"What will happen in the future?" A personal VTE journey

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Declaration of Interests

The authors declare they have no conflict of interest.

Introduction

Venous thromboembolism (VTE) includes deep vein thrombosis (DVT) and pulmonary embolism (PE) and is a huge contributor to global disease burden, affecting millions of people worldwide every year [1]. VTE has been reported to be the third commonest cause of death from cardiovascular disease after heart attack and stroke [2]. However, VTE does not just cause mortality, but also can be associated with major morbidity in survivors due to lifelong debilitating chronic conditions [3].

On 13th October every year we celebrate World Thrombosis Day (https://www.worldthrombosisday.org/) and renew our commitment to raise awareness of VTE and improve outcomes for all of our patients. In this manuscript, clinicians have partnered with an inspirational woman who is a VTE survivor and with the Irish Patient Organization, Thrombosis Ireland, to raise awareness of questions and issues that are important in the care of young women who have experienced VTE.

The patient voice

"I was first given my diagnosis of DVT in the Emergency Department (ED) of the Mater Hospital after my physiotherapist advised me to seek medical attention. I had been taking contraception. The conversation was very brief - I was told that there was a danger of the clot moving up to my lungs but that it was not a life changing diagnosis. I received an injection of blood thinner before going for a scan the next day. I went home and let the news sink in.

When I went back to ED for the scan, I was seen by two doctors who explained the diagnosis more thoroughly. They asked a lot of questions about my lifestyle and my family history to determine what might have been the cause of the DVT. It was the first time one of them mentioned the possible connection of this event with my contraception. I was put on rivaroxaban straight away - the only thing I was told at this stage about this medication was the dose and the fact that it was a new type of blood thinner negating the need for frequent blood tests. Unfortunately there was no discussion about which specific treatment would be best, the different types there are, or the potential side effects. I was told it was imperative I start on a high dose as soon as possible, as there was a real danger of the clot moving to my lungs. It is only at that moment that I realised how serious VTE was."

VTE risk during contraceptive use

Estrogen-containing contraceptives are associated with an approximately 2-6 fold increase in VTE risk over baseline [4, 5]. In general the absolute VTE risk is low in the majority of the >100 million contraceptive users worldwide, however VTE risk factors including severe inherited thrombophilia [6] increase this risk. "Third generation" combined oral contraceptives (COC) (containing progestagens such as desogestrel or gestodene) are associated with a higher VTE risk than "second generation" COC (which contain progestagens such as levonorgestrel (LNG) or norgestrel) [7, 8]. Hormone-releasing intrauterine devices (IUD) and some progesterone-only pills (POP) (when used at contraceptive doses) and are not associated with a significant increase in VTE risk [4, 9] and following counselling and full risk assessment, are often chosen as options for women with a personal or strong family history of VTE.

The patient voice

"For months after the diagnosis, the pain in my leg prevented me from walking very far, and I was scared of leaving the house in case I fell (and bled). Thanks to my job, I had access to electric bicycles. This was a revolutionary moment when I realised I could be mobile again with little pain - I started to go to the park and go outside a bit more. Although my symptoms have improved, even now post thrombotic symptoms mean I still have to stop working and be on pain medication from time to time. The heaviness and throbbing sensation of my leg means I am limited to short distance walks and electric bikes. I find the most difficult part is the psychological aspect, as it reminds me I had a DVT, and that I will carry the consequences of it. I am afraid of not being as active as I would want to be as I get older."

Post-thrombotic syndrome

Post-thrombotic syndrome (PTS) is a long term complication that is reported to affect 20-50% of patients within two years of a DVT diagnosis [10]. The constellation of symptoms that patients present with are secondary to chronic venous insufficiency (CVI); commonly lower limb complications including varicose veins, pain, edema, erythema, and inflammation [11, 12]. Cohorts that are more at risk for PTS include older individuals with a history of ipsilateral DVT, proximal DVT, a history of pre-existing CVI, and patients with obesity [11].

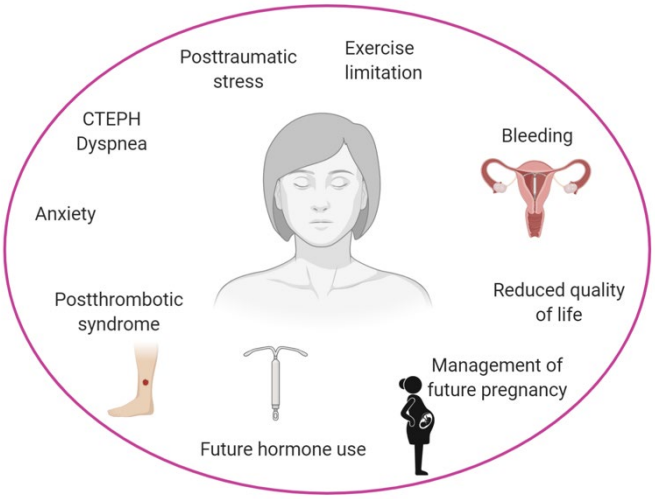
This debilitating complication can have serious adverse effects on the quality of life of patients; medically, socially, and economically [11, 13]. Thus, the treatment goals for patients are to reduce symptoms, to reduce the disease burden on lifestyle via shared-decision making management plans, and to reduce patient financial costs.

The patient voice

"I went home and started reading online about rivaroxaban - I always read up on a drug that is prescribed to me. I read about the excessive bleeding, the recommendation to have a bracelet in case of an accident to warn medical teams (I cycle everywhere so I thought it would be a good idea to get one). It was also through my own research that I realised that there was no antidote to this drug, that in the event of an accident or bleeding I would have to wait for it to leave my body. That scared me.

The oversight for women-specific issues [see figure 1] came to light when I experienced the impact that Rivaroxaban can have on periods - extremely heavy bleeding. Sometimes, the bleeding was so severe that I could not leave my home for a day or two every month as I had to change my protection every 45 minutes. Losing that much blood also made me extremely tired, and I was housebound for a lot of those first 3 to 4 months after the diagnosis."

Figure 1 : Challenges and complications facing patients and care providers during the shared management of VTE in women of childbearing age



Abnormal uterine bleeding during anticoagulation

Abnormal uterine bleeding (AUB) [14] represents a unique gender-specific complication of anticoagulant therapy. Up to one-third of women will experience AUB in their lives, most commonly occurring at menarche and perimenopause. [15] . Given that AUB is a relatively common phenomenon in women not on anticoagulation, it is perhaps unsurprising that in the absence of sufficient patient education, patients commonly attribute these symptoms to a consequence of natural biology or ageing rather than to their anticoagulant use.

Available evidence suggests that up to half of women afflicted by AUB do not seek medical advice for their symptoms, even if they have access to healthcare services [16], the reasons for which are poorly explored in the literature. Although data suggest that severe and life-threatening anticoagulant-associated AUB is rare, its detrimental psychosocial effects cannot be underestimated, with manifestations ranging from modest to severe disruption of work productivity and quality of life [17].

Published data suggest that AUB occurrence may vary between anticoagulation regimens:

Ferreira *et al* [18] conducted a retrospective single-centre review of 128 women of childbearing years treated with rivaroxaban for VTE during a two year period and reported heavy menstrual bleeding (HMB; a form of AUB) in 20%. Anemia was documented in 23% of women with HMB, with a mean hemoglobin drop of 18g/L and included one episode of major bleeding requiring hospitalization, blood transfusion and tranexamic acid. Only 6% discontinued rivaroxaban due to HMB. De Crem *et al* [19] performed a single centre retrospective study quantifying AUB in female VTE patients who were of reproductive age and who were treated with either rivaroxaban (n=52) or Vitamin K Antagonist (VKA) (n=52) using questionnaire data. They reported that approximately two thirds of women (73% and 67% in rivaroxaban and VKA groups respectively; no significant difference between groups) experienced AUB after starting anticoagulant therapy. Patients using rivaroxaban were more likely than those using VKA to experience prolonged (>8 days) menstrual bleeding (25% v 8.2%; p=0.031) and rivaroxaban (but not VKA) treatment increased the duration of menstrual bleeding. Patients treated with rivaroxaban reported more unscheduled contacts with a physician

for AUB (41% v 25%; p=0.096) and an increased need for medical or surgical intervention for AUB (25% v 9.4%; p=0.041). More rivaroxaban than VKA patients required changes in anticoagulant therapy (15% v 1.9%; p=0.031). Beyer-Westendorf *et al* [20, 21] reported on vaginal bleeding events in 178 women of reproductive age treated with direct oral factor Xa (FXa) inhibitors for either VTE (93%) or atrial fibrillation (7%) using two sources of prospectively collected data: the Dresden "novel oral anticoagulant" (NOAC) registry (NCT01588119) and locally archived data from phase 3 trials of direct oral FXa inhibitors conducted at a single university in Dresden. Patient-reported abnormal vaginal bleeding events were categorised as either unrelated to the menstrual cycle or, if related to the menstrual cycle, HMB. Vaginal bleeding events were reported in 33%, 32% and 25% of patients on apixaban, rivaroxaban and edoxaban respectively [21]. Overall, 57 of 178 women reported 72 vaginal bleeding events, of which 59 were cases of HMB and 13 were unrelated to menstrual cycle [20]. The median duration of follow-up was 586 days (290-997). According to the International Society on Thrombosis and Haemostasis (ISTH) definitions [22], 54% were minor, 38% were clinically-relevant non-major bleeding (CRNMB) events and 8% were major bleeding events. The majority (86%) of the HMB events were treated conservatively including 5 who were managed with a change of oral hormone therapy (COC discontinued in 2 patients, change of contraceptive type in 3 patients) with no recurrence. 6 (12%) had a change in direct oral anticoagulant (DOAC) therapy (temporary discontinuation or a reduced dose), of which 5 had no recurrence. For the remainder, no change to management was implemented. 14% underwent elective surgical or interventional treatment and surgical treatment was required for 89% of the women with anatomical abnormalities. In this series, no patients received plasma transfusions, factor concentrates or tranexamic acid. All patients continued anticoagulation for the intended minimum treatment duration. 23% and 4% of women had a second and third event respectively. 9/57 women had anatomical causes for bleeding established. All of these patients had HMB events [20].

In a post-hoc analysis of the combined "EINSTEIN" DVT and PE randomized trials [23, 24], Martinelli *et al* reported AUB more frequently in rivaroxaban than in VKA-treated patients (hazard ratio (HR) 2.13; 95% confidence interval (CI) 1.57-2.89)[25]. Brekelmans *et al* characterized AUB in patients with VTE receiving apixaban or enoxaparin/warfarin using data derived from another large randomized controlled trial (RCT) [26]. A CRNM vaginal bleeding event occurred in 2.5% and 2.1% of apixaban and enoxaparin/warfarin-treated women respectively (odds ratio (OR) 1.2; 95% CI 0.7-2.0). Scheres *et al* [27] conducted a post-hoc analysis of the Hokusai-VTE RCT [28] including women <50 years treated with edoxaban (n=628) and warfarin (n=665). AUB incidences were 15/100 person-years (py) (95% CI 11–19) and 9/100 py (95% CI 6–12) with edoxaban and warfarin respectively (HR 1.7, 95% CI 1.1–2.5). Major AUB events occurred in 1.3% and 0.9% of women on edoxaban and warfarin respectively (OR 2.8; 95% CI 0.8-10.8) and CRNM AUB events occurred in 8.4% and 5.6% (OR 1.6; 95% CI 1.0-2.4). Finally, Huisman *et al* [29] performed a post-hoc analysis of the pooled "RE-COVER" studies and the "REMEDY" trial [30-32], reporting incidences of AUB in 1280 female patients of reproductive age treated with dabigatran (n=643) compared with warfarin (n=637). AUB was reported in 8.1% women overall, 5.9% under dabigatran and 9.6% under warfarin treatment (OR for Dabigatran treated patients 0.59; 95% CI 0.39-0.90; p=0.015).

Optimal management strategies for anticoagulant-associated AUB in women with VTE have yet to be established and continue to pose a significant challenge for healthcare providers.

Planning duration of anticoagulation after a hormone-provoked VTE

VTE is associated with mortality and long-term morbidity. Additionally, anticoagulation confers bleeding risks (which can be increased by the presence of additional bleeding risk factors) [33]. Estimation of the probability of VTE recurrence is therefore very important, so that this probability

can be weighed against the complications of anticoagulation. A recent systematic review and meta-analysis reported rates of recurrent symptomatic VTE in patients who had completed at least 3 months of anticoagulation for unprovoked VTE and included 7515 patients from 18 studies. This study estimated that the risk of recurrent VTE was 10%, 16%, 25% and 36% at 1, 2, 5 and 10 years after treatment, with 4% of recurrent VTE events resulting in death [34].

It is important to understand an individual patient's recurrence risk so that prevention strategies can be given to the right patients. However, sometimes identification of patients who have the most to gain from extended anticoagulation can be challenging. In some patients, predicted recurrence risk is so high that continued anticoagulation is clearly of benefit. In others, the balance of competing recurrent thrombotic and bleeding risks is not so clear. Predicted VTE recurrence risk is primarily driven by the presence of risk factors at the time of the index event, and whether they are persistent or transient [33]. Patients whose initial VTE event was unprovoked have a higher recurrence risk compared with those whose initial event was provoked by a major transient provoking factor [35]. In a prospective follow up study of patients who had participated in a large population-based case control study [36], the thrombosis recurrence rate was highest in people whose first thrombotic event was unprovoked compared with those whose first event was provoked (33.2 per 1000 patient-years (95% CI, 25.4-42.6) and 17.7 per 1000 patient-years (95% CI, 11.9- 25.4) respectively; HR 1.9 (95% CI, 1.2-2.9).

Therefore, knowledge of concomitant risk factors at the time of the VTE event is central to decision-making surrounding duration of anticoagulation. Up to 50% of all people with a first VTE episode have no identifiable cause.

Predicting recurrence risk and making decisions on duration of anticoagulation in patients whose initial VTE event occurred in the context of an intermediate risk factor, such as estrogen therapy/contraception or pregnancy, is particularly challenging, especially as anticoagulation poses additional, gender-specific risks. Moreover, for transgender women with hormone-provoked VTE events, there are very important issues that need to be addressed, as recently summarized in a comprehensive review [37]. High-quality data are urgently needed for this group.

Studies have consistently reported a higher recurrent VTE rate for men than women [38]. However, the underlying mechanisms remain poorly understood. In a large retrospective cohort study, HR for male (versus female) sex were 1.29 (95% CI 1.06-1.57) and 2.07 (95% CI 1.6-2.67) respectively for VTE recurrence overall and "definite/probable" VTE [39] . An Austrian prospective cohort study including 826 patients with a first unprovoked VTE similarly reported a 5 year cumulative probability of recurrence of 30.7% (95% CI 23.8-37.6) in men and 8.5% (95% CI 5.0-12.0) in women. Male sex conferred a relative risk of recurrence of 3.6 (95% CI 2.3-5.8) [40]. In a single-centre prospective cohort study, Baglin *et al* reported a 2.5-fold higher risk of VTE in men than women at 2 years [41]. Similarly, Rodger *et al* reported annual VTE risks in men and women of 13.7% (95% CI 10.8-17.0%) and 5.5% (95% CI 3.7-7.8%) during mean follow-up periods of 72 and 84 weeks respectively ($p<0.001$) [42]. In a prospective follow-up of the Leiden Thrombophilia study, incidence rates for recurrent VTE were almost 3-fold higher for men than for women at 41.2 and 14.2 per 1000 person-years respectively (HR 2.8; 95% CI 1.4-5.7)[43]. Another prospective cohort study of thrombophilic families identified a higher relative risk (1.6; 95% CI, 1.3-2.0) for men compared with women [44]. A prospective study in Vienna leading to the derivation of a risk prediction model for recurrent VTE reported a two-fold elevated risk in men compared to women (crude HR 1.9; 95% CI 1.31-2.75)[38].

In some patients, predicted VTE recurrence risk is high and continued (indefinite) anticoagulation is suggested by guidelines in the absence of an elevated bleeding risk, for example following an unprovoked VTE event [33]. In others, the situation may not be so clear. Patients whose initial VTE

event was unprovoked have a higher recurrence risk compared with those whose initial event was provoked by a major transient provoking factor [35]. The optimal duration of anticoagulation in patients whose initial VTE event occurred in the context of an "intermediate" risk factor (as defined by recent guidelines) [33], such as hormonal contraception, remains sub-optimally characterized.

For women, VTE events in the context of hormone use have traditionally been regarded as provoked events for the purposes of decision-making surrounding duration of anticoagulation. However, emerging data suggest that personalized risk factors may prove to be relevant during decision-making. Studies evaluating the impact of hormone use on VTE recurrence risk have reported conflicting results [39-42, 45-54] due to heterogeneity in study design. However, recently, Kiconco *et al* [48] conducted a large retrospective well-designed population-based cohort study including 4170 women in order to determine whether women whose initial VTE event was hormone-related have a lower VTE recurrence risk than women whose initial event was unprovoked. Hormone users had a 29% lower VTE recurrence risk compared with non-users (adjusted HR 0.71; 95% CI 0.58-0.88). Among women aged 15-44 years, 562 were oral contraceptive (OC) users (82.6% of whom were COC users). In this group, OC users were 29% less likely to have VTE recurrence compared with non-users (HR 0.71; 95% CI 0.52-0.96).

The recently published "REVERSE II" prospective multinational management study [55] aimed to validate a clinical decision rule "HERDOO2" rule (**H**yperpigmentation, **E**dema, or **R**edness in either leg; **D**-dimer level ≥250 µg/L; **O**besity with body mass index (BMI) ≥30; or **O**lder age, ≥65 years) derived previously [42]. Women with ≤1 "HERDOO2" criteria discontinued anticoagulation, while men and women with ≥1 criteria were managed at the discretion of their physician. Recurrent VTE occurred in low risk women at a rate of 3.0% per patient year (95% CI 1.8%-4.8%). Amongst 429 women of premenopausal age (<50) who were at low "HERDOO2" risk and who discontinued anticoagulation, the risk of recurrent VTE was 1.4% (95% CI 0.4-3.7%) and 3.1% (95% CI 0.8-7.9%) in estrogen users (n=291) and non-users (n=138) respectively [55]. Le Gal *et al* [52] reported further on outcomes from the derivation phase "REVERSE" study [42] for women. Amongst estrogen contraceptive users who were high risk by "HERDOO-2" criteria, the annual recurrence risk was 4.1% (95% CI 0.0-12.2). Moreover, in women with an estrogen-provoked VTE, a high "HERDOO2" score was associated with a HR of 5.0 (95% CI 0.9-30.1) for recurrent VTE risk compared with those with an estrogen-provoked event and a low HERDOO2 score. Although the confidence intervals were wide due to small numbers, these data suggest that attention to personalized additional VTE risk factors may be relevant.

The patient voice

"I found myself wondering if all of this would have happened had I been given all the information from the beginning when deciding on contraception. When my contraception was prescribed to me I was told that it might increase the risk of clots because I was over 35 years old. However, there was no proper discussion about what VTE warning signs to look out for or what to do if I suspected one. I think this vital information should be given by every doctor prescribing estrogen contraception to women, young or old.

In retrospect I would have discussed alternative means of contraception with the doctor and my partner had I been aware of the potential consequences of a DVT. After my diagnosis, my partner got a vasectomy, so I was lucky that I did not have to consider the risks associated with re-starting hormonal contraception. In most cases though, the entire weight of contraception is on women, regardless of the risks and side effects."

Should a woman with a hormone-provoked VTE discontinue hormone use after anticoagulation has stopped? Are there safe alternative options?

During ongoing anticoagulation, continued estrogen use is suggested to be safe: Martinelli *et al*, in a post-hoc analysis of the "EINSTEIN" DVT and PE study cohorts, compared the incidences of recurrent VTE in women aged <60 receiving anticoagulant therapy for symptomatic VTE with either Rivaroxaban or low molecular weight heparin (LMWH)/VKA. VTE recurrence was similar in women who were exposed to hormonal therapy during anticoagulation and in those who were not exposed to hormonal therapy during this time (adjusted HR 0.56; 95% CI 0.23-1.39) [25].

However, continued estrogen use is associated with an increased risk of recurrent VTE and should be avoided for women with a history of VTE who require contraception **and who have discontinued anticoagulation.** Christiansen *et al* conducted a prospective follow-up of patients recruited to the Leiden Thrombophilia Study [36]. In a subanalysis of their initial study, they showed that amongst women whose *initial* VTE event was provoked by OC (n=128) or pregnancy (n=21), women who *continued* OCs after *discontinuation* of anticoagulation had a four-fold increased risk of recurrent VTE compared with women who *stopped* OCs (incidence rates (IR) 48.8; 95% CI 24.3-87.2 per 1000 patient-years and 10.5; 95% CI 4.5-20.7 per 1000 patient years respectively; IR ratio (IRR) 4.6 (95% CI 1.9-11.5)) [43]. The highest risk was in users of triphasic LNG-containing contraceptives (IRR 138.9; 95% CI 16.8-501.7).

Progestogen-only agents used at contraceptive (rather than therapeutic) doses (with the exception of injectable depot medroxyprogesterone acetate (DMPA)-containing agents) appear not to be significantly associated with an increased risk of first VTE [4, 9, 56-59]. Although a small but non-significant increase in OR (1.64; 95% CI 0.55–4.91) for VTE in association with oral *and* injectable progestogen-only contraceptives (POC) was reported by the WHO in 1998 [58], another nested case-control study conducted at the request of the WHO in 1999 (which differentiated between therapeutic and contraceptive indication for progestogen use) reported no significant increase in first VTE risk (adjusted RR estimate 1·3; 95% CI 0·3–6·8) [59]. Moreover, a Danish National historical registry- based cohort study reported that women using progesterone-only contraceptives - norethisterone, desogestrel or a LNG-releasing IUD - had a lower or similar risk of initial VTE to non-users (adjusted RR 0.56 (95% CI 0.29 to 1.07), 0.64 (95% CI 0.29 to 1.42) and 0.83 (95% CI 0.63 to 1.08) respectively) [4]. The safety of the LNG-releasing IUD was confirmed in a study conducted within the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA) case-control study: the use of a LNG IUD was not associated with an increased VTE risk (OR 0.3; 95% CI, 0.1 to 1.1), however injectable DMPA contraceptives were associated with a 3.6-fold (95% CI 1.8-7.1) increased risk of venous thrombosis compared with nonusers [9].

The few studies that have addressed VTE recurrence risk in women with prior VTE who are taking progestin-only agents have suggested no increased risk with oral progesterone-only pills and with LNG-IUD but an increased VTE recurrence risk in association with DMPA use. Conard *et al* [60] reported no increased VTE risk in association with chlormadinone acetate at anti-gonadotrophic doses in a retrospective cohort study of 204 consecutive women at high risk of VTE including 142 with prior VTE (HR 0.8; 95% CI 0.2-3.9). Christiansen *et al* reported a non-significant increased risk of recurrent VTE in women with prior hormone-provoked VTE who continued the use of progestin-only agents (which included both oral AND injectable preparations) during follow-up, relative to women who discontinued oral contraceptives [43]. However as numbers were small, confidence intervals were wide (IRR 3.7; 95% CI 0.8-17.2). Notably, the two recurrences were both related to injectable

medroxyprogesterone. Vaillant-Roussel *et al* [61] conducted a retrospective single-centre cohort study including all women (n=172) with a first objectively confirmed VTE event during or less than 1 month after discontinuation of COC use. For the entire cohort, incidence rates of recurrent VTE at 1, 2, 5 and 10 years were 5.1%, 7.8%, 14.2% and 28.6% respectively (a high rate, potentially influenced by the limitations of the study, including the fact that some women were referred for the first time at recurrence). Women who used COC during follow-up had a higher recurrence risk than those who did not (HR 8.2; 95% CI 2.1-32.2): all 4 patients who restarted COC experienced a recurrence. In contrast, no increased VTE recurrence risk was observed in the 34 women who restarted POC during follow up (HR 1.3; 95% CI 0.5-3.0). Le Moigne *et al* [62] subsequently conducted a prospective single-centre cohort study in France. Women aged ≤50 years with a first VTE diagnosis were included. Women taking estrogen contraception were instructed to discontinue and an alternative method (including a progestin only contraceptive) was recommended. Progestins used were predominantly oral LNG 30 µg/day or desogestrel 75µg/day (43%) and LNG-IUD (49%): they did not increase the risk of recurrent VTE (age-adjusted IRR 1.6; 95% CI 0.3-7.8). No women used injectable DMPA.

To date therefore, use of progestin-only agents (with the exception of injectable depot progesterone-containing agents) appear not to be associated with an increased risk of recurrent VTE (although larger studies are urgently needed).

How to best prevent VTE during a subsequent pregnancy in a woman who has experienced a prior VTE?

Women with a personal VTE history have a higher recurrent VTE risk during pregnancy [63, 64], with highest risks reported for women with an unprovoked or a hormone-provoked VTE [64-68]. It appears that this risk is reduced with LMWH [69]. Previous guidelines have suggested various approaches to VTE prevention in these women, with strategies including a low prophylactic or an intermediate (half-therapeutic) dose [70, 71]. The optimal LMWH dose for women with prior VTE in the context of no or a non-major transient risk factor (including hormones) is currently being investigated in the ongoing Highlow RCT (NCT 01828697), a multicentre, multinational RCT evaluating efficacy and safety of a fixed low dose of LMWH compared with an intermediate weight-adjusted dose in the prevention of VTE recurrence during pregnancy [64].

The patient voice

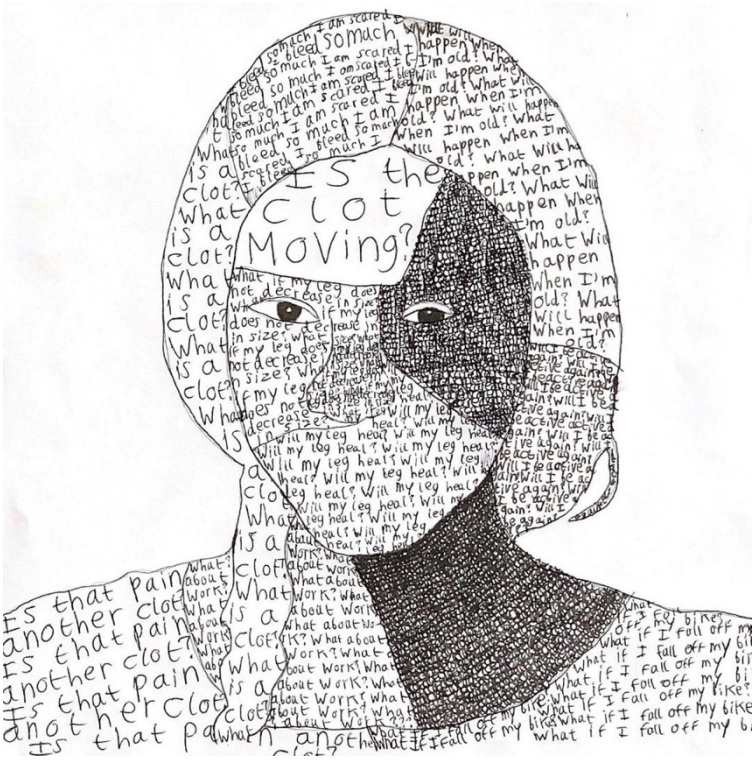
"I do not think I was educated or counselled enough, particularly at the beginning. I was not given any treatment options and was sent home without information about side effects or what to expect in terms of mental health. This was a very "targeted" medical intervention; everything was focused on the leg and the medical chart. A more holistic approach is necessary: guidance on self-care, how to keep active and how to keep calm if you suspect something is wrong. The medical profession also needs to consider gender specific issues - it is mind boggling that blood thinners are prescribed to women without them knowing about the potential of heavy periods. The emotional toll of the entire experience cannot be underestimated [see Figure 2] , and I'm acutely aware that only women with advantaged situations such as myself would be able to make their voice heard and talk to the right person and get the treatment that works for them.

Altogether, there was no real discussion about my treatment options initially. The shock and numbness when a diagnosis is given means that as patients we have a tendency to give in to the professional doctor in front of you and not question what s/he says. ***It is only when the medical***

professional starts opening the dialogue that you feel you are entitled to express an opinion. It is essential, to my mind, that doctors initiate that dialogue to make sure the patient feels comfortable asking questions about their own bodies and opening up about what is happening to it.

Now, I am much better. I think a lot about that first doctor who assured me having a VTE was no big deal. It was life changing, and I am very grateful to the medical professionals who listened to me. By doing so, they enabled me to be part of my own healing and treatment, and that is the example to follow."

Figure 2: Patient Word Cloud: crucial concerns during her diagnosis and treatment journey



Patient preferences, incorporating shared decision-making

In recent years there has been a strong move towards placing more weight on the preferences and priorities of patients. A model of shared decision-making (SDM) has therefore received increasing attention and is recommended in recently published guidelines, as it is the patient who best appreciates their preferences of proposed treatments and potential consequences of outcomes [72-75]. This approach encourages patient responsibility as the healthcare provider appropriately educates their patient of their treatment options and together, they develop a plan with shared responsibility [76]. SDM enhances patient satisfaction and adherence to treatment [74].

One proposed SDM model is based on introducing choice, describing options, and helping patients make decisions [77]. This model is especially useful in chronic diseases where there are multiple treatment options available with no one-size fits all plan. Engaging patients in the discussion and considering patient preference is imperative, as they live with the consequences of these decisions.

A striking example of this model is deciding on VTE prophylaxis during pregnancy. Guidance on the prevention and treatment of pregnancy-related VTE emphasize the importance of incorporating patient values and preferences alongside the risks and benefits of a proposed intervention [78]. Bates

et al. interviewed patients who were pregnant or planning a pregnancy. They identified that patients placed similar health state values on a pregnancy-related VTE and obstetric bleeding, but this varied among individuals [78, 79]. This variance among individuals reinforces the importance SDM has as a guiding principle in treatment plans.

In summary, patients are the drivers of their healthcare choices; by adopting shared-decision making in clinical practice, patients experience improved efficacy of treatment outcomes [74].

Thrombosis Ireland: giving the patient a voice

Thrombosis Ireland is a patient organization formed by patients Ann Marie O'Neill and Shay Kearney in 2016. Thrombosis Ireland is the only patient advocacy group in the Republic of Ireland dedicated to VTE (http://thrombosisireland.ie/awareness/). Thrombosis Ireland works closely with clinicians in Ireland caring for patients with VTE and with the World Thrombosis Day Campaign. Our goal is to raise awareness about VTE; to provide information to patients, the public and health care professionals; to support VTE survivors and their families and to support the families who have been bereaved as a consequence of VTE. Thrombosis Ireland wants to leave no patient group out and focus on particular on providing information to specific groups, including young women receiving hormones and pregnant women. We have a particular interest in reducing Hospital Acquired Thrombosis. Patients present to hospital to get well and do not expect to suffer a potentially fatal blood clot as a result of their hospital stay. It is crucial that every patient, carer and family is informed about risk factors for VTE, the signs and symptoms of VTE and the need to seek immediate medical attention if a patient thinks that he/she may have a VTE event. This information could save a patient's life. Few Irish people know that they remain at risk for 90 days after discharge from hospital. At an early stage, Thrombosis Ireland identified this knowledge gap and asked "How can a person protect him/herself or a loved one if they are not armed with the correct information the information?

Thrombosis Ireland members work with clinical colleagues in order to advocate for:

- A Mandatory VTE and Bleeding Risk Assessment for all who are admitted to hospital.
- Patients' right to the information to protect themselves from blood clots.
- A National Thrombosis Treatment Protocol in order to standardize therapy
- Greater awareness of the symptoms and signs of VTE and of the risk factors that can lead to VTE

In order to open the conversation, we have also developed a Blood Clot Alert Card which has been adopted by the HSE as a tool to inform Patients and to encourage healthcare providers to have this potentially life-saving conversation with their patients. All patients admitted to an Irish public acute hospital should receive a Blood Clot Alert Card, which are also available directly from Thrombosis Ireland.

Conclusions and next steps

Ms Bedos' words highlight the importance of communication and shared decision-making when planning a care pathway for patients affected by VTE. In particular, for women who have experienced hormone-provoked VTE, time must be devoted to providing personalized care, particularly as anticoagulation poses particular challenges. As Ms Bedos urges, we must "open a dialogue" with our

patients. We celebrate World Thrombosis day on October 13th, a global movement under the auspices of the ISTH. The campaign seeks to increase global awareness of thrombosis and ultimately, to reduce death and disability caused by the condition. On World Thrombosis Day 2020, Thrombosis Ireland and clinical colleagues renew our commitment to improving awareness of VTE and situation-specific challenges for all patients.

Figure legends

Figure 1: Challenges and complications facing patients and care providers during the shared management of VTE in women of childbearing age

CTEPH: Chronic Thromboembolic Pulmonary Hypertension

Figure 2: Patient Word Cloud: crucial concerns during her diagnosis and treatment journey

This illustration depicts Ms Bedos' most crucial concerns during her diagnosis and treatment journey, in her own words. The questions and phrases that were most important to her were: "Is the clot moving"; "Is that pain another clot?"; "I bleed so much; I am scared"; "What if my leg does not decrease in size"; "What about work?"; "Will my leg heal?"; "What if I fall off my bike"; "What will happen when I am old"; "Will I be active again".

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