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Prothrombin Thrombophilia

Synonym: Prothrombin G20210A Thrombophilia

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Summary

Clinical characteristics

Prothrombin thrombophilia is characterized by venous thromboembolism (VTE) manifest most commonly in adults as deep-vein thrombosis (DVT) in the legs or pulmonary embolism. The clinical expression of prothrombin thrombophilia is variable; many individuals heterozygous or homozygous for the 20210G>A *F2* variant never develop thrombosis, and while most heterozygotes who develop thrombotic complications remain asymptomatic until adulthood, some have recurrent thromboembolism before age 30 years. The relative risk for DVT in adults heterozygous for the 20210G>A variant is two- to fivefold increased; in children, the relative risk for thrombosis is three- to fourfold increased. Heterozygosity for 20210G>A has at most a modest effect on recurrence risk after a first episode. Although prothrombin thrombophilia may increase the risk for pregnancy loss, its association with preeclampsia and other complications of pregnancy such as intrauterine growth restriction and placental abruption remains controversial. Factors that predispose to thrombosis in prothrombin thrombophilia include: the number of 20210G>A alleles; presence of coexisting genetic abnormalities including factor V Leiden; and acquired thrombophilic disorders (e.g., antiphospholipid antibodies). Circumstantial risk factors for thrombosis include pregnancy and oral contraceptive use. Some evidence suggests that the risk for VTE in 20210G>A heterozygotes increases after air travel.

Diagnosis/testing

The diagnosis of prothrombin thrombophilia is established in a proband by identification of a heterozygous or homozygous 20210G>A variant (also known as c.*97G>A) in *F2*, the gene encoding prothrombin.

Management

Treatment of manifestations: Management depends on the clinical circumstances. The first acute thrombosis is treated according to standard guidelines. The duration of anticoagulation therapy is determined by assessment of the risks for VTE recurrence and anticoagulant-related bleeding. 20210G>A heterozygosity alone is not an indication for long-term anticoagulation in the absence of other risk factors.

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Surveillance: Individuals receiving long-term anticoagulation require periodic reevaluation to confirm that the benefits of anticoagulation continue to outweigh the risk of bleeding. 20210G>A heterozygotes who do not require long-term anticoagulation may benefit from evaluation prior to exposure to circumstantial risk factors such as surgery or pregnancy.

Agents/circumstances to avoid: Women heterozygous for 20210G>A with a history of VTE and women homozygous for 20210G>A with or without prior VTE should avoid estrogen-containing contraception and hormone replacement therapy (HRT).

Pregnancy management: No consensus exists on the optimal management of prothrombin thrombophilia during pregnancy; guidelines for treatment of VTE are derived from studies in non-pregnant individuals.

Genetic counseling

Prothrombin thrombophilia is inherited in an autosomal dominant manner: heterozygosity for the 20210G>A variant results in an increased risk for thrombosis; homozygosity for this variant confers a higher risk for thrombosis than heterozygosity. Occasionally (because of the relatively high frequency of the 20210G>A variant in the general population) one parent is homozygous for the 20210G>A variant or both parents are heterozygous for the 20210G>A variant. The genetic status of both parents and/or the reproductive partner of an affected individual needs to be evaluated before information regarding potential risks to sibs or offspring can be provided. If one parent of a heterozygous proband is heterozygous for the 20210G>A variant, the sibs of the proband are at 50% risk of being heterozygous; if one parent is homozygous, the sibs of the proband will be heterozygous. Once the 20210G>A variant has been identified in a family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

No clinical features are specific for prothrombin thrombophilia. The diagnosis **should be suspected** in individuals with at least one of the following more specific findings:

- A first unprovoked venous thromboembolism (VTE) before age 50 years
- A history of recurrent VTE
- Venous thrombosis at certain unusual sites such as the cerebral, mesenteric, portal, or hepatic veins
- VTE during pregnancy or the puerperium
- VTE associated with the use of estrogen-containing oral contraceptives or hormone replacement therapy (HRT)
- An unprovoked VTE at any age in an individual with a first-degree family member with a VTE before age 50 years

Prothrombin thrombophilia testing **may be considered** in individuals who have less specific findings, including the following:

- A history of unprovoked VTE considering discontinuation of anticoagulation
- A first VTE related to use of tamoxifen or other selective estrogen receptor modulators
- Age greater than 50 years with a first unprovoked VTE
- Neonates and children with non-catheter related idiopathic VTE or stroke

Molecular genetic testing for the *F2* 20210G>A variant is **not recommended** for the following:

- General population screening

- Routine initial testing prior to the use of estrogen-containing contraceptives, HRT, or selective estrogen receptor modulators
- Adults with VTE occurring in the setting of major transient risk factors (e.g., surgery, trauma)
- Routine initial testing in adults with arterial thrombosis
- Individuals with unprovoked VTE already receiving long-term anticoagulation treatment
- Routine initial testing during pregnancy
- Routine testing in women with recurrent fetal loss, placental abruption, fetal growth restriction, or preeclampsia
- Prenatal or newborn testing
- Neonates and children with asymptomatic central venous catheter-related thrombosis
- Routine testing in asymptomatic children
- Routine testing of unselected children with a first episode of VTE

Establishing the Diagnosis

The diagnosis of prothrombin thrombophilia **is established** in a proband with a heterozygous or homozygous pathogenic variant(s) 20210G>A in *F2* identified by molecular genetic testing (see Table 1).

Note: The range of plasma concentrations of prothrombin in heterozygotes overlaps with the normal range. Therefore, plasma prothrombin concentration is not reliable for diagnosis.

Molecular genetic testing approaches can include **targeted analysis** for the *F2* 20210G>A variant (see Table 1) or a **multigene panel** that includes the analysis of the *F2* variant and other genes of interest (see Differential Diagnosis). Note: The genes included and sensitivity of multigene panels vary by laboratory and are likely to change over time. For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Note: The diagnosis of prothrombin thrombophilia in the setting of liver transplantation requires molecular genetic testing of donor liver, the site of prothrombin synthesis.

Table 1. Molecular Genetic Testing Used in Prothrombin Thrombophilia

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
F2	Targeted analysis for 20210G>A [3]	100%

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. The official designation of the pathogenic variant is c.*97G>A per varnomen.hgvs.org guidelines.

Clinical Characteristics

Clinical Description

The clinical expression of prothrombin thrombophilia is variable. Many individuals who are heterozygous or homozygous for the *F2* 20210G>A variant never develop thrombosis. While most individuals with prothrombin thrombophilia do not experience a first thrombotic event until adulthood, some have recurrent VTE before age 30 years.

Venous Thromboembolism (VTE)

The primary clinical manifestation of prothrombin thrombophilia is VTE. The relative risk for VTE is increased two- to fivefold in 20210G>A heterozygotes [Gohil et al 2009, Lijfering et al 2009, Rosendaal & Reitsma 2009]. Deep-vein thrombosis (DVT) and pulmonary embolism (PE) are the most common VTE. The most common site for DVT is the legs, but upper-extremity thrombosis also occurs.

Among individuals with DVT, 20210G>A heterozygotes had a significantly higher rate of PE (32%) than those with the factor V Leiden variant (19%) or those without thrombophilia (17%). 20210G>A heterozygotes are also at increased risk of developing isolated PE [Martinelli et al 2006] and may develop VTE at a younger age than individuals without the variant [Martinelli et al 2006].

Upper-extremity thrombosis. Heterozygosity for 20210G>A is associated with a three- to sixfold increased risk for upper-extremity thrombosis [Martinelli et al 2004, Blom et al 2005a, Linnemann et al 2008]. Women heterozygous for 20210G>A who were using oral contraceptives had a nine- to 14-fold increased risk for idiopathic upper-extremity thrombosis [Martinelli et al 2004, Blom et al 2005a].

Cerebral venous thrombosis. 20210G>A heterozygosity is associated with a six- to tenfold increased risk for cerebral venous thrombosis [Dentali et al 2006, Lauw et al 2013, Gonzalez et al 2016]. The combination with this variant and other acquired risk factors greatly increases this risk. Women heterozygous for 20210G>A who used oral contraceptives had an 80- to 150-fold increased relative risk for cerebral venous thrombosis [Martinelli et al 1998].

Hepatic thrombosis and portal vein thrombosis. 20210G>A heterozygosity was associated with a fourfold increased risk for both idiopathic and liver disease-associated portal vein thrombosis [Dentali et al 2008a]. In contrast, a meta-analysis found that 20210G>A heterozygosity did not significantly increase the risk for hepatic vein thrombosis (Budd Chiari Syndrome) [Zhang et al 2014].

Thrombosis in unusual locations. Retinal vein thrombosis and other ocular thrombotic events have been reported in 20210G>A heterozygotes [Glueck & Wang 2009], although the association is much weaker than with DVT and/or PE. The risk for superficial venous thrombosis was increased nearly fourfold in 20210G>A heterozygotes [Martinelli et al 1999a]. These events are much less common than DVT or PE, and there is no evidence that identification of a 20210G>A variant should alter management [Tait et al 2012].

Risk for VTE in children. VTE in children is multifactorial, and is caused by acquired clinical risk factors, underlying medical conditions, and inherited predisposition to thrombosis [Klaassen et al 2015, van Ommen & Nowak-Göttl 2017, Nowak-Göttl et al 2018]. The most common clinical risk factors for thrombosis in children are central venous catheters and malignancy. Additional risk factors are present at the time of VTE in 92% [Young et al 2003, Young et al 2008].

Asymptomatic healthy children heterozygous or homozygous for 20210G>A are at low risk for thrombosis. Heterozygous children were found to have a three- to fourfold increase in relative risk for VTE [Junker et al 1999, Schobess et al 1999]. The relative risk for VTE was increased more than ninefold in children with two or more inherited thrombophilic disorders [Young et al 2008]. Other studies also found a higher risk in children compound heterozygous for the 20210G>A and factor V Leiden variants or with the 20210G>A variant in combination with other inherited thrombophilic disorders [Junker et al 1999, Young et al 2003]. Other reported manifestations in children include cerebral venous thrombosis [Kenet et al 2010] and hepatic, portal, and retinal vein thromboses.

Recurrent thrombosis. Due to conflicting data it is unclear to what extent the 20210G>A variant increases the risk of recurrent VTE. If there is an increased risk of recurrent thrombosis after initial treatment of a first VTE, the magnitude of the increase is small [Kyrle et al 2010, Berg et al 2011]. In children inherited thrombophilia appears to have at most a modest effect on the risk of recurrence, similar to the findings in adults [Klaassen et al 2015]. A two- to threefold increase in recurrence risk has been reported [Young et al 2009].

During pregnancy women with a prior history of VTE have an increased recurrence risk ranging from 0% to 15% in published studies. The risk is higher in women with a prior unprovoked episode or an estrogen-related VTE, and in those with coexisting genetic or acquired risk factors [Brill-Edwards et al 2000]. No studies have specifically evaluated the risk for recurrent VTE in pregnant women with a 20210G>A variant.

Pregnancy complications. It is unlikely that 20210G>A heterozygosity is a major factor contributing to pregnancy loss and other adverse pregnancy outcomes (e.g., preeclampsia, fetal growth restriction, placental abruption). Although multiple retrospective studies have suggested a modest increased risk of fetal loss, most prospective studies have not confirmed an association. The available data suggest that 20210G>A heterozygosity is associated with at most a two- to threefold increased relative risk for pregnancy loss [Rey et al 2003, Robertson et al 2006]. The association with preeclampsia, fetal growth restriction, and placental abruption is more controversial. At most, a 20210G>A variant is one of multiple largely unknown genetic and environmental predisposing factors contributing to these complications.

Homozygosity for 20210G>A variant. The risk of VTE is likely higher in individuals who are homozygous for the 20210G>A variant but the absolute risk has not been defined due to lack of data. 20210G>A homozygotes may develop thrombosis more frequently and at a younger age. The annual incidence of recurrent VTE was 12%/year in persons homozygous for 20210G>A, compared to 2.8% in those without a 20210G>A or factor V Leiden variant [González-Porras et al 2006]. Numerous reports of asymptomatic 20210G>A homozygotes emphasize the contribution of other genetic and acquired risk factors to thrombosis [Ridker et al 1999].

Additional Factors that Predispose to Thrombosis

In addition to the number of variants, the clinical expression of prothrombin thrombophilia is influenced by: family history, coexisting genetic abnormalities, acquired thrombophilic disorders, and circumstantial risk factors.

Family History

A family history of thrombosis affecting at least one first-degree relative is an additional risk factor for VTE even in those with a known inherited thrombophilic disorder (including 20210A heterozygosity) [Bezemer et al 2009]. A family history of thrombosis is associated with a three- to fourfold increased risk for VTE among individuals with a 20210G>A variant [Noboa et al 2008, Rossi et al 2011]. The risk is higher when multiple members are affected and thrombosis occurs at a young age.

Coexisting Genetic Abnormalities

Another inherited thrombophilic disorder is present in 8%-14% of 20210G>A heterozygotes, creating an additive effect on overall thrombotic risk. Individuals with multiple thrombophilic disorders develop VTE at a younger age and are at higher risk for recurrent thrombosis than those with a single thrombophilic variant [Makris et al 1997].

- **Factor V Leiden.** Heterozygosity for a factor V Leiden variant occurs in 20%-40% of symptomatic 20210G>A heterozygotes [Poort et al 1996, Emmerich et al 2001]. The risk for VTE was reported to increase seven to 20-fold in individuals heterozygous for both variants [Emmerich et al 2001, Segal et al 2009]. Compound heterozygotes were at a three- to fourfold higher risk than those with a single thrombophilic variant and were more likely to develop thrombosis in unusual locations (e.g., hepatic, mesenteric, or cerebral veins) [De Stefano et al 1999]. A three- to ninefold higher risk of recurrent VTE was found compared to those with neither variant, and a threefold higher risk compared to individuals heterozygous for factor V Leiden alone [De Stefano et al 1999, Meinardi et al 2002, Segal et al 2009]. The annual incidence of recurrent VTE was 12%/year in compound heterozygotes, compared to 2.8% in those with neither thrombophilia-related variant [González-Porras et al 2006].
- **Anticoagulant protein deficiency.** The combination of protein S deficiency and 20210G>A heterozygosity was associated with a nearly 13-fold increased risk for VTE, compared to a fourfold increased risk with 20210G>A heterozygosity alone [Tirado et al 2001]. In contrast, coinheritance of a 20210G>A variant did not increase the risk for thrombosis in a large kindred with protein C deficiency [Bovill et al 2000].

Other genetic factors (Note: Analysis of the following variants in *F8* and *SERPINE1* is not recommended in clinical practice.)

- ***F8*** (encoding factor XIII). The effect of *F8* Val34Leu has been extensively studied with conflicting results [Undas et al 2009, Bereczky & Muszbek 2011]. Two meta-analyses found a slight overall protective effect of *F8* Val34Leu against VTE [Wells et al 2006, Gohil et al 2009]. Note: The *F8* variant in exon 2 (NM_000132.3:c.157G>T) encodes a normal protein variant officially designated NP_000123.1:p.Val53Leu (commonly known as Val34Leu, which does not count the 19 amino-acid signal sequence) [Kohler et al 1998].
- ***SERPINE1*** (encoding plasminogen activator inhibitor type 1). A polymorphism commonly referred to as 4G/5G is a missense substitution located at -675 (NG_013213.1: g.4328G>T;rs114094261) that results in four or five G nucleotides in a row. Heterozygosity for *SERPINE1* 4G in combination with 20210G>A heterozygosity was associated with a sixfold increased risk for VTE. Homozygosity for *SERPINE1* 4G in combination with 20210G>A heterozygosity was associated with a 13-fold increased risk for VTE [Barcellona et al 2003].

Acquired Thrombophilic Disorders

Acquired thrombophilic disorders include antiphospholipid antibody syndrome, paroxysmal nocturnal hemoglobinuria, myeloproliferative disorders, and increased levels of clotting factors.

Circumstantial Risk Factors for VTE

The 20210G>A variant interacts with multiple environmental risk factors to increase the risk for VTE. At least 50% of thrombotic episodes in individuals with the 20210G>A variant are provoked by additional risk factors, with pregnancy being the most common [Gerhardt et al 2000, Campello et al 2019].

Table 2. Circumstantial Risk Factors: Increased Risk for Thrombophilia in Persons with the 20210G>A Variant

Circumstance	Relative Risk for VTE	Comment	Reference
Pregnancy	• 3x-15x ↑ risk (heterozygotes) • 31x ↑ risk during pregnancy or postpartum • 26x ↑ risk (homozygotes) • 8-47x ↑ risk in compound heterozygotes (w/factor V Leiden)	Incidence: • During pregnancy: 1:200 to 1:300 • Post partum:1:66 (highest risk: 1st 6 wks post partum) • In homozygotes: 1:40 • In compound heterozygotes (w/factor V Leiden): 1:20 to 1:125	Gerhardt et al [2000], Martinelli et al [2002], Gerhardt et al [2003], Robertson et al [2006], Martinelli et al [2008], Jacobsen et al [2010], Bates et al [2016], Gerhardt et al [2016]
Combined oral contraceptives	16x-59x ↑ risk (heterozygotes)	• Higher risk during 1st yr of use than subsequent yrs • Incidence 1/500/yr • Unopposed progestin is assoc w/↓ risk for thrombosis vs estrogen-containing contraception.	Martinelli et al [1999b], Bloemenkamp et al [2000], Emmerich et al [2001], Wu et al [2005], Mohllajee et al [2006]
Other contraceptives (e.g., transdermal, vaginal ring)	VTE risk at least as high as risk w/ combined oral contraceptives; not specifically studied in women w/ 20210G>A		Cole et al [2007], Jick et al [2007], Dore et al [2010]

Table 2. continued from previous page.

Circumstance	Relative Risk for VTE	Comment	Reference
Oral HRT	• 3x ↑ risk (heterozygotes) vs women using HRT w/o 20210G>A variant • 8x-25x ↑ risk (heterozygotes) vs women w/o 20210G>A variant not using HRT	5x ↑ risk w/conjugated equine estrogen use vs w/esterified estrogen	Straczek et al [2005], Smith et al [2006], Canonico et al [2008], Roach et al [2013]
Transdermal HRT	Preliminary data suggest may not ↑ risk.	Lower relative risk than oral HRT	Canonico et al [2010], ACOG [2013a]
SERMS	Risk uncertain but likely > risk assoc w/ SERMS alone		Abramson et al [2006]
Obesity	• 7x ↑ risk if BMI >30 kg/m^2 • 5x ↑ risk if BMI 25-30 kg/m^2	Risk ↑ w/↑ BMI	Pomp et al [2007]
Malignancy	• 17x ↑ risk of VTE • 20x ↑ risk of UE VTE • 5x ↑ risk of CVC thrombosis		Blom et al [2005a], Blom et al [2005b], Dentali et al [2008b]
Air travel	17x ↑ risk		Martinelli et al [2003]
Minor leg injury	9x-30x ↑ risk		van Stralen et al [2008]
Organ transplantation	Data unclear		Ghisdal et al [2010], Pereboom et al [2011]
CVC	Data unclear; CVC is most common risk factor for UE thrombosis in children. Studies evaluating risk in children w/ 20210G>A were not identified.	Studies found no ↑ or 2x-3x ↑ risk.	Vayá et al [2003], Van Rooden et al [2004], Linnemann et al [2008]
Surgery	Data unclear; any excess risk likely small compared to risk assoc w/surgery	Studies found no ↑ or 10x-13x ↑ risk.	Wåhlander et al [2002], Blom et al [2005a], Joseph et al [2005], Ringwald et al [2009]
Antiphospholipid antibody syndrome	Data unclear	1 study found 4x ↑ risk (heterozygotes).	DeSancho et al [2010]

BMI = body mass index; CVC = central venous catheter; HRT = hormone replacement therapy; SERMS = selective estrogen receptor modulators; UE = upper-extremity; VTE = venous thromboembolism

Pregnancy. Women with thrombophilia are at higher risk for VTE during pregnancy. In several studies 20210G>A heterozygotes had a three- to 15-fold higher risk for pregnancy-associated VTE than pregnant women without inherited thrombophilia [Gerhardt et al 2000, Martinelli et al 2002, Robertson et al 2006]. Heterozygous women without a family history of VTE have a lower thrombotic risk than women with prothrombin thrombophilia and a family history of VTE. Although 20210G>A heterozygosity increases the relative risk for pregnancy-associated VTE, the absolute risk in asymptomatic heterozygotes is low in the absence of other predisposing factors with an estimated probability in the range of 1:200 to 1:300 pregnancies [Gerhardt et al 2000, Gerhardt et al 2003]. The highest risk occurs during the first six weeks post partum but the risk does not return to pre-pregnancy baseline until three months post partum.

Women homozygous for 20210G>A or compound heterozygous for 20210G>A and factor V Leiden have a higher relative risk for pregnancy-associated VTE, but the absolute risk is less well defined [Robertson et al 2006, van Vlijmen et al 2011]. The probability of VTE during pregnancy and the puerperium is lower in compound heterozygous women younger than age 35 years (5.5%) than in older women (8.2%) [Gerhardt et al 2016].

Combined oral contraceptive (COC) use substantially increases the relative risk for VTE in women heterozygous for 20210G>A [Bistervels et al 2019]. The additive effect of both a 20210G>A variant and COC use was confirmed in multiple studies in which the odds ratios for VTE in women with both risk factors ranged from 16 to 59 [Martinelli et al 1999b, Wu et al 2005]. For women who are compound heterozygous for a 20210G>A variant and factor V Leiden, the odds ratios for VTE ranged from 17 to 110 [Mohllajee et al 2006, van Vlijmen et al 2016]. Despite the marked increase in relative risk, the absolute incidence of VTE is low because of the low baseline risk in young healthy women [van Vlijmen et al 2011]. The incidence of VTE in COC users with either factor V Leiden or a 20210G>A variant ranged from 0.49 to 2.0 VTE/100 pill-years compared to 0.19 to 0 VTE/100 pill-years in COC users without these variants. The absolute VTE risk is substantially higher in women who are compound heterozygous for 20210G>A and factor V Leiden variants or homozygous for either variant (0.86 vs 0.19 VTE/100 pill-years) [van Vlijmen et al 2016].

Other newer forms of combined hormonal, transdermal, and vaginal ring contraception have not been studied in 20210G>A heterozygotes but the risk is likely at least as great as the risk associated with COC use.

Oral hormone replacement therapy (HRT) is associated with a two- to fourfold increased relative risk for VTE in healthy postmenopausal users of HRT compared to non-users [Renoux et al 2010, Eisenberger & Westhoff 2014]. The risk of VTE in HRT users is threefold greater in postmenopausal women with a factor V Leiden or prothrombin 20210G>A variant than in HRT users without a thrombophilic variant [Roach et al 2013].

Transdermal HRT. Multiple observational studies consistently found that transdermal HRT did not increase the risk of VTE [Canonico et al 2010, Sweetland et al 2012, ACOG 2013a, Rovinski et al 2018]. There is also evidence that transdermal estrogen is associated with a lower thrombotic risk than oral estrogen in women with a thrombophilic variant including 20210G>A [Canonico et al 2010]. Women with a 20210G>A variant using transdermal estrogen had a risk of VTE similar to that of non-users with the variant [Straczek et al 2005]. However no prospective randomized trials have confirmed the safety of transdermal HRT in women with inherited thrombophilia.

Selective estrogen receptor modulators (SERMs). Limited data suggest that SERMs (e.g., tamoxifen, raloxifene) are associated with a twofold increased risk for VTE, similar to the risk associated with HRT [Barrett-Connor et al 2006]. The risk for VTE in 20210G>A heterozygotes who use SERMs is uncertain but likely higher than that associated with SERM use alone.

Arterial Thrombosis: NOT Convincingly Associated with Prothrombin Thrombophilia

The available evidence indicates that the 20210G>A variant is not a major risk factor for arterial thrombosis of any sort including myocardial infarction and stroke in fetuses, children, and adults.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified for other *F2* variants.

Nomenclature

Prothrombin thrombophilia may also be referred to as *F2*-related thrombophilia, factor II-related thrombophilia, or prothrombin 20210G>A thrombophilia.

Prevalence

F2 20210G>A heterozygosity is the second most common inherited thrombophilia, after factor V Leiden. The prevalence varies by population. Heterozygosity for 20210G>A occurs in 1.7%-3% of the general US and European populations. The highest heterozygosity rate is found in Europe; the variant is extremely rare in Asian,

African, and Native American populations. Within Europe, prevalence varies from 3% in southern Europe to 1.7% in northern countries [Rosendaal et al 1998]. In the US, the 20210G>A variant is present in 2%-5% of Americans of European origin, 2.2% of Hispanic Americans, and 0%-0.6% of African Americans [Dowling et al 2003, Chang et al 2009].

The 20210G>A variant is present in:

- 8.2% of Americans of European origin with VTE;
- 1.1% of African Americans with VTE;
- 6%-14% of adults with a first VTE;
- 18%-21% of adults with VTE and a personal or family history of recurrent VTE [Poort et al 1996, Tosetto et al 1999];
- 3.7% of children with a first spontaneous VTE [Nowak-Göttl et al 2001].

The frequency of homozygosity for the 20210G>A variant is 1:10,000. 20210G>A homozygosity is found in 1.8%-4.5% of individuals with VTE [Margaglione et al 1999, Barcellona et al 2003].

Genetically Related (Allelic) Disorders

Prothrombin deficiency (OMIM 613679), including hypoprothrombinemia and dysprothrombinemia, results from biallelic *F2* missense, nonsense, and splicing variants and deletions that inactivate or decrease prothrombin levels. Prothrombin deficiency is a rare bleeding disorder associated with easy bruising and hematoma formation, epistaxis, heavy menstrual bleeding, and bleeding after trauma and surgery.

Differential Diagnosis

The differential diagnosis of venous thromboembolism (VTE) includes several other inherited thrombophilic disorders (discussed here) and acquired thrombophilic disorders (outside of the scope of this GeneReview).

Factor V Leiden refers to the specific G-to-A substitution in *F5* that predicts a single amino-acid replacement (Arg506Gln) that destroys a cleavage site for activated protein C. Factor V Leiden thrombophilia (the most common inherited form of thrombophilia) is characterized by a poor anticoagulant response to activated protein C and an increased risk for VTE. Deep vein thrombosis (DVT) is the most common VTE, with the legs being the most common site. Factor V Leiden heterozygosity is found in 3%-8% of the general US and European population; the Leiden variant is present in approximately 15%-20% of individuals with a first DVT and up to 50% of individuals with recurrent VTE or an estrogen-related thrombosis.

Inherited deficiencies of the natural anticoagulant proteins C, S, and antithrombin are approximately tenfold less common than *F2* 20210G>A heterozygosity with a combined prevalence of less than 1%-2% of the population. Anticoagulant protein deficiencies are found in 1%-3% of individuals with a first VTE.

Hereditary dysfibrinogenemias (OMIM 616004) are rare and infrequently cause thrombophilia and thrombosis.

See Thrombophilia: OMIM Phenotypic Series, to view genes associated with this phenotype in OMIM.

Management

Evaluations Following Initial Diagnosis

To assess the risk for venous thromboembolism (VTE) in an individual found to have the *F2* 20210G>A variant, the following are recommended:

- An activated protein C resistance or DNA assay for factor V Leiden
- Serologic assays for anticardiolipin antibodies and anti-beta$_2$ glycoprotein 1 antibodies
- Multiple phospholipid-dependent coagulation assays for a lupus inhibitor

For high-risk individuals (e.g., those with a history of recurrent VTE, especially at a young age, or those with strong family history of VTE at a young age), evaluation should also include assays of the following:

- Protein C activity
- Antithrombin activity
- Protein S activity or free protein S antigen

Note: Measurement of the following is NOT recommended:

- Plasma concentration of homocysteine, since no data support a change in duration of anticoagulation or the use of vitamin supplementation in individuals with hyperhomocysteinemia and a history of VTE
- *MTHFR* variants, as no clinical rationale for this testing exists
- Factor VIII and other clotting factor levels [Moll 2015]

Treatment of Manifestations

Treatment of VTE in Adults

The management of thrombosis in individuals with prothrombin thrombophilia depends on the clinical circumstances.

The first acute thrombosis should be treated according to standard guidelines [Kearon et al 2012, Kearon et al 2016, Ortel et al 2020]. For initial treatment of VTE, current guidelines suggest a direct oral anticoagulant (dabigatran, edoxaban, rivaroxaban, or apixaban) over warfarin because of a lower bleeding risk and greater convenience [Kearon et al 2016, Ortel et al 2020]. Of note, low molecular-weight heparin (LMWH) is given before dabigatran and edoxaban but not before rivaroxaban or apixaban. Instead, a higher dose is administered for the first three weeks of therapy with rivaroxaban and for the first week of treatment with apixaban. The recommendation for a direct oral anticoagulant may not apply to certain subgroups such as individuals with severe renal insufficiency, antiphospholipid antibody syndrome, or extremes of body weight [Ortel et al 2020].

For individuals not treated with one of the direct oral anticoagulants, administration of warfarin is started concurrently with LMWH or fonadaparinux, a pentasaccharide (except during pregnancy), and monitored with the international-normalized ratio (INR). A target INR of 2.5 (therapeutic range: 2.0-3.0) provides effective anticoagulation, even in *F2* 20210G>A homozygotes [Tzoran et al 2017]. LMWH and warfarin therapy should be overlapped for at least five days, and until the INR has been within therapeutic range for 24 hours, at which time LMWH is stopped [Witt et al 2018].

Note: LMWH and warfarin are both safe in women who are breast-feeding (see Pregnancy Management for issues with anticoagulants).

The duration of oral anticoagulation therapy should be based on an individualized assessment of the risks for VTE recurrence and anticoagulant-related bleeding. Recurrence risk is determined by the clinical circumstances of the first event (provoked or unprovoked), adequacy of early treatment, and individual risk factors.

- 20210G>A heterozygosity alone is not an indication for long-term anticoagulation in the absence of other risk factors according to American College of Chest Physicians guidelines on antithrombotic therapy and American Society of Hematology guidelines for management of venous thromboembolism (see Published Guidelines / Consensus Statements).
- Anticoagulation for at least three months is recommended for persons with DVT and/or PE associated with a transient (reversible) risk factor [Kearon et al 2012, Kearon et al 2016, Ortel et al 2020].

Indefinite anticoagulation is recommended for individuals with a first or recurrent unprovoked (i.e., idiopathic) proximal DVT of the leg or pulmonary embolism who have a low or moderate bleeding risk [Kearon et al 2012, Kearon et al 2016, Ortel et al 2020]. The decision should be based on an assessment of potential risks and benefits regardless of 20210G>A status [Berg et al 2011]. Long-term anticoagulation is occasionally considered in selected individuals homozygous for 20210G>A or with multiple thrombophilic disorders particularly in the presence of additional risk factors [De Stefano & Rossi 2013], as the potential benefits of long-term anticoagulation may outweigh the bleeding risks.

Treatment of VTE in Children

Treatment recommendations for children with VTE are largely adapted from studies in adults. There is no evidence that identification of a 20210G>A variant should influence decisions about the intensity or duration of anticoagulation in children [Heleen van Ommen & Middeldorp 2011, Monagle et al 2012].

Children with a first VTE should receive initial treatment with either unfractionated heparin or LMWH for at least five days. American Society of Hematology guidelines suggest using either LMWH or warfarin in children with symptomatic DVT or PE. The decision on anticoagulant should be individualized based on preference of the affected individual, underlying condition, comorbidities, and other medications [Monagle et al 2018]. LMWH is often favored over warfarin for continued therapy, especially in very young children and those with complex medical problems [Monagle & Newall 2018]. Recommendations on the duration of antithrombotic therapy are based on the nature of the thrombotic event (e.g., spontaneous or provoked) [Monagle et al 2012]; see Published Guidelines / Consensus Statements.

Anticoagulation is recommended:

- For three months following a VTE provoked by a clinical risk factor that has resolved;
- At least three months and until the risk factor has resolved in children with ongoing but potentially reversible risk factor;
- For 6-12 months after a first unprovoked VTE.

Consensus guidelines and expert opinion emphasize the importance of a careful risk/benefit assessment in each individual.

Prevention of Primary Manifestations

In the absence of a history of thrombosis, long-term anticoagulation is not recommended for asymptomatic 20210G>A heterozygotes because the 1%-3%/year risk for major bleeding from anticoagulation is greater than the estimated less than 1%/year risk for thrombosis [Berg et al 2011].

Prophylactic anticoagulation may be considered in high-risk clinical settings such as surgery, pregnancy, or prolonged immobilization, although currently no evidence confirms the benefit of primary prophylaxis for asymptomatic 20210G>A heterozygotes. Factors that may influence decisions about the indication for and duration of anticoagulation include age, family history, and other coexisting risk factors. Recommendations for prophylaxis at the time of surgery and other high-risk situations are available in the American College of Chest Physicians and American Society of Hematology consensus guidelines [Guyatt et al 2012] (full text) [Anderson et al 2019, Schünemann et al 2018].

Surveillance

Individuals receiving long-term anticoagulation require periodic reevaluation to confirm that the benefits of anticoagulation continue to outweigh the risk of bleeding.

20210G>A heterozygotes who do not require long-term anticoagulation may benefit from evaluation prior to exposure to circumstantial risk factors such as surgery or pregnancy (see Prevention of Primary Manifestations).

Agents/Circumstances to Avoid

Women with a history of VTE who are heterozygous for 20210G>A should avoid estrogen-containing contraception and hormone replacement therapy (HRT).

Women homozygous for 20210G>A with or without prior VTE should avoid estrogen-containing contraception and HRT.

Asymptomatic women heterozygous for 20210G>A:

- Should be counseled on the risks of estrogen-containing contraception and HRT use and should be encouraged to consider alternative forms of contraception and control of menopausal symptoms;
- Electing to use oral contraceptives should avoid third-generation and other progestins with a higher thrombotic risk;
- Electing short-term hormone replacement therapy for severe menopausal symptoms should use a low-dose transdermal preparation, which has a lower thrombotic risk than oral formulations [Renoux et al 2010].

Evaluation of Relatives at Risk

The genetic status of apparently asymptomatic at-risk family members can be established using molecular genetic testing for the 20210G>A variant.

Note: The indications for family testing are unresolved.

- In the absence of evidence that early identification of the 20210G>A variant reduces morbidity or mortality, decisions regarding testing should be made on an individual basis.
- Clarification of 20210G>A variant status may be useful in at-risk female relatives considering hormonal contraception or pregnancy or in families with a strong history of recurrent venous thrombosis at a young age if the results are likely to affect management.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

No consensus exists on the optimal management of prothrombin thrombophilia during pregnancy; guidelines are derived from studies in non-pregnant individuals [Bates et al 2012, ACOG 2013b, Bates et al 2018]; see Published Guidelines / Consensus Statements. All women with inherited thrombophilia should undergo individualized risk assessment. Decisions about anticoagulation should be based on the number and type of thrombophilic defects, coexisting risk factors, and personal and family history of thrombosis.

LMWH is the preferred antithrombotic agent for prophylaxis during pregnancy. The oral direct thrombin inhibitor, dabigatran, and the direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) are contraindicated during pregnancy and breastfeeding because of (1) absence of data on fetal and neonatal safety and (2) animial studies that showed reproductive toxicity [Ageno et al 2012, Bates et al 2018].

Prophylactic anticoagulation during pregnancy **is recommended** for all women:

- With a history of unprovoked VTE, including those heterozygous for 20210G>A. LMWH should be given during pregnancy followed by six weeks of postpartum anticoagulation [ACOG 2013b, Bates et al 2018].

- Heterozygous for 20210G>A with a prior pregnancy or estrogen-related thrombosis who are also at an increased risk for recurrence [ACOG 2013b, Bates et al 2018].

Prophylactic anticoagulation during pregnancy **may be considered** for asymptomatic women who:

- Are homozygous for 20210G>A and have a family history of thrombosis [ACOG 2013b, Bates et al 2018].
- Are compound heterozygotes for 20210G>A and factor V Leiden, especially those with coexisting circumstantial risk factors (obesity, immobilization, multiple gestation) [ACOG 2013b, Bates et al 2018].

Prophylactic anticoagulation during pregnancy **is not routinely recommended** in asymptomatic women heterozygous for 20210G>A with no history of thrombosis. All women heterozygous for 20210G>A should be warned about potential thrombotic complications and counseled regarding the risks and benefits of anticoagulation during pregnancy [ACOG 2013b, Bates et al 2018].

Prevention of Thrombosis During the Postpartum Period

A six-week course of postpartum prophylaxis anticoagulation is recommended for:

- All women heterozygous for 20210G>A women with a prior history of VTE;
- All asymptomatic homozygous women and those with combined thrombophilia;

Postpartum prophylaxis may be considered in asymptomatic women heterozygous for 20210G>A with a positive family history of VTE, although consensus guideline suggestions differ for this group [Bates et al 2012, ACOG 2013b, Bates et al 2018].

Other

Unexplained pregnancy loss. Current consensus guidelines and expert opinion recommend against the use of antithrombotic therapy outside of clinical trials in women with inherited thrombophilia and unexplained pregnancy loss because of the absence of high-quality evidence confirming benefit [Bates et al 2012, ACOG 2013b, Skeith et al 2016].

Pregnancy complications. Current guidelines recommend against antithrombotic prophylaxis for women with inherited thrombophilia and a history of other pregnancy complications such as preeclampsia or placental abruption [Bates et al 2012, ACOG 2013b].

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Prothrombin thrombophilia (i.e., predisposition to the development of venous thrombosis) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- All individuals reported to date with prothrombin thrombophilia have had a parent who is heterozygous or homozygous for the *F2* 20210G>A variant.
- Prothrombin thrombophilia as the result of a *de novo* pathogenic variant has not been reported.
- Occasionally (because of the relatively high prevalence of the 20210G>A variant in the general population) one parent is homozygous for the 20210G>A variant or both parents are heterozygous for the 20210G>A variant.
- The family history of some individuals diagnosed with prothrombin thrombophilia may appear to be negative because no other family members developed thrombosis or because of failure to recognize prothrombin thrombophilia in affected family members. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing for the 20210G>A variant has been performed on the parents of the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If one parent is heterozygous for the 20210G>A variant, each sib of the proband is at a 50% risk of being heterozygous for the 20210G>A variant.
- If one parent is homozygous for the 20210G>A variant, each sib of the proband has a 100% chance of being heterozygous for the 20210G>A variant.
- If both parents are heterozygous for the 20210G>A variant, each sib of the proband has a 25% chance of being homozygous for the 20210G>A variant, a 50% chance of being heterozygous for the 20210G>A variant, and a 25% chance of inheriting both normal *F2* alleles.

Offspring of a heterozygous proband

- Each child has a 50% chance of inheriting the 20210G>A variant.
- If the proband's reproductive partner is also heterozygous for the 20210G>A variant, each of their children has a 25% chance of inheriting two 20210G>A variants, a 50% chance of inheriting one 20210G>A variant, and a 25% chance of inheriting neither 20210G>A variant.

Offspring of a homozygous proband

- A proband homozygous for the 20210G>A variant will transmit the 20210G>A variant to all offspring.
- If the proband's reproductive partner is heterozygous for the 20210G>A variant, each of their children has a 50% chance of inheriting two 20210G>A variants and a 50% chance of inheriting one 20210G>A variant.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: the family members of a person who is heterozygous or homozygous for 20210G>A variant are at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once the *F2* 20210G>A variant has been identified in a family member, prenatal testing for a pregnancy at increased risk for prothrombin thrombophilia and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Blood Clot Alliance**
  Phone: 703-935-8845
  Email: info@stoptheclot.org
  www.stoptheclot.org
- **Thrombosis UK**
  United Kingdom
  Phone: 0300 772 9603
  Email: admin@thrombosisuk.org
  www.thrombosisuk.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Prothrombin Thrombophilia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
F2	11p11.2	Prothrombin	F2 database	F2	F2

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Prothrombin Thrombophilia (View All in OMIM)

176930	COAGULATION FACTOR II; F2
188050	THROMBOPHILIA DUE TO THROMBIN DEFECT; THPH1

Molecular Pathogenesis

The 20210G>A variant is associated with elevated plasma levels of prothrombin [Poort et al 1996, Kyrle et al 1998, Simioni et al 1998, Soria et al 2000]. Experimental evidence suggests that the G>A transition increases the efficiency and accuracy of processing of the 3' end of the mRNA, resulting in an accumulation of mRNA and increased synthesis of the protein prothrombin. The observation that elevated prothrombin levels independently increase the risk for thrombosis suggests that the allele may act through this mechanism [Poort et al 1996, Legnani et al 2003]. The results of several experimental and clinical studies suggest that elevated prothrombin

levels contribute to increased thrombin generation and a prothrombotic state, although other mechanisms may also be involved [Kyrle et al 1998, Lavigne-Lissalde et al 2010].

Most 20210G>A heterozygotes have a mildly elevated plasma concentration of prothrombin that is approximately 30% higher than in healthy controls [Poort et al 1996, Soria et al 2000]. However, because the range of prothrombin concentrations in heterozygotes varies widely and overlaps significantly with the normal range, the plasma concentration of prothrombin is not reliable for diagnosis of prothrombin thrombophilia.

Individuals with one or two 20210G>A alleles often have elevated plasma levels of the prothrombin fragment F1+2, and other coagulation activation markers, reflecting the resulting mild hypercoagulable state [Eikelboom et al 1999, Gouin-Thibault et al 2002].

Mechanism of disease causation. Gain of function

Table 3. Notable *F2* Variants

Reference Sequences	DNA Nucleotide Change		Predicted Protein Change	Comment [Reference]
	Legacy [1]	Standard Nomenclature		
NM_000506.5 NP_000497.1		c.1621C>T	p.Arg541Trp	Uncertain significance [Mulder et al 2020]
		c.1787G>T	p.Arg596Leu	Uncertain significance
	20209C>T	c.*96C>T [2]	None	
	20210G>A	c.*97G>A [2]	None	Pathogenic; assoc w/↑ plasma levels of prothrombin

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions
2. * indicates that the variant is in the 3' untranslated region of *F2*; **96** indicates that the variant is the 96th nucleotide 3' of the translation stop codon. (Nucleotides are numbered *1, *2, …)

Pathogenic variant. The 20210G>A pathogenic variant is located in the 3' untranslated region of *F2* where it increases the efficiency and accuracy of processing of the 3' end of the mRNA.

Haplotype analysis of *F2* strongly suggests that the 20210G>A variant was a single event that occurred 20,000 to 30,000 years ago, after the evolutionary separation of individuals of European ancestry from Asians and Africans [Zivelin et al 1998]. A more recent analysis of single-nucleotide polymorphisms and microsatellites flanking *F2* suggests that the variant arose 21,000-24,000 years ago in whites toward the end of the last glaciation [Zivelin et al 2006].

Although the high prevalence of the 20210G>A allele among individuals of European ancestry suggests a balanced nucleotide variant with some type of survival advantage associated with the heterozygous state, no such advantage has been confirmed. Some investigators speculate that the mild hypercoagulable state conferred by the allele may have had a beneficial effect in reducing mortality from bleeding associated with childbirth or trauma in premodern times [Corral et al 2001, Zivelin et al 2006].

Variants of uncertain significance. Three allelic variants have uncertain clinical significance. Larger studies are needed to determine if they increase the risk for thrombosis in individuals with and without inherited thrombophilic disorders. Genetic testing for these variants is not routinely recommended.

- c.1621C>T, a novel missense variant in exon 12 resulting in increased thrombin potential and resistance to heparin was identified in a Dutch family with unexplained thrombosis [Mulder et al 2020].
- c.1787G>T, a novel missense variant in exon 14 (prothrombin Yukuhashi) results in resistance to antithrombin and a prothrombotic state. Prothrombin Yukuhashi (p.Arg596Leu) was identified in a Japanese family in which five members developed thrombosis at a very young age [Miyawaki et al 2012]. Several other missense variants involving Arg596 and resulting in resistance to antithrombin were identified in thrombophilic individuals (e.g., prothrombin Belgrade and prothrombin Amrita p.Arg596Gln, prothrombin Padua 2 p.Arg596Trp) [Djordjevic et al 2013, Sivasundar et al 2013, Bulato et al 2016].
- 20209C>T in the 3' untranslated region of the gene is a rare variant of unclear significance reported primarily in individuals of African descent with a history of thrombosis or obstetric complications. Data as to whether this variant is an independent risk factor for thrombosis are conflicting [Itakura et al 2005, Danckwardt et al 2006, Hooper et al 2006, Warshawsky et al 2009].

Chapter Notes

Revision History

- 4 February 2021 (sw) Comprehensive update posted live
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References

Published Guidelines / Consensus Statements

American College of Obstetricians and Gynecologists Women's Health Care Physicians. Practice Bulletin No.138: Inherited thrombophilias in pregnancy. Obstet Gynecol. 2013;122:706–17. PubMed PMID: 23963422.

Anderson DR, Morgano GP, Bennett C, Dentali F, Francis CW, Garcia DA, Kahn SR, Rahman M, Rajasekhar A, Rogers FB, Smythe MA, Tikkinen KAO, Yates AJ, Baldeh T, Balduzzi S, Brożek JL, Ikobaltzeta IE, Johal H, Neumann I, Wiercioch W, Yepes-Nuñez JJ, Schünemann HJ, Dahm P. American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. 2019;3:3898-944.

Baglin T, Gray E, Greaves M, Hunt BJ, Keeling D, Machin S, Mackie I, Makris M, Nokes T, Perry D, Tait RC, Walker I, Watson H; British Committee for Standards in Haematology. Clinical guidelines for testing for heritable thrombophilia. Available online. 2010. Accessed 1-25-22.

Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO; American College of Chest Physicians. VTE, thrombophilia, antithrombotic therapy, and pregnancy. In: *Antithrombotic Therapy and Prevention of Thrombosis*. 9 ed. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Available online. 2012. Accessed 1-25-22.

Bates SM, Middeldorp S, Rodger M, James AH, Greer I. Guidance for the treatment and prevention of obstetric-associated venous thromboembolism. Available online. 2016. Accessed 1-25-22.

Bates SM, Rajasekhar A, Middeldorp S, McLintock C, Rodger MA, James AH, Vazquez SR, Greer IA, Riva JJ, Bhatt M, Schwab N, Barrett D, LaHaye A, Rochwerg B. Amertican Society of Hematology 2018 guidelines for

management of venous thromboembolism: venous thromboembolism in the context of pregnancy. Available online. 2018. Accessed 1-25-22.

Committee on Bioethics, Committee on Genetics, and American College of Medical Genetics and Genomics Social, Ethical, Legal Issues Committee. Ethical and policy issues in genetic testing and screening of children. Available online. 2013. Accessed 1-25-22.

Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP Working Group: routine testing for Factor V Leiden (R506Q) and prothrombin (20210G>A) mutations in adults with a history of idiopathic VTE and their adult family members. Available online. 2011. Accessed 1-25-22.

Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuünemann HJ; American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Available online. 2012. Accessed 2-25-22.

Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, Nelson ME, Wells PS, Gould MK, Dentali F, Crowther M, Kahn SR; American College of Chest Physicians. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis. 9 ed. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Available online. 2012. Accessed 2-25-22.

Monagle P, Chan AK, Goldenberg NA, Ichord RN, Journeycake JM, Nowak-Göttl U, Vesely SK; American College of Chest Physicians. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. Available online. 2012. Accessed 2-25-22.

Monagle P, Cuello CA, Augustine C, Bonduel M, Brandão LR, Capman T, Chan AKC, Hanson S, Male C, Meerpohl J, Newall F, O'Brien SH, Raffini L, van Ommen H, Wiernikowski J, Williams S, Bhatt M, Riva JJ, Roldan Y, Schwab N, Mustafa RA, Vesely SK. American Society of Hematology 2018 Guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism. Available online. 2018. Accessed 1-25-22.

National Society of Genetic Counselors. Position statement on genetic testing of minors for adult-onset conditions. Available online. 2018. Accessed 1-25-22.

Ortel TL, Neumann I, Ageno W, Beyth R, Clark NP, Cuker A, Hutten BA, Jaff MR, Manja V, Schulman S, Thurston C, Vedantham S, Verhamme P, Witt DM, D Florez I, Izcovich A, Nieuwlaat R, Ross S, J Schünemann H, Wiercioch W, Zhang Y, Zhang Y. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. Available online. 2020. Accessed 1-25-22.

Tait C, Baglin T, Watson H, Laffan M, Makris M, Perry D, Keeling D; British Committee for Standards in Haematology. Guidelines on the investigation and management of venous thrombosis at unusual sites. Available online. 2012. Accessed 1-25-22.

Literature Cited

Abramson N, Costantino JP, Garber JE, Berliner N, Wickerham DL, Wolmark N. Effect of Factor V Leiden and prothrombin G20210-->A mutations on thromboembolic risk in the national surgical adjuvant breast and bowel project breast cancer prevention trial. J Natl Cancer Inst. 2006;98:904–10. PubMed PMID: 16818854.

ACOG. American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 556: Postmenopausal estrogen therapy: route of administration and risk of venous thromboembolism. Obstet Gynecol. 2013a;121:887–90. PubMed PMID: 23635705.

ACOG. American College of Obstetricians and Gynecologists. Women's Health Care Physicians Practice Bulletin No. 138: Inherited thrombophilias in pregnancy. Obstet Gynecol. 2013b;122:706–17. PubMed PMID: 23963422.

Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G; American College of Chest Physicians. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:e44S-88S.

Anderson DR, Morgano GP, Bennett C, Dentali F, Francis CW, Garcia DA, Kahn SR, Rahman M, Rajasekhar A, Rogers FB, Smythe MA, Tikkinen KAO, Yates AJ, Baldeh T, Balduzzi S, Brożek JL, Ikobaltzeta IE, Johal H, Neumann I, Wiercioch W, Yepes-Nuñez JJ, Schünemann HJ, Dahm P. American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. Blood Adv. 2019;3:3898–944. PubMed PMID: 31794602.

Barcellona D, Fenu L, Cauli C, Pisu G, Marongiu F. Allele 4G of gene PAI-1 associated with prothrombin mutation G20210A increases the risk for venous thrombosis. Thromb Haemost. 2003;90:1061–4. PubMed PMID: 14652637.

Barrett-Connor E, Mosca L, Collins P, Geiger MJ, Grady D, Kornitzer M, McNabb MA, Wenger NK; Raloxifene Use for The Heart (RUTH) Trial Investigators. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. N Engl J Med. 2006;355:125–37. PubMed PMID: 16837676.

Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO; American College of Chest Physicians. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:e691S-736S.

Bates SM, Rajasekhar A, Middeldorp S, McLintock C, Rodger MA, James AH, Vazquez SR, Greer IA, Riva JJ, Bhatt M, Schwab N, Barrett D, LaHaye A, Rochwerg B. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. Blood Adv. 2018;2:3317–59. PubMed PMID: 30482767.

Bereczky Z, Muszbek L. Factor XIII and venous thromboembolism. Semin Thromb Hemost. 2011;37:305–14. PubMed PMID: 21455864.

Berg AO, Botkin J, Calonge N, Campos-Outcalt D, Haddow JE, Hayes M, Kaye C, Klein RD, Offit K, Pauker SG, Piper M, Richards CS, Scott JA, Strickland OL, Teutsch S, Veenstra DL, et al. Recommendations from the EGAPP Working Group: routine testing for Factor V Leiden (R506Q) and prothrombin (20210G>A) mutations in adults with a history of idiopathic VTE and their adult family members. Genet Med. 2011;13:67–76. PubMed PMID: 21150787.

Bezemer ID, van der Meer FJ, Eikenboom JC, Rosendaal FR, Doggen CJ. The value of family history as a risk indicator for venous thrombosis. Arch Intern Med. 2009;169:610–5. PubMed PMID: 19307525.

Bistervels IM, Scheres LJJ, Hamulyák EN, Middeldorp S. Sex matters: Practice 5P's when treating young women with venous thromboembolism. J Thromb Haemost. 2019;17:1417–29. PubMed PMID: 31220399.

Bloemenkamp KW, Rosendaal FR, Helmerhorst FM, Vandenbroucke JP. Higher risk of venous thrombosis during early use of oral contraceptives in women with inherited clotting defects. Arch Intern Med. 2000;160:49–52. PubMed PMID: 10632304.

Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Old and new risk factors for upper extremity deep venous thrombosis. J Thromb Haemost. 2005a;3:2471–8. PubMed PMID: 16241945.

Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA. 2005b;293:715–22. PubMed PMID: 15701913.

Bovill EG, Hasstedt SJ, Callas PW, Valliere JE, Scott BT, Bauer KA, Long GL. The G20210A prothrombin polymorphism is not associated with increased thromboembolic risk in a large protein C deficient kindred. Thromb Haemost. 2000;83:366–70. PubMed PMID: 10744139.

Brill-Edwards P, Ginsberg JS, Gent M, Hirsh J, Burrows R, Kearon C, Geerts W, Kovacs M, Weitz JI, Robinson KS, Whittom R, Couture G. Safety of withholding heparin in pregnant women with a history of venous thromboembolism. Recurrence of Clot in This Pregnancy Study Group. N Engl J Med. 2000;343:1439–44. PubMed PMID: 11078768.

Bulato C, Radu CM, Campello E, Gavasso S, Spiezia L, Tormene D, Simioni P. New prothrombin mutation (Arg596Trp, Prothrombin Padua 2) associated with venous thromboembolism. Arterioscler Thromb Vasc Biol. 2016;36:1022–9. PubMed PMID: 27013614.

Campello E, Spiezia L, Adamo A, Simioni P. Thrombophilia, risk factors and prevention. Expert Rev Hematol. 2019;12:147–58. PubMed PMID: 30773075.

Canonico M, Fournier A, Carcaillon L, Olié V, Plu-Bureau G, Oger E, Mesrine S, Boutron-Ruault MC, Clavel-Chapelon F, Scarabin PY. Postmenopausal hormone therapy and risk of idiopathic venous thromboembolism: results from the E3N cohort study. Arterioscler Thromb Vasc Biol. 2010;30:340–5. PubMed PMID: 19834106.

Canonico M, Plu-Bureau G, Lowe GD, Scarabin PY. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. BMJ. 2008;336:1227–31. PubMed PMID: 18495631.

Chang MH, Lindegren ML, Butler MA, Chanock SJ, Dowling NF, Gallagher M, Moonesinghe R, Moore CA, Ned RM, Reichler MR, Sanders CL, Welch R, Yesupriya A, Khoury MJ, et al. Prevalence in the United States of selected candidate gene variants: Third National Health and Nutrition Examination Survey, 1991-1994. Am J Epidemiol. 2009;169:54–66. PubMed PMID: 18936436.

Chinthammitr Y, Vos HL, Rosendaal FR, Doggen CJ. The association of prothrombin A19911G polymorphism with plasma prothrombin activity and venous thrombosis: results of the MEGA study, a large population-based case-control study. J Thromb Haemost. 2006;4:2587–92. PubMed PMID: 17059428.

Cole JA, Norman H, Doherty M, Walker AM. Venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive system users. Obstet Gynecol. 2007;109:339–46. PubMed PMID: 17267834.

Corral J, Iniesta JA, Gonzalez-Conejero R, Villalon M, Vicente V. Polymorphisms of clotting factors modify the risk for primary intracranial hemorrhage. Blood. 2001;97:2979–82. PubMed PMID: 11342420.

Danckwardt S, Hartmann K, Katz B, Hentze MW, Levy Y, Eichele R, Deutsch V, Kulozik AE, Ben-Tal O. The prothrombin 20209 C-->T mutation in Jewish-Moroccan Caucasians: molecular analysis of gain-of-function of 3' end processing. J Thromb Haemost. 2006;4:1078–85. PubMed PMID: 16689762.

De Stefano V, Martinelli I, Mannucci PM, Paciaroni K, Chiusolo P, Casorelli I, Rossi E, Leone G. The risk of recurrent deep venous thrombosis among heterozygous carriers of both factor V Leiden and the G20210A prothrombin mutation. N Engl J Med. 1999;341:801–6. PubMed PMID: 10477778.

De Stefano V, Rossi E. Testing for inherited thrombophilia and consequences for antithrombotic prophylaxis in patients with venous thromboembolism and their relatives. A review of the Guidelines from Scientific Societies and Working Groups. Thromb Haemost. 2013;110:697–705. PubMed PMID: 23846575.

Dentali F, Crowther M, Ageno W. Thrombophilic abnormalities, oral contraceptives, and risk of cerebral vein thrombosis: a meta-analysis. Blood. 2006;107:2766–73. PubMed PMID: 16397131.

Dentali F, Galli M, Gianni M, Ageno W. Inherited thrombophilic abnormalities and risk of portal vein thrombosis. a meta-analysis. Thromb Haemost. 2008a;99:675–82. PubMed PMID: 18392325.

Dentali F, Gianni M, Agnelli G, Ageno W. Association between inherited thrombophilic abnormalities and central venous catheter thrombosis in patients with cancer: a meta-analysis. J Thromb Haemost. 2008b;6:70–5. PubMed PMID: 17988232.

DeSancho MT, Berlus N, Christos PJ, Rand J. Risk factors for clinical manifestations in carriers of Factor V Leiden and prothrombin gene mutations. Blood Coagul Fibrinolysis. 2010;21:11–5. PubMed PMID: 19474699.

Djordjevic V, Kovac M, Miljic P, Murata M, Takagi A, Pruner I, Francuski D, Kojima T, Radojkovic D. A novel prothrombin mutation in two families with prominent thrombophilia--the first cases of antithrombin resistance in a Caucasian population. J Thromb Haemost. 2013;11:1936–9. PubMed PMID: 23927452.

Dore DD, Norman H, Loughlin J, Seeger JD. Extended case-control study results on thromboembolic outcomes among transdermal contraceptive users. Contraception. 2010;81:408–13. PubMed PMID: 20399947.

Dowling NF, Austin H, Dilley A, Whitsett C, Evatt BL, Hooper WC. The epidemiology of venous thromboembolism in Caucasians and African-Americans: the GATE Study. J Thromb Haemost. 2003;1:80–7. PubMed PMID: 12871543.

Eikelboom JW, Ivey L, Ivey J, Baker RI. Familial thrombophilia and the prothrombin 20210A mutation: association with increased thrombin generation and unusual thrombosis. Blood Coagul Fibrinolysis. 1999;10:1–5. PubMed PMID: 10070829.

Eisenberger A, Westhoff C. Hormone replacement therapy and venous thromboembolism. J Steroid Biochem Biol. 2014;142:76–82. PubMed PMID: 24007716.

Emmerich J, Rosendaal FR, Cattaneo M, Margaglione M, De Stefano V, Cumming T, Arruda V, Hillarp A, Reny JL. Combined effect of factor V Leiden and prothrombin 20210A on the risk of venous thromboembolism--pooled analysis of 8 case-control studies including 2310 cases and 3204 controls. Study Group for Pooled-Analysis in Venous Thromboembolism. Thromb Haemost. 2001;86:809–16. PubMed PMID: 11583312.

Gerhardt A, Scharf RE, Beckmann MW, Struve S, Bender HG, Pillny M, Sandmann W, Zotz RB. Prothrombin and factor V mutations in women with a history of thrombosis during pregnancy and the puerperium. N Engl J Med. 2000;342:374–80. PubMed PMID: 10666427.

Gerhardt A, Scharf RE, Greer IA, Zotz RB. Hereditary risk factors for thrombophilia and probability of venous thromboembolism during pregnancy and the puerperium. Blood. 2016;128:2343–9. PubMed PMID: 27613196.

Gerhardt A, Scharf RE, Zotz RB. Effect of hemostatic risk factors on the individual probability of thrombosis during pregnancy and the puerperium. Thromb Haemost. 2003;90:77–85. PubMed PMID: 12876629.

Ghisdal L, Broeders N, Wissing KM, Saidi A, Bensalem T, Mbaba Mena J, Lemy A, Wijns W, Pradier O, Hoang AD, Mikhalski D, Donckier V, Cochaux P, El Housni H, Abramowicz M, Vereerstraeten P, Abramowicz D. Thrombophilic factors do not predict outcomes in renal transplant recipients under prophylactic acetylsalicylic acid. Am J Transplant. 2010;10:99–105. PubMed PMID: 19845577.

Glueck CJ, Wang P. Ocular vascular thrombotic events: a diagnostic window to familial thrombophilia (compound factor V Leiden and prothrombin gene heterozygosity) and thrombosis. Clin Appl Thromb Hemost. 2009;15:12–8. PubMed PMID: 18796459.

Gohil R, Peck G, Sharma P. The genetics of venous thromboembolism. A meta-analysis involving approximately 120,000 cases and 180,000 controls. Thromb Haemost. 2009;102:360–70. PubMed PMID: 19652888.

Gonzalez JV, Barboza AG, Vazquez FJ, Gándara E. Prevalence and geographical variation of prothrombin G20210A mutation in patients with cerebral vein thrombosis: a systematic review and meta-analysis. PLoS One. 2016;11:e0151607. PubMed PMID: 27031503.

González-Porras JR, García-Sanz R, Alberca I, López ML, Balanzategui A, Gutierrez O, Lozano F, San Miguel J. Risk of recurrent venous thrombosis in patients with G20210A mutation in the prothrombin gene or factor V Leiden mutation. Blood Coagul Fibrinolysis. 2006;17:23–8. PubMed PMID: 16607075.

Gouin-Thibault I, Arkam R, Nassiri S, de la Tourette A, Conard J, Horellou MH, Elalamy I, Samama MM. Markers of activated coagulation in patients with factor V Leiden and/or G20210A prothrombin gene mutation. Thromb Res. 2002;107:7–11. PubMed PMID: 12413582.

Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuünemann HJ, et al. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:7S-47S.

Heleen van Ommen C, Middeldorp S. Thrombophilia in childhood: to test or not to test. Semin Thromb Hemost. 2011;37:794–801. PubMed PMID: 22187402.

Hooper WC, Roberts S, Dowling N, Austin H, Lally C, Whitsett C. The prevalence of the prothrombin gene variant C20209T in African-Americans and Caucasians and lack of association with venous thromboembolism. Thromb Res. 2006;118:767–8. PubMed PMID: 16469364.

Itakura H, Telen MJ, Hoppe CC, White DA, Zehnder JL. Characterization of a novel prothrombin variant, Prothrombin C20209T, as a modifier of thrombotic risk among African-Americans. J Thromb Haemost. 2005;3:2357–9. PubMed PMID: 16194213.

Jacobsen AF, Dahm A, Bergrem A, Jacobsen EM, Sandset PM. Risk of venous thrombosis in pregnancy among carriers of the factor V Leiden and the prothrombin gene G20210A polymorphisms. J Thromb Haemost. 2010;8:2443–9. PubMed PMID: 20735725.

Jick S, Kaye JA, Li L, Jick H. Further results on the risk of nonfatal venous thromboembolism in users of the contraceptive transdermal patch compared to users of oral contraceptives containing norgestimate and 35 microg of ethinyl estradiol. Contraception. 2007;76:4–7. PubMed PMID: 17586129.

Joseph JE, Low J, Courtenay B, Neil MJ, McGrath M, Ma D. A single-centre prospective study of clinical and haemostatic risk factors for venous thromboembolism following lower limb arthroplasty. Br J Haematol. 2005;129:87–92. PubMed PMID: 15801960.

Junker R, Koch HG, Auberger K, Munchow N, Ehrenforth S, Nowak-Gottl U. Prothrombin G20210A gene mutation and further prothrombotic risk factors in childhood thrombophilia. Arterioscler Thromb Vasc Biol. 1999;19:2568–72. PubMed PMID: 10521389.

Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, Nelson ME, Wells PS, Gould MK, Dentali F, Crowther M, Kahn SR, et al. Antithrombotic therapy for VTE disease, In: *Antithrombotic Therapy and Prevention of Thrombosis.* 9 ed. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:e419S–94S. PubMed PMID: 22315268.

Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, Huisman M, King CS, Morris TA, Sood N, Stevens SM, Vintch JRE, Wells P, Woller SC, Moores L. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest. 2016;149:315–52. PubMed PMID: 26867832.

Kenet G, Lütkhoff LK, Albisetti M, Bernard T, Bonduel M, Brandao L, Chabrier S, Chan A, deVeber G, Fiedler B, Fullerton HJ, Goldenberg NA, Grabowski E, Günther G, Heller C, Holzhauer S, Iorio A, Journeycake J, Junker R, Kirkham FJ, Kurnik K, Lynch JK, Male C, Manco-Johnson M, Mesters R, Monagle P, van Ommen CH, Raffini L, Rostásy K, Simioni P, Sträter RD, Young G, Nowak-Göttl U. Impact of thrombophilia on risk of arterial ischemic stroke or cerebral sinovenous thrombosis in neonates and children: a systematic review and meta-analysis of observational studies. Circulation. 2010;121:1838–47. PubMed PMID: 20385928.

Klaassen IL, van Ommen CH, Middeldorp S. Manifestations and clinical impact of pediatric inherited thrombophilia. Blood. 2015;125:1073–7. PubMed PMID: 25564402.

Kohler HP, Stickland MH, Ossei-Gerning N, Carter A, Mikkola H, Grant PJ. Association of a common polymorphism in the factor XIII gene with myocardial infarction. Thromb Haemost. 1998;79:8–13. PubMed PMID: 9459313.

Kyrle PA, Mannhalter C, Beguin S, Stumpflen A, Hirschl M, Weltermann A, Stain M, Brenner B, Speiser W, Pabinger I, Lechner K, Eichinger S. Clinical studies and thrombin generation in patients homozygous or heterozygous for the G20210A mutation in the prothrombin gene. Arterioscler Thromb Vasc Biol. 1998;18:1287–91. PubMed PMID: 9714136.

Kyrle PA, Rosendaal FR, Eichinger S. Risk assessment for recurrent venous thrombosis. Lancet. 2010;376:2032–9. PubMed PMID: 21131039.

Lauw MN, Barco S, Coutinho JM, Middeldorp S. Cerebral venous thrombosis and thrombophilia: a systematic review and meta-analysis. Semin Thromb Hemost. 2013;39:913–27. PubMed PMID: 24129682.

Lavigne-Lissalde G, Sanchez C, Castelli C, Alonso S, Mazoyer E, Bal Dit Sollier C, Drouet L, Juhan-Vague I, Gris JC, Alessi MC, Morange PE. Prothrombin G20210A carriers the genetic mutation and a history of venous thrombosis contributes to thrombin generation independently of factor II plasma levels. J Thromb Haemost. 2010;8:942–9. PubMed PMID: 20096005.

Legnani C, Cosmi B, Valdrè L, Boggian O, Bernardi F, Coccheri S, Palareti G. Venous thromboembolism, oral contraceptives and high prothrombin levels. J Thromb Haemost. 2003;1:112–7. PubMed PMID: 12871547.

Lijfering WM, Brouwer JL, Veeger NJ, Bank I, Coppens M, Middeldorp S, Hamulyák K, Prins MH, Büller HR, van der Meer J. Selective testing for thrombophilia in patients with first venous thrombosis: results from a retrospective family cohort study on absolute thrombotic risk for currently known thrombophilic defects in 2479 relatives. Blood. 2009;113:5314–22. PubMed PMID: 19139080.

Linnemann B, Meister F, Schwonberg J, Schindewolf M, Zgouras D, Lindhoff-Last E, et al. Hereditary and acquired thrombophilia in patients with upper extremity deep-vein thrombosis. Results from the MAISTHRO registry. Thromb Haemost. 2008;100:440–6. PubMed PMID: 18766260.

Makris M, Preston FE, Beauchamp NJ, Cooper PC, Daly ME, Hampton KK, Bayliss P, Peake IR, Miller GJ. Co-inheritance of the 20210A allele of the prothrombin gene increases the risk of thrombosis in subjects with familial thrombophilia. Thromb Haemost. 1997;78:1426–9. PubMed PMID: 9423788.

Margaglione M, D'Andrea G, Colaizzo D, Cappucci G, del Popolo A, Brancaccio V, Ciampa A, Grandone E, Di Minno G. Coexistence of factor V Leiden and Factor II A20210 mutations and recurrent venous thromboembolism. Thromb Haemost. 1999;82:1583–7. PubMed PMID: 10613638.

Martinelli I, Battaglioli T, Bucciarelli P, Passamonti SM, Mannucci PM. Risk factors and recurrence rate of primary deep vein thrombosis of the upper extremities. Circulation. 2004;110:566–70. PubMed PMID: 15262837.

Martinelli I, Battaglioli T, De Stefano V, Tormene D, Valdrè L, Grandone E, Tosetto A, Mannucci PM, et al. The risk of first venous thromboembolism during pregnancy and puerperium in double heterozygotes for factor V Leiden and prothrombin G20210A. J Thromb Haemost. 2008;6:494–8. PubMed PMID: 18182035.

Martinelli I, Battaglioli T, Tosetto A, Legnani C, Sottile L, Ghiotto R, Mannucci PM. Prothrombin A19911G polymorphism and the risk of venous thromboembolism. J Thromb Haemost. 2006;4:2582–6. PubMed PMID: 16981886.

Martinelli I, Cattaneo M, Taioli E, De Stefano V, Chiusolo P, Mannucci PM. Genetic risk factors for superficial vein thrombosis. Thromb Haemost. 1999a;82:1215–7. PubMed PMID: 10544900.

Martinelli I, De Stefano V, Taioli E, Paciaroni K, Rossi E, Mannucci PM. Inherited thrombophilia and first venous thromboembolism during pregnancy and puerperium. Thromb Haemost. 2002;87:791–5. PubMed PMID: 12038778.

Martinelli I, Sacchi E, Landi G, Taioli E, Duca F, Mannucci PM. High risk of cerebral-vein thrombosis in carriers of a prothrombin-gene mutation and in users of oral contraceptives. N Engl J Med. 1998;338:1793–7. PubMed PMID: 9632445.

Martinelli I, Taioli E, Battaglioli T, Podda GM, Passamonti SM, Pedotti P, Mannucci PM. Risk of venous thromboembolism after air travel: interaction with thrombophilia and oral contraceptives. Arch Intern Med. 2003;163:2771–4. PubMed PMID: 14662632.

Martinelli I, Taioli E, Bucciarelli P, Akhavan S, Mannucci PM. Interaction between the G20210A mutation of the prothrombin gene and oral contraceptive use in deep vein thrombosis. Arterioscler Thromb Vasc Biol. 1999b;19:700–3. PubMed PMID: 10073976.

Meinardi JR, Middeldorp S, de Kam PJ, Koopman MM, van Pampus EC, Hamulyak K, Prins MH, Buller HR, van der Meer J. The incidence of recurrent venous thromboembolism in carriers of factor V Leiden is related to concomitant thrombophilic disorders. Br J Haematol. 2002;116:625–31. PubMed PMID: 11849222.

Miyawaki Y, Suzuki A, Fujita J, Maki A, Okuyama E, Murata M, Takagi A, Murate T, Kunishima S, Sakai M, Okamoto K, Matsushita T, Naoe T, Saito H, Kojima T. Thrombosis from a prothrombin mutation conveying antithrombin resistance. N Engl J Med. 2012;366:2390–6. PubMed PMID: 22716977.

Mohllajee AP, Curtis KM, Martins SL, Peterson HB. Does use of hormonal contraceptives among women with thrombogenic mutations increase their risk of venous thromboembolism? A systematic review. Contraception. 2006;73:166–78. PubMed PMID: 16413847.

Moll S. Thrombophilia: clinical-practical aspects. J Thromb Thrombolysis. 2015;39:367–78. PubMed PMID: 25724822.

Monagle P, Chan AK, Goldenberg NA, Ichord RN, Journeycake JM, Nowak-Göttl U, Vesely SK, et al. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:e737S-801S.

Monagle P, Cuello CA, Augustine C, Bonduel M, Brandão LR, Capman T, Chan AKC, Hanson S, Male C, Meerpohl J, Newall F, O'Brien SH, Raffini L, van Ommen H, Wiernikowski J, Williams S, Bhatt M, Riva JJ, Roldan Y, Schwab N, Mustafa RA, Vesely SK. American Society of Hematology 2018 Guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism. Blood Adv. 2018;2:3292–316. PubMed PMID: 30482766.

Monagle P, Newall F. Management of thrombosis in children and neonates: practical use of anticoagulants in children. Hematology Am Soc Hematol Educ Program. 2018;2018:399–404. PubMed PMID: 30504338.

Mulder R, Lisman T, Meijers JCM, Huntington JA, Mulder AB, Meijer K. Linkage analysis combined with whole-exome sequencing identifies a novel prothrombin (F2) gene mutation in a Dutch Caucasian family with unexplained thrombosis. Haematologica. 2020;105:e370–e372. PubMed PMID: 31582550.

Noboa S, Le Gal G, Lacut K, Mercier B, Leroyer C, Nowak E, Mottier D, Oger E, et al; EDITH Collaborative Study Group. Family history as a risk factor for venous thromboembolism. Thromb Res. 2008;122:624–9. PubMed PMID: 18281082.

Nowak-Göttl U, Junker R, Kreuz W, von Eckardstein A, Kosch A, Nohe N, Schobess R, Ehrenforth S. Risk of recurrent venous thrombosis in children with combined prothrombotic risk factors. Blood. 2001;97:858–62. PubMed PMID: 11159508.

Nowak-Göttl U, van Ommen H, Kenet G. Thrombophilia testing in children: what and when should be tested? Thromb Res. 2018;164:75–8. PubMed PMID: 29518638.

Ortel TL, Neumann I, Ageno W, Beyth R, Clark NP, Cuker A, Hutten BA, Jaff MR, Manja V, Schulman S, Thurston C, Vedantham S, Verhamme P, Witt DM. D Florez I, Izcovich A, Nieuwlaat R, Ross S, J Schünemann H, Wiercioch W, Zhang Y, Zhang Y. American Society of Hematology 2020 guidelines for

management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. Blood Adv. 2020;4:4693–738. PubMed PMID: 33007077.

Pereboom IT, Adelmeijer J, van der Steege G, van den Berg AP, Lisman T, Porte RJ. Prothrombotic gene polymorphisms: possible contributors to hepatic artery thrombosis after orthotopic liver transplantation. Transplantation. 2011;92:587–93. PubMed PMID: 21836539.

Pomp ER, le Cessie S, Rosendaal FR, Doggen CJ. Risk of venous thrombosis: obesity and its joint effect with oral contraceptive use and prothrombotic mutations. Br J Haematol. 2007;139:289–96. PubMed PMID: 17897305.

Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. Blood. 1996;88:3698–703. PubMed PMID: 8916933.

Renoux C, Dell'Aniello S, Suissa S. Hormone replacement therapy and the risk of venous thromboembolism: a population-based study. J Thromb Haemost. 2010;8:979–86. PubMed PMID: 20230416.

Rey E, Kahn SR, David M, Shrier I. Thrombophilic disorders and fetal loss: a meta-analysis. Lancet. 2003;361:901–8. PubMed PMID: 12648968.

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;99:999–1004. PubMed PMID: 10051291.

Ringwald J, Berger A, Adler W, Kraus C, Pitto RP. Genetic polymorphisms in venous thrombosis and pulmonary embolism after total hip arthroplasty: a pilot study. Clin Orthop Relat Res. 2009;467:1507–15. PubMed PMID: 18800213.

Roach RE, Lijfering WM, Helmerhorst FM, Cannegieter SC, Rosendaal FR, van Hylckama Vlieg A. The risk of venous thrombosis in women over 50 years old using oral contraception or postmenopausal hormone therapy. J Thromb Haemost. 2013;11:124–31. PubMed PMID: 23136837.

Robertson L, Wu O, Langhorne P, Twaddle S, Clark P, Lowe GD, Walker ID, Greaves M, Brenkel I, Regan L, Greer IA, et al. Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) Study: Thrombophilia in pregnancy: a systematic review. Br J Haematol. 2006;132:171–96. PubMed PMID: 16398652.

Rosendaal FR, Doggen CJ, Zivelin A, Arruda VR, Aiach M, Siscovick DS, Hillarp A, Watzke HH, Bernardi F, Cumming AM, Preston FE, Reitsma PH. Geographic distribution of the 20210 G to A prothrombin variant. Thromb Haemost. 1998;79:706–8. PubMed PMID: 9569177.

Rosendaal FR, Reitsma PH. Genetics of venous thrombosis. J Thromb Haemost. 2009;7 Suppl 1:301–4. PubMed PMID: 19630821.

Rossi E, Ciminello A, Za T, Betti S, Leone G, De Stefano V. In families with inherited thrombophilia the risk of venous thromboembolism is dependent on the clinical phenotype of the proband. Thromb Haemost. 2011;106:646–54. PubMed PMID: 21833444.

Rovinski D, Ramos RB, Fighera TM, Casanova GK, Spritzer PM. Risk of venous thromboembolism events in postmenopausal women using oral versus non-oral hormone therapy: a systematic review and meta-analysis. Thromb Res. 2018;168:83–95. PubMed PMID: 29936403.

Schobess R, Junker R, Auberger K, Munchow N, Burdach S, Nowak-Gottl U. Factor V G1691A and prothrombin G20210A in childhood spontaneous venous thrombosis--evidence of an age-dependent thrombotic onset in carriers of factor V G1691A and prothrombin G20210A mutation. Eur J Pediatr. 1999;158 Suppl 3:S105–8. PubMed PMID: 10650846.

Schünemann HJ, Cushman M, Burnett AE, Kahn SR, Beyer-Westendorf J, Spencer FA, Rezende SM, Zakai NA, Bauer KA, Dentali F, Lansing J, Balduzzi S, Darzi A, Morgano GP, Neumann I, Nieuwlaat R, Yepes-Nuñez JJ,

Zhang Y, Wiercioch W. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. Blood Adv. 2018;2:3198–225. PubMed PMID: 30482763.

Segal JB, Brotman DJ, Necochea AJ, Emadi A, Samal L, Wilson LM, Crim MT, Bass EB. Predictive value of factor V Leiden and prothrombin G20210A in adults with venous thromboembolism and in family members of those with a mutation: a systematic review. JAMA. 2009;301:2472–85. PubMed PMID: 19531787.

Simioni P, Tormene D, Manfrin D, Gavasso S, Luni S, Stocco D, Girolami A. Prothrombin antigen levels in symptomatic and asymptomatic carriers of the 20210A prothrombin variant. Br J Haematol. 1998;103:1045–50. PubMed PMID: 9886317.

Sivasundar S, Oommen AT, Prakash O, Baskaran S, Biswas R, Nair S, Mohan CG, Biswas L. Molecular defect of 'Prothrombin Amrita': substitution of arginine by glutamine (Arg553 to Gln) near the Na(+) binding loop of prothrombin. Blood Cells Mol Dis. 2013;50:182–3. PubMed PMID: 23265743.

Skeith L, Carrier M, Kaaja R, Martinelli I, Petroff D, Schleußner E, Laskin CA, Rodger MA. A meta-analysis of low-molecular-weight heparin to prevent pregnancy loss in women with inherited thrombophilia. Blood. 2016;127:1650–5. PubMed PMID: 26837697.

Smith NL, Heckbert SR, Lemaitre RN, Reiner AP, Lumley T, Rosendaal FR, Psaty BM. Conjugated equine estrogen, esterified estrogen, prothrombotic variants, and the risk of venous thrombosis in postmenopausal women. Arterioscler Thromb Vasc Biol. 2006;26:2807–12. PubMed PMID: 16973976.

Soria JM, Almasy L, Souto JC, Tirado I, Borell M, Mateo J, Slifer S, Stone W, Blangero J, Fontcuberta J. Linkage analisis demonstrates that the prothrombin G20210A mutation jointly influences plasma prothrombin levels and risk of thrombosis. Blood. 2000;95:2780–5. PubMed PMID: 10779421.

Straczek C, Oger E, Yon de Jonage-Canonico MB, Plu-Bureau G, Conard J, Meyer G, Alhenc-Gelas M, Lévesque H, Trillot N, Barrellier MT, Wahl D, Emmerich J, Scarabin PY, et al. Prothrombotic mutations, hormone therapy, and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration. Circulation. 2005;112:3495–500. PubMed PMID: 16301339.

Sweetland S, Beral V, Balkwill A, Liu B, Benson VS, Canonico M, Green J, Reeves GK, et al. Venous thromboembolism risk in relation to use of different types of postmenopausal hormone therapy in a large prospective study. J Thromb Haemost. 2012;10:2277–86. PubMed PMID: 22963114.

Tait C, Baglin T, Watson H, Laffan M, Makris M, Perry D, Keeling D, et al. Guidelines on the investigation and management of venous thrombosis at unusual sites. Br J Haematol. 2012;159:28–38. PubMed PMID: 22881455.

Tirado I, Mateo J, Soria JM, Oliver A, Borrell M, Coll I, Vallve C, Souto JC, Martinez-Sanchez E, Fontcuberta J. Contribution of prothrombin 20210A allele and factor V Leiden mutation to thrombosis risk in thrombophilic families with other hemostatic deficiencies. Haematologica. 2001;86:1200–8. PubMed PMID: 11694407.

Tosetto A, Missiaglia E, Frezzato M, Rodeghiero F. The VITA project: prothrombin G20210A mutation and venous thromboembolism in the general population. Thromb Haemost. 1999;82:1395–8. PubMed PMID: 10595625.

Tzoran I, Papadakis M, Brenner B, Fidalgo Á, Rivas A, Wells PS, Gavín O, Adarraga MD, Moustafa F, Monreal M, et al. Outcome of patients with venous thromboembolism and factor V Leiden or prothrombin 20210 carrier mutations during the course of anticoagulation. Am J Med. 2017;130:482.e1–482.e9. PubMed PMID: 27986523.

Undas A, Zawilska K, Ciesla-Dul M, Lehmann-Kopydłowska A, Skubiszak A, Ciepłuch K, Tracz W. Altered fibrin clot structure/function in patients with idiopathic venous thromboembolism and in their relatives. Blood. 2009;114:4272–8. PubMed PMID: 19690336.

van Ommen CH, Nowak-Göttl U. Inherited thrombophilia in pediatric venous thromboembolic disease: why and who to test. Front Pediatr. 2017;5:50. PubMed PMID: 28352625.

Van Rooden CJ, Rosendaal FR, Meinders AE, Van Oostayen JA, Van Der Meer FJ, Huisman MV. The contribution of factor V Leiden and prothrombin G20210A mutation to the risk of central venous catheter-related thrombosis. Haematologica. 2004;89:201–6. PubMed PMID: 15003896.

van Stralen KJ, Rosendaal FR, Doggen CJ. Minor injuries as a risk factor for venous thrombosis. Arch Intern Med. 2008;168:21–6. PubMed PMID: 18195191.

van Vlijmen EF, Veeger NJ, Middeldorp S, Hamulyák K, Prins MH, Büller HR, Meijer K. Thrombotic risk during oral contraceptive use and pregnancy in women with factor V Leiden or prothrombin mutation: a rational approach to contraception. Blood. 2011;118:2055–61. PubMed PMID: 21659542.

van Vlijmen EF, Wiewel-Verschueren S, Monster TB, Meijer K. Combined oral contraceptives, thrombophilia and the risk of venous thromboembolism: a systematic review and meta-analysis. J Thromb Haemost. 2016;14:1393–403. PubMed PMID: 27121914.

Vayá A, Mira Y, Mateo J, Falco C, Villa P, Estelles A, Corella D, Fontcuberta J, Aznar J. Prothrombin G20210A mutation and oral contraceptive use increase upper-extremity deep vein thrombotic risk. Thromb Haemost. 2003;89:452–7. PubMed PMID: 12624627.

Wåhlander K, Larson G, Lindahl TL, Andersson C, Frison L, Gustafsson D, Bylock A, Eriksson BI. Factor V Leiden (G1691A) and prothrombin gene G20210A mutations as potential risk factors for venous thromboembolism after total hip or total knee replacement surgery. Thromb Haemost. 2002;87:580–5. PubMed PMID: 12008938.

Warshawsky I, Makkar V, Rimmerman C, Kottke-Marchant K. Prothrombin 20209C>T: 16 new cases, association with the 19911A>G polymorphism, and literature review. J Thromb Haemost. 2009;7:1585–7. PubMed PMID: 19522744.

Wells PS, Anderson JL, Scarvelis DK, Doucette SP, Gagnon F. Factor XIII Val34Leu variant is protective against venous thromboembolism: a HuGE review and meta-analysis. Am J Epidemiol. 2006;164:101–9. PubMed PMID: 16740590.

Witt DM, Nieuwlaat R, Clark NP, Ansell J, Holbrook A, Skov J, Shehab N, Mock J, Myers T, Dentali F, Crowther MA, Agarwal A, Bhatt M, Khatib R, Riva JJ, Zhang Y, Guyatt G. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. Blood Adv. 2018;2:3257–91. PubMed PMID: 30482765.

Wu O, Robertson L, Langhorne P, Twaddle S, Lowe GD, Clark P, Greaves M, Walker ID, Brenkel I, Regan L, Greer IA. Oral contraceptives, hormone replacement therapy, thrombophilias and risk of venous thromboembolism: a systematic review. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) Study. Thromb Haemost. 2005;94:17–25. PubMed PMID: 16113779.

Young G, Albisetti M, Bonduel M, Brandao L, Chan A, Friedrichs F, Goldenberg NA, Grabowski E, Heller C, Journeycake J, Kenet G, Krümpel A, Kurnik K, Lubetsky A, Male C, Manco-Johnson M, Mathew P, Monagle P, van Ommen H, Simioni P, Svirin P, Tormene D, Nowak-Göttl U. Impact of inherited thrombophilia on venous thromboembolism in children: a systematic review and meta-analysis of observational studies. Circulation. 2008;118:1373–82. PubMed PMID: 18779442.

Young G, Becker S, Düring C, Friedrichs F, Goldenberg N, Kenet G, Manco-Johnson M, Scheffold C, Nowak-Göttl U. Influence of the factor II G20210A variant or the factor V G1691A mutation on symptomatic recurrent venous thromboembolism in children: an international multicenter cohort study. J Thromb Haemost. 2009;7:72–9. PubMed PMID: 18983482.

Young G, Manco-Johnson M, Gill JC, Dimichele DM, Tarantino MD, Abshire T, Nugent DJ. Clinical manifestations of the prothrombin G20210A mutation in children: a pediatric coagulation consortium study. J Thromb Haemost. 2003;1:958–62. PubMed PMID: 12871361.

Zhang P, Zhang J, Sun G, Gao X, Wang H, Yan W, Xu H, Zu M, Ma H, Wang W, Lu Z. Risk of Budd-Chiari syndrome associated with factor V Leiden and G20210A prothrombin mutation: a meta-analysis. PLoS One. 2014;9:e95719. PubMed PMID: 24755609.

Zivelin A, Mor-Cohen R, Kovalsky V, Kornbrot N, Conard J, Peyvandi F, Kyrle PA, Bertina R, Peyvandi F, Emmerich J, Seligsohn U. Prothrombin 20210G>A is an ancestral prothrombotic mutation that occurred in whites approximately 24,000 years ago. Blood. 2006;107:4666–8. PubMed PMID: 16493002.

Zivelin A, Rosenberg N, Faier S, Kornbrot N, Peretz H, Mannhalter C, Horellou MH, Seligsohn U. A single genetic origin for the common prothrombotic G20210A polymorphism in the prothrombin gene. Blood. 1998;92:1119–24. PubMed PMID: 9694698.

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