the disease, it's anonymous, but we'd like to know what sort of percentage of people go to various specialties. And this is a very still, I think my colleagues would agree, a very tricky diagnostic situation.

But the most severe worry of course is stroke, "I'm getting mini strokes. I have balance problems. I'm concerned". And this, as you've heard from the introductory comments, is probably one of the biggest things that we can do. We know there's a government run stroke incentive now, but so far very little on the antiphospholipid Hughes syndrome.

Now, there are other organs that don't like sticky blood. And if you think about it every organ is the same. This is a patient, the arrow shows a fractured foot, metatarsal, believe it or not that is a feature of the syndrome. I frequently say, "Have you ever had a march fracture?" "Yes doctor, as a jogger years ago and I fractured five times".

The big organs, the heart sadly can be involved; this is a clot inside the coronary artery. And some people one of their main complaints is angina. In the book that you have outside on sale there's a lot about angina and how this lady presented with chest pains. Again, very treatable.

And finally the arteries. It's really introducing us to work that in fact links sticky blood with perhaps a clogging of arteries. This is something very exciting. This is Yehuda Schoenfeld, one of the leaders in this field from Israel, and we collaborate a lot with his team.

Perhaps the most newsworthy is pregnancy, and once a year in this room we used to have a party for mothers and daughters. One of the ladies here had 14 miscarriages before being diagnosed and treated. So, we used to have this party every year until I left St Thomas' and I always thought it was quite fun with ice cream and vomiting and jelly. But the figures are fantastic. This is data that's reproduced throughout the world: back in '85 when we were looking at this first only 18% successful pregnancy if you had antibodies against phospholipid. Now most units are talking of 90% success or over.

One of the reasons is that we do collaborative studies. This shows my colleague Dr Khamashta, a mother with a new-born baby and haematologists and a paediatric doctor. So, collaborative studies like this have brought up the improvement.

But one of the things that I think is terribly sad and very important is that the media have ignored this Antiphospholipid syndrome in stillbirth. The Times last year or a year and a half ago said that stillbirth was one of the greatest tragedies known to man. There is an increased chance of stillbirth if you're sticky blood and not treated, and a very good group in America, Ware Branch's group, have shown this.

So, when you or your daughter or a friend goes for the first visit to the obstetrics department do they ask about Antiphospholipid syndrome? No, they don't. Do they

test? No, they don't. Could you predict who would need a test? Because at the moment you have to wait for three miscarriages to be eligible to test, and that's on economic grounds apparently; but for me it's very sad. And I've proposed a lot in publications any midwife or doctor in obstetrics should ask these three questions: Have you a thrombosis? Are you a migraine sufferer? And do you have a family history – it's so important – of autoimmune disease, that means lupus, rheumatoid, MS and thyroid disease?

Which brings me to the last couple of slides really and that is the treatment, which is going to be talked about by colleagues: aspirin traditionally for those without major problems; Heparin and Warfarin for those who have had a major clot. And this cartoon – showed it at the last meeting but it's something that epitomises what we see – many of our patients need a higher INR, I always think of Tesco's milk: it's got to be thin milk and not thick milk; and the ratio has got to be 3.5 or even more. I'm sure some of you in the audience run along nicely at four. And if the INR falls back come the symptoms of headaches, whatever.

For that reason it's been a feature of this meeting that we have had speakers on self-testing. And where appropriate I'm a real fan of this; it's my religion. I think if you can afford the 350 or whatever it is for a machine it opens up your life: you can travel, you can do normal things.

So, what's this patient teaching us? Well it teaches us, amongst other things, that it need not be Hughes syndrome alone; Hughes syndrome can be linked with other things. I talk about the big three: thyroid, lazy thyroid, Hughes syndrome and Sjögren's, which is aches and pains. And those three go in tandem all the time. But a new one has been described in the last five years and that is POTS. POTS goes for postural orthostatic tachycardia; which in plain English when you stand up you faint or the heart goes funny. It's due to a slightly abnormal nervous system, autonomic nervous system that monitors these things. So, these poor patients come to a regular doctor with 50 different things and are assumed to be neurotic, and so many cases that's not true.

To finish we have the twins: Jane who is strongly positive antiphospholipid antibodies – and this slide really is for Anisur who's going to be talking about testing next – and her identical twin, absolutely identical, Sarah, and she was negative.

Now, Jane had all the features of Hughes syndrome, migraine, balance problems, temporal lobe epilepsy, that's getting funny feelings and déjà vu, and memory loss. Her sister, who's APL negative, had the identical picture: migraine, balance problems, temporal lobe, memory loss. What shall we do with Sarah? Well, the answer is of course you treat. And we started her on aspirin, later Heparin and now she's completely well, asymptomatic on Warfarin.

What's this patient teaching us? Well, we're still a little naïve in testing; and I think this is important that you hear the next talk because it's not all that it seems. It's a passion of mine that there are patients who clinically fit the bill totally, they're often relative of patients already diagnosed or family members and whom the tests are negative, and what happens the patients sadly are often sent away. We call it seronegative, and that's simply because the tests are negative.

What's the importance of that? Well, you do wonder out there in the world of medicine how many patients with migraine have got Hughes syndrome and have not been picked up; how many recurrent pregnancy losses because the tests are borderline or negative; how many young strokes and heart attacks; how many unexpected fractures – who would think of that?; and stillbirth; and atypical MS. These are opening up, and such is the important of testing that we would hope to get better at it.

So, we wrote 33 years ago, 'the syndrome widens'. We think we have a better understanding of the mechanisms, although internationally people are working on this. I believe that this business of seronegative or the tests being negative is one of the most fundamental important aspects of our syndrome, and although in conferences a lot of people don't like the topic, it's a real one that hits us as busy clinicians. So, in 1983 I wrote, 'for those of us hardened by nihilism and years of study of various auto antibodies in SLE there's a rare sense of excitement at the implications of the associations now being reported'. And that's the same today I think. Thank you very much.

I was told to remind us that we have questions at the end of the fifth or sixth talk. So, it's a pleasure to welcome my friend and colleague, Anisur Rahman from UCH.

**Anisur Rahman**

Thank you very much Graham. Just two responses to what Graham has just said. Firstly his reference to Tesco's milk: I find it hard to credit that Graham buys his milk from Tesco's; I have him down as a Waitrose man or possibly Harrods. The other thing is Graham has given me a big build up with respect to seronegative Antiphospholipid syndrome, and it's shame to waste it, but in fact I'm not going to be talking about that today because I talked about it a couple of years ago. Although in the question and answer session later I'm sure we'll be able to cover it.

What I'm going to be talking about is testing. And the reason I'm going to be talking about testing is because it raises a lot of controversy and a lot of questions. So, people often ask, "Why can't I be tested? Why wasn't I tested earlier? Who should be tested? Is it worth my having the test?" And the tests themselves have confusing names like lupus anticoagulant and anticardiolipin. And now increasingly patients get their own results and their own letters, and there are numbers which you may not know exactly what they mean. So, I'm going to try and take away some of the mystery of these tests and show you how they work, and what a positive result means. And then I'm going to explain why we shouldn't test everybody; why it's bad to over-test. It's just as bad to over-test as it is to under-test. And given that, given that we have to select people how should we select? And I'm going to open up by telling you we don't know all the answers; none of us know to all of this. There are still unanswered questions about who should be tested.

So, what about tests? When are tests good for you, what's a good test? Well, a good test is one which gives you an absolutely clear result with no ambiguity. If the test is positive it tells you you've got something, you need treatment. If the test is negative it tells you you're completely safe from that thing. That is the perfect test: a test with no ambiguity. Plus it needs to lead to something useful to you. There's no point in having a test which just worries you and you can do nothing about it. So, that's what I think of as a very good test.

What are some examples of good tests? Well, the HIV test these days is very good because it's very, very accurate. If you have a positive HIV test you have been exposed to HIV; it's almost never wrong. And if you have a negative HIV test you probably haven't been exposed to HIV. So, that's a good test. Another good test is if you're a patient who's entering into kidney failure for some reason and nobody knows why a kidney biopsy is a very good test because it probably will tell you the

exact answer and the treatment for it. So, these are examples of test which are really good to have.

So, what about bad tests? When would a test be bad for you? So, you could argue: well a test will never be bad; it's always information. It's always useful to have information, isn't it? Well, not really, because sometimes the information can be ambiguous: it might mean one thing and it might mean another thing. Or it might be actively unhelpful; it might do something to you which is bad for you. Going back to the HIV test, I said HIV tests are good today, but back in the '80s and early '90s just having an HIV test was enough to make people deny you a mortgage or put up your premiums on life insurance, no matter what the result was, because they thought if you've had that test it means you're living a risky sort of a lifestyle. So, in that situation, not now, it was a bad test. So, if a test is ambiguous or confusing or for at least harmful consequences you would be better off not having that test.

So, what are some examples of that? In the Metro a few months ago I read an article showing that some parents of a primary school child were very upset, and they were upset because the school had tested the height and weight of all children and they'd found that their child had a high BMI, a high body mass index, in other words was more heavy – according to this number – than they thought he should be. Now, the BMI is a very crude number. If you test most of the England rugby team, for example, because they've got enormous amounts of muscle they'll have a high BMI, but they're perfectly healthy. So, this BMI figure could have been useful if for example they'd done a research study saying how many children have raised BMI. What wasn't useful is what the school had done, which was to write to all these parents saying, 'your child is overweight'. So, the children and the parents were very unhappy because it led to teasing and that sort of thing, and they said, "This is not a good use of this test" and they were right.

Another example of a test which is not useful, I met a man socially who had private health insurance and he was very proud of it and he said, "My super-duper gold-plated private life insurance gives me a whole body scan. I can have a whole body scan". But that's not a good thing to have because if you have a whole body scan probably they will find something a little bit abnormal in all of us. If you do a whole body scan on me you'll probably find a little bit of arthritis at some place or other. And it's not helpful because it will just worry me; there's no treatment for it; it's

probably not going to do me any harm. So, this is an example of a test which is not useful. So, tests are not always useful.

So, the value of any test depends on the accuracy and the clarity of the result, in other words, how you do the test, and the consequence of doing the result: why are you doing the test? And if you know the how and the why you can tell who you should do it on.

So, what about the test for APS? Now, there are three laboratory tests that are done in a laboratory for APS: anticardiolipin ELISA, anti-beta-2-glycoprotein ELISA and the lupus anticoagulant test. So, to start with I'm going to tell you how they work and what it means when you read the results.

So, an ELISA, two of those tests were called an ELISA and it's an acronym; it stands for enzyme linked immunosorbent assay. And it's very simple: if you take cardiolipin, cardiolipin is something we all have in our blood and people who have the antibodies have antibodies which attach to it. Most people don't have those antibodies; some people do. So, to test for it you get a plastic plate, you stick cardiolipin to it, you add the patient's blood and then you do various different things and add reagents, and if the blood has antibodies which stick to the cardiolipin then the well on the plate will turn yellow, and if there aren't any such antibodies it won't turn yellow. And how yellow it turns, whether it's dark yellow or light yellow, tells you how many of the antibodies there are. In other words this test gives a result which is a number. So, if you'd read your own results you might have a result saying: anticardiolipin level 25, or anticardiolipin 125. So, the higher the number the more of the antibodies you have in your blood. This is a picture of the plate, this is an empty plate, so what I want you to imagine is we take a blood sample from everybody in this room and everybody has one little well on that plate, so everybody's sample goes into one well on the plate, and then we do the test that I've just described to you; some of the wells will be yellow, some of the wells will be clear. And so we can tell who has the antibodies and who doesn't. And by seeing how dark the yellow is, which can be done by a machine, we can say who has high levels and who has low levels. So, that's what these two tests mean, the anticardiolipin and the anti-beta-2-glycoprotein one. The only difference is in one you put cardiolipin on the plastic plate and the other you put this beta-2 on the plastic plate.

So, what do the results of this test mean? The anticardiolipin test, if it's reported as positive it means your level is higher than the average level of healthy people. So, most people wouldn't have a level as high as you. That doesn't mean that you have dangerously high levels; it just means you have levels above the level you'd expect in a healthy person. But a strong positive test, which is over 40, is much more meaningful. That means you've got much higher levels of the antibodies. So, beware of people who have a weak positive test because that may not be harmful at all.

Similarly with the anti-beta-2-glycoprotein one test positive just means that you're above the 99$^{th}$ percentile of everyday folk, 99% of healthy people would be below you, but that doesn't mean it's going to cause you any problems. A strong positive is above 99%; a weak positive might be above about 90% or something like that. But levels of anticardiolipin and anti-beta-2 can vary over time: you might be positive one day and not as positive in a few months' time.

So, what about the lupus anticoagulant test? This isn't in ELISA; it's not like the tests I've just shown you. It doesn't give you a level. You can either be positive or negative. There's no concept of strong positive or weak positive. And what it means, a positively lupus anticoagulant test is that the blood contains some antibodies, some antiphospholipid antibodies that block clotting in a test tube. Now, some people at this point say, "This is very, very confusing because this is a disease which makes people clot, and yet the name of this test is a lupus anticoagulant. So, why is it called that? An anticoagulant is something which stops people clotting". And it is very confusing, and the answer is this: our tissues behave differently in the body than they do outside the body. So, if you imagine you took some skin off you, if you leave the skin on your body it will look one way, nice and moist and healthy; if you take the skin off your body then what it will do is it will curl up and become dry and so on. So, once you take something out of the body it will behave differently. And it's the same with the blood: if you take the blood out of the body into the test tube and it has some of these antibodies in it then it won't clot very well; it will stay runny, it won't clot. But if you leave that same blood in the person's body those antibodies make it clot. So, that's why it's called the lupus anticoagulant test, because when you take the blood out of the body the antibodies have a completely opposite effect to what they did in the body. That's why it's called that.

So, how do they do it? Well, actually in a way it's very simple: you take your blood and you let it clot, and it takes a certain time to clot. Now, people with the lupus anticoagulant it takes them longer to clot than other people. Now, there were two possible reasons for that: one reason could be that those people lack something, they don't have something that you need to clot. There are diseases like that, like haemophilia which was the last Tsarevich of Russia. You may have heard the story of how the last tsar of Russia, his son had this disease which made him bleed a lot, and that was because he didn't have a clotting factor. So, to check it's not something like that you mix your patient's with blood with blood or plasma derived from a healthy person. So, if that healthy person has the thing that was lacking it will correct the problem if it's haemophilia or something. But in this disease in Antiphospholipid syndrome you take the patient's blood, it takes too long to clot and you can't fix that by adding somebody else's blood. You can't fix it because your patient's blood has a thing which blocks clotting, that inhibits clotting, and that thing is the antiphospholipid antibodies. And you know that because if you add lots of phospholipids to block those antibodies you can correct the problem so the blood will clot normally. So, a positive lupus anticoagulant test is if the patient's blood takes too long to clot, you can't fix it by adding somebody else's blood, but you can fix it by adding lots of phospholipids. And that's what it means. And it can be either positive or negative.

So, lots of problems with this test. Number one, it's not always the same; it might be positive one day and then negative a few months later and then positive again. So, that's confusing. Sometimes it can vary from one hospital to another and some of you in the audience may have had this experience where you've had the test and it was positive at say, UCL, and then you went to Guy's and it was negative. And that's because it's that kind of test; it's very difficult to standardise it. It can't be done very easily in patients who are already taking Warfarin which makes their blood less likely to clot. It can be done but not easily. But the biggest problem I have with the test is it confuses patients. And the really big bugbear is it isn't a test for lupus. It's called the lupus anticoagulant because it was historically developed for people with lupus, but it is definitely not a test for lupus. Most people who have a positive test don't have lupus. And lots of people come to my clinic, they've been tested for this and they're worried they have lupus, but they haven't.

So, what do we mean by a positive test? For the anticardiolipin most people would say if it's more than 40 it's positive. For the anti-beta-2-GP1 if you're above 99% of

the healthy population you're positive. And lupus anticoagulant test is just positive or negative. Now, to diagnose this syndrome you should have it repeatedly positive. Some people it's just positive for a very short time and then it goes away. And an individual patient can be positive in one or two or all three of those tests. It's different for different people.

So, what's the problem with these tests, now I've explained them to you? Well, the first and the biggest problem is that they can be positive in healthy people. Some completely healthy people who are never going to get clots and never going to get miscarriages can be positive in these tests. So, how can that be? The answer is that some of these antibodies are harmful and some of them are not harmful. It's like snakes: some snakes are poisonous, some snakes are not poisonous, but they're all snakes. So, here we have anticardiolipin antibodies, some of them can cause harm, some of them don't cause harm, but they're all anticardiolipin antibodies. So, you can be positive in this test and yet not be at risk of thrombosis and miscarriage. And that's a problem with the test because about 5% of completely healthy people read positively. You don't want to treat those people but they're positive anyway. We're not sure what to make of those weak positive tests – you remember, the ones between 15 and 40 – we're not really sure what to make of those. Do those people need treatment or don't they need treatment? You can get different results from different hospitals, and your own tests can vary from positive to negative over time.

So, these tests are helpful but they're not as good as say an HIV test or a kidney biopsy; they're not as accurate as that. And that's the problem because now we come onto why: why were you doing the test? What is the outcome of somebody who has a positive test? And essentially the only reason you're going to do this test is if you want to diagnose Antiphospholipid syndrome. And if you diagnose Antiphospholipid syndrome currently the only established treatment is to be on anticoagulation for a long, long time. So, if you have a thrombosis in your calf, an ordinary one without APS, you'll be on Warfarin for three to six months. If you have it with APS you're on it forever or for a very, very long time. That is a big difference for a person. It is not a trivial thing to have to take Warfarin forever, which means you do not want to over-diagnose it; you don't want to make the diagnosis in somebody who doesn't have it. And the test is imperfect so there is a risk of over-diagnosing it because it is an imperfect test.

So, what about miscarriages? If you do this test and it's positive in a person with a miscarriage well you might treat their future pregnancies differently, with Heparin or aspirin. And what about people who have had neither a thrombosis nor a miscarriage, so somebody who's essentially perfectly healthy but has a positive test? And the honest answer is you just do not know; you do not know what you should do with those people, whether they should be treated or not. Now, you can have some ideas about it, you can try to estimate the risk, but there's no definite thing to do. So, we don't want to overuse the test because we don't want to over-treat people. It would be different if we had a better treatment.

So, let's say I imagine that we have a treatment, a single injection which I can give to a person and it takes their antiphospholipid antibodies away forever; one injection takes them away forever. Then I'd be perfectly happy to test everybody and give everybody who was positive the injection because it had no side effects, no downside and well, it would be good because they don't want to have those antibodies. But we don't have anything like that. All we have is these quite aggressive treatments like lifelong Warfarin. So, that's why it's important not to over-test and over-diagnose.

So, here's the question then: the tests are imperfect; the consequence of diagnosing it is not trivial, so if you test it in too many people and make those people have to have Warfarin you will actually be doing people harm; you'll be treating them unnecessarily. So, we're not going to test everybody, so who is going to get tested? Who should have the test? We have to be selective, but how do we select?

Now, I'm going to give you my answers on the next few slides, but I'm not going to tell you if these are the right answers because I don't think anybody has the right answers. And some of these I'll give you question marks because I honestly don't know what the answer is, but I can give you my opinion. All right? And all of the following slides are of the form 'not/but' because I'll tell you we do not test in all people like this, but we do test in some people like this.

So, first of all not the whole population. There is no argument at all for testing everybody for these antibodies. In fact it would be actually harmful to do that because if you tested say 100,000 people, 5,000 of those people would be positive, and they would be positive in such a way that it would never do them any harm; that

positivity is irrelevant to their health. So, if they're positive and then you treat them with Warfarin because they're positive you're treating 5,000 people unnecessarily, which is a bad thing to do. So, you do not want to test the whole population. But you do want to test some people, so who would you test? These are people who have never had a thrombosis or a miscarriage. So, would you test people with a strong family history? There's no guideline to say that you have to do that. Part of the reason there's no guideline is that it doesn't always run in families. There are lots of families where only one person has it. Now, personally it would be very easy to persuade me to do the test in a person with a strong family history. But even if I did the test I wouldn't necessarily know whether to treat that person; but I think the information would be useful. But I put a question mark because it isn't established but it's a good thing to do. It isn't established but it's good to do it in people with related diseases like SLE because we know that people with lupus have a higher risk of this condition than other people. So, all the people in our lupus clinic have the test.

But what about people that have suggestive symptoms, the sorts of things that Graham was just talking about? So, livedo reticularis is a rash that occurs on the thighs; it doesn't only occur in people with this syndrome but it's quite strongly linked. So, let's suppose somebody comes along to me with that rash and migraines; no thrombosis and no miscarriage. Am I going to do the antiphospholipid test? So, I put a question mark because nobody has come to me with that particular combination. If somebody did and said, "Do the test on me, Doctor" I don't know what I would do really, because if I did the test and it was positive what would I do about it? Would I put them on Warfarin? I probably wouldn't. But on the other hand if that person came along and said, "I've got these things. I've got a strong family history" you can see that you could argue for doing the test. But I don't have the answer. I don't know exactly what you should do about that. Nobody knows exactly what you should do about that.

We're on safer ground here when we talk about people with a thrombosis. Now, we don't test everybody who's had a thrombosis for Antiphospholipid syndrome. You could make an argument that we should do that – that's why I've put a question mark at the top. You could argue, okay, the person's had a clot, let's do the test, because if we do the test and it's positive it'll be good information and we'll change the treatment. The counterargument is: we know that most people just with ordinary thrombosis don't have the syndrome. So, then there's this question of worrying

people unnecessarily. So, currently we don't test everybody with one thrombosis. But there are circumstances in which you would do it. For example people who keep having thrombosis over and over and over again; you'd do it then. You might do it in people with an unexplained thrombosis: they've got a clot and we really don't know why. Let me give you an example: suppose I have a patient and this patient is a very heavy smoker and taking the oral contraceptive pill and has been on a long, long flight where they've kept still for a long time and they get a clot. That person has some risk factors; you might expect that person to be at risk of clots. Okay? But suppose I have a person who has no risk factors at all but just out of the blue they've got a clot. Maybe that person should be tested. Or a person who has a thrombosis in a very unusual place, just out of the blue, maybe in their vein going to their kidney they have a thrombosis, something really unusual. Maybe you should test it then. And people from the previous slide: so somebody with a thrombosis who also falls into one of these other groups, like somebody with a strong family history. Because we should have joined up thinking when we make this decision.

In other words if you're a clot doctor you should probably ask questions about pregnancy; if you're a stroke doctor you should probably ask questions about whether people have had lupus or miscarriages or so on, because it will help you to decide who gets the test.

Okay, so that's the thrombosis slide. What about people with a stroke? Now, we shouldn't test in every person with a stroke. Why not? Because particularly elderly people with a stroke it's unlikely that this disease has caused the stroke. It would be unlikely for somebody to get to the age of 80, never have had this syndrome, and then suddenly gets the syndrome which causes a stroke. That would be a really unlikely thing to happen. Plus some strokes are caused by bleeding and not clotting, and if you give a person Warfarin you make them more at risk of having those sorts of strokes, the bleeding ones. So, it's not negligible that risk. So, you don't necessarily want to test everybody with a stroke. But who would you test? Well, one set of people you might test are people under 50 because there is evidence that anybody who has a stroke under 50 they have a very high risk of being positive in these tests. And people from the previous two slides: somebody who has a stroke who has a strong family history or lupus or they've had recurrent thrombosis – you can see the evidence is adding up here to say who should be tested.

And what about people with miscarriages? Not all women with miscarriages because sadly we know that miscarriage is a very, very common thing. Many women suffer an early miscarriage even when they're perfectly healthy, so you wouldn't want to test every woman with a miscarriage because again you might get false positive results. But who would you test? People with recurrent early miscarriage. Now, Graham said that you have to have three before you get tested. And I'm like Graham, I don't really agree with that; I don't think should have to go through two and earn their test by having a third one. I think that's just unreasonable and cruel. So, I think you should test after two. But that's not what the national guidelines say at the moment. If there's a single late miscarriage late in pregnancy I think that it should be tested. And sometimes you would do it due to the mother's particular circumstances. I'm thinking now of a lady who I saw who was quite older than most first mothers, in her early 40s, she had had in-vitro fertilisation, IVF, it had failed many times, and she'd got pregnant, and this was probably her last chance. In that scenario I don't really mind over-treating. So if I give that lady Heparin and aspirin when she didn't really need it but she has a safe pregnancy I think that's a good outcome for the lady.

So, in some situations, somebody who's had just one early miscarriage or no miscarriage at all you might want to do it. And again the people on the previous three slides, the joined up thinking: the people with the family history, the people who have had the thrombosis and so on, these people you might want to test.

We don't have all the answers. None of us do. Not even Graham has all the answers – or maybe you do – but the tests are not perfect; there can be borderline results, there can be weak positive results. And so some people can be over-treated or under-treated based on these results. In other words there may be people who are positive in these tests and are having treatment and actually they didn't really need it – it might be the case. There may also be people who are under-treated, so people who have a weak positive result so it's not treated, and yet they really did need treating. It's not an exact science; there are grey areas. But the one thing I would say is awareness of the test is important. So, for doctors and patients to be aware of what the tests are, what the imperfections are and how we decide who to test. A good example of that is something I think we in this room can all be proud of, which is the fact that the Hughes Syndrome Foundation as an organisation for the first time has actually influenced testing on a national level. So, going back to that stroke slide I showed you: most strokes now are treated in stroke centres, so there are special

stroke centres that you will be sent to, and those stroke centres have national stroke guidelines, and those national stroke guidelines up till now have never said anything about Antiphospholipid syndrome. So, we have persuaded them to put something in. What they're going to put in is pretty much what I've said on the slide: in other words people under 50 should be tested, and people who have some of those other factors, like having SLE or having had recurrent thrombosis or having had recurrent miscarriages, clues that it might be this syndrome, should have the test. That's what the national guidelines from this September will now say, unless there's a last-minute change. And if the tests are positive they'll be referred to a haematologist. So, that's a big advance: people will be more aware; more tests will be done; more people will be picked up. And that was achieved not in a kind of flashy way – not all progress comes with banners and marches and so on – it was just very quietly by emails to people and making a case and persuading them. and it's something that I think the organisation has done. So, awareness of what the tests are, how they are done, why they are not perfect and how we use that to decide who to test is a good thing. Thank you.

**Graham Hughes**

Thank you very much Anisur. It's a pleasure next to welcome Beverley Hunt who's Professor of Haematology here and, as far as I'm concerned, the British expert, southeast corner of London particularly, on the new drugs used in the Antiphospholipid syndrome.

**Beverley Hunt**

So, what I normally do every year is we do a question and answer session about anticoagulation. I can't talk and help you individually because I don't know you all, but if you've got some general questions you want to ask now's your time. Do we have a roving mike? Let me get a roving mike. There we go.

Q1. Good afternoon. Moira Rigby, Sherborne. Professor Hughes mentioned that he would expect APS patients to be on a higher level INR, possibly four; and yet I read in a Canadian document that they found no benefit to be on the higher level, that it was between 2.5 was a good level to be on. Would you be able to clear that at all?

It's a controversial area, and the current practice that we do here and I think in most centres, I know Hannah does the same, is if you've had arterial events before, so that's a stroke or a heart attack, a clot in an artery, to run your INR between three to four. And if you've had a venous event, so a clot in the leg, pulmonary embolism, to run the INR between two to three. The Canadians and the Americans do it differently, and that's because they ran a trial and in their trial they found that if they ran the INR between two to three they didn't have the rate of thrombosis any higher than three to four, and the bleeding problems were greater with a higher INR. The problem is the trial was very flawed. So, they excluded people who'd already had a recurrent thrombosis and an INR of two to three, and they had very few patients with arterial problems before. So, it was good saying yes, INR two to three is okay for those who've had previous venous events, but it doesn't help us with those with arterial events.

And so many patients say, "When my INR is high I feel better, my head's less foggy, I can think more clearly" that that's how we go. I can see Hannah smiling at me because we agree on this one. Another question? This one. Oh Graham. Stand up straight.

**Graham Hughes**

This is my chance to get some help. If a patient has a bad time on Warfarin and needs an INR of say 3.9 do you find more problems with the new oral anticoagulants than with the others?

**Beverley Hunt**

We're not using the new oral anticoagulants in anybody who needs an INR of three to four. We don't know what dose of the new oral anticoagulants to use, and whether actually they have any benefit. I think that the new ones work in a very different way. So, when you're on Warfarin if you look at the whole day from nine o'clock in the morning, nine o'clock at night, nine o'clock the next morning, your anticoagulation is thin for 24 hours. Whereas when you're on Heparin and when you're on the new tablets your blood thinness does this. So, you've got periods of time when you've got very low levels of anticoagulation, and it seems to me, that's how I interpret it, that

you need the constant anticoagulation of Warfarin. I think that's the best way to explain it to lay people.

Q2. I've seen some suggestions of a link between medium and longer term of Apixaban and osteoarthritis; what's your experience and judgement?

Sorry, a connection between?

Q2. Medium to longer-term use of Apixaban and progress of osteoarthritis.

I'm not aware of any data around that. Do you want to tell us a bit more about it? Hannah? No, we don't know anything about that.

Q2. There's no point in pursuing it, is there?

And actually I'm quite surprised because Apixaban has been around for a very short period of time and osteoarthritis is a very slow disease, so I'm surprised that anyone has found that connection. I'll have to go back and google it.

Q3. You've just talked about the peaks and troughs of Heparin. For patients who aren't able to take Warfarin what other choices are there?

I think we all think that Warfarin is the bees' knees for Antiphospholipid syndrome. There are a few patients who seem to be better off on Heparin. Now, why that is, well I could give you an academic suggestion but really we don't know. So, some patients are on Heparin; a few patients are taking a drug called Fondaparinux which is a synthetic Heparin. Hannah is going to talk about using the new oral anticoagulants in a select group of patients with Antiphospholipid syndrome, so you'll hear about that in a minute.

Q4. I was just wondering whether or not you had any mechanism for making sure that your colleagues were aware of the differences of levels of anticoagulation. I've just been reviewed and it's been completely different; we've gone the Canadian way rather than the English way, and I have had arterial clots so I am obviously a bit concerned.

So, across the UK there isn't agreement either. The British Society for Haematology guidance says to start two to three and switch up to three to four if the patient has problems. So, there isn't even agreement across the country. And you have to slap our wrists because I don't think we've done enough research in this area to convince everybody. So, thank you for reminding me we need to do some more research.

Q5. I've never had a thrombosis but I have had lots of miscarriages. They were a very, very long time ago and I've been on Clopidogrel and aspirin, not together, one or the other, for over 15 years. And those drugs have caused me a huge amount of problems, gynaecological problems with excessive bleeding. And I'm wondering if I should have been on them at all, and if somebody hasn't had a thrombosis should there be a cut-off?

You do look remarkably well, I have to say. You're asking about just having an antibody, having had obstetric problems, never having a thrombosis. We've come a long way since 1983 when Graham described Antiphospholipid syndrome, and I think we were all pretty horrified the first few years when we started looking after patients because we saw the very worst end of the scale; so people were very damaged by lots of blood clots and things. We were fairly aggressive with the treatment. And as time has gone on we've found more and more people who have never had a thrombosis. In my clinics I have lots of women like you who are perfectly healthy, thank you very much, and they've had obstetric problems in the past, they've never had a thrombosis, and in actual fact some of them lose their antibodies as time goes on. And so we're getting much more conservative. Personally my practice is not to put people on long-term aspirin and/or Clopidogrel if they have antiphospholipid antibodies and they're healthy, they don't smoke, they have a good diet, they have regular exercise. There isn't enough evidence out there to support the use of long-term antiplatelet agents, which is what you're on.

Q6. I'm really enquiring for my daughter. Is there a re-test she can have?

You can always be re-tested. The tests have got better.

Q6. Does anyone ever get better?

She's asked me does anyone ever get better; and I think people's antibodies do go occasionally. It's not published unfortunately, but the women that I must have followed for five to ten years who had obstetric problems, who had little levels of antibody seems to disappear over a period of time. So, well worth getting yourself re-tested.

Q7. I just wanted to ask a question, I know it's been asked in previous years, about potential antidotes to the newer oral anticoagulants. I know to a certain extent they wear off over time and you don't need one; but when you do need one are there some licensed now?

So, we have one now available in all the hospitals for Dabigatran. Dabigatran was the first new oral anticoagulant, but we don't use much of it at all in this country. If you look at the prescription habits here most patients are on Rivaroxaban or Apixaban in the UK. We are trialling the antidote to Rivaroxaban and Apixaban at the moment. It will probably get licensed next year. The real problem with the trials is that we're all enrolled and no one's got any patients to put in the trial because very few patients have major bleeding on the new drugs. And you're going to tell me you know somebody, yes?

Q7. I was going to tell you I am that somebody.

Oh, you are that somebody!

Q7. That was why I was asking.

Okay. Are you all right now?

Q7. Now, well debatably. I had a major bleed while I was on Rivaroxaban and I was in hospital and I was taken off the Rivaroxaban and obviously because there was no antidote they had to wait for it to wear off. In that time I developed CAPS, so I am very interested in there being an antidote for people going forward so that that doesn't happen to anyone else.

Okay, I'm sorry to hear that.

Q8. I'm from the USA, which I think is probably the worst country to be in to have this disease. I've finally, with help of Professor Hughes, to get the doctors to

understand in the US. Currently I'm on Eliquis and Plavix both, but they seem to be exactly what you said: they have a tendency to go up and down and I can really feel the symptoms. But recently it's really kind of destroyed my stomach. I'm having a really hard time with it.

Okay, I'm really sorry you're having a bad time. I can't comment on your case; I don't know your details. Rivaroxaban we know is associated with dyspepsia a little bit, and perhaps slightly higher rates of gastric bleeding than Apixaban. And having an antiplatelet agent as well will make your risk of bleeding go up considerably. But I can't comment any more than that, sorry.

Am I done? Thank you Graham.

**Graham Hughes**

Thanks very much Beverley. Now the expert north of the river on these drugs is Hannah Cohen. Welcome to the south of the river.

**Dr. Hannah Cohen**

Thank you Graham. Good afternoon ladies and gentlemen. I'm very honoured to be invited here, and I thank Kate Hindle for that. Today I'm going to present the results of the Rivaroxaban in APS trial and, has already been mentioned, I would like to please request that whatever I say here is embargoed because the final version of what is going to be published, which we hope will come out in the next few months, may vary a little bit from what I'm saying today. So, this is the essence of what we have found.

So, what am I going to talk about? Firstly, why we did the RAPS trial. Then I'm going to tell you about the RAPS trial itself. I have to warn you now, a government health warning, there's going to be some scientific data. I thought about how I could tell you about it without showing that, and I then decided I couldn't, so that's going to be the case. So, I'm going to give you the results. And then I'm going to at the end say, "What does this all mean for a patient who has APS?"

So, Warfarin we all know, we may not love but we all know, and it's been around since the 1940s when Karl Link discovered it after he had Ed Carlson come, who was a Wisconsin farmer, who drove 200 miles in a blizzard and found the only

person who was still there in the hospital, in the research institute, and said, “Here’s a can of blood from my dead cow, my prize dead cow, who has unclottable blood, and you’ve got to sort it”. And he did, and he discovered Warfarin, which was hailed first of all as a rat poison, and then from that they moved to giving it to people. One of the earliest being President Dwight Eisenhower – so from rats to presidents – and he did very well. And so we know and we love Warfarin in terms of it being effective. However, as we all know, it’s got numerous problems, which I won’t go into in this lecture, and so because of its limitations there has been a major drive to identify new alternatives for anticoagulation.

So, the question is: can we do better? And the answer is: possibly. So, the new direct oral anticoagulants, which aren’t really that new anymore because they have now been around in dribs and drabs since about 2008 when they first started being licensed, have got definite advantages. So, these have got very specific effects on blood coagulation, unlike Warfarin which affects multiple parts of blood clotting.

So, what are the advantages? Well, the first thing is it’s fixed dose, so what you give is what you get. The second is, because of that you’ve got predictable anticoagulant effect i.e. you don’t need INRs, and so no routine anticoagulant monitoring. There are no dietary restrictions, unlike with Warfarin. There’s no interaction with alcohol, but that doesn’t mean you should drink yourself silly because alcohol has got other effects on blood clotting and obviously lots of other things in the body as well. And there are also fewer drug interactions than with Warfarin, which as anyone who’s on Warfarin will know, is a huge problem. Beverley’s touched on bleeding with the direct oral anticoagulants, and yes this is challenging at present, but there is national guidance and each Trust, each hospital should have guidance about how to deal with a patient who comes in bleeding.

Why did we do the RAPS trial? The RAPS stands for Rivaroxaban versus Warfarin in patients with thrombotic Antiphospholipid syndrome, with or without SLE. SLE being systemic lupus erythematosus or lupus. Why did we do the RAPS trial –I’ve sort of skipped a slide – so here I can say the first thing we know is with the direct oral anticoagulants they have been found to be both safe and effective compared to Warfarin to patients who have venous thrombosis i.e. deep vein thrombosis, usually thrombosis in the legs which if not treated the clot can dislodge and go to the lungs,

and that is called pulmonary embolism which can be very serious indeed. The big trials have shown that these new drugs are effective and safe compared to Warfarin.

However, it's uncertain whether their use could be extended to patients who have got Antiphospholipid syndrome. Why is this? Although APS is held to be a rare disease it has been estimated that it may be present in 10% of patients with DVT. However, APL antiphospholipid antibodies was not systematically documented in the DOAC trials. And the question also arises whether antiphospholipid antibodies could interfere with the anticoagulant or blood thinning effect of these new drugs. So, there were various questions to answer. So, whilst the manufacturers did not specifically excluded that DOACs could be used in patients with Antiphospholipid syndrome, the specialists in the field felt it was very important to actually do specific trials in our APS patients.

So, we set out to do this. The primary aim of RAPS was to demonstrate that the intensity of anticoagulation achieved with Rivaroxaban, which was the drug we chose because at the time of setting up the study Rivaroxaban was well established or better established than some of the other DOACs. So, the anticoagulant effect achieved with Rivaroxaban was not inferior to that of Warfarin, using a test called the thrombin generation test. And I will go into this with you on the next slide and in a bit more detail. And we thought it was important to also look at other things, so what we wanted to also do was to look at whether there were patients who had thrombosis as a result of having the Rivaroxaban and we wanted to see whether there were any problems with bleeding in comparison to Warfarin or any other adverse effects. And we also wanted to look at quality of life, because one might expect that if you don't need INR monitoring or there are no interactions with food or alcohol that quality of life might be better. And we also thought that we needed to see, by doing some laboratory tests, that patients were actually taking the drugs in both groups i.e. the Warfarin patients and the Rivaroxaban patients.

So, going back to the thrombin generation test. Why did we choose a laboratory test first of all? Well, we did this because we wanted to do the trial on relatively as small a group of patients as we could do and get a meaningful result. So, we worked out that in the group of patients we were going to study fortunately with Warfarin these patients have a very, very low rate of thrombosis and we would have needed

thousands of patients to actually answer the question. And that's why we went for a laboratory surrogate marker of blood coagulation.

So, thrombin, what is thrombin? Thrombin is a blood clotting protein and it's a really important protein because when thrombin is formed the next step in the blood clotting pathway is to form a blood clot, so it's a really important thing. And what we can do in the laboratory is we can simulate this by triggering off blood clotting and then measuring how thrombin is generated and how much thrombin is generated.

So, now I'm going to show you a graph of this. Here's a picture showing this, and what we have here is that we've simulated the blood clotting here. What we see first of all is that there is a peak of thrombin, this is all in the laboratory, and then this sort of goes on and then tails off. So, this is the peak here, and if we look at this whole area under this thrombin generation curve, which is also called a thrombogram, then what we get is literally the area under the curve, which is called the ETP or endogenous thrombin potential. So, in other words what is the potential for forming thrombin in this patient? And we used this test because it has been shown that this test, if the thrombin generation is high, it correlates or it predicts well for blood clotting and thrombosis to occur. And we thought because we're looking at two very different anticoagulants we could actually use this test to look at the effect of the anticoagulants and how much they reduce this based on their anticoagulant effect.

So, what we did in this trial is we took patients, and as Beverley mentioned, a very highly selective group of patients who had DVT and/or PE, and these patients needed a target INR of 2.5. So, with APS patients who have had a first event of DVT or PE, a target INR of 2.5 is appropriate. And what we did is we randomised them to either stay on the Warfarin, so we randomly allocated them to that, or to be switched to Rivaroxaban. And we looked at this thrombin generation at six weeks after starting and we continued the treatment for six months. At this point I'd like to say the trial, we had a trial steering committee, we had an independent data monitoring committee to see for any adverse effects going on, and we had Kate Hindle who was our lay member who was extremely helpful. And what we were looking at was to see if there was any new thrombosis as well. And we looked at other markers of blood clottability, so-called in vivo coagulation activation markers, and these are important to look at. And we looked at safety: we looked at safety from all perspectives, whether anything nasty was going on with the Rivaroxaban and also all bleeding

events, minor bleeding to major bleeding. We also looked at quality of life and, as I said, we looked at laboratory measures to see the Rivaroxaban levels in the Rivaroxaban patients and the INR in the Warfarin patients and also how well they stayed in their INR range through the trial.

So, now I'm going to show you the results. The first thing I'm going to show here – so don't all fall down – is the flowchart. We screened 941 patients, so we really cast the net wide to find the right patients for this trial, and we ended up with 116 which we had previously calculated and estimated was the right number to get the results that we needed for this trial. And we ended up with a virtually equal number in both patient groups: at the bottom we ended up with 54 patients in the Rivaroxaban group who were analysed for the laboratory thrombin generation and 56 in the other Warfarin group. And the only patients we excluded were those where the results were below the lower limit of detectability. And all patients received the treatment that they were supposed to receive. Here are the baseline characteristics. I'm just going to point out to show you that the patients were well-matched in both groups. What we did is we had two centres, so we had UCLH where I work, and we had Guy's and St Thomas' Hospital where Beverley works, and this was a collaborative trial between our two centres. What we did is we stratified the allocation so that there was not going to be any bias depending on which centre the patient was at or indeed whether or not the patient had lupus. And the patients, as you can see in the bottom row, were all DVT or PE patients. We also had patients with blood clots in the veins, not only in the legs but in other sites as well.

Now, this I'm going to have to show you. If we look at the EPT, if you remember I explained this, and this is getting higher and higher. These dotted lines here are the upper and lower limits of normal. I don't think it needs a scientist to say that the ETP was higher in the Rivaroxaban group – here's the middle value here and the middle value here – and lower in the Warfarin group. So, in other words there looks like there was more thrombin being generated in the Rivaroxaban group. But virtually all the results were below the upper limit of normal; they were in the normal range or below. Now, the peak thrombin, if you recall I mentioned, this on the other hand was the other way round: so the peak thrombin was actually lower in the Rivaroxaban group, implying more anticoagulant effect, and higher in the Warfarin group.

So, what does all this mean? This you've seen before, and this is just to remind you that here we have the peak thrombin here and the area under the curve. Okay? Now, I'm going to show you this in the Warfarin patients and the Rivaroxaban patients to try and explain what we're seeing. So, here we have a normal individual, and you can see it looks very much like the one we just saw, so here's the peak, it's a sharp peak and a short tail, and here's Warfarin patients, the green one, the same only less because there's less thrombin because the patients are on Warfarin. But if we look at Rivaroxaban what is this? It just goes on and on and on. So, what happens is when you look at the area under the curve it's big because it just goes on and on and on. And the way in which the machine is set up for this particular test that's what we get. So, what we did also is I said we looked at thrombosis and bleeding; we found no new thrombosis in any patient in the trial, both groups. We found no major bleeding event – this is bleeding where a patient will need to be hospitalised, where patient needs blood transfusion, this is serious bleeding – none of that. We looked also at minor bleeding and clinically relevant bleeding, which means if a patient say has to speak to a doctor or has to get some sort of advice or if it disrupts the patient's life – and there was no difference in the two groups.

The other thing is there was significantly better quality of life in the Rivaroxaban patients. I'm going to show you what I mean by this. It was a very small difference but this was significant. And this was based on a thing called the VAS, which is visual analogue score, and this is seriously not complicated. Let me show you what this is, so this is what this is: you literally give the patient this scale here, and bottom is the worst health you can imagine, i.e. rubbish, and the top is singing in the rain. So, you ask the patient themselves to put a cross where they feel they are that day and also to write the number. And that's as simple as it is. This actually is a very useful way, very simple, but very useful way to look at quality of life. And this was better in the Rivaroxaban patients, even with having to come for all the trial visits for example.

So, we can summarise to say Rivaroxaban was inferior to Warfarin based on the ETP; however the peak thrombin was better in the Rivaroxaban patients. And we believe that the higher ETP if you remember that curve I showed you that went on and on and on, is related to something to do with the way in which Rivaroxaban is working, rather than a real effect on blood clotting. The coagulation activation markers, the markers of blood clottability that we looked at other than the thrombin

generation, these were normal in virtually all the patients in both groups, and very much the sort of picture one might expect in a group of patients with thrombosis, and there was no difference in the two groups. And lastly the quality of life was better.

So, in conclusion we believe that we can say that there was no difference in thrombotic risk between patients taking Rivaroxaban at the standard dose and Warfarin at the standard INR of 2.5 in this very particular group of APS patients who have first event VTE, or if they've got a second event it would have been off Warfarin. This is based on the overall thrombograms, thrombin generation, the coagulation activation markers, and the fact that it's very encouraging that we saw no thrombosis or major bleeding in both groups, and improved quality of life.

So, what does all this mean? Well, we believe that we can say that Rivaroxaban is a suitable alternative to Warfarin for these patients, this very specific group of patients with blood clots in the veins needing INR of two to three. But further trials must be done to define the role of these new direct oral anticoagulants in APS patients who require higher intensity Warfarin. And I'd like to just acknowledge the huge number of people who were involved in this trial and also the funding which was primarily from Arthritis Research UK, and most of all the RAPS patients. Thank you.

**Graham Hughes**

Thank you very much indeed Hannah. Our last speaker in this session before we have questions is Lindsay Bearne, works with Sofia Georgopoulou and Heidi Lempp on 'It's as if I've hit a wall'.

**Heidi Lempp**

Thank you very much for inviting me. I came here about five years ago and was very shy, and I was invited by Kate saying, "If you want to meet patients with APS come to our patient day and you can talk to them". And what I was really interested about, because I didn't really know a lot about APS, what are the main complaints or the main difficulties, and everybody told me that they were very fatigued all the time. So, I looked in the literature and couldn't really find any study on fatigue in APS patients. And I'm a qualitative researcher; this means I'm doing interviews and focus groups. So, we decided we're doing a bigger study where we give people questionnaires and also interview them about their experience of having fatigue and APS.

What I'm going to present you with my colleague, Sofia, we've been doing this study together, is telling you about the interviews we did with patients. We won't tell you the findings from the questionnaires because we haven't completed that yet. So, it's work in progress but we have almost interviewed the amount of people we wanted to interview.

The topic of our talk is, 'It's as if I've hit a wall', this is the topic of our study. I will tell you a little bit about the background, the definition of fatigue, I will tell you what we did and what we found, and a discussion and conclusion.

So, a definition which I found very helpful because it seems very comprehensive and it was used in a lot of international studies means: fatigue is perceived as an unpleasant, unusual, abnormal or excessive whole body tiredness, disproportionate to or unrelated to activity or exertion and present for more than one month. Chronic fatigue is constant and recurrent. It is not dispelled easily by sleep or rest. And it can have a profound negative impact on the person's quality of life. Is that something which resonates with your experience? Yes, some people are nodding, it's good.

Another much shorter definition is: an overwhelming sustained sense of exhaustion and decreased capacity for physical and mental work. I also looked at other studies part of this in the background and there weren't really many interview studies or qualitative studies from other muscular skeletal conditions such as MS, osteoarthritis and rheumatoid arthritis. So, there seem to be a need to really do systematic study in the experience of fatigue in patients with muscular skeletal condition.

But what I also found when I talked to patients five years ago said they attribute a huge importance to fatigue as a symptom, and often feel it's overlooked by clinicians in the outpatient clinic. The clinicians told me as well that they often don't know what to do about it, but it would be good to have the experience of patients.

So, the main questions for the questionnaire study were: what is the occurrence of fatigue and physical inactivity in people with APS? We did this mainly in Guy's St Thomas' Hospital. For the research questions for the interviews were: what is the experience of fatigue and the impact it has on individual's life? What is the experience and impact of physical inactivity and its relationship with fatigue? What coping strategies do patients implement to manage fatigue in their daily life? And

what is the experience of discussing fatigue with the healthcare staff? So, these are the questions we wanted to find out when we interviewed the patients.

The inclusion criteria were that you had six-months' history of APS either thrombotic obstetric one, and was through the Sydney classification; you have to be an adult and you have to able to speak English, sorry, communicate. The exclusion criteria is that you have autoimmune diseases, that you have for example infections such as TB etc, you have a positive antinuclear antibody, you're pregnant or breastfeeding – probably tired because of that, and also if you have a BMI over 30 and are drug or alcohol dependent.

So, what did we do? It's work in progress, as I said, and has two components: one is a questionnaire, which we're still doing at the moment. We have recruited about a third of the patients; we need about 98. And we did one to one interview studies with 18 patients so far. We're hoping to do 20. And we have thrombotic and obstetric patients. We did first a pilot study which is very common where you try out your interview guide and see if patients understand the questions we wanted to ask them, and we got positive feedback. And we got also ethics approval in 2014.

So, we started in June 2015 with the interviews. We gathered the data, either face to face, we met the people in their homes or in the clinic, or we did it over the telephone. The duration of interviews took between 20 and 60 minutes. Some people had such a busy life they said, "I can only squeeze you in for 20 minutes so you have to ask your questions very quickly" which is fine. And we had two interviewers.

From the data analysis so far we have identified five main themes: the unpredictability of fatigue, which people talked to us about; the impact it has on their lives; the physical activity is really important to patients but it's often difficult; the individual coping strategies, which were amazing to me to see how you manage to live with fatigue and APS and anything else – sometimes I got fatigued reading about what you told us, it was just amazing; and what help and support you get from healthcare staff.

These are the characteristics from the patients, just to let you see it. Basically we found out that people in obstetric they're younger, that their disease duration was shorter, and they had less disability than people in the thrombotic one.

Just the metaphors you used we heard from you in the interviews were really, really interesting, and I always love to start with that when I do qualitative study. So, you said things like, “Fatigue hits you like a truck.” “It is as if you’ve hit the wall.” “You feel jet lagged.” “A physical weight pulling me down.” “It’s like a ragdoll with no stuffing left”. Then we’ve looked at this particular picture, which matches the next one, which is, “I’m climbing up a really big hill with a massive rucksack on my back and I’m struggling to get to the top” I thought this was a really lovely way to describe it. “I feel drained” and, “Like somebody pulled the plug”. These are ways of describing; we asked patients if they could describe to us their fatigue.

So, I’m handing over to Sofia now and she will tell you what we’ve found.

**Sofia Georgopoulou**

From the analysis that Heidi did we have two examples that patients use to describe their fatigue. And as you can see, we’ve split them into the thrombotic group and the obstetric group to see whether they were similar or different. One account from one patient belonging to the thrombotic group describing the fatigue is, “I consciously avoid trying to describe because you get quite frustrated trying to describe it to people. The only people I will happily discuss that are other APS people because they seem to get it. I find it extremely hard to describe my fatigue”. Which was quite a common response in many people we interviewed.

Now, to compare it to a person who has obstetric APS, “I literally had to fight sleep all day long, and I was scared of falling asleep. If I got onto public transport I’d think, ‘I must not fall asleep and go past my stop’. When I put the dinner on I’d think, ‘I must not fall asleep and burn this’. I was throwing away pans on a regular basis. I had a small child and I was thinking, ‘I must not fall asleep’. I’m in charge of a small child, and then literally the minute my head touched the pillow it was like a blessed relief that I no longer have to fight this; I’m allowed now to go to sleep”.

So, the analyses so far have uncovered five themes, as Heidi mentioned before: Theme one talks about fatigue and the unpredictability of it. To give you a little overview, people did say they couldn’t identify a pattern; they couldn’t identify any trigger of fatigue; and it wasn’t always easy to predict how long fatigue would take to go away or what they could do about it, because just taking some rest and pacing

themselves helped but didn't really make such a tremendous difference, so they just had to wait it out.

One account from a person with thrombotic APS was, "It can come in waves of three, four, five, six weeks, like I can be absolutely constantly fatigued with what I call bad fatigue. I get some kind of fatigue every day but not necessarily what I would consider bad. You know the fatigue like I said can happen any day and it comes out of the blue". And to compare it to a person with obstetric APS, "You never know quite what the day is going to be until you reach the end of it. It's a rollercoaster, you know; it's not something that is the same every day. Every day is different. You could wake up one morning and feel on top of the world and feel like you could run a marathon, yet the following day you could wake up and think, 'oh my god, I can't even get out of bed this morning'. It really does depend. It's a day to day thing; there is no pattern".

The next theme was what impact APS had on daily life. So, people tended to talk about the impact of the fatigue in the APS on work, on kids, on daily activities they had to undertake. So, one example from the thrombotic APS group, "I work flexitime, so on a day where I just think, 'I cannot do this anymore; I just need to get myself home' I can leave within reason". Or as far as kids are concerned, "She's quite demanding, as all children of her age – talking about her daughter – are. Wants to play or wants to go somewhere or go for a bike ride. I find it very hard because going on a bike ride isn't really what I want to do. And I can't at the moment do a bike ride, so I have to walk alongside her and try to keep up some sort of pace with her".

Obstetric account, "Oh yes, and they're teenagers so everything's a drama. But they're very understanding inasmuch as I've told them everything. They're aware of my condition; they're aware of my medication; how do I get tired. So, it doesn't stop them pressing my button sometimes. If I overdo things I get all sorts of strange symptoms which then grind me to a halt. Over the years I've learned what suits and what doesn't. I'm struggling a little bit today because I've spent two days at my daughter's looking after the children for her whilst she went to work. So, yes, it'll take me two or three days to get myself back on track".

Theme three that was identified talked about physical activity matters. Lots of you did say that you love to walk, to swim or go to the gym but it's not always feasible to do

so because of the fatigue. One account by a thrombotic patient was, “So, I do roughly between 15 and 20 minutes of walking a day, which is what the national guidelines say”. Another one, “I do go with my mum, who looks after me, and we sit and chat in the pool. So, it’s sort of a social event; I meet people in the pool as well. So, it’s a feel-good factor with swimming more so”. And equivalent to in the obstetric group, “I used to belong to a gym and go to a gym, and I had to stop that because when I got the fatigue I just couldn’t physically do what I need to do. I’d be going to my Pilates class and just lying on the floor because even lifting your legs doing the exercises was too much effort. And I remember saying to myself, ‘just do it, do the exercise because it will make you feel better’. But no, it never did. I used to be fine, there were other times when I could do spinning and everything, but not now. Swimming I like; swimming is good. As much as I like walking as well, but some days you just can’t be bothered really”.

And moving on to theme four, which refers to coping strategies that most of you employ when it comes to fatigue. People don’t really want to talk about it with their family to avoid overburdening them; they don’t want to show weakness; and they have to adjust the workload at their job or in the house to pace themselves and give them some room to recover from their fatigue.

So, thrombotic APS, “I think one of the things when you have fatigue is that you don’t want many people outside of your immediate family to know about it. I don’t talk to my children about it although they are all grown up because they don’t want to think of their mum as anything else but superwoman” and the obstetric account, “Now it’s not so bad because I’ve changed so many factors in my life to cope with it”. “Not working full time I’m having a lot less stressful job. Where I used to run a marketing department, I’m now a TA in a school so I’ve completely changed my lifestyle”. “I think I used to get anxious about how much there was to do. So, instead of not given myself a list of ten I’m doing seven and then worrying about the three; I’ll give myself the list of six and then say, ‘well done, you did all of that’.”

And the final theme identified so far was how people talk about, and if they talk about, their fatigue with healthcare professionals, which is not really on top of their list because there’s not much that healthcare professionals can do about it, and sometimes it’s not a priority symptom that they actually ask patients about. So, the account from the thrombotic group is, “I did obviously talk about it when I was first

diagnosed and they did take it seriously. But now there is no point keep going on about it to them". Another one, "No it's me who brings it up to them. They never ask me about my fatigue". And a third one, "My brilliant APS nurse she understood because her sister had APS, so she completely understood how it makes you feel". And the obstetric APS description, "I don't bother. There's nothing they can do about it, is there, so I don't. I plod on. My tiredness and things I can live with. It's the aches and pains and things like that that get on my nerves. But generally speaking I don't bother. I think they note it down as par for the course, but I wouldn't say they do anything with that information. I don't know what they do with that information anyway".

**Heidi Lempp**

So, that gives you a snapshot of what we found when we talked to patients with Aps. And we hope next year we'll be able to tell you a little bit more about it from the interview studies, but also from what the questionnaire showed as well. So, to finish off, the accounts from both groups of obstetric or thrombotic APS seems very similar in the account about the fatigue. All patients seem to employ coping strategies in order to manage their fatigue very well.

The physical activities are very important but it's often very difficult when they're very fatigued. And patients tend to avoid bringing up the issue of fatigue when they go to clinic due to the lack of observed response or empathy by clinicians.

So, in conclusion, the study is in progress and the initial data analysis suggests that fatigue is an overwhelming symptom for patients which is very challenging to manage. It is important to obtain, I think, the first study we know which has been done systematically in finding out about the impact of fatigue in people with APS, so I think it's really important to understand what patients have to say about this. And we hope to complete the questionnaire by next time when we come and introduce that.

So, before I stop I just want to acknowledge all the people who helped us, which are particularly the patients who talked to us; then the people who did the research, the researchers; then the people who transcribed your long, long interviews, which are really interesting; the administrators; then Professor Beverley Hunt; Doctors ((Preen?)) and Lewis Nell who gave us access to the patients; Kate Hindle and Yvonne who really encouraged to keep going with the interview study; and the

Hughes Syndrome Foundation who gave us money for the transcribing. Thank you very much.

**Graham Hughes**

Thank you very much. I wonder if Anisur and all the speakers, I think Beverley is here, could come up and have question and answer. Any hands up?

Q1. You mentioned earlier about being a fan of self-testing, how can I get my doctor to support this? I've already purchased my machine and I would really like his support.

**APS Patient's Day 2016**

**PART 2**

**Lynne Kirwin**

Right. We're going to start on the second half of this afternoon. And first on our list is Bethan Thomas. There you are, Bethan. A patient who's going to speak about her experiences. Thanks, Bethan.

**Bethan Thomas**

Okay. So, hi, I'm Bethan. And I was diagnosed with Antiphospholipid Syndrome in 2012. So I'm going to talk a little bit about how I've treated my mind and my body, and obviously everybody's very different, but this is a taster.

I don't have any kind of formal slides, but I have chosen this picture of me taking in the moment in Florida, on a beach. So enjoy that.

To set the scene, I grew up in a village in Hampshire. I moved to the bright lights of London over 12 years' ago now. And began a career in communications, very busy. I'm sure it's not an unfamiliar story to many people, but I spent ten years very much focused on my career. But in 2011, my finely tuned routine of keeping the plates spinning came to an end. I had my usual frantic run into a holiday, fitting ten days of work into five, very little sleep, and after a flight to see my sister in Florida, I started getting cramps in my leg. By the time I got back, I was feeling sick. Short of breath. About ready to chop my leg off. I'd suffered a DVT and a pulmonary embolism.

At that point, I took it all in my stride. I was in hospital for a few days. I had a week back in Wales to be looked after, and then I was back to London and back to work.

And from the outside, I think I looked okay. I looked like I was coping. I did do shorter hours for a while. And by shorter, I mean seven or eight hours a day, not the usual 12, 14. But outside work I was literally just existing. I was sleeping and eating and not much more. And the more I tried to make myself feel better by feeding myself worth through professional achievements, the more I struggled mentally. It

was the first time in years that I'd stopped to really question what I was doing all of this for. And this really hit me when I had the Hughes Syndrome diagnosis six months' later. That was when the realisation struck that it wasn't something that would just go away. It was something I had to adapt to and take as seriously as I had done my career.

So I knew I needed to change my life. I knew I needed to get fit and healthy physically. And I knew that mentally I had to find a way to shift my focus. And the way I was feeling about myself. So from the point of diagnosis, meeting with Nicky, a psychologist here at St Thomas's, really helped me to help myself. I could see that if I put the time and effort into taking on board the pointers from each session that I got more and more out of it.

I think it helps that I have a very inquisitive mind, and I love to learn, but I think everyone can spend more time kind of looking after themselves. So for me, my treatment of Hughes Syndrome has not just been about finding the right medicine and taking that, it's also… this journey has also been about me being the healthiest person I can be in my mind and my body.

So my natural instinct, after the DVT and PE, was to go back to what I knew. But actually what I needed more than anything was to change what I was doing. For starters, I couldn't work the same hours. I needed more sleep, and I couldn't respond as quickly because I would struggle to find certain words and articulate things properly. This was probably the biggest problem for me at work. It was something that other people noticed. Or I thought other people noticed. And it made me feel completely worthless. So I became more and more anxious about these speech problems.

So through the psychology sessions, I went through the process of questioning my own thoughts and feelings, challenging my own beliefs, and looking at what was triggering my emotions. This took a lot of practice. And I have to say that four years on I still think back to advice in those sessions, to try and alter my own perception of things.

So coming back to the words, though in reality many people struggle to find words, and we all have our own coping mechanisms to get around that. So I might have started phrasing things in a slightly different way, but I was still able to communicate what I meant in a roundabout way. So I now look at most things as an opportunity, and in a positive way, rather than assuming I've not done something right, or I could have improved. As they say in lots of those leaflets, eight or nine really is fine.

So I think the biggest change around challenging my beliefs has been me being able to let go more. I used to feel such huge responsibility for my family, for my friends, for my team at work, and maybe you might say that means I've become a bit more selfish. I don't think I have. I just don't assume that actions are expected of me. Or anyone else, for that matter. And I don't try and make sense of absolutely everything. For example, both of my sisters have moved to live abroad. That really affected me for a long time. Because I felt such a responsibility for my parents as the only remaining daughter here in the UK, and also in a way rejected by them. Not wanting to be here with us.

But over the years I've learned to let that go. I realised that decisions they've made are complex and personal, and that any negativity around those decisions is not going to do me or them any good.

So the second important thing that I started doing was living in the moment. I used to go through life in a bit of a daze, and I'd barely see daylight during the week and at weekends I would pack so much in that I was almost, you know, focusing on what was coming next, rather than enjoying what I was doing.

I started mapping out how I'd spend each week. Making sure I made time for relaxing, for exercise, for socialising, for learning. I thought about what I used to enjoy doing, and I joined a choir, I got in online dating. I got myself a good book. And part of that was thinking about the people that made me feel positive. And spending more time with those people. And either spending less time with people that made me feel negative, or actually talking to them about it and explaining how I was feeling.

And I had that conversation with someone very close to me. I found them incredibly critical and negative. It was really getting me down. So I didn't do it in a confrontational way, but I explained what I was trying to do in terms of spending time with positive people, how it was impacting my health, and they reacted really well, and they changed how they talked to me and reacted around me.

And the third thing I focused on was changing my relationship with work. So I tried for about six months to make changes to how things were in my agency. But as much as I tried, I just couldn't break out of that routine. I'd got stuck in it. So at the end of 2012, I handed in my notice and started looking for a new job.

I still wanted to work for a company that I believed in, but my priorities had changed. And I also wanted to make sure that I was giving myself time to focus on my health and my relationships.

So I spent two years in house with a tech company. I worked hard, I did my job to a good level, but I wasn't working every hour of the day. What I was doing was giving myself time and space to do things for me. I made sure I was going to the gym. I did yoga once a week. I downloaded Headspace and did meditation. I slept for seven or eight hours a night. And I signed up for a 10K run to give me something to work towards.

It also meant that I had the time and energy to change my relationship with food, something that I've always felt was an issue for me. And one that I'm sure has really impacted my health for many years. So I tried the paleo diet. I lost over three stone in weight. And since then I've moved more to a kind of gluten free vegan diet. So it's something that's constantly evolving. But I've found something that I'm really passionate about, and I really feel that it makes a real difference to how I feel day to day.

Importantly I think it's also given me like the mental stimulation in the same way that I used to get from my work.

So of course there are challenging times, and I still push myself too hard sometimes, but I'm now confident that I have the mechanisms to cope with it. I no longer feel

that I need to strive for perfection. I'm not looking for approval or in fear of disappointing other people or of losing control. I'm genuinely enjoying the moment and the journey, and when I feel like things are too much, I step back and reset.

So as an example, I was made redundant in February last year. And in my old world, that would have been about the worst thing that could have happened to me. The one thing that was giving me a real sense of self-worth being pulled from under my feet. But it was actually a welcome relief. It had become quite a negative environment for me. And it gave me the opportunity to do something different and take some time to explore what I wanted to do next. So I spent six months working with the Green Party on the election campaign, meeting some of the most inspiring people that I have known. I then started job hunting outside London, and in October last year I moved to Bristol to work for a sustainability company. So rather than feeling depressed and anxious, I actually felt energised and enthused.

Now, I'm not saying that moving cities hasn't been challenging. It really, really has. Mentally and physically. A few weeks' ago, I managed to faint in the middle of the night. Knocked myself out by head butting the bathroom floor. Not my best moment. It was scary. But it was also another chance for me to step back and to reset.

I've been doing way too much. And I know I need to be more aware of my own limitations with Hughes. But despite the hiccoughs, I am really proud that I've moved out of London, so I can lead the sort of life that I think I will be much more suited to. More relaxed, more community-focused, closer to nature, and closer to my family in Wales.

So, coming back to this image to finish. I had it as my Facebook cover photo for quite a few months. And to me it kind of contains a lot of meaning. It's in Florida. So it's somewhere that at one point I thought I'd never even want to go back to. So it symbolises to me not being scared. Not being put off from living my life. It shows me looking relatively slim and healthy. Something that I worked really hard for on a personal level. And it shows me taking in a moment. Appreciating the natural beauty of the sunset. So it's a reminder to me of what is important and the things that make me feel alive and happy.

So, for me, being diagnosed with a chronic condition, it was hard. And it changes your perspective on life. But in many ways that has been a very positive thing for me. So it certainly makes me who I am today. Which is something I wouldn't change.

That's my story.

Thank you.

[applause]

**Lynne Kirwen**

Thank you, Bethan. And I'm sure we've all shared some of those moments. Our next speaker is Yvonne Wren. You'll find in your goody bag a page about the INRTracker, and Yvonne, who works with the charity, she works with Kate and she'll be telling you more about the INRTracker.

**Yvonne Wren**

Hello. Just to let you know, I have APS, which was diagnosed after several TIAs. That was about 11 years' ago, and I've been self-managing the Warfarin, taking my INRs and adjusting my medication, for ten years. What I want to talk to you today briefly about is a free web application and mobile phone app which is a management tool for patients on Warfarin. It's called "INRTracker". It is available in English, Spanish, German and French, and adjusts to any time zone.

INRTracker is from a New Jersey based company in America that was established by a young couple, the co founders, Pavan Katepalli and Veronica Coulombe, in cooperation with a company called Reliant Heart Incorporated.

Victoria [sic] herself has Factor V Leiden, which is a genetic blood clotting disorder, and she herself has been prescribed Warfarin.

The company was founded in April 2012, as the definitive personal health management tool designed for Warfarin patients. It's entirely free to access, either on your mobile phone or on a laptop computer.

With INRTracker, Warfarin patients can log in to their daily activities, analyse their INR blood test results, learn from articles backed by University and government resources, you can use a selection of tools such as the Vitamin K Food Database, and a sodium food database, and you can even carry out quizzes to test your knowledge of Vitamin K and Warfarin interactions. The food pages also include a nutritional calculator.

There are sections within the website that give you information on wellness, such as exercise and weight control, and also in illness, where you can record if you've had any bruises or fevers, for example.

It explains about inactivity, time that you sit or length of time you travel, and explains about circulation and the effect of inactivity on that. Also the importance of exercise and weight control.

It explains how Warfarin can affect menstruation and gives information on things like compression sock usage and medication. All of these can be seen easily. You can see them on charts or on the information that is on their website.

INRTracker has an INR level tool to facilitate Warfarin management, as well as having a DVT and PE calculator. Which helps to determine the probability of a Deep Vein Thrombis or a Pulminary Embolis.

You can also talk to other patients using their discussion forum online.

There's also information on standard tests which take place, such as electrocardiograms and echocardiograms. With very clear explanations on the differences between them.

The website enables you to record your blood pressure and very usefully keeps a record of appointments. Previous ones and upcoming ones. And you can even set it to give you email alerts for your appointments.

You can also set goals, which will then appear on your charts.

From all of this information, you can generate printer-friendly reports, that include data and charts from all the features that I've mentioned.

These reports can be brought into your INR appointments and can help you and your doctor figure out what may be causing your INR fluctuations.

This is a very comprehensive website. Packed with useful information and advice for people who are taking Warfarin, whether under regular medical supervision or self-monitoring or self-managing. It's very clear and easy to negotiate.

It's really worth looking at as far as I'm concerned, and worth considering using.

I just would say that the website… I had trouble getting onto it with the www dot method, it's actually http, but if you Google INRTracker, you'll get into the right website.

So that's about the app. Thank you.

[applause]

**Lynne Kirwin**

And our next speaker is Cath Atkin. Many of you will know her book. About Warfarin. And her book is indeed on sale outside in the foyer. Thank you, Cath.

**Cath Atkin**

It's okay. I didn't bring my lunch. Don't worry about that. Thanks for the invite today, Kate. It's great to be here. And as you'll maybe have guessed, I've come

down from sunny Scotland, and I've brought you some lovely weather with us. So welcome to our world.

I too, like many of you here are, am an APS patient. And I was diagnosed, what, about three years' ago? After a stroke when I was on holiday. And basically what happened was… well, I'll not go into the whole story. I've got a blog here. You're more than welcome to have a look and put your own stories on as well to see the journey that I've been through.

Now I've basically kind of written this book as an idea of… a way to help people understand how I have dealt with Warfarin. Now, we are all very different. So we will all interact differently with Warfarin. And some people obviously don't like the Warfarin at all. I myself, I'm quite happy on it. But I have made it my journey to understand it and learn it, and this way, and putting it in a book, and putting it on my website, this way hopefully it can help other people out there, like yourselves.

So, I've gathered together some questions that I thought, "Well, maybe these are things that you might want to know", instead of going into the technical details of Warfarin itself. So what I did was I thought… well, one thing I was aware of was with Warfarin and APS, I didn't realise that actually there might be a difference to somebody who is on Warfarin and who may have afib. Or atrial fibrillation. I've got a friend who's on that. And actually his INR doesn't fluctuate very much at all. Whereas mine will go flying up in one minute and straight back down the next minute.

And then also what I found was that when I… my INR was under two, I started becoming really… feeling quite ill. I've had two years of this feeling ill, slurring my speech, some of that's maybe Scottish, but slurring my speech, I was getting the left sided weakness again, like after the stroke, and memory fog, and dizziness and complete exhaustion. And now I didn't realise, I thought this was all after effects of the stroke, but it wasn't until I spoke to Professor Kumash that I had the privilege of getting down to see him, and he said to me, "No, this is your INR is not high enough. You need to take more Warfarin".

So then I had a battle with my own doctors. But they've now agreed, and we've challenged it and we've now got it agreed, that my INR is between a 3 and a 4. So they want 2.5 to 3.5. They're quite happy with that. And they feel comfortable with that. I know for myself, if any… if I'm below 2, then I start to feel really quite ill. And I've got it agreed that I take a fragmen injection if I'm anywhere near below that.

So, that's one thing I certainly learned. These are things that… it doesn't seem to be that people with atrial fibrillation on Warfarin don't seem to have, and I don't know that everybody has it on APS, but this is one of the things that I've learned.

Another thing I've sort of learned was a lot on the Warfarin and diet and what I'm eating. I don't know what anybody else got told, but when I… I got administered with Warfarin, it's sort of like, "Well, here's the three colours of pills, and you'll take them in this order, and you'll take them at this time of night, and careful with green vegetables". Yeah. So you've had it as well? Did you get any other information? No. No. No. So that's when it's like… my INR started going down. And that's when I started looking into further about what foods affect the Warfarin. Because there's not a huge amount actually affects Warfarin. But it's actually knowing those key ones that really make the difference, and how much they make the difference.

So I decided as well that I wanted to change to… I wanted to lose weight. And one of… have you ever Googled, sort of, diets and then looked at the amount of green vegetables in all these diets? And so it just seemed to be so many green vegetables out there in these diets that I thought, "Well, which one am I going to choose?"

So I tried the paleo approach. Same as yourself. And I thought, "Well, this is going great". Nut granola. It's fantastic. I really enjoyed it. But only to find that my speech was getting slurred and I was starting to get exhausted, and this is where all the low INR was coming out. And eventually it was my colleague, Laurie, who is at the back of the room, and she said, "Is it maybe you're taking too much protein?" Now, not once had I ever heard of protein and Warfarin together. Never in the same sentence. If you Google it there's very little information on Warfarin and protein. I didn't realise the amount of protein that I'd been taking in the paleo diet was actually bringing my INR down.

And that's basically because Warfarin is a protein-based drug. So you put a protein-based drug with protein, and then it all attaches and it goes out your body.

So I didn't realise that actually I was making my Warfarin less effective. Once I found that out, I've basically then changed, I went to the 5:2 intermittent fasting diet. I thought, "I can easily calculate out my protein and my Vitamin K". So actually I've just really worked out a lot of the two days to make it a lot easier. And that is down to calculating my Vitamin K and my protein. And on my fast days actually, I don't know if anybody else did the same thing, it's like when you say, "Be careful of Vitamin K", and then you stop taking Vitamin K. You don't realise actually… I didn't realise that I wasn't taking enough. So it was about, "What can I add in on those fast days that will give me my Vitamin K allowance that I have said…?" Now, I think in the UK it's about 90 micrograms a day. Of Vitamin K. They recommend. I actually set mine at 150 micrograms a day. So do you know what that looks like? Have you ever had a look at what 50 or 90 micrograms of Vitamin K looks like? Let me just show you.

I prepared this earlier. Okay. For 50 grams of spinach, it's not a lot. So that's not much. Compare that to 50 grams of Iceberg lettuce. You can feed a family, nearly. 50 grams of peas. It depends how hungry you are. It's about one, maybe two servings. 50 grams of broccoli. That's what shocked me. I didn't realise that. Put that with 50 grams of cauliflower. I don't know if you can see all that. And 50 grams of Romaine lettuce. Cos lettuce. So what I did was on my fast days, I don't have enough Vitamin K, so in my… in the menus that I set out, so we worked out what it was and how much I had to take, so I actually take an additional two florets of broccoli. I eat them raw. Because I quite like that. But I have two of these a day on top of my… the foods that I eat.

Another thing I do is also if my INR is quite high… I've worked it out with my doctor to say instead of adjusting my Warfarin continually, so it fluctuates up and down so much and I can't get it stable, "Why can't I do this through food? And allow me to do this through food?" So that's how we work it now. If my INR's too high, I'll just say, "Well, I'll have an extra bit of spinach" or, "I'll have some extra broccoli".

It can also work the other way. So if you're out and about and you're worried about your INR, and you're eating at a restaurant, what you can do is start substitution. And things I looked at were say if you were wanting… it looks like I'm pulling a rabbit out of a hat here, doesn't it? Sorry. I will ask… instead of… if I'm quite stable in my INR, if the salad that I've ordered is going to be… what kind of lettuce is it going to be? So if they say to me it's the Cos lettuce or Romaine lettuce, I can only have this amount. Whereas the same size of salad, you can have less salad, it would be less for my INR. Less Vitamin K. If I use Iceberg lettuce.

So I'll ask them sometimes to substitute these things out. I've also found out that… in my research, that spinach is very, very high in INR. In Vitamin K. But I wanted all the goodness that comes with the spinach. So what I found was actually flaxseeds gives you very similar properties to spinach. Without the Vitamin K.

So it was things like that, that I've been looking at, and putting on the website, and things that I've found and people have shared with me.

So feel free to jump on, share your story, have a look at… if it helps out anybody, and the other thing I had was when I said about weight loss, it's… well, I've actually managed to now lose nearly two stone. And I've kept a pretty stable INR. And yet, there's always a surprise. The other day I actually had extra beetroot. I had a great big beetroot salad. I love beetroot. But I didn't realise my INR had shot up from 3.7 to 4.7. In such a short period of time. Just with beetroot salad. However, from that, what I do is I then took three parts of the broccoli, three florets of broccoli, and a little bit of spinach and salad, and I brought it back down to within my range. So perhaps it's like maybe not a case of always adjusting your Warfarin dose, but adjusting some of the foods that you eat. And for me it's been all about… Warfarin means to me is consistency. No more extremes. I still enjoy a glass of wine. But I balance it out with about three bits of broccoli. So there is always a balance there. You don't have to cut it all out completely. But there is no more extremes.

So I'm quite happy being on the Warfarin. It works for me. But please, if you want to know any more detail about Warfarin, it's like I've got the book outside and I've got a new one getting published about Vitaimin K and protein, and some of the recipes I've used in the diet. And hopefully maybe speak to somebody on the website.

Thank you very much.

[applause]

**Lynne Kirwin**

Unfortunately our next speaker, Abigail Wilson, hasn't been able to make it. So we'll go straight on to questions. If I can ask our speakers to come back up on stage, and we are aiming still to finish at five o'clock, because I know a lot of you have trains to catch, so this will sadly be quite brief. Just a little bit of housekeeping; in your goody bag you will find a feedback form. If you could please fill it out, it's you letting us know what you think of this day and how we can improve it. It would be very helpful. And you can leave them at the desk on the right as you go out. There's also on your chairs a very brief questionnaire… sorry, we're asking you to do rather a lot, actually, but Kate, if there's not time to fill out the feedback forms, what's best done?

**Kate**

You can post them?

**Lynne Kirwin**

They are helpful. If you could take a few minutes, it would be really helpful. So now we'll do questions. So if… if Bethan and Yvonne and Cath could join us again.

**Lynne Kirwin**

I've got a question for Cath, actually. How many grams of protein a day ideally should one have? Is there a hard and fast figure?

**Cath Atkin**

It's recommended at 50.

**Lynne Kirwin**

Recommended at 50?

**Cath Atkin**

50 grams. 50 grams. 50 grams. That's the recommendation.

**Lynne Kirwin**

Right. So there's quite a few websites which show you how much protein there is in food. It's something I'm particularly interested in, because I have a condition where I have to keep my protein up. So, anyway… right. First question, please.

Kate, this lady here? No. Sorry. The lady at the back.

**Question 1**

Hi, I just wondered if… it was a question about INR, really, whether or not sunshine was actually a factor in changing INRs.

**Cath Atkin**

I haven't… well, obviously I'm Scottish, so I haven't experienced that! So apart from this week, yes I have.

I wouldn't have said sunshine. I haven't experienced any of that. What I have found is dehydration really affects it. If you're not drinking enough water and you're not hydrated enough, then that affects it quite dramatically, actually.

**Lynne Kirwin**

Anybody else? No? The lady by Kate.

**Question 2**

Hi, I'm just curious about your comment about the 50 grams of protein per day. I'm quite anal about my diet, very much like you are. I've been taking Warfarin for 15 years. I self-monitor. You say 50, but without any regard to body size. To me it's grams of protein per kilo of bodyweight that's important. And I don't know whether 50 works for everybody. I mean, I actually take a lot more protein than that and a lot more veggies than you say, and I do it consistently on seven days, self-monitor and adjust accordingly. Works for me. Everybody's different. I'm just curious about your 50. As though it was the same for everybody.

**Cath Atkin**

All right. Basically I'm just going with whatever the UK guidelines, the NHS guidelines, that's what they recommend. I think there's more for women. There's 50. And I've just kept it at that, because actually 50 grams is a lot for me. That's enough for me.

**Questioner**

Mm. I guess it depends on lifestyle and activity levels?

**Cath Atkin**

Yeah. And also, for me, it was a case of, "Well, if I eat more protein and more Vitamin K, yes, that's great, however, I'm going to have to take more Warfarin".

**Questioner**

Yeah.

**Cath Atkin**

And then I'm already on 16mg a day.

**Questioner**

Yeah.

**Cath Atkin**

And I'd rather not be taking so much more. I'm trying to find some of the things that will balance it and thin the blood. So I now take fish oils and like a wee glass of wine.

**Questioner**

But isn't the level of Warfarin just dependant on how your liver metabolises it? I mean, it doesn't mean… you know, whether you take two or 20. I mean, I know somebody who's taking 70mg.

**Cath Atkin**

Yeah.

**Questioner**

You know? It's a huge variation.

**Cath Atkin**

Yeah. I just don't want to be taking more pills.

**Questioner**

No. No. No.

**Cath Atkin**

I'll take the least amount of pills possible.

**Lynne Kirwin**

Anybody else? Ah, yes, over there?

**Question 2**

Hello. How do you measure micrograms of food?

**Cath Atkin**

With very small scales.

**Questioner**

With small scales? As simple as that?

**Cath Atkin**

Yeah. You would need very small scales to get the… but there's… the databases that we've used in the book is from the American database and the UK database of foods. And we've broken that down and just divided in.

**Questioner**

Oh, I see. And micrograms, are they the same as grams, then?

**Cath Atkin**

No.

**Questioner**

I thought they were different. So it's a different set of scales, is it?

**Cath Atkin**

Yeah. Well, if you're wanting to weigh them out, yeah.

**Questioner**

I see. Okay.

**Cath Atkins**

And if you're wanting micrograms… down to 90 micrograms, yeah.

**Questioner**

Okay. Also, may I just ask how often do you test your INR?

**Cath Atkins**

I… it depends on how stable I am. If I've been pretty stable, it's every six weeks.

**Questioner**

Oh, right.

**Cath Atkin**

But I've also got a self-tester that I do at home. So that way I can say to myself as well if I don't feel right or I want to check where I'm at, or I fancy having a glass of wine, I can just test it, see where it's at, and think, "Well, actually I'll have a nice salad with it as well".

So I can do a little bit more. Testing myself. But my doctor does it about every six weeks.

**Questioner**

I see.  Thank you.

**Question 3**

I don't eat any green veg at all, basically.  And so… and is that why my INR is all over the place?  Is all up and down?  Because I don't eat green veg?

**Cath Atkin**

Well, it's pretty stable, isn't it?  If you…?  If you're not eating… I think it's the hidden foods that you're maybe not aware it's in.  Such as rapeseed oil is very high in Vitamin K.  Whereas I'll substitute it with coconut butter.  Cooking with coconut butter instead of rapeseed oil.  So you'll be getting Vitamin K in other means.  It could be your protein.  It could be sort of other things that you're doing.

**Questioner**

Yeah.  Because I have… I've been having blood tests for my INR.  I have… for 14 years every week.  So…

**Yvonne Wren**

Can I just ask… you don't have to answer, of course; do you not eat green vegetables because you've been told not to?  Or because you don't like green vegetables.

**Questioner**

I don't like green vegetables.  [laughter]

**Lynne Kirwin**

I hate them and I do juices instead, actually, which is a way of getting them without eating them.

One here?

**Question 4**

Sorry, I just want to say, I'm on Warfarin, and I know Vitamin K affects me when it's too high, but I just wondered if you're not on Warfarin, does Vitamin K make any difference to how you feel?

**Cath Atkin**

Does Vitamin K affect how you feel if you're not on Vitamin K?

**Questioner**

Yeah. When you're not on Warfarin.

**Cath Atkin**

Do you know, this is one thing I would love to get towards, is, I mean, we're setting out blood thinning foods and what's… we'd call it blood thinning and blood thickening foods. To make it easier to understand. We're trying to find out, "Well, actually, if you're not on Warfarin, how does that affect your blood?" That I don't know yet.

**Questioner**

Yeah. Yeah. I know, because when I went on a diet before I was on Warfarin, I used to feel… so when I… you know, when I was on Warfarin. So I felt that the Vitamin K affected me. Made my blood thicker. But whether that's…

**Cath Atkin**

Well, it does have some blood clotting properties. But that's a huge dietician question, I think, and I would love to be the fly on the wall to hear that answer.

**Lynne Kirwin**

One more question. No? Well, thank you, very much. Before we finish, just a couple of points. Just to remind you that the stroke guidelines won't actually come into effect until September. The GP learning module is a huge process. Which will be led for us by Anna Suraman. We will let you know when it is actually going out. And we will be asking your help to let your GP know about it. They will get email alerts from the Royal College, but your help in telling your GP, letting them know that the module is up there, because it's free to them, we're the ones who are paying for it. That would be enormously helpful.

Thank you, again, for coming today.

[applause]