Ulster Medical Society

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The Patient Voice in Collaborative Academic Research

Professor Fionnuala Ní Áinle
and
Ms Annmarie O'Neill

Professor Mary Frances McMullin:

Welcome. My name's Mary Frances McMullin, and I am President of the Ulster Medical Society, and as part of our research day for clinicians, we have an Ulster Medical Society lecture, which we're now going to have.

It is my great pleasure to introduce our speaker who accepted to come today, Professor Fionnuala Ní Áinle. Fionnuala, whom I've known for some years, because of course we're all in haematology circles, is a haematologist from Dublin. She trained in Trinity College, Dublin, originally; did her general medicine and haematology training, but then has very much taken the academic clinical-scientist path. She was an MMI clinical scientist, where she got her PhD of 2001, and since that, she has worked both as a professor in UCD, and consultant in the Mater Misericordiae and the Rotunda Hospitals, and she's clinical lead in thrombosis haemostasis and maternal haematology. She's an active researcher, she's a co-director of the SPHERE Research Group, but she's also very active with patient groups. She's a founder member of VTE Ireland, and a subject near to my own heart, is very active in guidelines, so it's with great pleasure, Fionnuala is going to speak to us today, and also Miss Annmarie O'Neill, a patient with her, so Fionnuala, I would like to ask you to come and give your talk on The Patient's Voice in Collaborative Academic Research. Thank you.

Professor Fionnuala Ní Áinle:

Thank you very much, Mary Frances, for the very kind introduction. Can everybody hear me?—fantastic. It's a real honour to be here, and it's a great honour to introduce my friend, my colleague, Annmarie O'Neill, who is a force of nature, and has really made things happen in terms of VTE awareness and research in Ireland over the past couple of years. Annmarie founded the patient organization, Thrombosis Ireland, a couple of years ago, and I'm going to start by asking Annmarie to say a few words about her own story, and what this means for VTE awareness and research in Ireland. Thank you, Annemarie.

Ms Annmarie O'Neill:

Thank you. Thanks for inviting me here to speak. My journey in VTE started about 24 years ago. I went into hospital to have my gall bladder removed, and ended up getting a pulmonary embolism, and at the time I was pretty sick. I'd had actually, there were complications, I'd had two surgeries in a matter of a week, two stomach surgeries, and I didn't really understand what had happened to me. I was six weeks in hospital, and really anxious to get home to my kids. I had just had a new baby in February, and this was June, and so my mum literally reared him for the first six months.

I left hospital on anticoagulation, knowing that I was going to be on it for six months, but with no real understanding about what had happened to me, or the fact that it could possibly happen again.

So roll on five years, I'm back working full-time, two kids back in school at this stage, and I got some chest pain. So I'd had pleurisy previously, I don't know if it's from scarring from PE or whatever, so I thought maybe it was a touch of pleurisy, or even a bit of pneumonia, but I was busy in work, and I suppose you can all relate to this. You're just busy, I had a presentation to do in two weeks' time. My husband was away on a work trip and wasn't available to mind the kids. I was thinking, I don't have a babysitter—I'll leave it. I'll leave it for about two weeks. I'll leave it till I'm ready to do it. I never made it to that presentation. I ended up being admitted as an emergency to another acute hospital, and diagnosed with a second PE.

I was really given out to, when I eventually, kind of, was able for them to give out to me, when I was well enough. I was basically told that I had put my own life at risk by delaying getting immediate action, and initially I was really upset about it, and then I thought about it, and I actually got a bit angry. I was like, actually, this was like a bolt out of the blue. I had no idea that first of all, it could happen to me again. I had no idea of the signs to look for. I had actually no means of protecting myself at all, and I certainly didn't know I had to act fast. I'd had no idea that I could have died. I had no idea it was potentially fatal.

So even though five years previous in hospital, I was sick anyway. I'd just had two surgeries. I knew I had nearly died, I knew I had been really unwell, but I didn't relate it because nobody had had any sort of conversation with me. I just remembered this time, and actually besides the fact that I was told that it was potentially fatal, nobody told me, God, you're actually ten times more likely for it to happen again after having it twice, or anywhere near it. Nobody had that conversation with me. There was a little conversation, that, just don't get pregnant—that's going to really increase your risk, because having young children, having kids at the time, and a year later I got pregnant—not intentionally, but I did. So then I had to go through the whole thing, where the maternity hospital really wanted me to go to the National Coagulation Centre, and that's kind of where my journey began, because the information, really, everything was explained to me. I had to inject every day of the pregnancy. I was really worried as well, that I was hurting my baby. I was really worried that we were both going to be okay, and there was nobody my age that I could reach out to and talk to, not in Ireland, there wasn't. I mean, I could get onto Thrombosis Canada or Stop

the Clot, or Thrombosis UK, or Anti-Coagulation Europe. All of that was available, but it didn't, there was nobody from my hospital or in my area that I could reach out and talk. It was a really lonely, lonely time.

So my son, Ryan, was born 18 years ago, and he is six foot three and not a [?] on him, and everything was fine, thank God. But then in 2012, because I was on anti-coagulation for so long as well, I had like a build up of fibroids and it was really affecting my life, and nobody would touch me with a ten-foot barge pole for a hysterectomy or anything, nobody wanted to operate on me. It was affecting me, that I couldn't really get on with my life normally, and I was recommended to have an embolization. So I organized the consultation, I went back to the Anti-Coagulation Centre and we got a plan, an anti-coagulation plan, and I had the procedure done, and as I woke from the procedure, my leg had a heart attack, is the only way I could describe it. I don't remember, it was sudden, immediate pain. I've never felt anything like it before in my life, and I never pressed this button, looking for the doctor, but I obviously hung onto this, I needed help as soon as possible, and somebody came to see me and said, "You're on anti-coagulation", "Give her two paracetamol", and three days later I was supposed to be sent home, and I still, my whole body just didn't feel well, and I was limping. My leg was hurting me, but I was sent home.

About four days later, I wasn't supposed to drive, but I really wanted to get my hair done, and I drove locally just to get my hair done, and when I came back, and was heading up the steps to my house, and my friend, who's a nurse across the way, spotted me and said, "I don't like the way you're dragging that leg. I think you need to get that checked" —that's all she said, so another friend of mine drove me back to the hospital, and they just freaked out. They were like, it was a private hospital, they had no wards available because it was a Friday. They needed to do CT scans. The doctor was holding his head, and he just confirmed I had a clot in my femoral artery, and sent me home. I got home, and I sat on the coach and I said, "Good God, do I walk? Do I not move? Am I supposed to drink lots of water? What am I supposed to do to protect myself?"—because he didn't want me, he said his secretary would contact me on Monday with a plan.

It was a terrifying couple of hours. I was like, what am I going to do? So, I decided to phone my anti-coagulation clinic, because it wasn't in the same hospital, but they had done the anti-coagulation plan, and I said "Look, this is what's actually happening. I don't know what I'm supposed to do. Can you just advise me what I should do for the weekend, to keep myself safe?"—and they said, "Call an ambulance, we want you in." So I didn't call an ambulance, we drove in, and it was confirmed with a scan, that I had a complete blockage in my femoral artery. So we bypassed it, I ended up getting surgery, and got a bypass, but it didn't work, it clotted again, and then we tried again and it clotted again, so I don't have that blood supply anymore. I just feel that a lot of it was unnecessary. I don't have any genetic reason to clot that we've found so far. So that was really my personal journey, and it's what drives me.

I got involved with a patient-partnership pal in St James's Hospital, and at that, I was on a panel with the Haemophilia Society, a lot of guys, very powerful, whatever they said would be done, and some consultants and nurses and whatever, but I was the only clotter. They called me the clotter, they were all the bleeders! So when I suggested something or wanted something done, nothing would happen. I'd send emails to the management in the hospital, because we wouldn't have access to CTs at certain times or whatever, and nobody would even answer my emails. Somebody said to me, "You need to get a group of you together and be a little bit more powerful, so at least have a better voice."

I went about looking at setting up Thrombosis Ireland. So we started small; we just had an evening meeting in St James's, and invited, I think we had 25 patients turn up, and every time I'd have these meetings, I'd say to people, "Would you like to join me? Would you like to help me try and set up something that patients would be able to reach out, just talk patient to patient, get a bit of support", because something I didn't mention was, that after my first PE, I was diagnosed with post-natal depression, but actually, subsequentl,y post-traumatic stress, so five years on Prozac during that time as well, to deal with, I was terrified of everything. It really had an effect on me, that kind of near-death experience, and in speaking with patients now, with my experience, I'm contacted weekly by patients who are really affected by post-traumatic stress after pulmonary embolism experiences. Thank you.

Professor Ní Áinle:

Incredible, thank you, Annmarie. As you've been hearing what Annmarie and Thrombosis Ireland have done in partnership with clinicians, is incredibly powerful, and we'll speak about that later on. As you've heard from Annmarie and her powerful words, venous thromboembolism, comprising most commonly deep vein thrombosis and pulmonary embolism, is affecting millions of individuals worldwide every year. One person in the western world dies every 37 seconds as a consequence, and a topic close to my own heart, is the top cause of direct maternal deaths in the UK and Ireland. A really staggering statistic is that VTE is responsible for more deaths than HIV or breast cancer, prostate cancer and motor vehicles combined.

So that is what has inspired both of us, and I'd like to start, I suppose, for those of you who are doing PhDs in the room, to talk a little bit about my journey from PhD to independent researcher. We'll then talk about our journey from translational research, as part of the SPHERE research group, to the formation of the Irish network for VTE clinical research; in particular, an area which, as I said, is very close to my own heart, VTE in pregnancy, and how that has

evolved in terms of excellent clinical trial information, which has guided guideline formation in the last six months; and finally, a very inspiring story towards VTE awareness in Ireland, which literally could save lives.

I was very fortunate, in 2011, to complete a PhD under the phenomenal supervision of Professor James O'Donnell, which was invasive science, and I was interested obviously in coagulation, and I was researching the very powerful anti-coagulant, protein C, or activated protein C, which is a fascinating molecule, because not only does it act as an anti-clotting or an anti-coagulant, but it can also signal on cells and has cellular protective functions. That was overall a tremendously formative experience, but for any of you doing PhDs, this should be very well known to all of you—there are highs and there are lows, and I think you learn more during the lows, and surround yourself with people who can inspire you and guide you through those lows, and sometimes they can lead you in directions that are not expected.

The second thing that really struck me during the PhD is the skill of writing—it's really powerful—and start early, write frequently, write every day, because the skills you learn are absolutely critical in terms of future grant writing, and when you're a clinician, business plan writing as well, so you can get what you want for your patients through these incredibly important skills.

So, as I said, I was blessed to be supervised by Professor James O'Donnell. I got experience in grant writing very early, and that, I suppose, I had the first big break back in 2012 and 2013, and that has led to a number of funding awards over the years, which has allowed my group to do the work that we want to do, but if I can be honest here with you, and this is very important for those of you that go into academic research, for every one of these successful grants, there are many, many others that were unsuccessful. It's absolutely heart-breaking sometimes, but it's something that you need to be aware of, and it is normal, so failure is part and parcel of academic research, I'm afraid, but for all the successes, you learn a lot through the not successful grants as well, and form collaborations that can lead you in phenomenal directions.

There isn't enough time to tell you every single story along that timeline, but I would like to share a patient-inspired journey that led to the first big break, which is a health research award back in 2013. I had been very fortunate to start a consultant post in the Rotunda Hospital in Dublin. The Rotunda is a very small hospital, but it's an incredibly busy maternity hospital, with 9,000 deliveries, 9,000 babies born every single year.

One of these women had the most devastating form of this condition called pre-eclampsia, and I won't go into detail with her story. It was absolutely heart-breaking over a number of years, but I can honestly say that it inspired me to go in a very different direction to what I'd done during my PhD, so not your standard journey.

For those of you that don't know, pre-eclampsia is a common multi-system disorder of pregnancy that can be both life-threatening and life-altering for both mothers and babies, and it is categorized by high blood pressure and protein in the urine for mothers, platelet-activated, and importantly, a thrombosis risk. Babies can be born prematurely, and that can lead to lifelong complications.

And at the time, as a thrombosis doctor, I was very interested in, I suppose, looking after these patients and the challenges that we're facing, reducing their risk of thrombosis, because obviously this is a potentially devastating pro-inflammatory condition, that is known to increase the risk of thrombosis, and therefore sometimes we have to make decisions on giving clot-reducing medication, so anti-coagulant medication, but these patients can also have really important competing bleeding risks, so it's an absolute nightmare sometimes to make decisions for this particular patient cohort. Therefore, understanding the true magnitude and the mechanisms underlying this VTE risk is absolutely central, and what really fascinated me at the time was that the risk associated with this incredibly pro-inflammatory condition was nowhere near what it was in other similar pro-inflammatory conditions. And we certainly knew that pro-clotting, or your clotting system, your likelihood to form a blood clot, was certainly turned on, for lots of different reasons. But not very much was known about the anti-clotting mechanisms that perhaps balance the pro-clotting mechanisms, and that's really important for an individual patient's overall risk of having a blood clot, and it's something we intuitively do every day when we assess.

So we were very fortunate to collaborate, I was very fortunate to collaborate, with my now friends and colleagues in the Rotunda Hospital, and we, over the course of two years, recruited patients with a form of pre-eclampsia that is quite pure and quite severe, called early-onset pre-eclampsia, happening at less than 34 weeks, and what you're looking at here is an assay of blood-clotting, so it's a thrombin generation assay, and the way it works is that you stimulate blood-clotting, and the generation of the clotting enzyme thrombin is automatically detected in real-time, and you're using a fluorogenic thrombin substrate. So the higher the curve, the more clotting there is; the lower the curve, the less clotting there is, so what you can see is that, in black we have women who are non-pregnant, who are matched to the women who are pregnant, and those with pre-eclampsia, and they have, I suppose, a baseline clotting risk that you can see. Women who were pregnant had higher clotting, as you can imagine, because in pregnancy the clotting system is very much turned on, but to our great surprise, in this assay, clotting appeared to be, or thrombin generation appeared to be reduced in women with this very severe form of pre-eclampsia, and this fitted very nicely with our hypothesis, that overall the thrombotic balance was slightly less than expected in these women, or in other words, the time taken in some cases for that

clotting to begin, or the time to peak thrombin, was significantly increased, and the amount of thrombin generated was decreased. In other words, there was less blood-clotting in these women, but why?

So the extra blood-clotting, if you can remember back to medical school, happens by two main pathways: the extrinsic, or tissue-factor pathway, and the contact pathway, and of particular relevance to pre-eclampsia, the tissue-factor pathway is turned off by a molecule called tissue-factor pathway inhibitor, so it's an anti-clotting mechanism, and it's increased in pre-eclampsia for lots of different reasons, and we hypothesized that perhaps tissue-factor pathway inhibitor was turning off blood clotting in pre-eclampsia, and that this was relevant to what we were seeing in this thrombin generation assay. We demonstrated that this indeed was happening, so there was an increase in tissue-factor pathway inhibitor in women with particularly severe early-onset pre-eclampsia, compared to non-pregnant and pregnant controls.

When we blocked tissue-factor pathway-inhibitor with an inhibitory antibody, we almost completely reverted thrombin generation to normal levels, suggesting that tissue-factor pathway inhibitor mediates this reduced thrombin generation or reduced blood-clotting in these women with early-onset pre-eclampsia.

So what does that mean? Well, we know, as I said before, that the pro-clotting mechanisms that increase your chance of having a blood clot are turned on in pre-eclampsia, and we've shown that again using the clotting assay, but what about the anti-coagulant methods?—and in this study, we showed that tissue-factor pathway inhibitor, the anti-coagulant protein, is increased in pre-eclampsia, and that it mediates this reduction in thrombin generation, and we also showed that another anti-coagulant pathway, activated protein C, that the resistance to that was lost, suggesting that, overall, women who have early-onset pre-eclampsia have lower overall clotting compared to pregnant controls.

So leading out of this initial research came a very fortunate cup of coffee, about a year into the research, and I suppose it led me in a direction that I wasn't expecting. I was very fortunate to meet a friend and a scientific colleague, Professor Patricia Maguire, who is very interested in platelets, and that worked very well, because with my own interest in blood clotting, we sat down and we shared an interest in maternal health. So as a basic scientist, Professor Maguire had a keen desire to improve health outcomes for pregnant women, particularly those affected with pre-eclampsia, and that has been a fantastic cup of coffee, because it led to the formation a year or two later of the UCD Conway SPHERE research group. And in fairness, it was made possible thanks to that initial funding from the Health Research Board, so not all the people in this photograph are members of SPHERE. That's our current Taoiseach, who a couple of years ago was Minister for Health, and attended the launch of SPHERE in 2015, and here is my colleague, Professor Patricia Maguire, who is a basic scientist, a huge patient advocate, and is a basic platelet researcher.

Since then, we have studied platelets in thrombosis and inflammatory disease, and to date have raised over €3 million in funding from a number of sources, including HRB, SFI, IRC and industry. The acronym SPHERE stands for 'Systemic inflammatory disorders: and the role of blood Particles, Haemostatic factors, and ExtRacEllular vesicles', and these [last] are tiny membrane-bound particles that circulate in the blood. They come from platelets, from endothelial cells, from white cells, from lots of different sources, and they can be, as we and others have shown, they are fundamentally altered in pro-inflammatory disease states, and this is a huge interest for us. The assays that we have available to us in the laboratory investigate both thrombin generation and focus on characterization of, as you'll hear later, platelet releasate, but also extracellular vesicles using quantification but also Omics technology.

So platelets are absolutely fascinating. They're so much more than just cells that initiate the blood-clotting system, because they and their contents also play a critical role in the immune response and in inflammation, and I suppose that explains the number of collaborations with fantastic colleagues in various hospitals around the country, but also internationally, that we have formed, looking at the non-anti-coagulant, in many cases, roles of platelets.

These platelets store their secrets in their 'releasate'. So what does that mean? Well, when platelets are activated, the contents of their granules are released, and these contents vary fundamentally, as we've shown, in patients with different disease states, and the contents contain both exosomes or extracellular vesicles, but also soluble proteins. Prior to us coming together, Professor Maguire and her group indeed coined the term "platelet releasate", which has been highly cited since then, back in 2004, so they have the copyright for the term, and since the formation of SPHERE, we have worked very hard to show that the contents of the platelet releasate, that it is stable; importantly, very reproducible, and I know it sounds awfully boring, but this is critical to any further research we have done. It has low variability in healthy people, and that therefore it is suitable for biomarker discovery, and a really nice example of this, coming out of that original research, has been the pregnancy test. Now, we are absolutely not advocating this as a replacement for the standard pregnancy test, but it is a beautiful proof of concept showing that the bar code of what is released from platelets fundamentally alters when a woman is pregnant—imagine that. The contents of her platelets are completely different when she's pregnant. Does this translate into a different thrombosis risk?—we don't know yet, but it would be fascinating to find out.

I suppose again, for any of you who are setting out on that transition from PhD to independent investigator, collaboration is absolutely essential, so look out for opportunities, and we have formed collaborations with a number of groups. I will talk much more about

the area of pregnancy and thrombosis, early-onset pre-eclampsia. We've worked with oncologists, cardiovascular colleagues, and I'll speak more about a very exciting collaboration we have with my friend and colleague, Clíona Ní Cheallaigh who set up an inclusion health service in St James's Hospital, working with homeless patients. There are huge opportunities, if you keep your eyes open, and very importantly, to plan the research journey with our patients, and this, we've been absolutely, Patricia and I as co-directors of the SPHERE research group, have been honoured to work very closely with Annmarie and with Thrombosis Ireland since the very beginning.

Ms O'Neill:

It has been a really exciting addition to our patient conference every year, so this year, for the second year, we had Dr Patricia Maguire join us, and give her talk on these magical EVs, and how she explained it to us was like, if you cut your finger, what's your first instinct to do, is to suck it, and these EVs are actually in our saliva, and they have healing qualities, but also it's wonderful for us as patients to know that people are working on trying to discover ways of maybe preventing thrombosis by spotting markers, or finding these magical things that actually have really good healing properties.

Professor Ní Áinle:

And Patricia and I have been so grateful for the opportunity to, I suppose, share the ideas and discoveries we've made in SPHERE with Annmarie and with her patients, and those ideas have translated into real research proposals on the ground, some of which are actually in the process of being funded.

Ms O'Neill:

Well, what Patricia and her team were saying was that they spend an awful lot of time in their lab, and they become completely detached from the real world of the research and why they're doing it, so we're able to put like a human element, a patient element to it.

Professor Ní Áinle:

Which is absolutely critical, I mean, it's fun, it's interesting, but if not for the benefit of our patients, then why are we doing what we are doing?—so thank you very much, Annmarie

These slides that I've shown you come from Professor Maguire's talk, at the Meet the Scientists session, which we were honoured to join at the patient parallel session of VTE Dublin this year.

So in parallel, I've talked a bit about the translational research that is ongoing in collaboration with our patients, but a very natural additional progression or arm to all of this has been the formation of a clinical research network, and this really started, the seeds for this were really sown for the first time at the very first international VTE Dublin conference, which happened five years ago, because it brought together patients, national, international experts in the field of thrombosis, and also care providers from a lot of very different multidisciplinary backgrounds, and we got together, we shared ideas. We had emergency colleagues, respiratory, cardiovascular, acute medicine, obstetrics, and out of this has come, it has been a breeding ground for ideas, that as you'll see has translated into real outcomes for patients, and ultimately guideline recommendations, and these people have become our friends, and through this five years of network building, ideas have come out leading to the formalized formation of the Irish network for VTE research, just last year at the fourth VTE Dublin conference, and we work side-by-side with Thrombosis Ireland, with the mission to develop and participate in excellent national, but also international, VTE-related research, and as Annmarie eloquently told you already, why do we do this?

Well, it's because VTE matters. It kills one person every 37 seconds.

Ms O'Neill:

I suppose what incenses us really, what keeps us going is, there's about 5,000 instances of VTE in Ireland, in the Republic of Ireland every year, of which about 50% are preventable. At the moment, in our hospitals there isn't a mandatory VTE assessment. It's done in a very willy-nilly way, and it's not really acceptable. It really depends on which hospital you go to, the kind of treatment differs from hospital to hospital. Whether you get an assessment differs, which I encourage our patients to ask for one as a start, while advocating for a mandatory VTE assessment. As well as the research piece, there's a huge awareness piece about, so we're trying to encourage medical staff to open the line of communication, because not only will the prophylaxis and whatever else you doctors do protect our patients, but we've got to explain to them what it is that's going on in their bodies, and how they can protect themselves, because what I've learnt is that those 90 days after discharge from our hospitals, the majority of these VTEs occur, so you're out of the care of your doctors and nurses and you're in your own home, and if you haven't been informed from what we call the thrombosis three, you haven't bee n informed of your risk. You're not going to be vigilant, because you don't know what to be vigilant about. If you don't know the signs to look for, you're not going to act fast, so basically we don't arm patients; if our hospital don't arm patients, they're responsible.

Professor Ní Áinle:

Absolutely, and that is what we're trying to do to gather data, to better inform our clinical pathways. So we have partner organizations all around the country. We would deeply love to have partners in the north, so a little plug for the INVITE network [Irish Network for VTE Research], if there is anybody who's interested in joining what has been a very exciting journey, please, please come to me at the end, and I'll be reaching out. We're also members of the international network for VTE clinical trial networks, and as I said, we were honoured to be launched by

Minister Heather Humphries, who's our Minister for Business, Enterprise and Innovation, last year, and you can see Annmarie delivering a stellar address.

So I'd like to share with you a little flavour of what's going on in INVITE, in terms of first of all our national studies, home-grown Irish research, and also our involvement in international research. So first of all, I suppose thrombosis after trauma can be an absolutely tragic event. The patient can be very fit and healthy leaving hospital, having had a lower limb fracture and a cast, and as we have heard very recently in stories that have been highlighted in the media in particular, but also other tragic stories, sometimes patients are not we might talk a bit at the end... but without awareness and adequate prophylaxis, and understanding which patients are at highest risk, tragedy and mortality can result, so to address this, so I suppose currently available randomized trials have shown us that routine implementation of thromboprophylaxis does not result in a statistically significant decrease in thrombotic events in patients after lower limb injury, and therefore a key research priority is to identify a high risk group who may get a benefit from thromboprophylaxis, and with this in mind, the TILLIRI study has been established about a year ago, led by one of our INVITE PIs, Dr Dennis O'Keeffe, who is a Clinical Director of Limerick, and inclusion criteria are adults with lower limb trauma and a requirement for lower limb immobilization, and we have a very large sample size in view of the fact that we were working on a predictive score, and we recruited, through the network, an incredible 400 patients already, with less than a year of recruiting, and we'll be expanding to a number of other sites, so a lot of this recruitment was done with only one, and then two sites.

Another study, which is again close to my own heart, is the OPTICA study, led by Professor Peter McMahon, which is a radiologist in the Mater, and this is addressing a very important area, which is the diagnosis of pulmonary embolism in pregnancy, and it's critically important that women who require investigation don't face barriers, and one of those barriers, as highlighted in the recent EFC guidelines on PE, is access to low-dose radiation—sorry, low radiation dose CTPA protocols, and unfortunately, despite the fact that often these protocols, modern protocols, do involve a very low radiation dose, there's surprisingly few data evaluating the safety of CTPA protocols associated with the low radiation dose in the literature, and with this is mind, our aims are to define a low dose CTPA protocol, which is optimized for pregnancy, and this is already running. We have recruited nearly 45 patients already, and the aim is to prospectively demonstrate safety, and ruling out pulmonary embolism in the pregnant and post-partum population, with the outcome of interest being incidence of pulmonary embolism at three months.

Finally, as I said, we were interested in understanding more about the drivers of venous thromboembolism in patients who are socially excluded, who are at a very high risk of thrombosis, and in fact represent, a thrombosis in patients who are marginalized represents a huge number of ED visits, certainly in the Dublin catchment area every year, and we are already recruiting to the VIP project in collaboration with not just Professor Ní Cheallaigh, but also Dr Vida Hamilton, our National Clinical Advisor in Acute Hospitals, the HSC Department of Health Intelligence, and the patient organization of Thrombosis Ireland, and De Paul, and the results from this study have a significant chance of impacting on policy down the line. And again we were very honoured to be invited to participate as a member of the International Network of Venous Thromboembolism Clinical Networks just last year, in recognition of the work that we've done.

I suppose through work that has been done nationally, but also through our involvement in international studies, we've had some very nice outputs in 2019, showing that collaborative research, without even a huge amount of funding up front, can result in real impact for patients.

I'd like to invite Annmarie to say a word or two about the BMJ open paper, which provided data for the very first time on VTE in one Irish hospital group, and you'll notice that Annmarie is actually a co-author on this paper, so congratulations, Annmarie.

Ms O'Neill:

I suppose when we started, it's back to the beginning of Thrombosis Ireland. In order to get any sort of funding, you have to have proof, so you need statistics, but also we didn't really have any idea what we were dealing with, how many people out there needed our help, how many people were having VTEs, and there was absolutely no data, nothing—zilch. I went to every department, I even went to the legal people to see, do they have any idea of the data?—and there was absolutely nothing, and no excuse, it was just ridiculous. If you name any of the other things, like cancer or diabetes or whatever, there's fantastic data and they're able to tell you, so basically we were totally starting from scratch. When I started the talks, I was doing it like individually in hospitals, but I realized, which I didn't know at the time, all different hospital groups, so really I wasn't really having a proper impact, and after meeting Dr Fionnuala, she asked me, did I want to join the VTE group in the Ireland East hospital group, and that kind of opened a real opportunity to look at this as a group, and then to voice the patient's concern that nobody is collecting—are we not important enough to know how many of us this is happening to?—or, how many are from trauma or breaking a leg, or how many are from surgery? We didn't know any of that data, so I suppose I brought it to the table, that we've got to do this, and if the government aren't doing it, that maybe as a hospital group we could start and give it as a shining example for the other groups, so that's really how it came about.

Professor Ní Áinle:

And it's been a real honour to make Annmarie's

vision a reality, as one of our key aims of last year through the INVITE network.

So just before the end, I'd like to talk a little bit about, I suppose, VTE research in pregnancy, which again through my work in the Rotunda, is a huge area of interest for me, and the impact it has already had on patient care, so obviously pulmonary embolism in pregnancy is a potentially devastating event, which is, as I said, the leading cause of direct maternal death in the UK and Ireland, and I suppose 1 in 1,000 pregnant women will experience a venous thromboembolic event, and this risk is increased through a number of different mechanisms, including stasis, compression, both by the gravid uterus, and also by the right iliac artery on the left iliac vein, and as we and others have shown, there are also fundamental changes in pro and anti-coagulant, and fibrinolytic pathways.

But not only is the baseline risk of thrombosis increased in pregnancy, but also women can have additional risk factors, that can further make them at risk of this potentially life-threatening and devastating condition, and there are surprisingly few data on how common these risk factors are, so recently we, in the Rotunda Hospital, performed a cross-sectional study of prospectively collected data in order to answer this question, and we collected data from a total of 21,000 women who had been risk assessed according to the Thrombocalc 2, an electronic VTE risk assessment tool, and this represented over 90% of all the women giving birth in the Rotunda Hospital during that time.

What is absolutely staggering is that nearly four-fifths of women had at least one additional risk factor, and that includes being overweight, a surprising one-third, being over 35, and not only that, but two-fifths had two or more VTE risk factors, and what's really important in terms of policy is that one-fifth of the women had no VTE risk factors prior to delivery, but they developed them during the delivery and post-partum period, and that is really important, because it is not good enough just to do a VTE risk assessment, to pick out whether women have additional risk factors at the time of booking, but it's also essential to repeat this VTE risk assessment after she has had her baby, because otherwise an opportunity to reduce risk and to prevent mortality and morbidity could be missed.

And of course, due to the lack of data over the years, due to the fact that women who are pregnant are so frequently excluded from high-quality clinical trials, there is a huge variation, a shocking variation in the percentage of women who would qualify for thromboprophylaxis, according to various international guidelines, and this ranges from just 7% under the American College of Chest Physician guidelines, right up to a whopping 37% under RCOG [Royal College of Obstetricians and Gynaecologists] guidelines, and this is really important, because it reflects the lack of good-quality data out there, and is really a call to action in terms of progressing excellent research for pregnant women, and not excluding them from clinical trials, and not allowing bureaucratic barriers to stand in our way.

This reflects the fact that guidelines are in fact based on expert opinion, rather than high-quality evidence. Thankfully this is changing in several important areas. The HighLow study is a randomized control trial of evaluating the optimal dose of heparin for pregnant women with a prior clot, in order to determine what the best dose is in order to prevent a recurrence of VTE, and we're very proud to be part of this study, which has nearly completed recruitment, in collaboration with a team of international colleagues. We would hope that, for the very first time, the optimal dose of low-molecular-weight heparin for prevention of this potentially devastating condition will be known through the highest possible level of evidence during 2021.

Finally, is it possible to, I suppose, risk assess all the pregnant women? Well, for women who have risk factors such as thrombosis in the past, and for women who have many other risk factors, it is important that we pick these risk factors up and I suppose through implementation of an electronic risk assessment tool in the Rotunda Hospital, we have shown that it is possible to assess nearly over 95% of pregnant women, and we have shown that a package consisting of VTE awareness, risk assessment and appropriate thromboprophylaxis, has the potential to reduce VTE. Now, we are seeing signals in the data from the Irish Maternity Indicator system showing a trend towards a reduction in reported pulmonary emboli since the roll out of the Rotunda VTE awareness initiative. These data are not yet statistically significant, I should point out, but work is ongoing, and we would hope to further this data in the next couple of years.

So I suppose it is possible to conduct excellent multicentre studies in pregnancy, and pregnant women should not be excluded from this level of data. They deserve this level of data, and we should make it possible.

Just this year, we had two clinical trials which permitted the adoption in international guidelines of new algorithms for suspected pulmonary embolism in pregnancy, and what this means is that in the past, every pregnant woman with a suspected pulmonary embolism had to undergo radiological investigations, which is potentially risky, and since the publication of these two independent prospective clinical management studies, it is now endorsed by the most recent European Society of Cardiology guidelines on acute pulmonary embolism, that women with suspected pulmonary embolism in pregnancy should under diagnostic imaging only after they have undergone D-dimer and clinical protection rule assessment, and according to these studies, a significant proportion of pregnant women do not need to proceed to formalized radiological diagnostic imaging, for the first time ever.

So the very final part of our talk, I will hand over to Annmarie, because this brings it right back to the beginning, which is awareness, because that really does drive research opportunities and shapes, I suppose, our direction, so thank you, Annmarie.

Ms O'Neill:

I suppose research on awareness seems really basic compared to your technical research, or clinical research, but it's so important for us to figure out how best to impart that information, that life-saving information, and talking about our pregnant girls, they get fantastic protection in the Rotunda, but if they don't get that information, I mean their highest risk of VTE is in that first week after having a baby, and I know they're only staying in one day, so they're at home on their own for that first week, that 100-fold increase in getting a VTE when they're at home, so we haven't figured a way to ensure that they've got the message and they understand how to protect themselves, so there's still a lot of research on that. So we are doing our level best, so from going from hospital to hospital, trying to raise awareness in the community, get the message, we've developed little alert cards to put all the information, and we're trying to ensure that everybody gets one of these, every inpatient, but now we've discovered actually, if you break a leg, and just get a cast, you're not an inpatient, but you still have a risk factor, so we need to get it to them as well, so it's really anybody who comes through the door of the hospital, we'd like them to get one. So we went from just doing hospital talks in the evening with patients, to a conversation about how we can raise awareness, and Mary Day, CEO of Ireland East's hospital group, backed us on an idea to wrap a big red double-decker bus with a big blood clot, and arrive into the town with this. I don't know if you're familiar, but most of our country towns don't have double-deckers, they're single-deckers, so it's only in and around Dublin, in the main city, that you'd see a double-decker. So Ireland East's hospital group has eleven acute hospitals, and they're spread out. I don't know who organized the groups, it's ridiculous, because they're all over the country instead of keeping them all together, but so we went from, we started off in Wexford, then the next day we were in Carlow, the next day we were in Kilkenny, and what we did was, we went into the town in the morning, into the community, right into the centre of the town, and beforehand we notified all the men's sheds, the ICAs, the women's groups, the pharmacists, the GPs, our community centres, mother and toddler groups, whatever—anybody we could. Thrombosis Ireland looked after the community event, and then the team in Ireland East hospital group organize everything they could through the hospitals, so we had a little gym upstairs with the physio and dietician. Healthy Ireland got involved; it was like a one-stop shop, but the whole idea was to get as much people as possible saying, "What are you talking about?"—like, "What is this clot?"—with these t-shirts, "Just ask us about clots", and just ask us the question, so we had an opportunity in the five, we did five weeks, two or three events a week, and we had community in the morning, and then the hospital in the afternoon. The hospital staff very nicely volunteered for the morning as well, to have extra, so we had a consultant, a senior pharmacist, and anybody else who wanted to get involved, so the patients, or the public that would board the bus, had the best of information, and a real conversation about blood clots, and just trying to create awareness, so in the five weeks, there was about 22 or 23 stops, if we include the conference. We distributed 10,000 cards individually into people's hands, and we know that everybody who received a card got the talk, so I can say it on my sleeve now at this stage, but we got kind of like, at the elevator pitch, but also an opportunity to share their own stories. And what we really discovered was, about one in three people that we came across in the shopping centres or towns, or even at the hospitals, whatever, that one in three had had a direct experience of VTE, either themselves or their family, or a close friend, like they actually knew about it, but they never thought it would ever affect them. They thought it was for old people. They didn't connect the fact that it can happen to anybody, and that they need to arm themselves with a bit of information, so it was also a learning curve on the hospitals, because the HSE released a document called the VTE Collaborative: Prevention of VTE in our Acute Hospitals, and it was released last August, and as part of the release, half-a-million of these were distributed to our acute hospitals, and as we went round the hospitals, we discovered that they were in storerooms in boxes, because we hadn't basically spoon-fed them with exactly how we thought it should be distributed, and who was going to distribute them, that it wasn't happening. And we also discovered that a lot of the hospitals didn't have a VTE working group, and we now know that that is actually an essential part of basically protecting the patients within the hospital, but also an arm to ensure that the patients are informed. So from our journey to the eleven hospitals, and having the conversation with everybody, we now believe that Ireland East's hospital group will have a VTE committee in each hospital, that will look after VTE assessments on arrival, and making sure that the information is imparted, so it was actually a fantastic success in that way.

Professor Ní Áinle:

All of the other hospital groups are still to do, but we forget that.

Ms O'Neill:

We still have seven hospital groups, so that's just one, and I've told them, we can't just do one a year, because it can't take seven years to impart this information, so we're hoping to hold onto the bus!

Professor Ní Áinle:

Do you want to say a word or two about the alert cards, Annmarie?

Ms O'Neill:

Yes, so I suppose the alert card just has all of the information that we try and impart it that elevator speech that I was talking about, so 60% of VTEs happen as a result of a hospital stay, and most people

think it's to do with long-haul flight, but only 3% happen as a result of a long-haul flight, and that's a surprise. But we also arm people with their risk factors, and these guidelines are on it, and the signs and symptoms to look for, and then in red, the important to act fast, but the other important message is, what you can do to help yourself, so we encourage them to ask for a VTE risk assessment, walk and move as much as possible when in hospital, keep hydrated, the water on the side of their bed isn't just for decoration, and explain why they need to stay hydrated, because it is another risk factor. To take their medications—medication is another interesting one, because VTE—there's been so many new medications now introduced, and many people don't really understand what they're taking, and how important it is to take it properly, particularly with the new DOACs [Direct Oral Anticoagulants], so there's a big learning piece on that as well.

Professor Ní Áinle:

Thank you, Annmarie, and congratulations on a phenomenally successful six weeks, which has just ended. We're both absolutely exhausted! So the final words, no matter what your research journey is, no matter what pathway you take, I think one piece of advice I would give is to surround yourself with colleagues and friends who really inspire you to answer the right questions, so thank you very much, and I'd be happy to take any questions.

Professor McMullin:

Thank you very much both, for an excellent and very inspiring talk. Do we have any questions?

Professor Peter Maxwell:

Can I just ask, beyond Caesarean section, what are the other risk factors, about delivery or post-partum, that increase the risk of VTE?

Professor Ní Áinle:

Thank you, Peter, so again, they're specific to the mother, to her condition, and to the pregnancy itself, so big ones around the time of labour and delivery would be actually a bleed or a post-partum haemorrhage; Caesarean section particularly if the Caesarean section has been an emergency section; infection; having a high body mass index; being confined to bed for a long time; having pre-eclampsia; inter-uterine growth retardation, so all of these conditions are known to be associated with significantly elevated risk of VTE, with significant odds ratios. I didn't have time to go through, how these, I suppose the knowledge gaps, we don't know precisely how these risk factors truly interact yet, and that's an ongoing interest for us in the Rotunda, but we are doing some work in collaboration with our Danish colleagues, looking at how the Rotunda risk assessment score translates into—can predict—VTE events in a large, much larger database, so we have some interesting signals from that work coming through. Thank you for highlighting that.

Audience member:

You mentioned 70% of women have a risk factor, or a blood clot. I thought that was high?

Professor Ní Áinle:

It is very high.

Audience member:

And obviously over 35 is going to be a lot of women. What are some of the other proportions of other risk factors?

Professor Ní Áinle:

Again, it's important to say that although 70% of women had at least one risk factor, that doesn't mean that each one of those women would qualify for a thromboprophylaxis, and there are risk factors that are associated with a much higher risk of thrombosis, than for example, age over 35, and one of those is the subject that is being evaluated in the HighLow trial, or having a previous VTE, or strong thrombophilia, but what's really interesting is, I'm so glad you asked that question, is that thrombophilia and prior VTE are the two areas that we have most data about. Put together, they comprise less than one percent of patients in our prospective study, so there are a myriad of other more common risk factors that can interact with each other to translate into an increased risk, but for those more common risk factors, there's shockingly poor data as to how to manage women with these risk factors, and it is a critical knowledge gap, but the good news is that there are various groups thankfully around the world, including ourselves, who are currently addressing this at the moment, but thank you.

Audience member:

We are quite proactive, I think, here, with our RCOG guidance, risk assessing people, both antenatal, as inpatients and post-partum. Why do you think that the South has been slower in [hospital diagnosis?]?

Professor Ní Áinle:

So you've done phenomenal work, as have our colleagues in the mainland UK, in terms of complying with thrombosis risk assessment, and not just in pregnancy, but in your hospitalized patients as well, and that has come on the back of tremendous advocacy work that has been done by leaders such as Professor Beverly Hunt, Andrew Cohen, et al, and that hasn't happened overnight, that has taken ten years, but how successful have they been? This is why it's so important to collaborate with our policy makers. So it's as you know, policy, to perform risk assessments and hospitals that don't comply can be financially penalized. We're quite far behind in Ireland. We don't have mandatory risk assessments in Ireland, I'm ashamed to say, in the South, but as you can see, we're working on that, we're working on it at grass roots level, through raising awareness. We are driven by our patients' needs and their interests. We're

working on it from a research perspective to provide data, to provide evidence. We're also working very hard knocking on the doors of our policy makers as well, and things have changed, so just in the last year we finally have a new KPI evaluation, hospital-acquired thrombosis, in Ireland, which is amazing. I think watch this space. A lot has happened in the last five years. I am embarrassed to say we're not quite as far ahead as you are, and that will translate into better outcomes for your patients, so congratulations. Are you an obstetrician?—fantastic.

Ms O'Neill:

I think it took us a while to have a patient voice as well, and I think, well certainly we've been to Brussels to try and advocate for action in Europe as well, and definitely the patient voice makes a difference, and it does encourage people to take action.

Professor Ní Áinle:

Together we are stronger, isn't that right?

Audience member:

I'm a GP and GP trainer, and I would just like advice on how to support GP trainees, in recognising patients at risk of VTE and supporting patients?

Professor Ní Áinle:

Oh, that is wonderful, thank you. So again, there are, are you aware of the organization, Thrombosis UK, as well? Both organizations work very closely together, and I know that they have a phenomenal—I'm sure Annmarie would be happy to share advice as well, but I think, one very simple step that doesn't require additional resources is to empower patients who have recently been discharged from hospital, with that one fact, and if everybody could take that one fact home with them, the one key message, that for 90 days after going home, they should not ignore the signs and symptoms of a VTE. I think that doesn't cost anything, and it could save a life. I think we're very happy to… are we, Annmarie?… to share our alert cards. I'm certain that our colleagues in Thrombosis UK have similar superb material available. I'm happy to help in any way.

Professor McMullin:

Well, thank you. That was an excellent talk and an excellent insight into the patient voice.