

# Thrombosis in the Young: Epidemiology and Risk Factors. A Focus on Venous Thrombosis

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## Introduction

Thrombosis is a disease that affects the young and the old. Differences between the ages concern the frequency of thrombosis and its risk factors. Here, we will present epidemiologic data on venous and arterial thrombosis with regard to the incidence for different age categories, with a view on morbidity and mortality. For the risk factors, the focus will be on venous thrombosis, with a review of the risk profiles specific to children in the first year of life, older children and young adults, which are three distinct groups with regard to venous thrombosis. Since in young adults the risk factors that play a role are qualitatively the same as those that play a role in older adults and the elderly, risk factors that are specific to young adults will be dealt with in detail: oral contraceptives, pregnancy and puerperium. Finally, we will present new data on the quantitative importance of several risk factors for venous thrombosis, concerning the frequency and the number of risk factors required for thrombosis in different age groups.

## Incidence of venous and arterial thrombosis

### Morbidity data

Thrombosis manifests itself mainly as myocardial infarction, cerebral infarction, and venous thromboembolism. Each of these occurs with an incidence of 1-3 per 1000 individuals per year (1,2,3). The incidence rates of thrombosis are only known by approximation, since they require very large studies or regional registries, that each have their specific shortcomings - for instance, even the largest studies will have considerable statistical uncertainty, hospital registries do not include individuals who died before admission, and statistics based on death certificates suffer from misclassified diagnoses. The incidence is distributed extremely unevenly over the ages, which on the one hand makes thrombosis uncommon in young individuals, while on the other hand thrombosis is the leading cause of death in the elderly. Table 1 shows

Table 1. Incidence of acute myocardial infarction (AMI), cerebral infarction (CI) and venous thromboembolism (VTE): morbidity data

age	Incidence per 100,000 per year		
	AMI <sup>1</sup>	CI <sup>2</sup>	VTE <sup>3</sup>
0-14	0.1	1.0	0.6
15-24	0.7	1.9	20.2
25-39	18.6	6.6	39.3
40-54	175.6	45.4	74.2

Information on hospital discharge diagnoses in 1994 kindly supplied by SIG Zorginformatie, Landelijke Medische Registratie (LMR), Utrecht (3). The 1994 discharge data cover 99.3 percent of the Netherlands. Incidence rates calculated with population age-distribution data for 1994 from the Central Bureau of Statistics, The Hague (4).

<sup>1</sup>ICD code 410: acute myocardial infarction, <sup>2</sup>ICD codes 434, 436: cerebral infarction, <sup>3</sup>ICD codes 415, 451, 453, 671.3, 671.4, 671.5: deep venous thrombosis, pulmonary embolism.

the incidence of the major types of arterial and venous thrombosis in the Netherlands, as calculated from hospital registries. Until age 40, venous thrombosis is the most common form of thrombosis, after which the incidence of myocardial infarction increases very rapidly and becomes the most common form of thrombosis. The incidence rates are also not evenly distributed over the sexes: myocardial infarction is more frequent among men than among women; up to age 55, myocardial infarction occurs four to five times more often in men than in women. Cerebral infarction is slightly (about two-fold) more common in women until age 40, after which this distribution reverses. Venous thrombosis is more often seen in women than in men, which difference is most pronounced in the reproductive age (two- to three-fold difference). Between age 15 and 39, a woman has a 5-fold higher risk of experiencing a venous thrombotic event than an arterial thrombosis (3).

### Mortality data

Table 2 shows Dutch mortality rates for acute myocardial infarction, cerebral infarction and venous thromboembolism (4). Until age 40, death from any form of thrombosis is very rare, and occurs in less than one per 100,000 individuals per year. After age 40, myocardial infarction and, to a lesser

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Table 2. Incidence of death from acute myocardial infarction (AMI), cerebral infarction (CI) and venous thromboembolism (VTE): mortality data

age	Mortality per 100,000 per year		
	AMI <sup>1</sup>	CI <sup>2</sup>	VTE <sup>3</sup>
0-14	0.03	0	0
15-24	0.3	0.1	0.3
25-39	3.0	0.4	0.4
40-54	31.5	3.6	1.1

National mortality statistics for 1994 from the Central Bureau of Statistics, The Hague (4).

<sup>1</sup>ICD code 410: acute myocardial infarction, <sup>2</sup>ICD codes 434, 436: cerebral infarction, <sup>3</sup>ICD codes 415, 451, 453, 673: deep venous thrombosis and pulmonary embolism

extent, cerebral infarction, begin to take their toll. When compared to the morbidity figures (which comparison should be made with some caution because of the shortcomings of these different estimates as mentioned above), it is clear that venous thrombosis has a much lower lethality than myocardial infarction: even though venous thrombosis is more common in the young than arterial thrombosis, less individuals die from venous than from arterial thrombosis. In children, thrombosis is so rare that mortality rates cannot be compared between the subtypes (venous and arterial) of thrombosis. Between age 15 and 24, mortality from venous thrombosis is slightly more frequent than from arterial thrombosis - the difference again being most pronounced in women.

### Risk factors for venous and arterial thrombosis

Table 3 lists several of the risk factors for myocardial infarction, cerebral infarction and venous thromboembolism (5-7). The risk factors for myocardial infarction and cerebral infarction show most overlap, although some risk factors are more pronounced for myocardial infarction (eg, male sex, hypercholesterolemia) than for cerebral infarction. Some factors are associated with an increased risk of all types of thrombosis, eg, oral contraceptives, hyperhomocysteinemia, lupus anticoagulant and high levels of fibrinogen (8,9).

The risk factors for venous thrombosis are different

Table 3. Risk factors for myocardial infarction, cerebral infarction and venous thromboembolism

Myocardial infarction	Cerebral infarction	Venous thromboembolism
hypertension	hypertension	surgery/trauma/ immobilisation
smoking	smoking	malignancy
diabetes mellitus	diabetes mellitus	pregnancy/puerperium
hypercholesterolemia	hypercholesterolemia	factor V Leiden
obesity	obesity	deficiency of PC/PS/AT
oral contraceptives	oral contraceptives	oral contraceptives
hyperhomocysteinemia	hyperhomocysteinemia	hyperhomocysteinemia
lupus anticoagulant	lupus anticoagulant	lupus anticoagulant
high fibrinogen	high fibrinogen	high fibrinogen
		high factor VIII levels

because they are not related to atherosclerosis. Classical risk factors for venous thrombosis are those associated with tissue damage and stasis, ie, trauma, surgery and immobilisation. Abnormalities associated with the hemostatic system are prominent in venous thrombosis, and together deficiencies of protein C (PC), protein S (PS), antithrombin (AT) and carriership of factor V Leiden or resistance to activated protein C (APC), account for 25-35 percent of all occurrences of venous thrombosis. This implies that heritability plays a more important, or at least a more obvious, role in venous than in arterial thrombosis.

### Venous thrombosis in children

Venous thrombosis in children is far less common than in adults and has a distinct presentation and etiology. In a registry of Canadian children with thrombosis, the incidence of venous thrombosis between ages 1 month and 18 years was estimated at 0.7 per 100,000 per year (10). This figure is in close accordance with the estimate of 0.6 per 100,000 per year for the ages 0-14 based on the Dutch hospital discharge registry shown in table 1.

In the first year of life, venous thrombosis occurs either in association with indwelling venous catheters, or as renal vein thrombosis. The association with venous access devices implies that the location of the thrombosis often involves the upper extremities. In the 60 children with venous thrombosis in the first year of life from the Canadian registry, 21 suffered renal vein thrombosis, while all but one of the 39 other patients had a venous catheter (11). These latter thromboses occurred in a variety of locations of which the superior vena cava and vena femoralis were the most common.

Renal vein thrombosis becomes manifest in the first few days after birth. Although its etiology is obscure, it is assumed that renal vein thrombosis has its onset before birth. In contrast to other forms of childhood thrombosis, renal vein thrombosis has a clear sex difference, affecting male newborns twice as often as newborn girls (11). An exceedingly rare and severe form of thrombosis in the newborn is caused by homozygous deficiencies of protein C or protein S (12-13). These children develop extensive thrombosis with purpura fulminans shortly after birth. Homozygous antithrombin deficiency may not be compatible with life (14).

In older children, venous catheters remain one of the most frequent triggering factors for thrombosis, and are reported in at least 25 percent of the patients (10,15,16). Other frequently encountered risk factors are surgery and trauma, malignancy, auto-immune disorders (systemic lupus erythematosus, lupus anticoagulant) and infections. Rarely, an inborn error of metabolism leads to a thrombotic tendency, eg homocystinuria, which has a prevalence of 1:335,000 live births (8,17). After the first year of life, thrombosis occurs about as frequently in male and female children (15). The incidence has a peak in the first year, becomes very low during the next 10 years and subsequently slowly increases with age (10). In children with venous thrombosis, it is only very rarely that no triggering event can be found; in almost half of the children three or four risk factors are present

simultaneously (10). In a substantial number of children disorders of hemostasis can be found: inherited deficiencies of antithrombin, protein C, protein S were reported in 25-30 percent of children with venous thrombosis (10,16). This clearly exceeds the prevalence of these disorders in consecutive adult patients with venous thrombosis (18,19). Even in these children with deficiencies, the thrombosis did not occur spontaneously, and the hemostatic defect only became apparent because thrombosis occurred when one or more acquired risk factors were also present (10,15). This has etiological and practical consequences: it shows that venous thrombosis is a multicausal disease, which becomes most evident in children, who have not yet accumulated age-associated risk factors; and it implies that in children contrary to the situation in adults it is worthwhile to investigate defects in hemostasis even if other risk factors seem to 'explain' the thrombotic event.

### Venous thrombosis in young adults

Among adults, the major risk factors for venous thrombosis can be divided in acquired and genetic risk factors. The importance of each depends on its prevalence in the general population and its relative risk. The prevalence of the acquired risk factors is strongly dependent on age, with pregnancy, puerperium and oral contraceptives being limited to the young, and malignancies, surgery and immobilisation being more prevalent among the elderly than among the young. The prevalence of some risk factors, such as use of oral contraceptives and hormonal replacement therapy will also vary between societies. For some risk factors, notably hyperhomocysteinemia and high levels of factor VIII, it is not clear to what extent they are affected by genetic or acquired determinants.

Although deficiencies of protein C, protein S and antithrombin have a high relative risk, they are not the most important risk factors for venous thrombosis because they are very rare. Common abnormalities are APC-resistance, which increases the risk of thrombosis seven-fold and is found in 3-7% of Caucasians (20-24), high levels of factor VIII, which are found (FVIII:C > 150 IU/dl) in 11 percent of the population and increase the risk of venous thrombosis six-fold (25), and hyperhomocysteinemia, which is found (homocysteine > 18.5 mol/l) in 5-10 percent of the population and increases the risk of thrombosis two-fold (26,27). The factor II variant (20210 G>A) has been found in 2.3 percent of healthy controls, and increases the risk three-fold (28). These figures allow the computation of population-attributable risks, which indicate how much of the total incidence in the population can be attributed to a specific exposure or risk factor (29). For factor VIII:C levels > 150 IU/dl this is 35 percent, ie, 35 percent of all events of deep-vein thrombosis can be attributed to high factor VIII levels; for protein C deficiency this is only three percent.

### Oral contraceptives and venous thrombosis

Numerous reports in the 1960s and 1970s have followed Jordan's case report of pulmonary embolism associated with

the use of a oral contraceptive in 1961 (30,31,32). Although over the decades the oestrogen content of the oral contraceptive pill has gone down in an attempt to lower the risk of thrombosis, this risk has not disappeared. In a recent study from the WHO, oral contraceptive use was associated with a 4.2-fold increased risk of thrombosis (33); in a Dutch study the age-adjusted relative risk of users versus non-users was six (34). Because oral contraceptives are used by young women who have a very low risk of venous thrombosis, the absolute risk remains low. On the other hand, since many young women use oral contraceptives, the majority of the thrombotic events in the younger age groups in women can be attributed to the use of oral contraceptives.

Recently, it has been shown in several studies that the progestagen component in oral contraceptives also has a thrombogenic potential: products containing desogestrel or gestodene, so-called third generation progestagens, confer a two-fold higher risk of thrombosis than oral contraceptives with a second generation progestagen (often levonorgestrel) (35-38). This higher risk associated with third generation progestagens remained after adjustment for age, family history, duration of use, parousness, obesity, factor V Leiden carriership (35-38). Among the youngest women, the relative risk was highest: among 15-19 year old women, a third-generation progestagen containing oral contraceptive led to a 7-fold higher risk than a second-generation progestagen containing oral contraceptive; in the age group 20-24 there was a four-fold risk increase (37).

The factor V Leiden genotype acts synergistically with the use of oral contraceptives on the risk of deep-vein thrombosis: the incidence of deep-vein thrombosis for the age-group 15-49 years was estimated at 0.8 per 10,000 women per year for non-users with the normal genotype, 3.0 per 10,000 women-years for users of oral contraceptives with the normal genotype, and 5.7 per 10,000 women-years for non-users with the factor V Leiden genotype, and the risk became 28.5 per 10,000 women-years for oral contraceptive users with the factor V Leiden genotype (34). This synergistic effect was most pronounced when women used a third-generation contraceptive (37). There is an excess of oral contraceptives using women among thrombosis patients with homozygous factor V Leiden (23); in one series, 80 percent of the homozygous women with thrombosis were users of oral contraceptives at the time of the thrombosis (39). A very high risk of thrombosis has also been shown for women with the more rare forms of familial thrombophilia who use oral contraceptives, especially in antithrombin deficiency (40).

### Pregnancy and venous thrombosis

It is unclear how large a risk of thrombosis is conferred by pregnancy and the puerperium. In two large series, venous thrombosis was reported in 0.13 per 1000 pregnancies (41) and 0.7 per 1000 pregnancies (42). Taking the average duration of pregnancy into account, these are incidence rates of 0.17 and 0.93 per 1000 pregnant-women-years. This is slightly higher than the risk of non-pregnant women in these age-groups. In a direct comparison in the Leiden Thrombophilia Study pregnancy was associated with a four-fold increased risk of venous thrombosis (43).

The risk of thrombosis is much greater in the puerperium than in pregnancy. It has been estimated that 2.3 to 6.1 of 1000 deliveries are followed by thrombosis (41,42). A woman therefore has a 3- to 5-fold higher risk of developing thrombosis shortly after than during pregnancy; since the postpartum is much shorter than the period of pregnancy, this implies that the incidence of thrombosis (ie, per unit of time) is at least 20-30 fold higher postpartum than during pregnancy.

All thrombophilias lead to an increased risk of thrombosis during pregnancy (44-46). Most of these are rare and therefore concerns only a fraction of all pregnancies. This is different for factor V Leiden, which has been found among 20-60 percent of women with thrombosis in pregnancy (47-49).

#### Frequency of risk factors for venous thrombosis

Whereas some types of thrombosis appear to be specific for young individuals, ie, renal vein thrombosis in the newborn, and some risk factors are only found in the young, ie, oral contraceptives and pregnancy, many risk factors increase the risk in the young and the old. The distribution of the risk factors over the age groups, however, may differ. Table 4 shows the prevalence of several major risk factors for thrombosis, as found in the Leiden Thrombophilia Study (LETS), for contrasting age categories:

Surgery, hospital admissions, factor V Leiden and high levels of factor VIII appear as important risk factors in young and older individuals alike. The prevalence of some factors is different for different age groups: the increased levels of factor VIII in those aged 55 and older is an age-effect, as is an increasing frequency of surgery, hospital admissions and other medical conditions that can be seen with finer age-stratification. The absence of a risk associated with high levels of homocysteine among young individuals is noteworthy; however, it is in contrast to other reports that showed a high prevalence of hyperhomocysteinemia in young individuals with thrombosis (50). The hereditary risk factors are more prevalent among patients who experience their first thrombotic event at a younger age than those who do so at an older age,

Table 4. Risk factors for deep-vein thrombosis by age

Risk factor	< 40 years		aged 55 +	
	cases (n=160) %	controls (n=161) %	cases (n=127) %	controls (n=124) %
surgery/hospital admission	30.0	5.6	24.4	4.8
factor V Leiden	23.1	3.7	18.1	3.2
factor II 20210G6A	6.9	3.7	4.7	2.4
PC/PS/AT deficiency	8.8	2.5	3.9	0.8
high factor VIII	25.0	11.8	48.0	29.8
hyperhomocysteinemia	11.2	10.6	24.4	12.2

Frequency of risk factors are shown for cases and controls younger than 40 (range 15-39) and older than 54 (range 55-72). Surgery and hospital admissions refer to all such events in the year prior to the thrombosis or a similar date in controls; deficiencies of protein C (PC), protein S (PS) and antithrombin (AT) were defined as results below the lower limit of normal on two separate occasions; high factor VIII are FVIII:C levels exceeding 150 IU/dl; hyperhomocysteinemia is a non-loading plasma homocysteine level exceeding 18.5 mol/l.

but this effect is not very pronounced. This seems in contrast to the marked relation with thrombosis at a young age reported in families with familial thrombophilia; however, that is the result of those families having been selected mainly on the occurrence of thrombosis at a young age (51). These genetic abnormalities are less prevalent in the older than in the younger healthy controls, which points to the high thrombotic risk of these defects: few individuals carrying these defects grow old without experiencing thrombosis.

#### Number of risk factors required for thrombosis

In children, three or four risk factors are often required to precipitate thrombosis. Recently, it has become clear that in adults, too, thrombosis is a multicausal disease. Protein C deficiency appeared more severe in families with familial thrombophilia than in relatives of asymptomatic blood donors (52-54), because in these families several abnormalities were present (55). It seems plausible that in order for thrombosis to occur, several risk factors, genetic and acquired, need to be present simultaneously, and that this is even more so for thrombosis to occur at a young age; hence the finding of several risk factors in young children, and in families with thrombophilia, which are often selected based on the occurrence of unexplained thrombosis at a young age.

Table 5 shows the number of risk factors, from a total of seven major risk factors, found in patients and controls in various age groups (data from LETS). Among individuals aged 40 and less, as well as among those aged 55 and more, a large proportion of the cases has one or more of these seven major risk factors. The relative risk of thrombosis rises sharply with the number of risk factors; among those aged less than forty, relative to those with none of these risk factors, those with one risk factor have a 2.4-fold increased risk, those with two risk factors a 7.7-fold increased risk, whereas for those with three or more risk factors the relative risk exceeds 20. Among the individuals aged 55 and older, a similar relation between the number of risk factors and the relative risk can be observed. A difference between the older and younger age groups is a higher proportion of individuals in the young age category, among cases and controls alike, with two or more risk factors. This indicates that in the young age group a combination of several risk factors will lead to thrombosis, leaving very few to grow old without thrombosis while carrying such a combination of risk factors.

Table 5. Number of thrombosis risk factors in different age categories

Risk factors	< 40 years		aged 55 +	
	cases (n=160) %	controls (n=161) %	cases (n=127) %	controls (n=124) %
none	16.9	47.8	22.8	54.8
1	31.9	37.3	37.8	38.7
2	35.6	13.0	33.9	4.8
3	11.9	1.2	3.9	1.6
4	3.8	0.6	1.6	0
5-7	0	0	0	0

The risk factors that are counted are those of table 4: surgery/hospital admission, factor V Leiden, factor II 20210 G6A, clotting inhibitor (PC/PS/AT) deficiency, high factor VIII, hyperhomocysteinemia, and oral contraceptive use.

## Conclusion

The incidence of thrombosis strongly depends on age: it is a very rare disorder in the young, and a common affliction in the elderly. Thrombosis occurs when a sufficient number of risk factors are present simultaneously. In children, three or four risk factors are required before thrombosis occurs, whereas in individuals aged 55 and older thrombosis will almost invariably occur when two or more risk factors are present. The number of risk factors required to cause thrombosis decreases with age, which itself therefore appears as a strong risk factor for thrombosis. It seems likely that ageing introduces additional risk factors, with vessel wall changes, with a different composition of the blood, or with altered mobility, which may all add to the risk profile, necessitating fewer additional risk factors for thrombosis to occur. Or, viewed from a different angle: the decreasing number of risk factors required to cause thrombosis with increasing age, explains why the incidence of thrombosis rises with age.

## Summary

Thrombosis occurs most often as myocardial infarction, cerebral infarction or venous thromboembolism, ie, deep-vein thrombosis and pulmonary embolism. The incidence of all types of thrombosis is strongly dependent on age. Among young individuals, up to age 40, venous thrombosis is the most common form of thrombosis. The risk factors for arterial and venous thrombosis differ, and among the latter disorders of hemostasis appear to be more prominent.

In children venous thrombosis appears almost exclusively in association with venous catheters, with an exception of the renal vein thrombosis of the newborn, which has an unknown etiology. In young adults, the risk factors for venous thrombosis are essentially the same as in older individuals, excepting oral contraceptives, pregnancy and puerperium which are limited to young women. In young women, most venous thrombotic events can be attributed to oral contraceptives.

Venous thrombosis is a multicausal disease: more than one risk factor needs to be present before thrombosis occurs. The younger an individual, the more risk factors are required to precipitate thrombosis: in children often three or four, and in young adults often two or more.

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