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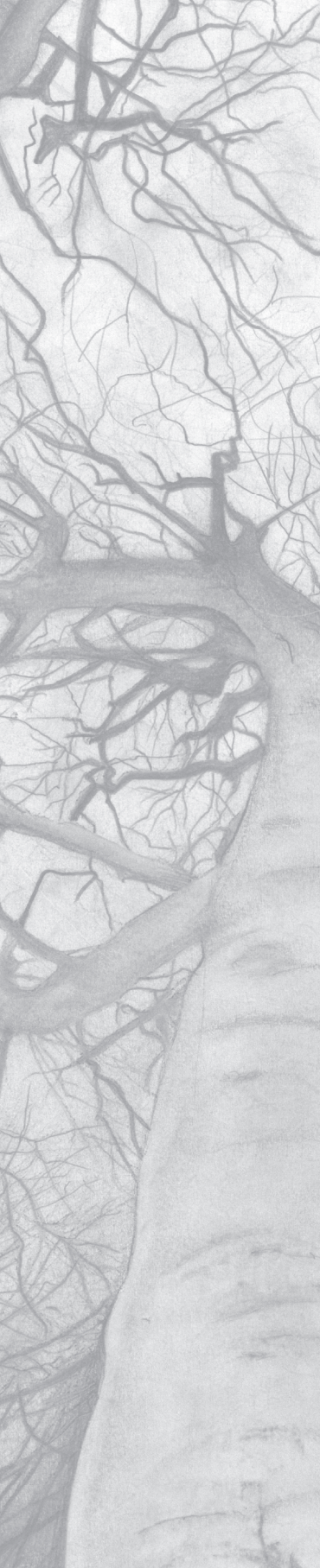


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CHAPTER 2

Venous thrombosis in the elderly: incidence, risk factors and risk groups

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ABSTRACT

Ageing is the strongest risk factor for venous thrombosis. The cause of this steep age-gradient is as yet, unexplained. The aim of this review was to provide an overview of studies on the effect of conventional risk factors as well as age-specific risk factors for venous thrombosis in the elderly.

Limited data are available on risk factors for venous thrombosis in the elderly, i.e., all results are based on small study groups. Results indicate that, of the conventional risk factors, malignant disease, the presence of co-morbidities and the genetic risk factors factor V Leiden and the prothrombin mutation seem to be associated with an increased risk of venous thrombosis in the elderly. Age-specific risk factors of thrombosis, i.e., endothelial dysfunction, diminished muscle strength, and frailty may be important in the explanation of the increased incidence of venous thrombosis in the elderly.

In conclusion, since ageing is the strongest risk factor for venous thrombosis, further identification of the risk factors for thrombosis in the elderly is needed to elucidate the age-gradient of the incidence of venous thrombosis and to target preventive measures.

INTRODUCTION

Thrombosis in the venous system, i.e., deep venous thrombosis or pulmonary embolism is a multicausal disease. The well-established or “conventional” risk factors are mostly identified in young and middle-aged populations. Conventional risk factors can be acquired, e.g., immobility, surgery, malignant disease, and hormone use, whereas the most well-known genetic risk factors are deficiencies of natural anticoagulants protein C, protein S, and antithrombin and the Factor V Leiden and prothrombin 20210A mutations [1-3].

The overall incidence of a first symptomatic venous thrombosis in the general population is 1-2 per 1000 person-years (py). In the age-group 25 to 30 years old, venous thrombosis occurs in ~1 per 10,000 py as compared to nearly 8 per 1000 py in the 85 years and older population [4]. The risk of developing venous thrombosis is therefore 80-fold increased in the older population, leading to a high attributable risk. The population attributable risk is more than 90%, indicating that 90% of the total incidence of thrombosis in the population can be ascribed to ageing. The life-time risk (cumulative incidence) of venous thrombosis is up to 15% in those aged 90, and ~60% of all venous thrombosis events occur in those aged 70 years and older [4].

It is therefore clear that ageing is by far the strongest risk factor for venous thrombotic disease, resulting in a high incidence of venous thrombosis in the elderly population (figure 1) [1-3]. The strong age-gradient can, at least in part, be explained

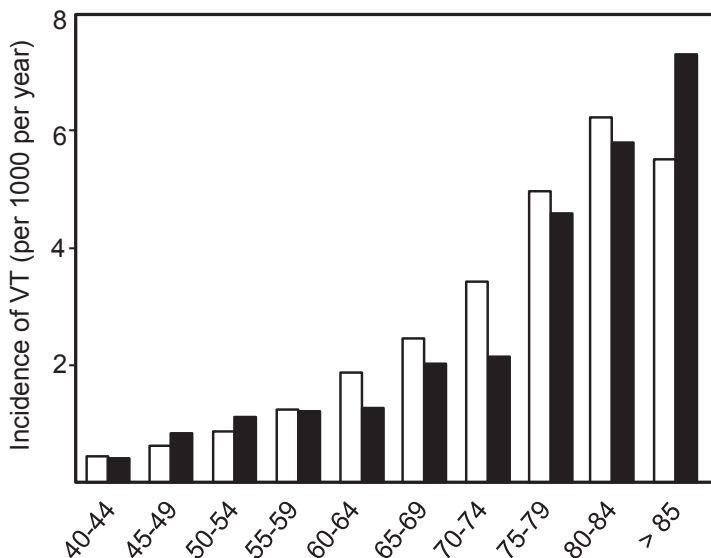


Figure 1. Incidence of first venous thrombosis (VT) [deep vein thrombosis (DVT) and pulmonary embolism (PE)] stratified by age group and gender. Rates are shown by 1000 per year, for man in open bars, for women in closed bars. *Adapted from Naess et al. (2007).

by an increased prevalence of conventional risk factors and the presence of other, age-specific, risk factors. The incidence of venous thrombosis is similar for men and women indicating that, given the excess of women in the old age groups, most elderly patients with venous thrombosis are women [5]. Furthermore, a difference in the distribution of deep venous thrombosis and pulmonary embolism between young and old people has been described. In one study in middle-aged individuals (40 to 44 years old) deep vein thrombosis (incidence of 0.3/1000 py) was three times more frequent than pulmonary embolism (incidence of 0.1/1000 py) [6]. In patients of 80 to 84 years old, pulmonary embolism (incidence of 5.5/1000 py) was more frequently diagnosed than deep vein thrombosis (incidence of 3.0/1000 py) [6]. These findings suggest that also an increase in the embolisation of clots may contribute to the age-gradient. However, in contrast, a large European registry found that deep vein thrombosis was more often diagnosed than pulmonary embolism in the 80 to 84 year old individuals (incidences of 3.8/1000 py for deep vein thrombosis compared to 2.2/1000 py for pulmonary emboli) [4].

In general, people over 60 years are considered to be 'the elderly' [5]. Why does thrombosis incidence increase with age? Several explanations can be postulated. Ageing may be associated with an increased prevalence of conventional risk factors or development of new, age-specific risk factors. In addition, risk factors may have synergistic effects conditional on age, i.e., the effect of a factor on the risk of thrombosis may be different in young and middle-aged populations compared with the elderly.

The interpretation of the effect of a risk factor for venous thrombosis in elderly populations is difficult as new risk factors may develop and accumulate during life. In addition, age-related changes of the association between a risk factors and venous thrombosis could be explained by the phenomenon: "attrition of susceptibles", i.e., individuals highly vulnerable to a risk factor are likely to develop thrombosis early in life, resulting in an elderly population that is less affected by this risk factor, leading to a weakened association between this risk factor and the occurrence of a first venous thrombosis in the elderly.

Several statistical measures can be used to express the importance of a risk factor in the development of disease. The rate difference ($I_e - I_o$), i.e. the difference of the incidence in the presence (I_e) or absence of the risk factor (I_o) indicates the excess number of cases due to the presence of a risk factor in a certain time period. The proportion of disease among those with the risk factor which can be attributed to that risk factor is expressed as the attributable risk (AR: $I_e - I_o / I_e$). A population attributable risk (PAR= $(I - I_o) / I$) indicates what proportion of the total incidence of a disease in the general population can be attributed to a certain risk factor. The latter is dependent on the prevalence of the risk factor in the general population. While the AR is also called 'aetiologic fraction', the PAR is the 'preventable fraction', for it indicates for a specific population which proportion of the burden of a certain disease could be removed by complete removal of the risk factor.

The role of many conventional and age specific risk factors in the explanation of the strong age-gradient of venous thrombosis has not before been summarised. This review will provide an overview of the prevalence and effect of conventional risk factors as well as age-specific risk factors for venous thrombosis in the older population. We will, wherever possible, calculate (population) attributable risks, to quantify the impact of risk factors on venous thrombosis and to compare the risk in young and the elderly populations. Furthermore, using available information on risk factors for venous thrombosis in the elderly, we will attempt to identify high-risk groups within the elderly population.

CONVENTIONAL RISK FACTORS

Table 1 shows conventional risk factors of venous thrombosis and attributable and population attributable risks in the young and older population are provided.

Immobility

Immobility, leading to rheologic changes by increasing blood viscosity and stasis, is associated with an increased risk of venous thrombosis. [7,8] There is no single definition of immobility. Differences in the definition for immobilisation, and the presence of underlying conditions while immobilised, such as hospitalisation because of surgery, make it difficult to provide one estimate of the strength of the association with thrombosis.

In a meta-analysis by Pottier *et al.*, a pooled odds ratio (OR) of more than two was reported for immobilised compared with non-immobilised medical patients, not taking into account the age of the patients. [9] In hospitalised patients aged >65 years,

Table 1. Conventional risk factors of venous thrombosis: attributable and population attributable risks in the young and older population

Conventional risk factors VT	Young AR (%)	Old AR (%)	Young Prev (%)	Old Prev (%)	Young PAR (%)	Old PAR (%)
Immobilisation*	50–90	66–83	10	25	9–47	33–56
Malignancy†	86	86	3	10	15	35
CHF‡	60–71	33–60	5	22	7–11	10–25
COPD§	50–80	33	1	11	1–4	5
DM	50	0–50	6	16	6	0–14
HRT use**	50	50	4	1	4	1
Genetic factors††	67–86	50–80	7	7	12–30	7–22

VT, venous thrombosis; Young, young and middle-aged population (< 65 years old); Old, older population (≥ 65 years old); AR, attributable risk; Prev, prevalence; PAR, population attributable risk; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HRT, hormone replacement therapy. *Ref. [7–13,18]. †Ref. [11,19–23]. ‡Ref. [10,24–28]. §Ref. [32–34]. ¶Ref. [35–40]. **Ref. [51–62]. ††Ref. [70–76].

short-term bed rest (up to 14 days) was associated with an almost six-fold increase in thrombotic risk compared with patients without bed rest. [10] Furthermore in young and middle-aged populations, hospitalisation was found to contribute to venous thrombosis in more than half of all cases in the general population (PAR: 50%), and a 8 to 10-fold increased risk of venous thrombosis during hospitalisation has been reported. [11] Surgery leads to a six-fold increased risk of venous thrombosis [12] and approximately three percent of individuals undergoing lower limb arthroplasty (whose average age is over 65) develop venous thrombosis even when they receive prophylactic medication. [13] The thrombotic risk associated with hospitalisation has not been studied specifically in the elderly population; however, since the prevalence of hospitalisation doubles with age (from ~ 10% in the population of 45 to 64 years to 25% in individuals of 65 years and older), the population attributable risks will be highest in the elderly. (PAR young ~10%, PAR old: ~40%). [9-15]

Numerous other causes for immobility can be identified, e.g., plaster cast and prolonged travel. Lower extremity injury and plaster casts often lead to immobilisation, and both have been identified as strong risk factors for venous thrombosis in the young and middle-aged population [14]; however, they have not been studied in the elderly.

Furthermore, long-haul travel leads to short-term immobility and was associated with a two-fold increased risk of venous thrombosis in the young and middle aged population in the MEGA study. [15,16] Air travel was found to affect the thrombotic risk also in the eldest subgroup of the study (50-71 years), but their absolute risk of thrombosis was lower than in the younger group. [17] The frequency of air travel is four-fold higher among young and middle aged than in the older population. Therefore, the population attributable risk will be lower in the elderly population than in the young and middle-aged indicating that air travel contributes mainly to the overall burden of thrombosis in the younger population. [18]

Long-term reduced mobility predominantly affects the elderly. In the Netherlands, ~10% of the people aged 45 to 64 years have disabilities affecting mobility, increasing to more than one third of the 75 years and older individuals. [19] Long-term immobility appears to be associated with the risk of venous thrombosis, although the risk appears to be strongest in the first four weeks of bed rest (3 to 4-fold increased). Similar results have been reported for arm chair immobilisation in a 65 years and older population. [10,20]

Malignancy

The overall risk of venous thrombosis in cancer patients is seven-fold increased compared with individuals without cancer. [11,21] This risk differs according to the type and location of the primary tumor, the extensiveness of the disease, and the cancer therapy. [22] Little information is available on the estimates of the risk of venous thrombosis

associated with malignancy in specifically the elderly patients. The absolute risk of venous thrombosis for ovarian cancer patients (treated with surgery and chemotherapy) of 61 years and older was reported to be ~250 per 1000 patients years. [23] Similar to the young and middle-aged population, pancreatic, ovarian and brain tumors are described to be associated most strongly with venous thrombosis in the elderly cancer patient. [4,22,24] Furthermore, cancer associated venous thrombosis is more prevalent in the population of 70 years and over than in a younger population. [25] This can be explained by the increase of the incidence of malignancy with age (i.e., three-fold increase of incidence for those over 65 years compared with those younger than 65 years). [19] As the present literature suggests that a seven-fold increased risk of development of thrombosis in cancer patients exists, we can conclude that the PAR is 15% in the younger population and 35% in the elderly.

Co-Morbidity

Diseases that have been identified to affect the risk of thrombosis are, e.g., heart failure, stroke, chronic obstructive pulmonary disease (COPD) and diabetes mellitus. Congestive heart failure has been associated with a 2.5 to 3.5-fold increase of the risk of venous thrombosis. [26,27] This risk was mainly increased for pulmonary emboli. These risk estimates were reported in studies among patients with a mean age of 60 years and older. In studies in which only patients older than 65 years (median 82 and 85 years) were included, risk estimate of ~1.5 to 2.5 were reported [10,28]. As congestive heart failure is > four times more prevalent in individuals of 75 years and older compared with those of 55 to 74 years old (prevalence ~22% versus ~5%), it contributes more to the incidence of thrombosis in the elderly than in the middle aged population. [29-32]

Stroke increases the risk of venous thrombosis 1.3-3.5-fold in elderly inpatients (>65 years old). The severity of stroke is positively associated with the risk of thrombosis. [28,33,34] The risk of venous thrombosis in younger stroke patients has not been studied. However, it is likely, as stroke is a disease of the elderly, [34,35] that the population attributable risk will be higher in older than in middle-aged populations.

Chronic obstructive pulmonary disease (COPD) is a risk factor for pulmonary embolism and deep venous thrombosis. In individuals aged over 60, the presence of COPD was associated with a 1.2-1.4 increased risk of pulmonary embolism. [36,37] In a younger population (aged 40 to 59 years) the relative risk was higher, i.e., 2 to 5. As COPD is ten times more prevalent in the elderly than in the younger population (75 to 79 years: prevalence ~11%; 45 to 49 years 1%), population attributable risks are less than 5% for the overall COPD population. In the elderly population with thrombosis the highest contribution of COPD is expected. [19,38]

In a meta-analysis it was shown that individuals with diabetes mellitus have an almost 50% increased risk of venous thrombosis compared with individuals without

diabetes. [39] However, individual studies report contradictory results on the risk of thrombosis associated with diabetes, i.e., risk estimates range between no effect (RR=1) to a twofold increased risk for those with diabetes compared with those without the disease. [40-42] The risk of venous thrombosis associated with diabetes was reported to be higher in the younger (RR = ~2) than in the older population (RR= 1.5). [40] Since diabetes mellitus is more prevalent in the elderly (16% vs. 6%) than in young and middle-aged individuals, this will indicate that the contribution of diabetes to the thrombosis incidence is approximately equivalent in the young and elderly population. [43,44]

Increasing age is positively associated with the prevalence of various chronic disorders. The prevalence of two or more chronic diseases has been estimated at 35% in 40 to 59 years old, and increases to almost 80% in people aged 80 and older. [45,46] Elderly with multi-morbidity are likely to be especially vulnerable to develop thrombosis as interaction of the separate effects of these risk factors may exist.

Hormone replacement therapy

Hormone replacement therapy (HRT) leads to a procoagulable state, with elevated levels of factors VII, IX, X, XII, and FXIII and decreased levels of the anticoagulant proteins antithrombin and protein S. [47,48] Hormone therapy is associated with a 2 to 3-fold increased risk of thrombosis in the middle-aged and elderly population. [49-54] Combined use of estrogen and progestin was reported to be associated with a higher thrombotic risk than with estrogen use only. [54] The relative risk of venous thrombosis associated with hormone use was similar for middle aged and elderly women, i.e., within age strata of 50-59 years, 60-69 years, and 70-79 years, the relative risk of venous thrombosis for hormone users was two-fold increased compared with non-use [55,56]. The publication of studies reporting an increased risk of complications associated with hormone use, e.g. breast cancer, led to a more than 50% decrease in the use of post-menopausal hormones. [57] In the Netherlands, HRT is used predominantly by middle aged women, and less so in the elderly, i.e., HRT use in 2004 was 4% in women aged 50 to 54 years and 1% in women aged 70 to 74 years. [58] Therefore, while HRT use is associated with a similar relative risk of thrombosis in the elderly compared with middle aged women, it is associated with a lower population attributable risk in the elderly due to its scarce use.

Haemostasis factors

Elevated levels of D-dimer, homocysteine, von Willebrand Factor (vWF) and coagulation factors, FVIII, FIX, FXI, fibrinogen, and prothrombin are all associated with increased risks of venous thrombosis, with roughly a doubling of the risk for those with a coagulation factor level in the upper 10 percent (P90) of the population distribution of levels. [59-63] With increasing age plasma levels of many haemostatic factors are also increasing e.g., fibrinogen, FVIII, FVII, d-dimer and homocysteine. [60,64]

Scarce data are present comparing high and low levels of haemostatic factors in the elderly and their associated risk of venous thrombosis. Thus far, for high FVIII and VWF levels an increased risk of thrombosis in the elderly has been reported (2 to 3-fold) [62]. However, the association between high fibrinogen levels and the risk of venous thrombosis is still controversial. [62,65]

Cut-off points used in young and middle-aged populations for low and high levels in young individuals are difficult to interpret within the older population. Therefore, population attributable risks are not provided.

Genetic Risk factors

The most common genetic risk factors for venous thrombosis are the prothrombotic mutations factor V Leiden (FVL, rs6025) and the prothrombin 20210A mutation (PT20210, rs1799963). The prevalence of these genetic variants are similar in the young and elderly. [66-68] However, they vary widely between ethnic groups. The factor V Leiden mutation increases the risk of venous thrombosis three to seven-fold in individuals younger than 70 years compared with non-carriers. [69-71] This mutation has also been associated with an increased risk of thrombosis in the elderly, i.e., in individuals over 60 years a five-fold increased risk of thrombosis has been reported. [72] Studies in the elderly population found a 1.5 to 4.5-fold increased risk of thrombosis for carriers of the PT20210A mutation as compared with wild type carriers. [73,74] Thus, the factor V Leiden and the PT20210A mutation increase the risk of thrombosis 2 to 5-fold, and their prevalence is 7%. This implies that these two mutations are responsible for ~25% of all thromboses (PAR), regardless of age.

AGE-SPECIFIC RISK FACTORS

Age-specific factors are factors that are almost exclusively present in the older population. Although not studied in great detail yet, we can speculate that these factors are likely to explain at least partly, the steep age gradient in the risk of venous thrombosis.

Muscle strength

The overall muscle strength declines with age starting from the age of 50 years. [75] It is likely that this also affects the calf muscle pump. Indeed, it has been reported that both the calf compliance and the capacitance response, a marker for the redistribution of peripheral venous blood to the central circulation, decline over time. [76] Although the role of muscle strength of the lower limbs and the concomitant deterioration in the venous hemodynamics is not yet clarified, diminished function or efficacy of the calf

muscle pump could lead to reflux and stasis, which subsequently may lead to thrombus formation.

Endothelial dysfunction

Endothelial dysfunction is the alteration of the actions of the endothelium toward reduced vasodilation, and more prothrombic properties. Endothelial dysfunction is an important age-associated cardiovascular phenomenon. [77] With increasing age the anatomy of the venous vessel wall is modified, e.g., muscle fibers atrophy and valves thicken by an increase the number of collagen fibers. [78] Moreover, ageing has been associated with a shift towards less anticoagulant properties of the endothelium, i.e., it has been suggested that endothelial thrombo-resistance in the valves diminishes with age. [79] In addition, changes in laminar shear stress that for example occurs in varicose veins could diminish the release of anti-inflammatory and anticoagulant factors. [80] Hence, remodeling of the venous vessel wall with increasing age may contribute to the age gradient in the risk of thrombosis. The finding of an increased risk of venous thrombosis associated with microalbuminuria which may be a reflection of endothelial dysfunction strengthens this hypothesis. [81]

Venous insufficiency

The pathophysiology of chronic venous insufficiency consists of failure of valves through dilation of the venous wall or remodelling of the valve leaflets, which subsequently can lead to stasis and elevation of distal venous blood pressure. The prevalence of this functional disease increases with age. [82,83] Histological findings associated with venous insufficiency are increased collagen content of the vessel wall and disruption of the smooth muscle cells and elastic fibers. Currently it is unknown whether venous insufficiency is associated with an increased risk of thrombosis in the elderly.

AGE SPECIFIC RISK GROUPS

Venous thrombosis is a multicausal disease, i.e., more than one risk factor needs to be present simultaneously to cause the disease. Especially in the elderly risk factors are likely to accumulate. Therefore, high risk-profiles may often be present in the elderly, which may be specifically of interest when considering preventive measures, e.g., prophylactic treatment with anticoagulants.

Female sex

Women have a higher life expectancy than men, leading to a sex-ratio in favour of women in the elderly population. [5] As no sex-difference is reported for the risk of

thrombosis in the general population, this will lead to a higher proportion of women among elderly patients with venous thrombosis. Interest should therefore focus on risk factors for venous thrombosis with a high prevalence in women. These are likely to be of great importance in the explanation of the age gradient of the risk of venous thrombosis.

Nursing home

In the Netherlands, approximately 6% of the people of 65 years and older are institutionalised and half of the residents of these institutions are 85 years and older. [84] It was reported that living in a nursing home increased the risk of venous thrombosis eight-fold as compared with similarly aged individuals not institutionalised. [85] An incidence of venous thrombosis of 13 events per 1000 py was reported in nursing home residents. [86] However risk estimates are not yet reported for this specific group. The potential high risk of venous thrombosis in nursing homes would likely be the result of a high prevalence of other risk factors discussed before, e.g., immobilisation and comorbidities.

Frailty

Buchner and Wagner defined the concept of frailty as “losses of physiologic reserve that increase the risk of disability” [87]. Many indices are used to objectify frailty. Most commonly deficits in health including restricted activity, disability in activities of daily living (ADL), and impairments in general cognition and physical performance are taken into account. Additionally, co-morbidity and self-rated health are often measured. It was shown that the percentage of individuals with frailty increases with age, from less than 4% in the 65-74 years old group to 25% in the 85 years and older age group, and the frail group appeared to have a 30% increased risk to develop venous thrombosis compared with the no-frailty. [88]

CONCLUSION

Despite the clear age gradient in the risk of venous thrombosis, limited data are available on risk factors for venous thrombosis in the age group that is mostly affected by the disease, i.e., the elderly population. Therefore, the risk estimates provided in this review are mostly based on small study groups and subgroup analyses.

Many conventional risk factors for venous thrombosis established in the young and middle-aged population are likely to also increase the risk of thrombosis in the elderly. Immobility, malignant disease, co-morbidities, and increased levels of coagulation factors remain associated with an increased risk of thrombosis in the elderly population. Furthermore, common genetic risk factors, e.g., the factor V Leiden and the prothrombin

20210A mutation are also associated with thrombotic risk in the elderly, although lower risk estimates as compared with the younger population were reported.

We found that many of the conventional risk factors such as, immobilisation, malignant diseases and co-morbidities are more prevalent in the elderly than in young and middle-aged individuals. The risk factors that contribute highly to the increased incidence of venous thrombosis in the elderly (i.e., with the highest PAR), are immobilisation and the genetic risk factors. We found that immobilisation contributes to more than 40% off all venous thrombotic events, and genetic factors explain between 7 to 22 % of the thrombotic events. Thrombotic risk factors that appear to contribute less in the incidence of thrombosis in the elderly are long haul travelling and the use of hormone replacement therapy.

We hypothesise that age-specific risk factors of venous thrombosis such as endothelial dysfunction and venous insufficiency in the elderly could in part clarify the strong age gradient of thrombosis. This also includes factors as frailty and institutionalised living.

The strong age-gradient in the risk of venous thrombosis has led to numerous reports on the association between risk factors and thrombosis in the elderly, however only in very small subgroups. Subsequently, only limited conclusions can be drawn. We speculated about the different factors that may play a role in the development of venous thrombosis and their role in the incidence gradient with ageing, though research specified on the most affected, older population is necessary to draw firm conclusions. Moreover, high risk groups need to be identified, in order to be able to target preventive measures such as prophylactic treatment with anticoagulants to high risk groups. This may result in the prevention of life-threatening side effects of this treatment such as major bleeding. In addition, complications and morbidities after a venous thrombotic event need to be evaluated in this potentially more vulnerable population.

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