Regular Physical Activity and Risk of Venous Thromboembolism

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Abstract

Venous thromboembolism (VTE) is a complex multifactorial disease that represents a growing public health concern. Identification of modifiable risk factors at the population level may provide a measure to reduce the burden of VTE. In this review, we summarize current knowledge of the role of physical activity on the risk of VTE and VTE-related complications. We also discuss methodological challenges related to research on physical activity, and put forward plausible mechanisms for an association between physical activity and VTE. Up to now, published studies have reported diverging results on the relationship between physical activity and VTE, and a complex picture has emerged. However, the available evidence appears to be balanced towards a small beneficial effect of physical activity on the risk of incident VTE, but not in a dose-dependent manner. Still, the lack of an operational definition and standardized assessment method for physical activity as well as several sources of bias, impair the interpretation of the available literature. Additional work is necessary to understand the role and how to apply physical activity in the VTE-setting. Future research should utilize objective assessment strategies of physical activity and physical fitness, account for the fluctuating nature in habitual activity levels, and explore the role of physical activity in the areas of secondary prevention and VTE-related complications.

Introduction

Despite improved knowledge of risk factors and preventive strategies, recent findings imply that the incidence of venous thromboembolism (VTE) has remained steady or slightly increased over the past decades.[1,2] Moreover, with increasing prevalence of important risk factors, such as cancer, obesity and an aging population, we may anticipate a further rise in the incidence of VTE in the years to come.[3-6] Hence, there is a great need to identify and take action on modifiable risk factors in order to combat the growing burden of VTE.

Initiated by the seminal study in 1953 by Dr. Jeremy Morris and colleagues[7] on the association between occupational physical activity and coronary heart disease, researchers in the field of physical activity epidemiology have established a firm dose-dependent inverse association between physical activity and risk of arterial thrombotic disease.[8,9] There is also overwhelming evidence that regular physical activity is associated with a reduced risk of premature all-cause mortality, type-2 diabetes and some types of cancer.[8,10,11] Nevertheless, a significant amount of the population worldwide fails to meet the minimum recommendations for physical activity, and physical *in*activity is now referred to as a global pandemic.[12,13]

Whether physical activity influences the risk of incident VTE is debated, and limited data exist on the role of physical activity in the prevention and treatment of VTE-related complications, such as recurrence, post-thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTEPH). The focus of this review is to summarize the existing epidemiological evidence on the association between physical activity and risk of VTE. We will also discuss methodological challenges related to research on physical activity, and put forward plausible mechanisms for an association between physical activity and VTE. The potential role of physical activity in the prevention of recurrent disease, PTS and CTEPH

will also be addressed. In addition to an analytical review of the existing literature, we will substantiate the discussion with results from a large Norwegian prospective cohort, The Tromsø Study.

The PubMed database was searched for articles on regular physical activity and VTE-risk by using combinations of the terms 'physical activity', 'physical inactivity', 'venous thromboembolism', 'deep vein thrombosis' and 'pulmonary embolism'. Relevant publications were also identified through PubMed links and by cross-referencing from the reference lists of the retrieved papers.

Epidemiological Evidence: Physical Activity, Sedentary Behavior and Risk of Incident VTE

Immobilization is a well-recognized risk factor for VTE, and logically, several researchers have hypothesized that a sedentary lifestyle or lack of regular physical activity could be associated with an increased risk of VTE. However, the reported results so far have shown an inconsistent pattern (Table 1).

In a large prospective cohort, the Atherosclerosis Risk in Communities (ARIC) Study,[14] middle-aged men and women participating in moderate or high amount of physical activity had 19 to 31% lower risk of VTE compared to those with a low amount of physical activity. Similarly, in The Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study,[15] participation in physical activity 1-3 times and more than 3 times per week, was associated with 30% and 41% lower risk of VTE, respectively. In the Million Women Study, Armstrong and colleagues[16] found that women who engaged in weekly physical activity had 4 to 34% lower risk of VTE compared to inactive women. However, apart from the REGARDS Study[15] where a dose-response relationship was observed, these studies provided limited evidence for a

4

progressive risk reduction with increasing amounts of physical activity.[14-16] On the contrary, in the Million Women Study,[16] there was a trend of a small increased risk of VTE in women participating in strenuous physical activity daily, when compared to women who were mostly inactive. Similarly, results from the Cardiovascular Health Study (CHS)[17] showed that weekly participation in strenuous physical activity was associated with a 75% higher risk of VTE compared to inactivity in the elderly, while participating in light-intensity exercise was associated with a non-significantly lower risk. Results from the Physicians' Health Study[18] indicated a higher risk of VTE with increasing weekly amount of vigorous physical activity, with a stronger association with provoked than unprovoked events. Thus, in contrast to the potential benefits related to low and moderate amounts of physical activity, excessive or highly intense activity might be associated with an increased risk of VTE.

The results from several other large prospective cohorts have suggested that physical activity has no influence on VTE-risk. In the Tromsø Study,[19] the weekly amount of moderate and high-intensity physical activity did not modify the risk of VTE in the general population during 12.5 years of follow-up. Likewise, results from the Iowa Women's Health Study[20] showed that physical activity was not associated with VTE-risk after adjusting for body mass index (BMI). Moreover, The Longitudinal Investigation of Thromboembolism Etiology (LITE),[21] The Nurses' Health Study[22] and the Copenhagen City Heart Study,[23] all reported no association between physical activity and risk of VTE. These apparently conflicting findings between studies may reflect methodological differences, which is further discussed below.

Sedentary behavior refers to activities that require very low amounts of energy expenditure.[24] Immobilization is an established risk factor for VTE, and essentially all circumstances that are associated with physical restriction, such as bed rest, plaster casts and

paralysis, have been shown to increase the risk of VTE.[25-28] Importantly, highly active individuals may well accumulate large amounts of sedentary time (e.g. sitting time) during a day, and physical activity and sedentary behavior may therefore be regarded as separate risk factors.[24] Using data from The Nurses' Health Study,[22] Kabrehl and colleagues found that women who spent most of their time sitting had more than a twofold higher risk of pulmonary embolism (PE). Similarly, in The Multiple Environment and Genetic Assessment (MEGA) Study,[29] men and women who were primarily sedentary on a daily basis had 20% and 40% higher risk of VTE, respectively, compared to those who were mostly active. Interestingly, in The Nurses' Health Study[22] the adverse association with sitting time was most pronounced in women who were also least physically active, suggesting that physical activity to some extent may mitigate the adverse effect of sedentary behavior.

Up to now, the association between objectively assessed physical fitness and risk of VTE has received little attention. However, high maximal aerobic workload (watt) per kilogram body weight on a bicycle test was recently reported to be associated with a lower risk of VTE in men.[30] Moreover, grip strength was reported to be inversely associated with VTE-risk in a recently published case-control study of elderly individuals.[31] In summary, the available data are suggestive of a curvilinear relationship between physical activity and risk of incident VTE in which a moderate amount of physical activity may be beneficial, while high amounts of strenuous physical activity may carry no further protection or an increased risk of VTE. Reducing the time spent on sedentary behaviors may also lower the risk of VTE. However, there is considerable heterogeneity between the published studies concerning design, confounding factors, assessment strategies, study populations and size, which precludes a proper comparison.

Methodological Challenges in Research on Physical Activity and Venous Thromboembolism

There are several aspects to consider related to study design, assessment strategy and data handling in the conduct and interpretation of epidemiological studies on physical activity. In general, studies with a prospective design have important advantages compared to retrospective (e.g. case-control) studies in that there is a clear temporal sequence between exposure and outcome, enhanced generalization of findings and unbiased exposure information. Particularly, recall bias is highly relevant in studies with a retrospective assessment strategy. In this context, it is striking that all studies with retrospective assessment of physical activity have reported a lower risk of VTE with higher amounts of physical activity,[32-34] whereas findings from prospective cohort studies have been less consistent.[16,18,19] It may be that subjects with an acute VTE-event recall or describe their activity habits differently compared to healthy controls, which introduces a form of differential misclassification resulting in biased risk estimates in retrospective studies.[35]

Accurate assessment of the variables under study is critical in all research. Physical activity is a complex behavior that lacks an operational definition and a standardized assessment method.[36,37] This is reflected in the range of available instruments, and the choice largely depends on the information of interest (intensity, frequency, total energy expenditure, domain etc.), study size, available resources and the required level of precision. Various self-report instruments, such as questionnaires, are most common in large observational studies.[38] However, these vary widely in the level of detail, time-perspective, and what dimensions (mode, frequency, duration, intensity) and domains (occupational, domestic, transport, leisure) that are in focus.[36] Self-administered questionnaires have valuable strengths in terms of cost-effectiveness, feasibility and ability to discriminate between inactive and active

individuals. However, compared to objective assessment methods, they are less accurate, and prone to error and bias due to recall and social desirability.[36]

The wide selection of available instruments is reflected in studies on the association between physical activity and the risk of VTE. The focus range from total weekly amount or frequency of physical activity of various intensities[15,16,18,19] via crude dichotomization[23] to estimation of caloric expenditure[17,21] and global assessment batteries.[14] Furthermore, the dimensions and time-perspectives, if specified, differ between studies, although the majority have displayed an interest in leisure-time activity with emphasis on frequency and intensity rather than the type of activity. Importantly, the different dimensions of physical activity relates to distinct physiological responses, e.g. high-intensity aerobic exercise relates to maximal oxygen uptake, while light-intensity activity is more strongly correlated with total energy expenditure.[39-41] Knowledge and validation of the actual physiological exposure is critical as it influences the interpretation of study findings and dictates the translation of findings into public health recommendations.[37]

A way to indirectly validate information of exposure (e.g. physical activity) gathered from self-administered questionnaires is to explore the effect on another outcome with a well-established association with the exposure variable. In the Tromsø Study, we have investigated the association between weekly physical activity during leisure time and the risk of incident myocardial infarction (MI) and VTE within the same cohort recruited from the general population (n=26215). The study design and population have been described in detail elsewhere.[19,42] As expected, we found an inverse association between physical activity and MI-risk of a magnitude of 20-29% that displayed a dose-response relationship across categories of increasing weekly amount of physical activity (*p* for trend<0.001, Table 2). In

contrast, there was no association between physical activity and the risk of VTE (Table 2). Our finding of an inverse association between physical activity and MI-risk corroborates previous research and supports the validity of our physical activity questionnaire.[9] Although we found no association between physical activity and VTE-risk in this study design, there could still be a small effect that is masked by fluctuations in activity habits and/or residual confounding variables (e.g. time spent in sedentary behavior that is independent of the overall amount of physical activity).

In longitudinal studies, a challenge emerges due to the potential fluctuating nature of physical activity during follow-up.[43,44] If not accounted for, this may lead to regression dilution bias and possibly an underestimation of the true association.[45] For instance, the risk of premature mortality according to physical inactivity was reported to increase 24-59% when change in behavior during follow-up was accounted for, as compared to analyses based on baseline data.[43] Up to now, we are aware of only two studies[14,17] investigating the association between physical activity and risk of VTE that have modelled physical activity as a time-varyingcovariate. Moreover, the studies that reported an association typically had shorter follow-up compared to the studies reporting null-findings (Table 1). Although the association between physical activity and MI remained during a 19-year follow-up in the Tromsø study (Table 2), it is likely underestimated due to regression dilution bias. Thus, a smaller effect size of physical activity on VTE-risk could still be present but not detected in a traditional cohort design with single measurements and long-term follow up.

Confounding variables may strengthen or weaken an association, and strategies to minimize such confounding variables include stratification or multivariable adjusted analysis.[46] In the context of physical activity and VTE, the influence of weight status is of

particular interest as physical activity is a key component in weight maintenance,[47,48] and obesity and weight gain are strong predictors of VTE.[49-51] Hence, obesity may act as a confounder, but is likely also in the causal pathway between physical activity and VTE. Most studies statistically adjust for the effect of BMI, which typically attenuate the risk estimates for the association between physical activity and VTE by 3-24%.[14,16,20] However, due to the potential interrelationship, such analyses may be over-adjusted and the true association underestimated.

The inconsistent findings reported up to now on the association between physical activity and risk of VTE may partly be due to aspects related to study design, exposure assessment strategy and data handling. Future studies that account for the fluctuating nature in human behavior and apply well-defined, preferably objective assessment strategies of both physical activity (e.g. accelerometry) and sedentary behavior, are needed. The role of physical fitness, such as cardiorespiratory endurance and muscle strength, should also be further explored in this context. This may not only clarify the nature of the potential association between physical activity and the risk of VTE, but also provide more valid effect sizes and generate hypotheses regarding potential mechanisms.

Plausible Mechanisms for an Association between Physical Activity and Venous Thromboembolism

Under normal physiological conditions the hemostatic system is regulated through a delicate balance between pro- and anticoagulant activity to maintain blood fluidity. In contrast, thrombosis refers to pathological clot formation that is not required for hemostatic function.[52] The framework for understanding the pathophysiology of thrombosis was proposed by Virchow in 1856, who suggested that thrombus formation results from changes in the vessel

wall, the blood flow and the blood composition.[53] There are several potential mechanisms for an association between physical activity and VTE, and all relate to the three aspects of Virchow's triad.

Blood flow

Physical activity increases energy turnover and requires rapid cardiovascular responses with increased blood flow to the working muscles. Cardiac output, the amount blood pumped by the heart every minute, increases 4-7-fold from rest to maximal exercise. This profound rise in blood flow results from an increase in heart rate and stroke volume, with the latter largely depending on enhanced ventricular filling (preload) and myocardial contractility. The skeletal muscle pump plays a vital role in emptying the veins of the lower extremities, where blood pools due to gravity, into the central circulation.[54,55] The blood flow profile is also influenced, and exercise has been shown to increase anterograde blood flow and decrease oscillatory shear rate.[56,57] It follows that during activity, the blood flow responses potentially create an antithrombotic environment.

Research on whether regular physical activity or exercise influence the blood flow profile during rest is limited. However, increased venous flow has been recorded up to 30 min after exercise cessation.[58] Moreover, in subjects with venous insufficiency, a six-month exercise program with focus on calf muscle strength improved the calf muscle pump function.[59] In addition, higher resting blood flow in femoral arteries has been reported in trained compared to untrained individuals.[60]

Vessel wall

Although venous blood clots most often form in the presence of an intact endothelium,[61,62] disruption of endothelial integrity potently activates the hemostatic system.[63] Participation in high-impact and high-intensity activities may increase the risk of injury,[64,65] and thus partly explain the increased thrombotic risk associated with physical activity reported in some studies.[17,66]

The endothelium is a multifunctional organ that exerts an expanding amount of important functions. In addition to regulating vascular tone and creating a physical barrier between blood and tissues, it also influences the hemostatic balance.[67,68] Diverging with time and location, the endothelium expresses anticoagulant/antithrombotic factors, such as thrombomodulin (TM), tissue-type plasminogen-activator (t-PA) and tissue factor pathway inhibitor (TFPI), as well as procoagulant/prothrombotic factors, such as tissue factor (TF), thrombin receptors, von Willebrand factor (VWF) and plasminogen activator inhibitor (PAI-1).[68] The exercise-related responses in the expression of these markers are discussed in the sections on "Blood composition" (below). The vasoactive hormones nitric oxide (NO) and prostacyclin that are released from the endothelium may also influence the hemostatic balance by regulating flow conditions and modulating platelet activity.[69,70] Although the endothelium normally displays an antithrombotic phenotype, a hallmark of endothelial dysfunction is an inability to release and respond to NO.[67,70] Endothelial dysfunction exerts an important role in the pathophysiology of atherosclerosis,[71] and impaired endothelial function has also been observed in patients with VTE.[72] Enhanced endothelial function, assessed by flow-mediated dilation (FMD), has been observed after a period of exercise in both healthy

individuals and in patients with established endothelial dysfunction, and is thought to be mediated by increased bioavailability of NO.[73,74]

Hemorheology

Exercise also alters hemorheology, i.e. the flow characteristics of the blood, as reviewed by El-Sayed et al.[75] Whole blood viscosity is largely determined by hematocrit and the rheological properties of the plasma and cellular components, and depends on shear rate.[76] Moreover, the relative influence of hematocrit on blood viscosity is higher under conditions with low shear rate.[77] The latter particularly applies to the venous system and may mediate the association between high hematocrit and an increased risk of VTE.[78] A transient increase in whole blood viscosity is typically observed following endurance exercise.[75,79,80] This is potentially due to increased hemoconcentration resulting from loss of total body water through perspiration and transition of fluid from the vasculature into the interstitial space, with subsequent increases in hematocrit and plasma viscosity.[75,79,80]

There is a paucity of data on the long-term effects of regular physical activity and exercise on the rheological properties of the blood.[75] An increase in blood volume is a well-documented response to endurance training.[54] In the early phases of training, this is mainly due to plasma volume expansion without a concomitant increase in red blood cell mass.[54,81,82] Further, inverse associations have been reported between both physical work capacity[83] and habitual physical activity,[84] and hematocrit and blood and plasma viscosity. Although not all studies have demonstrated any difference in hemorheological properties between trained and untrained individuals,[79] it has been suggested that endurance training probably is associated with a reduction in blood viscosity.[75] Thus, it appears that the short-term

hemorheological responses to exercise may result in an increased thrombotic risk, while the long-term adaptations potentially facilitates an antithrombotic milieu.

Blood composition – short-term effects

Physical activity is recognized as a potent modulator of the hemostatic system (reviewed in [85,86,87]). The most consistently reported short-term responses are summarized in Table 3. Several studies have shown that platelet count transiently increases in response to exercise in an intensity-dependent manner.[88-92] The rise is beyond what is explained by the change in plasma volume,[91] and returns to baseline values within two hours after termination of exercise.[91,92] In contrast, data on the effects of exercise on platelet function are conflicting, potentially due to large methodological variations.[86,93] However, it has been suggested that high intensity and maximal exercise may induce platelet activation as shown by increased plasma concentrations of β-thromboglobulin (β-TG) and platelet factor 4 (PF4).[88,91]

Exercise also transiently increases the coagulation potential as demonstrated by a shortening in clotting time and activated partial thromboplastin time (aPTT), while prothrombin time (PT) is negligibly affected.[94-98] A shortening in aPTT has been observed after both endurance and resistance-type exercise,[94,99] appears to be independent of exercise intensity,[91,95] and remains shortened at least one hour after termination of exercise.[91,97] The shortened clotting time is probably a result of a concomitant rise in coagulation factor VIII (FVIII) complex activity. Both components of the FVIII complex (FVIII and VWF) have been reported to increase in response to exercise in an intensity-dependent manner and may persist above resting levels for up to 10 hours after exercise.[94,97,100-103] The effect on other coagulation factors including fibrinogen is less certain and probably less pronounced.[86,103-105]

14

Moreover, intensity-dependent increases in markers of thrombin generation (prothrombin fragment 1+2 (F1+2) and thrombin-antithrombin (TAT) complex) have also been reported after exercise.[94,99,106-108]

Limited data exist on the acute effects of exercise on the anticoagulant pathways, such as antithrombin, protein C, and TFPI. However, while no effect was observed on the levels of protein C and antithrombin in one study,[109] antithrombin was reported to decrease after exercise when adjusted for changes in plasma volume in another study.[98] Moreover, a significant rise in TFPI has been reported immediately after and up to 10 hours following exercise with maximal effort, suggesting a role for TFPI in suppressing coagulation activation during and after extensive exercise.[108,110]

Exercise also transiently influences the fibrinolytic system. Specifically, enhanced fibrinolytic potential has been observed after exercise, assessed as shortened blood clot lysis time, and increased levels and activity of t-PA.[91,94,99,101,111] The rise in t-PA is dependent on exercise intensity, and potentially results from endothelial activation due to shear stress.[86] Moreover, decreased levels and activity of PAI-1 have also been reported after exercise, further supporting a greater fibrinolytic potential.[94,99,111,112] Notably, the response in t-PA appear to be highly transient, and returns to baseline levels earlier than the procoagulant markers.[97,101,113,114] In addition, a secondary inhibition of fibrinolysis has been observed two to four hours after strenuous exercise.[101] This imbalance may contribute to the increased cardiovascular risk observed shortly after strenuous exercise.[97,114]

Blood composition – long-term adaptations

The long-term hemostatic adaptations to regular physical activity and exercise are summarized in Table 4. Aerobic exercise interventions of 8 to 12 weeks duration have shown to decrease platelet activity during rest.[115-118] Furthermore, the platelet activation commonly observed after exercise appears to be attenuated after a period of aerobic exercise[88,116] and in trained compared to untrained subjects.[119] This is potentially mediated by a platelet-inhibiting effect of NO and prostacyclin, and associated with enhanced endothelial function.[69,115]

In contrast, markers of coagulation and thrombin generation during rest, including aPTT, PT, TAT and F1+2, appear not to be influenced by the amount of habitual physical activity[98,99,120] or after 12 weeks of aerobic exercise.[121,122] However, the literature is not entirely consistent, with one study reporting a prolongation in aPTT during rest after 12 weeks of aerobic exercise, [105] while a small reduction in basal F1+2 was reported in older adults after six months of aerobic exercise.[123] Furthermore, while habitual physical activity was inversely associated with resting fibrinogen, FVIII and VWF in a cross-sectional study of men,[84] these observations have not been confirmed in longitudinal studies with aerobic exercise interventions.[105,121,124]Accordingly, the plasma levels of FVIII and VWF under resting conditions in endurance-trained athletes do not appear to differ from less active controls.[125]

Few studies have investigated whether training status influences the short-term coagulation response to exercise. However, it has been suggested that endurance-trained athletes display a diminished response, as demonstrated by a lower increase in F1+2, compared to less trained controls.[120] Likewise, a less pronounced shortening of aPTT and attenuated increase in F1+2 was reported after a 12-week aerobic exercise intervention.[105] In

contrast, one study reported an augmented response in F1+2, and a more pronounced shortening of aPTT, in response to maximal exercise following 12 weeks of aerobic exercise.[122] However, the transient increase in FVIII activity evoked by exercise appears to be unaltered following an aerobic exercise intervention,[105,121] although an augmented response after training has also been suggested.[122,124]

An increase in t-PA activity and a decrease in PAI-1 activity during rest was reported after 6-months of aerobic exercise in elderly, while no such repose was observed in young subjects.[126] In contrast, two other studies did not observe any changes in resting activity of t-PA or PAI-1 after 12 weeks of aerobic exercise.[105,122] Further, in a cross-sectional study, resting t-PA activity was similar in active and inactive men, while PAI-1 activity was higher among the inactive.[112] Data on whether training status influences the fibrinolytic response to exercise are sparse. However, based on the available evidence, it can be suggested that trained individuals display an amplified fibrinolytic potential in response to maximal intensity exercise,[112,122,127] but probably not to submaximal exercise.[105,122]

In summary, although exercise evokes significant transient responses in both the coagulation and fibrinolytic systems, it remains unclear whether this results in a net hypercoagulable state.[86,128] Nevertheless, the more transient nature of the fibrinolytic response may induce a disturbed balance and contribute to the increased cardiovascular risk observed shortly after strenuous exercise.[97,114] There are inconsistent findings on the long-term adaptations to physical activity and exercise.[129] However, the available evidence imply that training status only moderately influences hemostasis assessed under resting conditions, while the fibrinolytic response to maximal intensity exercise may be amplified in trained subjects. Importantly, the available studies display large methodological variance related to

exercise-testing protocols, training interventions, study populations and analytical methods, which impedes firm conclusions on this topic.

Consequences of Venous Thromboembolism: Is There a Role for Physical Activity?

In addition to thrombus extension and embolization, potential complications following an acute VTE event include morbidity directly or indirectly related to the thrombus, recurrent disease and death.[130,131] The one-year all-cause mortality after VTE is reported to be 22-24%, [132-134] and in survivors the one- and five-year recurrence risks are 13-19% and 19-29%, respectively.[132,135,136]

To our knowledge, only one study has investigated the association between physical activity and the risk of VTE recurrence. In a follow-up arm of the MEGA study,[29] Flintermann and colleagues followed almost 4000 patients with incident VTE over a period of five years. They reported that individuals with a sedentary lifestyle prior to their incident VTE had an increased risk of recurrence that was more prominent in women (hazard ratio [HR] 1.5; 95% CI 1.1-2.0) than in men (HR 1.1; 95% CI 0.9-1.4).[29] It is currently not known whether physical activity after the incident VTE influences the risk of recurrence. Nevertheless, a sedentary lifestyle will increase the risk of other metabolic and cardiovascular diseases, and premature mortality.[8,10,11]

PTS occurs in 20-50% of patients with lower limb deep vein thrombosis (DVT), and manifests with pain, swelling and heaviness of the affected extremity.[131,137,138] The condition is associated with impaired quality of life and significant health care costs.[139,140] PTS most often occurs in patients with recurrent ipsilateral DVT, and predisposing factors include older age, insufficient anticoagulant treatment and impaired thrombus resolution.[131,141,142] As there

is currently no effective treatment strategy for PTS, prevention is pivotal.[142] A potential preventive role for physical activity has been suggested. Specifically, a small intervention study[143] reported that early mobilization, as compared to bed rest, was associated with a lower two-year incidence and severity of PTS symptoms in patients with acute DVT. In contrast, another study[144] did not find any significant association between self-reported physical activity one month after DVT and risk of developing PTS during the subsequent two years. Interestingly, a randomized controlled trial investigating the effect of supervised exercise on the risk of PTS is currently underway (NCT02148029). There is limited data on the effect of physical activity in the treatment of PTS. However, improved calf muscle pump function was reported after a six-month exercise program in patients with chronic venous insufficiency (50% with a history of DVT).[59] In addition, a pilot study in patients with established PTS, reported that a six-month exercise program improved quality of life, but the small beneficial effect on PTS symptoms did not reach statistical significance.[145]

Less prevalent but more debilitating, CTEPH, characterized by dyspnea, physical impairment and impaired quality of life, affects 0.5-4% of patients with PE.[146,147] The exact pathophysiology behind CTEPH is unclear, but is potentially driven by impaired thrombus resolution with subsequent development of fibrotic occlusions and vascular remodeling.[131,148] Previous PE, larger perfusion defects, lupus anticoagulant, antiphospholipid antibodies and elevated FVIII levels are reported to be associated with the development of CTEPH.[148] To our knowledge, no study has so far investigated the association between physical activity and the risk of CTEPH in patients with PE. However, exercise-based rehabilitation programs have shown promising effects on exercise capacity and quality of life in patients with pulmonary hypertension including CTEPH, although we are not aware of any studies restricted to patients with CTEPH only.[149,150]

It is now well established that early mobilization after an acute VTE does not increase the risk of disease progression or adverse events.[151,152] Moreover, one study on selected VTE-patients reported that maximal exercise testing and structured aerobic exercise early after acute VTE (≥6 weeks) was safe, feasible and efficient.[153] However, research on whether physical activity influences the risk and prognosis of VTE-related complications is limited.

Conclusions

Despite a considerable amount of research, the association between physical activity and risk of incident VTE has yet to be thoroughly established. As summarized in the present review, the available evidence is inclined towards a beneficial effect of physical activity on the risk of incident VTE, but not in a dose-dependent manner. There is, however, considerable methodological variance between the published studies, which largely precludes head-to-head comparisons. Future studies utilizing objective assessment strategies and accounting for fluctuations in behavior may aid to reveal the true association.

The potential role of physical activity in the secondary prevention of VTE and in relation to PTS and CTEPH has to date been investigated with a fragmented approach. Consequently, there is a need to explore the necessity and potential benefits of structured rehabilitation programs, equivalent to that in cardiac rehabilitation, in the VTE-setting.

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Table 1. Overview of prospective studies investigating the association between physical activity or sedentary behavior and the risk of incident venous thromboembolism (VTE) listed according to main findings

First author (year)	Cohort	Study population	VTE-events	PA assessment[a]	Reassessed PA	Follow-up	Main findings	Confounders	Comments
Beneficial association									
Armstrong (2015)[16]	Million Women Study	Women, 50-64 years	14550	Five categories of weekly frequency of any and high-intensity PA (sweating/fast heart rate)	No	9 years (first 4 years excluded)	Any PA vs inactive: 4-18% lower risk Strenuous PA vs inactive: 8-17% lower risk (U-shaped)	BMI (by age), smoking (by age), alcohol (by age), socioeconomic status and region	
Kabrehl (2011)[22]	Nurses' Health Study	Women, 30-55 years	268 (PE only)	Five categories based on weekly METs (calculated from hours/week spent in various activities). Five categories of sitting time based on sitting hours per week	Yes[b]	18 years	HR 2.34 (1.30-4.20) for the highest vs lowest category of sitting time	[c]	PA above the median partly attenuated the negative effect of sitting-time
Olson (2015)[15]	The Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study	Men and women, 45 and older	263	Three categories based on weekly frequency of PA (intensity and duration not provided)	No	5 years	HR for PA 1-3 times/week vs none: 0.70 (0.53-0.93), HR for PA ≥4 times/week vs none: 0.59 (0.43-0.81)	Age, sex, income, education, race and region.	The highest PA category was associated with 35% lower risk in the BMI-adjusted model
Wattanakit (2012)[14]	The Atherosclerosis Risk in Communities (ARIC) Study	Men and women, 45-64 years	468	Four categories based on the Baecke sports questionnaire	Yes	15.5 years	HR PA cat. 2 vs 1: 0.72 (0.53-0.93), HR PA cat. 3 vs 1: 0.74 (0.58-0.95). HR PA cat 4 vs 1: 0.81 (0.62-1.06).	Age, race, ARIC field centre, sex and BMI	All categories was associated with a significantly lower risk of VTE prior to BMI-adjustment
Adverse association									
Armstrong (2015)[16]	Million Women Study	Women, 50-64 years	14550	Five categories of weekly frequency of any and high-intensity PA (sweating/fast heart rate)	No	9 years	RR for strenuous PA daily vs none 1.08 (0.99-1.17)	BMI (by age), smoking (by age), alcohol (by age), socioeconomic status and region	
Glynn (2005)[18]	Physicians' Health Study	Men, 40-84 years	358	Six categories based on weekly frequency of vigorous exercise (sweating)	No	20 years	RR 1.09 (1.01-1.18) per exercise category	Age	Larger effect size for provoked VTE

Van Stralen (2008)[17]	The Cardiovascular Health Study (CHS)	Men and women, 65 years and older	171	Dichotomized as active or inactive based on total weekly kilocalories expended on leisure-time and household activities (≥or<500 kcal). Mild, moderate and strenuous exercise defined as METs <4, 4-6 and >6, respectively	Yes	11.6 years	HR 1.75 (1.08-2.83) for strenuous compared to no exercise	Age, sex, baseline BMI and self-reported health	Mild intensity exercise was associated with lower risk, HR 0.75 (0.49-1.169 when compared to no exercise

No association

Borch (2010)[19]	The Tromsø Study	Men and women, 25-97 years	460	Four categories based on weekly frequency of moderate and high intensity PA during leisure time (breathless/sweating)	No	12.5 years	No association between PA and VTE	Age, sex, BMI, diabetes, smoking and hormone therapy	
Holst (2010)[23]	Copenhagen City Heart Study	Men and women, aged 20 and older	969	Leisure time PA dichotomized into sedentary or moderately activity <4h/week, or moderate or intense activity >4h/week. Work-related activity assessed separately based as mostly sitting/standing versus lifting and heavy physical work	No	19.5 years.	No association between PA and VTE	Age and calendar time	
Kabrehl (2011)[22]	Nurses' Health Study	Women, 30-55 years	268 (PE only)	Five categories based on weekly METs (calculated from hours/week spent in various activities).	No	18 years	No association between PA and VTE		
Lutsey (2010)[20]	Iowa Women's Health Study	Women, 55-69 years	2137	Three level summary index based on the frequency of moderate (e.g. golf) and vigorous (e.g. aerobics) PA	No	13 years	No association between PA and VTE in multivariable analyses	Age, education, smoking status and BMI	Moderate and high intensity PA associated with 16% (HR 0.84 (0.76-0.93) and 19% (0.81 (0.72-0.90) lower risk of VTE in the age-adjusted model
Tsai (2002)[21]	The Atherosclerosis Risk in Communities (ARIC) Study & The Cardiovascular Health Study (CHS)	Men and women ARIC: 45-64 years CHS: 65 and older	ARIC: 130 CHS: 85	ARIC: Five-level index based on the Baecke leisure and sport questionnaires CHS: Five categories based on weekly kilocalories expended on leisure-time and household activities	No	7.8 years	No association between PA and VTE	Age, race and sex	Analyses was done separately for the two studies due to different assessment of physical activity

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; METs, metabolic equivalents; PA, physical activity; PE, pulmonary embolism; RR, relative risk; VTE, venous thromboembolism.

[a]All studies are based on self-reported physical activity, [b]Not analyzed as a time-varying covariate, [c]Adjusted for age, coronary heart disease, hypertension, menopausal status, multivitamin use, use of non-aspirin non-steroidal anti-inflammatory drugs, parity, race , rheumatologically disease, spouse's highest educational attainment, smoking status, pack-years, warfarin use, BMI, total energy intake, physical activity and dietary pattern.

Table 2. Incidence rates and hazard ratios with 95% confidence intervals for the risk of myocardial infarction (MI) and venous thromboembolism (VTE) by physical activity status. The Tromsø Study (1994-2013).

Physical activity status	Myocardial infarction				Venous thromboembolism			
	MI-events	IR (95% CI)[a]	HR (95% CI)[b]	HR (95% CI)[c]	VTE-events	IR (95% CI)[a]	HR (95% CI)[b]	HR (95% CI)[c]
Inactive[d]	621	7.25 (6.70-7.84)	1.00	1.00	195	2.19 (1.90-2.51)	1.00	1.00
Light PA 1-3 h/week	478	4.70 (4.30-5.14)	0.77 (0.68-0.87)	0.80 (0.71-0.91)	795	1.86 (1.62-2.14)	0.98 (0.81-1.20)	1.03 (0.84-1.26)
Light PA >3h/week	509	5.93 (5.44-6.47)	0.73 (0.65-0.82)	0.78 (0.69-0.88)	201	2.25 (1.96-2.58)	0.94 (0.77-1.15)	1.02 (0.84-1.25)
Hard PA 1-3h/week	255	3.03 (2.68-3.41)	0.63 (0.55-0.74)	0.71 (0.62-0.83)	98	1.14 (0.94-1.39)	0.84 (0.66-1.08)	0.92 (0.72-1.19)
Hard PA >3h/week	160	3.72 (3.18-4.34)	0.69 (0.58-0.82)	0.78 (0.65-0.93)	64	1.46 (1.14-1.86)	1.02 (0.77-1.36)	1.11 (0.83-1.49)
p for trend			<0.001	<0.001			0.432	0.928

Abbreviations: PA, physical activity; light PA, not sweating or out of breath; hard PA, sweating or out of breath.
[a]Crude incidence rates per 1000 person-years, [b]Adjusted for age (as timescale) and sex, [c] adjusted for age (as timescale), sex, BMI and smoking, [d]No or less than 1h of physical activity per week.

Table 3. Short-term hemostatic responses to exercise

Parameter	Effect	Magnitude of effect	Comment	Reference
Platelets				
Count	Increased	7-29%	Intensity-dependent Effect observed after both endurance and resistance exercise	[88-92]
Activation/reactivity	Uncertain/increased Unchanged/increased	β-TG: -13-155% PF4: -1-122%	Intensity-dependent Intensity-dependent	[88,91] [88]
Coagulation				
aPTT	Shortened	5-13%	Independent of intensity Effect observed after both endurance and resistance exercise	[91,94,95,97-99]
PT	Unchanged	n/a		[94,95]
F1+2	Increased	5-88%	Intensity-dependent Effect observed after both endurance and resistance exercise	[94,99,106,107]
TAT	Unchanged/increased	0-173%	Intensity-dependent Effect observed after both endurance and resistance exercise	[94,99,106,108]
FVIII activity	Increased	34-400%	Intensity-dependent Effect observed after both endurance and resistance exercise	[94,97,100,102,103]
VWF	Increased	96-200%	Dependent on intensity	[100,101]
Fibrinolysis				
t-PA activity	Increased	119-1525%	Intensity-dependent Effect observed after both endurance and resistance exercise	[94,99,111,112]
PAI-1 activity	Decreased	-19 - -83%	Probably not or less dependent on intensity Effect observed after both endurance and resistance exercise	[94,99,111,112]

Abbreviations: aPTT, activated partial thromboplastin time; β-TG, β-thromboglobulin; FVIII, coagulation factor VIII; PAI-1, plasminogen activator inhibitor-1; PF4, platelet factor 4; F1+2, prothrombin fragment 1+2; PT, prothrombin time; TAT, thrombin-antithrombin complex; t-PA, tissue plasminogen activator; VWF, von Willebrand factor

Table 4. Long-term adaptations to regular physical activity and exercise on resting hemostasis

Parameter	Effect	Magnitude of effect	Comment	Reference
Platelets				
Activation/reactivity	Reduced	Numbers not reported	Pre versus post intervention	[115,116]
	Reduced	Basal CD62P[a]: 42.7%	Pre versus post intervention	[118]
	Lower	Numbers not reported	Trained versus untrained	[118]
Coagulation				
aPTT	Prolonged	10.3%	Pre versus post intervention	[105]
	Unchanged	n/a	Trained versus untrained & pre versus post intervention	[98,99,121,122]
PT	Unchanged	n/a	Trained versus untrained	[98]
F1+2	Unchanged	n/a	Trained versus untrained & pre versus post intervention	[99,120,122]
	Decreased	4.8%	Pre versus post intervention	[123]
TAT	Unchanged	n/a	Trained versus untrained	[99,120]
FVIII activity	Decreased	5.6 %	Trained versus untrained	[84]
	Unchanged	n/a	Pre versus post intervention	[105,121,124]
VWF	Decreased	7.2%	Trained versus untrained	[84]
	Unchanged	n/a	Trained versus untrained & pre versus post intervention	[122,125]
Fibrinolysis				
t-PA activity	Increased	39%	Pre versus post intervention	[126]
	Unchanged	n/a	Trained versus untrained & pre versus post intervention	[105,112,122]
PAI-1 activity	Decreased	58%	Trained versus untrained & pre versus post intervention	[112,126]
	Unchanged	n/a	Pre versus post intervention	[105,124]

Abbreviations: aPTT, activated partial thromboplastin time; FVIII, coagulation factor VIII; PAI-1, plasminogen activator inhibitor-1; F1+2, prothrombin fragment 1+2; PT, prothrombin time; TAT, thrombin-antithrombin complex; t-PA, tissue plasminogen activator; VWF, von Willebrand factor
[a]Marker of platelet activation