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VTE epidemiology and challenges for VTE prevention at the population level

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ABSTRACT

Venous thromboembolism (VTE) is a frequent disease affecting more than 1 in 12 individuals during their lifetime. VTE is associated with a substantial disease burden due to long-term complications such as recurrence, the post-thrombotic syndrome, and the post-pulmonary embolism syndrome. Despite the knowledge of several risk factors and triggers, more than one third of the VTE events occur in the absence of an obvious provoking factor. In this narrative review, we summarize studies presenting time trends in incidence rates of VTE after year 2000 and discuss potential reasons for the incidence trends as well as challenges for VTE prevention at the population level. Studies from US, Europe and Asia indicate that the incidence rates of VTE have increased slightly during the last twenty years. Of note, this increase has persisted beyond the implementation of computed tomography pulmonary angiography (CTPA) into routine clinical practice. The persisting rates are likely attributed to the concomitant increase in major risk factors for VTE, such as obesity, major surgery, and cancer. Apparently, more widespread use of thromboprophylaxis to high-risk groups have not counteracted the rates noticeably, indicating that an approach to change the risk factor profile in the general population may be warranted. Obesity is recognized as the strongest causal lifestyle factor for VTE with a population attributable fraction of 10–30%. However, the mechanisms by which obesity increases the VTE risk are poorly understood. By integrating multi-omics and system biology approaches, future epidemiological studies should focus on identifying biological pathways that drive thrombogenesis to reveal disease mechanisms and potential targets for prevention.

1. Venous thromboembolism (VTE)

Deep vein thrombosis (DVT), the formation of a thrombus in the deep veins, occurs most often in the veins of the leg or thigh, with swelling and pain in the affected limb as major symptoms [1]. DVT can also occur in other deep vein segments of the body, causing a variety of symptoms [2]. Pulmonary embolism (PE) occurs when parts of the thrombus break away and travel along the venous blood stream to the lungs, eventually blocking a pulmonary artery. Typical symptoms and signs of PE are shortness of breath, respiratory-dependent chest pain, hemoptysis, syncope and in most serious cases death due to circulatory collapse [3,4]. DVT and PE are collectively referred to as venous thromboembolism (VTE) since the two conditions share the same underlying pathology and can present at the same time, although sometimes asymptomatic in one of the locations [5]. However, systematic whole body imaging studies have suggested that not all pulmonary emboli originate from thrombi in the peripheral deep veins, and that other sources of emboli, such as right sided cardiac thrombi, or *in situ* thrombus formation in the lungs, may contribute in the pathogenesis of PE [6]. This hypothesis is supported by studies showing that risk factors affecting the cardiopulmonary region, such as atrial fibrillation, heart diseases, and pulmonary infections, are more strongly associated with PE than with DVT [7–10].

VTE is a frequent disease, affecting more than one million people in Europe each year [11], and nearly 10 million people worldwide [12]. The incidence increases markedly with age, from around 1 per 10,000 persons per year in young adults (<25 years old) to 1 per 100 persons per year in the elderly (>75 years) [13–15]. Notably, the risk of VTE in men versus women also changes over age. In younger age-groups, the incidence is higher in women than in men, in middle-aged groups (55–75 years) the incidence is considerably higher in men than in women, while in the elderly it is higher again in women [13,14,16]. Since reproductive risk factors like oral contraceptive use and pregnancy

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Table 1
Studies on time trends in incidence of VTE after year 2000.

First author, year	Country	Study population	Time period	Main findings
Alotabi et al. [37] 2016	Canada	Data from administrative health databases in Alberta, 31,656 VTE cases	2002–2012	Overall incidence rate of VTE remained unchanged (mean 1.46/1000).
Arshad et al. [13] 2017	Norway	General population cohort from Tromsø, n = 26,855	2000–2011	Age-adjusted incidence rate of VTE increased by 7.5% (from 1.87/1000 to January 2, 1000)
Brahmandam et al. [40] 2017	USA	National Inpatient Sample >3 mill VTE admissions	2003–2013	Estimated hospitalization rate for VTE in the population increased by 6.5% (from 0.93/1000 to 0.99/1000)
Ghanima et al. [44] 2020	Norway	National Patient Registry, 63,274 VTE patients	2010–2017	Incidence rate of VTE remained stable (1.51/1000 to 1.53/1000)
Huang et al. [39] 2014	USA	4252 VTE cases, US Census denominator = 477,598	2001–2009	Age- and sex-adjusted annual events of incident VTE increased by 25.5% (from June 1, 1000 to 1.33/1000)
Kim et al. [43] 2021	Korea	National Health Insurance Database 133,956 VTE cases,	2009–2016	Age-standardized incidence rates increased by 41.7% (from 0.24/1000 to 0.34/1000)
Munster et al. [41] 2019	Denmark	Nationwide study based on health registry data: 67,426 VTE patients, 5.7 mill. Population	2006–2015	Hospitalization rates for first time VTE increased by 19.8% (from 1.26/1000 to 1.51/1000)
Scheres et al. [38] 2016	Netherlands	Data from three anticoagulation clinics, 14,253 VTE patients	2003–2012	No change in the overall age-adjusted incidence rate of VTE
Wändell et al. [42] 2019	Sweden	Administrative health data from Stockholm region: 14,849 VTE cases and 2 mill inhabitants.	2011–2018	Incidence of VTE increased by 2.7% (from 1.88/1000 to 1.93/1000)

contributes to increase the risk in women, it has been suggested that men have an inherently higher VTE risk [17]. However, two large population-based studies have reported that the overall life-time risk of VTE is similar in men and women, and corresponds to 8–9% after accounting for competing risk by death [16,18] and female cases attributed to reproductive factors [16]. Thus, VTE is a common disease in both men and women, as more than 1 in 12 will experience a VTE during their lifetime regardless of sex [16].

The health- and economic burden of VTE in society is substantial. In addition to hospital stays and initial diagnostics and treatment, VTE is associated with several short- and long-term complications. The risk of recurrence is high after a first VTE, and up to 30–40% of the patients experience a recurrence within 10-years following the first event [19–21]. The risk of recurrence varies depending on the presence of provoking factors preceding the index VTE, with highest risk in patients with major persistent risk factors (e.g. cancer) and unprovoked VTE, and lower risk in those with VTE provoked by a transient risk factor (e.g. surgery) [22]. Post-thrombotic syndrome, a condition characterized by pain, swelling, itching and, in severe cases, venous ulceration of the affected limb, affects up to 20–35% of patients with a proximal DVT [23]. Furthermore, post-PE syndrome, characterized by persistent dyspnea or functional limitations, affects up to 50% of PE patients [24,25]. Chronic thromboembolic pulmonary hypertension (CTEPH), the most severe presentation of the post-PE syndrome, affects 2–3% of PE survivors [26]. These conditions severely impair mobility and quality of life [27,28], and may influence working capacity. Recently, a study using nationwide Danish registry data showed that VTE patients have a 2- to 3-fold higher risk of permanent work-related disability pension compared to the general population after accounting for other comorbid conditions [29].

VTE is recognized as a multicausal disease, in which several genetic and environmental risk factors act together to increase an individual's thrombosis potential [30]. Family and twin studies have indicated a heritability of up to 60% [31], and a wide range of genetic risk factors for VTE have been identified [32,33]. The genetic risk factors vary substantially in prevalence and effect size, from the rare mutations causing antithrombin deficiency associated with a >10-fold increased VTE risk, to more common variants, such as the non-O blood type which is associated with approximately 1.5-fold increased risk [32]. Environmental or acquired risk factors for VTE include among others cancer, surgery, trauma, acute medical conditions leading to hospitalization, immobilization, estrogen use, pregnancy, obesity and chronic inflammatory conditions [34]. Environmental risk factors for VTE are often classified as major or minor, transient or persistent [22]. A VTE occurring shortly after exposure to a major transient risk factor (i.e. major surgery) can be readily categorized as having been provoked by this factor, while such categorization can be more vague in the presence of minor transient or persistent factors or for a combination of several minor factors. Around 40% of the VTE events occurring in the general population are classified as unprovoked, as they occur in the absence of an obvious provoking or triggering factor [13,14,35].

The incidence rate of VTE in the population has a great impact on the overall disease burden of VTE in society. Measuring time trends in the incidence rate of disease is important to provide a dynamic view of a population's health status, and can be useful to assess health care needs, make projections for future health services, and strategies for preventive actions. Following the introduction of computed tomography pulmonary angiogram (CTPA) to diagnose PE in the late 1990's, the rates of PE increased markedly due to improved diagnostic imaging [36]. However, changes in VTE risk factors and VTE prophylaxis during the last decades may have further influenced the rates. In this narrative review, we will therefore summarize studies presenting time trends in incidence rates of VTE after year 2000, with a particular focus on studies starting several years after the implementation of CTPA. For studies that also cover years before 2000, trends in rates from 2000 onwards will be extracted and presented, when applicable. Further, potential reasons for the observed trends and current challenges for VTE prevention at the population level will be discussed.

2. Global time trends in the incidence of VTE

Several studies have investigated time trends in the incidence of VTE in different settings and countries during the last two decades (Table 1). Using administrative health databases from Alberta Canada with 31,656 VTE cases, Alotaibi et al. reported that the overall incidence rate of VTE remained unchanged during the period 2002–2012 [37]. Similarly, data from three anticoagulation clinics in the Netherlands, including 14,253 VTE patients, indicated no change in the overall age-adjusted incidence of VTE in the period 2003–2012 [38]. In the Tromsø study, a Norwegian cohort of almost 27,000 participants with close follow-up on VTE events, the age-adjusted incidence rate of VTE increased by 7.5%, from 1.87/1000 person years (PY) to January 2, 1000 PY, in the period 2000–2011 [13]. In the Worcester study, which included >4000 validated VTE cases and US Census data as the population denominator, the age- and sex-adjusted annual incidence rate of VTE increased by 25.5%, from June 1, 1000 PY to 1.33/1000 PY, in the period 2001–2009 [39]. Applying data from the National Inpatient Sample in the US, including >3 million VTE admissions, Brahmandam et al. reported that the estimated hospitalization rate for VTE in the population increased by 6.5%, from 0.93/1000 PY to 0.99/1000 PY, in 2003–2013 [40]. Using high

quality registry data from the entire population of Denmark (>5.7 million people with >67,000 VTE events), Munster et al. showed that the hospitalization rates for first VTE increased by 19.8% in the period 2006–2015, from 1.26/1000 PY to 1.51/1000 PY [41]. In the Stockholm region in Sweden, results from administrative health data showed that the VTE rates remained fairly constant, with only 2.7% increase from 1.88/1000 PY to 1.93/1000 PY, in the period 2011–2018 [42]. A recent study using data from the National Insurance Health Database in Korea in 2009–2016 reported an increase in the age-standardized VTE incidence rates from 0.24/1000 PY to 0.34/1000 PY, corresponding to 41.7% increase [43]. A study based on data from the Norwegian Patient Registry in the period 2010–2017 showed that the incidence rates of VTE remained constant at May 1, 1000 PY [44].

Some of the studies described above were likely limited by their restrictions to report only rates of hospitalization for VTE (i.e., VTE cases treated solely in the community setting not covered) [40,41], some degree of coding errors and misclassification in administrative registry databases [37,40–42], and slight imprecision in the population denominator. However, as long as these limiting parameters do not vary over time, they are not expected to influence the time trends in incidence rates substantially. Nevertheless, summarizing the results from the reviewed studies, with particular emphasis on those of high methodological quality, we can conclude that the rates of VTE have not decreased, but rather remained constant or slightly increased, during the last two decades. This observation holds true also for studies presenting incidence trends after 2010 [41–44]. The persisting incidence rates of VTE are in sharp contrast to the incidence rates of arterial thromboembolic disease, in particular myocardial infarction and ischemic stroke, for which the incidence rates have declined substantially during the last decades [45,46].

3. Potential contributors to the persistent VTE rates

What factors contribute to the observed persistent or increasing rates of VTE? Introduction of CTPA for PE diagnostics in the late 1990's obviously had an important impact on the rates of VTE which probably lasted into the first decade of implementation in the clinic. However, the persisting rates reported by studies performed after 2010, indicate that also other factors have contributed. Awareness campaigns, such as the Surgeon General's Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism [47] and the World Thrombosis Day [48], have been launched to increase knowledge and attention of VTE among patients, health care personnel, and the public, and this may potentially have contributed. However, the most important contributor to the increasing VTE rates is presumably the concomitant rise in major VTE risk factors in the same period. Advancing age is one of the strongest risk factors for VTE, and as the life-expectancy in the population is increasing, and the longevity of people with chronic diseases is higher, aging may have contributed to increase the rates, particularly of PE [49]. However, most studies assessing time-trends have estimated age-standardized rates, thus to some extent accounting for the change in the age-distribution in the population over time. Other important risk factors for VTE that have increased during the last decades include obesity, surgery and cancer [50,51]. Using data from the period 1988–2010, Heit and co-workers reported that the proportion of VTEs in the population attributable to age, surgery and cancer increased slightly over time, while the attributable proportions of other risk factors, including hospitalization, nursing home, trauma and pregnancy, remained stable [52]. The prevalence of obesity, major surgery and cancer, as well cancer-related VTE [53], have continued to increase at the population level also after 2010, and have therefore likely contributed to the persistent trends in VTE rates [50,51]. The persisting rates call for improved preventive measures in order to lower the incidence and burden of VTE in society. In the next sections, current strategies and challenges for reducing the incidence of VTE in the population will be briefly discussed.

4. Risk assessment and prevention of VTE in high-risk situations

Many risk factors and conditions that predispose for VTE can lead to hospital admission, and it has been shown that around 40% of all the VTEs in society occur in hospital or in relation to a recent hospitalization [54]. Thus, a substantial proportion of these events can potentially be prevented. Even though there are already established strategies for prevention of VTE with thromboprophylaxis in high-risk situations [55–57], it is often challenging to assess the balance between thrombosis and bleeding risk in these situations. Risk assessment models for identification of individuals with high risk of VTE have been developed and implemented for several different settings (e.g., major surgery [58], acute medical conditions [59], and cancer [60]) but the performance of these models still has limitations, and few models incorporate concomitant bleeding risk assessment. Despite the above mentioned challenges, the awareness of hospital-related VTE and use of thromboprophylaxis has been more widespread during the last decades [54,61]. In the Rochester Epidemiology Project, the rates of prophylaxis in patients with indication for it increased from 40% to 90% in the period 2005–2010 [54]. However, despite this near-universal prophylaxis regimen, the rates of hospital-related VTE did not change. In a study from the UK, Roberts et al. reported that an increase in documented VTE risk assessment from <40% to >90% due to introduction of a comprehensive VTE prevention program, resulted in a 12% reduction in the incidence of hospital-related VTE [62]. Taken together, these findings imply that there is still room for improvement both with regards to risk assessment models in different hospital settings, and potentially also the duration of thromboprophylaxis in patients with particularly high risk, as a substantial amount of the hospital-related events occur in the period up to 90 days after hospital discharge [54].

5. Prevention of VTE at the population level

Despite the more widespread use of thromboprophylaxis to high-risk groups during the last decade the VTE incidence rates has persisted or slightly increased. As described by Rose [63], this may occur if the high-risk group represents a small proportion of the general population. Rose further exemplified that *"a large number of people at small risk may give rise to more cases than the small number who are at high risk"*. [63] Therefore, obtaining a shift in the risk factor profile for VTE in the general population could be the key for reducing the VTE incidence at the population level. Actually, we only need to look at arterial thrombosis to find a very good example of successful primary prevention at the population level. The incidence rates of both myocardial infarction and ischemic stroke have decreased substantially during the last decades [45,64,65], and the key factor for this decline lies in the identification of and intervention on major risk factors [64,65]. Today, there is a widespread use of antihypertensives, statins and antidiabetics for primary prevention of arterial cardiovascular disease. Using the Tromsø study, Mannsverk et al. reported that the age- and sex-adjusted incidence of total coronary heart disease decreased by 51% in the period 1995–2010, and that 66% of the decline in the incidence could be attributed to favorable changes in major risk factors such as lower cholesterol and blood pressure levels, smoking cessation and increased physical activity [64].

In contrast to arterial thrombosis, lifestyle factors have traditionally been considered to have low contribution to VTE. For instance, traditional cardiovascular risk factors associated with health behavior, such as hypertension, hyperlipidemia, type 2 diabetes, and atherosclerosis are not associated with VTE [66–71]. Furthermore, even though some studies have suggested a weak association between heavy smoking and VTE, this relationship is to a large extent explained by intermediate development of cancer or cardiovascular disease [67,72]. The available evidence on the association between physical activity and VTE has shown somewhat diverging results, but appears to be balanced towards a small beneficial effect of avoiding a sedentary life-style, with no

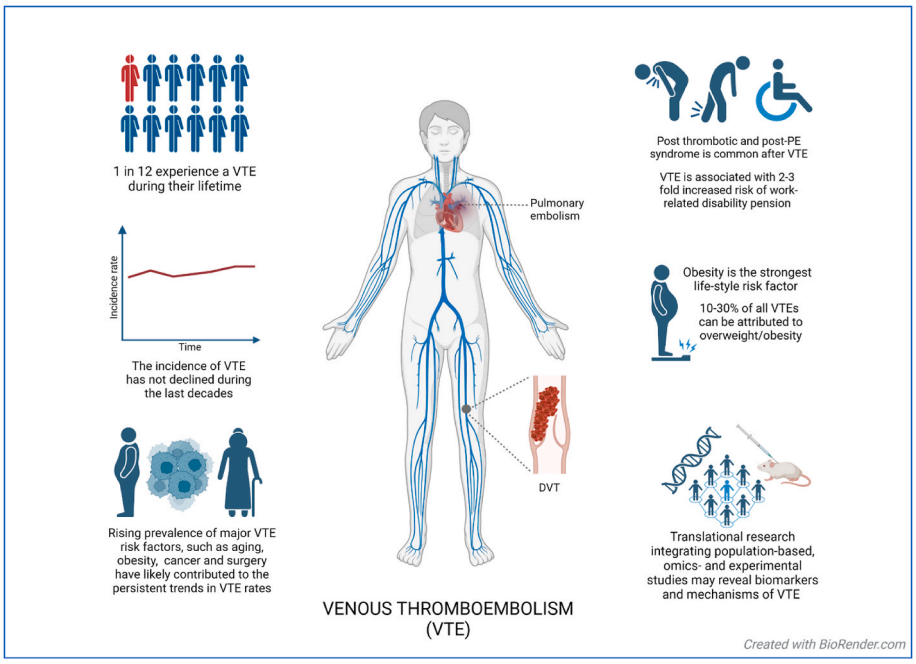

Fig. 1. Overview of VTE epidemiology and challenges for VTE prevention.

further gain in lowering the risk by increasing activity levels [73,74].

Apparently, the most important life-style factor for VTE is obesity. Obesity is recognized as a causal [75,76] risk factor associated with an approximately 2-fold increased risk of VTE [77,78]. The risk increases across all types of overweight and obesity measures (body mass index, waist circumference, hip circumference, waist-to-hip ratio, etc.) [78,79], and weight gain further increases the risk [80,81], particularly in those already obese [81]. As the prevalence of obesity is rising worldwide [82], the impact of obesity on VTE risk at the population level is substantial. This can be demonstrated by estimating the population attributable fraction (PAF), which denotes the proportion of all cases in a population that can be attributed to a certain risk factor. PAF is also called preventable fraction, as it represents the proportion of cases in the population that could be avoided if the risk factor could (hypothetically) be entirely removed [83]. The PAF is dependent on both the risk estimate and the prevalence of the disease in the population. In a cohort of 74,317 Swedish adults, the estimated PAFs of elevated BMI ($\geq$25 kg/m^2) and waist circumference ($\geq$94 cm in men and $\geq$80 com in women) were 12.3% and 23.7%, respectively, for overall VTE [76]. In a study using data from the Rochester Epidemiology Project in the US, the PAF of obesity was 33% for unprovoked VTE [52]. Although the effect of weight loss on risk of VTE is not established (as there are no randomized clinical trials performed), the PAF estimates indicate that a reduction in the prevalence of obesity could potentially lower the rates of VTE in society substantially. However, fighting the rising obesity epidemic has proven to be challenging, as no country has yet been able to reverse the rising prevalence despite extensive public health awareness and prevention campaigns [82].

The mechanisms by which obesity increases the risk of VTE are not fully elucidated, but stasis in the lower extremities due to enhanced intra-abdominal pressure, and changes in coagulation or fibrinolytic factors as well as inflammatory mediators are potentially involved [77]. Of note, obesity is also associated with increased risk of arterial CVD, but since the association is largely mediated by cardiometabolic risk factors such as lipid levels, hypertension and type 2 diabetes [84], the successful targeted intervention on these mediators have led to a decrease in CVD despite the rising obesity prevalence [64]. Therefore, in addition to continuing public health recommendations of maintaining normal weight, improved knowledge on the mechanisms by which obesity increases VTE risk and identification of potential targets for intervention may be of substantial importance for reducing the burden of obesity-related VTE in society.

6. Future directions of VTE research

We are gaining increasing knowledge about the mechanisms of VTE, but still some pieces in the puzzle are missing, particularly with regards to initiation of thrombus formation. Macfarlane stated in 1977 that thrombosis is "*hemostasis in the wrong place*" [85], but the mechanisms that differentiate thrombosis from normal haemostasis are still poorly understood. The fact that more than one third of the VTEs occur in the absence of obvious provoking factors underlines this knowledge gap. Venous thrombi likely occur due to a disturbed and complex interplay between vascular wall (dys)function, blood components and blood flow conditions. Although several abnormalities and mechanisms related to the coagulation system are known contributors to VTE, many people with such abnormalities still do not develop thrombosis. Thus, understanding the complex biological interplay between factors that promote thrombosis is of high importance.

So how should we proceed with epidemiological studies to try to identify risk factors and pathophysiological pathways for VTE that we can potentially intervene on at the population level? With the new omics-based technologies, there are promising opportunities to explore this within well-defined population-based cohorts with high quality biobank materials and validated VTE outcomes. Applying multi-omics on samples taken before disease development may open for system biology analyses that can potentially reveal biomarkers and pathways involved in the pathogenesis of VTE that can preferably be targeted without increasing the bleeding risk. Assessment of genetic regulation of key proteins or metabolites and Mendelian Randomization studies can be utilized to assess potentially causality [86] before further testing of candidate biomarkers in functional studies using cell lines, flow systems or animal models within a translational research framework. The Venous Thromboembolism Research Priorities statement from the American Heart Association and the International Society on Thrombosis and Haemostasis emphasizes that multidisciplinary approaches integrating epidemiologic, genomic, cellular, biochemical and biophysical strategies should be applied to advance understanding and

elucidate mechanisms for VTE [87].

7. Summary

VTE is a common disease with serious complications and a substantial disease burden (Fig. 1). Time-trend studies from both US, Europe and Asia indicate that the incidence of VTE has increased slightly during the last twenty years, particularly for PE, and that rates have been persistent also after the implementation of CTPA into clinical practice. The concomitant increase in major risk factors for VTE, such as advancing age, obesity and cancer have likely contributed to the increased rates. Prevention of VTE with anticoagulants comes with the risk of bleeding as a serious side effect, which limits its use to high-risk individuals or high-risk situations for VTE. Therefore, obtaining a shift in the risk factor profile for VTE in the general population could be essential for reducing the VTE incidence at the population level. Obesity is the strongest recognized life-style risk factor for VTE, with a reported population attributable fraction of 10–30% depending on the prevalence of obesity in the population. The mechanism by which obesity increases the risk of VTE are not fully understood. Future epidemiological studies should aim to identify risk factors and biological pathways that drive thrombogenesis, with particular focus on potential targets for intervention at the population level that does not comprise bleeding risk. The currently available omics-based platforms provide promising opportunities for integrated system biology studies which can be further transferred to *in vitro* and *in vivo* models for mechanistic studies using a translational research framework.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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