PREVALENCE OF THROMBOPHILIA MARKERS IN PATIENTS WITH SPONTONEOUS PERIPHERAL THROMBOTIC EVENTS

By

DR. AHSAN V P

Dissertation submitted to the National Board of Examinations, New Delhi.

In partial fulfillment of the requirements for the degree of

DNB Super-specialty

In

PERIPHERAL VASCULAR AND ENDOVASCULAR SURGERY

Under the guidance of

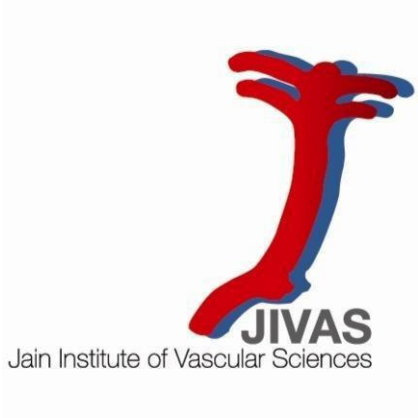
DR. VIVEKANAND

MBBS, MS (Gen Surgery), Fellowship in Vascular and Endovascular surgery,
Head of Department & Consultant in Vascular Surgery
at Jain Institute of Vascular Sciences, Bhagwan Mahaveer Jain Hospital

Bhagwan Mahaveer Jain Hospital
Bangalore – 560052 Karnataka
2021

PREVALENCE OF THROMBOPHILIA MARKERS IN PATIENTS WITH SPONTONEOUS PERIPHERAL THROMBOTIC EVENTS

Dissertation submitted to the National Board of Examinations, New Delhi, in partial fulfilment of the requirements for the award of the Diplomate of National Board in the super specialty of Peripheral Vascular Surgery



December 2021 **Dr. AHSAN V P**

Jain Institute of Vascular Sciences (JIVAS),
(A unit of Bhagwan Mahaveer Jain Hospital),
Bengaluru

DECLARATION CUM UNDERATKING FOR FRESH THESIS

I Dr. Ahsan V P, hereby declare that this thesis entitled **"PREVALENCE OF THROMBOPHILIA MARKERS IN PATIENTS WITH SPONTANEOUS PERIPHERAL THROMBOTIC EVENTS"** is 'bonafide' in nature and was carried out by me under the guidance and supervision of my guide Dr.Vivekanand. The interpretations put forth are based on my reading and understanding of the original texts and they are not published anywhere in the form of books, monographs or articles. The other books, articles and websites, which I have made use of are acknowledged at the respective place in the text. For the present thesis, which I am submitting to the National Board of Examinations, New Delhi, no degree or diploma or distinction has been conferred on me before elsewhere.

Place: Bengaluru

Date: 30-12-2021

Candidate Name: Dr Ahsan VP

Specialty:DNB- Peripheral Vascular Surgery

Registration Number: 333-27112-192-225221

COUNTERSIGNED & VERIFIED

Dr. Vivekanand, MBBS, MS, FVES
Head of Department
Jain Institute of Vascular Sciences
A Unit of Bhagwan Mahaveer Jain Hospital
Millers Road, Vasanthnagar
BANGALORE - 560 052

Dr. (Wg Cdr) M.D. Marker
Medical Director
BHAGWAN MAHAVEER JAIN HOSPITAL
Bangalore-560 052

Guide Name: Dr Vivekanand

Guide Designation: HOD,
Consultant Vascular Surgeon

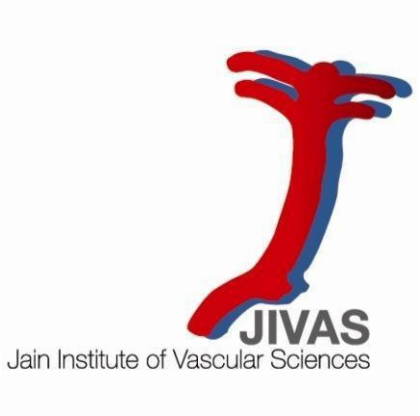
Institution: Jain Institute Of Vascular Sciences

HOI Name: Dr (Wg Cdr) M.D.Marker

HOI Designation: Medical Director

Institution: Bhagawan Mahaveer Jain Hospital

DECLARATION BY TE CANDIDATE



I hereby declare that this dissertation titled **"PREVALENCE OF THROMBOPHILIA MARKERS IN PATIENTS WITH SPONTONEOUS PERIPHERAL THROMBOTIC EVENTS"** is a bonafide and genuine research work carried out by me under the guidance and supervision of **Dr. VIVEKANAND**, HOD & Vascular surgeon, Jain Institute of Vascular Sciences (JIVAS), Bhagwan Mahaveer Jain Hospital, Bengaluru, in partial fulfilment of the requirement of National Board of Examinations regulation for the award of the Degree of DNB in Peripheral Vascular Surgery.

This has not formed the basis for the award of any degree or diploma me before and I have not submitted this to any other university or board previously.

Date: **Dr. Ahsan VP**

Place: Bengaluru

CERTIFCATE

This is to certify that the dissertation titled **"PREVALENCE OF THROMBOPHILIA MARKERS IN PATIENTS WITH SPONTONEOUS PERIPHERAL THROMBOTIC EVENTS"** is a bonafide research work done by **Dr. AHSAN VP, MBBS, MS (Gen surgery)** under my guidance at Jain Institute of Vascular Sciences (JIVAS), a unit of Bhagwan Mahaveer Jain Hospital, Bangalore in partial fulfilment of the requirement of National Board of Examinations regulation for the award of the degree of DNB in super specialty of ***Peripheral Vascular Surgery.***

DR. VIVEKANAND

MBBS MS

FVES

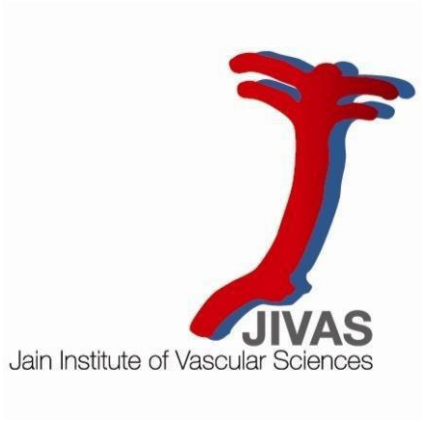
Head of the department and

Consultant Vascular Surgeon,

Jain Institute of Vascular Sciences

(JIVAS), Bangalore.

CERTIFICATE



This is to certify that the dissertation titled **"PREVALENCE OF THROMBOPHILIA MARKERS IN PATIENTS WITH SPONTONEOUS PERIPHERAL THROMBOTIC EVENTS"** is a bonafide research work done by Dr. AHSAN VP, MBBS, MS (Gen surgery) under my guidance at Jain Institute of Vascular Sciences (JIVAS), a unit of Bhagwan Mahaveer Jain Hospital, Bangalore in partial fulfilment of the requirement of National Board of Examinations regulation for the award of the degree of DNB in super specialty of *Peripheral Vascular Surgery.*

DR. K.R.SURESH
MBBS, DABS, FACS

Director and Consultant Vascular Surgeon,

Jain Institute of Vascular Sciences (JIVAS),
Bangalore.

CERTIFICATE

This is to certify that the dissertation titled **"PREVALENCE OF THROMBOPHILIA MARKERS IN PATIENTS WITH SPONTONEOUS PERIPHERAL THROMBOTIC EVENTS"** is a bonafide research work done by **Dr. AHSAN VP, MBBS, MS (Gen surgery)** under my guidance at Jain Institute of Vascular Sciences (JIVAS), a unit of Bhagwan Mahaveer Jain Hospital, Bangalore in partial fulfilment of the requirement of National Board of Examinations regulation for the award of the degree of DNB in super specialty of ***Peripheral Vascular Surgery.***

Dr. (Wg Cdr) M.D. MARKER

Medical Director,

Bhagwan Mahaveer Jain Hospital

Bangalore

ACKNOWLEDGEMENTS

During this journey of the compilation of my thesis, I have been helped, supported and encouraged by many, and I am feeling short of words to express my gratitude towards them.

I consider myself lucky to have **Dr. Vivekanand,** Head of the Department, Consultant Vascular Surgeon, Jain Institute of Vascular Sciences (JIVAS), as my supervisor and mentor. He has been a great teacher and a splendid personality. His clinical acumen, surgical skill and wisdom are well known and unparalleled. I will always cherish the time I spent under his guidance. He is, and will always remain as a source of inspiration for me.

I am extremely thankful to my co-supervisors **Dr. K.R. Suresh,** Director, JIVAS and **Dr. (Wg Cdr) M.D. Marker**, Medical Director, Bhagwan Mahaveer Jain Hospital for their helping attitude and invaluable guidance that has helped me bring this work to its logical conclusion.

I express my sincere thanks to **Dr. Vishnu Motukuru, Dr Sumanth Raj B, Dr. Indushekar, Dr. Mamatha S H,** and **Dr. Girija,** Consultants, JIVAS for their valuable help and the encouragement and support they provided me, during my work.

I am very grateful to my family for their encouragement, constant love and affection towards me.

I express my gratitude for the generous help and cooperation provided to me by my seniors **Dr Nishan, Dr. Vishal., Dr. Siva**

Krishna, and my colleagues **Dr. Surya Kiran I and Dr. Pavan** in completing my work. I would like to express my gratitude to all our department staff Mrs. Deepa, Mr Ashok, Mrs. Prema, Mrs. Sumati , Mrs. Hema, Mrs. Sophia, Mr. Sunil, Mr. Uday and Mr. Albert for their help in maintaining patient records and for data collection.

I am thankful to all my dear friends for the constant, unconditional support and inspiration which I received from them. All my friends were very co-operative and always helpful to me.

I sincerely thank all the patients who were part of the study for their cooperation

Place: Bengaluru
December, 2021

LIST ABBREVIATIONS

APCR	Activated Protein C Resistance
DIC	Disseminated Intravascular Coagulation
DVT	Deep Vein Thrombosis
EPCOT	European Prospective Cohort on Thrombophilia
HRT	Hormone Replacement Therapy
Lp [a]	Lipoprotein a
MTHFR	Methylenetetrahydrofolate reductase
OC	Oral Contraceptive
VTE	Venous Thromboembolism

CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Abstract

Objective: To determine the prevalence of positive thrombophilia marker/s in inpatients evaluated for spontaneous peripheral vascular thrombotic events at Jain Institute of Vascular Sciences, A unit of Bhagwan Mahaveer Jain Hospital.

Method: It was a single centre prospective observational study. During the study period of 18 months patients who were admitted with spontaneous peripheral – venous, arterial, both venous and arterial – thrombotic events and willing to undergo thrombophilia work up were recruited into the study. The work up included Factor V Leiden gene mutation (R506Q), Prothrombin gene mutation (G20210A), MTHFR gene mutation (C677T), Antiphospholipid syndrome, Hyperhomocysteinemia, Increased fibrinogen levels, Increased factor VIII levels, Increased factor IX levels, Increased factor XI levels Antithrombin deficiency, Protein C deficiency and Protein S deficiency.

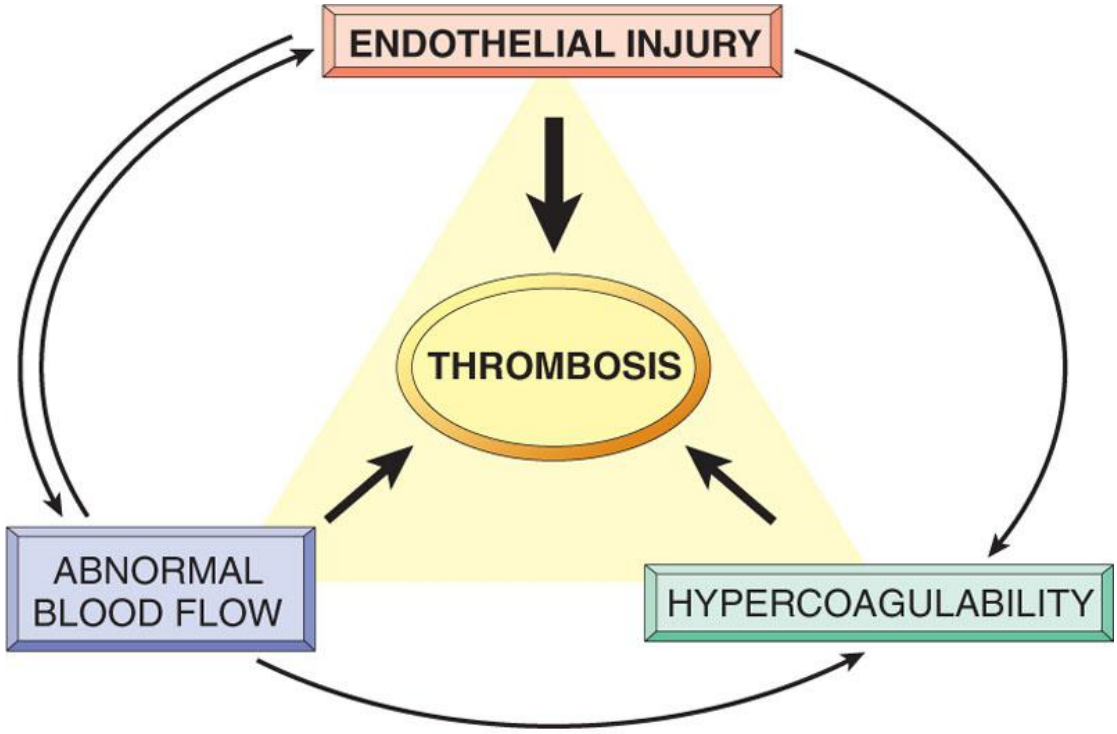
Result: During the study period 48 patients with unprovoked DVT, four patients with spontaneous arterial thrombosis, and two patients with both arterial thrombosis and DVT – total 54 patients – underwent thrombophilia work up. 62.96% (34 out of 54) of the patients had at least one thrombophilia marker positivity, with Hyperhomocysteinemia as the commonest marker 42.6% (23 out of 54), followed by Lupus anticoagulant 22.2% (12 out of 54), followed by increased Fibrinogen levels 18.5%, Increased Factor IX levels 11.1%, increased Factor VIII levels 9.2%. Other rare positive thrombophilia markers were as follows Cardiolipin Antibody IgM in one patient, Homozygous MTHFR mutation in one patient and increase factor XI level in three patients (5.6%). Other insignificant positive thrombophilia markers were Heterozygous MTHFR gene mutation in five (9.2%) patients, Heterozygous Factor V Leiden gene mutation in four (7.4%) patients, Antithrombin and Protein C deficiency in five and four patients respectively. All patients in the study population were tested negative for Beta 2 Glycoprotein, Protein S deficiency and Prothrombin gene mutation.

Conclusion: Selective testing of thrombophilia markers in patients with spontaneous / unprovoked peripheral thrombotic events is strongly recommend in view of above findings. Thrombophilia work up in the acute setting is an equally effective alternative in comparison to standard timing of thrombophilia work up as per different societal guidelines – that is after completion acute phase of illness and anticoagulation treatment course duration – especially with the poor long term follow up in Indian patient population and similar situation in other developing countries.

INTRODUCTION

Introduction

In the latter half of 19th century, the great German pathologist, Rudolf Virchow, proposed the concept of *Virchow's triad. As* He described thrombosis occurred when the following triad were present; vascular wall injury, stasis or abnormal blood flow , and changes in the consistency of blood (hypercoagulability).



Inherited and acquired thrombophilia increases the risk of thromboembolism. Determining whether a thrombophilia test is indicated and choosing the correct test from many available options is challenging. In most cases, the results of a thrombophilia test do not affect patient management. In addition, guidelines are not uniform as to when testing is appropriate. Moreover, testing for thrombophilia is costly. Unnecessary testing can cause harm to patients, particularly via the use of inappropriate anticoagulant therapy which increases the risk of bleeding or can give false assurance if negative. Moreover, many tests are affected by the acute phase of thrombosis and/or the presence of anticoagulation at the time of testing. Given the costliness and potential harm to patients due to inappropriate thrombophilia testing

and the lack of data from a Indian hospital setting, we conducted a prospective study to identify the incidence thrombophilia markers in spontaneous peripheral thrombotic events.

Though testing for inherited and acquired thrombophilia is often reflexively performed, the correct timing, appropriate utilization, and implications of such testing is poorly understood. The data are inconsistent and limited regarding the appropriate use of thrombophilia evaluation.

The prevalence of thrombosis is higher in individuals with a personal and/or family history of thrombosis than in the general population. Although patients with hypercoagulable risk factors are at a great risk for developing a thrombotic event, not all patients with hypercoagulable risk factors will develop clinically relevant thrombosis; conversely, not all patients with thrombosis will have an identifiable hypercoagulable state

AIMS AND OBJECTIVES

Aim

To determine the prevalence of factors predispose to thrombophilia in patients evaluated for spontaneous peripheral vascular thrombotic events at Jain Institute of Vascular Sciences.

Objectives

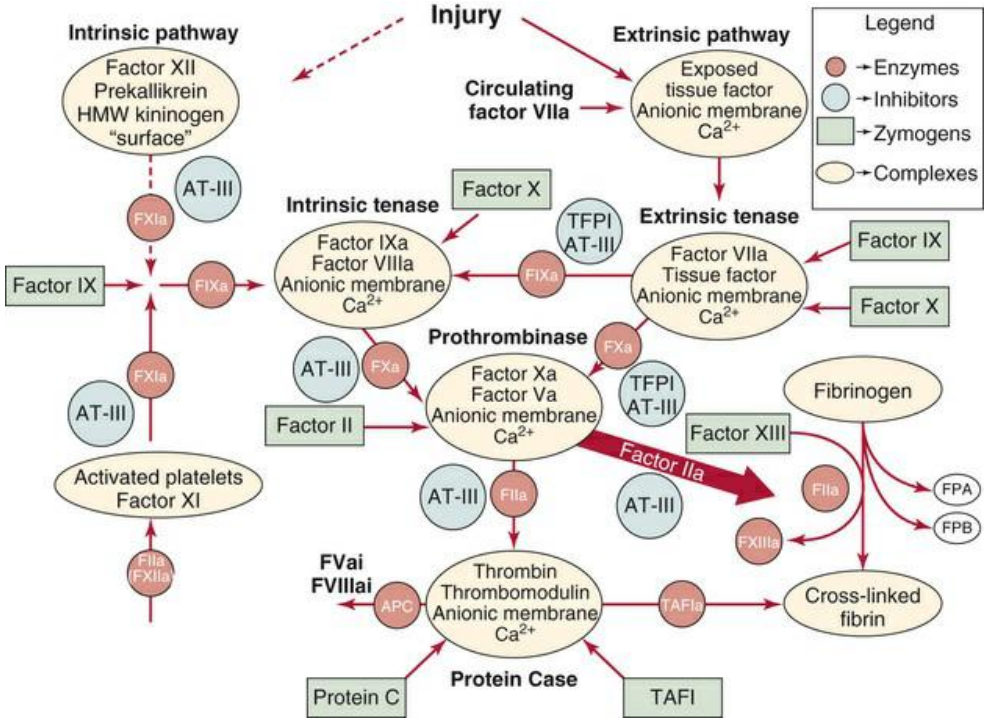
To identify positive thrombophilia marker/s in the study population.

REVIEW OF LITERATURE

Review of literature

In the last four decades, multiple inherited and acquired haemostatic disorders have been identified that are associated with an increased risk of venous and/or arterial thrombosis. The interactions of these hypercoagulable defects, alone or in combination, or when combined with other transient factors, such as vascular injury from surgery or trauma, can result in a significant increased risk of thrombosis.

The interaction between inherited hypercoagulable defects and acquired additional factors, such as age or acute illness, can result in what has been termed an increased "thrombosis potential," which, upon reaching a "thrombosis threshold," can result in symptomatic thromboembolism[1].



Overview of hemostasis. Two pathways can be used to initiate coagulation: the primary extrinsic pathway (shown on the right) and the intrinsic pathway (shown on the left). *AT,* Antithrombin; *HWM,* high-molecular-weight; *TAFI,* thrombin-activatable fibrinolysis inhibitor; *TFPI,* tissue factor pathway inhibitor. (Modified from Brummel-Ziedins K, et al. In: Lee GR, et al, eds. *Wintrobe's Clinical Hematology*. 11th ed. Philadelphia: Lippincott Williams & Wilkins; 2003: Chapter 21.)

Hemostasis is a highly organized series of reactions involving platelet adhesion and activation to form the platelet plug, followed by activation of

coagulation proteins in a series of controlled enzymatic reactions to generate thrombin. Thrombin potentiates platelet aggregation and activation, and acts on fibrinogen to generate the insoluble fibrin clot. Under normal conditions, these reactions occur on the endothelial surface only at sites of endothelial injury. This limits the size of the clot and allows blood to remain liquid and flowing. When this balance is altered, excess thrombin is generated, and abnormal thrombosis may occur. Therefore, thrombosis can result from defects in normal hemostasis that either increase the procoagulant activity or decrease the naturally occurring anticoagulants. These hypercoagulable defects have been termed thrombophilic syndromes and have been further classified as either congenital or acquired thrombophilias[1,2].

In addition, there is a group of other disorders whose prothrombotic mechanisms are poorly understood. These include elevations of homocysteine (hyperhomocysteinemia) and lipoprotein (a) (Lp[a]). The management of patients with thrombosis with these disorders remains controversial[3–9].

Arterial thrombosis, unlike VTE, is associated with conditions that primarily affect the vascular wall and endothelium. Endothelial disruption, which occurs with atherosclerosis, vasculitis (vascular inflammation), infection, trauma, or surgery, is most often associated with an arterial thrombotic event. In well-controlled population studies, the majority of congenital hypercoagulable defects associated with venous thrombosis are not associated with a statistical increased risk of arterial thromboembolism[10–13].

The few congenital hypercoagulable defects that may be associated with an increased risk of both venous and arterial thrombosis, such as hyperhomocysteinemia or increased Lp(a), are also associated with an increased risk of arterial atherosclerosis[4,8,14–16]. Other defects associated with an increased risk of arterial thromboembolism, such as those observed with increased levels of fibrinogen and von Willebrand factor, are known to enhance platelet function[17,18].

Although the thrombosis potential or risk of thrombosis for inherited prothrombotic defects have been well characterized in a number of prospective and retrospective population studies, it is important to understand that thrombosis is a multigenetic and multifactor disorder. The thrombosis potential for specific congenital

thrombophilic abnormalities is classically defined as a relative risk of thrombosis compared with a patient population without these abnormalities[1,2,9,10,12].

In most circumstances, patients who inherit more than one abnormality have a significantly higher risk of thrombosis potential or a relative risk of thrombosis[1,2,9,10,12,19]. However, patients may have additional risk factors, such as aging, oral contraceptive (OC) use, hormone replacement therapy (HRT), pregnancy, cancer, infection, trauma, or surgery. In these circumstances, a patient's individual risk also can be increased by a factor that is more than the sum of each individual risk fact[19].

Procoagulant Proteins

Protein	Molecular Weight (kD)	Plasma Concentration (nmol/L)	Plasma Concentration (μg/mL)	Plasma $t_{1/2}$ (Days)	Clinical Phenotype Associated With Deficiency	Functional Classification
Factor XII	80	500	40	2-3	None	Protease zymogen
HMW kininogen	120	670	80		None	Cofactor
LMW kininogen	66	1300	90			Cofactor
Prekallikrein	85/88	486	42			Protease zymogen
Factor XI	160	30	4.8	2.5-3.3	Sometimes bleeding	Protease zymogen
Tissue factor	44			N/A		Cell-associated cofactor
Factor VII	50	10	0.5	0.25	Bleeding (occasionally thrombotic)	VKD protease zymogen
Factor X	59	170	10	1.5	Bleeding	VKD protease zymogen
Factor IX	55	90	5	1	Bleeding	VKD protease zymogen
Factor V	330	20	6.6	0.5	Bleeding[a]	Soluble procofactor
Factor VIII	285	1.1-1.5[d]	0.3-0.4	0.3-0.5	Bleeding	Soluble procofactor
vWF	255	Varies	10		Bleeding	Carrier for factor VIII
Factor II	72	1400	100	2.5	Bleeding[b]	VKD protease zymogen
Fibrinogen	340	7400	2500	3-5	Bleeding[c]	Structural clot protein
Factor XIII	320	94	30	9-10	Bleeding	Transglutaminase zymogen

[a]Factor V Leiden mutation associated with thrombosis.

[b]Prothrombin 20210A mutation associated with thrombosis.

[c]Some fibrinogen mutations associated with thrombosis.

[d]Butenas S, Parhami-Seren B, Mann KG. The influence of von Willebrand factor on factor VIII activity measurements. *J Thromb Haemost*. 2009;7:132–137; Butenas S, Parhami-Seren B, Undas A, Fass DN, Mann KG. The "normal" factor VIII concentration in plasma. *Thromb Res*. 2010;126:119–123.

HMW, High-molecular-weight; *LMW,* low-molecular-weight; *VKD,* vitamin-K-dependent; *vWF,* von Willebrand factor.

Anticoagulant Proteins, Inhibitors, and Receptors

Protein	M_r (kD)	Plasma Concentration (nmol/L)	Plasma Concentration (μg/mL)	Plasma $t_{1/2}$ (Days)	Clinical Phenotype Associated With Deficiency	Functional Classification
Protein C	62	65	4	0.33	Thrombotic	Proteinase zymogen
Protein S	69	300	20	1.75	Thrombotic	Inhibitory cofactor
Protein Z	62	47	2.9	2.5	Sometimes thrombotic	Inhibitory cofactor
Thrombomodulin	100	N/A	N/A	N/A		Cofactor/modulator
Tissue factor pathway inhibitor	40	1-4	0.1	minutes		Proteinase inhibitor
Antithrombin	58	2400	140	2.5-3	Thrombotic	Proteinase inhibitor
Heparin cofactor II	66	500-1400	33-90	2.5	Often thrombotic	Proteinase inhibitor
α_2-Macroglobulin	735	2700-4000	2-3000	<1 h		Proteinase inhibitor
α_1-Proteinase inhibitor	53	28,000-65,000	1500-3500	6		Proteinase inhibitor
Endothelial protein C receptor						Receptor

1. Classification of Thrombophilia

Crowther and Kelton[2] proposed a simple classification system that divides the congenital hypercoagulable (thrombophilic) states into two broad groups. The first group constitutes reduced levels of the natural anticoagulants, such as antithrombin, protein C, and protein S[2], are much less common, but are associated with a significantly higher risk of thrombosis[2]. The second group is a "gain in procoagulant function" due to increased levels or function of coagulation factors[2]. These include factor V Leiden (activated protein C resistance [APCR]) and prothrombin G20210 mutations, increases in coagulation factors VIII, IX, and XI, and the dysfibrinogenemias. Although these defects have a lower thrombosis potential, they are more frequently found in the general population, and therefore, are more commonly ssociated with clinical thrombosis. The understanding that certain defects alone or in combination can be associated with a significantly higher risk of thrombosis may be important in determining the physician's approach to antithrombotic prophylaxis, the duration of anticoagulation after venous thrombosis, and family screening for patients with these defects.

Venous Thromboembolism and Inherited Thrombophilias

Abnormality	**Frequency in General Population (%)**	**Frequency in Patients With VTE (%)**	Relative Risk	Reference
Antithrombin	0.02	4-7.5	8.1-21	[15-17,19–22]
Protein C	0.2	2.5-6	7.3-11	[16,17,24,23]
Protein S	Unknown	1.3-5	8.5-32	[16,17,24,28]
Factor V Leiden (APCR) heterozygote	2-7	10-19	2.5-7	[7,17,18,24,24–30]
Factor V Leiden homozygote	0.015	1.5	80	[17,31,31]
PT G20210A heterozygote	1-4	5-10	1.7-3	[6,32–37]
PT G20210A Homozygote	Unknown	Unknown	Unknown	
Factor VIII	11	25	4.8	[1,38]
Homocysteine	5-10	10	2-4	[1,39–43]

APCR, Activated protein C resistance; *PT*, prothrombin; *VTE*, venous Thromboembolism

1.1.Group 1 Thrombophilia

Group 1 includes deficiencies of the naturally occurring anticoagulant factors antithrombin, protein C, and protein S. All are rare, representing less than 1% of the population[7]. However, they are highly prothrombotic, with 30% to 50% of carriers (heterozygote) having a symptomatic thrombotic event before they reach 60 years of age[7]. A significant number of carriers will have had a spontaneous thromboembolic event before the age of 40 years. Frequently, there is a strong family history of venous thrombosis. Although the risk of thrombosis is high, routine prophylactic anticoagulation in ambulatory healthy individuals has not been demonstrated to be of benefit and should be reserved for high-risk situations, such as surgery, sepsis, pregnancy, and immobilization[7]. Because of the high risk of recurrence, with group 1

deficiencies and patients homozygous for certain group 2 abnormalities, lifelong anticoagulation may be recommended after spontaneous thrombotic event[7,24].

1.1.1. Antithrombin Deficiency

Physiologically, antithrombin is the most important inhibitor of thrombin and other activated clotting factors (e.g., factors Xa, IXa, and VIIa). Antithrombin physiologic activity is enhanced 1000-fold by the binding of naturally occurring or administered heparin or heparin sulfates[44]. Antithrombin deficiency is rare, reportedly occurring in an estimated 0.02% of the general population in a study that screened samples from healthy blood donors[20,22]. It has been reported in 4% to 7.5% of patients with VTE[10,12,13,21,22].Antithrombin inheritance is autosomal dominant[45]. More than 250 mutations within the molecule have been described[46]. Homozygosity, particularly for antithrombin deficiency types I and II, is extremely rare and appears to be incompatible with life. Homozygosity for antithrombin deficiency results in a severe thrombophilic phenotype[47].

1.1.1.1.Types

There are three general subtypes of antithrombin deficiency. Type I is characterized by decreased antithrombin functional activity and antigen. Type II defects are antithrombin mutations that have reduced functional activity, but normal antigen levels resulting from a mutation in the active inhibitory site on the protein. Type III antithrombin mutations are characterized by moderate decreased activity due to impaired interaction with heparin. Screening for antithrombin deficiency should always be undertaken using a

functional assay, because screening with an antigen assay may fail to diagnose type II and III defects. In the presence of low antithrombin activity, further characterization can be made with an antigen assay.

Patients with antithrombin deficiencies are at a significantly higher risk of thrombosis than patients with other congenital deficiencies. Approximately 60% of carriers of type I and II deficiencies will have a thrombotic event by the age of 60 years. The risk for type III deficiency may be lower[48,49]. A strong family history of thrombosis is usually present. A Spanish Multi-Center study reported the relative risk of thrombosis in these thrombophilic families as 21-fold[21]. A multicenter, multinational European Prospective Cohort on Thrombophilia (EPCOT) study

reported an adjusted relative thrombotic risk of 17.5 (95% confidence interval [CI], 9.1 to 33.8)[19]. After the diagnosis of antithrombin deficiency is made in an individual with thrombosis, screening of family members is recommended.

1.1.1.2.Clinical Presentation and Management

Patients who have VTE usually present in the lower extremities. Unusual sites of thrombosis have been reported and are similar to those seen with antithrombin deficiency[23,50–52]. Although rare arterial events have been reported, large cohort studies do not support an increased risk of arterial events[53]. In protein C deficient patients from thrombophilic families who present with an unprovoked (idiopathic) thrombosis, recurrent thrombotic events are frequent. Life-long anticoagulation should be considered in these patients, particularly those who present before the age of 40 years.

The clinical presentation of antithrombin deficiency is predominantly lower extremity thrombosis with or withoutpulmonary embolism. Recurrent events are common, and atypical thrombotic events involving the portal, mesenteric, and hepatic venous system, or cerebral veins have been reported. Arterial events are rare, and patients are not at increased risk more than the unaffected adult population. Pregnancy is a particularly high-risk situation, and prophylaxis with heparin is The clinical presentation of antithrombin deficiency is predominantly lower extremity thrombosis with or without pulmonary embolism. Recurrent events are common, and atypical thrombotic events involving the portal, mesenteric, and hepatic venous system, or cerebral veins have been reported. Arterial events are rare, and patients are not at increased risk more than the unaffected adult population. Pregnancy is aparticularly high-risk situation, and prophylaxis with heparin is The clinical presentation of antithrombin deficiency is predominantly lower extremity thrombosis with or without pulmonary embolism. Recurrent events are common, and
atypical thrombotic events involving the portal, mesenteric, and hepatic venous system, or cerebral veins have been reported. Arterial events are rare, and patients are not at increased risk more than the unaffected adult population. Pregnancy is a particularly high-risk situation, and prophylaxis with heparin is indicated throughout pregnancy and in the immediate postpartum period. Patients with breakthrough events can receive antithrombin concentrates. An acquired form of Antithrombin deficiency has been reported in pregnant women with the fatty liver syndrome with disseminated

intravascular coagulation (DIC). Treatment with plasma or antithrombin concentrates rapidly reverses the Coagulopathy

1.1.2. Protein C Deficiency

Protein C is a vitamin K-dependent anticoagulation protein that is activated by thrombin to activated protein C. When thrombin levels are high, thrombin binds to the endothelial protein receptor, thrombomodulin, which changes the specificity of thrombin from cleaving fibrinogen or activating platelets to activating protein C. Protein C binds to its specific endothelial receptor, termed the endothelial protein C receptor, which enhances its activation. APC is a potent serine protease anticoagulant that cleaves the coagulant cofactors VIIIa and Va, thus modulating thrombin generation and subsequent clot formation. Deficiency of protein C is found in 0.2% of the general population, and in 2.5% to 6% of patients with VTE.

1.1.2.1. Types

Similar to antithrombin deficiency, multiple mutations resulting in protein C deficiency have been reported. These mutations have been classified into two general subtypes: type I mutations have reduced functional and antigenic protein levels; and type II mutations have reduced functional levels but preserved antigen levels of the protein.45 Adult heterozygous patients with protein C deficiency usually have activity levels of less than 60%. Clinical Presentation and Management Patients who have VTE usually present in the lower extremities. Unusual sites of thrombosis have been reported and are similar to those seen with antithrombin deficiency. Although rarearterial events have been reported, large cohort studies do not support an increased risk of arterial events.46 In protein C deficient patients from thrombophilic families who present with an unprovoked (idiopathic) thrombosis, recurrent thrombotic events are frequent. Life-long anticoagulation should be considered in these patients, particularly those who present before the age of 40 years.

Homozygosity for protein C deficiency, with absent protein C activity, may present at birth as a neonatal disorder termed purpura fulminans[54]. This disorder is characterized by diffuse microvascular thrombosis of the skin and systemic organs. Immediate treatment with heparin, plasma, or protein C concentrates can be lifesaving[54]. The majority of homozygous neonates with protein C deficiency will have functional levels less than 20% of normal[54].A similar severe disseminated

thrombotic disorder, characterized by skin necrosis, can occur in heterozygous patients with protein C deficiency treated with higher doses of warfarin, usually without concomitant anticoagulation with heparin[55,56].The syndrome, termed warfarin necrosis, results from the disproportional decrease in protein C in comparison to other procoagulant vitamin K- dependent coagulation factors. Patients presenting with this disorder should be treated with fresh frozen plasma, vitamin K, and heparin[55,56]. The syndrome can be prevented by initiating oral anticoagulation with lower doses of warfarin and concomitant use of heparin.

1.1.3. Protein S Deficiency

Protein S is the vitamin K-dependent cofactor necessary for the inactivation of factors Va and VIIIa by APC. A deficiency in protein S is phenotypically similar to protein C deficiency. Protein S exists in two forms: the functionally active free form that usually constitutes 20% to 40% of the total protein, and the remaining 60% to 80% that is active and bound to complement binding protein C4b[57,58]. Most patients with protein S deficiency will have activity levels between 50% and 75% of normal[57–59].

1.1.3.1. Types

Similar to the other natural anticoagulant proteins, protein S deficiency can be classified into 3 subtypes: type I is characterized by reduced functional and antigen protein levels; type II has reduced functional activity, but normal antigen levels; and type III has normal antigen levels, but reduced free active protein S due to enhanced C4b binding[60]. Type I and type III protein S deficiencies are the most common forms of the deficiency encountered, and do not appear to differ in their risk of venous thrombosis[61]. The measurement of protein S activity and antigen can be confounded by a number of physiologic and clinical conditions. In pregnancy, protein S levels fall in the second and third trimesters[62,63]. Reduced protein S levels have also been reported in patients with active cancer, lupus erythematosus, antiphospholipid antibody syndrome (APLAS), sepsis, chronic inflammatory disorders (e.g., inflammatory bowel disease) and in advanced HIV disease[25,26,72,64–71]

Protein S deficiency is clinically characterized by venous thrombosis and has been frequently reported in association with venous thrombosis in atypical sites[57–59,66,67]. These reports may be confounded by other comorbidities in these

patients that can be associated with acquired protein S deficiency. In addition, several eports have suggested a relationship between low protein S levels and arterial thrombosis, including a reported association between low free protein S and cardiolipin antibodies in stroke patients[68]. ike protein C deficiency, homozygous deficiency can be associated with neonatal purpura fulminans. Approach to management is similar to that of homozygous protein C deficiency[69]. Warfarin necrosis can also develop in heterozygote protein S patients[69].

1.2.Group 2 Thrombophilia

Although associated with a lower thrombosis potential than Group 1 thrombophilia, Group 2 hypercoagulable disorders are more frequently found in the general population and are found in a greater proportion of patients with VTE. They represent gain of function mutations resulting in increased thrombin generation. They are typified by either increased synthesis of specific coagulation factors or as observed with factor V Leiden, resistance to the inactivation of this cofactor by APC.

1.2.1. Factor V Leiden (Activated Protein C Resistance)

Factor V is a cofactor that accelerates the conversion of factor II (prothrombin) to thrombin by factor Xa. Under normal circumstances, factor V is degraded by the serine protease, APC, which cleaves the protein at two sites. Factor V Leiden has a mutation in the 506 position that results in a substitution of glycine for arginine. This renders one of the factor V cleavage sites resistant to the action of APC, which, like all coagulation serine proteases, cleaves arginine bonds[70–72]. This results in a slowing of the inactivation of the cofactor, which leads to increased thrombin generation. Factor V Leiden is a common mutation, occurring in approximately 2% to 7% of individuals of European ancestry[25,72]. It can be found in nearly 10% of people with VTE and in 30% to 50% of individuals being evaluated for thrombophilia[24–26,70–72]. The mutation is very rare in native Asians and Africans[25,26]. The mutation is also rare in African Americans (0.6%) and has not been reported in Native Americans[25,26]. Compared with patients with group 1 thrombophilia, patients with factor V Leiden have a lower relative risk of thrombosis, estimated between 2.5- and 7-fold[11,12,19,27]. A cross-sectional study from Italy found that only 6% of carriers of the mutation developed a thromboembolic event by the age of 65 years[73]. Homozygotes are at much higher risk than heterozygotes, with an estimated relative risk of 80-fold[12,27,31]. However, heterozygotes with combined defects have a significantly increased risk of

VTE. A second, very rare, mutation of the second factor Va cleavage site (Arg306Thr) has also been reported to be associated with increased risk of thrombosis, whereas other studies have failed to find a relationship of this mutation with the development of VTE.

The clinical presentation of thrombosis with factor V Leiden is overwhelmingly venous. Rare, unusual thrombosis sites, such as the cerebral vein and the retinal vein, have been reported.77,78 The onset of thrombosis is frequently at an older age than seen in patients with type 1 thrombophilia.17 In the Physicians Health Study, the risk of VTE in men with the factor V Leiden mutation did not become statistically significant until after the age of 50 years.17 The study also found no association with the factor V Leiden and an increased risk of stroke or myocardial infarction.17 Thrombosis is frequently triggered by transient risk factors, such as a prolonged plane flight, OC use, or pregnancy.79-82 In women carriers of the mutation, the reported thrombosis risk associated with the use of second-generation OCs varies widely, ranging from 6- to 50-fold.79-82 The wide variation reported in the thrombotic risk of OCs may be explained, in part, by a higher risk of thrombosis in women more than 30 years old who are taking OCs and some variation in the specific OCs used in the European studies, some of which contain prothrombotic progesterone substitutes.82 There is no excess mortality in carriers of the factor V Leiden mutation. No prophylaxis is recommended for carriers except what is recommended by guidelines for surgical interventions. Antepartum prophylaxis is not recommended for women who have not had a previous thrombotic event or a history of recurrent fetaoss.83 The risk of recurrent VTE after cessation of oral anticoagulation is not greater than that observed in other patients with unprovoked VTE.84

1.2.3.Prothrombin Gene Mutation G20210A

The prothrombin G20210A mutation is an abnormality located at the untranslated 3′ end of the prothrombin gene that results in increased plasma levels of prothrombin. The mutation affects the 5′ end cleavage signal, leading to increased prothrombin mRNA stability.85 The thrombotic risk is relatively low.86-88 The gene frequency in the European population is about 1% to 4%, with the greatest frequency in southern Europe and Spain.89,90 It is present in 5% to 10% of patients with VTE, and 15% of patients with thrombophilia.86-90 Similar to factor V Leiden, the prothrombin

G20210A mutation is very rare in Native Asians, Native Africans, African Americans, and Native Americans.91 Many carriers with a history of VTE have coinheritance of the factor V Leiden mutation.23,92 The relative risk of thrombosis is low in carriers of the prothrombin mutation, ranging from two- to threefold higher in carriers compared with noncarriers of the mutation.93,94

The clinical presentation is predominantly venous thrombosis of the lower extremities, and unusual sites are rare.86-88,93,94 Some controversy exists as to whether the prothrombin mutation is associated with an increased risk of arterial thrombosis.94-96 In carriers of the mutation who develop thrombosis, studies to date have shown either no increase in risk or only a slight increased risk of recurrent VTE after discontinuation of anticoagulation.94,97 The risk of VTE in women on OCs has been reported to be significantly increased, similar to that reported for factor V Leiden.93 Women who are carriers of both the prothrombin G20210A mutation and the factor V Leiden mutation have a markedly high risk of VTE.93 An association between the development of cerebral venous thrombosis in women carriers of the prothrombin mutation taking OCs has been reported, in which 20% of patients carried the mutation versus only 3% of controls.98

1.2.4. Elevated Factors VII, XI, and IX

Koster et al.99 first reported an increased risk of VTE in patients with an elevated factor VIII coagulant protein of more than the 90th percentile (>150%). Factor VIII activity levels more than 150% were associated with an adjusted relative risk of 4.8% compared with factor VIII levels 100% or less.99 These elevations appear to be independent of ABO blood type and were measured in patients without evidence of inflammation confirmed by a normal erythrocyte sedimentation rate (ESR) and C-reactive protein.100,101 Subsequent studies have supported this observation and found both a family and racial clustering suggestive of an inherited propensity for increased factor VIII levels.100,102 A study of African American women found a statistically higher level of factor VIII compared with the white and Asian population in the United States.103 Unlike female carriers of the factor V Leiden and prothrombin mutations, the use of OCs did not appear to significantly increase the risk of VTE.104 Elevations of factor VIII activity have also been associated with an increased risk of recurrent VTE.105 The measurement of factor VIII activity is

confounded by the fact that factor VIII, along with its carrier protein, von Willebrand factor, is an acute phase reactant and increases with bleeding and inflammation.100,101 Therefore, measurement of factor VIII activity should be performed with a simultaneous acute phase marker, such s the ESR or C-reactive protein. The assay should also be repeated at least twice at distant time intervals.99-101 Each laboratory must define the 90th percentile range for its own population to determine the patient population at risk.

The clinical presentation of patients with elevations in factor VIII activity is predominantly VTE of the lower extremities.99 Because factor VIII levels increase with inflammation, the elevation of this coagulation protein is an important cofactor in the development of thrombosis associated with infection, inflammatory bowel disease, and cancer. There is controversy as to whether increased levels of factor VIII are associated with arterial thrombosis, because elevations in factor VIII activity are associated with increases in von Willebrand factor. Increased levels of von Willebrand factor have been shown in population-based studies to be associated with an increased risk of arterial thrombosis.106 Increased levels of factors IX and XI have been associated with a twofold increase in the risk of VTE.107,108 These are relatively weak risk factors for thrombosis, but if combined with other defects, they may become significant. To date, no molecular markers have been reported to characterize these elevations in factors VIII, IX, and XI.

1.2.5. Other

1.2.5.1. Hyperhomocysteinemia

An association was made between markedly elevated levels of homocysteine and arterial vascular disease in individuals with homocysteinuria.110,111 Additional studies confirmed this association and found additional evidence that individuals with homocysteinuria also experience an increased incidence of VTE.110 Subsequent studies found an association between elevations of plasma homocysteine and an increased risk of atherosclerosis and arterial thrombosis in apparently healthy individuals.112-120 Additional studies that focused on risk factors for venous thrombosis reported a similar association.120-123 Homocysteine metabolism involves two enzymatic pathways that require essential vitamin cofactors: folate, vitamin B12, and vitamin B6 (pyridoxine).124 The vitamine B6-dependent pathway involves the

enzymatic conversion of homocysteine to cystathionine by the enzyme cystathionine-β-synthase (CBS).111,124 The second pathway involves remethylation of homocysteine back to methionine requiring folate, vitamin B12, and the two enzymes 5,10- methylenetetrahydrofolatate reductase (MTHFR) and methionine synthetase.124 The primary mutations responsible for homocysteinuria are in the CBS gene.111 However, in the general population, independent of deficiencies in the vitamin cofactors, a common mutation in the MTHFR gene at position 677 is most frequently associated with elevations in homocysteine.124 This C to T mutation results in a 50% reduction in the enzymatic activity of the gene.124 However, even in MTFR C677T homozygotes, folate supplementation or a diet intrinsically rich in folate can reduce

homocysteine levels into the normal range.124,125 The reported mechanisms by which homocysteine increases the risk of both arterial and venous thrombosis include (1) a direct toxic effect on endothelium; (2) enhanced platelet activation; (3) oxidation of low-density lipoprotein cholesterol; (4) an inflammatory decrease in endothelial TM; and (5) an increase in on Willebrand factor and factor VIII.124 However, no single reported effect of homocysteine adequately explains its prothrombotic effect in both the arterial and venous vasculature. A number of cohort studies and some prospective studies have found a statistically significant association between elevated homocysteine and an increased risk for myocardial infarction and stroke with estimated risks of 2- to 7.8-fold for individuals in the highest quartile.112-114 However, several prospective studies have failed to confirm this association.115-117 Data from the Physicians' Health Study,117 the Atherosclerosis Risk in Communities Study,118 and the Women's Health Study115,116 suggest a gender-defined risk for elevated homocysteine in which the risk is most significant in women. Elevations of homocysteine have also been found in case- controlled studies to be a weak risk factor for VTE, with a relative risk of only 2 to 4.117-123 Meta-analyses further confirmed an increased risk in patients with homocysteine levels more than the 95th percentile.123 Complicating the issue of elevated homocysteine as a risk factor for both arterial and VTE disease is the lack of response, in randomized controlled trials, to lowering homocysteine in reducing the risk of recurrent arterial10-12 and VTE13 disease in patients treated with vitamin therapy. The measurement of homocysteine in patients can be complicated by comorbid conditions, such as vitamin deficiency, renal

insufficiency, and improper plasma collection and handling. Measurements are best performed using freshly collected plasma, preferentially with patients in the fasting state. It is reasonable to repeat the assay on at least two separate occasions. Studies to date do not support an advantage for determination of the MTHFR genotype over direct measurement of homocysteine.125

1.2.5.2. Lipoprotein(a)

Lp(a) is a serum lipoprotein composed of a low-density lipid particle with a disulfide link to a long polypeptide chain, apolipoprotein(a).20,126 The protein has "kringle-like" domains that compete with tissue plasminogen activator, plasminogen, and plasmin for binding to fibrin and endothelial annexin II, thereby inhibiting fibrinolysis.126,127 The plasma levels of Lp(a) vary greatly within and between different racial populations, with African Americans having higher levels.128 Also, Lp(a) may increase as an acute phase reactant129,130 and has been reported to be elevated in certain inflammatory rheumatologic disorders.131 Early retrospective studies suggested a relationship between elevated levels of Lp(a) and the risk of premature atherosclerosis and arterial thrombosis.132-134 However, prospective studies have been less supportive and at the most suggest only a small increase in risk for individuals with elevated plasma Lp(a).135-141 Additional reports have suggested a role for elevated Lp(a) as an independent risk factor for VTE,142,143 although a failure to find an association has been reported by other investigators.144

1.2.5.3. Sticky Platelet Syndrome

Sticky platelet syndrome (SPS) is an inherited, autosomal dominant disorder associated with early-onset myocardial infarction and peripheral vascular disease.145-147 Although most often associated with arterial vasculopathy, VTE has been reported.145-147 A causal relationship to early miscarriage has also been reported. Patients usually present with a history of myocardial infarction or hromboembolism as young adults. The events often are precipitated by stress.145-147 The defect appears to be common in patients with unexplained thromboembolic events. In an analysis of 200 patients and family members identified with SPS, 21% had arterial thromboembolic events and 13.2% had VTE events.146 SPS platelets demonstrate hyperreactivity to epinephrine and adenosine diphosphate (ADP) even with dilution, but have normal responses to thrombin, collagen, and arachadonic

acid.145-147 Three types of platelet responses have been noted: type I is hyperreactive to both ADP and epinephrine; type II is hyperreactive to epinephrine only; and type III is hyperreactive to ADP only. Increased arterial events may be mediated through polymorphisms of glycoprotein IIIa allele PLA-A2.148 Although other investigators have reported similar hyperreactivity of platelets in patients with ischemic stroke,149 there remains controversy as to whether SPS represents a true congenital prothrombotic syndrome. In patients with documented platelet reactivity and thrombosis, low-dose acetylsalicylic acid (81 mg) appears to be effective in inhibiting platelet hyperreactivity.147

1.2.5.4 Idiopathic (Unprovoked) Venous Thrombosis

Unprovoked or idiopathic venous thrombosis is defined as the development of deep vein thrombosis and/or pulmonary embolism in the absence of known genetic prothrombotic mutations, permanent factors, or acquired risk factors. Patients who develop VTE provoked by surgery, trauma, immobilization, pregnancy, or female hormone intake are at low risk of recurrent thrombosis.150,151 Patients with unprovoked VTE have a recurrence risk of 5% to 10% per year, with nearly 50% developing a recurrent event by 10 years.150,151 A recent prospective clinical trial evaluated whether D- dimer screening 4 weeks after completion of 6 months of warfarin for unprovoked VTE could predict risk of recurrence off anticoagulation.152 The study found males, even with low D-dimer levels continue to have a greater than 7% annual risk of recurrent VTE.152 Women with low D-dimer levels and women with estrogen associated VTE have a significantly lower risk of recurrent VTE. A prospective study that screened 66 patients with idiopathic venous thrombosis found abnormalities in 26 (39.3%) patients when they were screened for thrombophilia (antithrombin, protein C, protein S, factor V Leiden, prothrombin G20210A, antiphospholipid antibodies).153 Therefore, 60% of patients with unprovoked VTE have no underlying known major inherited or acquired thrombophilia and still remain at high risk of recurrent VTE. It has been proposed that an underlying inflammatory state may be responsible for the increased risk of VTE in patients with unprovoked events.154,155 Laboratory assessment of patients with idiopathic VTE have demonstrated higher levels of interleukin (IL)-6 and IL-8 with low levels of IL-10 compared with age- and sex-matched controls.156 It is notable that the same inflammatory markers are linked to an increased risk of atherothrombotic

disease.154-157

1.3.Acquired Hypercoagulability

An increased risk of thrombosis can be associated with a variety of acquired abnormalities. Disorders such as the APLAS and cancer are significant prothrombotic syndromes.158,159 Common clinical situations such as cancer, pregnancy, infection, and estrogen use are transient causes of hypercoagulability.160-162 Surgery is a well-documented transient cause of hypercoagulability in which the risk of thrombosis is related to a number of factors, such as the type of surgery, the duration of surgery, the age of the patient, and other patient comorbidities.162 A significant iatrogenic thrombotic disorder is heparin-induced thrombocytopenia (HIT), in which early diagnosis and treatment may be lifesaving.163 Chronic inflammatory and autoimmune disorders, such as inflammatory bowel disease, Behcet's syndrome, or lupus erythematosus, with and without antiphospholipid antibodies, are also associated with a significant risk of thrombosis.164-167 Acquired elevations in factor VIII levels or depressions in protein S may be important contributing factors to a number of prothrombotic disorders, including cancer, pregnancy, infection, and chronic inflammatory disorders. In patients with cancer, the expression of tissue factor by the malignant cell further increases the thrombotic risk.168,169 Paroxysmal nocturnal hemoglobinuria, a rare hemolytic disorder in which nearly half of the patients develop symptomatic thrombosis, has been shown to be associated with both increased platelet activation and increased leukocyte tissue factor expression.170,171 Thrombosis in patients with myeloproliferative syndromes frequently involves unusual sites, such as the portal and hepatic veins, and is more often associated with syndromes associated with the Janus kinase-2 (JAK-2) mutation.172-175 The presence of JAK-2 mutation has also been shown to be associated with thrombosis in the splanchnic, portal, and hepatic veins, even in the presence of normal blood counts.175

1.3.1. Antiphospholipid Antibody Syndrome

The APLAS is one of the more common causes of acquired hypercoagulability.158,159 The syndrome is associated with an increased risk of both arterial and venous thrombosis.158,159 Although the APLAS can occur with systemic lupus erythematosus (SLE), 50% of the patients do not fulfill criteria for lupus or other autoimmune disorders.176 The syndrome is characterized by the presence of

antibodies that inhibit in vitro coagulation reactions, the lupus anticoagulant (LA), and antibodies that bind to anticardiolipin and β2-glycoprotein.158,159 Clinical criteria include a history of either thrombosis and/or pregnancy complications with fetal loss.177

There is strong epidemiologic evidence to support a relationship between the presence of these antiphospholipid antibodies and thrombosis.158,148,178 There appears to be a differential risk with the highest risk of thrombosis associated with the presence of an LA and high titer immunoglobulin-G (IgG) anticardiolipin antibody.158,178 The Leiden Thrombophilia Study, a large population-based, case-control study of unselected patients with a first episode of venous thrombosis, found a 3.6-fold increased risk for deep venous thrombosis for individuals positive for LA (odds ratio [OR], 3.6; 95% CI, 1.2 to 10.9).178 However, patients who were positive for both the LA and either antiprothrombin or anti-β2- glycoprotein-1 antibodies had an estimated 10-fold increased risk of VTE (OR, 10.1; 95% CI, 1.3 to 79.8). The syndrome is something of a paradox in that this thrombotic disorder is characterized by antibodies that prolong in vitro oagulation tests, most commonly, the activated partial thromboplastin time (aPTT). The mechanism(s) by which these antibodies result in thrombosis remains unclear. Activation of monocytes, platelets, and endothelial cells by antibody/β2- glycoprotein-1 complexes has been implicated in the etiology of thrombotic events. Antibodies to annexin II on endothelial cells, tissue plasminogen activator, and plasmin have been proposed as additional antigenic targets. Complement (C5a)- mediated inflammation has been demonstrated to be associated with increased thrombogenicity and recurrent fetal loss.

Laboratory diagnosis of the APLAS should include screening for LA with two different assay systems. Assessment of anticardiolipin antibodies should include screening for both IgG and IgM antibodies. Anti-β2-glycoprotein-1 screening can provide further confirmatory evidence for the diagnosis. Positive tests should be confirmed 12 weeks after the initial screen, because transiently positive values may be seen during infections, during autoimmune hemolytic anemia, and with malignancy.

APLAS has been associated with both arterial and VTE. No laboratory test can distinguish patients at risk for either an arterial or venous event. However, recurrent events most often recur in the vascular sites of previous thrombosis. Thrombosis at

unusual sites is well described with the APLAS, including multiple arterial emboli due to nonbacterial thrombotic endocarditis.184 Retrospective studies have reported a risk of recurrence as high as 50%.185,186 However, recent prospective treatment trials have estimated the risk to be somewhat lower, but still significant, with a relative risk of recurrence after stopping oral anticoagulants of 4- to 7.7-fold.187-189 This has led to consensus recommendations to consider extended or indefinite anticoagulation for patients with the APLAS and thromboembolism.24 Two prospective randomized trials in patients with APLAS associated thrombosis compared moderate- to high-intensity warfarin (prothrombin time [PT] international normalized ratio [INR] 2.0 to 3.0 vs. 3.0 to 4.0) for secondary antithrombotic prophylaxis. Both trials demonstrated that moderate-intensity warfarin was equivalent to high-intensity treatment with a lower risk of bleeding complications. Assessing adequate anticoagulation with the PT INR may, at times, be difficult in the rare patient with an LA that affects the PT test. A catastrophic form of APLAS designated as CAPS is a life- threatening variant of the disorder characterized by diffuse macro- and microvascular thrombosis with multiple organ involvement. Prompt recognition and treatment with corticosteroids and heparin, and in refractory cases, plasmapheresis, can be lifesaving.

MATERIALS AND METHODS

MATERIALS AND METHODS

Study design

A single centre, prospective observational study.

Study population

Inpatient with spontaneous venous and arterial thrombosis admitted in JIVAS, A Unit of Bhagwan Mahaveer Jain hospital.

Study period

1st November 2019 to 30th April 2021.

Inclusion criteria

Patients with spontaneous peripheral arterial or venous thrombotic events evaluated at JIVAS.

Exclusion criteria

A) Presence of any obvious cause that may have led to the thrombotic episode.

B) Patients with recent vascular interventions.

C) Not consenting for thrombophilia screen panel testing.

Sample Size

Arbitrarily taken as 50.

Data to be recorded

A. Demographics – Age, Sex.

B. Past history of arterial or venous disease including thrombosis, abortion with details of treatment especially past or current use of any forms of anticoagulation.

C. Comorbidities – DM, HTN, Thyroid disorder, IHD, CKD.

D. Tobacco use.

E. Routine baseline investigations (complete blood count, urea ,creatinine and electrolytes, liver function test, PT – INR, aPTT, ECG ,2D Echo, Ultrasound study of the abdomen).

F. Arterial Doppler scan of index limb / CT Angiogram / Venous duplex scan of index limb.

G. The recommended thrombophilia investigations include

- Inherited risk factors
    - Antithrombin deficiency
    - Protien C deficiency
    - Protein S deficiency
    - Factor V Leiden gene mutation (R506Q)
    - Prothrombin gene mutation (G20210A)
    - MTHFR gene mutation (C677T)
    - Acquired risk factor like Antiphospholipid syndrome
- Mixed risk factors
    - Hyperhomocystinemia
    - Increased fibrinogen levels
    - Increased factor VIII levels
    - Increased factor IX levels
    - Increased factor XI levels

Analysis

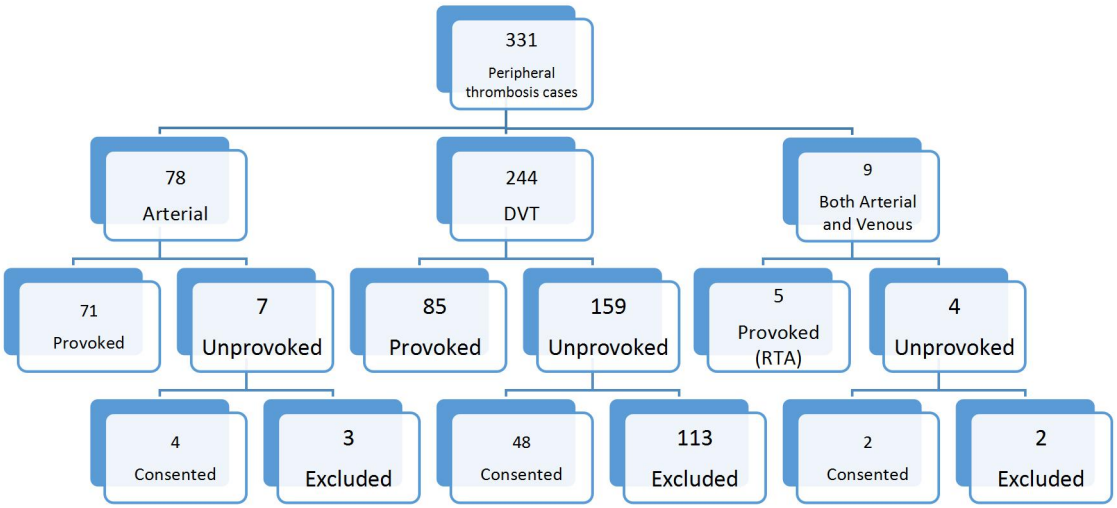
A. Data will be entered in Microsoft Excel and analyzed
B. Statistical Methods

The prevalence of thrombophilia was expressed in percentage for ease of comparison between each marker.

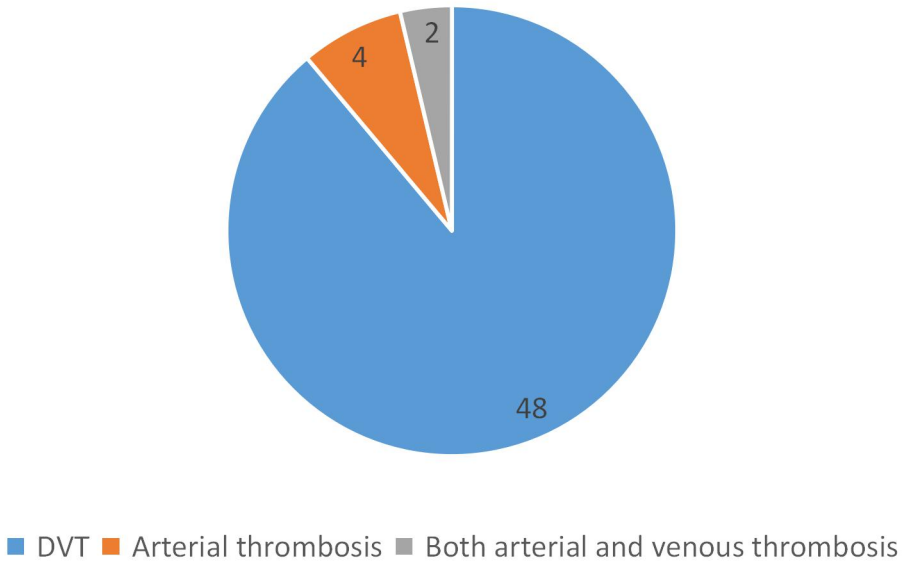
RESULTS

Results

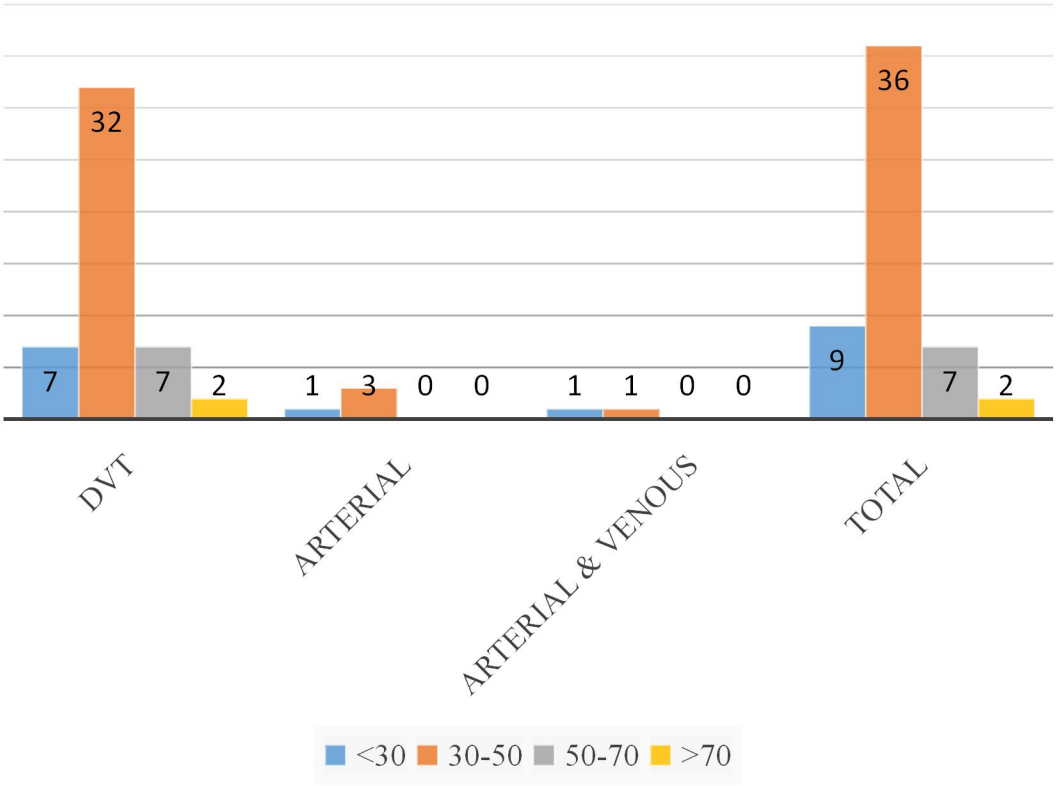
We were able to collect all the relevant data of 54 patients who were admitted to Jain Institute of Vascular Sciences, A Unit of Bhgawan Mahveer Jain Hospital with spontaneous peripheral thrombotic events who were evaluated with thrombophilia work up during the study period.



During the study period we had 331 admission with peripheral thrombotic events out of which maximum admissions were deep vein thrombosis followed by arterial and very few cases with both arterial and venous thrombosis. We had 54 selected patients who underwent thrombophilia work up, 48 patients with unprovoked DVT, four patients with arterial thrombosis and two patients with both arterial and venous thrombosis.


2
4
48
DVT
Arterial thrombosis
Both arterial and venous thrombosis

Age



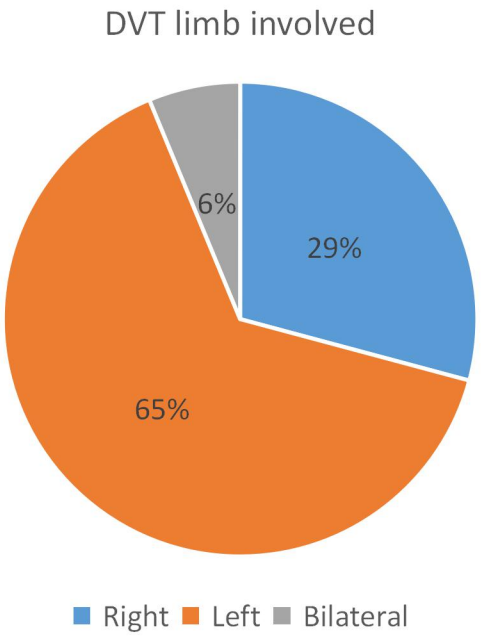
Majority of the patients were in 30 to 50 age group. With mean age of patients 42.09 +/- 11.48. In specific groups tha mean age was as follows DVT - 42.91 +/- 11.70, arterial thrombosis - 37.5 +/- 6.8, both arterial and venous 31.5 +/- 2.5.

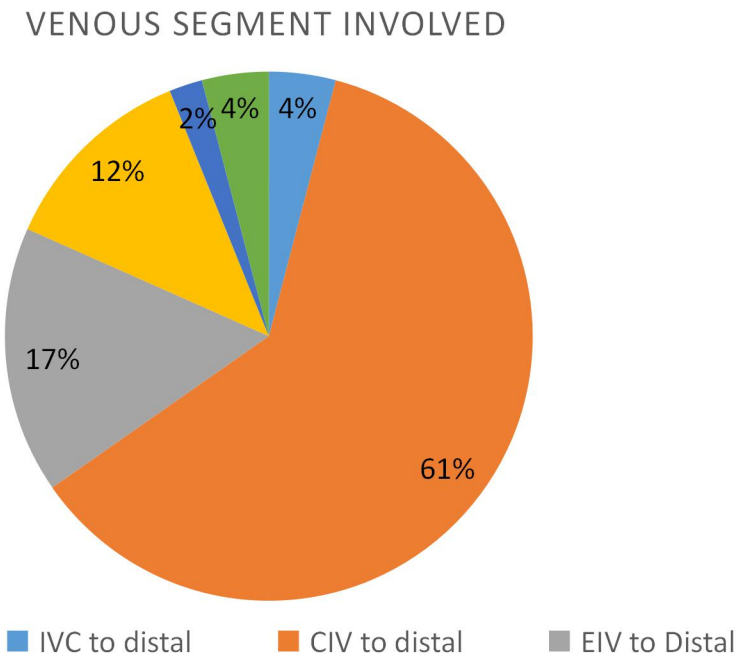
Characteristics of patients with unprovoked deep vein thrombosis

Unprovoked DVT forms the majority of the cases, 48 out of 54 (88.9%).

Variables		**Frequency**	**Percentage**
Gender	Female	21	43.75%
	Male	27	56.25%
Age	< 30 years	7	14.5%
	30-50 years	32	66.7%
	50-70 years	7	14.5%
	>70 Years	2	4.2%
Comorbidities	Diabetes Mellitus	Nil	
	Systemic Hypertension	Nil	
	Hypothyroidism	Nil	
Habits	Tobacco abuse	5	10.4%
	Chronic alcohol abuse	Nil	
Laterality	Left	31	65%
	Right	14	29%
	Bilateral	3	6%
Segment involved	IVC to distal	2	4%
	CIV to distal	30	61%
	EIV to distal	8	16%
	CFV to distal	6	12%
	SFV to distal	1	2%
	PV to distal	2	4%

In our study, 48 out of 54 patient (88.9%) had DVT. Predominant gender was male (56.25%), predominant age group was 30-50 yeas (66.7%). Tobacco use was the most common habit found (10.4%). Most common affected side was left(65%). In this study, it was found the CIV to distal was the most commonly affected segment in the DVT group (61%).


DVT limb involved
6%
29%
65%
Right
Left
Bilateral


VENOUS SEGMENT INVOLVED
4%
4%
2%
12%
17%
61%
IVC to distal
CIV to distal
EIV to Distal

Characteristics of patients with spontaneous arterial thrombosis

Variables		**Frequency**	**Percentage**
Gender	Female	2	50%
	Male	2	50%
Age	< 30 years	1	25%
	30-50 years	3	75%
Comorbidities	Diabetes Mellitus	0	
	Systemic Hypertension	1	25%
	CAD/CVA	0	
Habits	Tobacco abuse	0	
	Chronic alcohol abuse	0	
Laterality	Right	1	25%
	left	2	50%
	Bilateral	1	25%
Segment involved	Aorta bilateral distal	1	25%
	CIA to distal	1	25%
	CFA to distal	1	25%
	SFA to distal	1	25%

In our study, 4 out of 54 patient (7.4%) had spontaneous arterial thrombosis. 75% of the affected patients were in the age group of 30-50%. Because of the limited number no inference was made about this subgroup.

Characteristics of patients with both spontaneous arterial and venous thrombosis

Variables		Frequency	Percentage
Gender	Male	2	100%
Age	< 30 years	1	50%
	30-50 years	1	50%
Comorbidities	Diabetes Mellitus	0	
	Systemic Hypertension	0	
	CAD/CVA	0	
Habits	Tobacco abuse	0	
	Chronic alcohol abuse	0	
Laterality	left	2	100%
Segment involved Venous	CIV to distal	2	100%
Segment involved Arterial	CFA to distal	1	50%
	SFA to distal	1	50%

There were only 2 (3.7%) patients who had both arterial and venous thrombosis, both were males and less than 50 years of age. Because of the limited number no inference was made about this subgroup also.

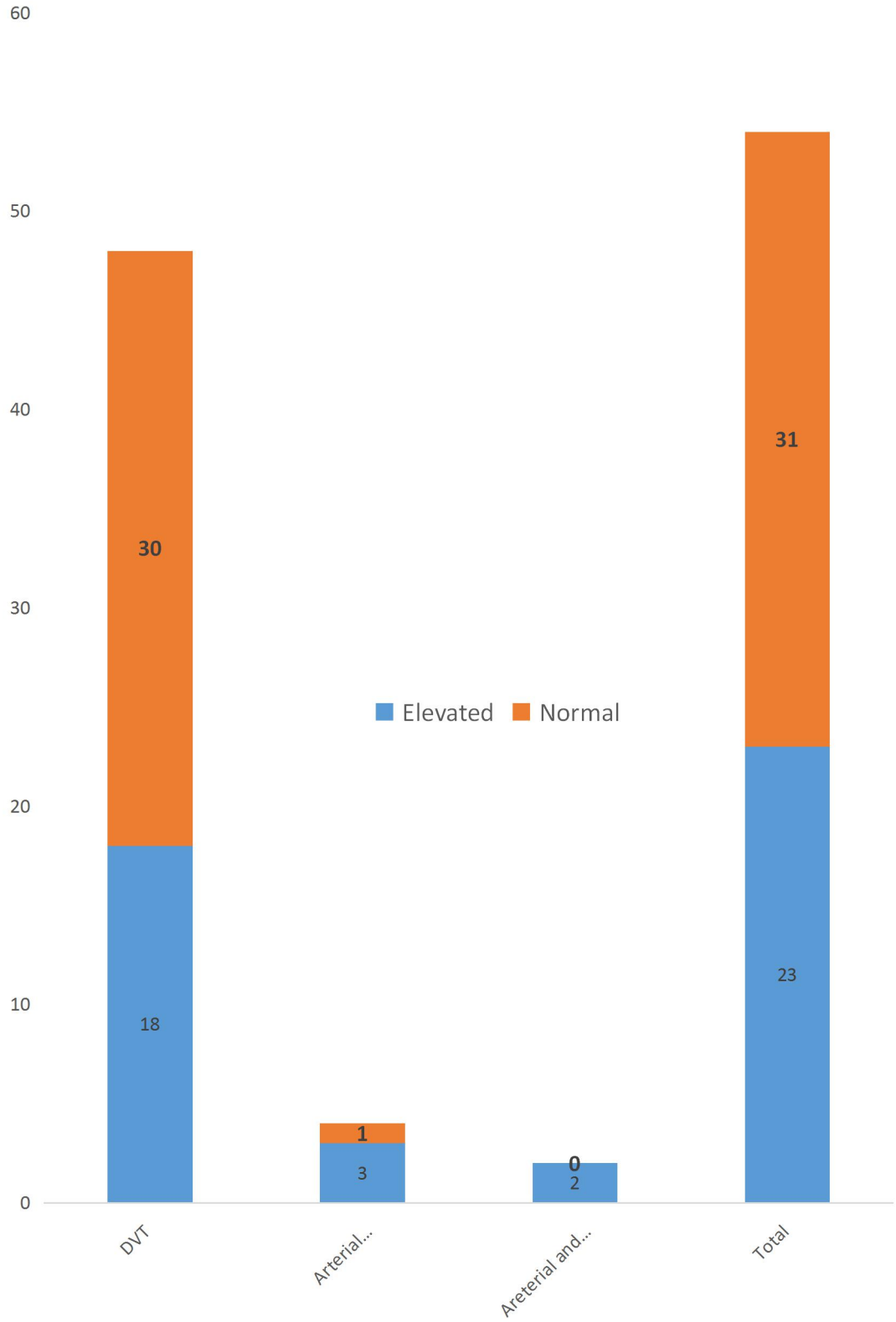
Thrombophilia workup results in study population

Variables	Frequency		Percentage	
Lupus Anticoagulant	12		22.2%	
Beta 2 Glycoprotien 1 IgG	0			
Beta 2 Glycoprotien 1 IgM	0			
Cardiolipin Antibody IgG	0			
Cardiolipin Antibody IgM	1		1.8%	
Antithrombin deficiency	5		9.2%	
Protein C deficiency	4		7.4%	
Protein S deficiency	0			
Factor V Leiden Mutation	Heterozygous 4	Homozygous 0	7.4%	0%
Prothrombin gene mutation	0			
MTHFR gene mutation	Heterozygous 5	Homozygous 1	9.2%	1.8%
Hyperhomocysteine	23		42.6%	
Increased Fibrinogen levels	10		18.5%	
Increased Factor VIII levels	5		9.2%	
Increased Factor IX levels	6		11.1%	
Increased Factor XI levels	3		5.6%	

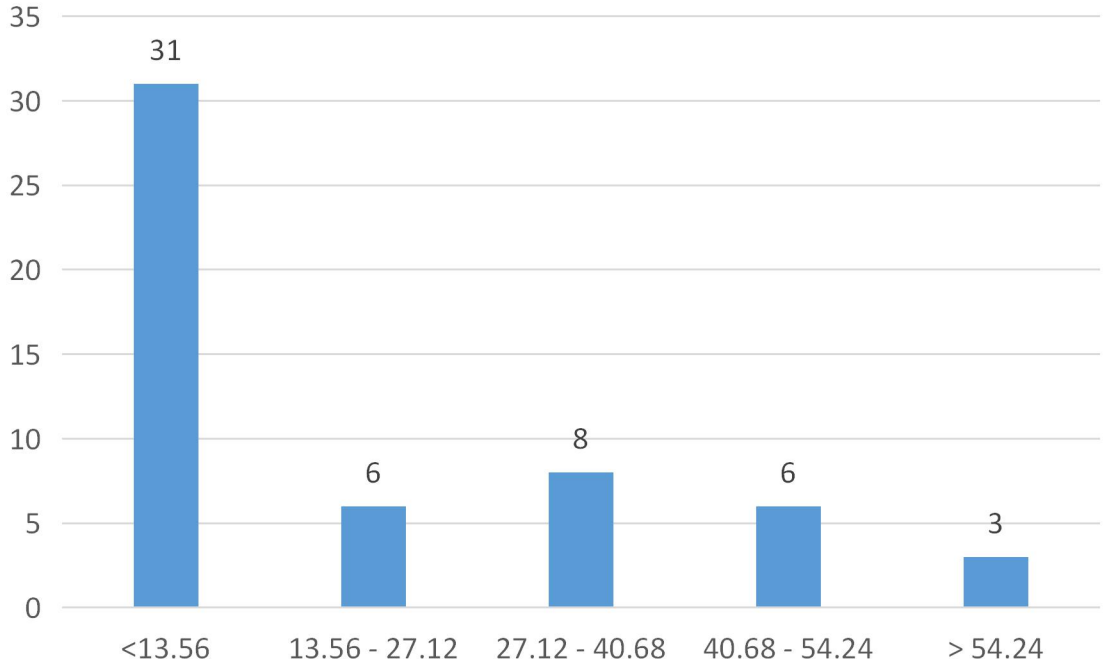
62.96% (34 out of 54) of the patients had at least one thrombophilia marker positivity, with Hyperhomocysteinemia as the commonest marker 42.6% (23 out of 54), followed by Lupus anticoagulant 22.2% (12 out of 54), followed by increased Fibrinogen levels 18.5%, Increased Factor IX levels 11.1%, increased Factor VIII levels 9.2%. Other rare positive thrombophilia markers were as follows Cardiolipin Antibody IgM in one patient, Homozygous MTHFR mutation in one patient and increase factor XI level in three patients (5.6%). Other insignificant positive thrombophilia markers were Heterozygous MTHFR gene mutation in five (9.2%) patients, Heterozygous Factor V Leiden gene mutation in four (7.4%) patients, Antithrombin and Protein C deficiency in five and four patients respectively. All patients in the study population were tested negative for Beta 2 Glycoprotein, Protein S deficiency and Prothrombin gene mutation.

Hyperhomocysteinemia

Serum Homocysteine quantitative assay was done in all patients. The reference normal range from our laboratory was 4.44 – 13.56 umol/L



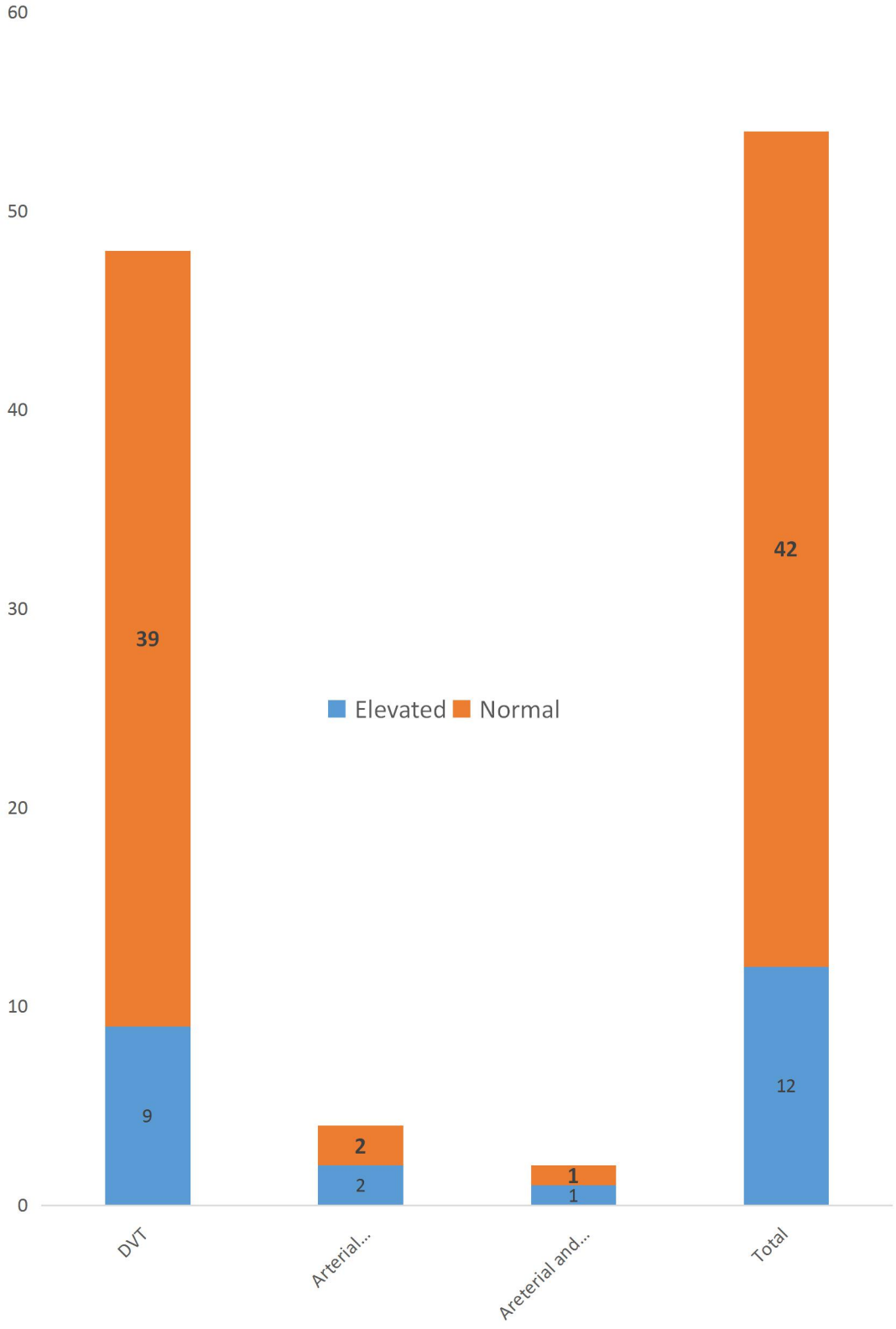
42.6% of the patient (23 out of 54) had a positive test result, 18 were from DVT (N=48), 3 from arterial sub group (N=4), 2 from both arterial and venous thrombosis sub group (N=2)



Among patients with hyperhomocysteinemia 61% had less than two times high normal elevation, which has very limited clinical relevance.

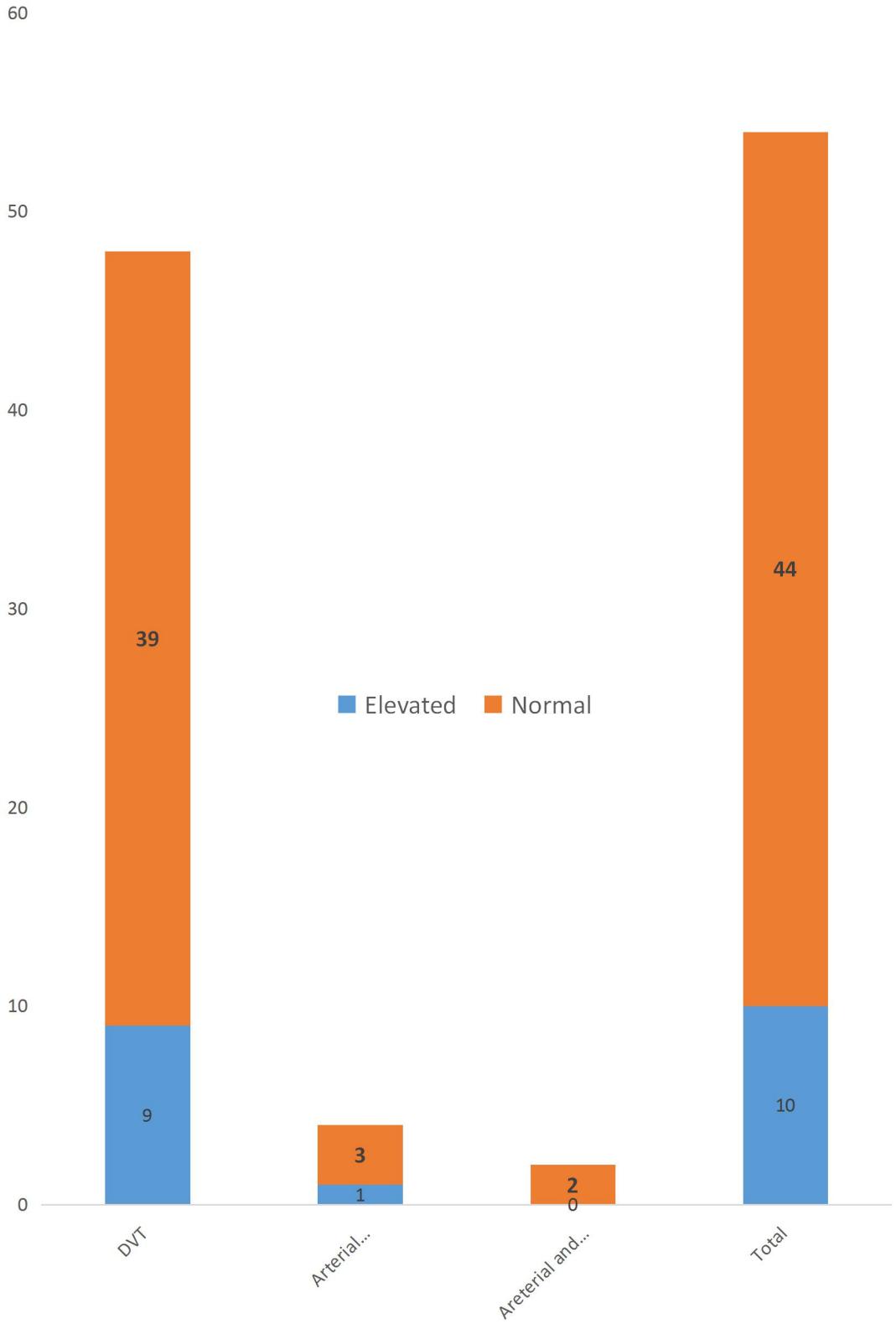
Lupus anticoagulant

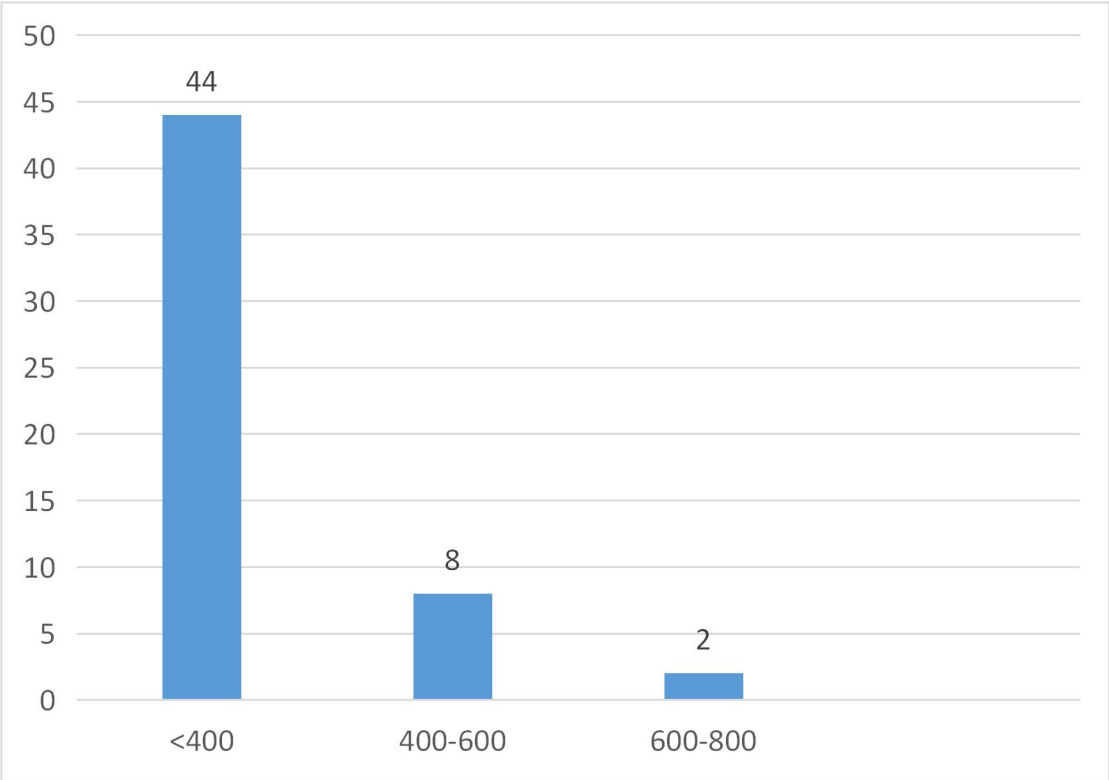
Lupus anticoagulant was estimated by Electromechanical clot detection dRVVT (diluted Russell viper venom time) with normalized ratio (Screen ratio/Confirm ratio) <1.2. 22.2% of the study population (12 out of 54 had a positive lupus anticoagulant study.



Increased Fibrinogen levels

Fibrinogen clotting activity reference normal range was 200.00-400.00 mg/dL. 18.5% of the study population (10 out of 54) had elevated test result





Distribution of Fibrinogen leves in study population

20 (37.1%) Patients in the study population (N=54) had negative result with all the tested thrombophilia marker. 22 (40.7%) Patients in the study population (N=54) gave positive result with more than one tested thrombophilia marker. 9 patients had 2 positive thrombophilia makers, 6 patients had 3 positive thrombophilia markers, 4 patients had 4 positive thrombophilia markers. 3 patients had 5 positive makers thrombophilia markers.

The following thrombophilia markers were negative in the entire study population namely Beta 2 Glycoprotien 1 IgG, Beta 2 Glycoprotien 1 IgM, Cardiolipin Antibody IgG, Protein S deficiency, Prothrombin gene mutation, Homozygous Factor V Leiden gene mutation.

DISSCUSSION

Disscussion

This study was undertaken to determine prevalence of thrombophilia markers inpatients who presented with spontaneous peripheral thrombotic events. In present study, 57.4% patients were male. The age group 30-40 years had maximum number of patients. This is similar to a study of 428 patients in South India where the mean age for venous thrombotic events reported was 31.3 years. Overall 81.6% events occurred in the third and fourth decade. A Danish study reported a steep increase in the incidence of cerebral ischemic events in young adults as a function of age.11 Cumulative effects of hereditary risk factors, aging and environmental factors play a role in contributing to the risk for thrombosis. This is probably the reason why majority of the thrombotic events occurred in the third and fourth decades.

In this study, a possible etiology of thrombophilia was detected in about 62.9% of the patients. 31 (62.9.7%) patients; 21 (67.7%) males and 10 (43.47.5%) females had at least one thrombophilia. This finding underlines the significance of thrombophilias in patients presenting with spontaneous arterial and venous thrombotic events. Patients with thrombophilias causing thrombotic vascular events can be treated with anticoagulants to prevent further episodes and thereby decrease morbidity and mortality.

Hyperhomocysteinemia was the most common thrombophilia amongst both genders and was observed in 23 (42.6%) patients. This is similar to the observations of a study in 428 patients of CVT from South India where the second most common risk factor was hyperhomocysteinemia (78, 18.2%), after anemia (79, 18.4%).[75] In present study, genetic mutations for methyl tetrahydrofolate reductase (MTHFR) C677T showed Homozygous mutation in one patient and Heterozygous mutation in 5 patients. It was the most common risk factor for thrombophilia. Hyperhomocysteinemia is known to cause both arterial and venous thrombosis. Since thrombosis in both arterial and venous vasculature was studied, it is possible that more cases of hyperhomocysteinemia were detected in this study. This is contrast to the aforementioned studies where

venous thrombosis were studied and Factor V Leiden was the most common risk factor.

There were 10 (32.3%) female patients and 13 (56.5%) male patients with no conventional risk factors or thrombophilias. There were a greater number of females without any risk factors who had thrombotic vascular events than males without any risk factors. It is possible that females are at a higher risk than males for thrombotic vascular events due to hormonal influences.

Thrombophilia workups are not supposed to be done in acute setting. Considering the poor follow up rates in Indian population we decided to do the workup in acute setting itself and our findings showed very less bias compared to previous studies which are conducted in ideal recommended timings.

Although at present, inherited thrombophilia testing should only be performed in a highly selective manner, acquiring more insight into genetic and environmental risk factors remains important. This should ultimately lead to better prediction of risk to make evidencebased decisions for patients with all clinical indications. The progress in genetic and bioinformatics techniques may facilitate finding more inherited thrombophilic defects, both in thrombophilic families as well as in population-based case control studies.81,82 In the future, multiple single nucleotide polymorphisms analyses of genes inside or outside the coagulation system may improve risk prediction and become feasible in clinical practice.83 With the current guidelines recommending indefinite anticoagulant therapy to most patients after a first episode of unprovoked VTE,73 being able to identify patients in whom this strategy is not justified is urgently needed. This goal has not been reached with testing for the currently known inherited thrombophilias.

CONCLUSION

Conclusion

Despite the increasing knowledge about the etiology of VTE, testing for inherited thrombophilia is most often not helpful to guide clinical decisions and should not be performed on a routine basis. Selective testing of thrombophilia markers in patients with spontaneous / unprovoked peripheral thrombotic events is strongly recommend in view of above findings. Thrombophilia work up in the acute setting is an equally effective alternative in comparison to standard timing of thrombophilia work up as per different societal guidelines – that is after completion acute phase of illness and anticoagulation treatment course duration – especially with the poor long term follow up in Indian patient population and similar situation in other developing countries

LIMITATIONS

Limitations

The main limitation of the study was small sample size, especially in comparison to the number of patients who dint give consent to undergo thrombophilia panel testing. Another major limitation of the study is the testing was conducted in acute stage of thrombotic illness which may give rise to spurious results and it was against existing societal recommendations.

SUMMARY

Summary

This is a single centre prospective observational trial conducted for a period of 18 months. In this study inpatient admitted with spontaneous peripheral venous, arterial or combined thrombotic events were included. Patients underwent thrombophilia workup and the prevalence of various markers were analysed. 54 for patients were included for the study, of which 48 were DVT cases, 4 were arterial and 2 were combined arterial and venous cases. 31 patients showed at least one thrombophilia marker positivity, with Hyperhomocysteinemia as the commonest factor followed by Lupus Anticoagulant positivity. Our findings are in favour of selective thrombophilia workup in patients with spontaneous peripheral thrombotic events.

BIBLIOGRAPHY

Bibliography

1. Rosendaal FR. Venous thrombosis: a multicausal disease. *Lancet (London, England)*. 1999;353(9159):1167-1173. doi:10.1016/S0140-6736(98)10266-0

2. Crowther MA, Kelton JG. Congenital thrombophilic states associated with venous thrombosis: a qualitative overview and proposed classification system. *Ann Intern Med*. 2003;138(2):128-134. doi:10.7326/0003-4819-138-2-200301210-00014

3. Den Heijer M, Willems HPJ, Blom HJ, et al. Homocysteine lowering by B vitamins and the secondary prevention of deep vein thrombosis and pulmonary embolism: A randomized, placebo-controlled, double-blind trial. *Blood*. 2007;109(1):139-144. doi:10.1182/BLOOD-2006-04-014654

4. Toole JF, Malinow MR, Chambless LE, et al. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: the Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. *JAMA*. 2004;291(5):565-575. doi:10.1001/JAMA.291.5.565

5. Jamison RL, Hartigan P, Kaufman JS, et al. Effect of homocysteine lowering on mortality and vascular disease in advanced chronic kidney disease and end-stage renal disease: a randomized controlled trial. *JAMA*. 2007;298(10):1163-1170. doi:10.1001/JAMA.298.10.1163

6. Lange H, Suryapranata H, De Luca G, et al. Folate therapy and in-stent restenosis after coronary stenting. *N Engl J Med*. 2004;350(26):2673-2681. doi:10.1056/NEJMOA032845

7. Lipoproteins and homocyst(e)ine as risk factors for atherosclerosis: assessment and treatment - PubMed. Accessed December 20, 2021. https://pubmed.ncbi.nlm.nih.gov/7750044/

8. Homocysteine and thrombotic disease - PubMed. Accessed December 20, 2021. https://pubmed.ncbi.nlm.nih.gov/9207431/

9. Den Heijer M, Willems HPJ, Blom HJ, et al. Homocysteine lowering by B vitamins and the secondary prevention of deep vein thrombosis and pulmonary embolism: A randomized, placebo-controlled, double-blind trial. *Blood*. 2007;109(1):139-144. doi:10.1182/BLOOD-2006-04-014654

10. Pabinger I, Schneider B. Thrombotic risk in hereditary antithrombin III, protein C, or protein S deficiency. A cooperative, retrospective study. Gesellschaft fur Thrombose- und Hamostaseforschung (GTH) Study Group on Natural Inhibitors. *Arterioscler Thromb Vasc Biol*. 1996;16(6):742-748. doi:10.1161/01.ATV.16.6.742

11. Ridker PM, Hennekens CH, Lindpaintner K, Stampfer MJ, Eisenberg PR, Miletich JP. Mutation in the gene coding for coagulation factor V and the risk of myocardial infarction, stroke, and venous thrombosis in apparently healthy men. *N Engl J Med*. 1995;332(14):912-917. doi:10.1056/NEJM199504063321403

12. Bucciarelli P, Rosendaal FR, Tripodi A, et al. Risk of venous thromboembolism and clinical manifestations in carriers of antithrombin, protein C, protein S deficiency, or activated protein C resistance: a multicenter collaborative family study. *Arterioscler Thromb Vasc Biol*. 1999;19(4):1026-1033. doi:10.1161/01.ATV.19.4.1026

13. Clinical manifestations and management of inherited thrombophilia: retrospective analysis and follow-up after diagnosis of 238 patients with congenital deficiency of antithrombin III, protein C, protein S - PubMed. Accessed December 20, 2021. https://pubmed.ncbi.nlm.nih.gov/7855783/

14. Coon WW, Willis PW, Keller JB. Venous thromboembolism and other venous disease in the Tecumseh community health study. *Circulation*. 1973;48(4):839-846. doi:10.1161/01.CIR.48.4.839

15. da Silva A, Widmer LK, Martin H, Mall T, Glaus L, Schneider M. Varicose veins and chronic venous insufficiency. *Vasa*. 1974;3(2):118-125. Accessed December 20, 2021. https://europepmc.org/article/MED/4831533

16. Hull RD, Raskob GE. Prophylaxis of venous thromboembolic disease following hip and knee surgery. *J Bone Jt Surg - Ser A*. 1986;68(1):146-150. doi:10.2106/00004623-198668010-00022

17. Tracy RP, Bovill EG, Yanez D, et al. Fibrinogen and factor VIII, but not factor VII, are associated with measures of subclinical cardiovascular disease in the elderly. Results from The Cardiovascular Health Study. *Arterioscler Thromb Vasc Biol*. 1995;15(9):1269-1279. doi:10.1161/01.ATV.15.9.1269

18. Wu KK, Folsom AR, Heiss G, Davis CE, Conlan MG, Barnes R. Association of coagulation factors and inhibitors with carotid artery atherosclerosis. Early results of the Atherosclerosis Risk in Communities (ARIC) Study. *Ann Epidemiol*. 1992;2(4):471-480. doi:10.1016/1047-2797(92)90097-A

19. Vossen CY, Conard J, Fontcuberta J, et al. Familial thrombophilia and lifetime risk of venous thrombosis. *J Thromb Haemost*. 2004;2(9):1526-1532. doi:10.1111/J.1538-7836.2004.00852.X

20. Wells PS, Blajchman MA, Henderson P, et al. Prevalence of antithrombin deficiency in healthy blood donors: a cross-sectional study. *Am J Hematol*. 1994;45(4):321-324. doi:10.1002/AJH.2830450409

21. Laboratory evaluation and clinical characteristics of 2,132 consecutive unselected patients with venous thromboembolism--results of the Spanish Multicentric Study on Thrombophilia (EMET-Study) - PubMed. Accessed December 21, 2021. https://pubmed.ncbi.nlm.nih.gov/9065991/

22. Ben-Tal O, Zivelin A, Seligsohn U. The relative frequency of hereditary thrombotic disorders among 107 patients with thrombophilia in Israel. *Thromb Haemost*. 1989;61(1):50-54. doi:10.1055/S-0038-1646525/ID/JR_13

23. Hereditary deficiency of antithrombin III, protein C and protein S: prevalence in patients with a history of venous thrombosis and criteria for rational patient screening - PubMed. Accessed December 21, 2021. https://pubmed.ncbi.nlm.nih.gov/1450321/

24. Lee DH, Henderson PA, Blajchman MA. Prevalence of factor V Leiden in a Canadian blood donor population. *C Can Med Assoc J*. 1996;155(3):285. Accessed December 21, 2021. /pmc/articles/PMC1487985/?report=abstract

25. Rees DC. The population genetics of factor V Leiden (Arg506Gln). *Br J Haematol*. 1996;95(4):579-586. doi:10.1046/J.1365-2141.1996.D01-1954.X

26. Ethnic distribution of factor V Leiden in 4047 men and women. Implications for venous thromboembolism screening - PubMed. Accessed December 21, 2021. https://pubmed.ncbi.nlm.nih.gov/9109469/

27. Dulíček P, Malý J, Šafářová M. Risk of thrombosis in patients homozygous and heterozygous for factor V Leiden in the East Bohemian region. *Clin Appl Thromb Hemost*. 2000;6(2):87-89. doi:10.1177/107602960000600207

28. Simioni P, Prandoni P, Lensing AWA, et al. The risk of recurrent venous thromboembolism in patients with an Arg506-->Gln mutation in the gene for factor V (factor V Leiden). *N Engl J Med*. 1997;336(6):399-403. doi:10.1056/NEJM199702063360602

29. Price DT, Ridker PM. Factor V Leiden mutation and the risks for thromboembolic disease: a clinical perspective. *Ann Intern Med*. 1997;127(10):895-903. doi:10.7326/0003-4819-127-10-199711150-00007

30. Factor V Leiden mutation and the risks for thromboembolic disease: a clinical perspective - PubMed. Accessed December 21, 2021. https://pubmed.ncbi.nlm.nih.gov/9382368/

31. High risk of thrombosis in patients homozygous for factor V Leiden (activated protein C resistance) - PubMed. Accessed December 21, 2021. https://pubmed.ncbi.nlm.nih.gov/7888671/

32. Prevalence of 20210 A allele of the prothrombin gene in venous thromboembolism patients - PubMed. Accessed December 21, 2021.

https://pubmed.ncbi.nlm.nih.gov/9684784/

33. Margaglione M, Brancaccio V, Giuliani N, et al. Increased risk for venous thrombosis in carriers of the prothrombin G-->A20210 gene variant. *Ann Intern Med*. 1998;129(2):89-93. doi:10.7326/0003-4819-129-2-199807150-00003

34. Increased risk for venous thrombosis in carriers of the prothrombin G-->A20210 gene variant - PubMed. Accessed December 21, 2021. https://pubmed.ncbi.nlm.nih.gov/9669991/

35. Franco RF, Trip MD, Ten Cate H, et al. The 20210 G-->A mutation in the 3'-untranslated region of the prothrombin gene and the risk for arterial thrombotic disease. *Br J Haematol*. 1999;104(1):50-54. doi:10.1046/J.1365-2141.1999.01149.X

36. Geographic distribution of the 20210 G to A prothrombin variant - PubMed. Accessed December 21, 2021. https://pubmed.ncbi.nlm.nih.gov/9569177/

37. Ridker PM, Hennekens CH, Miletich JP. G20210A mutation in prothrombin gene and risk of myocardial infarction, stroke, and venous thrombosis in a large cohort of US men. *Circulation*. 1999;99(8):999-1004. doi:10.1161/01.CIR.99.8.999

38. Koster T, Vandenbroucke JP, Rosendaal FR, Briët E, Blann AD. Role of clotting factor VIII in effect of von Willebrand factor on occurrence of deep-vein thrombosis. *Lancet (London, England)*. 1995;345(8943):152-155. doi:10.1016/S0140-6736(95)90166-3

39. Folsom AR, Nieto FJ, McGovern PG, et al. Prospective study of coronary heart disease incidence in relation to fasting total homocysteine, related genetic polymorphisms, and B vitamins: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation*. 1998;98(3):204-210. doi:10.1161/01.CIR.98.3.204

40. Falcon CR, Cattaneo M, Panzeri D, Martinelli I, Mannucci PM. High prevalence of hyperhomocyst(e)inemia in patients with juvenile venous thrombosis. *Arterioscler Thromb a J Vasc Biol*. 1994;14(7):1080-1083. doi:10.1161/01.ATV.14.7.1080

41. Fermo I, Vigano'D'Angelo S, Paroni R, Mazzola G, Calori G, D'Angelo A. Prevalence of moderate hyperhomocysteinemia in patients with early-onset venous and arterial occlusive disease. *Ann Intern Med*. 1995;123(10):747-753. doi:10.7326/0003-4819-123-10-199511150-00002

42. Hyperhomocysteinemia and deep-vein thrombosis. A case-control study - PubMed. Accessed December 21, 2021. https://pubmed.ncbi.nlm.nih.gov/8972005/

43. den Heijer M, Koster T, Blom HJ, et al. Hyperhomocysteinemia as a risk factor

for deep-vein thrombosis. *N Engl J Med*. 1996;334(12):759-762. doi:10.1056/NEJM199603213341203

44. Oates JA, Wood AJJ, Hirsh J. Heparin. *N Engl J Med*. 1991;324(22):1565-1574. doi:10.1056/NEJM199105303242206

45. Familial antithrombin III deficiency: its natural history, genetics, diagnosis and treatment - PubMed. Accessed December 21, 2021. https://pubmed.ncbi.nlm.nih.gov/6877092/

46. Antithrombin mutation database: 2nd (1997) update. For the Plasma Coagulation Inhibitors Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis - PubMed. Accessed December 21, 2021. https://pubmed.ncbi.nlm.nih.gov/9031473/

47. Bauters A, Zawadzki C, Bura A, et al. Homozygous variant of antithrombin with lack of affinity for heparin: management of severe thrombotic complications associated with intrauterine fetal demise. *Blood Coagul Fibrinolysis*. 1996;7(7):705-710. doi:10.1097/00001721-199610000-00008

48. Hellgren M, Tengborn L, Abildgaard U. Pregnancy in women with congenital antithrombin III deficiency: experience of treatment with heparin and antithrombin. *Gynecol Obstet Invest*. 1982;14(2):127-141. doi:10.1159/000299460

49. Different prevalence of thromboembolism in the subtypes of congenital antithrombin III deficiency: review of 404 cases - PubMed. Accessed December 21, 2021. https://pubmed.ncbi.nlm.nih.gov/3328320/

50. Protein C deficiency: a database of mutations, 1995 update. On behalf of the Subcommittee on Plasma Coagulation Inhibitors of the Scientific and Standardization Committee of the ISTH - PubMed. Accessed December 21, 2021. https://pubmed.ncbi.nlm.nih.gov/7482420/

51. Dahlbäck B. The protein C anticoagulant system: inherited defects as basis for venous thrombosis. *Thromb Res*. 1995;77(1):1-43. doi:10.1016/0049-3848(94)00138-4

52. Prevalence of protein C deficiency in the healthy population - PubMed. Accessed December 21, 2021. https://pubmed.ncbi.nlm.nih.gov/7740502/

53. Boekholdt SM, Kramer MHH. Arterial thrombosis and the role of thrombophilia. *Semin Thromb Hemost*. 2007;33(6):588-596. doi:10.1055/S-2007-985755

54. Manco-Johnson MJ, Martar RA, Jacobson LJ, Hays T, Warady BA. Severe protein C deficiency in newborn infants. *J Pediatr*. 1988;113(2):359-363.

doi:10.1016/S0022-3476(88)80284-1

55. Coumarin necrosis associated with hereditary protein C deficiency - PubMed. Accessed December 21, 2021. https://pubmed.ncbi.nlm.nih.gov/6547283/

56. McGehee WG, Klotz TA, Epstein J, Rapaport SI. Coumarin necrosis associated with hereditary protein C deficiency. *Ann Intern Med*. 1984;101(1):59-60. doi:10.7326/0003-4819-101-1-59

57. Comp PC, Nixon RR, Cooper MR, Esmon CT. Familial protein S deficiency is associated with recurrent thrombosis. *J Clin Invest*. 1984;74(6):2082-2088. doi:10.1172/JCI111632

58. Protein S deficiency - PubMed. Accessed December 21, 2021. https://pubmed.ncbi.nlm.nih.gov/9198178/

59. Plasma protein S deficiency in familial thrombotic disease - PubMed. Accessed December 21, 2021. https://pubmed.ncbi.nlm.nih.gov/6238642/

60. Comp PC. Laboratory evaluation of protein S status. *Semin Thromb Hemost*. 1990;16(2):177-181. doi:10.1055/S-2007-1002666

61. Castoldi E, Maurissen LFA, Tormene D, et al. Similar hypercoagulable state and thrombosis risk in type I and type III protein S-deficient individuals from families with mixed type I/III protein S deficiency. *Haematologica*. 2010;95(9):1563-1571. doi:10.3324/HAEMATOL.2010.021923

62. Functional and immunologic protein S levels are decreased during pregnancy - PubMed. Accessed December 21, 2021. https://pubmed.ncbi.nlm.nih.gov/2944555/

63. Faught W, Garner P, Jones G, Ivey B. Changes in protein C and protein S levels in normal pregnancy. *Am J Obstet Gynecol*. 1995;172(1 Pt 1):147-150. doi:10.1016/0002-9378(95)90104-3

64. Kemkes-Matthes B. Acquired protein S deficiency. *Clin Investig*. 1992;70(6):529-534. doi:10.1007/BF00210237

65. Vigano-D'Angelo S, D'Angelo A, Kaufman CE, Sholer C, Esmon CT, Comp PC. Protein S deficiency occurs in the nephrotic syndrome. *Ann Intern Med*. 1987;107(1):42-47. doi:10.7326/0003-4819-107-1-42

66. Mesenteric vein thrombosis associated with a familial deficiency of free protein S - PubMed. Accessed December 21, 2021. https://pubmed.ncbi.nlm.nih.gov/1828142/

67. A protein S deficient family with portal vein thrombosis - PubMed. Accessed December 21, 2021. https://pubmed.ncbi.nlm.nih.gov/2935967/

68. Vrethem M, Dahle C, Lindahl T, Ernerudh J. Association between deficiency of free protein S and anticardiolipin antibodies in patients = 65 years of age with acute ischemic stroke and TIA. *Eur J Neurol*. 1998;5(5):491-497. doi:10.1046/J.1468-1331.1998.550491.X

69. Anderson DR, Brill-Edwards P, Walker I. Warfarin-induced skin necrosis in 2 patients with protein S deficiency: successful reinstatement of warfarin therapy. *Haemostasis*. 1992;22(3):124-128. doi:10.1159/000216307

70. Dahlback B, Carlsson M, Svensson PJ. Familial thrombophilia due to a previously unrecognized mechanism characterized by poor anticoagulant response to activated protein C: prediction of a cofactor to activated protein C. *Proc Natl Acad Sci U S A*. 1993;90(3):1004. doi:10.1073/PNAS.90.3.1004

71. Bertina RM, Koeleman BPC, Koster T, et al. Mutation in blood coagulation factor V associated with resistance to activated protein C. *Nature*. 1994;369(6475):64-67. doi:10.1038/369064A0

72. (PDF) Inherited resistance to activated protein C is corrected by anticoagulant cofactor activity found to be a property of Factor V. Accessed December 21, 2021. https://www.researchgate.net/publication/15091673_Inherited_resistance_to_activated_protein_C_is_corrected_by_anticoagulant_cofactor_activity_found_to_be_a_property_of_Factor_V

73. Rodeghiero F, Tosetto A. Activated protein C resistance and factor V Leiden mutation are independent risk factors for venous thromboembolism. *Ann Intern Med*. 1999;130(8):643-650. doi:10.7326/0003-4819-130-8-199904200-00004

74. Chronic venous insufficiency of the lower limbs and its socio-economic significance - PubMed. Accessed December 20, 2021. https://pubmed.ncbi.nlm.nih.gov/1765717/

75. Narayan D, Kaul S, Ravishankar K, Suryaprabha T, Bandaru VS, Mridula KR, et al. Risk factors, clinical profile, and long-term outcome of 428 patients of cerebral sinus venous thrombosis: Insights from Nizam's Institute Venous Stroke Registry, Hyderabad (India). Neurol India. 2012;60:154-9

ANNEXURES

Study Performa

DVT											
Arterial thrombosis											
Sl No:		Date of OPD visit: ___/___/_____									
Name:	Date of OPD visit: / /	Age:									
Address with Phone number:	Age:	OP No:									
Address with Phone n	OP No:	IP No:									
umber:	IP No:										
Presenting complaints											
Limb affected	Right upper		Right lower			Left upper			Left lower		
Symptoms	Right upper	Yes	Right lower	No		Left upper	Duration		Left lower		
Pain	Yes		No			Duration					
Swelling											
Discolouration											
Cool limb											
Breathlessness											
Discolouration											
Relevant past history											
Weakness											
Arterial thrombosis											
Decreased touch sens											
Venous thrombosis											
ation											
Anti-coagulation											
Relevant past history											
Obstetric score											
Arterial thrombosis											
Diabetes											
Venous thrombosis											
Hyperlipidemia											
Anticoagulation											
Hypertension											
Obstetric score											
Smoking											
Diabetes											
Alcohol consumption											
Hyperlipidemia											
Remarks											
Hypertension											
Drug history											
Smoking											
Examination findings											
Alcohol consumption											
GCS	___/15		Pulse rate			Blood pressure					
Remarks											
Affected limb											
Drug history											
Swelling/Cyanosis											
Examination findings											
Peripheral Pulses											
GCS	/15		Pulse rate			Blood pressure					
Imaging and Laboratory reports											
Affected limbCyanosisGangreneMovementsColdness uptoMottlingPower											
Pulse											
Carotid /Brachial /Radial /Ulnar /Abdominal Aort a	Femoral /Popliteal /ATA /PTA /DPA /										
Imaging and Laboratory reports											

PATIENT CONSENT FORM

Study title: Prevalence of thrombophilia markers in patients with spontaneous peripheral thrombotic events

Study site: Jain Institute of Vascular Sciences, Bhagwan Mahaveer Jain Hospital, Bangalore.

I have been explained about the nature of the study. I have been explained that the study identifies Prevalence of thrombophilia markers in patients with spontaneous peripheral thrombotic events.

I have been read to about and understand the purpose of the study, type of study, risk and benefits associated with my involvement. I have been given the opportunity to ask questions regarding various aspects of the study. I understand that confidentiality is maintained in patient details. The information collected is only for research. I also understand that I am free to withdraw from the study at any point of time and standard of care provided to me does not change if I am quitting/not willing to take part in the study.

I the undersigned agree to voluntarily participate in this study and authorize the collection and disclosure of my personal information for the purpose of research.

Subject name and signature/ thumb impression: **Date:**

Name and signature/ thumb impression of witness: **Date:**

Name and signature of person obtaining consent: **Date:**

Scientific Committee Letter

Bhagwan Mahaveer
JAIN HOSPITAL
A Unit of Bhagwan Mahaveer Memorial Jain Trust
080 4087 5555 | 4110 0550
No. 17, Millers Road, Vasanthnagar
Bengaluru 560052
website - www.bmjh.org

caring
with
compassion

SCIENTIFIC COMMITTEE

APPROVAL CERTIFICATE OF DISSERTATION FOR NBE

Approval has been granted by Scientific Committee of Bhagwan Mahaveer Jain Hospital for the following Dissertation as per NBE requirement **PREVALENCE OF THROMBOPHILIA MARKERS IN PATIENTS WITH SPONTANEOUS PERIPHERAL THROMBOTIC EVENTS** Conducted by **DR. AHSAN V.P.** Department of **VASCULAR SURGERY** under the guidance of **DR. VIVEKANAND** approximate period of study is from **AUGUST 2019 to JULY 2020.**

Scientific Committee meeting held on **5/12/2019**

Date : 24/03/2020

Dr. (Wg Cdr) M.D.Marker
Medical Director
BMJH Scientific Committee

Dr. (Wg Cdr) M.D. Marker
Medical Director
BHAGWAN MAHAVEER JAIN HOSPITAL
Bangalore-560 052

Ethic Committee Letter

ETHICS COMMITTEE ON HUMAN RESEARCH
BHAGWAN MAHAVEER JAIN HOSPITAL
A UNIT OF BHAGWAN MAHAVEER MEMORIAL JAIN TRUST
Millers Road, Vasanthnagar, Bangalore - 560 052.
✆ : 4087 5555 (30 Lines), 4110 0550, Fax: 080 2226 1153
e-mail : bmjh.mdoffice@gmail.com

APPROVAL CERTIFICATE OF DISSERTATION FOR NBE

Approval has been granted by Ethics Committee of Bhagwan Mahaveer Jain Hospital for the following Dissertation as per NBE requirement **PREVALENCE OF THROMBOPHILIA MARKERS IN PATIENTS WITH SPONTANEOUS PERIPHERAL THROMBOTIC EVENTS** Conducted by **DR. AHSAN V.P.** Department of **VASCULAR SURGERY** under the guidance of **DR. VIVEKANAND** approximate period of study is from **DECEMBER 2019 to NOVEMBER 2020.**

Ethics Committee meeting held on **7/12/2019.**

Dr. (Wg Cdr) M.D.Marker
Member Secretary
BMJH Ethics Committee

Member Secretery
Ethics Committee on Human Research
Bhagwan Mahaveer Jain Hospital
Miller's Road, Vasanthnagar
Bangalore-560 052

Date : 24/03/2020

S L NO	AGE	SEX	INDEX LIMB	SEGMENT INVOLVED VENOUS	SEGMENT INVOLVED ARTERIAL	PAST HISTORY	TOBACCO ABUSE	HB	TC	PLATELETS	ESR	CREATININE	Na+	K+	Stool for occult blood	BILIRUBIN TOTAL	DIRECT BILIRUBIN	SGPT	SGOT	ALP	GGT	ALBUMIN	GLOBULIN	INR	APTT	CEA	AFP	CA125	CA19-9	PSA	ECG	2D ECHO	USG ABDOMEN	Venous Doppler	CT ANGIOGRAM	INTERVENTION IF ANY	Lupus anticoagulant	AT	Pro C	Pro S	Factor V Leiden Mutation	Prothrombin gene mutation	MTHFR Gene mutation	Beta 2 Glycoprotein IgG	Beta 2 Glycoprotein IgM	Cardiolipin antibody IgM	Cardiolipin antibody IgG	Homocysteine	Factor I…	Factor VIII	Factor XI	Fibrinogen
1	74	F	Left	CIV to distal	0	PE 2 years back, Hypothy	0	12	12	2.51	21	1.2	139	5	0	0.3	0.1	15	13	83	17	3.72	2.9	1.3	23.7	3.7	3.8	12	2.3	nil	Nor	56% N	Normal	CIV to di	0	0	1.26	83	82	87	0	0	Hetero	2.4	7.13	8.36	8.7	18.8	51	>200	101	455.7
2	48	F	Left	CIV to distal	0	0	0	12	7	3.6	14	0.94	129	4	0	1.2	0.4	21	18	65	44	3.5	3.1	1	34.1	2.6	1.6	9.8	1.03	nil	Nor	54% N	Normal	CIV to di	0	0	1.13	91	94	96	0	0	0	4.5	8.4	5.6	11	8.3	77	84	88.5	348.6
3	51	F	Left	CIV to distal	0	0	0	10	8	2.3	19	0.83	135	4	0	0.6	0.5	18	17	36	66	3.32	3.3	0.9	40.6	1.8	2.1	11	2.3	nil	Nor	60% N	Normal	CIV to di	0	0	1.27	84	83	66	0	0	0	3.6	2.6	3.1	5.6	7.2	86	85.6	96.1	256.3
4	36	F	Left	CIV to distal	0	0	0	14	7	2.15	9	0.68	132	5	0	0.7	0.4	32	34	61	45	4.02	3.5	1	38.2	nil	nil	nil	nil	nil	Nor	58% N	Normal	CIV to di	0	0	1.02	86	106	84	0	0	Hetero	1.5	4.8	2.8	7.1	29.1	92	79	141	374.2
5	32	F	Left	CIV to distal	0	0	0	12	9	4.5	21	1	137	3	0	0.65	0.3	24	17	44	38	3.45	3.1	1	38.3	nil	nil	nil	nil	nil	Nor	49% N	Normal	CIV to di	0	0	0.98	82	97	77	0	0	Hetero	6.1	3.8	7.74	2.8	48.1	78	64	76.1	386.2
6	41	F	Left	CIV to distal	0	0	0	13	10	1.19	23	1.2	133	5	0	1.1	0.3	15	31	38	29	3.26	2.8	1	39.1	2.1	1.9	13	3.1	nil	Nor	52% N	Normal	CIV to di	0	0	1.12	87	71	75	0	0	0	2.3	11.3	5.84	3.1	46.2	102	95	103	241.3
7	38	F	Left	CIV to distal	0	0	0	11	8	5.1	20	0.94	128	4	0	1.5	1	18	16	51	71	3.7	3.2	0.9	28.5	nil	nil	nil	nil	nil	Nor	54% N	Normal	CIV to di	0	0	1.31	94	88	93	0	0	0	3.5	5.1	3.15	4.5	10.2	86	83	87.9	256.3
8	54	F	Left	CIV to distal	0	0	1	16	11	3.2	8	0.71	141	4	0	0.9	0.5	21	37	42	37	3.1	2.8	1.1	36.5	2.7	1.2	8.9	2.53	nil	Nor	58% N	Normal	CIV to di	0	0	1.05	88	91	84	0	0	0	1.2	5.8	3.62	8.6	9.74	92	66.3	97.4	348.2
9	36	F	Left	EIV to distal	0	0	0	14	7	2.36	10	0.85	138	5	0	1.4	0.6	24	24	36	41	3.8	3.1	0.9	33.2	nil	nil	nil	nil	nil	Nor	54% N	Normal	EIV to di	0	0	1.07	97	84	81	0	0	0	4.8	6.4	3.82	3.5	7.34	78	78.5	78.2	396.3
10	36	F	Left	EIV to distal	0	0	0	11	11	3.1	19	0.81	136	5	0	0.8	0.2	17	40	91	72	2.9	3	1	37.6	nil	nil	nil	nil	nil	Nor	61% N	Normal	EIV to di	0	0	1.27	101	103	87	0	0	0	9.1	9.21	4.25	2.1	8.5	88	94.5	112	263.1
11	42	F	Left	EIV to distal	0	0	0	12	9	1.8	16	0.84	132	4	0	0.8	0.5	16	18	72	59	3.41	3.2	1	40	3	2.4	11	1.89	nil	Nor	52% N	Normal	EIV to di	0	0	1.26	77	78	73	0	0	0	1.3	5.7	5.16	7.6	42.3	142	112	94.3	342.1
12	28	F	Left	CFV to distal	0	0	0	13	8	4.6	15	1.1	135	4	0	0.6	0.4	26	28	35	38	3.57	2.6	1	37.4	nil	nil	nil	nil	nil	Nor	48% N	Normal	CFV to d	0	0	1.16	86	103	94	Hetero	0	0	6.5	10.6	11.5	4.3	52.1	80	103	102	390.1
13	51	F	Left	CFV to distal	0	0	0	15	8	4.1	9	0.81	133	4	0	0.9	0.3	21	21	38	41	3.54	3.3	1	37.6	2.9	4.1	9.5	1.12	nil	Nor	56% N	Normal	CFV to d	0	0	1.05	91	94	68	0	0	0	8.1	12.3	6.6	3.9	8.64	84	71.2	74.6	421.3
14	32	F	Left	PV to distal	0	0	0	13	8	2.1	14	0.85	137	3	0	1.2	0.8	19	37	54	29	3.33	3.2	1	29.6	nil	nil	nil	nil	nil	Nor	55% N	Normal	PV to dis	0	0	1.07	85	112	75	0	0	0	2.3	8.1	9.8	7.2	7.48	97	69.3	84.6	283.1
15	35	F	Bilatera	CIV to distal	0	0	0	13	11	3.2	18	0.76	142	3	0	0.8	0.1	14	16	46	60	3.45	3.1	1	38.4	nil	nil	nil	nil	nil	Nor	51% N	Normal	CIV to di	0	0	1.06	87	88	93	0	0	0	4.6	3.4	3.6	5.2	9.32	112	95.6	72.3	276.4
16	50	F	Right	CIV to distal	0	0	0	12	7	3.3	17	0.94	135	5	0	0.9	0.3	38	17	52	44	4.1	3.6	1.2	39.5	2.7	2.3	9.1	2.4	nil	Nor	58% N	Normal	CIV to di	0	0	1.3	84	96	84	0	0	0	2.5	1.9	5.4	2	7.14	101	118	114	371.2
17	62	F	Right	CIV to distal	0	DM, HTN	0	10	4	3.52	36	0.81	136	4	0	1.3	0.5	24	15	60	46	3.6	3.3	0.9	38.2	2.8	3.1	13	4.1	nil	Nor	60% N	Normal	CIV to di	0	0	0.99	90	84	76	0	0	0	11	7.4	6.12	4.1	8.75	89	116	97.6	390.5
18	39	F	Right	CIV to distal	0	0	0	14	10	3.15	7	0.84	134	4	0	1.1	0.6	17	31	57	37	3.51	3.12	1	39.2	nil	nil	nil	nil	nil	Nor	57% N	Normal	CIV to di	0	0	1.03	98	105	64	0	0	0	2.9	5.6	5.42	3.9	7.68	96	77.4	108	386.4
19	45	F	Right	CIV to distal	0	0	0	13	12	3.65	16	0.78	132	4	0	0.7	0.5	16	28	58	50	3.25	3.06	0.9	37.6	3.1	2.8	11	3.4	nil	Nor	60% N	Normal	CIV to di	0	0	1.01	93	73	95	0	0	0	3.4	121	10.5	5.1	8.64	72	85.6	94.5	375.2
20	26	F	Right	EIV to distal	0	0	0	13	10	2.5	14	0.86	138	3	0	1.2	0.2	24	24	45	47	3.8	3.24	1	34.7	nil	nil	nil	nil	nil	Nor	54% N	Normal	EIV to di	0	0	0.96	87	86	83	0	0	0	5.1	9.3	5.76	10	9.3	90	92.3	78.1	258.4
21	87	F	Right	CFV to distal	0	0	0	14	8	2.15	33	0.5	135	4	0	1.1	0.1	21	22	44	48	3.4	3.5	1	29.5	1.4	1.2	26	<2.0	nil	Nor	55% N	Normal	CFV to d	0	0	1.15	72	64	127	Hetero	0	0	7.8	7.11	8.87	8.8	27.3	51	77.6	40.4	200.3
22	42	M	Left	CIV to distal	0	0	0	14	6	1.56	12	0.84	135	3	0	0.87	0.2	17	40	62	57	3.2	3.1	0.9	34.1	nil	nil	nil	nil	nil	Nor	56% N	Normal	CIV to di	0	0	1.13	100	94	78	0	0	0	2.6	6.8	4.65	5.4	6.87	78	88.2	71.2	326.1
23	40	M	Left	CIV to distal	0	DM	1	13	9	1.77	17	0.7	135	4	0	1.1	0.7	43	49	88	73	4.76	2.9	1	32.5	2.9	8.9	nil	25.5	0.48	Nor	60% N	Normal	CIV to di	0	0	0.9	95	109	73	0	0	0	5.7	11.9	8.41	9.4	6.31	27	>150	95.4	378.2
24	51	M	Left	CIV to distal	0	0	0	13	11	1.69	23	1.2	131	4	0	0.9	0.4	25	31	74	60	3.1	3.2	1	33.8	1.2	1.4	nil	2.82	0.95	Nor	60% N	Normal	CIV to di	0	0	1.12	84	85	74	0	0	0	3.3	11	9.38	8.8	69.3	>150	26	110	443.9
25	44	M	Left	CIV to distal	0	0	0	13	12	3.3	18	1.2	128	4	0	0.78	0.3	18	16	48	42	4.3	3.6	1.1	39.1	2.3	2.8	nil	3.1	0.64	Nor	57% N	Normal	CIV to di	0	0	1.02	87	96	101	0	0	0	4.3	10.4	3.85	11	50.7	66	76.1	88.7	218.6
26	46	M	Left	CIV to distal	0	0	0	13	9	1.65	11	0.86	135	3	0	1.4	0.4	24	18	54	35	3.3	3.1	1	40.3	nil	nil	nil	nil	nil	Nor	54% N	Normal	CIV to di	0	0	0.96	94	102	98	0	0	0	7.2	4.6	6.21	2.7	41.5	84	103	94.3	327.8
27	28	M	Left	CIV to distal	0	0	0	10	11	5.1	29	0.94	134	4	0	0.89	0.3	27	24	35	40	2.9	3.2	0.9	37.8	nil	nil	nil	nil	nil	Nor	55% N	Normal	CIV to di	0	0	1.16	83	84	92	0	0	0	6.1	3.1	2.87	3.5	8.47	77	87.9	103	552.2
28	43	M	Left	CIV to distal	0	0	0	13	7	2.5	23	0.96	138	4	0	0.65	0.4	18	17	71	74	3.6	4.12	1	38.4	1.7	2.1	nil	1.6	0.78	Nor	54% N	Normal	CIV to di	0	0	1.08	94	76	88	0	0	0	3.2	2.7	6.4	4.8	9	75	97.4	96	294.6
29	49	M	Left	CIV to distal	0	0	0	13	9	1.38	16	1.1	129	3	0	0.8	0.1	17	13	52	35	3.4	3.1	1	36.6	2.1	3	nil	2.4	0.94	Nor	60% N	Normal	CIV to di	0	0	1.06	92	82	86	0	0	0	8.3	2.5	5.26	3.1	10.5	116	78.2	118	313.2
30	33	M	Left	CIV to distal	0	0	0	11	10	1.73	18	0.87	140	5	0	0.6	0.2	21	24	39	64	3.4	2.9	1	24.6	nil	nil	nil	nil	nil	Nor	55% N	Normal	CIV to di	0	0	1.12	88	94	67	0	0	0	3.4	12.6	7.12	5.1	11.3	77	84.6	116	284.5
31	52	M	Left	CIV to distal	0	0	0	15	11	1.68	9	0.64	136	5	0	0.5	0.2	22	26	34	51	4	3.2	0.9	40.5	nil	nil	nil	nil	nil	Nor	57% N	Normal	CIV to di	0	0	1.05	82	74	84	0	0	Hetero	3.8	3.4	12.3	3.614	7.1	135	103	77.4	266.4
32	25	M	Left	CIV to distal	0	0	0	15	5	1.45	10	0.8	132	5	0	0.7	0.1	15	18	44	38	3.2	3.3	1.1	33.1	nil	nil	nil	nil	nil	Nor	56% N	Normal	CIV to di	0	0	1.07	87	83	92	0	0	0	2.6	11.2	6.7	5.6	6.52	92	68.4	85.6	359.1
33	48	M	Left	CIV to distal	0	0	1	14	11	2.1	12	0.97	128	3	0	1.1	0.7	23	20	51	44	3.6	3.5	1	37.8	nil	nil	nil	nil	nil	Nor	59% N	Normal	CIV to di	0	0	1.03	83	97	101	0	0	0	5.4	2.5	2.3	4.1	9.8	78	114	92.3	273.9
34	26	M	Left	EIV to distal	0	0	0	11	11	3.59	33	0.7	140	4	0	0.4	0.2	38	25	99	46	3.5	4.1	1.3	30.4	nil	nil	nil	nil	nil	Nor	53% N	Normal	EIV to di	0	0	1.18	86	83	84	0	0	0	1.7	7.83	10.6	9.1	72.3	21	98	146	359.4
35	44	M	Left	EIV to distal	0	0	0	12	11	1.8	14	0.86	134	3	0	0.8	0.5	24	31	88	59	3.3	3.1	0.9	34.6	nil	nil	nil	nil	nil	Nor	54% N	Normal	EIV to di	0	0	1.11	91	91	78	0	0	0	2.8	5.9	1.5	3.2	8.74	70	102	94.6	281.4
36	46	M	Left	CFV to distal	0	0	0	14	10	3.2	12	1.4	136	4	0	0.74	0.2	11	17	81	53	3.7	3.3	1.1	28.9	nil	nil	nil	nil	nil	Nor	57% N	Normal	CFV to d	0	0	1.05	87	96	77	0	0	0	4.1	6.4	4.4	2.7	10.5	75	98.7	84.6	358.6
37	45	M	Left	SFV to distal	0	Heamorrhoidectomy 10 y	0	14	6	2.72	29	1	138	4	0	0.3	0.1	24	21	94	35	4.1	3.2	0.9	30.3	2.3	4.1	nil	4.69	2.65	Nor	55% N	Normal	SFV to di	0	0	1.11	76	131	140	Hetero	0	0	10	8.03	9.38	8.9	114	83	83	57.6	291.1
38	28	M	Left	PV to distal	0	0	0	16	10	3.27	18	0.9	138	4	0	1	0.5	32	23	##	28	4.44	3.2	1	35.5	nil	nil	nil	nil	nil	Nor	60% N	Normal	PV to di	0	0	1.14	107	96	137	0	0	0	1.4	7.36	8.65	8.7	21	48	111	65.6	494.5
39	28	M	Bilatera	IVC to bilateral	0	0	1	14	9	3.24	74	1.1	133	5	0	0.8	0.2	16	17	48	50	3.8	3.3	1.2	28.7	nil	nil	nil	nil	nil	Nor	62% N	Normal	Infraren	0	0	1.33	93	79	107	0	0	Hetero	9.1	7.09	8.04	8.7	26	120	145	93.9	730.9
40	50	M	Bilatera	IVC to bilateral	0	0	0	11	11	3.59	33	0.7	140	4	0	0.4	0.2	38	29	99	46	4.13	4.1	1.3	30.4	nil	nil	nil	nil	nil	Nor	60% N	Normal	Infraren	0	0	1.18	86	83	84	0	0	0	1.7	7.83	10.6	9.1	21.3	21	98	140	359.4
41	37	M	Right	CIV to distal	0	0	0	14	9	3.62	12	0.65	133	5	0	0.69	0.3	18	21	78	52	3.3	3	1	24.3	1.8	3.1	nil	8.1	0.74	Nor	58% N	Normal	CIV to di	0	0	0.98	88	85	75	0	0	0	3.3	2.4	1.87	3.1	8.6	85	64.9	82.1	199.7
42	42	M	Right	CIV to distal	0	0	0	13	5	5.1	31	1.1	136	5	0	0.8	0.2	14	18	48	44	3.5	3.4	1	35.8	2.3	1.8	nil	6.1	0.38	Nor	54% N	Normal	CIV to di	0	0	1.12	93	77	86	0	0	0	6.1	5.2	5.3	2.6	7.45	64	86.4	104	248.1
43	48	M	Right	CIV to distal	0	0	1	14	6	1.76	39	1.2	140	5	0	0.7	0.3	22	23	##	38	4.02	2.9	0.9	30.2	2.1	2.8	nil	<2.0	0.27	Nor	60% N	Normal	CIV to di	0	0	1.37	80	71	100	0	0	0	11	12.3	9.36	120	30.6	102	54.6	68.8	386.3
44	39	M	Right	EIV to distal	0	0	0	19	5	1.68	8	0.8	137	5	0	2.6	0.8	20	34	##	##	3.7	3.1	1.3	48.9	nil	nil	nil	nil	nil	Nor	60% N	Normal	EIV to di	0	0	1.13	74	67	138	Hetero	0	0	8.3	7.06	7.96	8.7	33.5	60	158	30	194.7
45	38	M	Right	EIV to distal	0	0	0	20	9	1.95	14	0.8	136	3	0	2.5	1.6	18	9	18	94	3.29	3.8	1.1	27.5	nil	nil	nil	nil	nil	Nor	61% N	Normal	EIV to di	0	0	1.07	91	66	93	0	0	Homo	1.1	8.06	9.44	9.1	28.3	70	88	63.3	342.2
46	48	M	Right	CFV to distal	0	0	0	13	11	4.6	9	0.95	132	5	0	0.7	0.3	21	24	45	32	2.9	3.1	1	44.1	3.2	1.8	nil	2.5	0.87	Nor	56% N	Normal	CFV to d	0	0	1.26	87	94	78	0	0	0	4.5	3.1	4.6	2.9	8.26	97	98.7	76.5	325.6
47	56	M	Right	CFV to distal	0	0	0	13	10	2.3	16	0.78	132	6	0	0.9	0.4	17	21	50	37	3.4	3.3	1	38.7	2.7	2.8	nil	3.1	0.45	Nor	58% N	Normal	CFV to d	0	0	1.28	84	87	82	0	0	0	3.6	7.2	3.52	6.3	9.48	84	94.3	97.4	387.5
48	41	M	Right	PV to distal	0	0	0	14	9	1.75	24	0.9	134	4	0	0.7	0.4	15	17	38	52	3.3	3.1	0.9	34.6	3.1	4.1	nil	9.1	0.66	Nor	60% N	Normal	PV to di	0	0	1.02	89	93	73	0	0	0	2.3	1.4	2.89	5.1	7.63	105	64.5	114	496.2
49	39	F	Left	0	SFA PA Infrapop	0	0	8	8	5.26	38	0.6	140	4	0	1.3	0.4	18	44	58	42	3.3	2.8	1.3	41.1	nil	nil	nil	nil	nil	Nor	63% N	Normal	0	Distal SF	Transpopli	1.15	81	147	138	0	0	0	3.4	11.1	8.24	9.1	38.1	>150	102	103	368.6
50	42	F	Left	0	CIA to distal	Appendicectomy 20 year	0	15	8	3.1	14	0.9	134	4	0	6	0.2	19	21	45	60	3.2	3	0.9	38	nil	nil	nil	nil	nil	Nor	58% N	nil	0	CIA to di	Left trasfer	0.98	87	111	126	0	0	0	7.6	9.3	6.3	10	32.1	106	114	105	278.3
51	43	M	Bilatera	0	Aorto bi iliac to d	HTN	0	8	7	2.49	44	0.9	136	5	1	0.7	0.3	11	20	##	15	3.66	3.1	1.1	38.2	1.4	2.8	nil	<2.0	0.56	Q w	58% N	Normal	0	Distal in	Bilateral tr	1.37	72	62	74	0	0	0	2	7.68	8.15	8.9	12.6	10	204	28.4	612.1
52	26	M	Right	0	CFA to distal	0	0	15	8	3.1	15	0.7	136	4	0	0.4	0.2	21	24	82	66	4.1	3.2	0.9	36.5	nil	nil	nil	nil	nil	Nor	61% N	nil	0	CFA to d	Right trans	1.24	105	92	132	0	0	0	1	6.84	8.06	8.7	33.4	>150	147	119	290.4
53	29	M	Left	CIV to distal	SFA PA Infrapop	0	0	14	11	4.5	13	0.9	132	4	0	0.9	0.2	38	24	45	51	3.8	4	0.9	40.3	nil	nil	nil	nil	nil	Nor	0	Normal	CIV to di	SFA to d	Transfemo	1.12	87	78	65	0	0	0	7.4	2.1	12.4	7.4	25.6	87	75.4	86.5	256.3
54	34	M	Left	CIV to distal	CFA to distal	0	0	15	12	1.78	9	0.78	129	3	0	0.8	0.3	25	35	62	70	3.7	3	0.9	28	nil	nil	nil	nil	nil	Nor	55% N	Normal	CIV to di	CFA to d	Transfemo	1.32	98	82	103	0	0	0	2.3	5.6	8.3	9.6	18.7	104	61.3	84.3	385.2