

The effects of obesity on venous thromboembolism: A review^{*}

Genyan Yang, Christine De Staercke, W. Craig Hooper[#]

Clinical and Molecular Hemostasis Laboratory Branch, Division of Blood Disorders, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia; [#]Corresponding Author: chooper@cdc.gov

Received 25 July 2012; revised 2 September 2012; accepted 8 October 2012

ABSTRACT

Obesity has emerged as a global health issue that is associated with wide spectrum of disorders, including coronary artery disease, diabetes mellitus, hypertension, stroke, and venous thromboembolism (VTE). VTE is one of the most common vascular disorders in the United States and Europe and is associated with significant mortality. Although the association between obesity and VTE appears to be moderate, obesity can interact with other environmental or genetic factors and pose a significantly greater risk of VTE among individuals who are obese and who are exposed simultaneously to several other risk factors for VTE. Therefore, identification of potential interactions between obesity and certain VTE risk factors might offer some critical points for VTE interventions and thus minimize VTE morbidity and mortality among patients who are obese. However, current obesity measurements have limitations and can introduce contradictory results in the outcome of obesity. To overcome these limitations, this review proposes several future directions and suggests some avenues for prevention of VTE associated with obesity as well.

Keywords: Obesity; Comorbidity; Deep Vein Thrombosis; Pulmonary Embolism; Venous Thromboembolism; Risk Factor; Prevention

1. INTRODUCTION

Venous thromboembolism (VTE) is the third most common cardiovascular disorder after ischemic heart attack and stroke [1,2]. It is estimated that VTE occurs among 1 to 2 per 1000 persons annually in the United

States [3-5]. VTE imposes a substantial burden on the US health care system. The initial clinical management, recurrence, and long-term complications of VTE including post-thrombotic syndrome (PTS) and other VTE-associated comorbid conditions compromise quality of life and cost about \$2 billion to 10 billion annually to the health care system in the United States [6,7].

Obesity is a major public health problem not only in the United States, but also rapidly is becoming a global threat [8]. While obesity can serve as a risk factor for some diseases, it also can affect preexisting diseases or lead to an array of comorbid conditions, including coronary artery disease (CAD), type 2 diabetes mellitus, hypertension, stroke, heart failure, obstructive sleep apnea syndrome, gastrointestinal disorders, depression, malignancies, and VTE [9,10]. In this review, we focus on the association between obesity and VTE, explore possible interactions between obesity and several other risk factors for VTE, discuss limitations of current obesity measurement, identify possible research gaps, and suggest some avenues for prevention of VTE associated with obesity. Although medical interventions are important, the clinical management of VTE is not in the scope of this review.

2. CLINICAL EPIDEMIOLOGY OF VTE

VTE encompasses two distinct clinical entities: deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT begins with formation of a blood clot in the deep veins of the body, usually in the legs or pelvis. PE occurs if the clot becomes detached and travels to the pulmonary arteries, and can result in death. Development of PTS is a common medical complication of DVT [11], while chronic thromboembolic pulmonary hypertension (CTEPH) can occur following a PE [12]. CTEPH is initiated by the obstruction of pulmonary arteries with thrombi that can lead to cardiac failure and death if left untreated [13]. PTS clinically manifests as persistent or intermittent pain, swelling, ulceration, or cramping in the limb affected [6]. In one longitudinal study, the cumulative incidence of PTS was reported to be 17% and 23%

^{*}Disclaimer: The findings and conclusions in this paper are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

at 1-year and 2-year follow-up post-DVT, respectively, and increased gradually to 29% over a period of 8 years [6]. In addition, approximately 30% of patients experienced recurrent VTE (DVT or PE) within 10 years of an initial VTE event [14]. Consequently, VTE can be considered a chronic rather than an acute disease.

The incidence of VTE varies widely across different racial populations and increases with age and hospitalization. Analysis of the California Patient Discharge Data Set showed that the total annual VTE incidence rate per 100,000 adults was 141 for Blacks or African Americans, 104 for Whites, 55 for Hispanics, and 21 for Asians [5]. Blacks or African Americans not only appeared to have the highest overall VTE incidence rate, but also were found to have a significantly greater PE case-fatality rate [5,15,16]. The incidences of PE and DVT also increase sharply with age [3,17]. Stein *et al.* investigated the database of the National Hospital Discharge Survey, which consists of data obtained during the period 1979 through 1999 from patients of over 400 nonfederal short-stay hospitals in all 50 states and the District of Columbia [17]. They found that the frequency of PE among patients 70 years of age or older was more than 4-times that among patients younger than 50 years of age [17]. Also, hospitalized patients and recently discharged patients were seen to have a remarkably increased risk for VTE [18]. Different from idiopathic or spontaneous VTE that occurs in the absence of known precipitating factors, VTE associated with hospitalization likely is provoked by multiple risk factors for VTE, including immobilization; surgery; trauma; childbirth; stroke; or the patient's comorbid medical conditions, such as infection, inflammatory bowel disease, or cancer [19].

3. DEFINITION OF OBESITY—MEASUREMENT TOOLS

The most frequently used indicator of obesity is the body mass index (BMI) [10], with a normal range of 18.5 - 24.9 kilograms per square meter (kg/m^2) among adults 20 years of age or older. Someone with a BMI of 25 - 29.9 kg/m^2 is considered overweight, and someone having a BMI $\geq 30 \text{ kg}/\text{m}^2$ is considered to be obese. According to World Health Organization (WHO) criteria established in 1997 [10], obesity among adults is further classified into three categories: Class I obesity is a BMI of 30 - 34.9 kg/m^2 ; Class II obesity is a BMI of 35 - 39.9 kg/m^2 ; and Class III obesity, or morbid obesity, is a BMI $\geq 40 \text{ kg}/\text{m}^2$. Childhood obesity is defined as a BMI greater than or equal to the 95th percentile of BMI-for-age for children and adolescents of the same sex (2 through 19 years of age) [20]. Wang *et al.* proposed that severe obesity among the pediatric population (2 through 19 years of age) be defined as BMI-for-age greater than or equal

to 120% of the 95th percentile of the Centers for Disease Control and Prevention growth charts [21].

Alternative anthropometric measures that reflect the distribution of body fat have been suggested as being superior to BMI in predicting certain diseases [22,23]. For example, waist circumference (WC), waist-to-hip ratio (WHR), and waist-to-height ratio (W/Hr) that define central obesity appear to be associated more closely with cardiovascular disease (CVD) than BMI [22,24]. WHO reference cutoff points for obesity were introduced in 2008 as a WHR (WC) > 0.9 (102 centimeters (cm)) for males and >0.85 (88 cm) for females [25].

Body fat percentage (BF%) directly calculates an individual's body composition. It can be measured accurately when using magnetic resonance imaging (MRI) [26] or dual-energy X-ray absorptiometry [27]. In the HERITAGE Family Study, Jackson *et al.* found that the BF% of females was 10.4% higher than that of males with the same BMI [28]. The American Council on Exercise recommended that cutoff value for obesity was a BF% $> 25\%$ for men and $>32\%$ for women [29]. In addition, BF% also is subject to change depending on age and race [28,30]. Asian populations generally have a higher BF% and appear to be more sensitive to the metabolic consequences of obesity than Whites of the same age, sex, and BMI [25]. Body fat generally increases and fat-free mass decreases with increasing age [28]. Consequently, older individuals usually have a higher percentage of body fat than younger individuals of the same BMI [30].

4. ASSOCIATION OF OBESITY WITH VTE

4.1. Obesity and First Occurrence of VTE

Obesity appears to be associated with an increased risk for VTE. A meta-analysis of 1 cohort and 8 case-control studies involving a total of 8125 patients with VTE and 23,272 control patients indicated that likelihood of first spontaneous VTE among people who were obese was more than twice that of individuals with a normal BMI (odds ratio (OR) = 2.33; 95% confidence interval (CI), 1.68 - 3.24) [31]. However, the OR reduced to 1.84 (95% CI, 1.55 - 2.18) after excluding three studies that had no adequate controls or BMI measurements [31]. In the Tromso study, Borch *et al.* found abdominal obesity as defined by WC was the only risk factor for VTE (PE or DVT) (OR = 2.03; 95% CI, 1.47 - 2.75) in a multivariable analysis that included hypertension, impaired glucose metabolism, a low level of high-density lipoprotein cholesterol (HDL-c), and hypertriglyceridemia [32]. Similarly, Steffen *et al.* found abdominal obesity was associated with idiopathic VTE among men (OR = 2.31; 95% CI, 1.48 - 3.62) and women (OR = 1.84; 95% CI, 1.19 -

2.84) after adjusting for age, race, education, smoking, triglycerides, HDL-c, glucose, and systolic blood pressure [33].

Increasing BMI above normal value has been reported to be associated with a rising risk of VTE [34-36]. A prospective cohort study of 87,226 women in the Nurses' Health Study (NHS) showed that the relative risk of unprovoked PE that was not associated with prior surgery, trauma, or cancer raised by about 8% per 1 kg/m² increase in BMI and approached a nearly sixfold greater risk among individuals with a BMI \geq 35 kg/m² ($p < 0.001$) [34]. In a prospective Danish study that enrolled 29,340 women and 26,674 men [36], Severinsen *et al.* found the OR of VTE was 1.45(0.98), 1.81(1.32), and 2.82(1.72) among women (men) with BMIs of 23.7 - 26.3 (24.4 - 26.8), 26.3 - 29.9 (26.8 - 29.4), and >29.9 (>29.4), respectively, after adjusting for age, physical activity, smoking, height, cholesterol, hypertension, diabetes mellitus, and use of hormone replacement therapy. The data have suggested the risk of VTE increases with a rising BMI among the individuals who are overweight or obese. Given about a 33% increase in obesity prevalence and a 130% increase in severe obesity prevalence through 2030 predicted by Finkelstein *et al.* [37], this positive association between increasing BMI and escalating risk of VTE might herald a parallel climbing of VTE incidence with the rising rates of obesity.

4.2. Obesity and Recurrent VTE

Several studies have addressed the relationship between obesity and recurrent VTE. Eichinger *et al.* followed 1107 patients for an average of 46 months after termination of anticoagulation therapy for a first spontaneous VTE. They found the frequency of recurrent VTE was 9.3% (95% CI, 6.0% - 12.7%) among patients with a normal BMI and 17.5% (95% CI, 13.0% - 22.0%) among patients who were obese [35]. In a prospective cohort study that followed 583 patients with a first idiopathic VTE for 28 months, Olie *et al.* found obesity was related to an increased risk of recurrent VTE (OR = 2.8; 95% CI 1.3 - 6.0) [32]. Similarly, Garcia-Fuster *et al.* also reported obesity was a risk factor for recurrent VTE (OR = 2.27; 95% CI 1.00 - 5.15) in a long-term prospective study of incidence of recurrent VTE that followed 98 patients and for 117 months after an initial episode of spontaneous VTE [38]. In contrast, Linnemann *et al.* showed no association between obesity and a risk of recurrent VTE in their cohort study that consisted of 1006 patients with history of VTE with an average follow-up time of 40 months after discontinuation of anticoagulation therapy [39]. It is worth noting that both spontaneous VTE and provoked VTE were included in Linnemann's study that investigated the effects of esta-

blished cardiovascular risk factors on the risk of recurrent VTE [35]. The potential VTE-provoking factors—such as thrombophilia, cancer, inflammation, hormone therapy, and surgery—in Linnemann's study might have masked the effect of obesity on recurrent VTE.

4.3. Obesity and VTE Mortality

PE is responsible for almost all mortality from VTE, but the association between obesity and PE case mortality has yet to be explained. Although obesity is associated with adverse comorbidities such as hypertension and stroke [10], some studies have indicated that mortality among patients with PE appeared to be paradoxically lower among patients who were obese than those who were not [40,41]. However, it still remains obscure whether this phenomenon—the so-called “obesity paradox” [42]—is attributable to a real protective role of increased body fat because the lower mortality was seen mostly among old people who were obese, but not among young adults and children who were obese [40, 41]. The observed lower PE mortality among old people who were obese might have been due in part to a number of factors. First, some obesity-related adverse effects take years to manifest. Therefore, those who become obese in old age might have lower mortality risk compared with those who were obese at midlife but were not obese in old age [43]. Next, being underweight is a strong predictor of mortality in the elderly [44]. Normal BMI due to unintentional weight loss caused by a wasting disease or unrecognized systemic illness can lead to an overestimation of the mortality among older adults with these “healthy” BMI, thereby making the elderly who are obese seem protected by obesity. Finally, an age-related decline in body height among the elderly [45] that might have introduced a false BMI increase and registered the individuals with merely an overweight BMI as being obese. Accordingly, PE mortality among the old population who are considered to be obese as defined by BMI might represent partially PE mortality among people who are not obese. Indeed, the studies that reported an obesity paradox used BMI to assess obesity [46,47]. After controlling for BMI, however, obesity as defined by WC or WHR in the same studies actually was associated positively with mortality [48].

5. INTERPLAY OF OBESITY WITH THE RISK FACTORS FOR VTE

VTE results from the complex interactions of genetic and environmental factors that influence the coagulant, inflammatory procoagulant, anticoagulant, and fibrinolytic system, leading to hypercoagulability or hypofibrinolysis, or both. In other words, VTE is a multifactorial chronic disease that most often involves two or more risk

factors. Although obesity appears to be a moderate risk factor for VTE [32,49], it can interact with other risk factors in VTE development and recurrence. Here, we have summarized the relationship of obesity with some common weak-to-moderate risk factors for VTE, including genetic factors, use of sex steroid hormones, inflammation, and insulin resistance [50,51].

5.1. In Relation to Genetic Factors

Identification of a positive family history of VTE as a risk factor for VTE suggests a contribution of genetic factors to VTE [52]. Common genetic factors reported to be associated with a greater risk of VTE include factor V Leiden (FVL), factor II (FII) G20210A, non-O blood group, sickle cell trait, and thalassemia intermedia (HbSC and HbS/ β^+) [53]. Among these inherited risk factors, FVL and FII G20210A are the most frequent prothrombotic mutations [54]. However, the incidence rate of VTE among individuals with FVL and FII G20210A is highly variable, suggesting other factors might be involved in shaping the effects of these genetic factors. In a prospective case-control study consisting of 732 patients with unprovoked VTE and 732 individuals without VTE who were matched to the cases by age, sex, risk factor for VTE—surgery, plaster cast, pregnancy, childbirth in the past 3 months, and active cancer [55], Delluc *et al.* reported an OR for VTE among patients with the FII G20210A mutation who were obese was 12.03 compared with the matched controls with the FII G20210A mutation who were obese. In contrast, the OR for VTE among patients with the FII G20210A mutation who had a BMI < 25 kg/m² was only 1.67 compared with the matched controls with the FII G20210A mutation who had a BMI < 25 kg/m² [55]. The data suggest FII G20210A mutation interacts with obesity to increase risk of VTE. However, the association between FVL and increasing BMI lacked statistical significance [55]. Similar findings have been reported by Severinsen *et al.*, who analyzed the effects of the FVL and FII G20210A mutations on the risk of VTE among a subcohort of 1803 individuals randomly selected from the Danish Diet, Cancer, and Health Study [56]. The ORs for VTE were 5.27 and 2.63 for patients with FVL who were obese and of normal BMI, respectively compared with the patients without FVL who had normal BMI [56]. This approximate two-fold increase in the risk of VTE was essentially equivalent to the risk of VTE associated with obesity alone (OR = 2.34; 95% CI, 1.73 - 3.16) [56], suggesting there was no interaction between obesity and FVL. In contrast, the risk of VTE was nearly fivefold higher among patients carrying the FII G20210A mutation who were obese than among those with the mutation who were of normal weight [56]. These findings are in line with those of Del-

luc *et al.* that suggested obesity might interact with FII G20210A—but not with FVL—in modifying the risk of VTE [55,56].

5.2. In Relation to Use of Sex Steroid Hormones in Women

Steroid hormone applications, mainly estrogen derived compounds, appear to be associated with a risk of VTE [57,58]. At least 10 million women in the United States and 100 million women worldwide use oral contraceptive pills (OCPs) [59]. In spite of a sustained decline in hormone replacement therapy (HRT) due to adverse health risks reported by Ettinger *et al.* from the Women's Health Initiative (WHI) study [60], HRT still is prescribed widely for women who are postmenopausal to prevent osteoporosis or other medical conditions [61,62].

The combination of oral steroid usage and obesity has been associated with higher risk of VTE than use of oral steroids or obesity alone [57,63]. In the WHI estrogen plus progestin clinical trial, Cushman *et al.* found that the risk of VTE further increased among women who were overweight or obese and who were taking oral steroids compared with women who were normal weight and were taking a placebo [58]. Analysis of the data from the EStrogen and THromboEmbolism Risk (ESTHER) study by Canonico *et al.* also indicated that obesity alone or oral estrogen use by itself each increased the risk of VTE by 4.0- and 5.6-fold, respectively; however, the OR approached more than 20-fold when these two risk factors were combined among women who were obese and were taking oral estrogen [63], suggesting an interaction between obesity and oral estrogen use. However, transdermal delivery of estrogen did not impose an additional risk of VTE on women who were overweight or obese [57,63]. Transdermal hormone delivery bypasses hepatic metabolism and, hence, might have less pronounced effects on the hepatic synthesis of coagulation and anticoagulation factors [64]. However, little is known about the molecular mechanism underlying the disparity in the risk of VTE between oral and transdermal steroid administration.

Thrombin generation that enhances overall coagulation potential has been shown to be elevated among patients who are obese and is reduced following weight loss after bariatric surgery [65]. Oral estrogen can shift hemostasis balance toward a prothrombotic state by increasing resistance to activated protein C [66,67] and upregulating plasma concentration of coagulation factors (II, VII, VIII, and X) [68] and prothrombin activation peptide (F1 + 2) [69], while decreasing the antigen level and activity of protein S [70] and antithrombin [71]. Therefore, obesity is considered as a prothrombotic state that can be enhanced further by the use of oral steroids,

especially among elderly women who are obese and who have been reported to attain higher concentrations of estrogen than women with a normal BMI who received an oral HRT [72].

5.3. In Relation to Inflammation and Insulin Resistance

Excessive visceral adipose tissue causes hypoxia and increases delivery of inflammatory adipocytokines and free fatty acids (FFA) to the liver, where coagulation factors are synthesized abundantly [73,74]. FFA can induce mitochondrial production of reactive oxygen species (ROS) [75]. Alone or in combination with inflammatory adipocytokines, ROS is able to activate endothelial cells and can initiate systemic coagulation [76].

Overactivation of the rennin-angiotensin system (RAS) and an elevated level of circulating free fatty acids (FFAs) among those who are obese, especially among those with visceral obesity, has been postulated to cause insulin resistance by interfering with insulin-mediated glucose uptake in its target tissues [9,77]. The subsequent hyperglycemia can lead to ROS generation and oxidative stress [77], which can trigger systemic inflammation and mediate further FFA production [9]. This process ultimately leads to a prothrombotic tendency by enhancing coagulation while inhibiting fibrinolysis [78,79], which in some cases can contribute to the pathogenesis of VTE associated with abdominal obesity [32]. Indeed, insulin resistance has been reported to increase the risk of VTE in a BMI-dependent manner [80].

6. PREVENTION OF VTE ASSOCIATED WITH OBESITY

With the high prevalence of obesity [21,81] and potential interplay of obesity with other risk factors for VTE discussed previously, implementation of effective, safe, and practical prevention strategies is critical in reducing the incidence of VTE associated with obesity and minimizing recurrence of VTE.

Intentional weight loss through diet control and physical activity may modulate risk factors for VTE among the population with obesity. Regular physical activity may reduce risk of VTE through a reduction of the activity of plasminogen activator inhibitor-1 (PAI-1) that was accompanied with body-weight loss [82] and an increase in endothelial release of tissue-type plasminogen activator (t-PA) upon bradykinin stimulation among the individuals who were obese [83]. Lutsey *et al.* reported that moderate to high intensity physical exercise was associated with reduced risk of VTE compared with low level of physical activity [84]. However, others did not find a significant impact of regular physical exercise on the risk of VTE [85-87]. It is not clear whether in-

creasing intensity and frequency of exercises, or whether exercises in conjunction with diet control to an extent that can result in weight loss may decrease risk of VTE among individuals who are obese. In the NHS and Health Professionals Follow-Up Study (HPFS), Varraso *et al.* found that a diet intake rich in vitamins E and B6 and fiber was associated with a decreased risk for VTE [88]. These results were corroborated by findings from the WHI study (n = 39,876) [89] and the Longitudinal Investigation of Thromboembolism Etiology (LITE) study (n = 14,962) [90]. However, Lutsey *et al.* observed no significant association between VTE and food nutrients, including vitamins E and B6 and whole grains, in the Iowa Women's Health Study (IWHS) [91]. A noticeable difference among these studies was the age of their participants. Lutsey *et al.* pointed out in the IWHS that the mean age of their study participants at the midpoint of follow-up was 72 years compared a mean age of 60 years among participants in the LITE study [91]. The nurses were 30 through 55 years of age in both the NHS/HPFS and more than 90% of the participants in WHI were younger than 64 years of age [88,89]. A general decline in food-nutrient digestion, absorption, and metabolism among old adults in the IWHS might have contributed in part to the less significant effect of diet on VTE than among younger people in the NHS/HPFS and WHI and LITE studies. Nevertheless, Lutsey *et al.* found alcohol intake was inversely related to risk of VTE in the IWHS [91]. Moderate wine consumption modulated expression of fibrinolytic proteins, including PAI-1 and t-PA [92,93] and the effects appeared to be alcohol dependent [94]. Although some studies have suggested that alcohol intake conferred a reduced risk of VTE [91,95], the effects have not been confirmed by others [85,96,97]. Given these inconsistent findings about alcohol and VTE, extensive epidemiological investigations are warranted to determine if alcohol consumption might be beneficial in reducing the risk for VTE among individuals who are obese.

Effective DVT prophylaxis (mechanical and pharmacological) can reduce the morbidity and mortality of VTE among hospitalized patients [98], but studies examining thromboprophylaxis of patients who are obese are limited [99]. The American College of Chest Physicians (ACCP) guidelines do not recommend using mechanical prophylaxis alone for VTE prevention among patients with morbid obesity unless a high bleeding risk precludes the use of pharmacological prophylaxis; however, the ACCP guidelines do suggest weight-based dosing for certain anticoagulation medications for VTE prophylaxis [100]. Several studies have demonstrated the necessity of adjusting the anticoagulant loading dose and dosing interval to achieve optimal anticoagulation among patients who are morbidly obese [99,101]. Suboptimal

adherence to prophylaxis schemes or inappropriate prophylaxis (underprophylaxis of patients who are severely obese or overprophylaxis of patients who are of normal weight or who are underweight) has been reported [98, 99,102]. Moreover, both the ACCP and the National Institute for Health and Clinical Excellence underscore the importance of individualized prophylaxis according to the estimated risk of VTE [103]. Therefore, education of at-risk individuals (e.g., people who are obese), VTE patients, and health care providers to improve clinical awareness and knowledge of VTE is essential to ensure proper and timely thromboprophylaxis [99].

7. LIMITATIONS AND GAPS

The WHO-defined BMI cutoff points for obesity classification have been accepted generally and used widely. However, BMI does not account for the wide variation in body fat distribution and, hence, might not be appropriate for use in all populations to predict accurately disease development as a risk factor. For example, in a cohort study of Italian children recruited from 15 national clinical centers ($n = 1479$, 5 - 15 years of age), Maffeis *et al.* reported that children with a normal BMI but with an increased W/Hr were at high risk for metabolic disorders and CVD compared with those with a lower W/Hr ($OR > 7$, $p < 0.001$) [24].

Although growing evidence has suggested an association between obesity and VTE, several questions remain to be answered. For instance:

1) Does the interplay between obesity and other risk factors for VTE additively or synergistically intensify the clinical severity of VTE (besides the frequency of VTE)?

2) Will the frequency or severity, or both, of VTE differ between those who are obese in their early life and those who gain weight and become obese at midlife or in old age?

3) Is there any dose-dependent effect between interacting risk factors for VTE? As discussed previously, the association between the risk of VTE and alcohol consumption is inconsistent. Could this controversy be attributable to the difference in amount of alcohol intake? Light to moderate alcohol consumption has been seen to reduce risk of VTE [95,96], but frequent binge drinkers have been subjected to an increased risk of VTE compared with those with restrained alcohol intake [95, 104], suggesting alcohol might have a dose-dependent effect on VTE occurrence. Nevertheless, it remains unclear if a given amount of alcohol might have a differential effect on patients depending on their level of obesity.

8. FUTURE DIRECTIONS

As discussed previously, epidemiological studies have suggested that obesity is associated with a significantly

higher frequency of VTE in the context of multiple risk factors than obesity by itself. Dire future efforts should be directed to:

1) Develop thromboprophylaxis schemes and other prevention strategies suitable for patients of different obesity categories (*i.e.*, Class I obesity, Class II obesity, and morbid obesity). A fixed dose of FDA-approved anticoagulant regimens might not provide optimal VTE prophylaxis among patients who are severely obese. For example, subcutaneous injection of 40 mg of enoxaparin twice daily generated an anti-Xa concentration of 0.14 international units per milliliter (IU/mL) among patients who were overweight, but only 0.06 IU/mL among patients who were morbidly obese [101].

2) Identify novel interactions among risk factors for VTE among the population with obesity. For example, observations that body height was an independent risk factor for VTE among men [105-107] warrant further studies to understand the sex-specific influence of body height on VTE occurrence and take this parameter into consideration when assessing risk of VTE among people who are obese.

3) Research molecular and pathogenic mechanisms responsible for VTE onset, development, and recurrence among patients who are obese, which might help us to better understand the differential effects between oral and transdermal administration of HRT on the risk of VTE among women who are obese [57,63].

4) Examine the dose-dependent effect on the interactions between obesity and other risk factors for VTE. For instance, low amounts of alcohol might enhance thrombolysis through regulation of the expression and activity of t-PA and PAI-1 among individuals who are obese and have elevated levels of circulating PAI-1 [92, 93,108], whereas consistently high levels of alcohol can cause liver diseases such as cirrhosis [109] that might predispose the individuals to the risk of VTE [110].

In future studies, a combination of two or more methods should be considered in obesity measurement [48]. Some individuals with a normal BMI might have excessive adiposity as determined by more sensitive methods, such as BF% [27]. This so-called “normal weight obesity” suggests that exclusively relying on a single measurement for obesity might be of limited value and might result in inconsistent findings regarding excessive body fat as a risk factor for disease. Given WC (positively) and BMI (negatively) were differently associated with mortality [48], the “obesity paradox” phenomenon among patients with PE [31,32] might be reconciled by using WC or WHR in combination with BMI for obesity assessment.

9. CONCLUSION

People who are obese are at an increased risk for VTE

compared with individuals who are of normal weight. The extent of the effects of obesity on VTE depends not only on total body fat, but also on the distribution of adipose tissue (e.g., central obesity) and the interplay among risk factors for VTE, such as genetic mutations, hospitalizations, and OCP use. The dimension and strength of possible interactions between obesity and these VTE risk factors may vary across different racial populations and can differ by age and sex as well. Therefore, consideration of other proper anthropometric measurements (not relying on BMI solely) for accurate identification of obesity may be needed to understand the etiology of VTE and to assess the need for and effectiveness of interventions to reduce the risk of VTE among individuals of different races who are obese. With the high prevalence of obesity in the United States [21,81,111], it is likely that the incidence of VTE also will increase with time. Commensurate attention is needed to develop effective VTE prevention strategies aimed at the large population who are obese.

10. ACKNOWLEDGEMENTS

We thank Drs. Michael Soucie, Scott Grosse, and Sheree Boulet for their critical comments on our manuscript.

REFERENCES

- [1] Giuntini, C., Di Ricco, G., Marini, C., Melillo, E. and Palla, A. (1995) Pulmonary embolism: Epidemiology. *Chest*, **107**, 3S-9S. [doi:10.1378/chest.107.1_Supplement.3S](https://doi.org/10.1378/chest.107.1_Supplement.3S)
- [2] Goldhaber, S.Z. (2012) Venous thromboembolism: Epidemiology and magnitude of the problem. *Best Practice & Research Clinical Haematology*, **25**, 235-242. [doi:10.1016/j.beha.2012.06.007](https://doi.org/10.1016/j.beha.2012.06.007)
- [3] Silverstein, M.D., Heit, J.A., Mohr, D.N., Petterson, T.M., O'Fallon, W.M. and Melton, L.J., III. (1998) Trends in the incidence of deep vein thrombosis and pulmonary embolism: A 25-year population-based study. *Archives of Internal Medicine*, **158**, 585-593. [doi:10.1001/archinte.158.6.585](https://doi.org/10.1001/archinte.158.6.585)
- [4] Spencer, F.A., Emery, C., Lessard, D., Anderson, F., Emani, S., Aragam, J., *et al.* (2006) The Worcester venous thromboembolism study: A population-based study of the clinical epidemiology of venous thromboembolism. *Journal of General Internal Medicine*, **21**, 722-727. [doi:10.1111/j.1525-1497.2006.00458.x](https://doi.org/10.1111/j.1525-1497.2006.00458.x)
- [5] White, R.H., Zhou, H., Murin, S. and Harvey, D. (2005) Effect of ethnicity and gender on the incidence of venous thromboembolism in a diverse population in California in 1996. *Journal of Thrombosis and Haemostasis*, **93**, 298-305.
- [6] Kahn, S.R. (2006) Frequency and determinants of the postthrombotic syndrome after venous thromboembolism. *Current Opinion in Pulmonary Medicine*, **12**, 299-303. [doi:10.1097/01.mcp.0000239543.40078.17](https://doi.org/10.1097/01.mcp.0000239543.40078.17)
- [7] Ruppert, A., Steinle, T. and Lees, M. (2011) Economic burden of venous thromboembolism: A systematic review. *Journal of Medical Economics*, **14**, 65-74. [doi:10.3111/13696998.2010.546465](https://doi.org/10.3111/13696998.2010.546465)
- [8] Popkin, B.M., Adair, L.S. and Ng, S.W. (2012) Global nutrition transition and the pandemic of obesity in developing countries. *Nutrition Reviews*, **70**, 3-21. [doi:10.1111/j.1753-4887.2011.00456.x](https://doi.org/10.1111/j.1753-4887.2011.00456.x)
- [9] Schelbert, K.B. (2009) Comorbidities of obesity. *Primary Care*, **36**, 271-285. [doi:10.1016/j.pop.2009.01.009](https://doi.org/10.1016/j.pop.2009.01.009)
- [10] Nejat, E.J., Polotsky, A.J. and Pal, L. (2010) Predictors of chronic disease at midlife and beyond—the health risks of obesity. *Maturitas*, **65**, 106-111. [doi:10.1016/j.maturitas.2009.09.006](https://doi.org/10.1016/j.maturitas.2009.09.006)
- [11] Kahn, S.R. (2011) The post thrombotic syndrome. *Thrombosis Research*, **127**, S89-S92. [doi:10.1016/S0049-3848\(11\)70024-X](https://doi.org/10.1016/S0049-3848(11)70024-X)
- [12] Kim, N.H. and Lang, I.M. (2012) Risk factors for chronic thromboembolic pulmonary hypertension. *European Respiratory Review*, **21**, 27-31. [doi:10.1183/09059180.00009111](https://doi.org/10.1183/09059180.00009111)
- [13] Hardziyenka, M., Campian, M.E., Reesink, H.J., Surie, S., Bouma, B.J., Groenink, M., *et al.* (2011) Right ventricular failure following chronic pressure overload is associated with reduction in left ventricular mass evidence for atrophic remodeling. *Journal of the American College of Cardiology*, **57**, 921-928. [doi:10.1016/j.jacc.2010.08.648](https://doi.org/10.1016/j.jacc.2010.08.648)
- [14] Schulman, S., Lindmarker, P., Holmstrom, M., Larfars, G., Carlsson, A., Nicol, P., *et al.* (2006) Post-thrombotic syndrome, recurrence, and death 10 years after the first episode of venous thromboembolism treated with warfarin for 6 weeks or 6 months. *Journal of Thrombosis and Haemostasis*, **4**, 734-742. [doi:10.1111/j.1538-7836.2006.01795.x](https://doi.org/10.1111/j.1538-7836.2006.01795.x)
- [15] Schneider, D., Lilienfeld, D.E. and Im, W. (2006) The epidemiology of pulmonary embolism: Racial contrasts in incidence and in-hospital case fatality. *National Medical Association*, **98**, 1967-1972.
- [16] Stein, P.D., Kayali, F., Olson, R.E. and Milford, C.E. (2004) Pulmonary thromboembolism in Asians/Pacific Islanders in the United States: Analysis of data from the national hospital discharge survey and the United States bureau of the census. *American Journal of Medicine*, **116**, 435-442. [doi:10.1016/j.amjmed.2003.11.020](https://doi.org/10.1016/j.amjmed.2003.11.020)
- [17] Stein, P.D., Hull, R.D., Kayali, F., Ghali, W.A., Alshab, A.K. and Olson, R.E. (2004) Venous thromboembolism according to age: The impact of an aging population. *Archives of Internal Medicine*, **164**, 2260-2265. [doi:10.1001/archinte.164.20.2260](https://doi.org/10.1001/archinte.164.20.2260)
- [18] Amin, A.N., Varker, H., Princic, N., Lin, J., Thompson, S. and Johnston, S. (2012) Duration of venous thromboembolism risk across a continuum in medically ill hospitalized patients. *Journal of Hospital Medicine*, **7**, 231-238.
- [19] Stein, P.D. and Matta, F. (2010) Epidemiology and incidence: The scope of the problem and risk factors for development of venous thromboembolism. *Clinics in Chest Medicine*, **31**, 611-628. [doi:10.1016/j.ccm.2010.07.001](https://doi.org/10.1016/j.ccm.2010.07.001)
- [20] Barlow, S.E. (2007) Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: Summary

- report. *Pediatrics*, **120**, S164-S192.
[doi:10.1542/peds.2007-2329C](https://doi.org/10.1542/peds.2007-2329C)
- [21] Wang, Y.C., Gortmaker, S.L. and Taveras, E.M. (2011) Trends and racial/ethnic disparities in severe obesity among US children and adolescents, 1976-2006. *International Journal of Pediatric Obesity*, **21**, 176-182.
- [22] Czernichow, S., Kengne, A.P., Stamatakis, E., Hamer, M. and Batty, G.D. (2011) Body mass index, waist circumference and waist-hip ratio: Which is the better discriminator of cardiovascular disease mortality risk?: Evidence from an individual-participant meta-analysis of 82,864 participants from nine cohort studies. *Obesity Reviews*, **12**, 680-687.
- [23] Borch, K.H., Braekkan, S.K., Mathiesen, E.B., Njolstad, I., Wilsgaard, T., Stormer, J., *et al.* (2010) Anthropometric measures of obesity and risk of venous thromboembolism: The Tromso study. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **30**, 121-127.
[doi:10.1161/ATVBAHA.109.188920](https://doi.org/10.1161/ATVBAHA.109.188920)
- [24] Maffeis, C., Banzato, C. and Talamini, G. (2008) Waist-to-height ratio, a useful index to identify high metabolic risk in overweight children. *Journal of Pediatrics*, **152**, 207-213. [doi:10.1016/j.jpeds.2007.09.021](https://doi.org/10.1016/j.jpeds.2007.09.021)
- [25] WHO (2008) Waist circumference and waist-hip ratio: Report of a WHO expert consultation. WHO, Geneva.
http://whqlibdoc.who.int/publications/2011/9789241501491_eng.pdf
- [26] Thomas, E.L., Saeed, N., Hajnal, J.V., Brynes, A., Goldstone, A.P., Frost, G., *et al.* (1998) Magnetic resonance imaging of total body fat. *Journal of Applied Physiology*, **85**, 1778-1785.
- [27] Wang, Z., Heymsfield, S.B., Chen, Z., Zhu, S. and Pierson, R.N. (2010) Estimation of percentage body fat by dual-energy x-ray absorptiometry: Evaluation by *in vivo* human elemental composition. *Physics in Medicine and Biology*, **55**, 2619-2635. [doi:10.1088/0031-9155/55/9/013](https://doi.org/10.1088/0031-9155/55/9/013)
- [28] Jackson, A.S., Stanforth, P.R., Gagnon, J., Rankinen, T., Leon, A.S., Rao, D.C., *et al.* (2002) The effect of sex, age and race on estimating percentage body fat from body mass index: The heritage family study. *International Journal of Obesity and Related Metabolic Disorders*, **26**, 789-796.
- [29] Muth, N.D. (2009) What are the guidelines for percentage of body fat loss? American Council on Exercise (ACE). Ask the Expert Blog.
- [30] Deurenberg, P., Yap, M., van Staveren, W.A. (1998) Body mass index and percent body fat: A meta analysis among different ethnic groups. *International Journal of Obesity and Related Metabolic Disorders*, **22**, 1164-1171.
[doi:10.1038/sj.ijo.0800741](https://doi.org/10.1038/sj.ijo.0800741)
- [31] Ageno, W., Becattini, C., Brighton, T., Selby, R. and Kamphuisen, P.W. (2008) Cardiovascular risk factors and venous thromboembolism: A meta-analysis. *Circulation*, **117**, 93-102. [doi:10.1161/CIRCULATIONAHA.107.709204](https://doi.org/10.1161/CIRCULATIONAHA.107.709204)
- [32] Borch, K.H., Braekkan, S.K., Mathiesen, E.B., Njolstad, I., Wilsgaard, T., Stormer, J., *et al.* (2009) Abdominal obesity is essential for the risk of venous thromboembolism in the metabolic syndrome: The Tromso study. *Journal of Thrombosis and Haemostasis*, **7**, 739-745.
[doi:10.1111/j.1538-7836.2008.03234.x](https://doi.org/10.1111/j.1538-7836.2008.03234.x)
- [33] Steffen, L.M., Cushman, M., Peacock, J.M., Heckbert, S.R., Jacobs, D.R., Jr., Rosamond, W.D., *et al.* (2009) Metabolic syndrome and risk of venous thromboembolism: Longitudinal investigation of thromboembolism etiology. *Journal of Thrombosis and Haemostasis*, **7**, 746-751.
[doi:10.1111/j.1538-7836.2009.03295.x](https://doi.org/10.1111/j.1538-7836.2009.03295.x)
- [34] Kabrhel, C., Varraso, R., Goldhaber, S.Z., Rimm, E.B. and Camargo, C.A. (2009) Prospective study of BMI and the risk of pulmonary embolism in women. *Obesity*, **17**, 2040-2046. [doi:10.1038/oby.2009.92](https://doi.org/10.1038/oby.2009.92)
- [35] Eichinger, S., Hron, G., Bialonczyk, C., Hirschl, M., Minar, E., Wagner, O., *et al.* (2008) Overweight, obesity, and the risk of recurrent venous thromboembolism. *Archives of Internal Medicine*, **168**, 1678-1683.
[doi:10.1001/archinte.168.15.1678](https://doi.org/10.1001/archinte.168.15.1678)
- [36] Severinsen, M.T., Kristensen, S.R., Johnsen, S.P., Dethlefsen, C., Tjonneland, A. and Overvad, K. (2009) Anthropometry, body fat, and venous thromboembolism: A Danish follow-up study. *Circulation*, **120**, 1850-1857.
[doi:10.1161/CIRCULATIONAHA.109.863241](https://doi.org/10.1161/CIRCULATIONAHA.109.863241)
- [37] Finkelstein, E.A., Khavjou, O.A., Thompson, H., Trogon, J.G., Pan, L., Sherry, B., *et al.* (2012) Obesity and severe obesity forecasts through 2030. *American Journal of Preventive Medicine*, **42**, 563-570.
[doi:10.1016/j.amepre.2011.10.026](https://doi.org/10.1016/j.amepre.2011.10.026)
- [38] Garcia-Fuster, M.J., Forner, M.J., Fernandez, C., Gil, J., Vaya, A. and Maldonado, L. (2005) Long-term prospective study of recurrent venous thromboembolism in patients younger than 50 years. *Pathophysiol Haemost Thromb*, **34**, 6-12. [doi:10.1159/000088541](https://doi.org/10.1159/000088541)
- [39] Linnemann, B., Zgouras, D., Schindewolf, M., Schwonberg, J., Jarosch-Preusche, M. and Lindhoff-Last, E. (2008) Impact of sex and traditional cardiovascular risk factors on the risk of recurrent venous thromboembolism: Results from the German MAISTHRO registry. *Blood Coagulation & Fibrinolysis*, **19**, 159-165.
[doi:10.1097/MBC.0b013e3282f54558](https://doi.org/10.1097/MBC.0b013e3282f54558)
- [40] Barba, R., Zapatero, A., Losa, J.E., Valdes, V., Todoli, J.A., Di Micco, P., *et al.* (2008) Body mass index and mortality in patients with acute venous thromboembolism: Findings from the RIETE registry. *Journal of Thrombosis and Haemostasis*, **6**, 595-600.
[doi:10.1111/j.1538-7836.2008.02907.x](https://doi.org/10.1111/j.1538-7836.2008.02907.x)
- [41] Stein, P.D., Matta, F. and Goldman, J. (2011) Obesity and pulmonary embolism: The mounting evidence of risk and the mortality paradox. *Thrombosis Research*, **128**, 518-523. [doi:10.1016/j.thromres.2011.10.019](https://doi.org/10.1016/j.thromres.2011.10.019)
- [42] Kalantar-Zadeh, K., Horwich, T.B., Oreopoulos, A., Kovesdy, C.P., Younessi, H., Anker, S.D., *et al.* (2007) Risk factor paradox in wasting diseases. *Current Opinion in Clinical Nutrition & Metabolic Care*, **10**, 433-442.
[doi:10.1097/MCO.0b013e3281a30594](https://doi.org/10.1097/MCO.0b013e3281a30594)
- [43] Janssen, I. and Bacon, E. (2008) Effect of current and mid-life obesity status on mortality risk in the elderly. *Obesity*, **16**, 2504-2509. [doi:10.1038/oby.2008.400](https://doi.org/10.1038/oby.2008.400)
- [44] Newman, A.B., Yaney, D., Harris, T., Duxbury, A., Enright, P.L. and Fried, L.P. (2001) Weight change in old age and its association with mortality. *Journal of the*

- American Geriatrics Society*, **49**, 1309-1318.
[doi:10.1046/j.1532-5415.2001.49258.x](https://doi.org/10.1046/j.1532-5415.2001.49258.x)
- [45] Sorokin, J.D., Muller, D.C. and Andres, R. (1999) Longitudinal change in height of men and women: Implications for interpretation of the body mass index: The Baltimore longitudinal study of Aging. *American Journal of Epidemiology*, **150**, 969-977.
[doi:10.1093/oxfordjournals.aje.a010106](https://doi.org/10.1093/oxfordjournals.aje.a010106)
- [46] Oreopoulos, A., Kalantar-Zadeh, K., Sharma, A.M. and Fonarow, G.C. (2009) The obesity paradox in the elderly: Potential mechanisms and clinical implications. *Clinics in Geriatric Medicine*, **25**, 643-659.
[doi:10.1016/j.cger.2009.07.005](https://doi.org/10.1016/j.cger.2009.07.005)
- [47] Zamboni, M., Mazzali, G., Zoico, E., Harris, T.B., Meigs, J.B., Di Francesco, V., *et al.* (2005) Health consequences of obesity in the elderly: A review of four unresolved questions. *International Journal of Obesity*, **29**, 1011-1029.
[doi:10.1038/sj.ijo.0803005](https://doi.org/10.1038/sj.ijo.0803005)
- [48] Chang, S.H., Beason, T.S., Hunleth, J.M. and Colditz, G.A. (2012) A systematic review of body fat distribution and mortality in older people. *Maturitas*, **72**, 175-191.
[doi:10.1016/j.maturitas.2012.04.004](https://doi.org/10.1016/j.maturitas.2012.04.004)
- [49] Vaya, A., Martinez-Triguero, M.L., Espana, F., Todoli, J.A., Bonet, E. and Corella, D. (2011) The metabolic syndrome and its individual components: Its association with venous thromboembolism in a Mediterranean population. *Metabolic Syndrome and Related Disorders*, **9**, 197-201.
[doi:10.1089/met.2010.0117](https://doi.org/10.1089/met.2010.0117)
- [50] Eikelboom, J.W. and Weitz, J.I. (2011) Importance of family history as a risk factor for venous thromboembolism. *Circulation*, **124**, 996-997.
[doi:10.1161/CIRCULATIONAHA.111.048868](https://doi.org/10.1161/CIRCULATIONAHA.111.048868)
- [51] Osinbowale, O., Ali, L. and Chi, Y.W. (2010) Venous thromboembolism: A clinical review. *Postgraduate Medicine*, **122**, 54-65. [doi:10.3810/pgm.2010.03.2122](https://doi.org/10.3810/pgm.2010.03.2122)
- [52] Mili, F.D., Hooper, W.C., Lally, C. and Austin, H. (2011) The impact of co-morbid conditions on family history of venous thromboembolism in whites and blacks. *Thrombosis Research*, **127**, 309-316.
[doi:10.1016/j.thromres.2010.12.012](https://doi.org/10.1016/j.thromres.2010.12.012)
- [53] Margaglione, M. and Grandone, E. (2011) Population genetics of venous thromboembolism. A narrative review. *Thrombosis and Haemostasis*, **105**, 221-231.
[doi:10.1160/TH10-08-0510](https://doi.org/10.1160/TH10-08-0510)
- [54] Emmerich, J., Rosendaal, F.R., Cattaneo, M., Margaglione, M., De Stefano, V., Cumming, T., *et al.* (2001) Combined effect of factor V Leiden and prothrombin 20210A on the risk of venous thromboembolism—pooled analysis of 8 case-control studies including 2310 cases and 3204 controls. Study group for pooled-analysis in venous thromboembolism. *Thrombosis and Haemostasis*, **86**, 809-816.
- [55] Delluc, A., Le Moigne, E., Tromeur, C., Noel-Savina, E., Couturaud, F., Mottier, D., *et al.* (2011) Site of venous thromboembolism and prothrombotic mutations according to body mass index. Results from the EDITH study. *British Journal of Haematology*, **154**, 486-491.
[doi:10.1111/j.1365-2141.2011.08592.x](https://doi.org/10.1111/j.1365-2141.2011.08592.x)
- [56] Severinsen, M.T., Overvad, K., Johnsen, S.P., Dethlefsen, C., Madsen, P.H., Tjønneland, A., *et al.* (2010) Genetic susceptibility, smoking, obesity and risk of venous thromboembolism. *British Journal of Haematology*, **149**, 273-279. [doi:10.1111/j.1365-2141.2010.08086.x](https://doi.org/10.1111/j.1365-2141.2010.08086.x)
- [57] Canonico, M., Plu-Bureau, G., Lowe, G.D. and Scarabin, P.Y. (2008) Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: Systematic review and meta-analysis. *British Medical Journal*, **336**, 1227-1231. [doi:10.1136/bmj.39555.441944.BE](https://doi.org/10.1136/bmj.39555.441944.BE)
- [58] Cushman, M., Kuller, L.H., Prentice, R., Rodabough, R.J., Psaty, B.M., Stafford, R.S., *et al.* (2004) Estrogen plus progestin and risk of venous thrombosis. *Journal of the American Medical Association*, **292**, 1573-1580.
[doi:10.1001/jama.292.13.1573](https://doi.org/10.1001/jama.292.13.1573)
- [59] Petitti, D.B. (2003) Clinical practice. Combination estrogen-progestin oral contraceptives. *New England Journal of Medicine*, **349**, 1443-1450.
[doi:10.1056/NEJMc030751](https://doi.org/10.1056/NEJMc030751)
- [60] Ettinger, B., Wang, S.M., Leslie, R.S., Patel, B.V., Bouliware, M.J., Mann, M.E., *et al.* (2011) Evolution of postmenopausal hormone therapy between 2002 and 2009. *Menopause*, **19**, 610-615.
- [61] Davey, D.A. (2012) Update: Estrogen and estrogen plus progestin therapy in the care of women at and after the menopause. *Women's Health*, **8**, 169-189.
[doi:10.2217/whe.12.1](https://doi.org/10.2217/whe.12.1)
- [62] Schmidt, P. (2012) The 2012 hormone therapy position statement of: The North American Menopause Society. *Menopause*, **19**, 257-271.
- [63] Canonico, M., Oger, E., Conard, J., Meyer, G., Levesque, H., Trillot, N., *et al.* (2006) Obesity and risk of venous thromboembolism among postmenopausal women: Differential impact of hormone therapy by route of estrogen administration. The ESTHER study. *Journal of Thrombosis and Haemostasis*, **4**, 1259-1265.
[doi:10.1111/j.1538-7836.2006.01933.x](https://doi.org/10.1111/j.1538-7836.2006.01933.x)
- [64] Goodman, M.P. (2012) Are all estrogens created equal? A review of oral vs. transdermal therapy. *Women's Health*, **21**, 161-169. [doi:10.1089/jwh.2011.2839](https://doi.org/10.1089/jwh.2011.2839)
- [65] Ay, L., Kopp, H.P., Brix, J.M., Ay, C., Quehenberger, P., Scherthaner, G.H., *et al.* (2010) Thrombin generation in morbid obesity: Significant reduction after weight loss. *Journal of Thrombosis and Haemostasis*, **8**, 759-765.
[doi:10.1111/j.1538-7836.2010.03766.x](https://doi.org/10.1111/j.1538-7836.2010.03766.x)
- [66] Rosing, J., Middeldorp, S., Curvers, J., Christella, M., Thomassen, L.G., Nicolaes, G.A., *et al.* (1999) Low-dose oral contraceptives and acquired resistance to activated protein C: A randomised cross-over study. *Lancet*, **354**, 2036-2040. [doi:10.1016/S0140-6736\(99\)06092-4](https://doi.org/10.1016/S0140-6736(99)06092-4)
- [67] Hoibraaten, E., Mowinckel, M.C., de Ronde, H., Bertina, R.M. and Sandset, P.M. (2001) Hormone replacement therapy and acquired resistance to activated protein C: Results of a randomized, double-blind, placebo-controlled trial. *British Journal of Haematology*, **115**, 415-420.
[doi:10.1046/j.1365-2141.2001.03111.x](https://doi.org/10.1046/j.1365-2141.2001.03111.x)
- [68] Middeldorp, S., Meijers, J.C., van den Ende, A.E., van Enk, A., Bouma, B.N., Tans, G., *et al.* (2000) Effects on coagulation of levonorgestrel- and desogestrel-containing low dose oral contraceptives: A cross-over study. *Thrombosis and Haemostasis*, **84**, 4-8.

- [69] Scarabin, P.Y., Alhenc-Gelas, M., Plu-Bureau, G., Taisne, P., Agher, R. and Aiach, M. (1997) Effects of oral and transdermal estrogen/progesterone regimens on blood coagulation and fibrinolysis in postmenopausal women. A randomized controlled trial. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **17**, 3071-3078. doi:10.1161/01.ATV.17.11.3071
- [70] Post, M.S., Christella, M., Thomassen, L.G., van der Mooren, M.J., van Baal, W.M., Rosing, J., *et al.* (2003) Effect of oral and transdermal estrogen replacement therapy on hemostatic variables associated with venous thrombosis: A randomized, placebo-controlled study in postmenopausal women. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **23**, 1116-1121. doi:10.1161/01.ATV.0000074146.36646.C8
- [71] Conard, J., Samama, M., Basdevant, A., Guy-Grand, B. and de Lignieres, B. (1983) Differential AT III-response to oral and parenteral administration of 17 beta-estradiol. *Thrombosis and Haemostasis*, **49**, 252.
- [72] Karim, R., Mack, W.J., Hodis, H.N., Roy, S. and Stanczyk, F.Z. (2009) Influence of age and obesity on serum estradiol, estrone, and sex hormone binding globulin concentrations following oral estrogen administration in postmenopausal women. *Journal of Clinical Endocrinology & Metabolism*, **94**, 4136-4143. doi:10.1210/jc.2009-0643
- [73] O'Rourke, R.W., White, A.E., Metcalf, M.D., Olivas, A.S., Mitra, P., Larison, W.G., *et al.* (2011) Hypoxia-induced inflammatory cytokine secretion in human adipose tissue stromovascular cells. *Diabetologia*, **54**, 1480-1490. doi:10.1007/s00125-011-2103-y
- [74] Tordjman, J., Guerre-Millo, M. and Clement, K. (2008) Adipose tissue inflammation and liver pathology in human obesity. *Diabetes & Metabolism*, **34**, 658-663. doi:10.1016/S1262-3636(08)74601-9
- [75] Subauste, A.R. and Burant, C.F. (2007) Role of FoxO1 in FFA-induced oxidative stress in adipocytes. *American Journal of Physiology Endocrinology and Metabolism*, **293**, E159-E164. doi:10.1152/ajpendo.00629.2006
- [76] Gorlach, A. (2005) Redox regulation of the coagulation cascade. *Antioxidants & Redox Signaling*, **7**, 1398-1404. doi:10.1089/ars.2005.7.1398
- [77] Kalupahana, N.S. and Moustaid-Moussa, N. (2012) The renin-angiotensin system: A link between obesity, inflammation and insulin resistance. *Obesity Reviews*, **13**, 136-149. doi:10.1111/j.1467-789X.2011.00942.x
- [78] Miyagawa, R., Asakura, T., Nakamura, T., Okada, H., Iwaki, S., Sobel, B.E., *et al.* (2010) Increased expression of plasminogen activator inhibitor type-1 (PAI-1) in HEPG2 cells induced by insulin mediated by the 3'-untranslated region of the PAI-1 gene and its pharmacologic implications. *Coronary Artery Disease*, **21**, 144-150. doi:10.1097/MCA.0b013e328335790e
- [79] Meerarani, P., Badimon, J.J., Zias, E., Fuster, V. and Moreno, P.R. (2006) Metabolic syndrome and diabetic atherosclerosis: Implications in vascular complications. *Current Molecular Medicine*, **6**, 501-514. doi:10.2174/156652406778018680
- [80] Van Schouwenburg, I.M., Mahmoodi, B.K., Veeger, N.J.G.M., Bakker, S.J.L., Meijer, K., *et al.* (2012) Insulin resistance and risk of venous thromboembolism: Results of a population-based cohort study. *Journal of Thrombosis and Haemostasis*, **10**, 1012-1018. doi:10.1111/j.1538-7836.2012.04707.x
- [81] Sturm, R. (2007) Increases in morbid obesity in the USA: 2000-2005. *Public Health*, **121**, 492-496. doi:10.1016/j.puhe.2007.01.006
- [82] Lindahl, B., Nilsson, T.K., Jansson, J.H., Asplund, K. and Hallmans, G. (1999) Improved fibrinolysis by intense lifestyle intervention. A randomized trial in subjects with impaired glucose tolerance. *Journal of Internal Medicine*, **246**, 105-112. doi:10.1046/j.1365-2796.1999.00537.x
- [83] Van Guilder, G.P., Hoetzer, G.L., Smith, D.T., Irmiger, H.M., Greiner, J.J., Stauffer, B.L., *et al.* (2005) Endothelial t-PA release is impaired in overweight and obese adults but can be improved with regular aerobic exercise. *American Journal of Physiology Endocrinology and Metabolism*, **289**, E807-E813. doi:10.1152/ajpendo.00072.2005
- [84] Lutsey, P.L., Virnig, B.A., Durham, S.B., Steffen, L.M., Hirsch, A.T., Jacobs Jr., D.R., *et al.* (2010) Correlates and consequences of venous thromboembolism: The Iowa Women's Health Study. *American Journal of Public Health*, **100**, 1506-1513. doi:10.2105/AJPH.2008.157776
- [85] Tsai, A.W., Cushman, M., Rosamond, W.D., Heckbert, S.R., Polak, J.F. and Folsom, A.R. (2002) Cardiovascular risk factors and venous thromboembolism incidence: The longitudinal investigation of thromboembolism etiology. *Archives of Internal Medicine*, **162**, 1182-1189. doi:10.1001/archinte.162.10.1182
- [86] Borch, K.H., Hansen-Krone, I., Braekkan, S.K., Mathiesen, E.B., Njolstad, I., Wilsgaard, T., *et al.* (2010) Physical activity and risk of venous thromboembolism. The Tromso study. *Haematologica*, **95**, 2088-2094. doi:10.3324/haematol.2009.020305
- [87] Glynn, R.J. and Rosner, B. (2005) Comparison of risk factors for the competing risks of coronary heart disease, stroke, and venous thromboembolism. *American Journal of Epidemiology*, **162**, 975-982. doi:10.1093/aje/kwi309
- [88] Varraso, R., Kabrhel, C., Goldhaber, S.Z., Rimm, E.B. and Camargo, C.A., Jr. (2012) Prospective study of diet and venous thromboembolism in US women and men. *American Journal of Epidemiology*, **175**, 114-126. doi:10.1093/aje/kwr377
- [89] Glynn, R.J., Ridker, P.M., Goldhaber, S.Z., Zee, R.Y. and Buring, J.E. (2007) Effects of random allocation to vitamin E supplementation on the occurrence of venous thromboembolism: Report from the women's health study. *Circulation*, **116**, 1497-1503. doi:10.1161/CIRCULATIONAHA.107.716407
- [90] Steffen, L.M., Folsom, A.R., Cushman, M., Jacobs, D.R., Jr. and Rosamond, W.D. (2007) Greater fish, fruit, and vegetable intakes are related to lower incidence of venous thromboembolism: The longitudinal investigation of thromboembolism etiology. *Circulation*, **115**, 188-195. doi:10.1161/CIRCULATIONAHA.106.641688
- [91] Lutsey, P.L., Steffen, L.M., Virnig, B.A. and Folsom, A.R. (2009) Diet and incident venous thromboembolism: The Iowa women's health study. *American Heart Journal*, **157**,

- 1081-1087. [doi:10.1016/j.ahj.2009.04.003](https://doi.org/10.1016/j.ahj.2009.04.003)
- [92] Booyse, F.M., Pan, W., Grenett, H.E., Parks, D.A., Darley-Usmar, V.M., Bradley, K.M., *et al.* (2007) Mechanism by which alcohol and wine polyphenols affect coronary heart disease risk. *Annals of Epidemiology*, **17**, S24-S31. [doi:10.1016/j.annepidem.2007.01.006](https://doi.org/10.1016/j.annepidem.2007.01.006)
- [93] Canali, R., Ambra, R., Stelitano, C., Mattivi, F., Scaccini, C. and Virgili, F. (2007) A novel model to study the biological effects of red wine at the molecular level. *British Journal of Nutrition*, **97**, 1053-1058. [doi:10.1017/S0007114507657870](https://doi.org/10.1017/S0007114507657870)
- [94] Ridker, P.M., Vaughan, D.E., Stampfer, M.J., Glynn, R.J. and Hennekens, C.H. (1994) Association of moderate alcohol consumption and plasma concentration of endogenous tissue-type plasminogen activator. *Journal of the American Medical Association*, **272**, 929-933. [doi:10.1001/jama.1994.03520120039028](https://doi.org/10.1001/jama.1994.03520120039028)
- [95] Lindqvist, P.G., Epstein, E. and Olsson, H. (2009) The relationship between lifestyle factors and venous thromboembolism among women: A report from the MISS study. *British Journal of Haematology*, **144**, 234-240. [doi:10.1111/j.1365-2141.2008.07460.x](https://doi.org/10.1111/j.1365-2141.2008.07460.x)
- [96] Wattanakit, K., Lutsey, P.L., Bell, E.J., Gornik, H.,ushman, M., Heckbert, S.R., *et al.* (2012) Association between cardiovascular disease risk factors and occurrence of venous thromboembolism. A time-dependent analysis. *Thrombosis and Haemostasis*, **108**, 291-302.
- [97] Hansen-Krone, I.J., Braekkan, S.K., Enga, K.F., Wilsgaard, T. and Hansen, J.B. (2011) Alcohol consumption, types of alcoholic beverages and risk of venous thromboembolism—The Tromso study. *Thrombosis and Haemostasis*, **106**, 272-278. [doi:10.1160/TH11-01-0043](https://doi.org/10.1160/TH11-01-0043)
- [98] Sharif-Kashani, B., Shahabi, P., Raeissi, S., Behzadnia, N., Shoaraka, A., Shahrivari, M., *et al.* (2012) Assessment of PRophylaxis for venous thromboembolism in hospitalized patients: The MASIH study. *Clinical and Applied Thrombosis/Hemostasis*, **18**, 462-468.
- [99] Freeman, A.L., Pendleton, R.C. and Rondina, M.T. (2010) Prevention of venous thromboembolism in obesity. *Expert Review of Cardiovascular Therapy*, **8**, 1711-1721. [doi:10.1586/erc.10.160](https://doi.org/10.1586/erc.10.160)
- [100] Guyatt, G.H., Akl, E.A., Crowther, M., Gutterman, D.D. and Schunemann, H.J. (2012) Executive summary: Antithrombotic therapy and prevention of thrombosis, 9th ed. American college of chest physicians evidence-based clinical practice guidelines. *Chest*, **141**, 7S-47S.
- [101] Lewis, T.V., Johnson, P.N., Nebbia, A.M. and Dunlap, M. (2011) Increased enoxaparin dosing is required for obese children. *Pediatrics*, **127**, e787-e790. [doi:10.1542/peds.2010-0746](https://doi.org/10.1542/peds.2010-0746)
- [102] Roth-Yelinek, B. (2012) Venous thromboembolism prophylaxis of acutely ill hospitalized medical patients. Are we under-treating our patients? *European Journal of Internal Medicine*, **23**, 236-239. [doi:10.1016/j.ejim.2011.11.005](https://doi.org/10.1016/j.ejim.2011.11.005)
- [103] Brunelli, A. (2012) Deep vein thrombosis/pulmonary embolism: Prophylaxis, diagnosis, and management. *Thoracic Surgery Clinics*, **22**, 25-28. [doi:10.1016/j.thorsurg.2011.08.014](https://doi.org/10.1016/j.thorsurg.2011.08.014)
- [104] Masoomi, H., Buchberg, B., Reavis, K.M., Mills, S.D., Stamos, M. and Nguyen, N.T. (2011) Factors predictive of venous thromboembolism in bariatric surgery. *American Journal of Surgery*, **77**, 1403-1406.
- [105] Borch, K.H., Nyegaard, C., Hansen, J.B., Mathiesen, E.B., Njolstad, I., Wilsgaard, T., *et al.* (2011) Joint effects of obesity and body height on the risk of venous thromboembolism: The Tromso study. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **31**, 1439-1444. [doi:10.1161/ATVBAHA.110.218925](https://doi.org/10.1161/ATVBAHA.110.218925)
- [106] Pomp, E.R., le Cessie, S., Rosendaal, F.R. and Doggen, C.J. (2007) Risk of venous thrombosis: Obesity and its joint effect with oral contraceptive use and prothrombotic mutations. *British Journal of Haematology*, **139**, 289-296. [doi:10.1111/j.1365-2141.2007.06780.x](https://doi.org/10.1111/j.1365-2141.2007.06780.x)
- [107] Braekkan, S.K., Borch, K.H., Mathiesen, E.B., Njolstad, I., Wilsgaard, T. and Hansen, J.B. (2010) Body height and risk of venous thromboembolism: The Tromso study. *American Journal of Epidemiology*, **171**, 1109-1115. [doi:10.1093/aje/kwq066](https://doi.org/10.1093/aje/kwq066)
- [108] Correia, M.L. and Haynes, W.G. (2006) A role for plasminogen activator inhibitor-1 in obesity: From pie to PAI? *Arteriosclerosis, Thrombosis, and Vascular Biology*, **26**, 2183-2185. [doi:10.1161/01.ATV.0000244018.24120.70](https://doi.org/10.1161/01.ATV.0000244018.24120.70)
- [109] Polednak, A.P. (2012) US mortality from liver cirrhosis and alcoholic liver disease in 1999-2004: Regional and state variation in relation to per capita alcohol consumption. *Substance Use & Misuse*, **47**, 202-213. [doi:10.3109/10826084.2011.635462](https://doi.org/10.3109/10826084.2011.635462)
- [110] Ali, M., Ananthkrishnan, A.N., McGinley, E.L. and Saeian, K. (2011) Deep vein thrombosis and pulmonary embolism in hospitalized patients with cirrhosis: A nationwide analysis. *Digestive Diseases and Sciences*, **56**, 2152-2159. [doi:10.1007/s10620-011-1582-5](https://doi.org/10.1007/s10620-011-1582-5)
- [111] Ogden, C.L., Carroll, M.D., Kit, B.K. and Flegal, K.M. (2012) Prevalence of obesity in the United States, 2009-2010. *NCHS Data Brief*, **56**, 1-8.