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Prescription of venous thromboembolism assessment. Evaluation of medical practices

A Dissertation Submitted to the Faculty of medicine Department of pharmacy, in Partial Fulfillment of the Requirements for diploma Degree of doctor in pharmacy.

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With every beat of my heart, I dedicate this work to

My mother, who has always encouraged me to pursue higher education and supported me throughout this journey.

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LIST OF ABBREVIATIONS

ATCD: antecedent

BRF: Biological risk factor

DVT: Deep vein thrombosis

FACTOR X a: Factor x activated

PC: protein C

PS: protein S

PTS: Post thrombotic syndrome

USA: United States American's

VTE: venous thromboembolism

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ABSTRACT

Venous Thromboembolic Disease (VTE) is a serious and frequent pathology. Etiological investigation is essential for its management. The guideline published in 2019 give precise recommendations for cancer research and an update of the guidelines for biological thrombophilia has been carried out. The objective was to analyze the practices of specialist practitioners of the Algeirs region regarding the prescription of the etiological assessment according to the recommendations.

Material and method: An observational, descriptive and cross-sectional study was carried

Out using an anonymous questionnaire sent to 184 specialist Practitioners in the Algeirs region.

Results: 100 doctors were included in the study. The 2019 recommendations were known by 47 (47%) doctors. All practionners carried out the search for cancer, but 90% carried out the search for cancer in accordance with the 2019 recommendations. Thrombophilia, 100% were looking for it, 55% prescribed thrombophilia work-up as recommended.

Discussion and Conclusion: This study shows that despite the 2019 recommendations, the majority of Practitioners report difficulties in carrying out the etiological assessment of VTE according to the guideline.

Key words: venous thromboembolism, recommendation, etiological assessment, Algeirs region.

الملخص

تعد الجلطة الدموية الوريدية مرضا خطيرا وشائعا كما ان البحث عن أسبابه يعد ضروريا من اجل التحكم بالمرض

التوصيات التي تم نشرها سنة 2019 تحدد بدقة كيفية البحث عن السرطان وكذلك مجموعة التحاليل التي يجب عملها وترتيبها كما تم نشر توصيات للبحث في أسباب تخثر الدم أيضا

الأهداف: تحليل ممارسات الأطباء المختصين في منطقة الجزائر العاصمة بليدة الدويرة الجزائر بخصوص وصف التقييم السببي للمرض وفقا للتوصيات الدولية التي تم نشرها

الطريقة: تم اجراء دراسة وصفية باستخدام استبيان تم ارسالها الى 184 طبيبا مختصا في المنطقة.

النتائج: تم تظمين 100طبيبا في الدراسة وكانت التوصيات معروفة لدى 47% من الأطباء، قام جميع الأطباء بالبحث عن السرطان ولكن 90% منهم فقط فعل ذلك في الحالات الموصي بها.

بالنسبة لتخثر الدم 100% من الأطباء قام بالبحث عن أسبابه ولكن 55% يصفون التحاليل كما هو موصى بها

النقاش والاستنتاج: توضح هذه الدراسة انه بالرغم من التوصيات التي نشرت عام 2019 يواجه اغلبية الأطباء صعوبة في اجراء التقييم السببي للمرض وفقا للمعايير الموصي بها.

الكلمات المفتاحية: الجلطة الوريدية، التوصيات، التقييم السببي منطقة الجزائر العاصمة.

RÉSUMÉ

La maladie thromboembolique veineuse (VTE) est une pathologie grave et fréquente. L'investigation étiologique est essentielle pour sa gestion. Les recommandations publiées en 2019 donnent des directives précises pour la recherche sur le cancer et une mise à jour des directives pour la thrombophilie biologique a été effectuée. L'objectif était d'analyser les pratiques des médecins spécialistes de la région algéroise concernant la prescription de l'évaluation étiologique conformément aux recommandations.

Matériel et méthode : Une étude observationnelle, descriptive et transversale a été menée à l'aide d'un questionnaire anonyme envoyé à 184 médecins spécialistes à la région algéroise.

Résultats : 100 médecins ont été inclus dans l'étude. Les recommandations de 2019 étaient connues par 47 (47%) médecins. Tous les médecins ont effectué la recherche de cancer selon les indications, mais seulement 10% ont effectué la recherche de cancer conformément aux recommandations de 2019. Pour la thrombophilie, 100 (100%) ont effectué des recherches, mais seulement 10% ont prescrit le bilan de thrombophilie conformément aux recommandations.

Discussion et conclusion : Cette étude montre que malgré les recommandations de 2019, la majorité des praticiens signalent des difficultés à réaliser le bilan étiologique de la VTE conformément aux directives.

Mots-clés : thromboembolie veineuse, recommandation, bilan étiologique, la région algéroise.

INTRODUCTION

Venous thromboembolism (VTE) is a severe and potentially fatal disease affecting millions of people worldwide. Effective diagnosis and treatment of VTE require etiological assessments to identify the underlying cause of the condition. However, prescribing these assessments can be a complex issue, as multiple factors need to be taken into account, such as patient history, risk factors, and latest medical recommendations. Despite the availability of new guidelines for prescribing etiological assessments for VTE, there is still a significant gap between what is recommended and what is actually being prescribed by doctors, resulting in missed diagnoses, inadequate treatment, and unnecessary costs.

Therefore, we conducted a descriptive observational study in the Algerian region to assess the knowledge of doctors regarding the latest updates in recommendations according to their age, duration of work, and mode of work. Our focus was on specialists in internal medicine, cardiology, hematology, and neurology due to the high frequency of venous thromboembolic disease in these services. Our interest in this topic is to highlight the lack of knowledge among doctors about the recommendations for prescribing etiological assessments and to explore the reasons for this gap and find ways to improve the prescription of etiological assessments for VTE according to the latest recommendations.

PART 1

CHAPTER 1: VENOUS THROMBOEMBOLISM

I – GENERALITY

Venous thromboembolism (VTE) is the formation of a Blood Clot in a deep vein that can leadto complications, including deep vein thrombosis (DVT), a pulmonary embolism (PE), or postthrombotic syndrome (PTS). Venous thromboembolism is a serious condition, with an incidence of 10% to 30% of people dying within 1 month of diagnosis, and half of those diagnosed with a DVT have long-term complications. Even with a standard course of anticoagulant therapy, one third of individuals will experience another VTE within 10 years. For those who survive a VTE, quality of life can be decreased due to the need for long-term anticoagulation to prevent another VTE .[1]

I - 1 Epidemiology

Afflicting worldwide nearly 10 million people of all ethnicities per year, venous thromboembolism is a substantial contributor to the global burden of disease [2]

The incidence of VTE in Europe and the USA is estimated to be ~1–2 per 1,000 person-years,but varies widely by age, sex, race and medical conditions.

In Asia, the rates of VTE are thought to be lower than in Europe and the USA. For instance, theincidence of VTE in South Korea was estimated to be 0.2 per 1,000 person-years.

Fewer data exist for South America and Oceania. A study from Buenos Aires, Argentina, founda VTE incidence of 0.7 per 1,000 person-years24, and a study from Perth, Australia, found a VTE incidence of 0.8 per1, 000 person-years. Very little is known about VTE incidence in Africa.[3]

The most robust data on VTE incidence come from the USA and Europe. An American Heart Association report from 2021 estimated that approximately 1,220,000 total cases of VTE occurin the USA annually. This estimate was based on previously unpublished data from the National Inpatient Sample, and showed ~370,000 cases of pulmonary embolism and ~857,000 cases of DVT in 2016 and assumed 30% of DVTs were treated in the outpatient setting. A modelling study estimated that the annual VTE incidence in six countries in Europe (total population 310.4million) was 296,000 cases of pulmonary embolism and ~466,000 cases of DVT.[4]

The annual incidence of acute venous thromboembolism is 1–2 cases per 1000 population, 1– 3 which rises exponentially with age for both men and women, 2 and is 4-times higher in high-income than low-income countries. The lifetime risk of venous thromboembolism does

not differ by sex, but women have a higher risk during the ages of 20–40 years reflecting exposure to reproductive risk factors, whereas men have a higher risk in other age groups. Among patients with active cancer, the annual incidence of first venous thromboembolism differs according to cancer type (3% for bladder and breast cancers, 4–7% for colon and prostate cancers, 10–12% for lung, stomach, ovary, and brain cancers, and 15% for pancreatic cancer).[5]

Statistical data in Algeria are not listed in the scientific literature.

II – COAGUALATION

II – 1 Introduction

The coagulation pathway is a cascade of events that leads to hemostasis. The intricate pathway allows for rapid healing and prevention of spontaneous bleeding. Two paths, intrinsic and extrinsic, originate separately but converge at a specific point, leading to fibrin activation. The purpose is to ultimately stabilize the platelet plug with a fibrin mesh.[6]

II - 2 Function

The function of the coagulation pathway is to keep hemostasis, which is the blockage of a bleeding or hemorrhage. Primary hemostasis is an aggregation of platelets forming a plug at thedamaged site of exposed endothelial cells. Secondary hemostasis includes the two main coagulation pathways, intrinsic and extrinsic, that meet up at a point to form the common pathway. The common pathway ultimately activates fibrinogen into fibrin. These fibrin subunits have an affinity for each other and combine into fibrin strands that bind the platelets together, stabilizing the platelet plug.[7]

II – 3 Mechanism

The mechanism by which coagulation allows for hemostasis is an intricate process that is done through a series of clotting factors. The intrinsic pathway consists of factors I, II, IX, X, XI, and XII. Respectively, each one is named, fibrinogen, prothrombin, Christmas factor, Stuart-Prowers factor, plasma thromboplastin, and *Hageman factor*. The extrinsic pathway consists of factors I, II, VII, and X. Factor VII is called *stable factor*. The common pathway consists of factors I, II, V, VIII, and X. The factors circulate through the bloodstream as zymogens and are activated into serine proteases. These serine proteases act as a catalyst to cleave the next zymogen into more serine proteases and ultimately activate fibrinogen. The following are serine proteases: factors II, VII, IX, X, XI and XII. These are not serine proteases: factors V, VIII, XIII. The intrinsic pathway is activated through exposed endothelial collagen, and the extrinsic pathway is activated through tissue factor released by endothelial cells afterexternal damage.

II – 3.1 Intrinsic Pathway

This pathway is the longer pathway of secondary hemostasis. It begins with the activation of Factor XII (a zymogen, inactivated serine protease) which becomes Factor XIIA (activated serine protease) after exposure to endothelial collagen. Endothelial collagen is only exposed when endothelial damage occurs. Factor XIIA acts as a catalyst to activate factor XI to Factor XIA. Factor XIA then goes on to activate factor IX to factor IXA. Factor IXA goes on to serve as a catalyst for turning factor X into factor Xa. This is known as a cascade. When each factor is activated, it goes on to activate many more factors in the next steps. As you move further down the cascade, the concentration of that factor increases in the blood. For example, the concentration of factor IX is more than that of factor XI. When factor II is activated by either intrinsic or extrinsic pathway, it can reinforce the intrinsic pathway by giving positive feedback to factors V, VII, VIII, XI, and XIII. This makes factor XII less critical; patients can actually clot well without factor XII. The intrinsic pathway is clinically measured as the partial thromboplastin time (PTT).

II – 3.2 Extrinsic Pathway

The extrinsic pathway is the shorter pathway of secondary hemostasis. Once the damage to the vessel is done, the endothelial cells release tissue factor which goes on to activate factor VII to factor VIIa. Factor VIIa goes on to activate factor X into factor Xa. This is the point where both extrinsic and intrinsic pathways become one. The extrinsic pathway is clinically measured as the prothrombin time.

II – 3.3 Common Pathway

This pathway begins at factor X which is activated to factor Xa. The process of activating factor Xa is a complicated reaction. Tenase is the complex that cleaves factor X into factor Xa. Tenase has two forms: extrinsic, consisting of factor VII, factor III (tissue factor) and Ca2+, or intrinsic, made up of cofactor factor VIII, factor IXA, a phospholipid, and Ca2+. Once activated to factor Xa, it goes on to activate factor II (prothrombin) into factor IIa (thrombin). Also, factor Xa requires factor V as a cofactor to cleave prothrombin into thrombin. Factor IIa (thrombin) goes on to activate fibrinogen into fibrin. Thrombin also goes on to activate other factors in the intrinsic pathway (factor XI) as well as cofactors V and VIII and factor XIII. Fibrin subunits come together to form fibrin strands, and factor XIII acts on fibrin strands to form a fibrin mesh. This mesh helps to stabilize the platelet plug.

II – 3.4 Negative Feedback

To prevent over-coagulation, which causes widespread thrombosis, there are certain processes to keep the coagulation cascade in check. As thrombin acts as a procoagulant, it also acts as negative feedback by activating plasminogen to plasmin and stimulating the production of antithrombin (AT). Plasmin acts directly on the fibrin mesh and breaks it down. AT decreases the production of thrombin from prothrombin and decreases the amount of activated factor X. Protein C and S also act to prevent coagulation, mainly by inactivating factors V and VIII.

II – 3.5 Organs Involved

One of the organs intimately involved in the coagulation process is the liver. The liver is responsible for the formation of factors I, II, V, VII, VIII, IX, X, XI, XIII, and protein C and S. Factor VII is created by the vascular endothelium. Pathology to the liver can cause lack of coagulation factors and lead to hemorrhage. A decrease in coagulation factors typically means severe liver damage. Factor VII has the shortest half-life, leading to elevated PT first in liver disease. INR can be greater than 6.5 (normal is close to 1.0). Coagulopathy in liver disease is treated with fresh frozen plasma.[8]

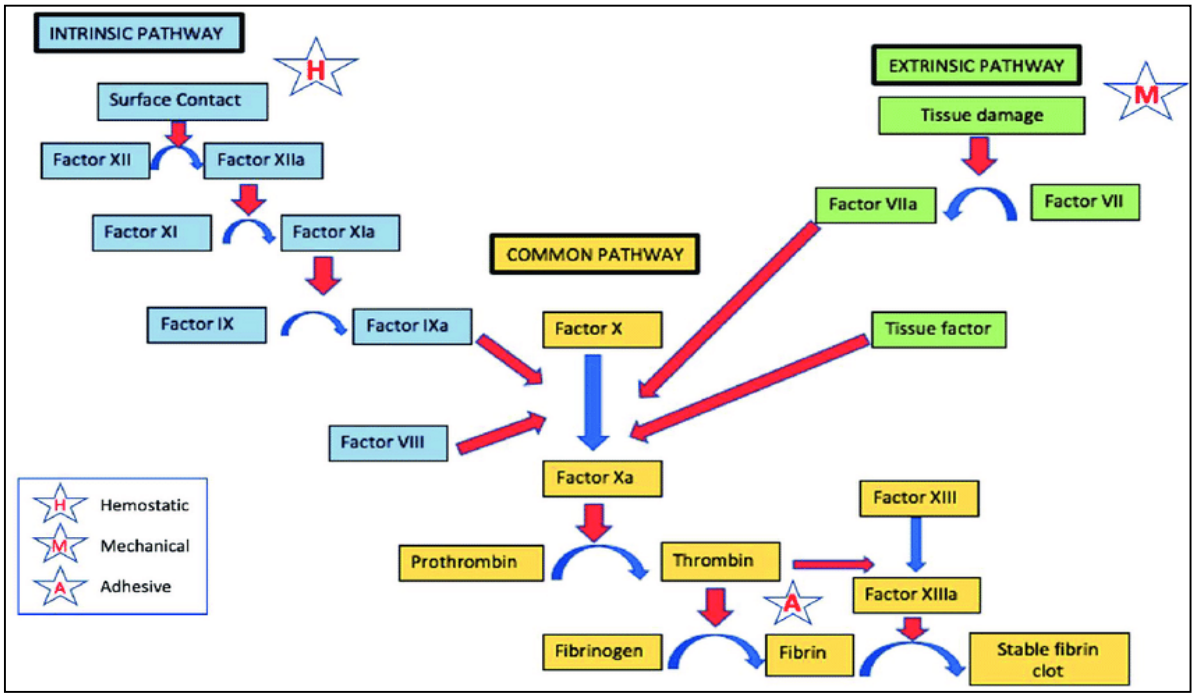

Figure 1: Overview of coagulation cascade. Diagram of the multistep intrinsic (left, blue and extrinsic pathway (right, green) and common pathway.

III - PATHOPHYSIOLOGY

Venous thromboembolism (VTE) is a condition where a thrombus (blood clot) is formed in a vein. The term VTE is usually restricted to thrombi located in deep veins, as opposed to superficial vein thrombosis. This definition of VTE is used throughout this thesis. Most venous thrombi are formed in the lower extremities. Venous thrombi differ from arterial thrombi; venous thrombi are primarily composed of fibrin and red blood cells, whereas the main content of arterial thrombi is platelets. Arterial thrombi form at or around ruptured atherosclerotic plaques, whereas venous thrombi can occur even if the endothelium is intact. The formation of a thrombus is facilitated by the presence of abnormalities of blood flow, vascular wall and blood clotting components. These three factors are known as Virchow's triad.[9]

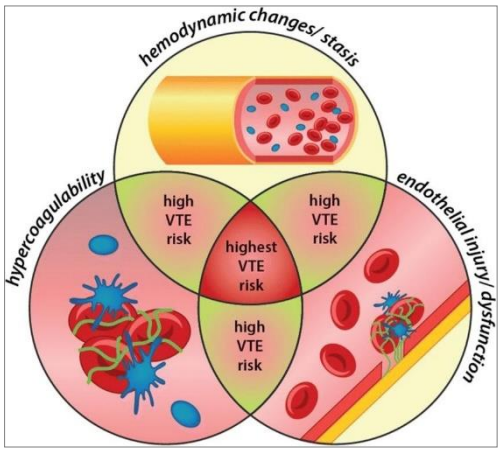

Figure 2: Virchow's triad describes the three broad categories of factors contributing to the risk of venous thrombosis.

The first component of Virchow's triad is abnormal blood flow. The majority of venous thrombi have their origin in regions with slow blood flow, for example the large venous sinuses of the calf and thigh, or in the valve cusp pockets upstream of venous valves. Thrombi can also originate in bifurcations of the venous system where blood flow irregularities are present. Blood pooling can cause activation of the coagulation system, which in turn leads to local hypercoagulability. Endothelial damage due to the distention of the vessel wall can potentially contribute to activation of the clotting system. Examples of conditions that can result in venous stasis are obesity, pregnancy, heart failure, and tumors causing external compression of veins. The veno-muscular pumps, i.e., the pumping action of extremity skeletal muscles that promotes venous return, have an important role in preventing venous stasis. In situations where skeletal muscles, the calf muscles in particular, are less active, venous stasis can form. Examples of Such situations are extremity fractures, orthopedic casts or restraints, paralysis

and hospitalization with bed rest.[10]

Vascular wall abnormalities, the second component of Virchow's triad, can occur in the form of endothelial damage in the setting of surgery, trauma or presence of indwelling venous catheters.[8] Increased levels of markers of endothelial dysfunction have been found in persons with previous VTE compared to matched controls, but it is uncertain whether endothelial dysfunction is a cause or a consequence of the VTE event.

The third component of Virchow's triad is hypercoagulability. The risk of VTE increases when the balance between the pro- and anticoagulant forces is shifted towards blood coagulation, [8] this imbalance can be inherited or acquired. Examples of inherited conditions causing hypercoagulability are activated protein C resistance, prothrombin mutation and antithrombin deficiency. Such conditions, called hereditary thrombophilia's, cause a lifelong hypercoagulability. Acquired hypercoagulability can for example be caused by medication (e.g., estrogen therapy), pregnancy, cancer and autoimmune disorders. The duration of an acquired hypercoagulability depends on its cause.[11]

III – 1 Deep vein thrombosis

DVTs of the lower extremities are predominantly located in the left lower extremity. Of patients with DVT, about one fourth of patients have a distal DVT (i.e., an isolated calf vein DVT or muscular vein DVT), half the patients have a proximal DVT involving femoropopliteal veins, but not veins above the inguinal ligament, and one fourth have a proximal DVT involving veins above the inguinal ligament. Common symptoms of lower extremity DVT are erythema, tenderness and swelling. [12]

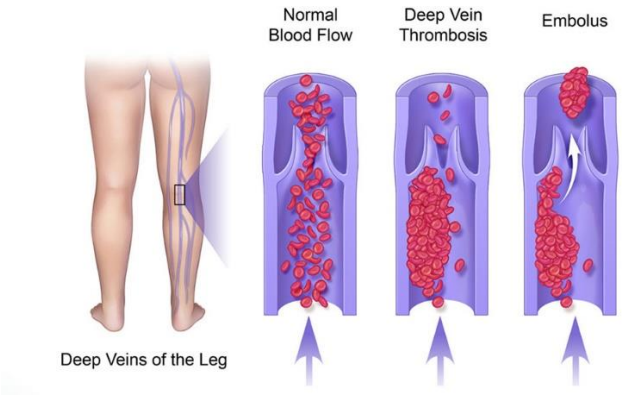

Figure 3: deep vein thrombosis developing.

The gold standard for diagnosis of DVT has been venography, but this method is not recommended in current guidelines. Instead, the first-line method for identifying lower

extremity DVTs is venous ultrasound, preceded by D-dimer testing in patients with low pre-test probability of DVT. The sensitivity and specificity of venous ultrasound for identifying proximal lower extremity DVTs is greater than 90%, whereas for distal lower extremity DVTs, the sensitivity is about 70% Due to thelower sensitivity of venous ultrasound in the diagnosis of distal lower extremity DVT, it is likely that the true prevalence of distal DVTs is underestimated. DVT of the upper extremities is a rare condition; only about 5% of DVTs affect the upper extremities. Symptoms of upper extremity DVT are similar to those caused by lower extremity DVT, and the condition can be diagnosed using venous ultrasound .[12]

III – 2 pulmonary embolism

PEs are thought to be fragments of DVTs that move through the blood stream to the pulmonary vasculature. A lower extremity DVT can be identified in about 60% of the patients with PE.[13] The origin of the PEs in the remaining 40% of patients is not known. Right-sided cardiac thrombi and local thrombus formation in the pulmonary arteries have been suggested as explanations.[14] Symptoms of PE include sudden onset dyspnea, chest pain, syncope and hemoptysis.[15] the gold standard diagnostic method for PE is pulmonary angiography, but this method is associated with a mortality of 0.5% [16] and is more costly compared to other diagnostic methods.[17]

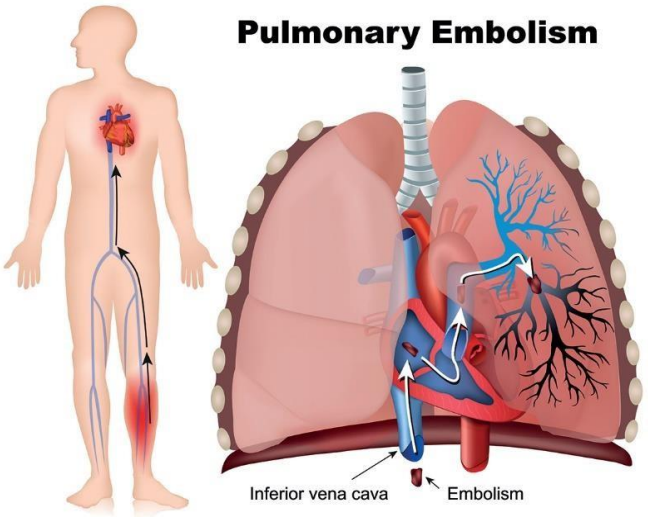

Figure 4: pulmonary embolism American venous forum.

For these reasons, it has fallen out of favor. Current guidelines regarding suspected PE in a patient without shock or hypotension advocate a strategy where the clinical probability 4 of PEis assessed using clinical judgment or a prediction rule. If the clinical probability of PE is low or intermediate, D-dimer testing is performed. If the D dimer test is positive, the patient is recommended to undergo computed tomography (CT) angiography. In patients with a high clinical probability of PE, CT angiography is performed without previous D-dimer testing.[18]In patients with shock or hypotension where PE is suspected, a CT angiography is

performed if immediately available. Otherwise, an echocardiography is performed. If right ventricular overload is present and the patient can be stabilized, a CT angiography can be made to confirmthe diagnosis of PE. If right ventricular overload is present and no other diagnostic test for PE is available, or if the patient is unstable, PE-specific treatment can be initiated. If no right Ventricular overload can be detected on echocardiography, other causes of hemodynamic instability should be considered .[18]

III – 3 Post thrombotic syndrome

Despite appropriate anticoagulant therapy, at least 1 of every 2-3 patients with deep-vein thrombosis (DVT) of the lower extremities will develop post-thrombotic sequel. These vary from minor signs (i.e., stasis pigmentation, venous ectasia, slight pain and swelling) to severe manifestations such as chronic pain, intractable edema and leg ulcers [19]. The established post thrombotic syndrome (PTS) remains a significant cause of chronic illness, with considerable socio-economic consequences for both the patient and the health care services [20]

The post-thrombotic syndrome is characterized by aching pain on standing, dependent edema, and the frequent development of brawny, tender induration of the subcutaneous 144 Deep Vein Thrombosis tissues of the medial lower limb, a condition that has been termed "lipodermatosclerosis". Pruritus and eczematous skin changes are frequently present, and a proportion of patients develops secondary superficial varicose veins as the syndrome evolves. Ulceration, often precipitated by minor trauma, arises in a considerable number of patients and is characteristically chronic and indolent with a high recurrence rate, once healing has been achieved. Uncommonly, patients with persistent obstruction may experience venous claudication, a bursting pain in the leg during exercise, which, in some respects, mimics arterial claudication [21].

III – 4 rare thrombosis localizations

Of these uncommon localizations of thrombosis, deep vein thrombosis of the arms is one of themost frequent entities, accounting for about 5% of all thrombosis .[22] Most cases of deep arm vein thrombosis develop secondary in patients with indwelling central venous catheters, pacemakers, malignant disease, or after surgery. Conversely, primary upper extremity deep venous thrombosis is observed in patients after strenuous arm exercise (“thrombosis par effort”), in thoracic outlet syndrome and inherited or acquired thrombophilia.[23] Acute and long-time complications of upper extremity thrombosis may be significant and include pulmonary embolism, post-thrombotic syndrome and recurrent thromboembolism. In this chapter, the

clinical presentation, diagnostic procedures, treatment and prevention of thrombosis of the upper extremity will be reviewed. It is not unusual to find thrombosis of proximal arm veins and deep veins of the neck region at the same time. Therefore, thrombosis of the internal jugular Vein, which are also most often observed in the presence of indwelling central venous catheters,will also be discussed. In this review, special emphasis will be given to the practical aspects ofthe disease, like risk factors, clinical presentation, diagnosis, and treatment of arm veinthrombosis. For a detailed, comprehensive overview of pathophysiological mechanisms, the reader will be referred to other, excellent reviews within this field. [24]

VTE events can also occur in other locations. Cerebral venous thrombosis is a rare type of stroke that can occur at any age. Headache is the most frequently reported symptom of cerebral venous thrombosis. Other symptoms and signs include seizures, focal neurological signs, impaired consciousness and papilledema.[25] Abdominal VTE is another rare form of VTE. Persons experiencing an abdominal VTE are, in general, younger than persons with lower extremity DVT or PE. Abdominal VTE events can for example occur in the hepatic, portal, splenic, mesenteric or renal veins, or in the inferior vena cava. Patients with abdominal VTE can present with pain, edema, and symptoms and signs related to organ dysfunction. [26]

IV - RISK FACTORS

An array of different factors contributes to the risk of VT. It is notable that women and men of all ages, races, and ethnicities are at risk for VTE. Age and obesity are important risk factors for VTE and, after the age of 40, the risk for VTE doubles with each decade of life. Prior episodes of VTE and atherothrombosis also contribute to the increased risk. A recent study demonstrated that MI is associated with an increased risk of transient VTE and PE independent of traditional atherosclerotic risk factors.[27] Fibrin degradation products, as measured by plasma D-dimer levels are associated with acute VTE. The concentration of D-dimer remains increased in VTE patients even after treatment. Higher basal level of plasma D-dimer is a strong, long-term risk marker for first VTE.[28] An increase in estrogen levels due to pregnancy, obesity, or, oral contraceptive use is also a risk factor for VTE. Elevated levels of estrogen lead to a rise in coagulation factors which are crucial to prevent blood loss during child birth but concomitantly increase risk for deep vein thrombosis (DVT).[29] the risk is further increased in overweight or obese women who use oral contraceptives. Similarly, the risk for cerebral VT (CVT) was associated with an increased body mass index (BMI). The dose-dependent association between BMI and CVT was not found in women who did not take oral contraceptives.[30] multiple pregnancies and older maternal age are risk factors for VTE. Immobility due to bed rest, long distance travel or surgery is associated with a higher risk of VTE. Anemia may be an important risk factor for CVT. A stronger association between anemia and CVT was found in men as compared to women and hemoglobin was inversely associated with CVT.[31] It has been suggested that endothelial hypoxia may be responsible for the increased VT.[29] Advanced stages of cancer as well as chemotherapy treatment are also associated with increased risk for VTE. Cancer patients have an approximately four-fold increased risk of VTE as compared with the general population, and cancer patients with VTE have reduced survival. This VTE risk is notable for pancreatic and cerebral cancer followed by stomach and bladder cancer. [35] Certain hematological malignancies such as acute leukemia are also associated with a high incidence of VTE.[33] Evidence shows that TF-containing micro vesicles secreted by malignant tissues are able to activate platelets via thrombin and lead to increased coagulability and VTE.[34] The process could be further complicated by increases in platelet and leukocyte number, soluble P-selectin, and D-dimer all contributing to platelet prothrombotic properties and VTE.[35] In addition to environmental and acquired risk factors, there are particular genetic mutations that also increase the risk for VTE. A classic example is Factor V Leiden mutation that leads to hypercoagulability. This particular variation leads to the inability of activated protein C to degrade and inactivate fact. Other genetic risk factors that increase risk for VTE are mutations

in prothrombin (G20210A) and fibrinogen (C10034T) [29] and mutations in proteins mediating anticoagulation. The last are mutations in antithrombin, protein C and protein S.

IV – 1 PROVOKING FACTORS

A) Institutionalization

The most common transient provoking factor for VTE is institutionalization. Of all cases of VTE, 35% can be attributed to nursing home stays or hospital stays without surgery, and 24% to hospital stays combined with surgery.[39] both hospital stays with and without immobilization are associated with increased risk of VTE. The age- and sex-adjusted incidence of VTE in hospitalized patients is more than 100 times that of community residents.[40]

B) Hospitalized Medical Patients

Approximately 70–80% of fatal hospital acquired thrombosis (HAT) occurs in medical patients. Venous thrombosis is increased in most acute medical conditions, necessitating hospitaladmission. The risk of VTE is also increased in a number of chronic medical disorders (see Table 1.3). Medical inpatients are usually elderly, often with several conditions to compound VTE risk.

Stroke patients, whether due to ischemic or hemorrhagic events, are at increased risk of VTE, with a wide range of estimates reported, namely, 15–60%. Prevention with chemical thromboprophylaxis is dependent on safety, with hemorrhagic risk often high. In the absence of hemorrhage, the presence of additional factors, such as severity of immobilization and comorbidities, are important for risk assessment. Acute respiratory infection in hospitalized patients is a particularly high risk for VTE. Other medical conditions included in clinical trials for thromboprophylaxis in medical patients include congestive heart failure, respiratory failure,and acute rheumatological and inflammatory bowel disorders. Clinical studies have shown therisk of DVT to be between 4–5%, with mortality at 90 days 6–14%.

Congestive heart failure patients commonly develop DVT in the absence of thromboprophylaxis, affecting 20–40% of patients, with a similar risk for medical intensive care patients. All hospitalized medical inpatients, therefore, require a risk assessment for VTE in order to reduce morbidity and mortality from HAT. Several chronic medical conditions carry an increased life-time risk of VTE. Rheumatological disorders such as systemic lupus erythematosus, particularly associated with the anti-phospholipid syndrome, are pro-thromboticconditions. Inflammatory bowel disease is associated with a 2–3 fold

An increased life-time risk of VTE. Rheumatological disorders such as systemic lupus erythematosus, particularly associated with the anti-phospholipid syndrome, are pro-thrombotic conditions. Inflammatory bowel disease is associated with a 2–3 fold increased VTE risk. Less common medical conditions at high risk include Bechet's disease, nephrotic syndrome, sickle cell disease, and some porphyria. Paroxysmal nocturnal hemoglobinuria, while rare, is complicated by thrombotic problems in over 50% of cases. Medical treatments may also be associated with VTE, with hormone therapies and erythropoietin being common examples. These medical conditions should evoke a high index of suspicion for VTE, particularly in those with a previous proven event.[41]

C) Surgery

Surgery is another transient risk factor for VTE. A case-control study showed an odds ratio of 22 for increased risk of VTE in patients who had undergone surgery requiring anesthesia during the past three months.[42] the increased risk of VTE in persons who have undergone surgery decreases with time, but is detectable for at least one year after the procedure. The risk of VTE is higher in patients that undergo inpatient surgery compared to day surgery, [43] and the duration of the surgical procedure is positively associated with risk of VTE.[44] the risk of VTE also varies depending on the type of surgery performed. Patients undergoing major orthopedic surgery or cancer surgery are at particularly high risk of VTE [42]

D) Trauma

Trauma requiring hospital admission is associated with an over 12-fold increase in risk of VTE.[42] Injury severity score, number of operative procedures, pelvic injuries and concomitantmedical conditions have been identified as markers of increased risk of VTE in trauma patients.In-hospital mortality in trauma patients with VTE is about double that of trauma patients without VTE.[45] A 7 below-knee orthopedic cast seems to be a stronger risk factor for VTE whenthe indication for the cast is a traumatic injury.[46] Minor injuries of the leg (not requiring surgery, orthopedic casts or extended bed rest) are also associated with an increased risk of VTE.[47]

E) Central venous catheters

Presence of central venous catheters or pacemaker electrodes is also associated with increased risk of VTE.[42] In studies where routine diagnostic screening was used, the percentage of patientswith a clinically manifest catheter-related DVT ranged between 0 and

12%. The risk of VTE inthis setting varies depending on the catheter type and material.[48] Patients With peripherally Inserted central venous catheters seem to be at higher risk of VTE compared to patients with centrally inserted catheters.[49]

F) Pregnancy, puerperium and hormone therapy

The risk of VTE is increased during pregnancy and puerperium. The incidence of VTE is 96 per 100,000 woman-years in pregnancy, and 511 per 100,000 woman-years during the first three months after delivery[50] During pregnancy clotting factor concentrations increase concentrations of endogenous anticoagulants decrease, and within the fibrinolysis system, bothactivator and inhibitor concentrations increase.[51] The overall activity of the fibrinolysis systemis reduced. These changes are most likely a physiologic response to maintain normal placentalfunction and reduce the risk of massive hemorrhage at delivery.[52] Use of combined oral contraceptives and hormone replacement therapy are also associated with increased risk of VTE, especially in women with a family history of VTE.[53] Transdermal administration of hormone replacement therapy may be associated with a lower risk of VTE compared to oral administration.[54] In contrast, high endogenous concentrations of sex hormones are not associated with increased risk of VTE. [55]

Although the risk of VTE is higher among users of oral estrogen-containing contraceptives than nonusers, 62,63 the absolute risk is low.[56] An absolute risk of VTE of less than 1/10,000 patients/y increased to only 3 to 4/10,000 patients/y during the time oral contraceptives were used.56 The relative risk for VTE in women using oral contraceptives containing 50 mg of estrogen, compared with users of oral contraceptives that contained less than 50 mg was 1.5.65The relative risk for VTE in women using oral contraceptives containing more than 50 mg of estrogen, compared with users of oral contraceptives that contained less than 50 mg was 1.7.65No difference in the risk of VTE was found with various levels of low doses of 20, 30, 40, and50 mg/d.[59] With doses of estrogen of 50 mg/d, the rate of VTE was 7.0/ 10,000 contraceptive users/y and with more than 50 mg/d, the rate of VTE was 10.0/10,000 oral contraceptive users/y.[57] However, some found no appreciable difference in the relative risk of VTE in relationto low or higher estrogen doses. Reports of the risk of VTE in relation to the duration of use oforal contraceptives are inconsistent. Some showed relative risks increased as the duration of use of estrogen-containing oral contraceptives increased. The relative risks were 0.7 in womenwho used oral contraceptives for less than 1 year, 1.4 for those who used oral contraceptives for 1 to 4 years and 1.8 in those who used it for 5 years or longer.[58] others

Showed the oppositeeffect, with a decreasing relative risk with duration of use. The relative risk for DVT or PE was .5.1 with use for less than 1 year, 2.5 with use for 1 to 5 years, and 2.1 with use for longer than5 years.[59] Some showed the risk to be unaffected by the duration of use.[60] A synergistic effect of oral contraceptives with obesity has been shown the odds ratio of DVT in obese women (BMI _30 kg/m2) who were users of oral contraceptives ranged from 5.2 to 7.8 compared withobese women who did not use oral contraceptives and among women with a BMI 35 kg/m2 orhigher, the odds ratio was 3.1 compared with similarly obese nonusers of oral contraceptives.[61]

There is a 2- to 3-fold increased risk of VTE with the use of hormone replacement therapy in postmenopausal women.[62] Among postmenopausal women who had coronary artery disease and received estrogen plus progestin, the relative hazard of VTE was 2.7 compared with nonusers.[63] Review showed that the risk of VTE is highest in the first year of hormone replacement therapy. The risk of VTE is increased for oral estrogen alone, oral estrogen combined with progestin, and probably for transdermal hormone replacement therapy.[64]

G) cancer

Active cancer is the most important persistent provoking risk factor for VTE,[65] as cancer is a common condition , as well as a strong risk factor for VTE.[42] The term "active cancer" is not well-defined, but a suggested definition includes cancer that has not received potentially curative therapy, cancer where there is evidence that the therapy has not been curative, and cancer where treatment is ongoing or the disease-free interval after treatment is too short to properly evaluate treatment effect.[65] There are many reasons for the increased risk of VTE in cancer patients. Tumor cells can have procoagulant activity. Aberrant tissue factor expression has been found in many human cancers,[66] and some tumor cells produce cancer procoagulant which activates coagulation factor X independently of coagulation factor VII.[67] Circulating micro particles can have procoagulant properties, and tissue factor-bearing micro particles are associated with increased risk of VTE in persons with cancer.[68] Both activating and inhibitory factors of the fibrinolysis pathway can be expressed on the surface of tumor cells.[67] They can also secrete pro inflammatory cytokines that can affect the endothelium in a procoagulant direction. Tumor cells that adhere to the vascular endothelium and/or extracellular matrix can promote localized clotting by releasing cytokines that attract other cells.[69] Tumor cells can interact with the monocyte-macrophage system and induce these cells to express tissue factor.[70]

Furthermore, tumor cells can induce platelet activation and aggregation. Anti-cancer treatments such as surgery, [71] hormonal therapy, and some anti-cancer drugs are associated with an Increased risk of VTE.[72] Long-term central venous catheters, commonly used in patients with cancer, are also associated with increased risk of VTE.

IV – 2 HERIDETARY RISK FACTOR

A) Family history

Persons with a history of VTE in a first-degree relative have an approximately 2.5-fold higher risk of VTE.[75 76] Studies of risk of VTE in adoptees, extended families, and spouses and siblings with varying age-differences[77] have indicated that the increased risk of VTE in persons with family history of VTE is due to hereditary risk factors, rather than shared environmental risk factors. Family history of VTE is a risk factor for VTE, both in persons with and without an identifiable hereditary thrombophilia. In patients with VTE, the positive predictive value of family history of VTE for hereditary thrombophilia is 30%, and the negative predictive value is 78%, which means that the value of family history of VTE to rule out or rule in presence of hereditary thrombophilia is limited.[75]

B) Ethnicity

The risk of VTE may vary between persons with different ethnicities. In the US, an increased Of VTE was seen in blacks compared to whites in some study cohorts and regions. Asians and Pacific Islanders seem to have a lower risk of VTE compared to persons of other ethnicities.[78]

C) ABO blood type and coagulation factor VIII

ABO blood type is the most common hereditary risk factor for VTE. Persons with non-O blood type have an approximately doubled risk of VTE compared to persons with O blood type.[79] This could possibly be explained by the fact that persons with non-O blood type have higher levels of von Will brand factor,[80] which is important for primary hemostasis, as well as serving as a carrier protein for factor VIII, thereby preventing its degradation.[81] High levels of coagulation factor VIII are associated with increased risk of VTE.[82] The levels of coagulation factor VIII are only partly genetically determined; 60% of variations in factor VIII coagulant activity depend on non- genetic factors.[83] Age, obesity, diabetes and malignancy are all associated with increased levels of coagulation factor VIII.[84] The association 10 between high levels of coagulation factor VIII and risk of VTE may be partially mediated through an acquired

Activated protein C resistance, and partially through an increased rate of formation of thrombin and fibrin.[85]

D) Antithrombin deficiency

Antithrombin is a serine protease inhibitor of thrombin and also inhibits factors IXa, Xa, XIa, and XIIa. Thrombin is irreversibly bound by antithrombin and prevents thrombin's action on fibrinogen, on factors V, VIII, and XIII, and on platelets.[86] this anticoagulant is synthesized inthe liver and endothelial cells, and has a half-life of 2.8 days.[87]

Historically, Egeberg (1965) was the first to associate cases of venous thrombosis with a hereditary defect in the Coagulation system; namely AT deficiency. AT is an inhibitor for thrombin, and its inhibition action is largely enhanced by heparin as a co-factor. AT deficiency causes lower control over thrombin, and therefore the Coagulation process becomes overactive (hypercoagulability) leading to VTE. Also, decreased control over thrombin in cases with AT deficiency may have a positive effect on an inhibitor of fibrinolysis called thrombin-activatable fibrinolysis inhibitor (TAFI), which may add to the hypercoagulable status in these patients, aswill be explained later. [88]

Hereditary AT deficiency has been found in 1-5 % of thrombotic cases, with a prevalence of one in 500-5000 in different populations.[89] It has an autosomal dominant mode of inheritance, and it accounts for a 10-fold increased risk of developing VTE.[90] AT deficiency maybe divided into two types: Type I (quantitative; lower amount) and Type II (qualitative; abnormal function). Type II AT deficiency is also subdivided into three subtypes based on the kind of abnormality in function it has: affecting inhibition of thrombin, affecting the binding to heparin, or affecting both. More than 80 genetic abnormalities (missense, nonsense, deletions) were reported to cause AT deficiency.[91] more than half of the patients with hereditary AT deficiency Have been reported to suffer from VTE at an age less than 40 years.[92] No reports are present on cases of homozygous AT deficiency, suggesting it is incompatible with life to have complete absence of AT in the blood.[93]

E) Protein C and protein S deficiency

Protein C is a vitamin K dependent anticoagulant protein that, once activated by thrombin, will inactivate factors VA and VIIIa, thereby inhibiting the generation of thrombin.[94] additionally, activated protein C stimulates the release of t-PA. It is produced in the liver and is the dominant endogenous anticoagulant with an eight-hour half-life. Protein C deficiency has a prevalence

of1 in 200–300 with more than 150 mutations and an autosomal dominant inheritance.[94 95] Protein S is also a vitamin K dependent anticoagulant protein that is a cofactor to activated protein C. The actions of protein S are regulated by complement C4b binding protein and only the free form of protein S serves as an activated protein C cofactor.[96] Additionally, protein S appears to have independent anticoagulant function by directly inhibiting procoagulant enzymecomplexes.[95] The prevalence of protein S deficiency is about 1: 500 with an autosomal dominant inheritance.

Clinically, protein C and S deficiencies are essentially identical. With homozygous protein C and S deficiencies, infants typically will succumb to purpura fulminant, a state of unrestricted clotting and fibrinolysis. In heterozygotes, venous thrombosis may occur at an early age especially in the lower extremity.[97] Thrombosis may also occur in mesenteric, renal, and cerebral veins.

F) Activated protein C resistance

Activated protein C resistance is a form of hereditary thrombophilia in which active coagulation factor V is more resistant to inactivation by activated protein C. This leads to increased thrombin generation as well as decreased activated protein C anticoagulant activity. The most common cause of activated protein C resistance is a mutation in the factor V gene that causes one amino acid to replace another in the gene product, also known as factor V Leiden [98 99]. Heterozygotes for factor V Leiden have a doubled risk of DVT, but no increase in risk of PE, [100] whereas homozygotes have an increased risk of both DVT and PE.100. Activated protein Cresistance can also be an acquired hypercoagulable state, for example in users of oral contraceptives.[101]

G) Prothrombin mutation

Prothrombin (Factor II) is a zymogen synthesized in the liver and dependent on vitamin K. When prothrombin is activated, it forms thrombin (Factor IIa). A single mutation where adenine is substituted for guanine occurs at the 20210 position. The mechanism for increased thrombotic risk is not well understood, but individuals with this genetic variant have supra normal levels of prothrombin. The mutation is inherited as an autosomal dominant trait and is associated with both arterial and venous thrombosis. Clinically, patients may present with deep venous thrombosis of the lower extremity, cerebral venous thrombosis, as well as arterial thrombosis. The risk of thrombosis increases in the presence of other genetic coagulation defects and with acquired risk factors. [102 103]

H) Hyperhomocysteinemia

Homocysteine is an amino acid formed during the metabolism of methionine and may be elevated secondary to inherited defects in two enzymes that are part of the conversion of Homocysteine to cysteine. The two enzymes involved are N5, N10–methylene tetrahydrofolatereductase (MTHFR) or cystathionine beta-synthase. Hyperhomocysteinemia has been shown to increase the risk of atherosclerosis, atherothrombosis, and venous thrombosis. Elevated plasma Homocysteine levels cause various dysfunctions of endothelial cells leading to a prothrombotic state. Hypercoagulable syndromes include inherited and acquired thrombophilia. The former isdiscussed in detail in the article by Weitz in this issue. The latter includes the antiphospholipid syndrome, heparin-induced thrombocytopenia, acquired dysfibrinogenemia, myeloproliferative disorders, and malignancy. Myeloproliferative disorders and malignancy are described elsewhere in this article. Regarding the antiphospholipid syndrome, antiphospholipid antibodiesare associated with both arterial and venous thrombosis.[104] The most commonly detected subgroups of antiphospholipid antibodies are lupus anticoagulant antibodies, anticardiolipin antibodies and anti-b2- glycoprotein I antibodies.[105] DVT, the most common manifestation of the antiphospholipid syndrome, occurs in 29% to 55% of patients with the syndrome, and about half of these patients have pulmonary emboli.[106] The risk of heparin-associated thrombocytopenia is more duration related than dose related. Heparin-associated thrombocytopenia occurs more frequently with unfractionated heparin when used for an extended duration than with LMWH used for an extended duration. When used for prophylaxis, there was a higher prevalence of heparin-associated thrombocytopenia in those receiving unfractionated heparin (1.6%, 57 of 3463) than in those receiving LMWH (0.6%, 23 of 3714).[107] However, treatment resulted in only a small difference in the prevalence of heparin associated thrombocytopenia comparing unfractionated heparin (0.9%, 22 of 2321) with LMWH (0.6%, 18 of 3126).[107] Acquired dysfibrinogenemia occurs most often in patients withsevere liver disease. The impairment of the fibrinogen is a structural defect caused by an increased carbohydrate content impairing the polymerization of the fibrin, depending on the degree of abnormality of the fibrinogen molecule.[108]

IV – 3 ACQUIRED RISK FACTORS

A) Age

Age is a strong risk factor for VTE. As previously described, the incidence of VTE increases markedly with age.[109] about 60% of all VTE events occur in persons aged 70 years and above. One reason for the association between advancing age and risk of VTE is that elderly persons tend to have a higher burden of provoking factors and risk factors for VTE when compared to younger persons. Institutionalization, surgery and cancer are all more common in older personscompared to younger persons.[110] Age is also associated with changes in coagulation factors levels, for example levels of coagulation factor VIII and activated coagulation factor VII increase with age.[111] Muscle strength declines with age, and it is probable that this overall decline also affects the function of the veno-muscular pumps. Venous compliance decreases with increasing age. Moreover, venous valve thickness increases with age. This could be one mediator of the association between age and risk of VTE.[112]

B) Antiphospholipid antibodies

Lupus anticoagulants, anticardiolipin antibodies and anti-beta 2-glycoprotein I antibodies are collectively known as antiphospholipid antibodies. The presence of antiphospholipid antibodiescan be associated with increased risk of VTE. Antiphospholipid antibodies can occur in conjunction with autoimmune conditions, such as systemic lupus erythematosus, or as an isolated phenomenon.[113] in patients with systemic lupus erythematosus, there is an associationbetween presence of antiphospholipid antibodies and increased risk of VTE with an OR of 5.6for the association between lupus anticoagulants and risk of VTE. The association between anticardiolipin antibodies and risk of VTE is weaker (OR 2.2).[114] in a meta-analysis where thevast majority of study participants did not have systemic lupus erythematosus, there was an association between lupus anticoagulants and risk of VTE with ORs between 5 and 16 in different studies.[115] the association between anticardiolipin antibodies and risk of VTE in persons without systemic lupus erythematosus is debated. The aforementioned 12 meta-analysis concluded that there is a possible association between anticardiolipin immunoglobulin G antibodies in medium or high titers and risk of VTE, [115] whereas two prospective population- based studies found no association between anticardiolipin antibodies and risk of VTE.[116]

C) Smoking

Several studies have reported an association between smoking and increased risk of VTE.[117] The risk of VTE seems to increase with exposure to smoking, measured as number of pack-years.[118] The smoking-related increase in risk of VTE is thought to be driven by an association between smoking and an increased risk of provoked VTE events.[119] For example, smoking is associated with an increased risk of cancer in many different organs, and cancer is an important provoking factor for VTE. [120]

D) Obesity

Obesity is associated with increased risk of death, as well as increased risk of a range of cardiovascular events such as myocardial infarction, stroke, heart failure and atrial fibrillation [121] A higher body mass index is also associated with increased risk of VTE. The association between the metabolic syndrome and risk of VTE seen in some studies is attributable to obesity.[122] possible mechanisms for the association between obesity and increased risk of VTE could be the association between obesity and development of an inflammatory and prothrombotic state, [123] increased intra-abdominal pressure [124] and altered venous hemodynamics of the lowerlimbs. A Mendelian randomization study showed an association between an obesity- specific genetic locus and DVT complicated by PE. These findings indicate that there may be a causal association between obesity and risk of VTE.1[25] Body height also influences venous pressure physiology, [126] and there seems to be a synergistic effect of tall stature and obesity on the risk of VTE.[127]

IV – 4 MEDICAL ILLNESS

A) Inflammatory bowel desease

The incidence of VTE among hospitalized medical patients with ulcerative colitis was 1.9%and the incidence with Crohn disease was lower (1.2%). Among medical patients who had neither ulcerative colitis nor Crohn disease the incidence was 1.1%.[128] the relative risk of VTE among Patients with ulcerative colitis compared with patients who did not have inflammatory bowel disease was 1.9 and with Crohn disease it was 1.2. Among patients younger than 40 years with ulcerative colitis, the relative risk of VTE compared with patients who did not have inflammatory bowel disease was 2.96 and in patients younger than 40 years with Crohn disease the relative risk was 2.23.[128]

B) Liver disease

Patients with chronic liver disease (both alcoholic and nonalcoholic) seem to have a lower riskof PE than patients without liver disease,[129] but data are inconsistent.[130] Chronic liver disease may result in impaired production of vitamin-K dependent procoagulant factors.[131] However, decreased production of vitamin-K dependent endogenous anticoagulants, such as protein C, protein S, and antithrombin III, may counter the hypercoagulability in such patients.[131] Other prothrombotic factors may counteract the impaired production of vitamin K dependent procoagulant factors including lupus anticoagulant, activated protein C resistance, PT20210A mutation, Factor V Leiden, MTHFR mutation, and increased levels of factor VIII.[132] Based on data from the National Hospital Discharge Survey, among 4,927,000 hospitalized patients withchronic alcoholic liver disease from 1979 to 2006, the prevalence of VTE was 0.6% and among4,565,000 hospitalized patients with chronic nonalcoholic liver disease it was 0.9%. The prevalence of VTE was higher in those with chronic alcoholic liver disease than with nonalcoholic liver disease, but the difference was small and of no clinical consequence.[129] Bothshowed a lower prevalence of VTE than in hospitalized patients with most other medical diseases. It may be that both chronic alcoholic liver disease and chronic Nonalcoholic liver disease have protective antithrombotic mechanisms although the mechanisms differ.

C) Hypothyroidism

Among 19,519,000 hospitalized patients with a diagnosis of hypothyroidism from 1979 to 2005, 119,000 (0.61%) had PE. DVT was diagnosed in 1.36% of hypothyroid patients. The relative risk for PE in patients with hypothyroidism was highest in patients younger than 40 years and the relative risk for DVT was also highest in patients younger than 40 years. Hyperthyroidism was not associated with an increased risk for VTE.[133]

D) Rheumatoid arthritis

Rheumatoid arthritis is not generally considered a risk factor for VTE, although abnormalities of coagulation factors have been found in patients with rheumatoid arthritis.[134] Among 4,818,000 patients hospitalized in short-stay hospitals from 1979 to 2005 with rheumatoid arthritis who did not have joint surgery, the incidence of PE was 2.3%, and the relative risk of VTE compared with those who did not have rheumatoid arthritis was 1.99. Among patients younger than 50 years the relative risk was higher (2.13).[135]

E) Diabetes mellitus

Among 92,240,000 patients with diabetes mellitus hospitalized from 1979 to 2005, 1,267,000 (1.4%) had VTE.[136] The relative risk for VTE was increased only in patients younger than 50 years and was highest in patients aged 20 to 29 years. In patients with diabetes mellitus who did not have obesity, stroke, heart failure, or cancer, compared with those who did not have diabetes mellitus and did not have any of these comorbid conditions, the relative risk for VTE was 1.52 in patients aged 20 to 29 years and 1.19 in patients 30 to 39 years. In older patients, the relative risk of VTE in patients with diabetes mellitus was not increased. Among all adultswith diabetes mellitus, the relative risk of VTE was 1.05.[136]

F) Human immunodeficiency virus

Among 2,429,000 patients older than 18 years hospitalized in short-stay hospitals from 1990 through 2005 with human immunodeficiency virus (HIV) infection; the prevalence of VTE was1.7%. The prevalence of VTE in patients aged 30 to 49 years was also 1.7%, but the relative risk compared with patients who did not have HIV infection was higher (1.65).[137]

G) Nephrotic syndrome

From 1979 to 2005, 925,000 patients were discharged from short-stay hospitals with nephroticsyndrome and 14,000 (1.5%) had DVT (relative risk 5 1.72). In patients aged 18 to 39 years therelative risk for DVT was 6.81. Renal vein thrombosis was so uncommon that too few were reported to calculate its prevalence. Therefore, PE, if it occurs, is likely to be due to emboli from the lower extremities and not the renal vein.[138]

H) Sickle cell disease

Sickle cell disease does not seem to be a risk factor for DVT / Among 1,804,000 patients hospitalized in short-stay hospitals with sickle cell disease from 1979 to 2003, 11,000 (0.61%)had a discharge diagnosis of DVT, which was not more than in African Americans without sickle cell disease (0.81%). Among patients with sickle cell disease, a discharge diagnosis of PE was made in 0.50% compared with 0.33% who did not have sickle cell disease. Regarding patients younger than 40 years, 0.44% had PE, whereas among patients who did not have sickle cell disease, 0.12% had PE.[139] The higher prevalence of apparent PE in patients with sickle cell disease compared with African American patients the same age

who did not have sickle cell disease, and the comparable prevalence of DVT in both groups, is compatible with the conceptthat thrombosis in situ may be present in many.

I) Systemic lupus erythematosus

Systemic lupus erythematosus is believed to be independently associated with the risk of developing DVT. The odds ratio for DVT in patients with systemic lupus erythematosus, compared with those without it, was 4.3. [140]

J) Behest disease

Behcet disease is a rare multisystem inflammatory disorder of unknown cause. VTE occurs in about one-fifth of patients with Behcet disease.[141]

K) Paroxysmal nocturnal hemoglobinuria

Review of 13 retrospective studies of patients with paroxysmal nocturnal hemoglobinuria showed a 30% prevalence of venous thrombotic events in patients from Western nations. The majority was within the hepatic and mesenteric veins.[142]

L) Sepsis

Initiation of coagulation takes place when TF is exposed, such as by fibroblasts, when there istissue damage or by cytokine-stimulated monocytes and endothelial cells, as in sepsis. While TF is the major initiator of coagulation, endotoxin, foreign bodies, and negatively charged particles may initiate coagulation via contact system activation. TF binds to factor VIIa, and this complex (TF: VIIa) may then activate factor X and factor IX. Factor Xa, associated with factor VA, forms the prothrombinase complex, which subsequently turns prothrombin into thrombin. The relationship between coagulation and inflammation is complex and, as yet, not completely understood. It is known that blood clotting not only leads to fibrin deposition and platelet activation, but it also results in vascular cell activation, which contributes to leukocyte activation[145]. On the other hand, inflammation can induce TF expression in monocytes, via nuclear factor kappa-B (NF-kB) activation, thus initiating coagulation[144]. Examples of this interaction are readily seen. First, leukocytes are found at relatively high concentrations in venous thrombi, and leukocytes and activated platelets can form rosettes mediated by P-selectin expression on the surface of the activated platelet.[146]

These microscopic observations are probably elicited from the actions of thrombin, which canactivate platelets and endothelium, increasing the surface expression of P-selectin.[147] P-electinis the primary initial mediator of leukocyte-endothelial cell rolling and is critical for

leukocyteadhesion. Second, TF: VIIa and factor Xa have been shown to activate cells and generate responses similar to those mediated by thrombin.[145] Third, GAG and TM expression on cell surfaces are inhibited by inflammatory cytokines and lipopolysaccharide (LPS),[148] thusblocking the augmentation of AT action by GAG, and APC formation by TM.

CHAPTER 2: THE NEW RECOMMENDATIONS FOR THE MANAGEMENT OF VENOUS THROMBOEMBOLIC DISEASE

I - European Society for Vascular Surgery (ESVS) 2021 Clinical Practice Guidelines on the Management of Venous Thrombosis.

I – 1 GENERAL ASPECTS

The European Society for Vascular Surgery (ESVS) has developed a series of clinical practice guidelines for the care of patients with vascular diseases. Their aim is to assist clinicians in selecting the best management strategies to achieve optimal patient outcomes.

These are the first ESVS guidelines on venous thrombosis. In 2017, the ESVS Guidelines Committee (GC), initiated a process to develop these guidelines. The present guideline document addresses acute deep vein thrombosis (DVT) of the lower extremity (unless otherwise stated), upper extremity DVT (UEDVT), superficial vein thrombosis (SVT), and thrombosis inunusual sites. The guideline document also covers topics in addition to treatments, including investigations and health economics, and includes special patient populations. The topic of venous thrombosis is large and therefore the remit of the guideline has been limited to conditions and situations likely to be commonly encountered by clinical teams/end users managing patients with venous thrombosis and others exposed to this condition. Furthermore, all recent ESVS guidelines have considered the patient's perspective the recommendations represent the best available knowledge at the time of publication.[149]

I – 2 WEIGHING THE EVIDENCE

To define the current guidelines, members of the GWC reviewed and summarized the relevant peer reviewed published literature. Conclusions were drawn based on the available scientific evidence. In keeping with other published ESVS guidelines, the clinical practice recommendations in this document are presented using the European Society of Cardiology grading system. For each recommendation, the letter A, B, or C indicates the level of current Evidence guiding the recommendation.

Table 1: levels of evidence.

Level of evidence A	Data derived from multiple randomised clinical trials or meta-analyses
Level of evidence B	Data derived from a single randomised clinical trial or large non-randomised studies
Level of evidence C	Consensus of experts opinion and/or small studies, retrospective studies, and registries

Depending on whether the recommendation is strongly supportive of an intervention, weakly supportive, or strongly against an intervention, each recommendation is categorized as either Class I, IIa/IIb, or III.

Table 2: classes of recommendations.

Class of recommendation	**Definition**
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, and effective
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy*
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion*
Class III	Evidence or general agreement that the given treatment or procedure is not useful/ effective, and in some cases may be harmful

Recommendation 1:

When deep vein thrombosis is suspected, a clinical assessment of the pre-test probability isrecommended as part of the diagnostic process. **Class I level C**

Recommendation 2:

All healthcare professionals involved in the diagnosis of deep vein thrombosis should use avalidated diagnostic pathway. **Class I level C**

Table 3: Wells score for the prediction of lower extremity deep vein thrombosis.

Clinical characteristic	Score
Active cancer (treatment ongoing, within previous six months, or palliative)	1
Paralysis, paresis, or recent plaster immobilisation of the lower extremities	1
Recently bedridden > 3 days, or major surgery within 12 weeks requiring general or regional anaesthesia	1
Localised tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling 3 cm larger than asymptomatic side (measured 10 cm below tibial tuberosity[a])	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)[b]	1
Alternative diagnosis at least as likely as DVT	–2
Probability of DVT: Low ≤ 0, intermediate 1-2, and high ≥ 3	

Recommendation 3:

For patients with suspected deep vein thrombosis requiring imaging, ultrasound is recommended as the first modality. **Class I level C**

Recommendation 4:

For patients with suspected deep vein thrombosis with a likely pre-test probability and negative compression ultrasound scanning, repeat ultrasound assessment should be considered after 5e7 days. **Class IIa level C**

Recommendation 5:

For patients with suspected proximal deep vein thrombosis where ultrasound assessment is Inconclusive or not feasible, computed tomography venography, magnetic resonance venography, or venography should be considered. **Class IIa level C**

Recommendation 6:

When performing ultrasound imaging in patients with suspected calf deep vein thrombosis, whole leg ultrasound is recommended. **Class I level C**

Recommendation 7:

For patients with deep vein thrombosis, routine investigation for occult pulmonary embolism in the absence of symptoms or signs is not recommended. **Class III level C**

Recommendation 8:

For patients with unprovoked deep vein thrombosis, clinical examination and sex specific cancer screening, as opposed to routine extensive screening, for occult malignancy is recommended. **Class I level A**

Recommendation 9:

For patients with provoked deep vein thrombosis, thrombophilia testing is not recommended **Class III level C**

Recommendation 10:

For patients with unprovoked deep vein thrombosis, routine testing for inherited thrombophilia's is not recommended. **Class III level C**

Recommendation 11:

For patients with unprovoked deep vein thrombosis and a family history of venous thromboembolism in a first degree relative, testing for hereditary thrombophilia should be considered. **Class IIa level C**

Recommendation 12:

For patients with unprovoked deep vein thrombosis, testing for antiphospholipid antibodies should be considered if a decision to stop anticoagulation is contemplated. **Class IIa level C**

Table 4: Definition of transient or persistent provoked risk factor for deep vein thrombosis.

Provoked risk factor	Definition
Transient	
Major*	Half the risk of recurrent VTE after stopping anticoagulant therapy (*vs.* if there was no transient risk factor), when the risk factor occurred up to three months before the VTE
	A >10 fold increase in the risk of having a first VTE
Minor†	Half the risk of recurrent VTE after stopping anticoagulant therapy (*vs.* if there was no transient risk factor), when the risk factor occurred up to two months before the VTE
	A 3–10 fold increase in the risk of having a first VTE
Persistent‡	Cancer, if: • has not received potentially curative treatment • there is evidence that treatment has not been curative (e.g., recurrent or progressive disease) • treatment is ongoing
	Ongoing non-malignant condition associated with at least a twofold risk of recurrent VTE after stopping anticoagulant therapy

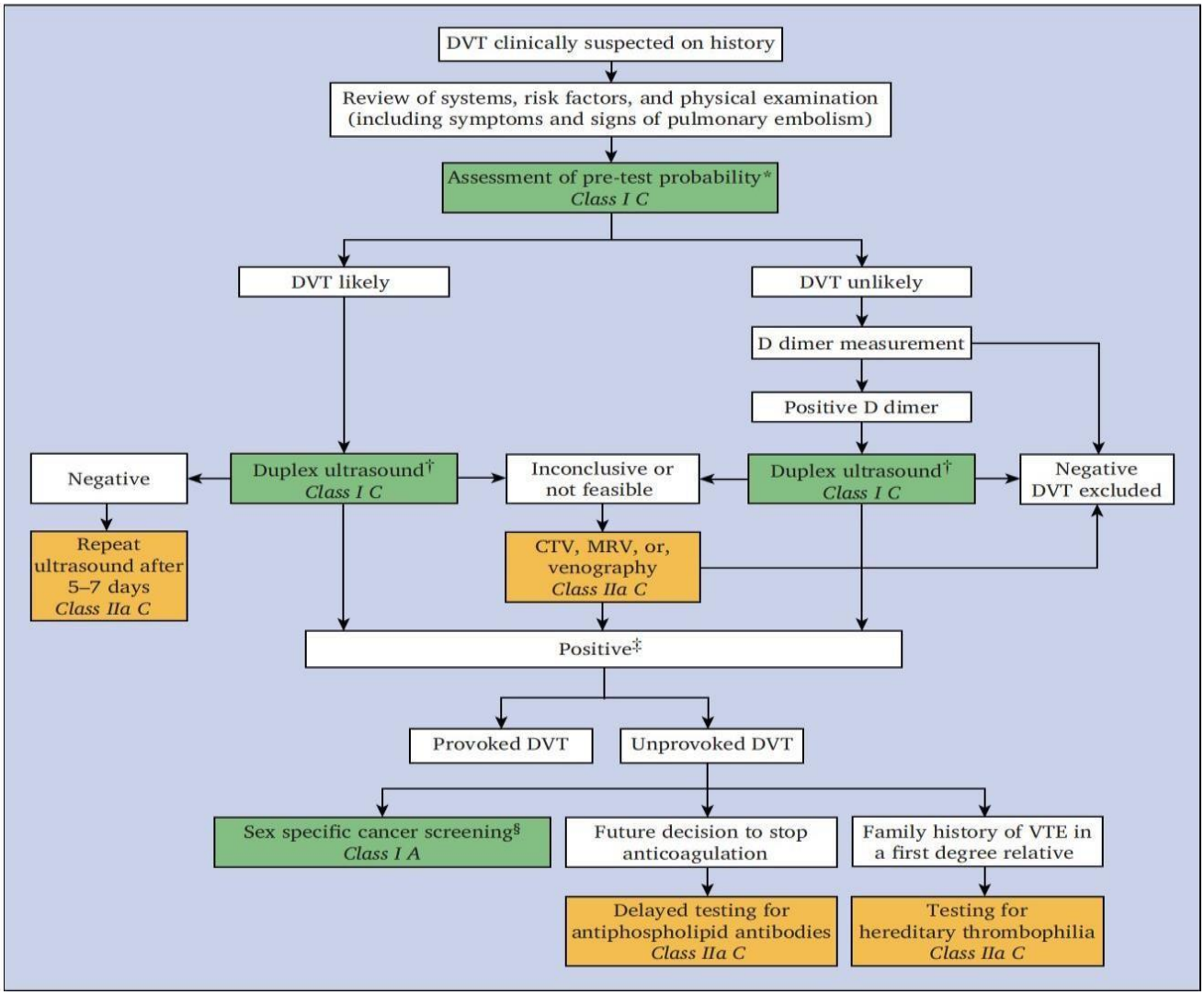

Figure 5: Flowchart of recommendations for the diagnosis and investigation of deep vein thrombosis (DVT).

Recommendation 13:

For patients with suspected lower limb superficial vein thrombosis, a whole leg ultrasound scanis recommended to determine thrombus extent and exclude asymptomatic deep vein thrombosis. **Class I Level B**

Recommendation 14:

For patients with lower limb superficial vein thrombosis, acute superficial venous intervention is not recommended. **Class III Level C**

Recommendation 15:

For patients with suspected upper extremity deep vein thrombosis, ultrasound is recommended

as the initial imaging investigation. **Class I Level C**

Recommendation 16:

In most patients with symptomatic primary upper extremity deep vein thrombosis, early thrombus removal is not recommended. **Class III Level C**

Recommendation 17:

The management of children with deep vein thrombosis should be guided by clinicians with specific expertise in pediatric thrombosis and hemostasis. **Class I Level**

Recommendation 18:

For patients with proximal deep vein thrombosis, use of below knee compression stockings should be considered in order to reduce the risk of post-thrombotic syndrome.

Class IIa Level A

Recommendation 19:

For patients with proximal deep vein thrombosis and with limited symptoms and signs, as described in the Villalta score, it is recommended to limit the use of below knee stockings to six or 12 months.[154] **Class I Level A**

Table 5: The Villalta scale and its interpretation for post-thrombotic syndrome (PTS).

Clinical findings*	None	Mild	Moderate	Severe
Symptoms				
Pain	0	1	2	3
Cramping	0	1	2	3
Heaviness	0	1	2	3
Pruritis	0	1	2	3
Paraesthesia	0	1	2	3
Signs				
Oedema	0	1	2	3
Induration	0	1	2	3
Hyperpigmentation	0	1	2	3
Venous ectasia	0	1	2	3
Redness	0	1	2	3
Calf tenderness	0	1	2	3
Interpretation of severity of post thrombotic syndrome				
Villalta score	< 5	5–9	10–14	> 14 or the presence of venous ulceration

* Each variable is given a score of between 0 and 3 indicative of a severity of none, mild, moderate, or severe, respectively, with a maximum score of 33.

II - Good practice guidelines for the management of venous thromboembolic disease in adults (French Language Pneumology Society) 2019

These recommendations are based on an exhaustive and systematic review of the literature, including meta-analyses. All of the data and analyses are detailed in the supporting documentation, which led to the development of recommendations graded according to the "Grade" method.

In summary, the level of evidence from studies is evaluated based on quality (high: randomized controlled trials, meta-analyses; low: cohort studies, case-control studies, diagnostic studies) and the importance of the effect and outcome criteria, resulting in a high grade (1 or "recommendation") with a high level of evidence or a low grade (2 or "suggestion") with a low level of evidence. Each grade is divided into positive action ("prescribe" or "do") or negative action ("do not prescribe" or "do not do"). Four grades are defined as follows:

- Grade 1+: strong and positive recommendation, "it is recommended to do or prescribe";

- Grade 2+: optional and positive recommendation, "it is suggested to do or prescribe";

- Grade 1-: strong and negative recommendation, "it is recommended not to do or prescribe";

- Grade 2-: optional and negative recommendation, "it is suggested not to do or prescribe".

1 - Some recommendations from the guideline of good practice for venous thromboembolic.

R1 - It is recommended to consider the hypothesis of a pulmonary embolism (PE) in the presence of suggestive symptoms, particularly unexplained dyspnea or chest pain that cannot be attributed to another diagnosis (grade 1+).

R2 - It is recommended not to investigate the hypothesis of a PE in the absence of any respiratory or hemodynamic symptoms, either permanent or transient (dyspnea, chest pain, discomfort, etc.) suggestive of a PE (grade 1-).

R3 - It is suggested to use the PERC rule to exclude a PE, except during pregnancy and postpartum, provided that the patient has a low clinical probability of PE, which is evaluated implicitly by the clinician (grade 2+).

R5 - It is suggested to use the Geneva score with a 3-level probability stratification (low, intermediate, high) for non-hospitalized patients instead of a 2-level probability stratification (unlikely, likely) (grade 2+).

R130 - It is recommended to determine the provoked or unprovoked nature of a first episode of venous thromboembolism (VTE) when assessing the risk of recurrence (Table 12), regardless of any known biological risk factors (grade 1+).

R131 - In patients with a first episode of provoked VTE caused by a major transient risk factor, systematic screening for occult cancer is not recommended (grade 1-).

R132 - In patients with a first episode of unprovoked VTE, the following is recommended:

- Conduct a careful physical examination and obtain personal and family history of neoplasms, and repeat this evaluation during the first six months of follow-up. Investigations should be guided by any observed abnormalities (grade 1+).

- In addition to standard anticoagulant treatment monitoring (blood tests for electrolytes and creatinine, liver function tests), perform a chest X-ray (if a thoracic CT scan was not performed for the diagnosis of PE), complete blood count, and serum calcium (grade 1+).

- Update recommended screening in the general population (grade 1+): perform a cervical smear test for all women, mammography after age 50, and a PSA test for all men over 50, unless these tests were performed in the previous year.

- Other investigations should be guided by the results of the initial tests (grade 1+).

R133 - In patients with a first episode of unprovoked VTE and a normal complete blood count, it is suggested not to test for mutations associated with myeloproliferative disorders, except in

cases of atypical site thrombosis such as splanchnic, upper limb, or cerebral thrombosis (grade 2-).

R134 - In patients with an unprovoked recurrent VTE (i.e., ≥ 2 events) despite well-conducted anticoagulant therapy:

- It is recommended to search for cancer by conducting the same tests as during the first episode (grade 1+).

- It is suggested to actively search for occult cancer (JAK2 mutation, thoraco-abdomino-pelvic CT scan and/or PET scan, etc.) (Grade 2+).

- Other investigations should be guided by the results of the initial tests (grade 1+).

R137 - Systematic testing for inherited thrombophilia after a first episode of VTE is not recommended (grade 1-).

R138 - Testing for inherited thrombophilia is not recommended in patients with a first episode of proximal DVT or PE after age 50, regardless of whether the thrombosis is provoked or unprovoked (grade 1-).

R139 - It is suggested to perform testing for inherited thrombophilia in the following situations:

- In patients with a first unprovoked episode of proximal DVT or PE before the age of 50 and with a first-degree family history of thrombosis (grade 2+).

- In patients with recurrent venous thromboembolism (at least one episode of proximal DVT or PE and at least one unprovoked episode before age 50) (grade 2+).

- In patients with unprovoked venous thrombosis in atypical sites (splanchnic, upper limb, cerebral) (grade 2+).

R140 - In other situations, given the complexity of analyzing medical records and potential therapeutic consequences, it is suggested to seek the advice of a multidisciplinary expert thrombosis center (grade 2+).

R141 - When testing for inherited thrombophilia is indicated, it is suggested to search for the following abnormalities in a specialized laboratory, between the 3rd and 6th month after the diagnosis of thrombosis: deficiencies in AT, PC, PS, Leiden mutations of FV and G20210A of FII (grade 2+).

R142 - In case of inhibitor deficiency (AT, PC, PS), it is suggested to determine the phenotype precisely and even the genotype (grade 2+).

R143 - It is suggested to test asymptomatic relatives for inherited thrombophilia in case of severe inherited thrombophilia in the proband (deficiency in AT, PC, PS, double heterozygote and homozygote FV and FII) (grade 2+).

R144 - When testing asymptomatic relatives for inherited thrombophilia is indicated, it is recommended to refer the subject to an accredited expert thrombosis center (grade 1+).

R145 - When testing asymptomatic relatives for inherited thrombophilia is indicated, it is suggested to limit testing initially to the abnormality identified in the probed (AT, PC, PS, or double heterozygote or homozygote FV Leiden and FII G20210A). If the abnormality is found, it is suggested to perform a complete thrombophilia workup (grade 2+).

PART 2

CHAPTER 1: REPRESENTATION OF THE STUDY

I – PROBLEMATIC AND OBJECTIVES OF THE STUDY

I - 1 PROBLEMATIC OF STUDY

Management of VTE involves multiple specialists, including internists, cardiologists, hematologists, and neurologists, who are responsible for screening, coordinating care, long-term follow-up, and therapeutic management of VTE.

While the etiological investigation is essential for proper management of VTE, as it allows for the adaptation of the duration of anticoagulant treatment, the etiological assessment remains complex and difficult to perform on an outpatient basis.

No study has been conducted in Algeria on the evaluation of the clinical practice of specialist physicians in the face of venous thrombophilia.

The evidence suggests that many doctors who are not familiar with the management recommendations have difficulties in prescribing a comprehensive etiological assessment, which includes the search for an occult cancer.

All of these elements raise questions about the practices of specialist physicians in the Algeirs region regarding the etiological assessment of VTE compared to the 2019 recommendations.

- What are the current practices of specialist physicians in the Algeirs region regarding the prescription of etiological assessments for VTE, and how do these practices compare to the 2019 recommendations?
- How knowledgeable are doctors in the Algerian region about the latest updates in recommendations for prescribing etiological assessments for VTE, and how does this knowledge vary by age, duration of work, and mode of work?

It is necessary to assess these shortcomings and implement tools to facilitate the dissemination of these recommendations and thus facilitate the management of VTE.

I – 2 THE MAIN OBJECTIVE

a descriptive and observational study was conducted with the main objective of analyzing the practices of specialists' practionners in the Algeirs region regarding the prescription of the etiological assessment, specifically the search for occult cancer and biological thrombophilia.

I – 3 THE SOCONDARY OBJECTIVES

The secondary objectives of this study are to describe the practice of specialists' practitioners in the Algeirs region regarding the etiological assessment of VTE, including the search for risk factors (BRF) and occult cancer. The specific objectives are:

- Identify the BRFs searched for when a thrombophilia assessment is prescribed.

- Understand in what clinical circumstances the thrombophilia assessment is prescribed in the presence of VTE.

- Evaluate how the result of the thrombophilia assessment conditions the management of VTE.

- Identify the situations that require a search for occult cancer and the first-line examination for this search.

These objectives will help to better understand the practices of specialists' doctors in the region.

II – METHODS

It is a descriptive observational epidemiological study, in the form of a declarative survey of specialist practitioners in the Algeirs region

Population: only Internalist; hematologist; neurologist; and cardiologist were included likewise, general practitioners practicing vascular medicine were not included in the study so as not to bias the survey responses. Finally, all incomplete responses were excluded from the analysis.

Data collection: Questionnaires were distributed in the offices of a large number of doctors. A part of the selected doctors was contacted by telephone where they were offered in the event of acceptance, either a subsequent telephone interview, or an email with the computerized questionnaire (site Google forms.com) and in Word format. All questionnaires were completed anonymously. The responses were filed in an Excel spreadsheet and IBM SPSS statistics 22

The questionnaire was divided into 3 parts:

A first part on the general data of the doctors interviewed (sex, age, method of exercise, year of start of exercise, estimation of knowledge on the subject, training on the subject, and frequency of confrontation with VTE).

A second part on the search for occult Cancer, risk factors, prescription of the thrombophilia assessment, and biological (PC, PS, antithrombin, mutation of coagulation factors) parameters were proposed. With the possibility multiple choice answers, A first closed question was established on their probability of prescribing this assessment in the face of a VTE (Yes / No), a question in major risk factors, search for idiopathic cancer (provoked / unprovoked VTE, before / after 50 years and recurrence) and First-Intention Examinations for Occult Cancer.

A third part on care. Several clinical (personal or family ATCD of VTE, idiopathic VTE, provoked VTE, clinical context) and biological (FV or FII mutation in heterozygous, homozygous). The questions were closed (yes or no).

Statistical analyzes: The doctors were drawn FRANTS FANON hospital, FABOUR hospital, MUSTAPHA BACHA hospital and liberal practitioners in Blida and DOUERA region. A sample of 100 doctors from each department was selected. In order to be the most representative of the population of the Algeirs region, the Proportion of doctors practicing by department has been respected 47% from FRANTZ FANON (15% Internalist, 7% hematologist, 15% neurologist and 10% cardiologist.), 10 % from FABOUR hospital (internal medicine),18% from DOUERA and 25% from MUSTAPHA BACHA hospital. The data were classified by Microsoft EXCEL® 2013 the quantitative variables were represented in numbers and percentages.

CHAPTER 2: RESULTS

I - DEMOGRAPHIC DATA

Table 6: Demographic data of the sample study.

DEMOGRAPHIC QUESTIONS		Percent
GENDER OF DOCTORS	Female	58%
	Male	42%
AGE OF DOCTORS	30 years and less	43%
	30 to 40 years	26%
	40 to 60 years	27%
	60 years above	4%
HOW LONG HAVE YOU PRACTICING MEDECINE?	10 years and less	44%
	10 to 20 years	30%
	20 years above	26%
EXCERCISE MODE	Liberal	32%
	Hospital	46%
	Mixed	22%

From the table (6), we found that the highest percent of the total sample were female by (58%), while male were (42%) of the total sample.

About age, they were (30 years or less) by 43% of the total sample, followed by 27% for (40 to 60 years), 26% for (30 to 40 years) and 4% for (60 years above) with average age 35, 9 years.

About ancientity, the highest percent was for (10 years or less) by 44% of the total sample, followed by (10 to 20 years) with 30% of the total sample, while 26% of the total sample were 20 years above.

About exercise mode, the highest percent was for (hospital doctors) by 46 of the total sample, followed by (liberal doctors) with 32% of the total sample, while 22% of the total sample had a mixed exercise

II- DESCRIPTION OF THE KNOWLEDGE OF DOCTORS CONCERNING THE PRESCRIPTION OF ETIOLOGICAL ASSESSMENT OF VTE.

II – 1 Assessing doctor's Knowledge of Best Practice Recommendations for the Management of Venous Thromboembolic Disease

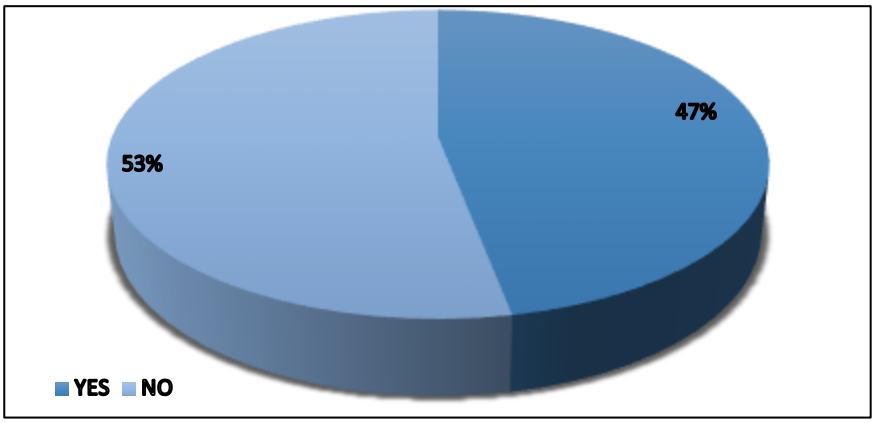

Figure 6: A relative circle representing the percent of doctor's who are familiar with the recommendations.

In the sample, 53% of doctor's are not familiar with the 2019 recommendations. It was known only by 47% of doctors

II – 2 the knowledge of doctors about major risk factor of venous thromboembolism

From figure 7, we found that 100% of doctors in the sample considered the surgery as a major risk factor followed by 93% (anti phospholopid syndrome), 76% for (active cancer) and 73% for (pregnancy and postpartum), while only 48% of all doctors taught inflammatory bowel desease as a major risk factor.

The next figure shows these results.

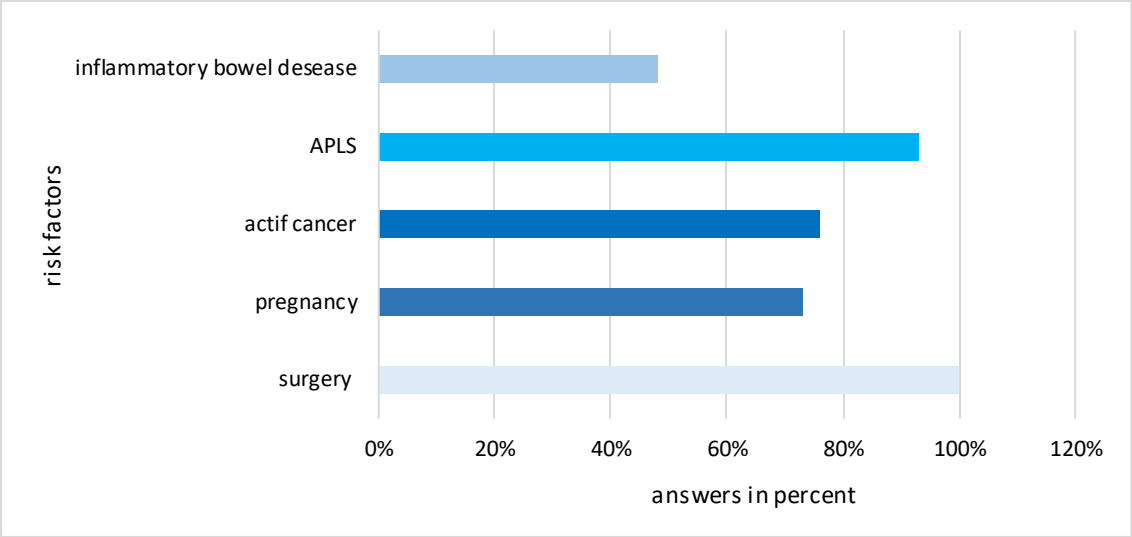

Figure 7: major risk factor of venous thromboembolism.

II – 3 clinical cases, thrombophilia assessment

A) 65-year-old patient who has never had a VTE; but her sister had a prothrombin mutation without thromboembolic event, is there any indication to look for this deficit?

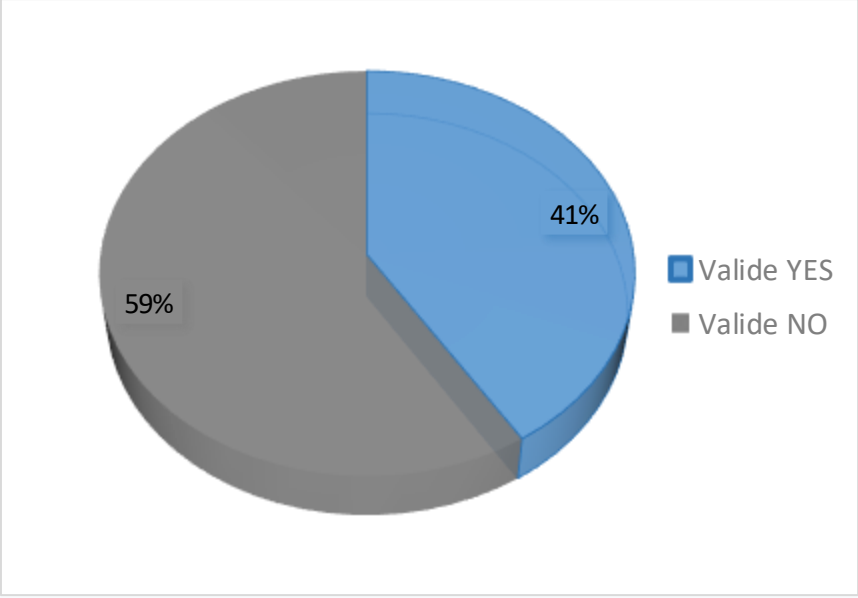

Figure 8: search for prothrombin mutation.

In the sample, 41% of doctors answered by (YES), while 59% answered by (NO).

B) Would you have carried out a thrombophilia assessment on the same patient? If you knew that her sister, a prothrombin mutation carrier, decided from a pulmonary embolism 20 years ago.

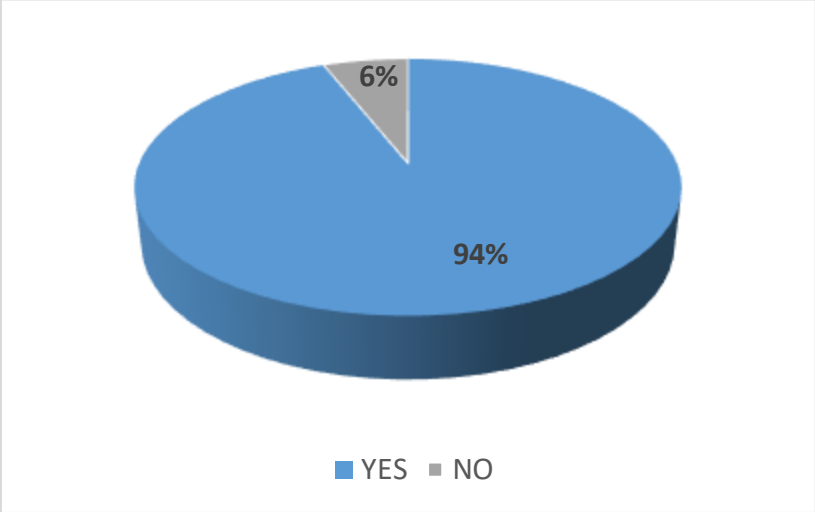

Figure 9: prescription of thrombophilia assessment

In the sample, the majority of doctors (94%) answered by (YES).

C) What assessment would you suggest to a 43-year-old patient who presented a first episode of unprovoked proximal venous thrombosis knowing that his brother is a carrier of a homozygous factor V mutation?

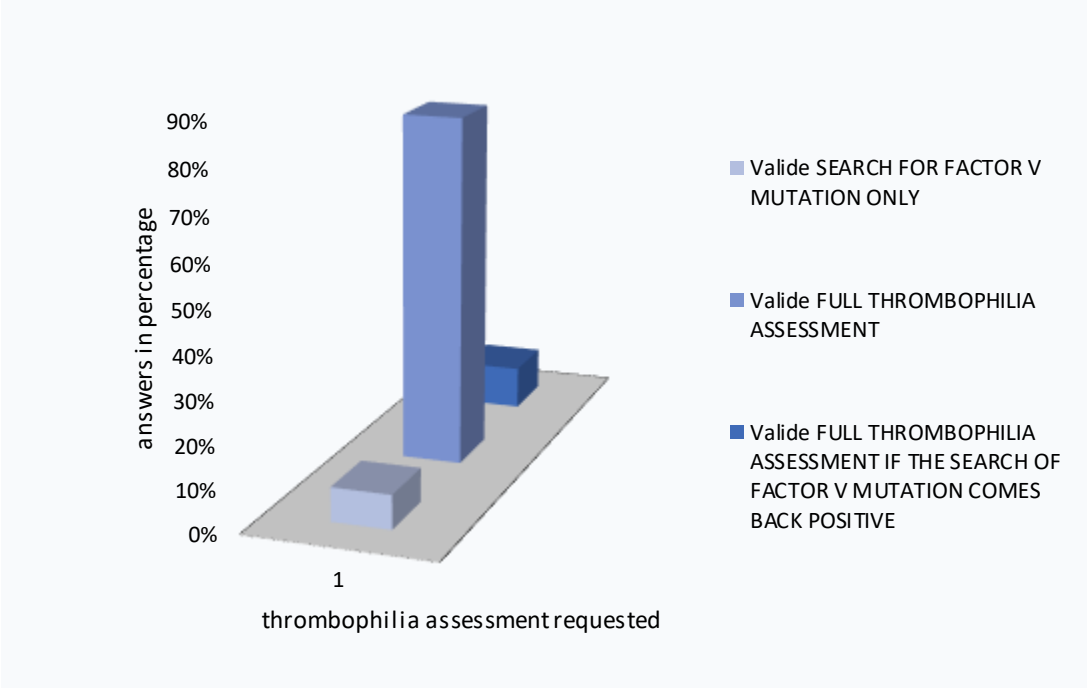

Figure 10: the most thrombophilia assessment requested.

In the sample, 82% of doctors achieve a full thrombophilia assessment.

D) Would you prescribe a thrombophilia assessment to a 15-year-old girl with no history of VTE who wants to take estrogen – progestogen pills?

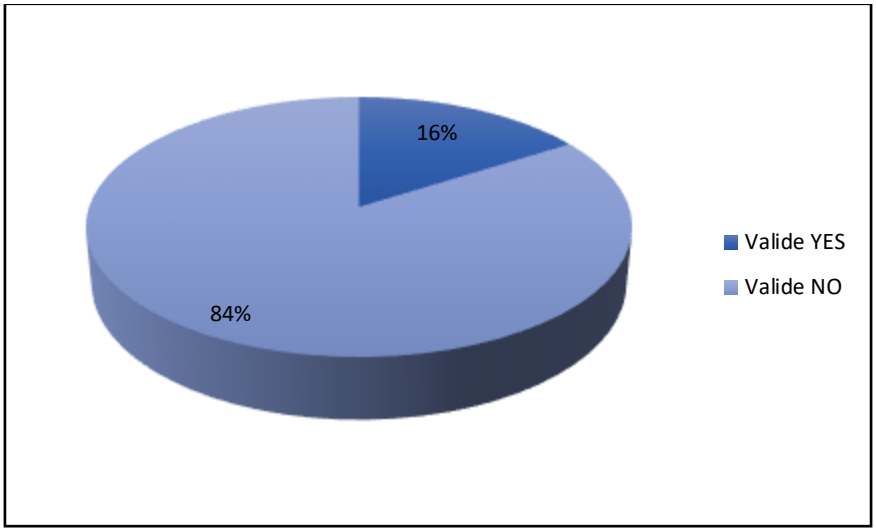

Figure 11: prescription of thrombophilia assessment before prescribing of estrogen-progestogen pills.

In the sample, the majority of doctors 84% answered by (NO).

E) In the same girl whose mother is suffering from antithrombin deficiency would you have looked for abnormalities in the thrombophilia assessment before prescribing estrogen-progestogen contraception?

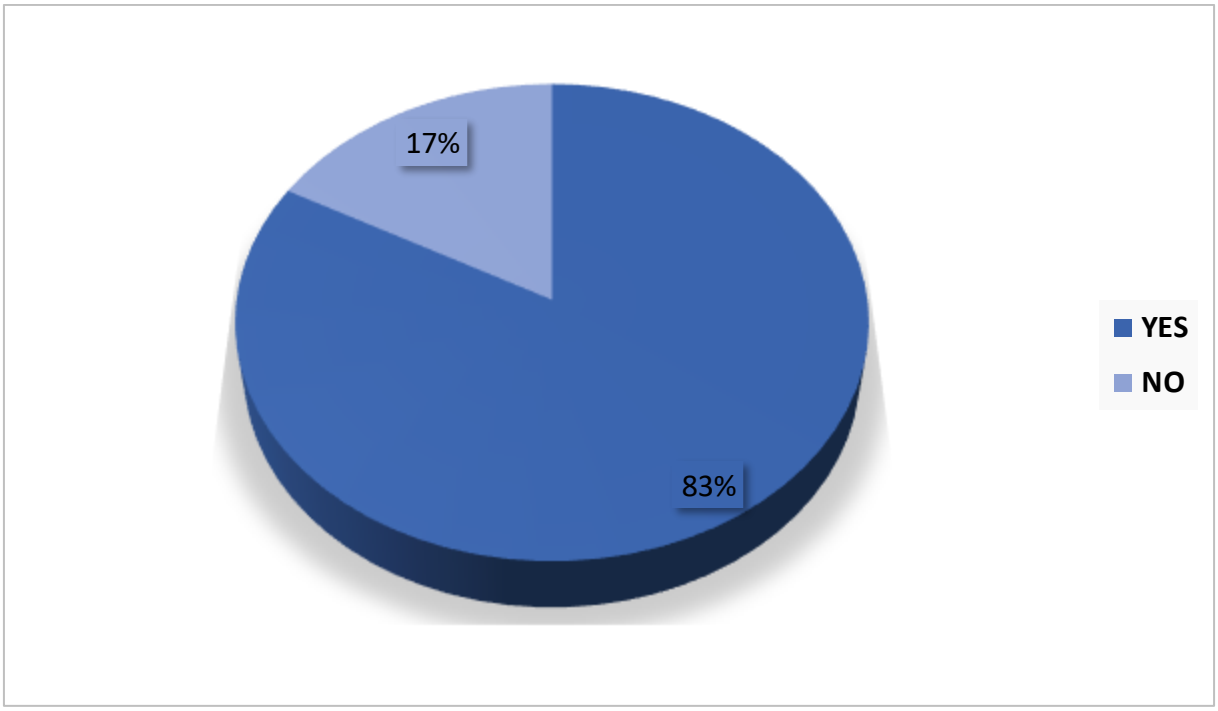

Figure 12: prescription of thrombophilia assessment before prescribing of estrogen-progestogen pills in case of antithrombin deficiency.

In the sample, 83% of doctors answered by (YES).

III - DESCRIPTION OF THE CLINICAL PRACTICE OF DOCTORS CONCERNING THE PRESCRIPTION OF ETIOLOGICAL ASSESSMENT OF VTE.

III – 1 the frequency of patient management for venous thromboembolism

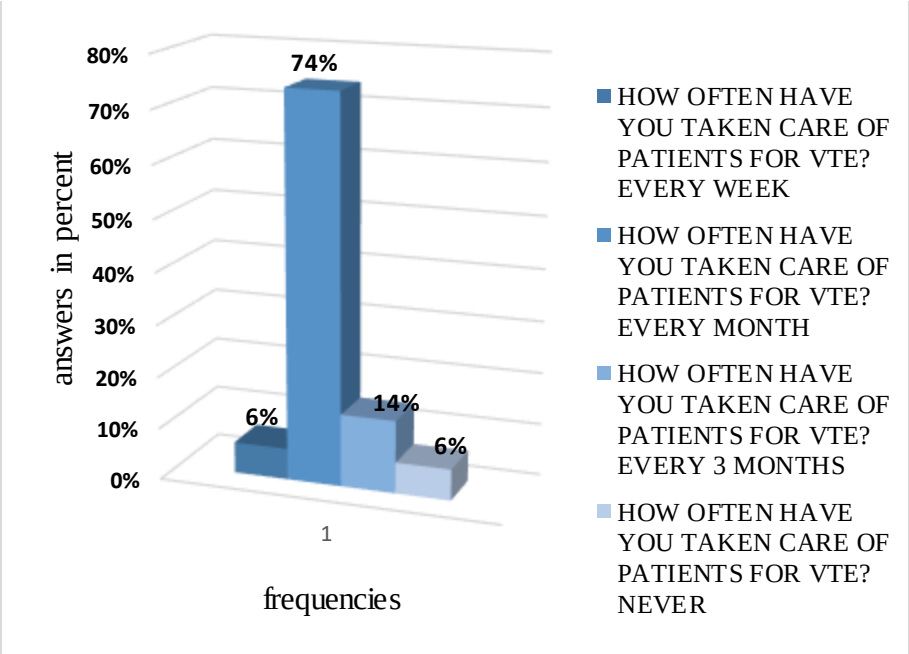

Figure 13: the frequency of patient management for venous thromboembolism

The majority of doctors in the sample were confronted every month or every 3 months with a patient presenting with a venous thromboembolic disease, respectively 74 (74%) and 14 (14%).

III – 2 Practionners Comfort with Etiological Assessment Prescription for Venous Thromboembolism (VTE).

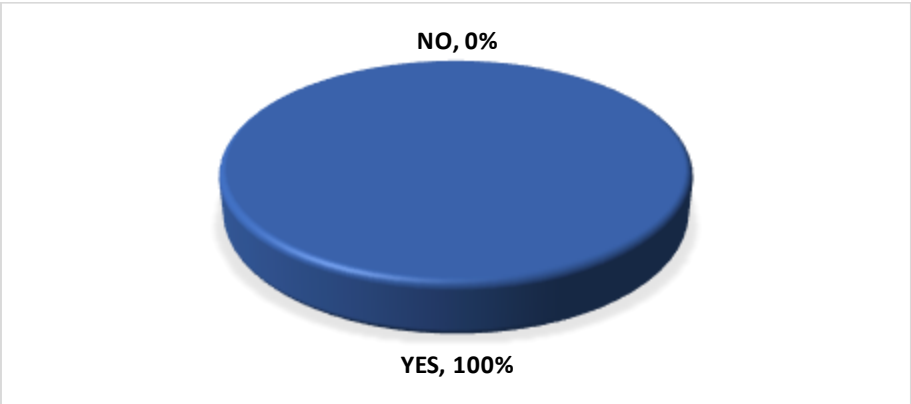

Figure 14: practionners Comfort with Etiological Assessment Prescription for Venous Thromboembolism (VTE).

All the doctors felt comfortable with the prescription of the etiological assessment of venous thromboembolic disease.

III – 3 Referring Patients with venous thromboembolism to Specialists.

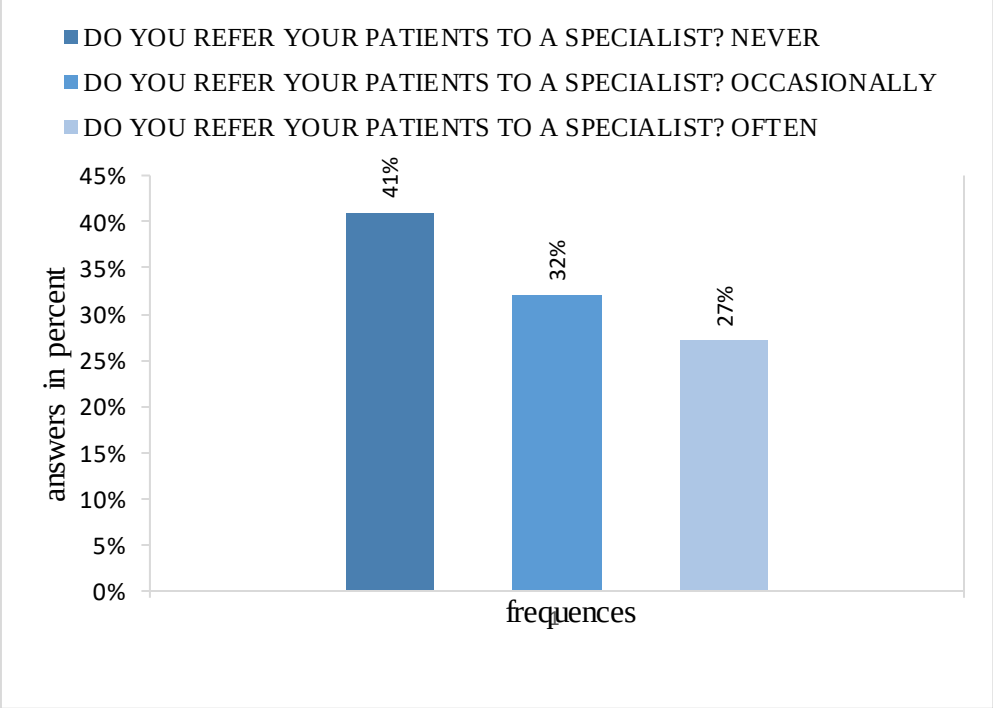

Figure 15: histogram represent the frequencies of referring patients to specialists.

In the sample, 41% of doctors didn't refer patients to a medical specialist, while 32% and 27% answered respectively by sometimes and often.

III – 4 prescription of etiological assessment for provoked VTE

Table 7: prescription of etiological assessment in the case of provoked VTE

	Frequency	Percent
YES	68	68.0%
YES EXCEPT FOR PATIENTS UNDER 30	4	4.0%
YES EXCEPT FOR PATIENT AMONG 30 YEARS	4	4.0%
NO	18	18.0%
OCCASIONALLY	6	6.0%
Total	100	100.0%

In the case of provoked VTE, 68 (68%) doctors who participated declared that they achieved an etiological assessment.

III – 5 Use of validated scores for the prediction of venous thromboembolism

Table 8: use of validated scores for the prediction of venous thromboembolism.

		FREQUENCY	PERCENT
DO YOU USE THE SCORE METHOD IN YOUR EXAMS?	YES	42	42%
	NO	58	58%
	TOTAL	100	100%

Table 9: Scoring Systems for Predicting Venous Thromboembolism.

		FREQUENCY	PERCENT
WICH SCORE YOU USE ?	PERC	0	0%
	WELLS	23	23%
	REVISED GENEVA	19	19%
	TOTAL	42	42%

In the sample, we found that 58% of doctors didn't use a validated diagnostic pathway. While 42% of doctors use a validated score, 23% for (wells) and 19% for (revised Geneva).

III – 6 search for occult cancer according to episode of VTE and age of patients

From the 100 doctors questioned, 90 (90%) searched for an occult cancer in the case of the first episode of unprovoked VTE after 50 years, whereas 84% of doctors did likewise in the case of a recurrence of VTE in patients who were using anticoagulants.

The majority of doctors agreed to look for occult cancer in cases of recurrent VTE and the first episode of unprovoked VTE beyond 50 years.

The next figure shows these results

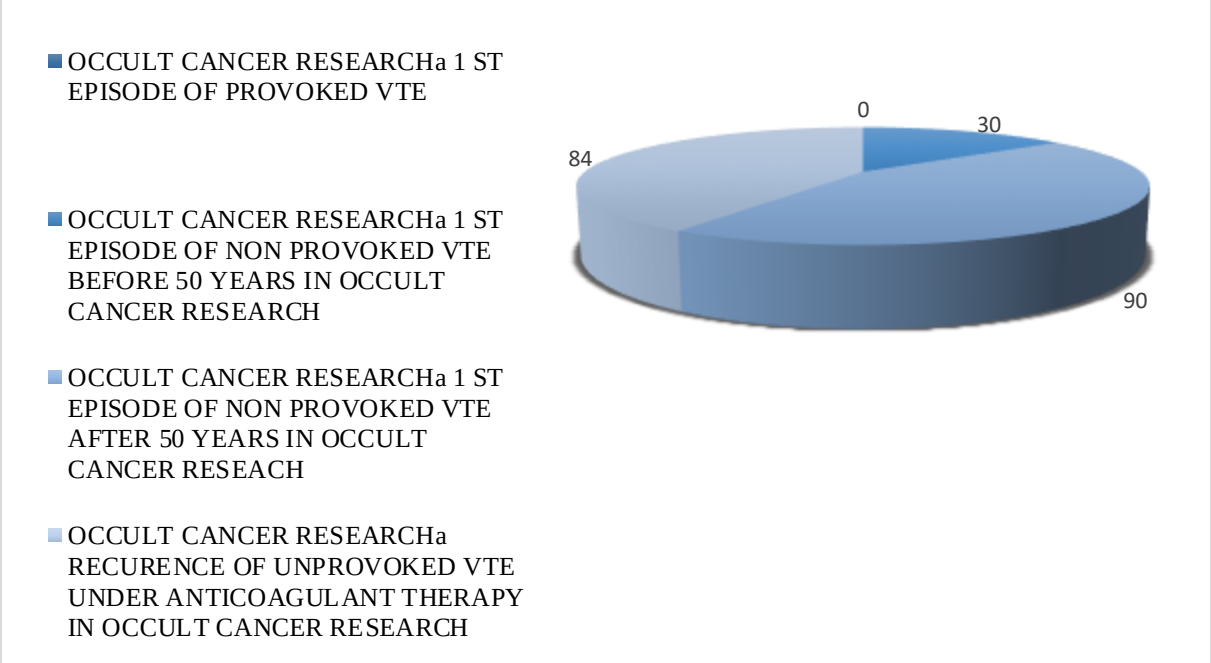

Figure 16: search for occult cancer according to episode of VTE and age of patients.

III – 7 First-line examinations done to look for occult cancer.

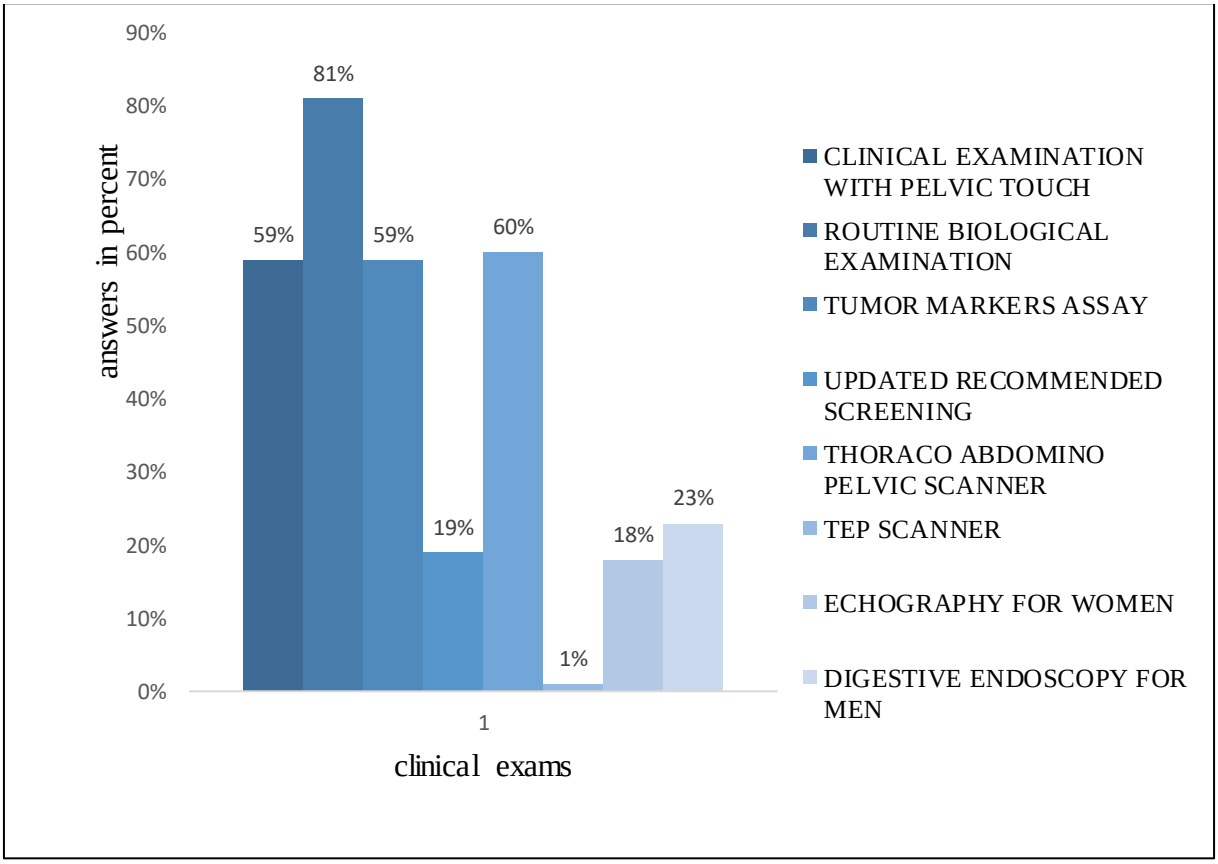

Figure 17: First-line examinations done to look for occult cancer.

To search for occult cancer, most of the doctors in the sample, 81% carried out routine biological examination as first intention, 60% carried out abdominal-pelvic scanner and 59% doctors in the sample looked for tumor markers and clinical examination with pelvic touch. Whereas, we found that a few doctors release echography for women or digestive endoscopy for men respectively 18% and 23%. Also, few doctors were updating the general public's recommended screenings

III – 8 search for thrombophilia according to episode of VTE and age of patients

Table 10: thrombophilia in patients with VTE desease.

EPISODES OF VTE	Percent
1 ST EPISODE OF PROVOKED VTE BEFOR OR AFTER 50 YEARS	37,0%
1 ST EPISODE OF UNPROVOKED VTE BEFORE OR AFTER 50 YEARS WITHOUT HISTORY OF 1ST DEGREE THROMBOSIS	15,0%
1 ST EPISODE OF UNPROVOKED VTE AFTER 50 YEARS WITH HISTORY OF 1 ST DEGREE THROMBOSIS	28,0%
1 ST EPISODE OF UNPROVOKED VTE AFTER 50 YEARS WITH HISTORY OF 1 ST DECREE THROMBOSIS	26,0%
RECURENT VTE INCLUDING AT LEAST 1 ST UNPROVOKED EPISODE	55,0%
UNPROVOKED VTE ON ATYPICAL LOCATION	17,0%

From the table (10), we found that 55% of doctors in the sample search for thrombophilia in the case of recurrent VTE, 37% of them chose first episode of provoked VTE after or before 50 years as situation to search for thrombophilia, 28% for (first episode of unprovoked VTE before 50 years with history of first degree of thrombosis), 26% for (first episode of unprovoked VTE after 50 years with history of first degree of thrombosis), 17% for (unprovoked VTE on atypical location), and 15% for (first episode of unprovoked VTE before or after 50 years without history of first degree of thrombosis).

III – 9 the parameters asked when prescribing a thrombophilia assessment

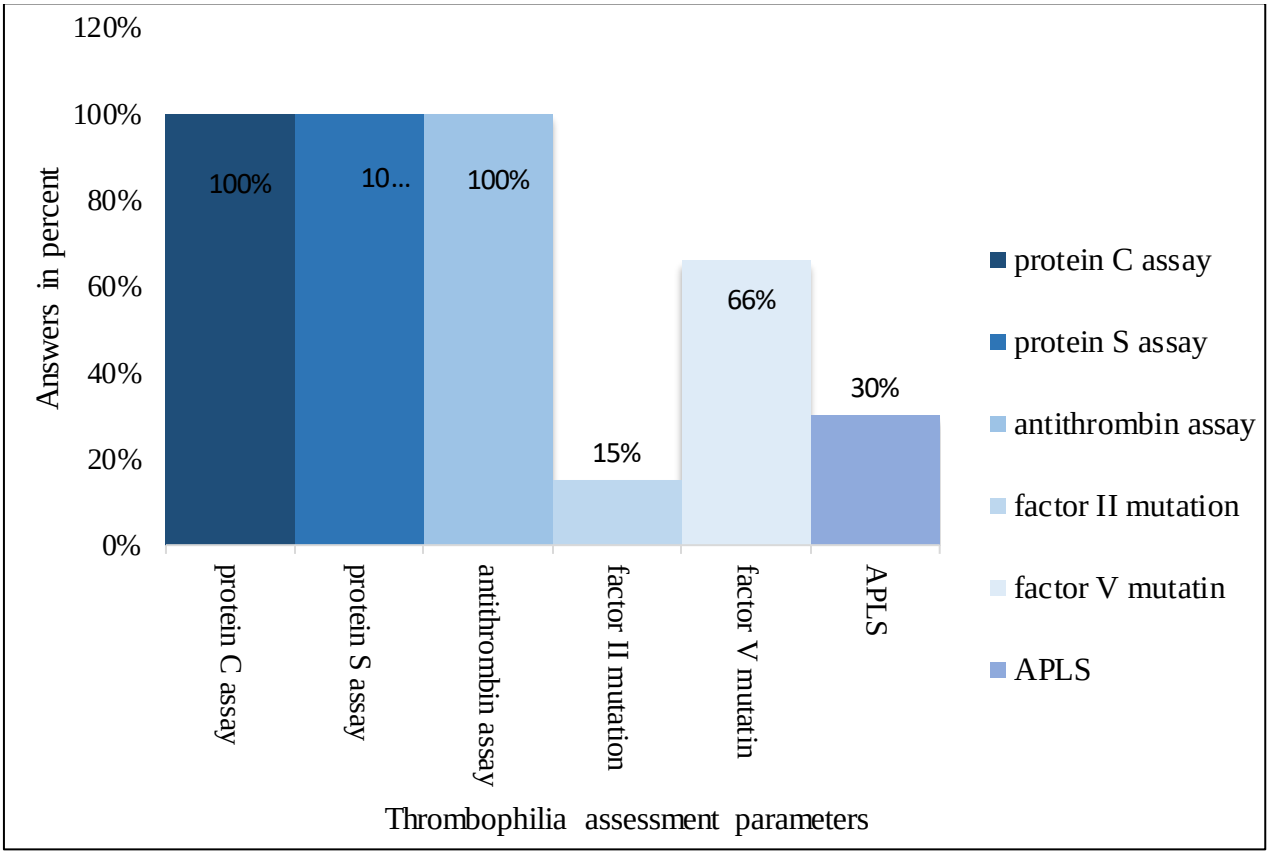

Figure 17: the parameters asked when prescribing a thrombophilia assessment.

In the sample, we found that 100% of doctors ask for the protein C, S and antithrombin dosage in the thrombophilia assessment, while 66% of them are asking for factor v mutation, 30% for APLS and only 15% of doctors ask for factor II mutation.

IV - ANALYSES ACCORDING TO THE CHARACTERISTICS OF THE DOCTORS QUESTIONED

IV – 1 According to the age

Table 11: Cross table between the knowledge of recommendation and the age.

		AGE OF DOCTORS			
		UNDER 30 YEARS	BETWEEN 30 AND 40 YEARS	BETWEEN 40 AND 60 YEARS	60 YEARS ABOVE
		Number	Number	Number	Number
DO YOU KNOW THE RECOMMANDATIONS FOR GOOD PRACTICES FOR TAKING CHARGE OF VTE	YES	19	16	12	0
	NO	24	10	15	4

The data in the table suggests that a higher proportion of doctors who are under 30 years (19 out of 47) are familiar with the recommended best practices for taking charge of VTE, as compared to doctors in other age ranges. On the other hand, all doctors who are 60 years above (4) are not familiar with the recommended best practices for taking charge of VTE, as compared to doctors in other age ranges.

IV – 2 According to the frequency of patient care

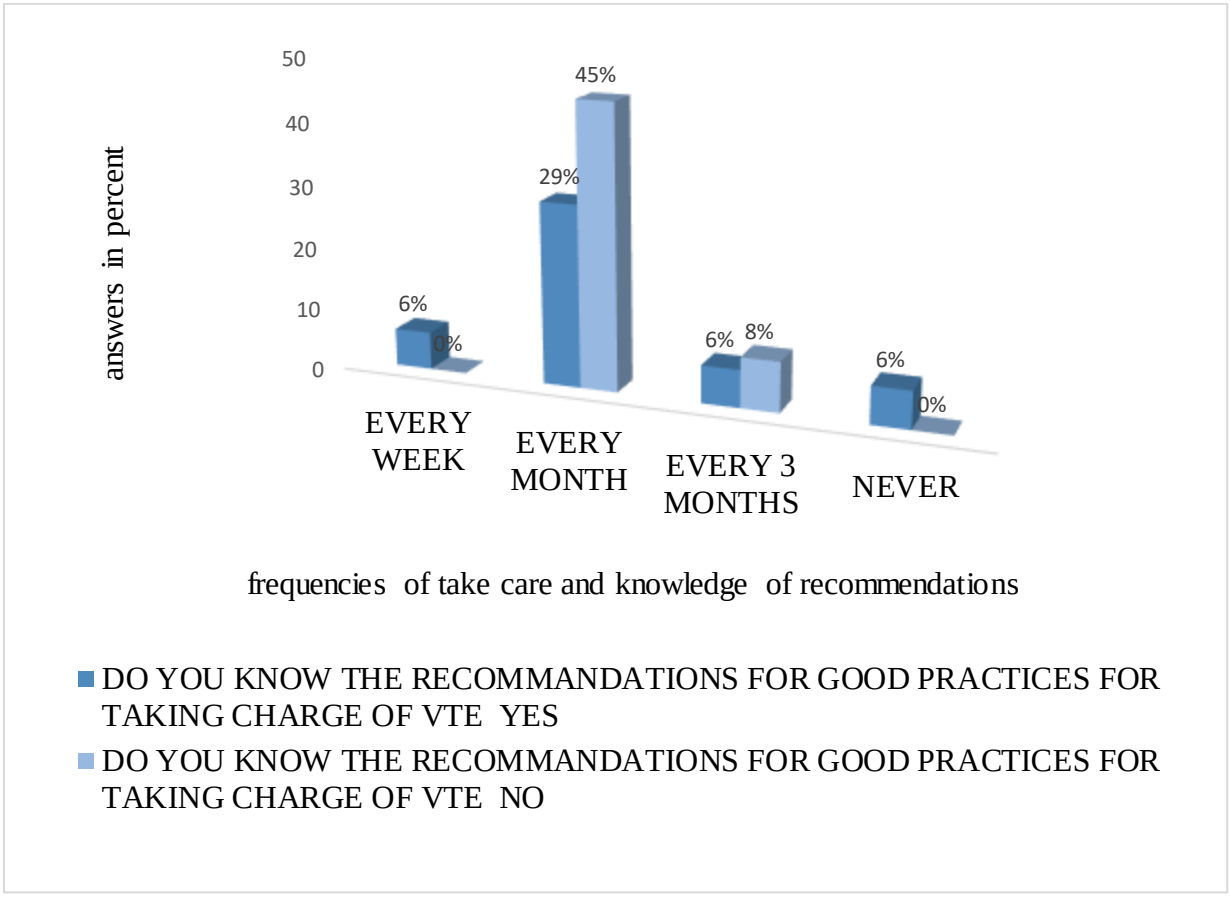

Figure 18: Frequency of patient care according to the knowledge of recommendations.

The findings of the survey suggest that a significant proportion of doctors, approximately 45%, provide care for VTE patients on a monthly basis. However, the results also highlight a knowledge gap among healthcare professionals, as a considerable number of doctors are not familiar with the recommended best practices for managing venous thromboembolism. Out of the doctors who provide monthly care for VTE patients, only 29 of them reported familiarity with the guidelines.

IV – 3 According to the exercise mode

Table 12: Cross table between the exercise mode and the knowledge of recommendations.

		EXCERCICE MODE		
		LIBERAL	HOSPITAL	MIXED
		Number	Number	Number
DO YOU KNOW THE RECOMMANDATIONS FOR GOOD PRACTICES FOR TAKING CHARGE OF VTE?	YES	17	30	0
	NO	15	16	22

The data in the table suggests that a higher proportion of respondents who exercise in a hospital setting (30 out of 46) are familiar with the recommended best practices for taking charge of VTE, as compared to respondents who exercise in a liberal setting (17 out of 32) or a mixed setting (none out of 22). On the other hand, a higher proportion of respondents who exercise in a mixed setting (22 out of 22) are not familiar with the recommended best practices for taking charge of VTE, as compared to respondents who exercise in a hospital setting (16 out of 46) or a liberal setting (15 out of 32).

CHAPTER 3: DISCUSSION

DISCUSSION

To our knowledge, no publication regarding the prescription of an etiological assessment for venous thromboembolic disease has been found in the literature. Our study aimed to gain a better understanding of the practice of specialist physicians in internal medicine, cardiology, hematology, and neurology regarding the prescription of an etiological assessment for venous thromboembolic disease, specifically in the search for occult cancer and biological thrombophilia.

I - Analysis of the population studied

Through research of articles in the literature, there are no epidemiological studies on the sociodemographic data of Algerian doctors. However, according to the estimates of the Minister of Health, the public sector has 40,000 general practitioners and 17,000 specialists. This number is sufficient to cover the health issues of the Algerian population, which is estimated to be 44 million inhabitants.[152] The Council of the Order reports a figure of 55% female practitioners and 45% male practitioners.

In fact, there were 58% women and 42% men in our study, which corresponded to the population of doctors in Algeria.

In our survey, the majority of medical practitioners are between 30 and 40 years old, with an average age of 35.95 years. This could be interpreted to mean that the medical profession in Algeria is relatively young, with a significant proportion of doctors in the early stages of their careers.

Most healthcare professionals are employed in the public sector (hospitals). This implies that the public sector is the primary employer of healthcare professionals in Algeria. That the public sector is where most of the demand for healthcare services is concentrated.

II – ANALYSIS OF THE DOCTOR'S KNOWLEDGE

II – 1 Analysis of doctor's knowledge about recommendations

The breakdown of the results based on practitioners' characteristics sheds more light on the extent of the knowledge gap regarding the 2019 recommendations for taking charge of VTE.

It is concerning that only 47% of responding doctors were knowledgeable about the recommendations, which suggests that there is a need for more widespread education and awareness initiatives targeted towards doctors. However, it is encouraging to see that knowledge varied based on the duration of practice, mode of exercise, age, and frequency of patient care, which indicates that targeted interventions may be effective in improving knowledge and adherence to the recommendations.

The finding that the recommendations were better known by doctors with less than 10 years of practice and those with 10-20 years and more than 20 years of practice, respectively (25%, 14%, and 8%) suggests that younger doctors may have received more comprehensive training on VTE prevention and management. However, it is also possible that older doctors may have had less exposure to updated recommendations or may be less likely to prioritize continuing education.

The finding that hospital doctors were more knowledgeable about the recommendations than private doctors (30% vs 17%) may be due to differences in access to educational resources or team work efficiency that can improve communication and spreading information. It is important to note that private doctors still play a critical role in VTE prevention and management, and efforts to improve knowledge and adherence to the recommendations should target all healthcare providers.

Overall, these results highlight the need for targeted education and awareness initiatives for doctors, particularly those with less experience or who work in private practice. Efforts to increase knowledge and adherence to the recommendations can help reduce the incidence and impact of VTE and improve patient outcomes. This can include continuing education programs, clinical guidelines, and quality improvement initiatives for healthcare providers, as well as public awareness campaigns and patient education materials. By addressing the knowledge gap and increasing awareness of VTE and its management, we can potentially improve patient outcomes and reduce the burden of VTE on the healthcare system.

II – 2 Analysis of doctor's knowledge about major risk factor

The most common risk factor for venous thromboembolism (VTE) observed in the study was surgery, accounting for 100% of cases. This is consistent with previous research, as surgery is a known risk factor for VTE due to the immobility that often follows the procedure.

The second most common risk factor observed in the study was pregnancy or postpartum, accounting for 73% of cases. This is also consistent with previous research, as pregnancy is known to increase the risk of VTE due to hormonal changes and decreased mobility.

The third most common risk factor observed in the study was active cancer, accounting for 76% of cases. This is also consistent with previous research, as cancer is a known risk factor for VTE due to its effect on the blood and blood vessels.

The fourth risk factor observed in the study was APLS, accounting for 93% of cases. This refers to antiphospholipid syndrome, which is an autoimmune disorder that increases the risk of blood clots. Patients with APLS are often advised to take blood-thinning medication to reduce their risk of VTE.

The final risk factor observed in the study was inflammatory bowel disease (IBD), accounting for 48% of cases. This is a less commonly recognized risk factor for VTE, but previous research has shown that patients with IBD may be at increased risk due to inflammation and other factors. Patients with IBD may benefit from taking preventive measures, such as staying active and taking blood-thinning medication, to reduce their risk of VTE.

Overall, the study highlights the importance of recognizing and addressing risk factors for venous thromboembolism. By identifying and managing these risk factors, healthcare providers can help reduce the incidence of VTE and improve patient outcomes.

Based on the results of the survey, it appears that the doctors have a good understanding of the common risk factors for venous thromboembolism. The fact that they were able to identify surgery, pregnancy or postpartum, active cancer, antiphospholipid syndrome, and inflammatory bowel disease as significant risk factors for VTE indicates that they have a solid understanding of the medical conditions that can contribute to the development of blood clots.

However, it's worth noting that the survey only covers a limited number of risk factors, and there may be other risk factors that the doctors were not asked about or did not consider. Additionally, knowledge of risk factors is only one aspect of VTE prevention and management,

and doctors also need to be aware of appropriate prevention strategies, diagnostic tests, and treatment options.

Overall, while the survey results suggest that the doctors have a good baseline understanding of VTE risk factors, it's important to continue to educate and update them on the latest developments in VTE prevention and management to ensure that they can provide the best possible care to their patients.

III – ANALYSIS OF DOCTOR'S CLINICAL PRACTICE

III – 1 Analysis of doctor's practice about the use of score method

Many doctors in our study did not use a validated scoring system for etiological assessment of venous thromboembolism (VTE), despite it being recommended in the guidelines. Instead, many doctors relied on their own experience.

Using a validated scoring system, such as the Wells score or the Revised Geneva score, can help healthcare providers more accurately assess the probability of VTE and guide appropriate diagnostic testing and treatment. Relying solely on experience may lead to unnecessary testing and treatment or missed diagnoses.

It is important to address this gap in knowledge and practice by promoting the use of validated scoring systems in clinical practice. This may require ongoing education and training for healthcare providers, as well as the development of tools and resources to facilitate the use of scoring systems in clinical practice. In addition, further research may be needed to better understand the barriers to using validated scoring systems for VTE and to develop strategies to overcome these barriers. This can help ensure that patients receive the most appropriate and effective care for VTE.

III – 2 analysis of prescription a biological thrombophilia assessment's complexity

We established 5 clinical situations, 1 multiple-choice and 4 closed, and 2 multiple choice questions in order to evaluate the prescription choices of practitioners with regard to the recommendations.

The answers being answered by prescribing practitioners, the interpretation of the results is therefore not altered and representative.

In the sample, few of the surveyed doctors were found to investigate for thrombophilia in a patients who met the criteria for thrombophilia assessment according to the 2019 recommendations. Specifically, some doctors were found to investigate biological risk factors in patients with provoked VTE or in patients over 50 years old who had experienced a first episode of unprovoked VTE with or without a first-degree family history of thrombophilia. This may be due to a lack of knowledge or understanding of the recommendations or the clinical impact of these biological risk factors.

The Connors study of 2017 showed that the risk of recurrence between provoked VTE with or without the presence of biological risk factors was identical, which suggests that thrombophilia assessment should not be performed for provoked VTE regardless of age.[153] Additionally, several studies have shown that the first episode of VTE in a population with thrombophilia mostly occurs at an age younger than 45 years old, which supports the recommendation not to perform thrombophilia assessment after 50 years old, as it does not lead to any modification of therapeutic management.[154]

Furthermore, it is recommended to perform a constitutional thrombophilia assessment in patients with recurrent venous thromboembolism (at least one episode of proximal DVT or PE and at least one unprovoked episode before the age of 50) and in patients with unprovoked venous thrombosis in atypical sites (splanchnic, upper limb, cerebral). Only 55% of the doctors in the study responded correctly to the recommendation, and only 17 doctors responded according to the latter recommendation.

The survey results indicate that some doctors are not adhering to the current recommendations for thrombophilia assessment. Specifically, the survey found that only a small percentage of doctors ordered all of the recommended tests for thrombophilia assessment, including protein C, protein S, antithrombin, factor II mutation, factor V mutation, and antiphospholipid

antibodies. This suggests that there is a gap between the guidelines and the actual practice of doctors.

Additionally, the analysis of specific cases aimed at evaluating the doctors' attitude towards investigating thrombophilia based on family history of thrombophilia showed that the majority of doctors followed the 2019 recommendations. Notably, in the case of a patient over 65 years old without thromboembolic events presenting with prothrombin mutation without thromboembolic events in the first-degree family (Cases 1 and 2), and in Cases 3, 4, and 5, which include patients with no family history of VTE or with a first-degree family history of major thrombophilia and a patient of 43 years old with a first episode of unprovoked VTE and a first-degree family history of homozygous factor V mutation.

The discrepancies between the current guidelines and the actual practice of doctors regarding thrombophilia assessment could be due to their lack of knowledge about minor and major thrombophilia's, which have different clinical and therapeutic impacts. Minor thrombophilia's are often associated with a lower risk of thrombosis, while major thrombophilia's are associated with a higher risk.[155]

Although few studies have evaluated the risk of recurrence of unprovoked MTEV based on the type of thrombophilia (major or minor),

Although few studies have evaluated the risk of recurrence of unprovoked MTEV based on the type of thrombophilia (major or minor), the study by Mean et al. demonstrated that the number of recurrences was not higher in patients with a heterozygous mutation of factor V Leiden or factor II, indicating that there is no indication for long-term anticoagulation in these patients. However, the study by De Stefano et al. showed a higher risk of recurrence of MTEV in patients with congenital deficiencies in antithrombin, protein S, and protein C, indicating the importance of screening for major thrombophilia's.

To address the knowledge gap among doctors, efforts should be made to increase awareness and adherence to the recommended thrombophilia assessment. This can be achieved through continuing medical education programs, clinical decision support tools, and electronic health record systems. Additionally, health policies and insurance coverage may need to be revised to ensure that patients have access to appropriate testing and preventive measures.

It is important to evaluate the benefit of thrombophilia screening individually, and specialized advice is necessary, especially in cases of family history, as recommended by the 2019

guidelines. By improving doctors' knowledge of thrombophilia assessment and ensuring that patients have access to appropriate testing and preventive measures, we can better identify patients at increased risk of VTE and provide them with the appropriate care.

III – 3 Analysis of doctor's practice about looking for occult cancer

In our study, we found that 100% of doctors did not perform an etiological assessment before a provoked MTEV, which was in line with the recommendations. The majority of practitioners (90%) searched for cancer according to the indications of good practices in 2019 for an unprovoked MTEV. However, regarding the exploration methods, 60 (60%) of the doctors in the sample performed a thoraco-abdominal-pelvic CT scan as a first-line test, 81% performed routine blood tests, 21% searched for tumor markers, and only 19 performed the recommended screening update.

According to the SOME study by Mac Carrier published in 2015, which evaluated the usefulness of limited screening (review of medical history, standard blood tests, clinical examination, and update of screenings such as PSA, mammography, and Pap smear) compared to intensive screening (limited screening plus a thoraco-abdominal-pelvic CT scan with virtual colonoscopy) for a first unprovoked episode of MTEV, with the primary outcome being the discovery of newly diagnosed cancer during a 1-year follow-up period. Mac Carrier found that the prevalence of cancer was low, at 3.9% (95% CI: 2.8%-5.4%), and that an intensive search for occult cancer did not significantly influence the primary outcome. However, the low incidence rate of cancer in the SOME study may be due to selection bias, as the mean age was 54 years and patients were recruited from hospitals.[156] the applicability of this trial may be limited in the general population of older and more comorbid patients seen in daily practice by general practitioners.

Furthermore, the MVTEP study published in 2016 corroborates the findings of the SOME study. This study evaluated the usefulness of intensive screening with a PET scan compared to limited screening during the 2 years following an unprovoked MTEV episode. The study found that the prevalence of cancer was low, at 6.5%, and that no difference was observed between the two screening strategies. The low incidence of cancer in the MVTEP study may be due to patient selection bias, such as the inclusion of patients under 50 years old, hospital recruitment of patients, non-exclusion of patients on oral contraceptives, patients who had recently traveled, or those who had previously had an MTEV.[157]

A meta-analysis published in 2017 reviewed data from 10 prospective studies, including the SOME and MVTEP studies with a total of 2316 patients with unprovoked MTEV, and showed that intensive cancer screening did not reduce mortality related to cancer or the frequency of cancer diagnosis compared to limited screening. This meta-analysis also showed that the prevalence of cancer was associated with age, ranging from 0.5% in patients less than 40 years old to 9.1% in those over 80 years old in 7 of the 10 studies, and 5.2% in the overall population in this study.[158] Despite possible selection biases in SOME and MVTEP studies, particularly related to hospital recruitment, which may have underestimated the incidence of cancer, the EPIGETBO study confirmed the low prevalence of cancer (i.e., 4.94%) in the year following the diagnosis of unprovoked MTEV. After the initial MTEV assessment, the incidence rate of MTEV during follow-up at one year was 2.6% in this study.[159] these results confirm that a limited strategy is preferable, as recommended by the 2019 guidelines.

In our study, the fact that 80.5% of doctors performed a thoraco-abdominal-pelvic CT scan as a first-line test highlights that the 2019 recommendations were not followed by the doctors. Furthermore, patients seen in medicine for an unprovoked MTEV are often older than in the studies mentioned above, and therefore the prevalence of cancer is likely to be higher, explaining the doctor's decision to conduct a broader search than recommended. There is thus a disparity between recommendations and daily medical practice. It is therefore worth questioning the value of studies focusing on the population seen in medicine in order to clarify the characteristics of patients seen for an MTEV in daily practice.

STRONG POINT AND LIMITS OF OUR STUDY

One potential limitation of the study is that many doctors may have been hesitant to participate, even though the survey was anonymous. This could have led to a bias in the results, as those who chose to respond may have had different attitudes and behaviors compared to those who did not participate.

Another limitation is that the study did not include demographic data on Algerian doctors, which could have provided valuable insights into how factors such as age, gender, and location may influence our demographic data discussion.

Additionally, the study was based on a declarative survey, which relied on self-reported data from the doctors. This may not accurately reflect their actual knowledge.

Lastly, during the interview process, some doctors expressed satisfaction with their experience and did not feel the need to use guidelines or recommendations. This may indicate a potential limitation in the effectiveness of guidelines or recommendations in influencing doctors' behavior and decision-making in clinical practice.

Despite the limitations of the study, it can still be considered original in the region and provide valuable insights into the use of guidelines for managing venous thromboembolism (VTE) among doctors in Algeria. The choice of the region is ideal, as many Algerian people seek medical care and diagnoses in this area.

One important finding from the study is that some doctors may have limited knowledge of the guidelines for managing VTE etiological assessment, which could impact their behavior and decision-making in clinical practice. This highlights the importance of ongoing education and support for healthcare providers to ensure that they have the knowledge and skills necessary to provide high-quality care to patients with VTE.

By identifying this gap in knowledge and behavior, the study can help to inform interventions and strategies to improve the uptake and implementation of VTE etiological assessment guidelines among doctors in Algeria. This could include the development of educational resources and training programs that are tailored to the specific needs and preferences of doctors in the region.

Overall, the study has the potential to make a contribution to the understanding of doctors' use of guidelines for managing VTE in Algeria and beyond. By addressing the limitations and building on the findings, future research can further inform and improve the quality of care for patients with VTE.

CONCLUSION AND PROSPECT

Healthcare practionners are responsible for screening, coordinating care, long-term follow-up, and therapeutic management of VTE. Etiological investigation is essential for the management of VTE and should be performed according to the 2019 recommendations, taking into account the balance of benefits and risks as well as cost-effectiveness when searching for cancer and/or biological thrombophilia.

Our study showed that doctors are aware of the indications for cancer screening, but it is often done through thoraco-abdomino-pelvic scanning or tumor marker testing, which has not demonstrated benefits compared to limited screening strategies. Few doctors think of updating recommended screenings for the general population such as PSA for all men over 50, cervical cancer screening for women aged 25 to 65, and mammography for women aged 50 to 74. This discrepancy could be due to a lack of time, resources, communication, or incentives. It could also be a result of a lack of awareness of the latest screening protocols or a lack of training on how to effectively implement them.

We have shown that doctors do not encounter difficulties in knowing when and what biological thrombophilia assessment to perform, especially when there is a family history of thrombophilia. Short training programs, including periodic seminars for specialist doctors, particularly hospital residents, could improve patient care and, in some cases, avoid unnecessary, incomplete, and/or costly thrombophilia assessments. During our study, we observed that the more junior doctors are, the better they know the 2019 recommendations, which allows them to feel comfortable with ordering etiological assessments. VTE is exacerbated by the COVID-19 pandemic. Therefore, it is important to improve access to new European or American recommendations by improving their dissemination and adapting them to the needs of Algerian doctors.

Finally, Doctors should stay up-to-date with the latest screening protocols and guidelines by attending regular training programs and continuing education opportunities. It's important to communicate effectively with patients about the importance of cancer screening, and doctors should have access to essential resources like equipment and trained staff. Limited screening strategies should be promoted, as they are effective at detecting cancer while minimizing unnecessary testing and reducing costs. Finally, regular follow-up and monitoring are critical for patients who have been diagnosed with cancer or are at high risk of developing cancer.

PROSPECT

The issue of doctors not using the guidelines for management of venous thromboembolism (VTE) and prescribing unnecessary tests is a significant concern in the region. This practice can lead to increased healthcare costs, longer hospital stays, and potentially harmful outcomes for patients.

One potential reason for this practice is a lack of awareness or understanding of the guidelines for VTE management among doctors in the region. This highlights the need for ongoing education and training for healthcare providers to ensure that they are up-to-date on the latest evidence-based guidelines and recommendations.

Another potential reason for this practice is the pressure to provide comprehensive and thorough care to patients, which may lead to the overuse of tests and procedures. This can be addressed through the development of clinical decision support tools and standardized protocols that guide doctors in their practice and promote evidence-based care.

Overall, addressing the issue of doctors not using guidelines for management of VTE and prescribing unnecessary tests requires a multi-faceted approach that involves education, training, and the development of tools and protocols to support evidence-based practice. By improving the uptake and implementation of guidelines and recommendations, healthcare providers can provide high-quality, cost-effective care to patients with VTE.

ANNEXES

ANNEX 1: Questionnaire distributed to different doctors.

PRESCRIPTION DE BILAN ETIOLOGIQUE DEVANT UN MALADIE THROMBOEMBOLIQUE VEINEUX. EVALUATION DES PRATIQUES DES MEDECINS.

L'objectif principal est d'évaluer la prescription de bilan étiologique notamment la prescription de bilan de thrombophilie et la recherche de cancer occulte.

CRITERES D'INCLUSION

Tous les médecins spécialistes ou généralistes de ces services

- ✓ ***Médicine interne***
- ✓ ***Hématologie***
- ✓ ***Neurologie***
- ✓ ***Cardiologie.***

DONNEES GENERALES

1. **Quel est votre sexe ?**

   ☐ **Homme** ☐ **Femme**

2. **Quel est votre Age ?**

   ☐ **Moins de 30 ans**

   ☐ **De 30 ans a 40 ans**

   ☐ **De 40 ans a 60 ans**

   ☐ **Plus de 60 ans**

Depuis combien de temps exercez-vous la médecine ?

☐ **Moins de 10 ans**

☐ **Entre 10 ans et 20 ans**

☐ **Plus de 20 ans**

3. **Mode d'exercice ?**

   ☐ **Libéral**

   ☐ **Hospitalière**

   ☐ **Mixte**

4. **Au cours des 6 derniers mois, à quelle fréquence avez-vous pris en charge les patients pour MTEV ?**

   ☐ **Chaque semaine**

   ☐ **Chaque mois**

   ☐ **Chaque 3 mois**

   ☐ **Jamais**

5. **Connaissez-vous les recommandations de bonnes pratiques pour la prise en charge de la maladie thromboembolique veineux chez l'adulte (SPLF 2019) ?**

   ☐ **OUI** ☐ **NON**

6. **Vous sentez vous a l'aise avec la prescription du bilan étiologique de la MTVE ?**

☐ **OUI** ☐ **NON**

7. **Adressez-vous vos patients à un spécialiste pour le bilan étiologique de la maladie thromboembolique veineux ?**

☐ **Jamais**

☐ **Parfois**

☐ **Souvent**

I) – BILAN ETIOLOGIQUE DE LA MTVE

1). En cas de MTVE provoquée prévoyez-vous un bilan étiologique ?

☐ **Oui**

☐ **Oui, sauf pour les patients de moins de 30 ans**

☐ **Oui, sauf pour les patients de plus de 65 ans**

☐ **Non**

2). Quel (s) sont les facteurs de risques majeurs de maladies thromboembolique veineux parmi les contextes cliniques suivants ?

☐ **Chirurgie, alitement, réduction de mobilité d'un membre**

☐ **Grossesse ou post partum**

☐ **Cancer actif**

☐ **Syndrome des anti phospholipides**

☐ **Maladie inflammatoires chronique de l'intestin**

☐ **Autre ……**

3). Utilisez-vous la méthode de score TEV dans votre examen ?

☐ **OUI** ☐ **NON**

4). Si oui, quel score utilisez-vous ?

☐ **Règle de PERC**

☐ **WELLS**

☐ **Genève révisé**

☐ **A partir de votre expérience**

☐ **Autre**

a)- recherche d'un cancer occulte.

1)- selon vous, dans quel (s) cas faut-il rechercher un cancer occulte ?

☐ **1 ère épisode de la MTVE provoquée**

☐ **1 ère épisode de la MTVE non provoquée avant 50 ans**

☐ **1 ère épisode de la MTVE non provoquée après 50 ans**

☐ **Récidive de la MTVE non provoquée sous traitement anticoagulant**

2)- quel (s) examen (s) de première intention faites-vous pour chercher un cancer occulte ?

☐ **Examen clinique avec toucher pelvien**

☐ **Examen biologique de routine**

☐ **Dosage marqueurs tumoraux**

☐ **Mise à jour des dépistages recommandés**

☐ **Scanner thoraco-abdomino-pelvien**

☐ **TEP scanner**

☐ **Autre ……..**

b)- Bilan de thrombophilie

1)- Selon vous dans quel (s) cas faut-il rechercher une thrombophilie ?

☐ **1er épisode de MTVE provoquée avant ou après 50 ans**

☐ **1er épisode de MTVE non provoquée avant ou après 50 ans sans antécédent de thrombose au 1er dégrée**

☐ **1er épisode de MTVE non provoquée avant 50 ans et 1 antécédent de thrombose au 1er dégrée**

☐ **1er épisode de MTVE non provoquée après 50 ans et 1 antécédent de thrombose au 1er dégrée**

☐ **MTVE récidivante dont au moins 1 er épisode non provoqué. Thrombose veineuse non provoquée de localisation atypique**

2)- Quel bilan faites-vous pour rechercher une thrombophilie ?

☐ **Dosage de l'activité de la protéine C**

☐ **Dosage de l'activité de la protéine S**

☐ **Antithrombine**

☐ **Mutation de facteur II (G20120A)**

☐ **Mutation de leiden du facteur V**

☐ **Autre ……..**

II)- CAS PARTICULIERS : BILAN DE THROMBOPHILIE.

1)- chez une patiente de 65 ans qui n'a jamais présenté de MTVE, mais sa sœur avait une mutation de la prothrombine sans évènement thromboembolique, y-a-t-il une indication à rechercher ce déficit ?

☐ **OUI** ☐ **NON**

2)- chez la même patiente, toujours asymptomatique, auriez-vous réalisé un bilan de thrombophilie en sachant que sa sœur porteuse de la mutation de la prothrombine est décédée d'une embolie pulmonaire, il y a 20 ans

☐ **OUI** ☐ **NON**

3)- quel bilan auriez-vous proposé à un patient de 43 ans ayant présenté un 1er épisode de thrombose veineuse proximale non provoquée sachant que son frère est porteur d'une mutation de facteur V homozygote ?

☐ **Recherche seulement de la mutation du facteur V**

☐ **Bilan de thrombophilie complet**

☐ **Bilan de thrombophilie complet si la recherche de la mutation de facteur V revient positive**

☐ **Aucun**

4)- prescririez-vous un bilan de thrombophilie a une fille de 15 ans ne présentant aucun antécédent, qui souhaite prendre une pilule oestro-progestative ?

☐ **OUI** ☐ **NON**

5)- chez la même fille dont la mère est atteinte D'un déficit en antithrombine, auriez-vous cherché des anomalies du bilan de thrombophilie avant de prescrire une contraception oestro-progestative ?

☐ **OUI** ☐ **NON**

III- avez-vous des commentaires ou des propositions pour améliorer la prise en charge étiologique de la MTVE en soins primaires ?

……

……

Merci pour votre réponse.

ANNEX 2: thrombophilia testing guideline.

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GUIDELINE

Thrombophilia testing: A British Society for Haematology guideline

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METHODOLOGY

This guideline was compiled according to the BSH process at [https://b-s-h.org.uk/media/16732/bsh-guidance-development-process-dec-5-18.pdf]. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org. A literature search was carried out using the terms given in Appendix S1 until April 2021.

Review of the manuscript

Review of the manuscript was performed by the BSH Haemostasis and Thrombosis Task Force, the BSH Guidelines Committee and the sounding board of BSH. It was also placed on the members section of the BSH website for comment. It has also been reviewed by Royal College of Obstetricians and Gynaecologists, Royal College of Paediatrics and Child Health, Royal College of Physicians and Thrombosis UK, a patient-centred charity dedicated to promoting awareness, research and care of thrombosis; these organisations do not necessarily approve or endorse the contents.

INTRODUCTION

This guideline updates and widens the scope of the previous British Society for Haematology (BSH) Clinical guidelines for testing for heritable thrombophilia[1] to include both heritable and acquired thrombophilia.

Abbreviations: aCL, anticardiolipin antibodies; anti-β2GPI, anti-β2-glycoprotein-I antibodies; APS, antiphospholipid syndrome; AT, antithrombin; BCS, Budd–Chiari syndrome; BSH, British Society for Haematology; CAPS, catastrophic antiphospholipid syndrome; CVADs, central venous access devices; CVC, central venous catheter; CADASIL, Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; *CALR*, calreticulin gene; CVST, cerebral venous sinus thrombosis; DOACs, direct oral anticoagulants; GEL, Genomics England Limited; GWAS, genome wide association study; ET, essential thrombocythaemia; FBC, full blood count; FVL, factor V Leiden; FGA, fibrinogen-alpha; FGB, fibrinogen-beta; FGG, fibrinogen-gamma; LA, lupus anticoagulant; MVT, mesenteric vein thrombosis; MPN, myeloproliferative neoplasms; MTHFR, methylenetetrahydrofolate reductase; NICE, National Institue for Health and Excellence; PNH, paroxysmal nocturnal haemoglobinuria; PFO, patent foramen ovale; PCR, polymerase chain reaction; PVT, portal vein thrombosis; PMF, primary myelofibrosis; ZPI, protein Z-dependent protease inhibitor; PC, protein C; PS, protein S; RVO, retinal vein occlusion; RCPCH, Royal College of Paediatrics and Child Health; *SERPINIC*, serine protease inhibitor 1C; SVT, splanchnic vein thrombosis; TFPI, tissue factor pathway inhibitor; NICE, The National Institute for Health and Care Excellence; VTE, venous thromboembolism.

The term thrombophilia is generally used to describe hereditary and/or acquired conditions associated with an increased predisposition to thrombosis. Heritable thrombophilia refers to genetic disorders of specific haemostatic proteins. These guidelines focus only on the factors that are identified from laboratory testing and therefore exclude disorders such as cancer, inflammatory conditions and obesity that are associated with thrombosis through multiple mechanisms.

The most clearly defined heritable thrombophilias are the factor V Leiden (*FVL*) variant (*F5* G1691A), the prothrombin gene variant (*F2* G20210A), protein C (PC) deficiency, protein S (PS) deficiency, and antithrombin (AT) deficiency.[2] Important acquired thrombophilias include the antiphospholipid syndrome (APS), paroxysmal nocturnal haemoglobinuria (PNH), myeloproliferative neoplasms (MPN) and the presence of a *JAK2* mutation in the absence of an MPN phenotype. Pregnancy is a hypercoagulable state due partly to physiological changes in both the coagulation and fibrinolytic systems. Heritable and acquired thrombophilias can interact to further increase the risk of thrombosis, for example during pregnancy and the puerperium. As there is evidence that some thrombophilias may be associated with pregnancy failure and complications, testing for this purpose is included.

THROMBOPHILIA TRAITS: CLINICAL SIGNIFICANCE AND MEASUREMENT OR ASSESSMENT OF DEFECTS

Procoagulant factors and risk of thrombosis

Elevated levels of procoagulant factors may increase the risk of thrombosis but the relationship is not straightforward. First, part of the variance is genetic, and therefore lifelong, but some is acquired so that comorbidities such as obesity or inflammation confound the estimate of effect. Second, some factors, most notably factor V (FV), have anticoagulant effects that counterbalance a procoagulant effect from their elevation.

A meta-analysis of 12 genome-wide association studies (GWAS) for venous thromboembolism (VTE) identified variants in *F2, F5, F11,* and *FGG* (encoding fibrinogen gamma chain) linked to thrombosis as well as non-O alleles of *ABO* which mediate their effect via elevation of von Willebrand factor (VWF) and secondarily factor VIII (FVIII).[3] This approach does not detect rare variants with functional effects increasing thrombotic risk as reported in factor IX (*F9*), factor II (*F2*) and fibrinogen-alpha (*FGA*), fibrinogen-beta (*FGB*), and *FGG*.[4–6] However, the relevance of these genetic variants to routine clinical practice is not clear at present.

A phenotypic analysis was carried out as part of the Multiple Environmental and Genetic Assessment (MEGA) case–control study of VTE. After adjustment for age and sex, levels of factors II, X, IX, XI, VIII and fibrinogen all showed a positive association with risk of thrombosis. After additional correction for FVIII levels, only FIX and FXI retained significance with odds ratios (ORs) for levels >95th centile of 1.8 (95% confidence interval [CI]: 1.1–2.9) and 1.8 (1.1–3.0), respectively. In contrast, the OR for FVIII>95th centile was 16.0 (9.7–26.3) after correction for age, sex, and all the other coagulation factors.[7] However, because of interacting heritable and acquired influences on FVIII activity, variability in levels over time, and as yet, lack of evidence of a role in the management of individuals with thrombosis or asymptomatic family members, routine testing for FVIII is not currently recommended.

Despite results from animal studies, there remains no genetic or phenotypic[8–10] evidence that variation in FXII is associated with thrombosis in humans.[11] FXIII has a complex relationship with thrombosis due to interactions with other factors and the effects of genetic variants on FXIII activity assays. Genetic studies showed that the Val24Leu variant was associated with a reduced risk of venous thrombosis (OR: 0.85; 95% CI: 0.77–0.95).[12,13]

Recommendations

- Routine testing of coagulation factors to assess the risk of thrombosis is not currently recommended (Grade 2C).

Deficiency of natural anticoagulants and risk of thrombosis

The associations of PC, PS and AT deficiencies with increased risks of VTE are well-established.[14] The degree of deficiency is variable and sensitive to assay type but in general thrombosis risk rises as soon the levels of protein C, S or AT fall below the normal range. In contrast, although tissue factor pathway inhibitor (TFPI), heparin cofactor II, and protein Z-dependent protease inhibitor (ZPI) and its cofactor, protein Z, are also natural anticoagulants, the clinical significance of genotypic or phenotypic variation in these is uncertain and testing for clinical purposes is not recommended.

Guidelines on laboratory aspects of testing for deficiencies of natural anticoagulants have recently been published by the British Society for Haematology[15] and the International Society on Thrombosis and Haemostasis.[16–18]

The risk of a first episode of VTE is increased around 15-fold in heterozygous AT deficiency.[19] Overall, the risks are similar in those with type I and type II defects with the exception of most type II heparin binding defects, which appear to have a 4-fold lower risk.[19] In contrast, homozygous heparin binding site defects appear to be associated with a high thrombotic risk.[20] Further differences within antithrombin subtypes have also been observed.[21] However, data on differences in risk between and within different subtypes are limited, and findings vary according to study design, the

population being studied (family or non-family members), and whether all or only unprovoked venous thrombotic events were included in the analysis.

In those with heterozygous PC or PS deficiency, the risk of a first episode of VTE is increased around 5–7-fold.[19,22,23] There are no clinically useful differences in thrombotic risk between type I and type II PC deficiency[15] and no clear evidence of a difference in risk between different subtypes of PS deficiency. These risks for heterozygous PC and PS deficiency are similar to or greater than those associated with *FVL* variant or *F2* G20210A variant, but deficiencies of the natural anticoagulants are much less common (population prevalence of <0.5% for each deficiency), at least in those of European origin, and contribute relatively little to the population burden of VTE.

Deficiencies of physiological anticoagulants interact with acquired risks and a transient provoking factor is present in approximately 50% of episodes of VTE in genetically predisposed individuals.[24,25] Since deficiencies of these natural anticoagulants are caused by multiple different genetic variants, clinical laboratory assessment is generally based on measurement of plasma activities or concentrations rather than molecular analysis.[15] Acquired causes of deficiencies (Table 1) should always be considered before testing and when interpreting results as, if present, it may not be possible to reliably diagnose a heritable deficiency. Acquired problems include warfarin and the potential assay-dependent impact of direct oral anticoagulants (DOACs).[15] When the decision has been made to test for deficiencies of physiological anticoagulants, this should be performed only after 3 months of anticoagulation for acute thrombosis, as there is uncertainty over the validity of the results obtained earlier, leading to repeat testing and increased costs, and with there being no evidence that it influences acute management.

Genomics England have made a panel available for "thrombophilia with a likely monogenic cause." The criteria for using this panel are[26]:

- Clinical features indicative of a likely monogenic venous thrombophilia as assessed by a consultant haematologist or clinical geneticist.
- Testing should typically be targeted at those with venous thromboembolic disease at less than 40 years of age, either spontaneous or associated with weak environmental risk factors and which is also present in at least one first degree relative.
- Testing should only be used where it will impact clinical management.

Identification of patients who fulfil these criteria is at the discretion of the responsible haematologist or clinical geneticist. The panel (R97) currently comprises 15 genes and includes *SERPINC, PROS1* and *PROC* as well as *F2, F5* and the fibrinogen genes but some of the genes have an uncertain relationship to risk of thrombosis.[27,28]

Recommendations

- Genetic testing to identify causative variants responsible for phenotypically identified deficiencies of AT, PC, PS should be performed when the results will influence management (Grade 2B).
- Testing for deficiencies of physiological anticoagulants should be performed only after 3 months of anticoagulation for acute thrombosis (Grade 2B).

TABLE 1 Factors commonly affecting measurement of protein C, protein S and antithrombin

Protein C activity Chromogenic assay	Protein S Free protein S antigen	Antithrombin activity Chromogenic assay
Physiological reduction	Physiological reduction	Physiological reduction
Neonates and children (different normal range from adults)	Neonates (Different normal range from adults)	Neonates (Different normal range from adults)
Other causes of reduction	Pregnancy and puerperium	Late pregnancy, early postpartum[a]
Vitamin K antagonists (e.g., warfarin)	Other causes of reduction	Other causes of reduction
Vitamin K deficiency	Vitamin K antagonists (e.g., warfarin)	Liver disease
Liver disease	Vitamin K deficiency	Disseminated intravascular coagulation
Disseminated intravascular coagulation	Liver disease	Nephrotic syndrome
Severe sepsis	Nephrotic syndrome	Severe sepsis
Artefactual increase	Disseminated intravascular coagulation	Recent thrombosis
DOACs or heparin if using clotting-based assay	Severe sepsis	Heparin therapy
Artefactual decrease	Recent thrombosis	L-asparaginase therapy
Factor V Leiden if using clotting-based assay	Oral oestrogen therapy (e.g., combined oral contraceptive pill or hormone therapy)	Artefactual increase
	Acute phase response	DOACs:
	Sickle cell disease	Xa inhibitors – if using Xa-based assay
	Artefactual increase	Thrombin inhibitors – if using thrombin-based assay
	DOACs or heparin if using clotting-based assay.	
	Artefactual decrease	
	Factor V Leiden if using clotting-based assay	

Abbreviation: DOAC, direct acting oral anticoagulant.

[a]James et al. 2014.[176]

FV Leiden, prothrombin gene variant and other genetic variants (except AT, PC and PS deficiency) and risk of thrombosis

The *FVL* and *F2* G20210A variants are the most commonly tested genetic variants predisposing to VTE.[29] These are detected using polymerase chain reaction (PCR)-based methods. Their prevalence varies in populations of different ethnicity. For example, heterozygosity for *FVL* is present in about 5% of individuals of European descent but is rare or absent in peoples from sub-Saharan Africa, East Asia and indigenous populations of the Americas and Australia. Similarly, heterozygosity for the prothrombin gene variant is present in 1%–2% of Europeans and is rare or absent in other ethnic populations.[30]

The *FVL* variant abolishes a cleavage site for activated PC in factor V increasing procoagulant activity. The prothrombin gene variant is a point mutation (G20210A) in the 3′ untranslated region of the gene[31] causing increased levels of prothrombin.[32] These variants result in increased relative risks for first venous thrombosis of 5- and 3-fold, respectively.[33]

A large number of variants in other genes with a wide range of prevalences have been reported to confer an increased risk of thrombosis. These include variants of methylenetetrahydrofolate reductase (*MTHFR*), *SERPINE1* (encoding plasminogen activator inhibitor type 1) (PAI-1) and factor XIII as well as variants linked to the quantitative changes in procoagulant factors discussed above.[28] However, either their association with thrombosis is not convincingly consistent or their effect is too small to alter management and they should not be included in thrombophilia panels at present. Although it has been shown that multiple variants present in an individual can combine to identify a significant risk of recurrence,[34] this requires validation and we do not yet know how and when to introduce this oligogenic model into practice.

Recommendations

- Genetic testing to predict a first episode of venous thrombosis is not recommended (Grade 2B).

Acquired genetic traits and risk of thrombosis

Paroxysmal nocturnal haemoglobinuria (PNH) and myeloproliferative neoplasms (MPN) are acquired genetic traits that increase the risk of thrombosis. PNH is an acquired clonal stem cell disorder characterised by the expansion of a population of blood cells deficient in glycosylphosphatidylinositol anchored proteins (GPI-AP) due to *PIGA* gene mutation resulting in a deficiency or absence of all GPI-anchored proteins including CD55 and CD59 on the cell surface. Absence of CD59 leads to chronic complement activation resulting in the classical clinical features of intravascular haemolysis and thrombosis.[35] Up to 10% of patients with PNH will present with thrombosis. The neutrophil clone size correlates best with thrombosis risk and patients with a clone of over 50% have a cumulative 10-year incidence of thrombosis of 34.5% compared to 5.3% in those with a clone of <50%.

MPNs are characterised by clonal expansion of an abnormal haematopoietic stem/progenitor cell and include polycythaemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). MPN or presence of a clone characterised by a *JAK2* mutation in the absence of an MPN phenotype are associated with arterial and venous thromboses.[36]

The thromboses associated with PNH and MPN can occur anywhere in the venous or arterial systems but particularly in unusual sites for example, splanchnic vein thrombosis (SVT) (which includes portal vein (PVT), mesenteric vein (MVT) and splenic vein thrombosis, and the Budd–Chiari syndrome (BCS)) and cerebral venous sinus thrombosis (CVST).[37,38] In MPN, thrombosis often precedes disease recognition. Molecular abnormalities, primarily the V617F mutation in *JAK2* exon 14, are found in 95% of PV (and an exon 12 mutation in most remaining patients) and in 60%–70% of ET and PMF patients.[39] Isolated *JAK2* mutations occur in approximately 0.1%–0.2% of the general population without an MPN phenotype and in 2.9%–5.6% of patients with CVST with no MPN phenotype[40] (Table 2). A proportion of patients positive for *JAK2* mutation with normal full blood count at presentation progressed into MPN during follow-up.[41] Mutations of *MPL* exon 10 are present in about 5% of those with ET or PMF.[42–44] In patients without *JAK2* or *MPL* mutations, 67%–71% of those with ET and 56%–88% of those with PMF are positive for a calreticulin gene (*CALR*) mutation.[45] In a study by Rumi et al. of 1235 consecutive patients diagnosed with ET or PV, the incidence of thrombosis associated with *JAK2*-mutated patients with ET and PV was similar; 7.1 and 10.5% respectively and was four times that of patients with ET and the *CALR* mutation (2.8%). The incidences of thrombosis associated with the *JAK2* exon 12 and *MPL* mutations are not well documented due to the small number of patients with these mutations.

Testing for *JAK2, CALR, MPL* variants in peripheral blood is sensitive and bone marrow samples are not required.[39] Detailed guidance on assays used for detection of *JAK2* mutations is available in separate guidelines.[46] Diagnosis of

TABLE 2 Studies investigating patients presenting with cerebral venous sinus thrombosis and *JAK2* mutation but normal full blood count

Study	CVST number	*JAK2* mutated and full blood normal count *n* (%)
De Stefano et al.[93]	45	2 (4.8%)
Shetty et al.[94]	70	2 (2.9%)
Passamonti et al.[41]	152	4 (2.6%)
Lamy et al.[95]	125	7 (5.6%)

Abbreviation: CVST, cerebral venous sinus thrombosis.

PNH is based on flow cytometric analysis using antibodies directed against GPI-AP.[47]

Recommendations

- We suggest testing for PNH in patients with thrombosis at unusual sites and abnormal haematological parameters (i.e., cytopenia and abnormal red cell indices) or evidence of haemolysis (i.e., raised lactate dehydrogenase, bilirubin and reticulocyte count) (Grade 2C).
- We recommend testing for MPN panel (including *JAK2* V617F, JAK2 exon 12, CALR, *MPL* mutation analysis) in patients with thrombosis at unusual sites and with full blood count abnormalities suggestive of a myeloproliferative neoplasm (Grade 1C).
- We suggest testing for *JAK2* mutation in patients with splanchnic vein thrombosis or CVST in the absence of clear provoking factors and a normal FBC (Grade 2C).

Acquired non-genetic traits

Antiphospholipid syndrome

The diagnosis of APS is dependent on the presence of at least one clinical feature (thrombosis or pregnancy morbidity) and at least one laboratory feature of antiphospholipid antibodies (aPL) which include lupus anticoagulant (LA), immunoglobulin (Ig) G or IgM anticardiolipin antibodies (aCL) or anti-β2-glycoprotein-I (anti-β2GPI) antibodies).[48] The aPL need to be persistent, that is, present on two or more occasions at least 12 weeks apart.[49] Of the three tests, a positive LA appears to be the most strongly associated with recurrent thrombosis, but individuals who are positive for all three assays ("triple positives") have the highest thrombotic risk.[50–52] Although the BSH guidelines (2012) on the investigation and management of antiphospholipid syndrome stated that in patients with thrombosis, measuring IgM antibodies does not add useful information,[53] both IgG and IgM aCL and anti-β2GPI are part of the international consensus on laboratory diagnostic criteria for APS.[49] There is increasing evidence that IgM anticardiolipin and anti-β2GPI antibodies have a pathogenic role in patients with APS.[54–57]

In patients with thrombotic APS, uncertainties remain as to the recurrence risk in patients with an initial unprovoked, compared to provoked, VTE and in those with venous compared to an initial arterial thrombosis.[58] There is increasing evidence that the recurrence risk of VTE provoked by minor risk factors is similar to that with unprovoked VTE.[59,60] Therefore, such patients may also benefit from extended anticoagulation therapy as in those with unprovoked VTE. As the presence of antiphospholipid antibodies may alter management including choice of antithrombotic therapy in these patients, it may be reasonable to test for antiphospholipid antibodies.

Catastrophic APS (CAPS) is a rare, but potentially fatal, variant of APS characterised by sudden onset of extensive microvascular thrombosis at multiple sites leading to multiorgan failure.[61] CAPS tends to occur usually in patients with triple positive APS. Recommendations on the timing of, and indications for, antiphospholipid antibody testing following venous or arterial thrombosis are provided in the Addendum to British Society for Haematology Guidelines on Investigation and Management of Antiphospholipid Syndrome (2020).[62]

In asymptomatic individuals with triple positive antiphospholipid antibodies (mostly identified because of a prolonged activated partial thromboplastin time or presence of an autoimmune disorder), the incidence of first thrombotic events (which were equally distributed between venous and arterial thrombosis) was estimated to be 5% per year.[52] Lower incidences of thrombosis of 1% and 0.5% annually respectively have been described in asymptomatic single antibody positive individuals and in women with the obstetric antiphospholipid syndrome.[63,64]

Recommendations

- Screening for antiphospholipid antibodies is recommended following unprovoked VTE because this may alter management including choice of antithrombotic therapy (Grade 1B).
- Screening for antiphospholipid antibodies is suggested in patients with VTE provoked by a minor risk factor as this may alter management including choice of antithrombotic therapy (Grade 2C).
- Patients with acute multiple thrombotic events and evidence of organ failure suggestive of CAPS should be tested for antiphospholipid antibodies (Grade 1A).
- As APS is an acquired thrombophilia, screening for antiphospholipid antibodies is not recommended in family members of patients with thrombosis (Grade 1A).

General guidelines on the role of thrombophilia testing

In situations where the clinical utility of testing is not clear, testing is clearly not mandatory (clinical utility is defined as the ability of a test to improve clinical outcome). It is important that patients are counselled in advance of any decision on whether or not to undertake testing. This should include discussion of the aims of testing and how it might alter management decisions.

What is the utility of identifying a heritable thrombophilic trait in a patient who has had a venous thrombotic event in modifying their future management or the management of asymptomatic family members?

The relative risk of thrombophilic traits for recurrent VTE is less than that for a first episode of thrombosis because the comparator group is different. Moreover, the

risk is managed differently, and no clinical trials have been undertaken. There are conflicting data on the association of *FVL* and *F2* G20210A variants with risk of recurrence in the overall population of patients with VTE.[33,65] Observational data suggest that *FVL* Leiden but not *F2* G20210A is associated with an increased risk of recurrence.[33,65] However, in a study with of 354 consecutive patients aged ≥65 years with a first unprovoked VTE, 9.0% of patients had *FVL* and 3.7% had a *F2* G20210A variant.[66] After adjustment for age, sex, and periods of anticoagulation as a time-varying covariate, at 3-year follow up neither the *FVL* (HR 0.98; 95% CI: 0.35–2.77) nor the *F2* G20210A mutation (HR 1.15; 95% CI: 0.25–5.19) was associated with recurrent venous thromboembolism compared to controls.[66]

Patients with natural anticoagulant deficiencies were excluded from prospective studies from which predictive models for recurrent VTE after completion of treatment for a first event were derived.[67] A meta-analysis of individuals with AT deficiency concluded the odds of recurrence were increased 2-4-fold with an absolute annual recurrence risk without long-term anticoagulant therapy of 8.8% (95% CI: 4.6–14.1) for AT-deficient and 4.3% (95% CI: 1.5–7.9) for non-AT-deficient VTE patients.[19] A further cohort study in which AT was measured in percentage points on only one occasion found the odds of recurrent VTE were increased 3.7-fold (95% CI: 1.4–9.9) in those with AT activity <70% (fifth centile 87%) and 1.5-fold (95% CI: 1.0–2.3) in those with AT activities of 70%–87%.[68]

In a prospective study of familial thrombophilia, the annual risk of recurrent VTE in patients who did not receive long-term anticoagulant treatment was 5.1% (95% CI: 2.5–9.4) in those with PC deficiency and 6.5% (95% CI: 2.8–11.8%) in those with PS deficiency.[69] In a meta-analysis, the odds of recurrent VTE were increased 2.9-fold (95% CI: 1.4–6.0) in PC deficient patients and 2.5-fold (95% CI: 0.9–7.2) in those with PS deficiency (25). At 10 years, the rates of recurrence were 31, 43 and 41% among patients with FXI activity <34th centile, between the 34th and 67th centiles, or >67th centile, respectively.[70] Patients with the highest factor VIII level category (>200 iu/dL^{-1}) had a hazard ratio for recurrence of 3.4; (95% CI: 2.2–5.3) compared to those with FVIII ≤100 iu/dL^{-1}.[71] In absolute terms this corresponded to a recurrence rate of 5% per annum compared to 1.4% per annum.

Although these effects are significant, their utility is limited. Clinical history, in conjunction with simple tests such as D-dimer in selected patients, can identify those whose risk of recurrence is high enough to warrant long-term anticoagulation and which is not lowered significantly by the absence of a thrombophilic trait. These factors also identify patients with low risk of recurrence not requiring long-term anticoagulation, even in the presence of heritable thrombophilic traits.[72–75]

There is no evidence that the presence of heritable thrombophilia influences the intensity, choice or the monitoring of anticoagulant therapy when treating thrombosis except potentially in those with AT deficiency.[76] In AT deficiency, diagnosis makes specific treatment (antithrombin concentrate) available,[77] which can be valuable and can also facilitate interpretation of laboratory monitoring of heparin. Nonetheless, this is a rare disorder and so routine testing is not advised in the absence of a strong family history (defined as two or more first-degree relatives with VTE).[78]

For patients with a strong personal and/or family history of thrombosis in the absence of a clear risk factor, genetic analysis via Genomics England Limited (GEL) is available as noted above and should be combined with phenotypic testing where available. The likelihood of detecting a genetic trait increases with the strength of the family history.[26]

The major heritable thrombophilic traits follow Mendelian inheritance albeit with variable penetrance. Levels of FVIII and FXI have clear genetic components but also significant acquired modifiers so the likelihood of relatives being affected is less certain. Identification of a heritable trait in a family member does not indicate a risk of thrombosis high enough to warrant anticoagulation and does not alter most thromboprophylaxis regimens. However, some guidelines include knowledge of heritable thrombophilic traits in their risk assessment schemes with a consequent impact on management.[79] Absence of that trait in a family member significantly reduces their risk of thrombosis but does not return it to normal and the utility of testing will depend on their personal circumstances and the circumstances of the proband's VTE event.[80,81] Overall, the recurrence risk for VTE is determined by the clinical situation (e.g., provoked vs. unprovoked) along with non-Mendelian risk factors (e.g., body mass index and age) rather than the inherited thrombophilia panel. Therefore, when a patient is known to have a heritable thrombophilic trait, it may be reasonable to consider selective testing of first-degree relatives when this will alter their management choices, for example, highly penetrant deficiencies of PC, PS or AT deficiency in a woman of childbearing age. Routine screening for *FVL* is not required in women with a first degree relative with *FVL* but no history of thrombosis (i.e., mother or siblings) prior to starting combined oral contraceptive pills or oestrogen replacement therapy.[82,83] However, the influence of family history of thrombosis, thrombophilia testing and risk of thrombosis related oestrogen-progesterone content of therapies should be discussed with all women to determine whether they will alter their therapy choices and should be documented clearly.

Recommendations

- Testing for heritable thrombophilic traits after a venous thrombotic event is not recommended as a routine to guide management decisions (Grade 2B).
- We do not recommend offering routine thrombophilia testing to first-degree relatives of people with a history of VTE (Grade 2B).

- We suggest selective testing of asymptomatic first-degree relatives of probands with protein C, protein S and antithrombin deficiency where this may influence the management and life choices depending on personal circumstances (Grade 2B).
- Genetic testing for variants in genes (e.g., *MTHFR*, *SERPINE1* variants (PAI-1plasma level)) without a clinically significant link to thrombosis is not recommended (Grade 2C).

Thrombosis in unusual sites

Investigation and management of thrombosis at unusual sites are discussed in another BSH Guideline.[84] For thrombosis at unusual sites, which often involves local or systemic conditions triggering the event, testing for thrombophilia should be reserved for selected patients with unexplained events. The association of MPN and PNH with thrombosis at unusual sites, especially SVT which includes portal, mesenteric, splenic vein thrombosis and the Budd-Chiari syndrome, has been demonstrated in many studies[85,86] and these disorders should be tested for in the absence of a clear reason for the SVT, such as abdominal sepsis, cancer or cirrhosis. Analysis of data from pooled incidence-cases found that in 19% of patients, splanchnic vein (hepatic, mesenteric, portal, splenic, inferior vena cava) thrombosis preceded the diagnosis of PNH.[87] For the remaining patients, visceral thrombosis occurred at a median of 5 years (range, 0–24) after diagnosis. Diagnosis of PNH and MPN is important because these diseases have specific treatments in addition to anticoagulation to prevent recurrent thrombosis.

In a systematic review and meta-analysis of nine small observational studies to assess the prevalence of heritable thrombophilia in patients with PVT and BCS (total 4 studies), the pooled prevalence of AT, PC, and PS deficiencies were 3.9, 5.6, and 2.6% in PVT, and 2.3, 3.8, and 3.0% in BCS, respectively. Only three studies compared the prevalence of heritable thrombophilia between PVT patients and healthy individuals. The pooled odds ratios of heritable AT, PC and PS deficiencies for PVT were 8.89 (95% CI: 2.34–33.72, $p = 0.0011$), 17.63 (95% CI: 1.97–158.21, $p = 0.0032$), and 8.00 (95% CI: 1.61–39.86, $p = 0.011$), respectively.[88] These studies are only for the first thrombotic event and the risk of recurrent events associated with heritable thrombophilia and thrombosis at unusual sites is not well established but seems to be low. Therefore, the value of testing for heritable thrombophilia is unknown and testing should be considered only if the thrombotic event occurs in the absence of a clear risk factor for the index event at a young age (median ~46 years).[88]

CVST is a rare entity accounting for <1% of all strokes.[89] The majority (85%) of CVST patients will have an identifiable risk factor, the most common of which are oestrogen-containing oral contraceptive use and pregnancy.[90] Other rare causes that can contribute to CVST include APS, vasculitis, MPN, PNH, chronic inflammatory disorders, and local factors such as infection, malignancy, trauma or surgery.[90] CVST is reported in 2%–8% of patients with PNH[91,92] and around 3.8% of patients with MPN.[93] Around 2.6%–5.6% of patients diagnosed with CVST are found to have a *JAK2* mutation with normal full blood count at presentation[41,94–96] (Table 2). CVST are reported in 2% to 8% of patients with PNH.[90,97–99] However, it is not clear how many of these patients had a normal full blood count at presentation with CVST.

Several studies have shown the presence of aPL increases the risk of thrombosis at unusual sites such as SVT and CVST.[100,101] As the type and duration of anticoagulation are affected by the presence of antiphospholipid antibodies, testing for these antibodies is recommended in an updated BSH guideline.[62] In the absence of a clear risk factor, patients with CVST may need long-term anticoagulation and routine testing for heritable thrombophilia is not required.

There is no evidence to suggest an association of heritable thrombophilia with retinal vein occlusion (RVO). The pathogenic role of antiphospholipid antibodies in RVO is uncertain. A meta-analysis of 11 studies showed that presence of antiphospholipid antibodies was significantly associated with incidence of RVO (OR = 5.18, 95% CI: 3.37, 7.95).[102] A more recent study that included 331 consecutive patients with RVO and 281 controls, also showed that antiphospholipid antibodies were more prevalent in RVO-patients than in controls (33, 10% vs. 12, 4.3%; OR 2.47; 95% CI: 1.25–4.88; $p = 0.009$) with RVO-APS patients having more frequently lupus anticoagulant or triple positive antiphospholipid antibody than controls.[103] Testing for aPL may be considered in patients without local risk factors and no other explanation for RVO such as diabetes, hypertension, and hpercholesterolaemia as those with persistently positive aPL would be considered for anticoagulation.

Recommendations

- We do not recommend testing for heritable thrombophilia in patients with thrombosis if the only indication is thrombosis at an unusual site because the association is weak, and management would not be changed by their presence (Grade 2B).
- We recommend testing with MPN panel in patients with thrombosis at unusual sites with full blood count abnormalities suggestive of a myeloproliferative neoplasm (Grade 1C).
- We suggest genetic testing with *JAK2* mutation in patients with splanchnic vein thrombosis or CVST in the absence of clear provoking factors and a normal FBC (Grade 2C).
- We recommend testing for antiphospholipid antibodies in patients with thrombosis at unusual sites in the absence of clear provoking factors as the type and duration of anticoagulation are affected by the presence of these antibodies (Grade 1A).

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