FACULTY OF MEDICINE AND HEALTH SCIENCES

A COMPREHENSIVE LITERATURE REVIEW ON THE ROLE INHERITED THROMBOPHILIA PLAYS IN VENOUS THROMBOEMBOLISM

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Preface

A lot of people helped me accomplish this thesis, so I would like to start by thanking them.

First I would like to thank my promotor, Prof. Dr. Fransiska Malfait, for the guidance and positive outlook during the making of this thesis. And in addition, for choosing this interesting topic.

I would also want to thank my parents for their never-ending support and encouragement these past few years. Without them I would not have been able to get to this point. A special thank you to my father for reading this thesis multiple times.

Furthermore I want to thank my fellow students and friends, for the incredible solidarity. Because of them I never felt alone, even when I was struggling.

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Abstract

Venous thromboembolism (VTE) is a common disease, often with a fatal outcome. It is the third leading cardiovascular cause of mortality and morbidity in the Western world. VTE is a multifactorial disease, and the risk factors are often divided into an inherited predisposition and non-inherited risk factors.

Inherited thrombophilia, which can be found in approximately 50 % of patients with an episode of unprovoked or idiopathic VTE, is usually divided in mild thrombophilia and high-risk thrombophilia. Mild thrombophilias include the more common forms of inherited thrombophilia, the Factor V Leiden mutation and prothrombin G20210A mutation (heterozygous carriers). High-risk thrombophilias are the more rare types of inherited thrombophilia: antithrombin deficiency, protein C and S deficiency, homozygous carriers of any thrombophilic abnormality and carriers of multiple abnormalities. Besides carriers of these mutations, individuals with a non-O blood group or a positive family history of VTE also have a higher risk of VTE.

Non-inherited risk factors are age, antiphospholipid syndrome, obesity, smoking, pregnancy and the postpartum period, oral contraception, hormone-replacement therapy, surgery, immobilization and cancer.

The association between inherited thrombophilia and venous thromboembolism has been well established. There is a synergistic relationship between inherited thrombophilia and other thrombopilic risk factors. Studies found that the relative VTE risk due to pregnancy was 3 to 41 times higher in women with thrombophilia (the magnitude of the VTE risk depends on the type of thrombophilia) compared to women without thrombophilia. However, the absolute VTE risk during pregnancy remains low. There is still some controversy whether or not inherited thrombophilia plays a causal role in adverse pregnancy outcome. Most studies showed a higher risk of recurrent pregnancy loss in women with inherited thrombophilia. The use of oral contraception increases the relative VTE risk among women with inherited thrombophilia. The magnitude of this increase of VTE risk is depending on the type of thrombophilia. The absolute risk of VTE during the use of contraception remains low.

A lot of contradictory results can be found surrounding the impact of inherited thrombophilia in cancer patients. Inherited thrombophilia is a risk factor that needs to be taken into account when assessing the risk of VTE before a surgery.

The combination of inherited thrombophilia and a non-O blood group have a supra-additive effect on the VTE risk.

Testing and screening for inherited thrombophilia is still a matter of great debate. Many studies have showed that the presence of inherited thrombophilia does not increase the risk of VTE

recurrence and that it does not have an impact on treatment. Since inherited thrombophilia is a risk factor and not a disease, many carriers remain asymptomatic. Therefore, routine screening for inherited thrombophilia in asymptomatic individuals is not indicated.
Inherited thrombophilia does not influence the acute treatment of VTE. Acute VTE treatment consists of thrombolysis in limb- or life-threatening situations. After thrombolysis or in case thrombolysis is not indicated, anticoagulant therapy is started. Standard anticoagulant therapy is heparin (unfractionated heparin or low-molecular-weight heparin), followed by vitamin K antagonists. There are arguments that non-vitamin K antagonist oral anticoagulants could replace vitamin K antagonists. The subject of thromboprophylaxis, when and how long, still causes much disagreement. The clinician often takes a decision based on experience. More studies, especially higher-quality studies, are necessary to get better guidelines on the management of inherited thrombophilia.

Nederlandstalige samenvatting

Veneuze trombo-embolie (VTE) is een frequent voorkomende aandoening, die vaak een fatale afloop kent. Het is de derde meest voorkomende oorzaak van mortaliteit en morbiditeit in de Westerse wereld. VTE is een multifactoriële aandoening en de risicofactoren worden onderverdeeld in erfelijke en niet-erfelijke risicofactoren.
Erfelijke trombofilie kan gevonden worden in ongeveer 50% van de patiënten met een idiopathische VTE-episode. Er wordt meestal een opsplitsing gemaakt in milde trombofilie en hoog-risico trombofilie. Tot de groep van de milde trombofilieën behoren de meer frequente vormen van erfelijke trombofilie, zijnde Factor V Leiden en de protrombine G20210A mutatie (heterozygote dragers). De hoog-risico trombofilieën zijn zeldzamer, hiertoe behoren antitrombine deficiëntie, proteïne C of S deficiëntie, homozygote dragers van gelijk welke abnormaliteit, en dragers van meerdere abnormaliteiten. Naast dragers van deze mutaties hebben ook individuen met een niet-O bloedgroep of een familiale voorgeschiedenis van VTE een verhoogd risico op VTE.
Niet-erfelijke risicofactoren zijn leeftijd, antifosfolipidensyndroom, obesiteit, roken, zwangerschap en de postnatale periode, orale anticonceptie, hormoonvervangende therapie, heelkunde, immobilisatie en kanker.

Er is een bewezen associatie tussen erfelijke trombofilie en VTE. Tevens is er een synergistische relatie tussen erfelijke trombofilie en andere risicofactoren voor VTE. Studies hebben aangetoond dat bij vrouwen met erfelijke trombofilie het relatieve risico op zwangerschap-gerelateerde VTE 3 tot 41 keer verhoogd was ten opzichte van vrouwen zonder erfelijke trombofilie. De stijging in risico is sterk afhankelijk van het type trombofilie. Het

absolute risico op VTE blijft echter vrij laag. Of erfelijke trombofilie een oorzakelijke rol heeft in adverse zwangerschapsuitkomsten is nog een punt van discussie. Orale anticonceptie zorgt ook voor een verhoging van het relatieve VTE-risico bij vrouwen met erfelijke trombofilie. Het absolute risico op VTE blijft laag.
De combinatie van erfelijke trombofilie en een bloedgroep anders dan O geeft een supra-additief effect op het VTE-risico. Over de impact van erfelijke trombofilie op kanker zijn er nog veel tegenstrijdige resultaten. Bij operaties is erfelijke trombofilie een risicofactor die in achting moet genomen worden.

Er is nog steeds veel discussie over erfelijke trombofilie screening. Vele studies hebben bewezen dat de aanwezigheid van een erfelijke trombofilie geen verhoging geeft van het risico op herhaalde VTE's. Bovendien heeft erfelijke trombofilie geen impact op de behandeling van VTE. Aangezien erfelijke trombofilie een risicofactor is en geen ziekte, blijven vele dragers asymptomatisch. Daarom is het niet aangewezen om routine screening uit te voeren bij asymptomatische individuen.
Erfelijke trombofilie zorgt niet voor een verandering in de acute behandeling van VTE. Deze behandeling bestaat uit trombolyse in het geval van levensbedreigende situaties. Na trombolyse of in het geval trombolyse niet uitgevoerd kon worden of niet geïndiceerd was, wordt anticoagulatietherapie gestart. Standaard anticoagulatietherapie is heparine (laagmoleculair gewicht heparine of niet-gefractioneerd heparine) gevolgd door vitamine K-antagonisten. Er zijn argumenten om deze vitamine K-antagonisten te vervangen door nieuwe of direct orale anticoagulantia. Voor profylaxe behandeling, wanneer en hoe lang te geven, is er nog geen consensus bereikt. Vaak is het de clinicus die de beslissing moet maken op basis van zijn/haar eigen ervaring. Er zijn meer studies nodig, vooral studies van hogere kwaliteit, om duidelijke richtlijnen te krijgen over de zorg van individuen met erfelijke trombofilie.

1. Introduction

Venous thromboembolism (VTE) includes both deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE is the result of a disturbance of hemostasis, which is centered on Virchow's triad (blood flow stasis, hypercoagulability and vascular damage). [1, 2] It is a common disease, often with a fatal outcome. Untreated, VTE ends in death for 1 out of 3 patients. [3, 4] VTE is the third leading cardiovascular cause of mortality and morbidity in the Western world. In Europe, the estimated annual incidence rate of VTE ranges from 104 to 183 per 100 000 person-years (which is similar to the incidence rate of stroke). [5, 6] An annual death rate of 500 000 patients has been estimated. Besides the high fatality rate, VTE also has a high recurrence rate, which makes secondary thromboprophylaxis necessary. [2] Around 30% of the patients who have experienced VTE, have a recurring VTE within 10 years. Even with adequate anticoagulant therapy, there is still a risk of VTE recurrence. The risk of recurrence increases with the presence of inherited and non-inherited risk factors. [6, 7]

VTE is a multifactorial disease, and the risk factors are often divided into an inherited predisposition and non-inherited risk factors.

Inherited thrombophilia can be found in approximately 50 % of patients with an episode of unprovoked or idiopathic VTE. [8-10] Inherited thrombophilia can be divided into two groups. One group consists of the more rare forms of inherited thrombophilia. These are deficiencies of natural anticoagulant proteins: antithrombin, protein C and protein S. The other group includes the more common forms of inherited thrombophilia. These are the result of mutations that lead to an overactivity of coagulation factors. The most common ones in a Caucasian population are Factor V Leiden (FV Leiden) and prothrombin G20210A.

Antithrombin deficiency and protein C and S deficiency have a combined prevalence in the Western population that is less than 1% (See Table 1), [2, 3, 11], but they form a more severe risk of VTE than the more common forms of inherited thrombophilia. Together with homozygous carriers of any abnormality and carriers of multiple abnormalities, these deficiencies of anticoagulant proteins are called high-risk (for VTE) thrombophilias. [5, 12] Studies show that for antithrombin deficiency the risk of VTE rises with an odds ratio (OR) in order of 20-25 and for protein C and S deficiencies the risk rises with an OR in order of 10. [7] Antithrombin is a serine protease inhibitor, which mainly interacts with activated coagulation factors IIa and Xa, but also with factors VIIa, IXa, XIa and XIIa (intrinsic pathway), see Figure 1. [5] The interaction is accelerated by heparin and some patients with antithrombin deficiency may exhibit heparin resistance, which is something to keep in mind when administering thromboprophylaxis. Many gene variations in the antithrombin gene (*SERPINC1*) can lead to antithrombin deficiency, and also acquired conditions like nephrotic syndrome, some liver

diseases and asparaginase treatment can cause a deficiency of antithrombin. [5, 13-15] Protein C is activated by thrombin, and inactivates coagulation factor Va and factor VIIIa, these factors are required for the activation of factors II and X (see Figure 2). [5] Over 200 mutations in the *PROC* gene have been reported. Protein S acts as a cofactor of activated protein C (APC) and as a cofactor of tissue factor pathway inhibitor. Most of the mutations that cause protein S deficiency are mutations on the *PROS1* gene. [5, 13, 16, 17]

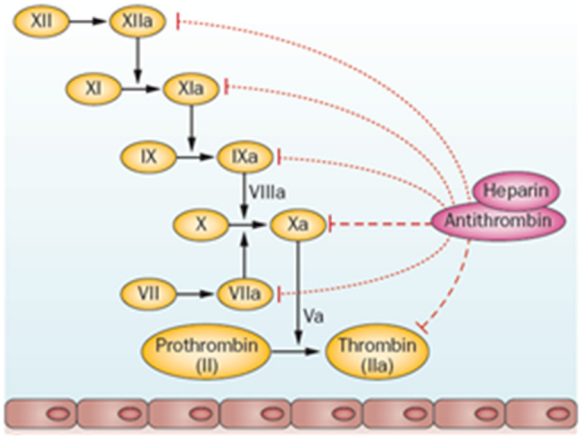

Figure 1 [5]: Anticoagulant mechanisms of antithrombin. The rate of interaction with target proteases is accelerated by heparin. Solid lines denote activation and broken lines inhibition (dashed lines, strong inhibition; dotted lines, weak inhibition).

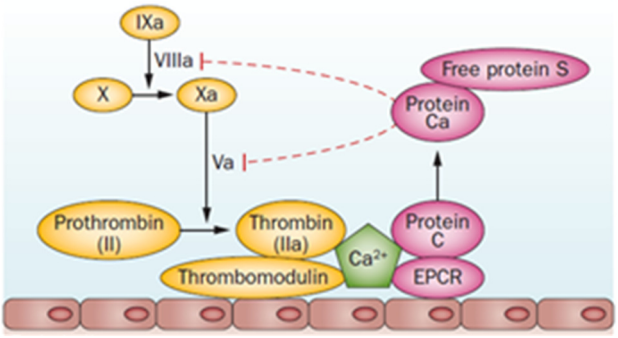

Figure 2 [5]: Anticoagulant mechanisms of the protein C and protein S system. Protein S acts as a cofactor of protein C and the complex inhibits factors VIIIa and Va. Protein C is activated by the EPCR bound to the complex thrombin–thrombomodulin. Solid lines denote activation and broken lines inhibition.
EPCR: endothelial protein C receptor, Protein Ca: activated protein C.

Heterozygous carriers of the FV Leiden or prothrombin G20210A mutation present a milder risk of VTE. FV Leiden is caused by a mutation that leads to activated protein C-resistance. Because of this mutation, the inactivation of factor Va happens at a slower pace and coagulation lasts longer. Heterozygous FV Leiden patients have a prevalence of approximately 5% in the general white population. Homozygous FV Leiden is less prevalent, but carriers tend to develop VTE at a younger age and more frequently than carriers of the heterozygous type. The prothrombin G20210A mutation causes a high plasma level of prothrombin. Heterozygous prothrombin G20210A can be found in about 2% of the Western population and like Factor V Leiden, the homozygous form of prothrombin G20210A is more rare. A combination of multiple thrombogenic disorders, which is not found frequently, makes for a very strong risk factor for VTE. [5, 7, 11, 13]

Table 1: Prevalence of inherited thrombophilia and association with risk of venous thromboembolism. [3, 11, 13, 17]

Thrombophilic abnormality	Prevalence (%)		First VTE		Recurrent VTE
	General population	Individuals with VTE	Relative Risk (OR)	Annual Incidence (%)	Relative Risk
Antithrombin deficiency	0.02-0.2	0.5-4.9	5-20	1-4	2.5
Protein C deficiency	0.2-0.4	3-9	5-8	1-2	2.5
Protein S deficiency	<0.5	1-3	1.7-8	0.7-2	2.5
FV Leiden (heterozygous)	3-7	12-20	4.9-9.7	0.19-0.67	1.3
FV Leiden (homozygous)	0.004-0.065	0.01	9-80	1.3	NA
Prothrombin G20210A (heterozygous)	1-3	6-8	1.9-3.8	0.13	1.4
Prothrombin G20210A (homozygous)	0.001-0.012	0.2-4	30	1.1	NA
FV Leiden + prothrombin G20210A	0.01	2-4.5	20-58.6	0.57	2.5

NA: not available

A special form of an inherited risk factor for VTE is the patient's blood group. Non-O blood group individuals have a higher risk of VTE compared to O blood group individuals. The reason for this increased risk is a higher level of von Willebrand factor and coagulation factor VIII in non-O individuals. [7, 18, 19] A high plasma level of factor VIII also increases the risk of VTE, but whether or not there is a genetic basis is still unknown. Another type of inherited thrombophilia is dysfibrinogenemia. Mutations in the fibrinogen genes are very rare and lead to various thrombophilia settings. [3, 5, 11]

Family history of VTE also poses an increased risk of VTE. A first-degree relative with a history of VTE increases the risk of a first VTE by 2-3 times. If there are multiple family members with a history of VTE, and at least one of them had symptoms before the age of 50, the risk of VTE is 4 times higher. Patients with a first-degree relative with VTE history also qualify for inherited thrombophilia testing. [3, 5, 11, 20]

Non-inherited risk factors can be divided into non-modifiable risk factors and acquired risk factors. Non-modifiable risk factors are age and antiphospholipid syndrome. The risk of VTE increases with advancing age. However, if the patient has an inherited form of thrombophilia, VTE tends to develop at a much younger age. Adolescents with VTE are more likely to have a genetic predisposition, and often qualify for screening after an unprovoked VTE.

Among the acquired risk factors (with the most evidence) are pregnancy and the postpartum period, oral contraception, hormone-replacement therapy, surgery, immobilization, long-distance travel, obesity and cancer.

The incidence rate of VTE is around 0.5-2 per 1000 pregnancies. It is one of the leading causes of mortality and morbidity amongst pregnant women. Pregnant women are 4 to 6 times more at risk for VTE than women of the same age who are not pregnant. The postpartum period holds an even higher risk, up to 14 times higher. [3, 11, 14, 21]

The use of oral contraceptives increases the risk of VTE 3 to 6 times. The risk of VTE is higher for third-generation contraceptives and high ethynylestradiol doses. The increased risk is primarily due to the estrogen component of oral contraceptives, because of an estrogen-induced protein C resistance. [22] The risk of oral contraceptive use is highest in the first 6-12 months, and in women using oral contraceptives for the first time. After those first 12 months, the risk of VTE decreases. [22, 23] Overall the absolute thrombotic risk of oral contraceptives is still low because of the generally low risk profile of patients taking oral contraceptives (young and healthy women). Some studies show an increase of VTE risk with the use of transdermal patches, others show a similar risk as the oral contraception. Vaginal ring users also have an increased risk of VTE compared to non-users. [22] Hormone-replacement therapy increases VTE risk similar to oral contraceptives, but the absolute risk is higher. Hormone-replacement therapy is usually given to older, post-menopausal women and these women have a higher baseline risk for VTE than the average woman using oral contraceptives.

All types of surgery pose a risk for VTE, with major surgery posing a higher risk than minor surgery. The risk surgery contains, is also very dependable on the patient's individual risk profile. The immobilization that follows surgery and other types of immobilization like lower extremity plaster casts, long-distance travel and paralysis or muscle weakness caused by a neurological disorder, increases the risk of VTE as well. The longer the immobilization lasts, the higher the risk of VTE gets. Similar to surgery, the risk immobilization poses is depending on individual risk factors. The absolute risk of long-distance travel, for patients without any other risk factors, is low.

Cancer can also pose a risk for VTE. Studies show that in almost 20% of all patients with an unprovoked episode of VTE, active cancer is found. Immunosuppressive or cytotoxic

chemotherapy increases the risk of VTE even more. [6] The magnitude of VTE risk in patients with cancer depends of the type of cancer and possible treatment. [3, 11, 24]
Obesity (a body mass index ≥ 30 kg/m²) increases the risk of VTE 2-3 times. But the bigger issue with obesity is that it amplifies other risk factors. [3, 5, 11, 24]
Smoking still remains a controversial VTE risk factor. Some studies have failed to find a significant association between smoking and VTE risk. Others have found modest associations, with an increased VTE risk according to the number of cigarettes per day. [13, 22, 25, 26]

Screening for inherited thrombophilia does not happen often at the moment. The reason for this is that the diagnosis of an inherited thrombophilia does not have much impact on the course of treatment. Also inherited thrombophilia is a risk factor, not a disease and many carriers remain asymptomatic. Therefore screening of asymptomatic individuals in the general population is not justified, even if they have multiple risk factors of VTE. [2, 5]

Since VTE is a common and potentially fatal disease, we will look into the risks of inherited thrombophilia, the impact it has on other, non-inherited risk factors of VTE, and its role in recurring VTE. If inherited thrombophilia increases the risk of VTE substantially, would screening for inherited thrombophilia and subsequent early thromboprophylaxis help reduce this risk? We will look into the advantages and disadvantages of screening and investigate what the criteria for this screening are. And finally, we will explore the different types of thromboprophylaxis, when and where it is best used.

2. Method

Full-text studies that reported data of VTE and inherited thrombophilia were evaluated for inclusion. In order to find enough studies to support this thesis, a systematic search of studies listed in the Pubmed database was conducted. First the following search strategy was used: "Venous Thromboembolism"[Mesh] AND "Thrombophilia"[Mesh]. But after a little evaluation of the results, it was not found a suitable search strategy. The following strategy was then chosen: "venous thromboembolism inherited". This resulted in 688 articles. After applying the filters "full text" and "English", the decision was made to only use articles that were published in the last 5 years, starting November 2012. This resulted in 180 studies. In addition to the previous search strategy, another one was included to focus more on prevention: "inherited thrombophilia prevention". The same filters were used and the time cutoff was also November 2012. This search strategy resulted in 63 studies. All these studies were evaluated for inclusion, based on relevance to the topic of this thesis. A couple of studies were also found in

the 'similar articles' section. Some articles were found by scanning through the references of articles that were already included.

3. Results

3.1 Risk factors

There is a synergistic relationship between inherited thrombophilia and the non-inherited risk factors. [8] In the next chapter, the effect on the VTE risk of inherited thrombophilia (FV Leiden, prothrombin G20210A mutation, protein C and S deficiency and antithrombin deficiency) in combination with some of the most common non-inherited risk factors will be investigated.

3.1.1 Pregnancy

Pregnancy has been proven to be associated with a hypercoagulable state in order to maintain hemostatic balance. This hypercoagulable state is caused by the increase of procoagulant factors and at the same time a decrease of anticoagulant factors. Inherited thrombophilia leads to a hypercoagulable state because of a similar mechanism. In some types of inherited thrombophilia there are deficiencies of natural anticoagulant proteins and in other types there are mutations that lead to an overactivity of coagulation factors. Pregnancy also causes venous stasis in the lower extremities. This stasis is due to compression of the pelvic veins and the inferior vena cava, hormones mediate an increase in venous capacitance and pregnancy causes hyperlipidemia and insulin resistance. All of this leads to an increased risk of VTE. [2, 27]

According to James et al., in 20%-50% of the women who have experienced VTE during their pregnancy or the postpartum period, some type of thrombophilia can be found. [28] Lussana et al. found that the relative VTE risk due to pregnancy was 3 to 41 times higher in women with thrombophilia (the magnitude of the VTE risk depends on the type of thrombophilia) compared to women without thrombophilia. [21]

Table 2 shows the risk of pregnancy-related VTE for the different inherited thrombophilias, according to the American College of Obstetricians and Gynecologists (ACOG). [27] Hotoleanu et al. has found that in almost half of the FV Leiden carriers, a VTE episode can occur during pregnancy. [8] According to Davenport et al. less than 0.3% of the heterozygous FV Leiden carriers will have a VTE episode during pregnancy. [29] Lussana et al. showed that the highest VTE risk can be found in homozygous FV Leiden carriers, the association between these carriers and pregnancy gives an OR of 34.4 with a 95% confidence interval (CI) of 9.9-120.1. The heterozygous mutation increases the risk 8.3 times (95% CI 5.4-12.7). However, the

absolute VTE risk during pregnancy remains low, and the FV Leiden mutation only slightly increases this absolute risk. [21] The ACOG found the heterozygous FV Leiden mutation in no more than 5-12/1000 deliveries. A personal history of VTE increases the risk of VTE up to 10% of the pregnant heterozygotes. Pregnant homozygous FV Leiden carriers without personal or first-degree relative history of VTE have a 1-2% VTE risk, those with history of VTE have a 17% VTE risk. [27]

Table 2: Risk of Venous Thromboembolism (VTE) with different inherited thrombophilias. [27]

	VTE risk per pregnancy, no history (%)	**VTE risk per pregnancy, with previous VTE (%)**	**Percentage of all VTE**
Antithrombin deficiency	3.7	40	1
Protein C deficiency	0.1-0.8	4-17	14
Protein S deficiency	0.1	0-22	3
FV Leiden (heterozygous)	0.5-1.2	10	40
FV Leiden (homozygous)	4	17	2
Prothrombin G20210A (heterozygous)	<0.5	>10	17
Prothrombin G20210A (homozygous)	2-4	>17	0.5
FV Leiden + prothrombin G20210A	4-5	>20	1-3

Looking at pregnant women who have suffered a VTE, the prothrombin G20210A mutation can be found in 17% of these women. [8, 27, 30] Without personal history of VTE, pregnant heterozygous carriers of the prothrombin G20210A mutation have less than 1% risk of VTE. With personal history of VTE, the risk increases to 10%. [27] Lussana et al. found a relative VTE risk related to pregnancy in heterozygous carriers of 6.8 times (95% CI 2.5-18.8) and 26.4 (95% CI 1.2-559.3) in homozygous carriers of the prothrombin mutation. [21]

Pregnant women with either protein C or S deficiency have a VTE risk up to 7% in the presence of personal of family history of VTE. In the absence of VTE history, the absolute risk of VTE is 0.1-0.8% for protein C deficiency and 0.1% for protein S deficiency. [27, 29] Lussana et al. found a relative VTE risk of 4.8 (95% CI 2.2-10.7) for pregnant women with protein C deficiency and 3.2 (95% CI 1.50-6.0) for pregnant women with protein S deficiency, compared to women without a deficiency. [21] Newborns who are homozygous carriers of protein C or S deficiency

will develop neonatal purpura fulminans, and they will need to take anticoagulant therapy for the rest of their lives. [3, 27]
Rogenhofer et al. found that, compared to women without antithrombin deficiency, pregnant women with antithrombin deficiency and a positive family history for VTE have a significantly elevated risk of ante- and postpartum VTE (OR 4.7). [31] Rheaume et al. found an increased risk of VTE (OR 6.09, 95% CI 1.58-23.43) among asymptomatic pregnant women with antithrombin deficiency compared to women without antithrombin deficiency. [14] James et al. reported that a systematic review found an association between antithrombin deficiency and pregnancy with an OR of 4.76 (95% CI 2.15-10.57). [28] Lussana et al. reported a similar association (OR 4.7, 95% CI 1.30-17.0). [21] Hotoleanu et al. reported that 31% of the pregnant women with antithrombin deficiency may present VTE, increasing up to 50% if they have VTE history. [8]

Because both pregnancy and inherited thrombophilia increase the risk of VTE in a similar way, many studies have tried to find evidence for a correlation between inherited thrombophilia and adverse pregnancy outcomes (these include pregnancy loss, preeclampsia, intrauterine growth restriction, placental abruption and stillbirth). [8, 29, 32]
Pregnancy loss is quite frequent, up to 15% of women experience a spontaneous loss of a clinically recognized pregnancy at least once their life. The absolute percentage of pregnancy loss is estimated to be even higher, because pregnancy loss at a very early gestation often goes unnoticed. Recurrent pregnancy loss affects 1% of women if recurrent pregnancy loss is defined as three or more pregnancy losses. When recurrent pregnancy loss is defined as two or more pregnancy losses, 3-5% of women are affected. The definition of recurrent pregnancy loss depends on the country where the study is executed. [30, 32-34] The pathophysiology of pregnancy loss is still not completely understood, but it is believed to involve both coagulation and inflammation. However, there is some controversy whether or not inherited thrombophilia plays a causal role in adverse pregnancy outcome. The cause of adverse pregnancy outcomes remains unknown in almost half of the cases, it is most likely multifactorial. [27, 30, 33, 34]
According to the ACOG, meta-analyses and a retrospective cohort study have been able to find an association between inherited thrombophilia and first-trimester pregnancy loss, while prospective cohort studies have not found an association. [27] Areia et al. conducted a meta-analysis that showed there is a significant association between inherited thrombophilias and first-trimester pregnancy loss, however the magnitude of this association depends on the type of pregnancy loss and the type of inherited thrombophilia. [35]
De Jong et al. found that first-trimester recurrent pregnancy loss was most associated with FV Leiden, active protein C resistance, and the prothrombin G20210A mutation. Late non-

recurrent pregnancy loss was associated with FV Leiden, the prothrombin G20210A mutation and protein S deficiency. [32]

Table 3 shows the association between inherited thrombophilia and pregnancy loss (including stillbirth). [33]

Table 3: Association between inherited thrombophilia and pregnancy loss. [31]

Type of thrombophilia	Miscarriage: 1st or 2nd trimester loss (OR (95% CI))	Recurrent 1st trimester miscarriage (OR (95% CI))	Non-recurrent 2nd trimester miscarriage (OR (95% CI))	Stillbirth: 3rd trimester loss (OR (95% CI))
Antithrombin deficiency	0.9 (0.2-4.5)	NA	NA	7.6 (0.3-196.4)
Protein C deficiency	2.3 (0.2-26.4)	NA	NA	3.1 (0.2-38.5)
Protein S deficiency	3.6 (0.4-35.7)	NA	NA	20.1 (3.7-109.2)
FV Leiden (heterozygous)	**1.7** (1.1-2.6)	1.9 (1.0-3.6)[a]	**4.1** (1.9-8.8)[a]	**2.1** (1.1-3.9)
FV Leiden (homozygous)	**2.7** (1.3-5.6)			2.0 (9.7)
Prothrombin G20210A (heterozygous)	**2.5** (1.2-5.0)	**2.7** (1.4-5.3)	**8.6** (2.2-34.0)	**2.7** (1.3-5.5)

Odds ratios in bold are statistically significant
NA: not available
[a] Only the odds ratios for heterozygous and homozygous carriers together are available.

Skeith et al. found only a small increased risk of pregnancy loss with carriers of the FV Leiden mutation (4.2%) compared to the women without the mutation (3.2%). The OR 1.52 (95% CI 1.06-2.19) suggests a weak causal effect. [34] Hotoleanu et al. showed that the presence of the FV Leiden mutation increases the risk of adverse pregnancy outcomes 2 to 3 times compared to non-carriers. [8] Davenport et al. found 2 comprehensive reviews where FV Leiden carriers had an increased risk of recurrent pregnancy loss (OR 1.52, 95% CI 1.06-2.19 and OR 2.02, 95% CI 1.60-2.55). It also showed a low absolute risk of pregnancy loss (4.2%) in women carrying the FV Leiden mutation. [29]

Some studies have shown that women with the prothrombin G20210A mutation are two times more likely to have recurrent pregnancy loss than women without the mutation. Other studies have failed to find an association. [29] McNamee et al. reported two European case-control studies where no association was found. It also gave results of a systematic review where an OR of 2.70 (95% CI 1.37-5.34) was found for recurrent pregnancy loss in women with the prothrombin mutation compared to women without the mutation. [30]

Hotoleanu et al. found no association between protein C deficiency and adverse pregnancy outcome. They also found that for women with protein S deficiency, pregnancy or the

postpartum period acts as a trigger for VTE in about 20% of the cases. Patients with protein S deficiency have a 3 times higher risk of pregnancy loss than non-carriers. [8] McNamee reported a case-control study where no significant association was found between protein S deficiency and adverse pregnancy outcome. [30]
De Jong et al. reported family studies that showed an increased risk of pregnancy loss among women that have an inherited thrombophilia, especially antithrombin deficiency or combined defects. [32] Hotoleanu et al. also found an increased risk of adverse pregnancy outcome among pregnant women with antithrombin deficiency. These women had less complications when given antithrombotic therapy. [8] Davenport et al. found that pregnant women with antithrombin deficiency had an increased risk of embryonic demise and pregnancy loss, compared to the general population. [29]

Intrauterine growth restriction (IUGR) or fetal growth restriction (FGR) can lead to small gestational weight (estimated fetal weight is below the 10^{th} percentile of the gestational age reference curve) and a low birth weight. IUGR can lead to fetal death. Coriu et al. found a statistically significant association between IUGR and the prothrombin G20210A mutation with an OR of 4.81 (95% CI 1.05-22.02, p=0.043). An association between IUGR and the FV Leiden (OR 1.58, 95% CI 0.61-4.08) was also found, however this association was not statistically significant (p=0.347 and the cut-off was set at p=0.05). Coriu et al. also showed results of another study where an association between IUGR and FV Leiden was found (OR 6.9, 95% CI 1.4-33.5) as well as an association between IUGR and the prothrombin G20210A mutation (OR 5.9, 95% CI 1.2-29.4). Another study showed an OR of 1.0 (95% CI 0.80-1.25) for FV Leiden and an OR of 1.25 (95% 0.92-1.70). [36] The ACOG reported studies where no significant association was found between IUGR and FV Leiden or the prothrombin G20210A mutation. [27]

Until now, there is insufficient evidence of an association between inherited thrombophilia and preeclampsia or placental abruption. [27, 29, 35]

3.1.2 Oral contraceptives

Hormonal contraceptives are used by hundreds of millions of women all over the world. The most commonly used are combined oral contraceptives (COC). [10, 22] Therefore a great number of women are exposed to a VTE risk. Studies showed that the incidence of VTE is in fact higher among women with some type of inherited thrombophilia. The magnitude of this increase of VTE risk is depending on the type of thrombophilia. [3]

For patients with Factor V Leiden who also use oral contraception, the risk of VTE increases 34-35 times compared to non-users without the mutation. This is much higher than the sum of the separate risks, respectively 4-7 times and 3-6 times higher. However, even with a VTE risk increase of 34-35 times, the absolute risk for FV Leiden carriers on oral contraception is still very low. [8, 22, 25, 37] Van Vlijmen et al. found that FV Leiden in users of oral contraception increased the VTE risk more than 6-fold (OR 6.14, 95% CI 2.58-14.46), compared to oral contraception users without FV Leiden. [38] O'Brien et al. reported a prospective cohort study of asymptomatic FV Leiden carriers where the annual VTE incidence was 1.8% per year oral contraception was used. [22]

Hotoleanu et al. showed that women carrying the prothrombin G20210A mutation on oral contraception had a 7-fold increase in VTE risk, and a 17-fold higher risk if these women also had a concomitant heterozygosity for FV Leiden. [8] Van Vlijmen et al. found that the prothrombin mutation in patients using oral contraception causes a 5-fold increase in VTE risk (OR 5.24, 95% CI 2.69-10.20), compared to women on oral contraception without the mutation. [38]

For women with protein S deficiency, Hotoleanu et al. reported that the use of oral contraception could increase the VTE risk up to 600 times, compared to women without the deficiency. [8] According to Van Vlijmen et al., the presence of high-risk (severe) thrombophilia, like antithrombin deficiency and protein C and S deficiency, could increase the risk of VTE up to 7 times in oral contraception users (OR 7.15, 95% CI 2.93-17.45). [38]

Table 4: Effect of duration of oral contraception and inherited thrombophilia on venous thromboembolism. [22]

	OR (95% CI)	**Adjusted OR (95% CI)**
Non-users without thrombophilia	Reference	Reference
Non-users with thrombophilia	4.1 (3.0-5.5)	4.0 (2.9-5.4)
Long and very long users without thrombophilia	6.1 (4.6-8.1)	6.6 (4.9-8.8)
Long and very long users with thrombophilia	23.9 (15.6-36.5)	25.4 (16.5-39.2)
Short users without thrombophilia	7.2 (5.1-10.3)	7.5 (5.3-10.8)
Short users with thrombophilia	62.6 (30.1-130.1)	62.2 (29.8-129.6)

There is a synergistic association between inherited thrombophilia and the use of oral contraceptives. However, the strength of this association changes according to the duration of

oral contraceptive use. The risk of VTE is highest in the first year of oral contraceptive use, especially with first time users. The risk of VTE decreases in the following years, however it still remains quite high. (Table 4) The use of oral contraceptives has a much smaller impact on the VTE risk in older (>40 years) women. [23]

Because of the increased risk of VTE, some studies suggested that inherited thrombophilia is a contra-indication for the use of oral contraception. [26] Others claimed only women with high-risk thrombophilias should be withheld from the use of oral contraception. Women with a mild thrombophilia have a much lower absolute risk of VTE and should not be denied the benefits of oral contraception. These patients should be given an informed decision, whether or not they want to use oral contraception. [22, 38]

3.1.3 Other risk factors

3.1.3.1 Surgery and hospitalization

It is well known that surgery is a risk factor for VTE, especially orthopedic surgery. The combination with inherited thrombophilia amplifies this VTE risk. Parajuli et al. found that inherited thrombophilia in patients undergoing kidney transplantation, increases the risk of complications. [39] Dubsky et al. found that FV Leiden was significantly associated with unsuccessful percutaneous transluminal angioplasty (PTA). In patients with the prothrombin G20210A mutation an association was also found, however this was not statistically significant. [40]

3.1.3.2 Cancer

Heit et al. found that in almost 20% of all patients who have experienced incident VTE, active cancer can be found. Immunosuppressive or cytotoxic chemotherapy increases the risk of VTE even more. [6] Hotoleanu et al. reported that cancer patients with FV Leiden mutation have a 13% risk of VTE, which is twice the risk cancer patients without the mutation have. A lot of contradictory results can be found surrounding the impact of inherited thrombophilia in cancer patients. [8]

3.1.3.3 ABO-blood group

In a retrospective case-control study performed by Spiezia et al. the impact of having an inherited thrombophilia combined with a non-O blood group was examined. The combination of inherited thrombophilia and non-O blood group increased the risk of VTE 7 times (OR 7.06, 95% CI 4-85-10.28), compared to non-carriers of inherited thrombophilia with blood group O. The study showed that the impact on VTE risk of non-O blood group and inherited thrombophilia separately, was similar (respectively OR 2.21, 95% CI 1.78-2.75 and OR 2.28, 95% CI 2.18-3.66). So the combination showed a supra-additive effect on VTE risk. [18]

Franchini et al. also found that the combination of a non-O blood group and FV Leiden had a supra-additive effect on the risk of VTE (OR 7.60, 95% CI 3.21-17.99). [19]

3.2 Screening

Table 5: Guidelines concerning the value of testing for inherited thromboembolism. [12]

	To determine VTE reason	Prediction of recurrent VTE after unprovoked VTE	Prediction of VTE and prescribing thromboprophylaxis in asymptomatic relatives	Prediction of VTE and prescribing thromboprophylaxis in general population
International Consensus Statement (2015)	In all patients, except those with a single provoked VTE >50 years	Yes	Yes, especially females of childbearing age	No
French Consensus Guideline (2009)	In patients with a single unprovoked proximal VTE <60 years, patients with recurrent proximal VTE, and patients with recurrent, unprovoked distal DVT < 60 years	Yes	Yes	No
British Committee for Standards in Hematology (2010)	No (possible exception for patients with strong family history of unprovoked recurrent VTE)	No (possible exception for patients with strong family history of unprovoked recurrent VTE)	No, possible exception for relatives of carriers of AT, PC, PS deficiency	No
Evaluation of Genomic Applications in Practice and Prevention (2011)[a]	No	No	No	NA
National Institute for Health and Clinical Excellence (NICE) (2012)	In patients with unprovoked VTE and with a first-degree relative with VTE <50 years (deficiency of AT, PC, PS testing)	In patient with a first-degree relative with VTE <50 years, if anticoagulation is stopped (deficiency of AT, PC, PS testing)	No, possible exception for females of childbearing age, with a first-degree relative with VTE and known thrombophilia, who are planning pregnancy or oral contraception	NA

VTE: venous thromboembolism, DVT: deep venous thrombosis, AT: antithrombin, PC: protein C, PS: protein S, NA: not analyzed

[a] Only Factor V Leiden and prothrombin G20210A were analyzed

Table 5 gives a summary of the different guidelines on testing for thrombophilia. [12]
Screening for inherited thrombophilia is still a highly-discussed, controversial subject. Many studies claim testing for inherited thrombophilia should always be done with the intent to give tailored treatment (for example prolongation of anticoagulation), if testing turns out positive. [3, 5, 8, 12, 41] However, whether or not the diagnosis of inherited thrombophilia has an impact on patient management is uncertain, and often therapy is not adjusted in patients with thrombophilia. [2, 10-12, 42-45] The only indications for IT testing, according to the NICE recommendations, are patients with a first-degree relative with a history of VTE, and patients with an unprovoked VTE. [2] Hotoleanu et al. suggested that diagnosing an inherited thrombophilia only has an impact on anticoagulant therapy in selected cases: children with purpura fulminans, pregnant women at risk for VTE, patients with a VTE episode before the age of 40 and patients with positive family VTE history. For these last two groups, testing for inherited thrombophilia can help to compute the risk of VTE recurrence. [8] Varga et al. recommended against routine thrombophilia testing, because of inadequate evidence of the clinical utility. [11]
Another argument against routine testing is that having an inherited thrombophilia does not strongly predict the risk of VTE recurrence. [2, 8, 10, 20, 44, 46]

Bleker et al. suggested testing for thrombophilia should not be performed with the objective to decrease the risk of VTE recurrence, but testing could help identifying asymptomatic family members so that they could take VTE-preventive measures. [10] De Stefano et al. found that 12-16% of thrombophilia testing is performed on asymptomatic individuals with positive family history of VTE. Patients with VTE or relatives with VTE are the main group that are tested for inherited thrombophilia. [12] Since family history of VTE is a strong risk factor for VTE on its own, Martinelli et al. found family studies the most appropriate instrument to examine the risk of VTE and incidence of VTE in patients with thrombophilia compared to those without. [5] Suchon et al. found that family history is not a good predictor of inherited thrombophilia (sensitivity = 12% and specificity = 92%). It did show that inherited thrombophilia was significantly more prevalent (35.3%) in patients with a high family history profile, compared to patients with a low family history profile (23.9%). However, there was little difference between patients with a lower family history profile and patients with no family history at all. [26] Zöller et al. reported that using positive family history as a tool for identifying inherited thrombophilias showed a sensitivity of 16-63% and a positive predictive value of 6-50%, concluding family history is not a good predictor. [20] Grimes et al. found similar results. [47]
Coppola et al. found indiscriminate testing in the general asymptomatic population to be cost-ineffective. Routine thrombophilia screening before starting oral contraception is not recommended, even with a positive family history of VTE. Screening could be considered in

asymptomatic family members if there is a known history of higher-risk inherited thrombophilia. [3] Van Vlijmen et al. also suggested that screening for inherited thrombophilia could be useful in asymptomatic women from families with a known severe thrombophilia. However, testing negative could give a false sense of reassurance, since for example, women with a positive family history have a higher chance of oral contraception-related VTE even without an inherited thrombophilia. [38]

There are arguments as well to perform thrombophilia testing in adolescents with multiple VTE risk factors. [22, 48]

3.2.1 Factor V Leiden

Table 6: Indications for Factor V Leiden testing. [8]

° Age <50, any VTE
° VTE in unusual sites (such as hepatic, mesenteric, and cerebral veins)
° Recurrent VTE
° VTE and a strong family history of thrombotic disease
° VTE in pregnant women or women taking oral contraceptives
° Relatives of individuals with venous thrombosis under age 50
° Myocardial infarction in female smokers under age 50

The indications for FV Leiden mutation testing, according to Hotoleanu et al. can be found in Table 6. They suggested female relatives of patients with a FV Leiden mutation could be tested before starting oral contraception, women contemplating pregnancy, or women with recurrent pregnancy loss or unexplained complications, in order to manage their future pregnancies better.[8] Davenport et al. found there is not enough evidence to recommend screening for FV Leiden in women who have had adverse pregnancy outcomes. [29] Hotoleanu et al. did not recommend routine prenatal testing or newborn screening. Routine FV Leiden testing should also not be performed on adults with unprovoked VTE (for secondary prophylaxis against recurrent VTE) and asymptomatic adult relatives of patients with FV Leiden (for primary prophylaxis, being anticoagulation, against a first episode of VTE). [8]

3.2.2 Prothrombin G20210A mutation

According to Hotoleanu et al., indications for testing for the prothrombin G20210A mutation are the same as the indications for FV Leiden. Routine prothrombin G20210A mutation testing should also not be performed in adults with unprovoked VTE and asymptomatic adult relatives of patients with VTE and an inherited thrombophilia. The prothrombin mutation was found not to be a risk factor for adverse pregnancy outcome in female relatives, so screening of these relatives is not advised. [8] The ACOG also recommends against screening for prothrombin G2210A mutation in women with history of adverse pregnancy outcome. [27, 29]

3.2.3 Protein C deficiency

Hotoleanu et al. found that in symptomatic families, protein C deficiency posed a higher risk of VTE than in asymptomatic families. This shows the interaction of protein C deficiency and other genetic factors. Protein C testing during an acute VTE episode gives valid results (even though protein C and S levels decrease during the acute phase) and a normal test result rules out a deficiency. [8]

3.2.4 Protein S deficiency

Hotoleanu et al. found that low free protein S and low total protein S levels can rarely identify individuals of the general population at risk for VTE. Therefore routine protein S deficiency screening is not recommended. [8] Alhenc-Gelas found that only individuals with specific mutations in the PROS1 gene and a free protein S level below 30% have an increased VTE risk, whereas low free protein S without a mutation showed no association to VTE. This suggested that PROS1 genotyping could be used for protein S deficiency diagnosis. [16]

3.2.5 Antithrombin deficiency

According to Hotoleanu et al. genetic analysis and prenatal testing for antithrombin deficiency is not advised, because there are too many mutations that lead to antithrombin deficiency. [8]

3.2.6 Special conditions

The ACOG found that increased screening for inherited thrombophilia in pregnant women, has not resulted in significant treatment benefits. Thrombophilia screening should only be done if the patient either has a personal history of VTE, related to a non-recurrent risk factor (trauma, surgery or immobilization), or has a first-degree relative with high-risk thrombophilia. [27] Areia et al. also found that routine inherited thrombophilia screening for pregnant women was not recommended, as the use of antenatal thromboprophylaxis in all women with thrombophilias is still controversial. [35] Davenport et al. found that screening pregnant women with a personal history of VTE is accepted. Screening of pregnant women with family history of VTE is controversial, since there is no evidence of its benefit. There is also controversy surrounding screening of women with history of adverse pregnancy outcome, therefore it is recommended not to screen these women. [29, 49]

De Stefano et al. reported recommendations against indiscriminate screening of women before prescription of oral contraceptives or hormone replacement therapy or when considering pregnancy. However, in clinical practice testing for thrombophilia is still common with these women. [12] According to Martinelli et al., pregnancy, the use of oral contraceptives, hormone-replacement therapy, surgery… are not indications for thrombophilia screening, except in

patients with family history of VTE or families with known natural anticoagulant deficiencies (high-risk thrombophilia). [5]

O'Brien et al. recommended against the routine laboratory thrombophilia screening before initiation of oral contraceptives. The routine testing before oral contraception was also found not to be cost-effective. They found that over 92 000 carriers of the FV Leiden mutation should be identified and discontinue the use of oral contraception in order to prevent one VTE-related death. O'Brien et al. did recommend testing for inherited thrombophilia before the use of oral contraceptives in adolescents with positive family history of VTE. [22]

Since the combination of inherited thrombophilia and a non-O blood group increases the VTE risk caused by inherited thrombophilia up to 3 times, Spiezia et al. recommended that in patients who already have been diagnosed with inherited thrombophilia, the blood group should be determined. Especially in patients with additional circumstantial risk factors. For patients without a known inherited thrombophilia, blood group testing is of little use, because of the high prevalence of non-O blood groups in the general population and the low VTE risk in that population. [18]

3.3 Diagnosis

Table 7: Testing for inherited thrombophilia. [27]

Thrombophilia	**Testing method**	**Testing reliable during pregnancy?**	**Testing reliable during acute VTE?**	**Testing reliable with anticoagulation?**
FV Leiden	Activated protein C resistance assay	Yes	Yes	No
	-> if abnormal: DNA analysis	Yes	Yes	Yes
Prothrombin G20210A	DNA analysis	Yes	Yes	Yes
Protein C deficiency	Protein C activity (<60%)	Yes	No	No
Protein S deficiency	Functional assay (<55%)	No	No	No
Antithrombin deficiency	Antithrombin activity (<60%)	Yes	No	No

Table 7 shows a summary of how to test for each inherited thrombophilia and it also shows if those tests are reliable in specific situations, like pregnancy, an acute episode of VTE and with anticoagulation therapy. [27]

FV Leiden can be diagnosed via functional assay and a DNA-based genotyping test. If the functional assay is positive, further DNA testing is necessary to confirm and identify the mutation. As a functional test, the active protein C (APC) resistance assay can be used. This test analyses the activated partial thromboplastin time (aPTT) and the response to APC. Patients with an APC resistance will have a minimal prolongation of the aPTT. The test should not be used in patients with a prolonged aPTT (patients receiving oral anticoagulants or patients with lupus anticoagulants). [8, 13]
Polymerase chain reaction (PCR) is used to detect the prothrombin mutation. [8, 13]

Protein C deficiency is detected through functional and immunologic assays. [13] The immunological assays include electroimmunoassays, radioimmunoassay and ELISA (enzyme-linked immunosorbent assay). Patients with protein C levels less than 50% are likely to have a protein C deficiency. Because anticoagulant therapy could interfere with protein C levels, it is recommended to stop oral anticoagulation 10 days before thrombophilia testing. [8]
Protein S deficiency is detected by measuring protein S antigen (total or free protein S antigen) through ELISA and functional protein S activity tests. These tests are based on the prolongation of blood clotting. Whenever protein S deficiency is suspected, free protein S antigen testing should be executed. Decreased levels of protein S occur not just in the inherited deficiency, but also with liver diseases, pregnancy, vitamin K deficiency and vitamin K antagonist therapy, nephrotic syndrome, varicella, sickle cell disease, HIV infection, malignancy… Patients with FV Leiden can also present with decreased protein S levels. Plasma should be diluted to get a more accurate result. [8]

Antithrombin deficiency testing can be done by using the antithrombin-heparin cofactor assay, to measure antithrombin activity. This test measures heparin binding to a coagulation factor that requires antithrombin activity. If this antithrombin activity is low, an antithrombin antigen test is done. [8, 13] Functional antithrombin tests are influenced by heparin (lowers antithrombin levels) and vitamin K antagonists (increase antithrombin levels). [8]

Skelley et al. found that testing for thrombophilia can be complex, because many laboratory values necessary for diagnosis are affected by medication or other conditions. An example of medication that interferes with thrombophilia testing are the non-Vitamin K antagonist oral anticoagulants (NOACs). They prolong clotting times, which can cause false-positive results

for protein C and protein S levels. It is suggested that thrombophilia testing either happens before administration of anticoagulants, or 4-6 weeks after anticoagulant therapy has been halted. [41]

3.4 Treatment & Prevention

The first 5-10 days following a DVT or PE is considered the acute phase of VTE. The acute management of VTE contains the following: acute resuscitative measures, the start of anticoagulation or an alternative for patients with an anticoagulation contraindication, and short-term follow up. Figure 3 shows the flowchart for acute management after confirmation of VTE. [4]

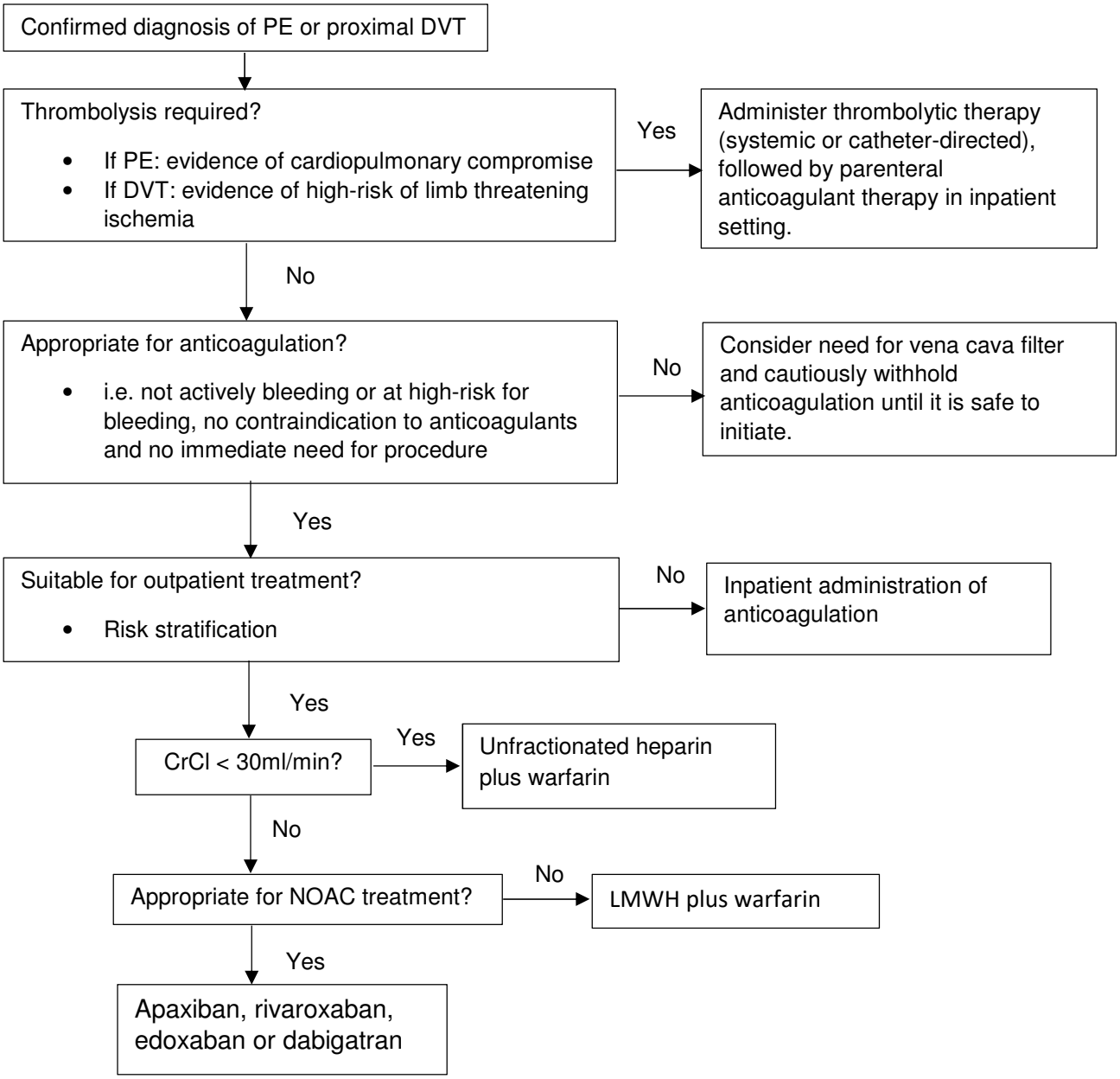

Figure 1: Flowchart for acute treatment of venous thromboembolism. [4]
PE: pulmonary embolism, DVT: deep venous thrombosis, CrCl: creatinine clearance, NOAC: non-vitamin K antagonist oral anticoagulant, LMWH: low-molecular-weight heparin

3.4.1 Thrombolysis

If possible and when necessary (in life- or limb-threatening situations), thrombolysis should be considered after a VTE episode. According to Hillis et al., catheter directed thrombolysis (CDT) is current practice. Studies still need to confirm if CDT actually increases vein patency in comparison to anticoagulation and does not increase VTE recurrent rate or increase adverse event. In controlled trials, thrombolysis after acute PE did not result in mortality benefit, a meta-analysis however did find a lower mortality rate in some high-risk patients given thrombolysis, compared to patients only given anticoagulant therapy. [4] Wang et al. also reported that systematic thrombolysis was not recommended, because of the increase in major bleeding. It also did not find a significant reduction in VTE recurrence after CDT. [2] Studies suggested the need of further evaluation.

3.4.2 Vena Cava Filter

Some patients have a (temporary) contraindication for anticoagulation, are bleeding or have a high bleeding risk, or they require a procedure within the following four weeks. For these patients, a temporary vena cava filter could be considered instead of anticoagulation. Patients who are eligible for anticoagulant therapy do not benefit from a vena cava filter. It should be taken into account that the filter itself poses a risk of thrombosis, so anticoagulation should start as soon as it is safe enough to do so and the filter should be removed as soon as full-dose anticoagulation is reached. Hillis et al. found that in clinical practice, the vena cava filter was often left in place unnecessary long, exposing the patients to unneeded long-term risks without benefit. [4]

3.4.3 Anticoagulation

For patients without any contra-indications and patients who do not require thrombolysis, anticoagulation should be the first choice for acute treatment of VTE. Before starting anticoagulant therapy, the clinician has to determine the bleeding risk for each patient individually, since there is no prospectively validated standardized bleeding prediction tool. Age, history of bleeding, comorbidities and medication should all be taken into account. [4]

The available anticoagulant therapies are: unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), aspirin or acetylsalicylic acid (ASA), vitamin K antagonists (VKA) and non-vitamin K antagonist oral anticoagulants (NOACs).

3.4.3.1 Heparin

Hillis et al. reported a meta-analysis, showing the safety and efficacy of LMWH treatment for VTE patients. LMWH is a rapidly acting anticoagulant, it can be used as long-term VTE treatment. However, LMWH is most frequently followed after 4-5 days by VKAs. These VKAs are more slow-onset anticoagulants, so LMWH takes care of the initial response against the

VTE attack, until the VKAs have reached their full anticoagulant capacity. The LMWH treatment can only be discontinued if the International Normalized Ratio (INR) is between 2.0 and 3.0, for 2 consecutive days. Patients who are at a high risk of bleeding can also be started on intravenous UFH. [2, 4] Wang et al. preferred twice-daily LMWH over once-daily LMWH or UFH because twice-daily LMWH posed a lower risk of major bleeding or heparin-induced thrombocytopenia. [2]
Renal failure is a contra-indication for the use of LMWH. Hillis et al. found increasing amount of literature challenging this. [4]

Patients with antithrombin deficiency may not have an adequate response to heparin. Antithrombin has a binding site for heparin, and if heparin is bound to antithrombin, there is amplification of the inhibition of coagulation caused by antithrombin. Therefore, in patients with antithrombin deficiency, where no antithrombin or a reduced concentration is present, heparin has little effect. Some of these patients could be helped by a higher dose of heparin, however the response may be variable in different patients. [3, 8, 14, 28]

The available LMWH agents are: dalteparin, enoxaparin, nadroparin and tinzaparin.

3.4.3.2 Aspirin

Prandoni et al. found that aspirin decreases the risk of VTE recurrence, compared to placebo (hazard ratio 0.58, 95 % CI 0.36–0.93). Another trial showed no significant decrease in VTE recurrence with aspirin therapy compared to placebo (hazard ratio 0.74, 95 % CI 0.52–1.05). However, aspirin was associated with a significant reduction of major vascular events compared to placebo (hazard ratio 0.66, 95 % CI 0.48–0.92). Low dose aspirin is a highly cost-effective option for long-term thromboprophylaxis, but other anticoagulants have a higher decrease of VTE recurrence rate, and aspirin probably causes more major bleeding. [42]

Areia et al. found no evidence that supported adding LMWH to aspirin alone in patients with inherited thrombophilia. [35] Neither did McNamee et al. [50]

3.4.3.3 Vitamin K antagonists

As shown before, VKAs are often used in the treatment and secondary prevention of VTE, following LMWH. Because VKAs have a slow-onset action, oral VKA therapy is best started on the same day as the LMWH therapy. [2] The efficacy of VKAs has been demonstrated before, but VKAs also have disadvantages. VKA therapy requires laboratory monitoring, VKA's have a narrow therapeutic index range, complex dosing regimens and there are a lot of drug-

drug and drug-food interactions. [41] For example, a subtherapeutic VKA dose leads to a higher VTE recurrence rate. [2]

Coppola et al. found that in patients with protein C deficiency and less frequently protein S deficiency, the use of warfarin could induce skin necrosis. The skin necrosis can be observed on the third to eighth day of warfarin therapy. After warfarin initiation, protein C levels drop dramatically, leading to a temporary imbalance of anti- and procoagulant pathways. Other vitamin K-dependent coagulation factors experience a much smaller decrease in concentration. [3]

3.4.3.4 Non-vitamin K antagonist oral anticoagulants (NOACs)

NOACs are the newest anticoagulant medicines. They have an advantage with regards to the VKAs because they have predictable pharmacokinetics, a rapid-onset of action and shorter half-lives. There are also less drug-drug and drug-food interactions with NOACs than with VKAs. [4, 42]

Table 8: Clinical factors excluding NOACs as acute venous thromboembolism treatment. [4]

° Acquired or inherited thrombophilia
° Active bleeding or other contraindications for anticoagulation
° Active cancer
° Younger than 18 years
° obesity
° Pregnant or breastfeeding
° Post-thrombolysis
° Vena cava filter
° Dual antiplatelet therapy
° Rare VTE location
° Renal failure (creatinine clearance <25 ml/min)

Hillis et al. reported that for NOACs the case-fatality rate for major bleeding is less than the rate for VKAs. [4] Wang et al. also found NOACs to be safer than VKAs, looking at the major bleeding risk. [2] Prandoni et al. found a better benefit-to-risk profile for NOACs in the first 6-12 months after VTE, compared to conventional treatment (LMWH + VKA). [42] Hillis et al. recommended that NOACs, even though their efficacy is proven and they are easier to use than VKAs, should only be used in limited situations. Table 8 shows some of the reasons for not choosing NOACs as first-choice acute VTE treatment. Other contra-indications for NOACs are: patients who take potent P-glycoprotein inhibitors or inducers, patients with renal failure (creatinine clearance CrCl <25-30 ml/min). However, randomized controlled trials have found no difference in efficacy and safety for patients with a CrCl of 30-50ml/min on NOACs compared to VKAs. [4] A disadvantage of NOACs is the cost. NOACs are a much more expensive than VKAs. Another disadvantage of NOACs is that only a limited amount of reversal

agents are available for patients with major bleeding. For VKAs, more reversal agents are available. [41]

Wang et al. reported results of 4 NOACs that have been comprehensively tested in clinical trials on patients who have experienced an episode of VTE. Dabigatran, rivaroxaban, apixaban and edoxaban are approved in Europe and North America. Edoxaban was used in the largest clinical trial for VTE treatment ever. Table 10 shows the difference in selected outcomes between these NOACs and VKAs. Wang et al. found that rivaroxaban or apixaban as single-drug therapy or parenteral heparin followed by dabigatran or edoxaban is as effective as LMWH followed by warfarin for recurrent VTE prophylaxis. [2]

Hillis et al. found no specific studies on the effect of NOACs in patients with thrombophilia. But for patients with heterozygous FV Leiden or heterozygous prothrombin G20210A mutation the use of NOACs should be acceptable. [4] Skelley et al. also suggest that in theory, the NOACs could be used for patients with inherited thrombophilia. But one has to consider that the efficacy of the NOACs in patients with inherited thrombophilia might be different to the efficacy in patients without thrombophilia. Skelley et al. found that dabigatran and rivaroxaban can be used in VTE treatment for patients with inherited thrombophilia. [41]

Hillis et al. found no studies that showed superiority of one of the NOACs. [4]

Table 9: Odds ratio (95% confident interval) of NOACs compared to VKAs on selected outcomes. [2]

	Dabigatran vs. VKAs	Rivaroxaban vs. VKAs	Apixaban vs. VKAs	Edoxaban vs VKAs
Recurrent VTE	1.09 (0.76-1.57)	0.89 (0.66-1.19)	0.84 (0.60-1.18)	0.82 (0.60-1.14)
Major bleeding	0.73 (0.48-1.11)	0.54 (0.37-0.79)	0.31 (0.17-0.55)	0.84 (0.59-1.21)
death	1.00 (0.67-1.51)	0.89 (0.67-1.18)	0.79 (0.53-1.19)	1.05 (0.82-1.35)

NOACs: non-vitamin K antagnonist oral anticoagulants, VKAs: vitamin K antagonists

Dabigatran

Prandoni et al. reported the RE-SONATE study. This study showed a relative reduction of 92% of the relative VTE recurrence risk in patients on dabigatran compared to patients on placebo. The use of dabigatran only posed a small risk for major bleeding (0.3% vs 0% in the placebo group). [42] Prandoni et al. and Skelley et al. reported results of the REMEDY study. This study included patients with a higher VTE risk that had been treated with VKAs after a first VTE for 6 months. The study focused on long-term prevention of recurrent VTE. It found that patients on dabigatran had a significant reduction of recurrent or fatal VTE compared to warfarin. It also showed a lower major bleeding rate for dabigatran (0.9%), compared to warfarin (0.9% versus 1.8% respectively, giving a relative risk reduction of 48%). Dabigatran did show more acute coronary events during treatment (0.9%) than warfarin (0.2%). [41, 42] Wang et al. reported

the RECOVER trials (see Table 9). In these trials dabigatran was compared to warfarin, both after initial parenteral heparin (LMWH or UFH) for a period of 6 months. The trials showed dabigatran to be non-inferior to warfarin for VTE recurrence. Dabigatran did show significantly less major bleeding than warfarin. [2]
In patients with thrombophilia, Skelley et al. found no inferiority of dabigatran compared to warfarin, with regards to recurrent VTE or VTE-related deaths. [41]

Rivaroxaban

Wang et al. reported the EINSTEIN trial. This study showed no inferiority of rivaroxaban compared to LMWH followed by VKA, in regards to recurrence of VTE. Rivaroxaban did not cause excessive major bleeding. There was significantly less major bleeding found in patients on rivaroxaban, compared to LMWH-treatment followed by VKA (see Table 9). [2] Prandoni et al. reported the EINSTEIN extended trial. In this trial patients with previous unprovoked VTE and 6-12 months of anticoagulant therapy were tested. Recurrent symptomatic VTE occurred in 1.3% of the patients on rivaroxaban and in 7.1% of the patients taking placebo (relative risk reduction = 82%). Major bleeding was recorded in 0.7% of the patients given rivaroxaban, compared to 0% in the placebo group. [42]
Skelley et al. found that rivaroxaban looks promising in the treatment of patients with FV Leiden or protein C deficiency. [41]

Apixaban

Wang et al. reported the AMPLIFY study (see Table 9). Patients with acute VTE were either given apixaban or LMWH followed by warfarin for 6 months. In this study apixaban showed no inferiority to LMWH followed by warfarin in regards to VTE recurrence. Patients given apixaban showed significantly less major bleeding than patients on VKAs. [2] Prandoni et al. reported the AMPLIFY extension study. Patients who had experienced unprovoked VTE and were given 6-12 months of VTE treatment were tested. Apixaban showed a significant reduction of both primary and secondary outcome of recurrent VTE and fatality, compared to placebo. The study found a similar major bleeding rate in the apixaban group as in the placebo group. [42]

Edoxaban

Wang et al. found that edoxaban showed no inferiority to warfarin (both given after initial parenteral heparin) in regards to VTE recurrence. Patients given edoxaban did have significantly less major bleeding than patients given warfarin (see Table 9). [2]

3.4.4 Guidelines

According to Hillis et al. stable patients at low risk for complications should be given a NOAC or LMWH transitioning to VKA as acute treatment after a VTE episode. Unstable patients, patients who have received thrombolysis, or patients that have a high bleeding risk, should be given intravenous UFH. Treatment of patients with inherited thrombophilias is up to the clinician's judgement (based on experience), with LMWH transitioning to a VKA as the standard treatment. Pregnant patients or patients with active cancer should receive LMWH in monotherapy. [4]

Skelley et al. recommended choosing an anticoagulant therapy based on patient specific factors and patient preference. NOACs were preferred over traditional therapy like VKA therapy. For patients with inherited thrombophilia there are not yet specific evidence-based guidelines. Usually there is no modification of treatment with thrombophilia patients, however thromboprophylaxis given for a longer period could potentially be beneficial. In order to reverse the warfarin-induced skin necrosis, patients with protein C and protein S deficiency can be treated with rivaroxaban or dabigatran. Rivaroxaban should be given in a higher dose than for VTE treatment. [41]

Prandoni et al. suggested that patients, after a first episode of unprovoked VTE, should take VKA therapy for at least 3 months. An INR of 2.0-3.0 should be obtained. Continuing this anticoagulant therapy longer than 3 months could be considered in patients at low bleeding risk. The annual incidence of major bleeding with patients on long-term anticoagulation is 1.5-2.0%, and major bleeding poses a higher fatality risk than recurrent VTE. [42]

Wang et al. suggested to start parenteral anticoagulation before the diagnosis of VTE is confirmed, for patients with high or intermediate probability of acute VTE. They suggested a 3-phase anticoagulation treatment. An initial intensified anticoagulation phase should be followed by at least 3 months of long-term oral anticoagulant therapy. After these 2 phases, patients may or may not need extended anticoagulation, depending on VTE recurrence risk, bleeding risk and preference of the patients. [2]

According to Coppola et al. acute VTE treatment should not be altered if the patients are carriers of inherited thrombophilia. However, inherited thrombophilia could have an effect on the efficacy of oral anticoagulation. They found no specific evidence to treat antithrombin deficiency patients with antithrombin concentrates for acute VTE, but it might be useful in patients with extensive or severe VTE. Also, patients with very low protein C levels might benefit from protein C concentrates or fresh-frozen plasma. [3]

Hotoleanu et al. recommended that patients with protein S deficiency could be given lifelong warfarin therapy, in case of life- or limb-threatening VTE, if VTE occurred in multiple unusual locations and in cases of recurrent VTE. The NOACs dabigatran and rivaroxaban could also be used with protein S deficiency carriers. Asymptomatic protein S deficiency carriers should

not take thromboprophylaxis, unless these carriers have a major acquired risk factor. For patients with antithrombin deficiency long-term thromboprophylaxis is not recommended, but short-term prophylaxis is recommended in situations that increase the VTE risk (pregnancy, postpartum, surgery). If VKAs or NOACs give insufficient response, antithrombin concentrates could be considered. Antithrombin levels should be increased to at least 120%, and maintained at a minimum of 80% after the initial phase. [8]

Heit et al. recommended that secondary prophylaxis is effective in prevention of VTE recurrence, but anticoagulant therapy for more than 3 months does not show a decrease in VTE recurrence. [6]

Yilmaz et al. recommended that asymptomatic relatives of patients with inherited thrombophilia should be given anticoagulation in situations with elevated risk for VTE. [44]

3.4.5 Special conditions

3.4.5.1 Pregnancy

Table 11 shows different guidelines for thromboprophylaxis indications during pregnancy and the postpartum period in women with an inherited thrombophilia. [12]

Table 11: Guidelines for thromboprophylaxis during pregnancy for asymptomatic women with inherited thrombophilia. [12]

	Antenatal prophylaxis with LMWH	**Postpartum prophylaxis with LMWH for 6 weeks**
International Consensus Statement (2015)	- AT, PC or PS deficiency - Heterozygous FV Leiden or prothrombin G20210A [a] - Multiple abnormalities or homozygotes	- AT, PC or PS deficiency - Heterozygous FV Leiden or prothrombin G20210A - Multiple abnormalities or homozygotes
Pregnancy and Thrombosis Working Group (2007)	- AT deficiency - PC or PS deficiency [a] - Heterozygous FV Leiden or prothrombin G20210A [a] - Multiple abnormalities or homozygotes	- No formal recommendation
Italian Society for Haemostatics and Thrombosis (2009)	- AT deficiency - PC or PS deficiency - Heterozygous FV Leiden or prothrombin G20210A [a] - Multiple abnormalities or homozygotes	- AT, PC or PS deficiency - Heterozygous FV Leiden or prothrombin G20210A - Multiple abnormalities or homozygotes - Women
Royal College of Obstetricians and Gynaecologists (2009)	- AT deficiency - PC or PS deficiency [a] - Heterozygous FV Leiden or prothrombin G20210A [a] - Multiple abnormalities or homozygotes	- AT deficiency - PC or PS deficiency [a] - Heterozygous FV Leiden or prothrombin G20210A [a] - Multiple abnormalities or homozygotes

		- Women with PC or PS deficiency or heterozygous FV Leiden or prothrombin G20210A without family history of VTE or other risk factors, duration of LMWH therapy can be limited to 7 days.
Scottish Intercollegiate Guidelines Network (2010)	- AT deficiency - PC or PS deficiency [b] - Heterozygous FV Leiden or prothrombin G20210A [b] - Multiple abnormalities - Homozygous FV Leiden	- AT, PC or PS deficiency - Heterozygous FV Leiden or prothrombin G20210A - Multiple abnormalities or homozygotes
American College of Obstetricians and Gynecologists (2011)	- AT deficiency - PC or PS deficiency - Heterozygous FV Leiden or prothrombin G20210A - Multiple abnormalities or homozygotes - For women with PC or PS deficiency or heterozygous FV Leiden or prothrombin G20210A, surveillance without anticoagulation could be an option.	- AT deficiency - PC or PS deficiency [a] - Heterozygous FV Leiden or prothrombin G20210A [a] - Multiple abnormalities or homozygotes
American College of Chest Physicians Guidelines (2012)	- Homozygous FV Leiden or prothrombin G20210A [b]	- AT, PC or PS deficiency [b] - Heterozygous FV Leiden or prothrombin G20210A [b] - Multiple abnormalities [b] - Homozygous FV Leiden or prothrombin G20210A - VKAs (INR 2.0-3.0) can be an alternative to LMWH, except with PC or PS deficiency
Australian Society of Thrombosis and Haemostasis (2012)	- AT deficiency [a] - PC or PS deficiency [a] - Heterozygous FV Leiden or prothrombin G20210A [c] - Multiple abnormalities [a] - Homozygous FV Leiden [a]	- AT, PC or PS deficiency - Heterozygous FV Leiden or prothrombin G20210A - Multiple abnormalities - Homozygous FV Leiden

LMWH: low-molecular-weight heparin, AT: antithrombin, PC: protein C, PS: protein S
[a] Thromboprophylaxis is only recommended if family history of VTE or other risk factors are present.
[b] Thromboprophylaxis is only recommended if family history of VTE is present.
[c] Thromboprophylaxis is only recommended if other risk factors are present.

Thromboprophylaxis in pregnant women has not yet been standardized. During pregnancy, LMWH can be given. LMWH is found to be safe for the fetus, since it does not cross the placenta. LMWH is preferred over UFH, because of a better risk-benefit ratio. [27, 32, 49, 51]

De Jong et al. also found that aspirin is safe to use during the second and third trimester. [32] Bates et al. recommend not to use NOACs during pregnancy. [49] VKAs are not recommended during pregnancy, because it is associated with fetal abnormalities. In the postpartum period, VKAs are an acceptable anticoagulant therapy. Warfarin and heparin can be used in women who are breastfeeding, they do not have anticoagulant effects on the infant. The therapeutic range for LMWH prophylaxis is uncertain, which makes that clinicians choose the dose based on their own clinical judgement. [27, 37]

The European Society of Human Reproduction and Embryology (ESHRE) found that pregnant women with high-risk thrombophilia, acquired thrombophilia or positive VTE family history, should be given primary thromboprophylaxis (anticoagulant therapy before a first VTE episode). However, the indications of primary thromboprophylaxis during pregnancy are a matter of debate and there is no consistent approach. It is important to take other thrombotic risk factors into account as well, when considering thromboprophylaxis. [37] According to the ACOG, all patients with inherited thrombophilia should undergo an individual risk assessment. [27] Rheaume et al. recommended that women with antithrombin deficiency should be given a more aggressive care concerning ante- and postpartum prophylaxis, because antithrombin deficiency poses a high risk of VTE during pregnancy. [25] The American College of Chest Physicians recommended that even though antithrombin deficiency is a high-risk thrombophilia, anticoagulation should only be given to pregnant women with history of VTE. [28] Bates et al. suggested not to give thromboprophylaxis to women with inherited thrombophilia and history of pregnancy complications, and also not to women with recurrent pregnancy loss that do not carry an inherited thrombophilia. [49] Martinez-Zamora et al. recommended that women with an inherited thrombophilia and a history of recurrent pregnancy loss should be given thromboprophylaxis in their next pregnancy. However, long-term prophylaxis in these patients is not recommended if they do not have a personal history of VTE. [52]

Rheaume et al. reported that thromboprophylaxis should be restricted to the postpartum period, and only be given to those with a positive family history. Pregnant women without family history should be treated with clinical vigilance. [14] According to ESHRE, in the postpartum period, all women with an inherited thrombophilia and all women with a personal history of VTE should receive LMWH thromboprophylaxis. [37] Bates et al. also recommended that all pregnant women with history of VTE should be given LMWH or VKAs for at least 6 weeks postpartum. [49] Table 12 shows the guidelines for thromboprophylaxis during pregnancy according to the ACOG. [27]

Table 12: Thromboprophylaxis during pregnancy for carriers of inherited thrombophilia. [27]

Clinical Scenario	Antepartum Management	Postpartum Management
Low-risk thrombophilia[a] without previous VTE	Surveillance without anticoagulation	Surveillance without anticoagulation or anticoagulation if the patient has other thrombotic risk factors
Low-risk thrombophilia with a first-degree relative with VTE history	Surveillance without anticoagulation	Intermediate-dose LMWH or UFH VKAs
Low-risk thrombophilia with a single previous VTE episode, not receiving long-term anticoagulation	Prophylactic-dose LMWH or UFH or surveillance without anticoagulation	Intermediate-dose LMWH or UFH VKAs
High-risk thrombophilia[b] without previous VTE	Surveillance without anticoagulation or LMWH or UFH	VKAs
High-risk thrombophilia with a single previous VTE episode, not receiving long-term anticoagulation	Prophylactic, intermediate-dose or adjusted-dose LMWH or UFH	VKAs or intermediate or adjusted-dose LMWH or UFH for 6 weeks (therapy levels should be at least as high as in the antepartum therapy)
No thrombophilia with previous single VTE episode associated with a transient risk factor that is no longer present (pregnancy or estrogen-related risk factors excluded)	Surveillance without anticoagulation	VKAs
No thrombophilia with previous single VTE episode associated with a transient risk factor that was pregnancy- or estrogen-related	Prophylactic-dose LMWH or UFH	VKAs
No thrombophilia with previous single VTE episode without associated risk factor (unprovoked), not receiving long-term anticoagulation	Prophylactic-dose LMWH or UFH	VKAs
Thrombophilia or not thrombophilia with two or more VTE episodes, not receiving long-term anticoagulation	Prophylactic or therapeutic-dose LMWH or UFH	VKAs or therapeutic-dose LMWH or UFH for 6 weeks
Thrombophilia or not thrombophilia with two or more VTE episodes, receiving long-term anticoagulation	Therapeutic-dose LMWH or UFH	Resuming long-term anticoagulation

VTE: venous thromboembolism, LMWH: low-molecular-weight heparin, UFH: unfractionated heparin, VKAs: vitamin K antagonists

For secondary thromboprophylaxis (prophylaxis after an episode of VTE, with the objective of preventing recurrent VTE), triggering factors of the previous VTE are more important than the presence of an inherited thrombophilia. ESHRE found that if a previous VTE was idiopathic, pregnancy-related or related to the use of oral contraception, the VTE recurrence risk is higher than if the previous VTE occurred after trauma or surgery. There is little evidence supporting that women whose previous VTE was related to trauma, surgery or immobilization, could be refrained from secondary LMWH prophylaxis during the pregnancy. [37]

Skeith et al. found that for women with inherited thrombophilia, the use of LMWH showed no significant increase of livebirth rates compared to no LMWH (OR 0.81, 95% CI 0.55-1.19), therefore LMWH prophylaxis should not be administrated with the object to prevent recurrent pregnancy loss in carriers of inherited thrombophilia. [34] Tan et al. also found that LMWH does not substantially improve livebirth rates in women with inherited thrombophilia. [9] Hotoleanu et al. reported that thromboprophylaxis shows little benefit regarding adverse pregnancy outcomes in women with inherited thrombophilia. [8] The Jong et al. found there is not enough evidence to recommend thromboprophylaxis for pregnant patients with inherited thrombophilia and a history of pregnancy complications. [33]

3.4.5.2 Oral contraception

Most studies agree that patients with high-risk thrombophilias should not use COC. Some studies also suggested that non-oral contraception like transdermal patches or vaginal rings, should also be avoided because of the increased risk of VTE. Progestogen-only pills or intra-uterine devices (IUDs) could be an alternative for these patients. COC use for patients with mild thrombophilia is controversial. Some studies found that, if other alternatives were found unacceptable, and no other thrombotic risk factors were present, patients with mild thrombophilia could use COC with the lowest VTE-risk. [38]

3.4.5.3 Surgery and immobilization

Major orthopedic surgeries (like hip and knee replacements) pose a relatively high risk for VTE, so most patients are treated with LMWH prophylaxis, prior to these surgeries. Non-orthopedic or trauma surgical patients have a more moderate VTE risk, but usually they are also given LMWH or UFH. The presence of inherited thrombophilia does not really effect the choice of prophylaxis, and a higher dose or longer duration of anticoagulation is also not recommended. Antithrombin deficiency patients are an exception to this, because they may show a resistance to heparin. So empirical recommendations were made to give a higher dose of heparin and prolong heparin treatment in antithrombin deficiency patients. [2, 3]

4. Discussion

Inherited thrombophilias clearly increase the risk of a first episode of VTE. In combination with other thrombotic risk factors, they amplify that VTE risk even more. All inherited thrombophilias increase the VTE risk, but certain types pose a higher risk for VTE than others. This can also be said about the association of inherited thrombophilia with other VTE risk factors.

The association between inherited thrombophilia and venous thromboembolism has been well established. Testing for inherited thrombophilia however is still a matter of great debate. Most studies recommend that routine screening is not indicated, because it is found not to be cost-effective and the presence of inherited thrombophilia does not significantly increase the risk of VTE recurrence. But for the indications in which testing for inherited thrombophilia is useful, a consensus has not yet been reached. There are a few guidelines, but these do not completely align. Further research should be conducted to get enough evidence to formulate definitive guidelines for thrombophilia testing.

Family history in itself is a strong risk factor for VTE. However, it is not a good predictor for inherited thrombophilia in asymptomatic relatives. It is suggested that thrombophilia screening is acceptable in families with a history of high-risk inherited thrombophilia, considering that the combination of both risk factors (positive family history and high-risk thrombophilia) increases the risk of VTE substantially.

Many studies have shown that inherited thrombophilia does not impact treatment. However, those studies also claim that testing for inherited thrombophilia should always be done with the intent to give tailored treatment. Most studies recommend that treatment of acute VTE is not changed in the presence of inherited thrombophilia, since there is not enough evidence to support a certain change. More extensive study should be performed in patients with inherited thrombophilia, in order to see if standard VTE treatment (LMWH + VKA) is the best option for these patients or if NOACs are the better option.

Because inherited thrombophilia is considered a risk factor, patients are usually not treated unless in a specific situation. However, there is still a lack of definitive guidelines on what that treatment should be, and for what specific situations it should be given. This is also a reason for many clinicians to screen and treat patients the way they seem fit, based on their experience rather than the recommendations.

A major problem with inherited thrombophilia is that there are not a lot of large, high-quality randomized clinical trials. Some types of inherited thrombophilia, like antithrombin deficiency and protein C and S deficiency, are very rare. Therefore, most available studies are small case-control and cohort studies. FV Leiden is more prevalent, and consequentially, more evidence

is available. Another problem is the heterogeneity of the tested populations, both the control group and inherited thrombophilia group. For example, antithrombin deficiency can be caused by many mutations and given antithrombin deficiency's rare incidence, those patients are all put into the same category while they may not have the same symptoms. Also, many of these studies have a different study design, which makes it difficult to compare results, since it is not always clear if contradictory results are because of the different approach in study design or because of a different study population.

Because of the small number of patients in most studies, the coincidence intervals are wide. This lowers the quality of the studies. In order to get higher-quality controlled trials, international cooperation is necessary. This way the magnitude of the study can be increased, so an attempt can be made to compose studies with a less heterogeneous study population, ultimately resulting in high-quality, evidence-based guidelines.

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