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CONTEMPORARY REVIEW

Exploring Opportunities for Primary Prevention of Unprovoked Venous Thromboembolism: Ready for Prime Time?

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ABSTRACT: Venous thromboembolism (VTE) is an important vascular disease and public health problem. Prevention of VTE has focused mainly on using thromboprophylaxis to avoid provoked VTE or recurrent VTE, with little attention paid to the possibility of preventing the one third to one half of VTEs that are unprovoked. We review growing research suggesting that unhealthy lifestyle risk factors may cause a considerable proportion of unprovoked VTE. Using epidemiologic data to calculate population attributable risks, we estimate that in the United States obesity may contribute to 30% of VTEs, physical inactivity to 4%, current smoking to 3%, and Western dietary pattern to 11%. We also review possibilities for VTE primary prevention either through a high-risk individual approach or a population-wide approach. Interventions for outpatients at high VTE risk but without VTE provoking factors have not been fully tested; yet, improving patient awareness of risk and symptoms, lifestyle counseling, and possibly statins or direct oral anticoagulants may prove useful in primary prevention of unprovoked VTE. A population approach to prevention would bolster awareness of VTE and aim to shift lifestyle risk factors downward in the whole population using education, environmental changes, and policy. Assuming the epidemiological associations are accurate, causal, and independent of each other, a reduction of obesity, physical inactivity, current smoking, and Western diet by 25% in the general population might reduce the incidence of unprovoked VTE by 12%. We urge further research and consideration that primary prevention of unprovoked VTE may be a worthwhile public health aim.

Key Words: primary prevention ■ pulmonary embolus ■ venous thromboembolism ■ venous thrombosis

Venous thromboembolism (VTE), comprising deep vein thrombosis and pulmonary embolism, is a major health burden. Annually in the United States there are an estimated 857 000 deaths from deep vein thrombosis, 370 000 from pulmonary embolisms, and 52 000 with VTE among the listed causes of death.[1] The lifetime VTE risk is 1 in 12 US adults.[2] Care of each VTE costs $18 000 to $23 000,[3] for $7 to $10 billion in US total annual cost.

Depending on the population and definition,[4] approximately one half to two thirds of VTEs have strong triggering or persistent risk factors and are classified as "provoked."[1] The remaining one third to one half are classified as "unprovoked," as they occur without warning or identifiable causes, typically outside of a medical setting. Major identified causes of VTE include inherited traits (eg, thrombophilias, such as factor V Leiden or prothrombin G20210A mutation), acquired long-term risk factors (eg, relative immobility, cancer, inflammatory conditions, obesity), and acute triggers (eg, hospitalization, surgery, immobilization, pregnancy/puerperium, long distance travel).[5,6] Lifestyle factors have generally been considered minor contributors to VTE.

There are established clinical guidelines and methods—the foremost involving anticoagulation—used to treat acute VTE, prevent recurrence, and prevent provoked VTE in high-risk medical settings.[7–12] Although there are calls to action to prevent VTE from advocacy organizations[9] and the US Surgeon

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Nonstandard Abbreviations and Acronyms

ACC-AHA	American College of Cardiology-American Heart Association
AHA	American Heart Association
ARIC	Atherosclerosis Risk in Communities study
ERFC	Emerging Risk Factors Collaboration
LS7	Life's Simple 7
UKB	UK Biobank Study

General,[13] current strategies for preventing VTE fail to address the one third to one half of VTEs that are unprovoked. Herein, we review recent research relevant to primary prevention of unprovoked VTE. First, we review growing evidence for modifiable lifestyle factors being risk factors for VTE. We cite heavily relative risks from several of the most comprehensive large US or UK prospective cohorts, consortia of cohorts, or meta-analyses, as these publications generally provide stable relative risk estimates. Where relative risk information was less available and diverse (eg, for diet and VTE), we searched online databases and reference lists for published articles. Where possible, we cite the most recent US data for population risk factor prevalences. Second, after summarizing general concepts of primary prevention, we address specifically whether more emphasis should be devoted to the primary prevention of unprovoked VTE. Because few relevant clinical or community trials on primary prevention of VTE are available, we again relied heavily on inferences from prospective studies.

LIFESTYLE RISK FACTORS FOR VTE

Primary prevention of unprovoked VTE might rely fundamentally on healthy lifestyle. Epidemiologic research on lifestyle risk factors for VTE in the general population has grown steadily. One of the largest and most recent reports was the combined ERFC (Emerging Risk Factors Collaboration) and UKB (UK Biobank) study, together totaling 1.1 million participants.[14] This pooled prospective investigation used administrative data to examine risk factors for either incident VTE (in the UKB) or fatal VTE (in the ERFC). Of relevance to our review, this large study found risk factor hazard ratios (HRs) to be largely similar between unprovoked and provoked VTE.

Obesity

Adiposity consistently shows a positive, dose-response association with incidence of VTE. The HRs per 1-SD higher body mass index (BMI) were 1.43 (95% CI, 1.35–1.50) for fatal VTE in the ERFC and 1.37 (95% CI, 1.32–1.41) for all incident VTE in the UKB.[14] LITE (Longitudinal Investigation of Thromboembolism Etiology) reported a comparable HR per 1-SD of BMI (1.3 [95% CI, 1.2–1.5]), similar for unprovoked and provoked VTE.[15]

Obesity, defined as BMI ≥30 kg/m^2, approximately doubles the risk of VTE.[16] The prevalence of obesity is substantial—42.4% in the United States,[17] such that population attributable risk calculations based on a doubling of VTE risk suggest that obesity may explain 30% of all VTEs in the United States (Table 1).

Mendelian randomization studies indicate that obesity is likely a true cause of VTE.[21,22] The most likely direct mechanisms are venous stasis and elevated hemostatic and inflammatory factors,[16] but obesity also contributes to other chronic conditions (eg, cancer) that increase VTE risk. Although there are no large randomized clinical trials to prove that weight loss can reduce VTE risk, observational studies show conclusively that avoiding obesity prevents VTE, and preventing excessive weight gain may be an effective way to reduce VTE risk. For example, the Tromsø Study (n=17 802, with 302 incident VTEs over median of 6 years) reported that subjects who gained most weight (7.5–40.0 kg) had a 1.92-fold higher risk of VTE (95% CI, 1.38–2.68) compared with those with no or a moderate (0–7.4 kg) weight gain.[23] Similarly, among 9710 participants in the ARIC (Atherosclerosis Risk in Communities) study with 529 incident VTEs, those in the highest quintile of 9-year weight change (>7.71 kg) had a 1.46-fold (95% CI, 1.09–1.95) higher risk of incident VTE over an average of 19 years follow-up compared with those whose weight gain was –1.81 to +1.36 kg.[24]

Physical Inactivity

A thorough 2018 review reported that approximately half of 11 epidemiologic studies found that physically active adults had lower risk of VTE compared with inactive adults. The review concluded that physical activity may modestly reduce the risk of incident VTE but not in a dose-dependent manner.[25] Plausible mechanisms

Table 1. Lifestyle Risk Factors for Venous Thromboembolism

Risk Factor	Prevalence (P)*	Relative Risk (RR)†	Population Attributable Risk (PAR)‡
Obesity	42.4%	2	30%
Physical inactivity	25.4%	1.15	4%
Current smoking	13.7%	1.23	3%
Western diet pattern	20%	1.6	11%

*Sources: 2017–2018 US obesity,[17] 2018 US physical activity,[18] 2018 US smoking,[19] Western diet pattern.[20]

†Sources: see text.

‡PAR=[P(RR–1)/[1+P(RR–1)].

suggested include beneficial effects of physical activity on the venous endothelium, blood flow, blood rheology, and hemostasis. A 2019 systematic review and meta-analysis of 14 epidemiologic studies estimated the relative risk of VTE was 13% lower for those with high habitual physical activity compared with low physical activity (relative risk=0.87 [0.79–0.95]).[26] Using population attributable risk estimation, if the relative risk of low physical activity is 1.15 (taking the reciprocal of 0.87) and its prevalence is 25.4%,[18] then 4% of VTE risk might be attributable to habitual physical inactivity (Table 1).

Immobility—for example, from paresis, bed rest, or fracture treatment—is a strong and well-established risk factor for VTE, carrying a relative risk >5.[27,28] Less extreme sedentariness also seems to increase risk of VTE, as evidenced by episodic long-distance travel being a VTE trigger with a pooled relative risk of 2.8 (95% CI, 2.2–3.7) for travelers versus nontravelers in a 2009 meta-analysis and an 18% higher risk for VTE for each 2-hour increase in duration of travel (P=0.01).[29] In addition, habitual sitting at work or from TV watching is a moderate long-term VTE risk factor.[30–32] For example, the frequency of TV viewing in the ARIC study (299 767 person-years of follow-up and 691 VTE) showed a positive dose-response relation with VTE incidence (P for trend=0.04), in which "very often" viewing TV carried 1.71 (95% CI, 1.26–2.32) times the risk of VTE compared with "never or seldom" viewing TV. Even among individuals who met a recommended level of physical activity, viewing TV "very often" carried 1.80 (1.04–3.09) times the risk of VTE, compared with viewing TV "never or seldom."[30] Although there is no large-scale randomized clinical trial proof, observational data suggest that reducing sedentary time should modestly reduce the risk of unprovoked VTE.

Diet

Research has linked various dietary components with makers of coagulation and inflammation, providing rationale that diet should affect VTE occurrence. Yet, observational studies of diet and VTE itself are difficult to interpret because of low between-person variability and high within-person variability in diet, general difficulty in measuring diet, inconsistent dietary components studied (eg, foods, nutrients, patterns), and other methodologic issues. We found only 11 epidemiologic reports from 1 case-control and 8 cohort studies addressing diet and VTE,[20,33–42] and results were mostly inconsistent. The foods most strongly associated with VTE were fish or n-3 fatty acids (inversely), coffee (inversely), and red and processed meat (positively). Fruit and vegetable intake showed inverse associations with VTE in approximately half of existing studies but no associations in the remainder.

Among 3 studies of dietary patterns and VTE risk, 2 found a "Western" dietary pattern associated positively with VTE whereas the other found an inverse association. The same 3 studies found no association of a "prudent" diet with VTE. For example, the ARIC study reported a relative risk of noncancer VTE over 12 years of follow-up for the highest versus lowest quintile of the Western dietary pattern to be 1.60 (95% CI, 0.97–2.66 and P trend=0.04).[20] The corresponding relative hazard for a prudent dietary pattern was 0.69 (95% CI, 0.44–1.09 and P trend=0.12). These HRs for ARIC have persisted, with smaller P values, after longer follow-up (unpublished). Using the ARIC estimate that the 20% of participants with the most Western diet pattern had a relative risk of VTE of 1.6, then Western diet might explain up to 11% of VTE in the US population (Table 1).

The Dutch component of the European Prospective Investigation into Cancer and Nutrition is the only study of the Mediterranean diet and VTE. Using a Mediterranean Diet Score (range 0–9) derived from a validated food-frequency questionnaire in a cohort of 34 708, a 2-unit stronger Mediterranean dietary score was associated with 0.74-fold lower pulmonary embolism risk (95% CI, 0.59–0.92), suggesting it might also prevent VTE.[37] A single study reported the Dietary Approaches to Stop Hypertension dietary pattern, which lowers blood pressure,[43] was not associated with VTE.[38] There are no randomized clinical trials to prove that specific dietary patterns or foods can reduce risk of VTE.

Intakes of individual nutrients have for the most part not been associated with VTE. A recent meta-analysis of 10 prospective studies with a total of 441 128 individuals and 10 221 VTE cases found no association of alcohol intake with VTE.[44] However, the review did not include a report that alcohol drinking (current versus other) was associated with reduced risk of fatal VTE in the ERFC (HR, 0.82; 95% CI, 0.71–0.94) and with incident VTE in the UKB (HR, 0.75; 95% CI, 0.61–0.93).[14] A clinical trial to evaluate whether moderate alcohol might prevent unprovoked VTE is certainly not feasible, as any effect of alcohol on VTE likely would be modest and carry other risks.

A randomized 10-year clinical trial demonstrated that 600 IU vitamin E every other day reduced VTE 21% compared with placebo in healthy women.[45] This trial has not been replicated, and there is other, albeit inconsistent, trial evidence that vitamin E doses at this level may increase risk of prostate cancer, total mortality, or other adverse outcomes. Thus, advocating vitamin E supplementation to prevent unprovoked VTE remains speculative.

Cigarette Smoking

Epidemiologic studies show that current smoking is associated with modestly increased risk of VTE, most directly via hypercoagulability or endothelial damage or over the long term by increasing other chronic diseases.

The HR for current smoking compared with nonsmoking in the ERFC was 1.38 (95% CI, 1.20–1.58) and was 1.23 (95% CI, 1.08–1.40) in the UKB.[14] The association was similar for unprovoked and provoked VTE in UKB.

An earlier 2014 meta-analysis of 32 observational studies of 4 million participants reported a similar, modest positive association, similar for provoked and unprovoked VTE.[46] Compared with never smokers, the overall combined relative risks for developing VTE were 1.17 (95% CI, 1.09–1.25) for ever smokers, 1.23 (95% CI, 1.14–1.33) for current smokers, and 1.10 (95% CI, 1.03–1.17) for former smokers. The risk of VTE was 10.2% (95% CI, 8.6%–11.8%) higher for every additional 10 cigarettes per day smoked or 6.1% (95% CI 3.8%–8.5%) higher for every additional 10 pack-years. Using the relative risk of 1.23 for current smoking, which is prevalent in 13.7% of US adults,[19] the population attributable risk is 3% suggesting smoking avoidance should modestly reduce unprovoked VTE risk (Table 1).

Other Individual Lifestyle-Related Health Characteristics

Most prospective studies, including the ERFC and UKB[14] and another large consortium,[16] have found no appreciable associations of diabetes mellitus, hypertension, or hypercholesterolemia with VTE. Yet, a large Mendelian randomization study suggested that hypercholesterolemia may, in fact, increase VTE risk.[47] Statins seem to moderately reduce VTE risk, although, because they improve procoagulant profile and lower inflammation,[48] it is unclear whether this is owing to their cholesterol lowering effect.

Multiple Lifestyle Characteristics Considered Together

The American Heart Association (AHA) has promoted "Life's Simple 7" (LS7) for primary prevention of cardiovascular disease (CVD).[49] LS7 assigns ideal, intermediate, and poor levels to 7 CVD health factors: smoking, BMI, diet, physical activity, blood pressure, blood cholesterol, and glycemia. Three prospective studies have confirmed that a greater number of ideal LS7 components is strongly associated with reduced risk of VTE.[50–52] For example, in the ARIC study,[51] HRs of VTE between 1987 and 2011 for 0 to 1, 2, 3, 4, 5, or 6 to 7 ideal LS7 components were 1 (reference), 1.00, 0.91, 0.64, 0.41, and 0.54 (*P* trend <0.001) (see also Figure 1). Thus, an optimal overall lifestyle pattern may greatly reduce the risk of unprovoked VTE.

Socioeconomic and Race/Ethnic Disparities in VTE

Incidence rates of VTE in the United States are 70% lower in Asian American people than White people, 50% lower in Hispanic people than White people, but

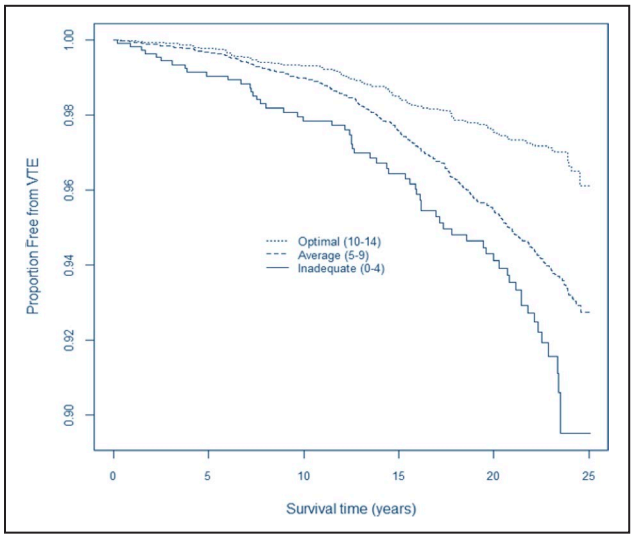

Figure 1. Cumulative incidence of venous thromboembolism (VTE) in relation to 3 categories of a Life's Simple 7 Score, ARIC (Atherosclerosis Risk in Communities) study, 1987 to 2011.
Reprinted from Folsom et al[51] with permission. Copyright ©2015, John Wiley and Sons.

are 30% to 100% higher in Black people than White people.[53,54] Lifetime risk of VTE (provoked plus unprovoked) in the ARIC study was 11.5% in Black people but 6.9% in White people. Race is mainly a sociocultural construct,[55] and therefore root causes of the higher VTE rate in Black people may include social disadvantages, racist policies, healthcare inequities, and cultural influences that affect lifestyle-determined VTE risk factors (eg, diet, physical inactivity, obesity). In the ARIC study, the nearly 2-fold higher incidence rate of VTE in Black people than White people appeared largely explained by higher BMI, lower family income, and higher factor VIII concentrations in Black people, and not by ethnic differences in the frequencies of 5 major genetic variants for VTE. Others have pointed out health disparities in VTE care, for example, patients with VTE who had lower income were less likely to fill prescriptions for direct oral anticoagulants.[56] In another study, Black patients were less often given VTE pharmacoprophylaxis in hospital.[57] Thus, socioeconomic and race/ethnic disparities, including structural racism, warrant due consideration in strategies of primary prevention of unprovoked VTE.

CONCEPTS OF PRIMARY PREVENTION

Primary prevention of disease entails reducing incident (or first) events to reduce the burden of disease in the population. Geoffrey Rose distinguished 2 complementary approaches to primary prevention, often termed the "high-risk" and "population" approaches.[58]

The 2 approaches focus on downward shifts of different parts of the distribution of disease risk in the population (Figure 2). The strategy for the high-risk approach is to screen for risk factors in each individual to distinguish those having an actionable level of risk, and then to provide individual interventions to reduce modifiable causes of the target disease. Potential interventions might include raising awareness, prescribing medication, lifestyle counseling, vaccination, and so forth. The high-risk approach often can greatly reduce the target disease in the high-risk group; yet, if the high-risk group represents a small proportion of the general population, their risk factor reduction may have a limited impact on the overall incidence the disease.

The strategy for the population approach, in contrast, is to intervene broadly to shift lifestyle norms to prevent or reduce risk factors for disease in the entire population. Interventions typically encompass public health approaches and population-wide promotion of healthy lifestyle through education, environmental changes, or policies. Because the entire population is targeted, an advantage of the population approach is to not require screening to assess disease risk of every person in every generation. Notably, even small improvements in highly common risk factors in the entire population often can have a big impact in the incidence of the target disease.

Which general primary prevention approaches to pursue (high risk versus population versus both) and which specific interventions to adopt depend on several epidemiologic characteristics. These include the incidence rate, fatality, and importance of the target disease; the existence of risk markers by which to estimate risk of the disease; the frequency and modifiability of the target causes of disease; evidence that risk factor modifications can reduce the disease; and the risk-benefit, cost-benefit, acceptability, and equity of potential interventions. Of course, the high-risk and population approaches are not mutually exclusive and can be complementary in prevention.

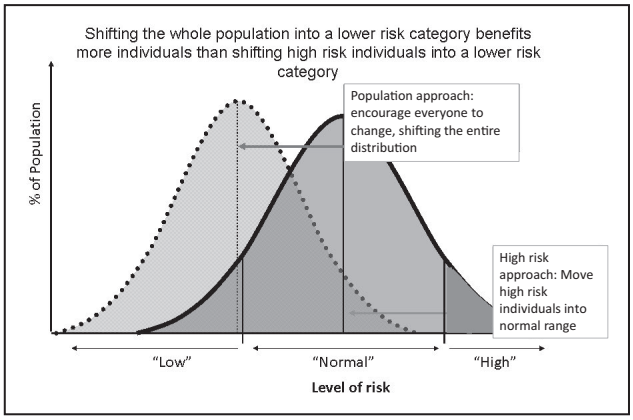

Figure 2. Primary prevention by the population approach vs the high-risk approach.

Atherosclerotic CVD offers a good example of the rationale and strategy for primary prevention. CVD is common and is the leading cause of death in many countries. Epidemiologic studies identified frequent and likely causal major risk factors (age, hypertension, cigarette smoking, hypercholesterolemia, diabetes mellitus), and yielded equations to identify high CVD risk and target interventions. Randomized primary prevention trials in high-risk individuals demonstrated that control of hypertension, hypercholesterolemia, and smoking decrease CVD incidence rates, with acceptable risk- and cost-benefit ratios. Furthermore, population-wide approaches using cardiovascular health promotion in the general population have proved cost effective. Current professional guidelines to prevent CVD advocate both high-risk and population strategies. These prevention strategies, along with improved treatment of CVD, have contributed to the major decline in CVD incidence and death rates over the past 4 decades.

Table 2 summarizes in the first 2 rows the clinically accepted strategy toward VTE prevention, which is currently focused only on preventing provoked or recurrent VTE. These quite high-risk patients are readily identified and treated, but represent a small proportion of the entire population at risk. The high-risk strategy for preventing unprovoked VTE (third row in Table 2) would target a larger proportion of the population that is at lower VTE risk and more difficult to identify. The population approach to prevent unprovoked VTE (fourth row) targets the entire population, because much of the population is at some risk of VTE by virtue of unhealthy lifestyles. All 4 approaches are potentially useful, but little focus has been paid previously to primary prevention of unprovoked VTE.

CONSIDERATIONS FOR A HIGH-RISK APPROACH TO PRIMARY PREVENTION OF UNPROVOKED VTE

Before considering the high-risk strategy for unprovoked VTE, several questions should be addressed.

Can We Actually Identify People at "High Risk" of Unprovoked VTE in the General Population to Justify Widespread Risk Estimation?

There currently is no widely accepted method to accurately estimate risk of unprovoked VTE. Ideally, the method to estimate risk would use routinely collected clinical data that might even be available in electronic health records or be simple to apply to large-scale screening of the general population. Some risk scoring methods to consider might be a strong family history

Table 2. Targets, Goals, and Strategies of Venous Thromboembolism Prevention

Target Population	Population Size	VTE Risk	Prevention Goal	Strategy
Patients after acute VTE	Small	High	Prevent VTE recurrence and complications	Identify high risk of VTE recurrence per existing clinical algorithms (eg, Refs 10, 11); pharmacoprophylaxis per clinical guidelines
High-risk patients (eg, cancer, some genetic thrombophilias, or VTE triggers)	Medium	Moderate	Prevent first provoked VTE	Identify high risk of VTE per existing clinical algorithms (eg, Ref 12); pharmacoprophylaxis per clinical guidelines
High estimated VTE risk in the general population	Medium	Low	Prevent first unprovoked VTE	Identify high risk of unprovoked VTE (risk score needed); increase awareness, lifestyle counseling/behavior modification, pharmacoprophylaxis?
General population	Very large	Very low	Lower the population-wide rate of unprovoked VTE	Population/public health approach to everyone via education, environmental modification, policies

VTE indicates venous thromboembolism.

of VTE; carriage of 1 or more thrombophilic mutations or an elevated polygenetic VTE risk score; an elevated American College of Cardiology (ACC)-AHA 10-year risk of CVD; a low AHA's LS7 score; or some combination of these. Some recent observational studies have evaluated how strongly these predict VTE risk, but evidence remains sparse on their clinical utility.

Family History of VTE

Epidemiologic studies have documented that a history of VTE in first-degree relatives is a moderate risk factor for VTE. For example, a large Dutch case-control study found that a history of VTE in 1 first-degree relative increased risk of VTE 2.2-fold (1.9–2.6) and 3.9-fold (2.7–5.7) when more than 1 relative was affected.[59] A nationwide family study in Sweden reported that a family history increased the risk of recurrent unprovoked VTE hospitalization by 1.20-fold (95% CI, 1.10–1.32) for individuals with affected parents, 1.30-fold (95% CI, 1.14–1.49) for those with affected siblings, and 1.92-fold (95% CI, 1.44–2.58) for individuals with 2 affected parents.[60] A recent review concluded that a first-degree family history of VTE increases VTE risk 2- to 3-fold.[61] History of VTE in a first-degree relative is common (possibly 5%–10%) and perhaps easily assessed in clinical settings. It could be a means of identifying patients at moderately high risk of unprovoked VTE, especially if the general population were more aware of VTE and could accurately report family history.

Carrying Known Thrombophilic Variant(s) or High VTE Genetic Risk Score

Classical thrombophilias, such as resistance to activated protein C or deficiencies of antithrombin, protein C, or protein S, substantially increase VTE risk, but their rarity makes population-wide screening for them currently impractical. Genome-wide screening is becoming cheaper and may someday be used on a population-wide basis, for example, to identify risks of adult diseases in childhood. Meanwhile, epidemiologic studies have developed polygenic risk scores to discriminate and predict risk of VTE. The first, by de Haan et al, demonstrated that a genetic risk score based on 5 variants—*F5* Leiden rs6025, *F2* rs1799963, *ABO* rs8176719 (O versus non-O groups), *FGG* rs2066865, and *F11* rs2036914—discriminated VTE moderately well (c-statistic 0.68) in a European case-control study[62] (Figure 3). They found this c-statistic to be lower than the c-statistic of 0.77 for a nongenetic risk score composed of clinical factors and was 0.82 for the combined genetic plus nongenetic score. We replicated prospectively the moderate predictivity of the 5 single nucleotide polymorphism score in White participants in the ARIC study, but the score did not predict well in Black participants.[63]

More recently, a large prospective study showed a 297 variant polygenetic risk score strongly predicted VTE in populations of European ancestry.[47] Those in the upper 5% of the population on the risk score had at an incident VTE risk equivalent to carriers of *F5* Leiden or the *F2* G20210A mutation. If and when widespread genome screening is adapted clinically, a comprehensive polygenetic risk score might prove helpful in identifying patients at high risk of unprovoked VTE, but the utility of genetic risk scores in nonwhite populations needs examination.

High ACC-AHA 10-Year Risk of CVD

Many clinicians already routinely assess 10-year risk of atherosclerotic CVD using the ACC-AHA risk equation[64] or some other risk score. To our knowledge, no one has examined how well estimates of future CVD risk might predict VTE incidence. We therefore examined incidence of VTE from 1987 through 2015 in relation to 10-year risk of CVD in the ARIC study (A.

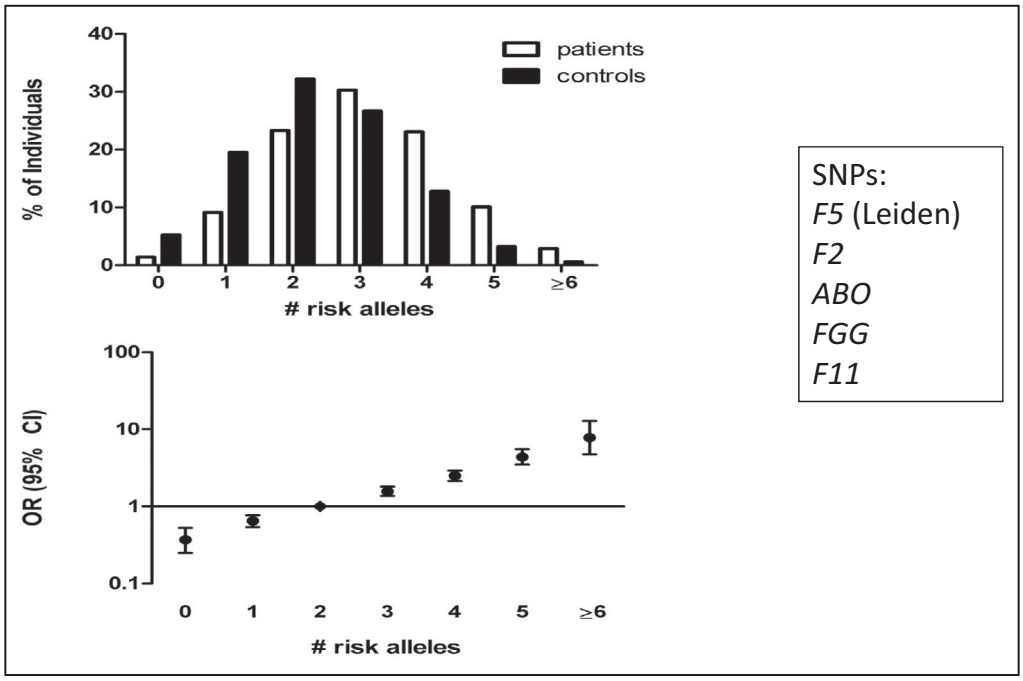

Figure 3. 5-SNP (single nucleotide polymorphism) risk allele distribution in patients with venous thromboembolism and controls and corresponding odds ratios (OR).
Reprinted from de Haan et al[62] with permission. Copyright ©2012, The American Society of Hematology.

R. Folsom, MD, previously unpublished data, Table 3). The hazard ratios (95% CI) for participants with 10-year CVD risks of <5%, 5% to 7.49%, 7.5% to 19.9%, and ≥20% were quite modest: 1, 1.08 (0.88–1.33), 1.23 (1.01–1.50), and 1.29 (0.93–1.79). After further adjustment for BMI, estimated CVD risk did not predict VTE at all. Thus, the widely-accessible ACC-AHA CVD risk equation unfortunately does not readily identify people in the general population at high-risk of VTE.

Low Compliance With AHA LS7

As noted earlier (Figure 1), having <4 ideal LS7 factors seems to identify adults at high risk of VTE in the general population. Many of the LS7 factors are already assessed clinically, but wide-scale assessment of physical inactivity and diet in a clinical setting may be challenging.

In the ARIC study (422 VTE events in 9026 White participants over 23 years), high genetic risk and less than optimal LS7 contributed independently to increase VTE risk 2.6-fold,[65] suggesting that a combined genetic and lifestyle risk score may identify patients at high risk. This finding needs confirmation in other studies.

If We Could Accurately Define Patients at High Risk of Unprovoked VTE in the General Population, What Interventions to Reduce Risk Might Be Considered Safe and Appropriate?

Improve Awareness—Safe and Appropriate

The 2008 US Surgeon General advocated that physicians become better aware of thromboprophylaxis

Table 3. Relative Risks of Venous Thromboembolism by 10-Year Atherosclerotic Cardiovascular Disease Risk Score, Atherosclerosis Risk in Communities, 1987 to 2015

	ASCVD 10-y Predicted Risk*			
	<5%	5–7.49%	7.5–19.9%	≥20%
Incident VTE, n	409	142	291	51
Person-years at risk	182 142	49 688	85 954	14 517
VTE incidence rate (per 1000 person years)	2.3	2.9	3.4	3.5
Age, race, sex-adjusted RR (95% CI)	1	1.08 (0.88–1.33)	1.23 (1.01–1.50)	1.29 (0.93–1.79)
Also body mass index-adjusted RR (95% CI)	1	0.99 (0.80–1.22)	1.09 (0.89–1.32)	1.08 (0.78–1.51)

ASCVD indicates atherosclerotic cardiovascular disease; RR, relative risk; and VTE, venous thromboembolism.
*American College of Cardiology-American Heart Association risk score.[64]

guidelines and that patients at high risk of VTE should be made aware of their risk.[13] Only 25% the US general public at the time had heard of deep vein thrombosis, and of these, <50% knew signs, symptoms, or triggering factors and <25% believed deep vein thrombosis could be prevented. A more recent survey of 9 countries similarly showed lower public awareness of causes of VTE than for causes of many other chronic diseases.[66] Trying to increase awareness of patients at high risk of VTE seems simple and safe, but there is no clinical trial evidence that awareness motivates patients to reduce risk factors for VTE. It might be worthy to consider studying the impact of an office alert system to identify patients at risk and provide counseling and education on VTE prevention.

Nonpharmacological Interventions—Safe and Appropriate

Physicians can and do make clinical decisions based on perception of a patient's risk. For example, they now largely avoid prescribing thrombogenic medications (eg, oral contraceptives or hormone replacement therapy) to patients at perceived risk of VTE, and they may recommend strategies (eg, leg exercises or compression stockings) to prevent VTE during long distance travel.[8] The degree to which practitioners actually consider VTE risk before prescribing thrombogenic medications is unknown, but this high-risk approach to primary VTE prevention may be effective.

Clinical counseling of high-risk patients to improve lifestyle (ie, weight control, prudent diet, exercise, and smoking avoidance) would seem safe to do and warranted based on epidemiologic data, though there is no clinical trial evidence that such counseling is cost effective in preventing unprovoked VTE. Lifestyle counseling certainly is underutilized, and even without clinical trial evidence might still be considered for those at very high risk of VTE. Innovative and effective web-based, smartphone, or other mobile applications to promote healthy lifestyle may have an increasing role in medicine generally.

Pharmacological Interventions—Unclear Safety for Primary Prevention of Unprovoked VTE

Identifying high-risk patients to provide prophylaxis before major surgery or extended immobility is an evidence-based method to prevent a provoked VTE.[8,67] However, a major drawback to pharmacoprophylaxis for primary prevention of unprovoked VTE is that, because an unprovoked VTE cannot be anticipated, pharmacoprophylaxis would need to be given indefinitely. We do not have clinical trials showing acceptable risk-benefit ratios and numbers needed to treat for pharmacologic agents that might be used.

Anticoagulation

Long term, low-intensity anticoagulation therapy can prevent recurrent VTE.[68] Yet, no clinical trial has tested whether low-dose anticoagulation or direct oral anticoagulants given to high-risk patients can prevent a first unprovoked VTE. The risk-benefit and number needed to treat may be unfavorable. Thus, experts have not recommended thromboprophylaxis for primary prevention of VTE, even in most patients with high-risk medical conditions or documented thrombophilia.[8] Whether very low doses of direct oral anticoagulants could be beneficial in this regard, as they seem to be for patients with CVD,[69] is an intriguing hypothesis to pursue, because bleeding risk with this approach might be minimal.

Aspirin

Another high-risk approach for primary prevention of unprovoked VTE might be aspirin prophylaxis. Yet, a secondary analysis of a placebo-controlled clinical trial of 100 mg of aspirin every other day showed no efficacy for preventing a first VTE in healthy women.[70] Recent evidence suggests the risk-benefit ratio of aspirin for primary prevention of atherosclerotic CVD is unacceptable and would likely also be unacceptable for use in prevention of unprovoked VTE.

Statins

A meta-analysis of VTE as a secondary end point in 23 randomized clinical trials (1031 VTEs) suggested that statins, particularly rosuvastatin, might reduce incidence of VTE by 15% (95% CI, 1–27%)[71,72] The effect may not be because of cholesterol lowering, as statins have many pleotropic effects on inflammation and hemostasis.[48,73–75] Others have discussed in detail the possible use of statins to prevent provoked or recurrent VTE,[73,76] but the risk-benefit of giving statins long term specifically for primary prevention of unprovoked VTE, with no other indication for statins, needs further evaluation. Of course, it is conceivable that the widespread use of statins in many countries could be serendipitously preventing unprovoked VTEs.

Proprotein Convertase Subtilisin/Kexin Type 9 Inhibition

Mendelian randomization studies suggest higher lipoprotein(a) is not a VTE risk factor.[77] Yet, 2 recent

clinical trials reported that PCSK9 (proprotein convertase subtilisin/kexin type 9 inhibition) reduced VTE risk in patients with atherosclerotic disease who have persistent hypercholesterolemia while on statins, and that this VTE reduction might be mediated by lowering lipoprotein(a).[78,79] However, giving PCSK9 inhibitors to high-risk patients in the general population in order to prevent unprovoked VTE has unproven efficacy and would certainly not be cost effective.

Other Anti-Inflammatory Interventions

Three recent trials reported on novel anti-inflammatory drug interventions for secondary prevention of arterial CVD, evaluating canakinumab, methotrexate, and colchicine.[80–82] Given that inflammation is important in pathogenesis of VTE, it might be expected that these agents would reduce VTE risk. Of these 3 agents, only the colchicine trial reported VTE outcomes, amounting to a small absolute risk reduction of VTE (0.4% in placebo versus 0.3% in patients treated with colchicine over 22.6 months).[82] It is unknown whether future guidelines will recommend these agents for arterial CVD prevention, but it is reasonable to consider trials addressing their use in VTE prevention settings.

Summary of the Feasibility of a High-Risk Approach to Preventing Unprovoked VTE

It seems that we cannot currently identify high-risk individuals well enough in the general population to consider broad screening and application of the high-risk approach to prevent unprovoked VTE. Yet, additional development and testing of combined polygenetic and nongenetic risk scores for VTE seem warranted, because use of electronic health records could simplify the screening process and broad genetic testing for prevention may eventually prove cost effective.

Counseling of patients at high VTE risk may be risk beneficial for primary prevention, but there currently is no clinical trial evidence of counseling's efficacy. It follows to surmise that such counseling could improve awareness, at the least, and lead to earlier diagnosis and possibly less morbidity from VTE. If we could identify patients at quite high VTE risk, clinical trials of direct oral anticoagulants for primary prevention could be considered. Warfarin or aspirin likely would have unacceptable risk-benefit ratios for use in primary prevention of unprovoked VTE. A high-risk approach using statins in patients at risk of VTE also warrants additional consideration, along with the expectation that giving statins for other indications is serendipitously reducing VTE risk.

CONSIDERATIONS FOR A POPULATION APPROACH TO PRIMARY PREVENTION OF UNPROVOKED VTE

If most of the risk of unprovoked VTE were genetic, then population strategies would not be effective or warranted. Yet, when many in the general population have modifiable VTE risk factors, as may be the case in many countries, the population approach to primary prevention may complement or be more efficient than a high-risk approach. As noted previously, several modifiable lifestyle risk factors, including having more ideal LS7 factors, are associated with reduced risk of VTE. It is therefore plausible that promotion of healthy lifestyles can lower risk of unprovoked VTE in the whole population, and this is true even for those at high genetic risk.[65] Nevertheless, some key questions should be addressed to verify a population approach could be useful.

Are the Lifestyle-VTE Associations Sufficiently Strong, and Are the Risk Factors Common Enough, Causal, and Modifiable so That a Downward Shift of Population Risk Factors Might Be Successful?

In fact, the modifiable VTE risk factors—obesity, physical inactivity, cigarette smoking, and unhealthy diet—are all common in the general population, and this is reflected cumulatively by few adults in the United States having optimal LS7. The published relative risks of VTE with obesity and cumulative LS7 are particularly strong, but those for physical inactivity, diet, and smoking are modest. Obesity, physical inactivity, ever smoking, and a Western dietary pattern might contribute, respectively, to 30%, 4%, 3%, and 11% of VTE risk in the population (Table 1).

Are There Public Health Approaches That Could Effectively Reduce VTE Risk Factors and Therefore VTE Incidence?

Population-based trials have shown that primary prevention strategies of health promotion, through education, environmental changes, or health policy, can reduce lifestyle risk factors, and professional organizations have published comprehensive and effective population strategies, like AHA's 2012 "Population Approaches to Improve Diet, Physical Activity, and Smoking Habits"[83] and the "2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease."[84] These approaches have contributed in recent decades to a dramatic decline in the United States in smoking

and modest changes in diet and physical activity. These same approaches could be used safely in primary prevention of unprovoked VTE. Of course, current population strategies have not been successful in reversing the obesity epidemic, and better interventions for obesity are needed.

Summary on Feasibility of a Population Approach to Preventing Unprovoked VTE

Arguments favoring the use of a population approach are that the individual high-risk approach poorly identifies patients at risk, and there few established interventions for preventing unprovoked VTE in high-risk patients. In contrast, the prevalence of poor lifestyle risk factors is high. Although we do not have definitive community trial evidence that population approaches will prevent VTE, observational data suggest that sustained population risk factor reduction, with better obesity strategies, should indeed reduce incidence of unprovoked VTE. Of course, population-wide efforts to improve lifestyles are already underway for prevention of CVD, diabetes mellitus, and cancer; these may spill over to prevent unprovoked VTE as well. Because it is unrealistic that we could ever totally eliminate obesity, physical inactivity, and unhealthy diet, the population attributable risk estimates in Table 1 certainly reflect the most that VTE could be reduced by lifestyle improvement. Nevertheless, broader support and advocacy for population approaches from health professionals interested in preventing VTE could significantly bolster current primary prevention efforts.

SUMMARY

Evidence is growing to support the possibility of primary prevention of unprovoked VTE. Although existing evidence on the efficacy and feasibility of interventions is limited and definitive guidelines may be premature, some strategies represent "low hanging fruit" (Table 4). These include both high-risk patient and population-wide approaches to reduce obesity, physical inactivity, cigarette smoking, and a Western dietary pattern. In fact, primary prevention of VTE, which has been largely ignored in previous lifestyle guidelines (eg,[83,84]), needs to be promoted in the future as another benefit of adopting a healthy lifestyle. Assuming the epidemiological estimates of association of lifestyle factors with VTE are accurate, causal, and independent of each other, simultaneous reduction of obesity, physical inactivity, current smoking, and Western diet by 25% in the general US population might reduce the incidence of unprovoked VTE by 12% (Figure 4).

We certainly need more research to develop feasible and effective prevention strategies against unprovoked VTE. Some priorities for research for the high-risk approach are (1) continued development and testing of polygenic and clinical risk scores applicable to the general population, (2) modeling of the costs of identifying high-risk patients in the population using different approaches including electronic health records, (3) testing of the efficacy and risk-benefit of various clinical interventions directed toward high-risk patients, and (4) continued research on how to help patients lose weight and maintain weight loss.

Recommended research on the population approach includes (1) understanding how to better increase population awareness of VTE, its risk factors, and how to prevent VTE; (2) testing of the efficacy of novel population-wide intervention strategies to reduce risk, including education, environment changes, or policies, especially those directed toward obesity; and (3) testing how to mobilize existing public health resources and health systems to provide interventions at the population level.

Table 4. Lifestyle Strategies to Prevent Unprovoked Venous Thromboembolism

Targets	High-Risk Approach	Population Approach
Obesity Physical inactivity Cigarette smoking Western diet Socioeconomic and racial disparities	Expand clinical guidelines Screen patients to identify those at high risk (methods need development and could use electronic health records) Individual high-risk patient interventions • Increase patient awareness • Increase provider awareness to socioeconomic and racial barriers to prevention, and mitigate barriers • Behavioral modification or lifestyle counseling, potentially using mobile health "apps" • Pharmacotherapy for obesity, smoking • Avoid thrombogenic medications Risk-benefit uncertain for • Thromboprophylaxis • Statins	Education, awareness, eg: • Mass media; health "apps" • Schools, workplaces • Health advocacy Environmental change, eg: • Access to healthy foods, especially to disadvantaged groups • Smoking restriction • Built environment improvements, especially in disadvantaged neighborhoods Policies, including those to eliminate health disadvantages, eg: • Food labeling • Food taxation • School health and physical education • Food and agriculture policies • Insurer-offered incentives • Laws and industry regulations

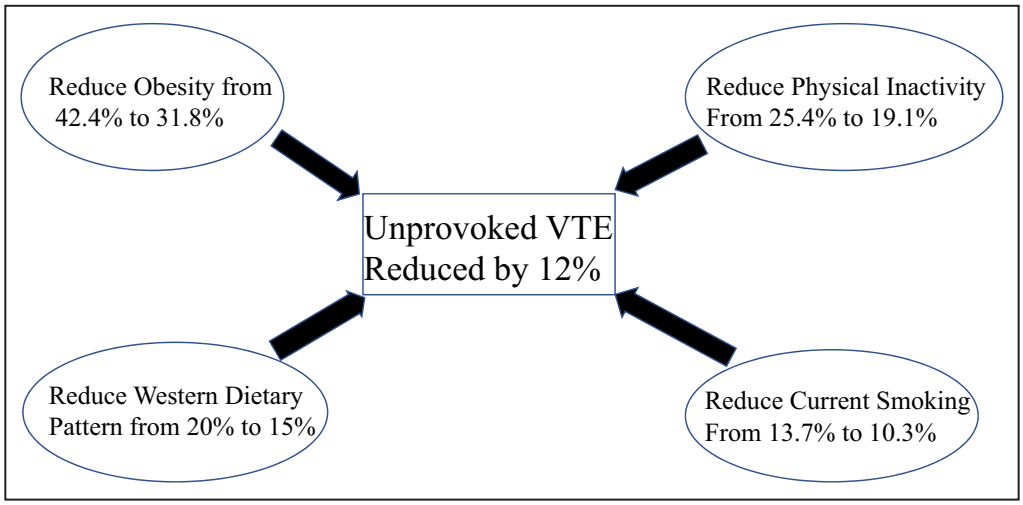

Figure 4. Potential reduction in unprovoked venous thromboembolism (VTE) by simultaneously lowering 4 lifestyle factors by 25% in the population*.
*Based on population attributable risks (PARs) in Table 1, assuming causal and independent associations.

A key factor in determining success of population approaches to prevent VTE is the ability to determine VTE incidence in the population. In the United States, there currently is no population surveillance for VTE, so we rely on hospitalization rates as a surrogate.[1] With increasing use of outpatient treatment for VTE, even for pulmonary embolism, the lack of surveillance data will continue to hamper efforts to reduce VTE incidence in the population.

ARTICLE INFORMATION

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Disclosures

None.

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