Association Between the Metabolic Syndrome, Its Individual Components, and Unprovoked Venous Thromboembolism: Results of a Patient-Level Meta-Analysis

Walter Ageno, Matteo N.D. Di Minno, Cihan Ay, Moon Ju Jang, John-Bjarne Hansen, Lyn M. Steffen, Amparo Vayà, Marcello Rattazzi, Ingrid Pabinger, Doyeun Oh, Giovanni Di Minno, Sigrid K. Braeckkan, Mary Cushman, Elena Bonet, Paolo Pauletto, Alessandro Squizzato, Francesco Dentali

Objective—The metabolic syndrome (MetS) may contribute to the pathogenesis of venous thromboembolism (VTE), but this association requires additional investigation.

Approach and Results—We performed a patient-level meta-analysis of case–control and cohort studies that evaluated the role of MetS and risk of unprovoked VTE. For case–control studies, odds ratios and 95% confidence intervals were calculated using logistic regression analysis to estimate the influence of individual variables on the risk of VTE; χ² tests for trend were used to investigate the effect of increasing number of components of MetS on the risk of VTE and to explore the influence of abdominal obesity on this relationship. For cohort studies, hazard ratios and 95% confidence interval were calculated using multivariable Cox regression analysis. Six case–control studies were included (908 cases with unprovoked VTE and 1794 controls): in multivariate analysis, MetS was independently associated with VTE (odds ratio, 1.91; 95% confidence interval, 1.57–2.33), and both MetS and abdominal obesity were better predictors of unprovoked VTE than obesity defined by the body mass index. Two prospective cohort studies were included (26531 subjects and 289 unprovoked VTE events): age, obesity, and abdominal obesity, but not MetS were associated with VTE.

Conclusions—Case–control but not prospective cohort studies support an association between MetS and VTE. Abdominal adiposity is a strong risk factor for VTE. (Arterioscler Thromb Vasc Biol. 2014;34:2478-2485.)

Key Words: metabolic syndrome X obesity pulmonary embolism venous thromboembolism venous thrombosis

Venous thromboembolism (VTE) is a multifactorial disease that can affect apparently healthy individuals and hospitalized patients. In most cases, the occurrence of VTE is associated with the presence of major provoking factors, such as a recent surgical procedure, trauma, fracture, pregnancy or puerperium, the use of oral contraceptives, prolonged immobilization, or a severe medical disease. However, in ≤45% of cases, none of these risk factors is identified and VTE remains classified as unprovoked.1–3

During recent years, several studies have reported an increased risk of cardiovascular events in patients with VTE.4–9 The results of a recent meta-analysis reported that the overall risk of cardiovascular events, as well as the risk of acute myocardial infarction or stroke after VTE, is significantly higher in patients with unprovoked VTE than in patients with VTE secondary to a major provoking factor.9

One of the hypotheses for this association between cardiovascular disease and VTE is that the 2 diseases may share common risk factors. Among traditional cardiovascular risk factors, obesity and age have been demonstrated to be consistently independent risk factors also for VTE.10,11 In a systematic review of the literature and meta-analysis, we found that arterial hypertension, diabetes mellitus, and dyslipidemia are also associated with VTE.12 Although the estimated odds ratios (ORs) for these variables were less robust than those reported for established major risk factors for VTE, such as cancer or surgery, the findings are relevant because cardiovascular risk factors are more common, often coexist and their...
The metabolic syndrome is a cluster of cardiovascular risk factors, including abdominal obesity, hypertension, insulin resistance, and dyslipidemia, with high triglycerides levels and low high-density lipoprotein cholesterol. The interaction of these risk factors results in a significantly increased risk of developing coronary artery disease and ischemic stroke. Recent studies suggest that the metabolic syndrome may also be associated with VTE, but several issues remain unclear. In particular, whether this association is attributable to the metabolic syndrome or to abdominal obesity alone, with no additional contribution by the other components, and whether this association is sex specific remain to be established.

To explore these issues further, we performed a systematic search of the literature and an individual patient-level meta-analysis of published studies, evaluating the association between unprovoked VTE and the metabolic syndrome.

Materials and Methods
Materials and Methods are available in the online-only Supplement.

Results
The results of study search and selection process are summarized in Figure 1. The interobserver agreement for the study selection was excellent, with a $\kappa$ of 0.92. After the selection process, 8 studies were eligible for this analysis, of which 6 were case–control studies and 2 were prospective cohort studies. All contacted investigators agreed to provide their full database of the study.

Table 1 summarizes the characteristics of the 6 case–control studies included in the analysis, and Table 2 summarizes the characteristics of the 2 prospective cohort studies. Briefly, among case–control studies, 1 study included patients with deep vein thrombosis only, whereas the remaining studies included patients with both deep vein thrombosis and pulmonary embolism. Five studies enrolled patients with a single episode of VTE and 1 study enrolled patients with recurrent VTE. One study was conducted in Asian patients only, and the other 5 studies enrolled white patients. Mean age of study patients in case–control studies was <50 years in 4 studies, between 50 and 60 years in 1 study, and >60 years in 1 study. According to our predefined quality score for case–control studies, 2 studies scored 6, thus were high quality, 4 studies scored 5, thus were medium quality. According to our predefined quality score for cohort studies, both studies scored 6 and were thus high quality.

In prospective cohort studies, the mean time elapsed between the measurement of the features of the metabolic syndrome and VTE events was 7.6 years (range, 0.6–15.1) in one study and 6.7 years (range, 0.2–12.7 years) in the second study. Information was collected on both deep vein thrombosis and pulmonary embolism. At baseline, mean age of study subjects was 58 years in one study and between 60 and 63 years (metabolic syndrome negative and positive patients, respectively) in the second study. The definition of unprovoked VTE slightly differed among all selected studies (Tables 1 and 2).

![Figure 1. Process of study selection. ISTH indicates International Society on Thrombosis and Haemostasis; and VTE, venous thromboembolism.](http://atvb.ahajournals.org/)}
Results of the Analysis of Case–Control Studies

We initially analyzed aggregate data, and the presence of the metabolic syndrome was significantly associated with VTE with an OR of 2.64 (95% confidence interval [CI], 2.19–3.18). There was no heterogeneity among the studies (I²=0%; Figure 2).

We subsequently performed the patient-level analysis. Overall, we received data for 908 patients with unprovoked VTE and 1794 controls. No cases or controls were excluded from the analysis for insufficient data. Baseline characteristics of the 2702 cases and controls enrolled in this study are summarized in Table 3. The 2 groups were significantly different according to sex, mean age, and the prevalence of obesity. Dyslipidemia was significantly more prevalent in cases of unprovoked VTE than in controls. The metabolic syndrome and each of its components were also significantly more prevalent in the group of cases than controls.

Table 1. Description of Case–Control Studies Included in the Meta-Analysis

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Inclusion Criteria</th>
<th>Definition of Unprovoked VTE</th>
<th>Timing Between VTE and Assessment of MS</th>
<th>Quality of Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ageno et al15</td>
<td>Cases: consecutive patients with DVT; controls: suspected and objectively excluded DVT</td>
<td>Absence of surgery, trauma, pregnancy, acute medical disease, oral contraceptives, and cancer</td>
<td>&lt;6 mo</td>
<td>5</td>
</tr>
<tr>
<td>Ay et al17</td>
<td>Cases: patients with recurrent VTE, ≥1 unprovoked</td>
<td>Absence of surgery, trauma with immobilization, pregnancy, and cancer</td>
<td>Median, 2.55 y</td>
<td>5</td>
</tr>
<tr>
<td>Jang et al18</td>
<td>Cases: consecutive patients with VTE; controls: healthy, unrelated individuals with negative history of VTE</td>
<td>Absence of recent surgery, trauma, fracture, immobilization, and cancer</td>
<td>6 mo</td>
<td>6</td>
</tr>
<tr>
<td>Vayà et al21</td>
<td>Cases: patients with VTE (VTE related to pregnancy or cancer excluded); controls: healthy, unrelated individuals with negative history of VTE</td>
<td>Absence of surgery, trauma, fracture, immobilization, and other nondefined risk factors</td>
<td>3–6 mo</td>
<td>5</td>
</tr>
<tr>
<td>Di Minno et al22</td>
<td>Cases: consecutive patients aged &lt;50 y with unprovoked VTE; controls: healthy subjects with negative history of VTE</td>
<td>Absence of pregnancy, cancer, trauma, fracture, and acute medical disease</td>
<td>&lt;6 mo</td>
<td>6</td>
</tr>
<tr>
<td>Rattazzi et al23</td>
<td>Cases: patients with ≥1 episode of VTE; controls: healthy, unrelated individuals with negative history of VTE</td>
<td>Absence of surgery, trauma, fracture, immobilization, acute medical disease, and pregnancy</td>
<td>Median 60 mo</td>
<td>5</td>
</tr>
</tbody>
</table>

DVT indicates deep vein thrombosis; MS, metabolic syndrome; and VTE, venous thromboembolism.

Table 2. Description of Prospective Cohort Studies Included in the Meta-Analysis

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Inclusion Criteria</th>
<th>Definition of Unprovoked VTE</th>
<th>Mean Time Between Assessment of VTE and MS</th>
<th>Quality of Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borch et al19</td>
<td>Population study of individuals assessed for the MS and with no previous VTE</td>
<td>Absence of major surgery, trauma, or acute medical condition within 8 wk before event; active cancer at time of event, immobilization within 14 days before event</td>
<td>6.7 y</td>
<td>6</td>
</tr>
<tr>
<td>Steffen et al20</td>
<td>Population study of individuals assessed for the MS and with no previous VTE</td>
<td>Absence of surgery, trauma, recent hospitalization, or severe immobility. Cancer-related VTE excluded patients from analyses</td>
<td>7.6 y</td>
<td>6</td>
</tr>
</tbody>
</table>

MS indicates metabolic syndrome; and VTE, venous thromboembolism.
In our subgroup analyses, the OR for VTE for metabolic syndrome in men was 1.88 (95% CI, 1.46–2.42) and in women was 2.77 (95% CI, 2.16–3.56). The OR for VTE with metabolic syndrome in patients <50 years was 1.99 (95% CI, 1.57–2.53), and in patients aged ≥50 years was 2.07 (95% CI, 1.61–2.66). Heterogeneity between male and female patients was significant (χ² = 4.63; P for interaction, 0.03), whereas there was no statistically significant difference according to age (P for interaction >0.10).

In multivariable logistic regression analysis, the metabolic syndrome remained associated with odds of VTE after adjusting for age, sex, and obesity, with an OR of 1.91 (95% CI, 1.57–2.33; Table 4).

The analysis was repeated after the exclusion of the study by Ay et al17 because it was the only study including patients with recurrent VTE only. The results were unchanged (data not shown, available on request). The association between the metabolic syndrome and VTE was significant both in male and in female patients (OR, 1.61; 95% CI, 1.22–2.20 and OR, 2.32; 95% CI, 1.74–3.09, respectively) after adjusting for age and obesity. The observed association remained statistically significant when the multivariate analysis was repeated after the exclusion of patients with increased waist circumference with an OR of 2.19 (95% CI, 1.51–3.16) after adjusting for age and obesity.

Results of multiadjusted regression models on the association of the individual components of the metabolic syndrome and VTE are reported in Table 4.

**Results of the Analysis of Prospective Cohort Studies**

We initially analyzed aggregate data, and the presence of the metabolic syndrome was significantly associated with VTE, with an OR of 1.15 (95% CI, 0.90–1.47). There was no heterogeneity among the studies (I²=0%; Figure 3). We subsequently performed the patient-level analysis. Overall, we received data on 26544 subjects who had 552 VTE events during follow-up. Excluding 13 subjects with incomplete data and considering only unprovoked events, 26531 participants had 289 events during follow-up.

Baseline characteristics of patients who developed and who did not develop unprovoked VTE during follow-up are summarized in Table 5. The 2 groups were significantly different according to mean age, prevalence of obesity, abdominal obesity, and hypertension, whereas other baseline characteristics and prevalence of metabolic syndrome were similar in the 2 groups.

### Table 3. Baseline Characteristics of the Study Population and Prevalence of the Metabolic Syndrome and of Its Components in Case–Control Studies

<table>
<thead>
<tr>
<th></th>
<th>Total Population</th>
<th>VTE Patients</th>
<th>Controls</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>2702</td>
<td>908</td>
<td>1794</td>
<td></td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>1162 (43.0)</td>
<td>475 (52.3)</td>
<td>687 (38.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean age, y (SD)</td>
<td>51.4 (14.3)</td>
<td>52.7 (15.3)</td>
<td>50.7 (13.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Obesity*, n (%)</td>
<td>686 (25.4)</td>
<td>313 (34.5)</td>
<td>373 (20.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholesterol &gt;200 mg/dL†, n (%)</td>
<td>1253 (46.4)</td>
<td>475 (52.3)</td>
<td>778 (43.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL cholesterol &gt;160 mg/dL†, n (%)</td>
<td>548 (20.3)</td>
<td>257 (28.3)</td>
<td>291 (16.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Metabolic syndrome, n (%)</td>
<td>703 (26.0)</td>
<td>341 (37.6)</td>
<td>362 (20.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abdominal obesity‡, n (%)</td>
<td>1066 (39.5)</td>
<td>466 (51.3)</td>
<td>600 (33.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting glucose ≥100 mg/dL†, n (%)</td>
<td>720 (26.6)</td>
<td>314 (34.6)</td>
<td>406 (22.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood pressure ≥130/85 mm Hg†, n (%)</td>
<td>1052 (38.9)</td>
<td>440 (48.5)</td>
<td>612 (34.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL cholesterol &lt;40/50 mg/dL†, n (%)</td>
<td>773 (28.6)</td>
<td>365 (40.2)</td>
<td>504 (28.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides ≥150 mg/dL†, n (%)</td>
<td>641 (23.7)</td>
<td>283 (31.2)</td>
<td>358 (20.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and VTE, venous thromboembolism.

*White patients: BMI>30 kg/m²; Asian patients: BMI>25 kg/m².
†Patients currently receiving drug therapy for hypertension, diabetes mellitus, or dyslipidemia (only statins) were defined as having those disorders.
‡White patients: waist circumference >102 cm for men and >88 cm for women; Asian patients: waist circumference >90 cm for men and >80 cm for women.
The results of this patient-level meta-analysis do not convincingly support the role of the metabolic syndrome as an independent risk factor for VTE but support the role of abdominal adiposity, as assessed by waist circumference, as a strong risk factor for VTE. The association between the metabolic syndrome and unprovoked VTE was confirmed in the analysis of case–control studies in different patient subgroups but not in the analysis of prospective cohort studies. Likewise, individual components of the metabolic syndrome were also independently associated with VTE, and their coexistence resulted in an additive effect in case–control studies, but not in longitudinal studies, with the exception of abdominal obesity.

The fact that the importance of the coclustering of the various components of the metabolic syndrome or their complete expression did not play a role in prospective studies on VTE occurrence may suggest a minor contribution of the atherogenic pattern found in the metabolic syndrome to the pathogenesis of VTE. Conversely, the state of chronic, low-grade inflammation that is associated with the metabolic syndrome, but that most of all depends on the presence of abdominal adiposity, may result in a prothrombotic state that predisposes to VTE. Both chronic inflammation and insulin resistance, which plays a key role in the pathogenesis of the syndrome, are associated with increased levels of fibrinogen, and low-grade chronic inflammation has also been associated with increased release of soluble tissue factor and factor VII.24 The simultaneous increase in both soluble tissue factor and factor VII clearly enhances the risk of activation of the coagulation cascade. Furthermore, increased levels of plasminogen activator inhibitor-1 and decreased plasma tissue-type plasminogen activator activity are common in these patients, thus leading to a hypofibrinolytic state.23 Recent studies have shown that plasminogen, thrombin-activatable fibrinolysis inhibitor, plasminogen activator inhibitor-1, and tissue plasminogen activator are all associated with the risk of venous thrombosis, thus supporting the potential relevance of hypofibrinolysis as a link between VTE and both abdominal obesity and the metabolic syndrome.25 Furthermore, hypofibrinolysis was also reported to be associated with an increased risk of recurrent VTE.26 Taken together, these coagulation abnormalities have the potential to predispose patients to an increased risk of VTE. This hypothesis was initially suggested by the results of case–control studies,15–18,21–23 and to a much lesser extent, by the results of prospective cohort studies.19,20 In fact, the main finding of 1 of the 2 longitudinal studies, the Tromso study, was that abdominal obesity is a necessary component for the association between the metabolic syndrome and VTE because after the removal of abdominal obesity this association is lost. This observation, substantially confirmed by the results of the present study, is relevant because abdominal adipose tissue, which is best viewed as an endocrine organ,27 plays a central role in the cause of the metabolic syndrome and in predisposing to the

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic syndrome and VTE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>1.91</td>
<td>1.57–2.33</td>
</tr>
<tr>
<td>Age</td>
<td>1.00</td>
<td>0.99–1.01</td>
</tr>
<tr>
<td>Obesity*</td>
<td>1.56</td>
<td>1.28–1.89</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.67</td>
<td>1.42–1.97</td>
</tr>
<tr>
<td>Components of the metabolic syndrome and VTE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal obesity†</td>
<td>1.66</td>
<td>1.36–2.02</td>
</tr>
<tr>
<td>HDL cholesterol &lt;40/50 mg/dL‡</td>
<td>1.48</td>
<td>1.24–1.77</td>
</tr>
<tr>
<td>Blood pressure ≥130/85 mm Hg‡</td>
<td>1.41</td>
<td>1.17–1.70</td>
</tr>
<tr>
<td>Fasting glucose ≥100 mg/dL‡</td>
<td>1.26</td>
<td>1.04–1.53</td>
</tr>
<tr>
<td>Triglycerides≥150 mg/dL‡</td>
<td>1.24</td>
<td>1.02–1.51</td>
</tr>
<tr>
<td>Age</td>
<td>1.00</td>
<td>0.99–1.01</td>
</tr>
<tr>
<td>Obesity*</td>
<td>1.22</td>
<td>0.99–1.52</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.64</td>
<td>1.38–1.94</td>
</tr>
</tbody>
</table>

*BMI indicates body mass index; CI, confidence interval; HDL, high-density lipoprotein; OR, odds ratio; and VTE, venous thromboembolism.

§White patients: BMI>30 kg/m²; Asian patients: BMI>25 kg/m².

†White patients: waist circumference >102 cm for men and >88 cm for women; Asian patients: waist circumference >90 cm for men and >80 cm for women.

‡Patients currently receiving drug therapy for hypertension, diabetes mellitus, or dyslipidemia (only statins) were defined as having those disorders.

Discussion

In the random effects Cox model age ≥65 years (hazard ratio, 1.80; 95% CI, 1.39–2.34), obesity (hazard ratio, 1.56; 95% CI, 1.15, 2.11) and abdominal obesity (hazard ratio, 1.55; 95% CI, 1.15, 2.08) were significantly associated with the development of unprovoked VTE during follow-up, whereas hypertension was not (hazard ratio, 1.12; 95% CI, 0.86–1.46). The metabolic syndrome was not significantly associated with an increased risk of developing VTE when added to a multivariate model with obesity and age ≥65 years. The metabolic syndrome was also not significantly associated with an increased risk of VTE in a multivariate model that included all other covariates that were significantly associated with VTE in univariate analysis or considering the prespecified subgroups according to age and sex (data not shown). Given the absence of association between the metabolic syndrome and VTE, no further analysis on the additive role of the individual components was performed.

![Figure 3. Forest plot of cohort studies. CI indicates confidence interval.](http://atvb.ahajournals.org/)

Table 4. Results of Multiadjusted Regression Models of Case–Control Studies on the Association Between the Metabolic Syndrome, Its Components, and VTE
chronic inflammatory state. For this reason, the International Diabetes Federation proposed the presence of abdominal obesity as a necessary condition for the diagnosis of the metabolic syndrome.24 In the second longitudinal study, the LITE (Longitudinal Investigation of Thromboembolism Etiology) study, this finding was observed in men only.20 In this study, abdominal obesity, but not the metabolic syndrome, was related to VTE in women. In men, the metabolic syndrome was associated with VTE, but when abdominal obesity was removed, this association between the metabolic syndrome and VTE was no longer statistically significant. Sex-related differences have been reported by some authors also for the association between the metabolic syndrome and the cardiovascular disease.29,30 but have not been confirmed by other studies, and the mechanisms underlying this finding have not been elucidated. The results of our individual patient data meta-analysis of case–control studies confirmed a statistically significant interaction by sex, but, differently from the study by Steffen et al,20 the association between the metabolic syndrome and VTE was no longer statistically significant. This association could not be confirmed when the individual patients data of the 2 prospective cohort studies were analyzed.

The reasons for the observed discrepancies are, at least in part, attributable to the study designs. In the case–control studies included in our meta-analysis, the components of the metabolic syndrome were measured within 6 months after VTE in 4 studies,15,18,21,22 and after a median of 2.5 years and 60 months in 2 studies.17,23 In the longitudinal studies, the features of the metabolic syndrome were measured at baseline and VTE events occurred after years.19,20 Because all components of the metabolic syndrome are modifiable, and individuals with a higher cardiovascular risk profile at baseline may have been managed more aggressively, there is a chance that the effect of some of the metabolic risk factors may have been diluted at the time of the VTE event. Regular physical activity and a healthy diet are key elements for the primary intervention in patients with the metabolic syndrome and have been shown to reduce the incidence of VTE in some31,32 but not in all studies.33,34 Likewise, statins are among the main therapeutic strategies in patients with the metabolic syndrome and have also been recently shown to reduce the risk of VTE.35 Another potential explanation for the observed discrepancies is that the prevalence of the metabolic syndrome increases with increasing age,36,37 and the distribution of risk factors may have changed in longitudinal studies during time between patients who subsequently developed VTE and patients without VTE. Of note, in 4 of the 5 case–control studies,17,18,21,22 the mean age of study patients ranged between 41 and 47 years, and only in 1 study the mean age of patients with VTE was 63 years.23 Conversely, the mean age at baseline in the 2 prospective cohort studies was ≈60 years,19,20 and, thus VTE occurred in these studies at an older age when compared with the case–control studies. However, in the case–control studies, we separately assessed the association between the metabolic syndrome and the VTE in patients aged ≤50 years and in patients ≥50 years; this association remained statistically significant in both groups and the magnitude of the association was actually greater in older patients. Finally, a third explanation of the discrepancy between study designs is that the retrospective nature of case–control studies may have contributed to overestimation of the magnitude of the observed associations. In addition, also the time elapsed between VTE and the measurement of the components of the metabolic syndrome in the case–control studies included in our analysis might have contributed to bias because obesity is a known

### Table 5. Baseline Characteristics of the Study Population and Prevalence of the Metabolic Syndrome and of Its Components in Cohort Studies

<table>
<thead>
<tr>
<th></th>
<th>Total Population</th>
<th>Patients With VTE</th>
<th>No VTE</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>26531</td>
<td>289</td>
<td>26242</td>
<td>...</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>11 986 (45.2)</td>
<td>128 (44.3)</td>
<td>11 858 (45.2)</td>
<td>0.77</td>
</tr>
<tr>
<td>Mean age, y (SD)</td>
<td>59.4 (10.0)</td>
<td>63.3 (8.9)</td>
<td>59.3 (10.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obesity*, n (%)</td>
<td>5987 (22.6)</td>
<td>105 (36.3)</td>
<td>5882 (22.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholesterol &gt;200 mg/dL†, n (%)</td>
<td>12 142 (45.8)</td>
<td>126 (43.6)</td>
<td>12 016 (45.8)</td>
<td>0.46</td>
</tr>
<tr>
<td>LDL cholesterol &gt;160 mg/dL†, n (%)</td>
<td>4742 (17.9)</td>
<td>44 (15.2)</td>
<td>4698 (18.9)</td>
<td>0.24</td>
</tr>
<tr>
<td>Metabolic syndrome, n (%)</td>
<td>9720 (36.6)</td>
<td>113 (39.1)</td>
<td>9607 (36.6)</td>
<td>0.38</td>
</tr>
<tr>
<td>Abdominal obesity†, n (%)</td>
<td>11 724 (44.2)</td>
<td>172 (59.5)</td>
<td>11 552 (44.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting glucose ≥100 mg/dL†, n (%)</td>
<td>10 507 (39.6)</td>
<td>115 (39.8)</td>
<td>10 392 (39.6)</td>
<td>0.92</td>
</tr>
<tr>
<td>Blood pressure ≥130/85 mm Hg†, n (%)</td>
<td>14 740 (55.6)</td>
<td>187 (64.7)</td>
<td>14 553 (55.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>HDL cholesterol &lt;40/50 mg/dL†, n (%)</td>
<td>9282 (35.0)</td>
<td>88 (30.4)</td>
<td>9194 (35.0)</td>
<td>0.11</td>
</tr>
<tr>
<td>Triglycerides ≥150 mg/dL†, n (%)</td>
<td>8206 (30.9)</td>
<td>81 (28.0)</td>
<td>8125 (31.0)</td>
<td>0.26</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and VTE, venous thromboembolism.

*White patients: BMI>30 kg/m²; Asian patients: BMI>25 kg/m².
†Patients currently receiving drug therapy for hypertension, diabetes mellitus, or dyslipidemia (only statins) were defined as having those disorders.
‡White patients: waist circumference >102 cm for men and >88 cm for women; Asian patients: waist circumference >90 cm for men and >80 cm for women.
risk factor for VTE and weight loss counseling after VTE in overweight individuals might have been proposed to at least some of the patients. However, reduced mobility after acute VTE may have favored weight gain with consequent increased waist circumference and changes in lipid profile, thus resulting in a revers association.

There are several limitations to our study. First, inclusion criteria and the definition of unprovoked VTE differed among studies. When the analysis was repeated for case-control studies with the exclusion of the study that used different inclusion criteria (patients with recurrent VTE as opposed to patients with a first episode), the results were unchanged. With regard to the different definitions of unprovoked VTE, these mainly related to the inclusion of hormone-associated VTE in 2 studies, and of long-distance travel in another study. However, both hormone-therapy and long-distance travel are considered as weak risk factors for VTE, and it is unlikely that the low number of patients included with either one of these risk factors may have significantly affected our results. Second, one of the studies was only performed in Asian patients. To reduce the potential bias of ethnic differences, we used ethnic-specific definitions of obesity and components of the metabolic syndrome.

In conclusion, only the individual patient data meta-analysis of case-control studies confirmed an association between unprovoked VTE and the metabolic syndrome. This association was not present in longitudinal studies. Conversely, the meta-analysis of both case-control and longitudinal studies supports the role of abdominal adiposity as a strong risk factor for VTE. The modifiable nature of the individual components of the metabolic syndrome, but also bias that are intrinsic in the design of case-control studies, may explain this discrepancy. Additional studies that are specifically designed to address this issue taking into account all potential sources of bias are warranted. Furthermore, the role of the metabolic syndrome in the pathogenesis of VTE secondary to traditional major risk factors should also be explored.

Acknowledgments
We thank the staff and participants of the ARIC (Atherosclerosis Risk in Communities Study) and CHS (Cardiovascular Health Study) studies for their important contributions. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Study concept and design: W. Ageno, F. Dentali, A. Squizzato; acquisition of data: W. Ageno, F. Dentali, M.N.D. Di Minno, C. Ay, M.J. Jang, L.M. Steffen, M. Rattazzi, S.K. Braekkan, E. Bonet; analysis and interpretation of data: W. Ageno, F. Dentali, J.-B. Hansen, L.M. Steffen, M. Cushman, A. Squizzato; drafting of the article: W. Ageno, F. Dentali, A. Squizzato; critical revision of the article for important intellectual content: M.N.D. Di Minno, C. Ay, J.-B. Hansen, L.M. Steffen, A. Vayá, I. Pabinger, D. Oh, G. Di Minno, M. Cushman, P. Pauletto, A. Squizzato; final approval of the article: W. Ageno, M.N.D. Di Minno, C. Ay, M.J. Jang, J.-B. Hansen, L.M. Steffen, A. Vayá, M. Rattazzi, I. Pabinger, D. Oh, G. Di Minno, S.K. Braekkan, M. Cushman, E. Bonet, P. Pauletto, A. Squizzato, F. Dentali. W. Ageno and F. Dentali had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of all the data analysis.

Sources of Funding
The Atherosclerosis Risk in Communities Study is performed as a collaborative study supported by National Heart, Lung, and Blood Institute (NHLBI) contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C) and the Longitudinal Investigation of Thromboembolism Etiology was funded by grant HL59367 from the NHLBI. CHS research was supported by contracts HHSN268201200036C, HHSN268200800007C, N01 HC5222, N01 NC85079, N01 HC85080, N01 HC85081, N01 HC85082, N01HC85083, N01HC85086, and grant HL080295 from the NHLBI, with additional contribution from the National Institute of Neurological Disorders and Stroke. Additional support was provided by AG2023629 from the National Institute on Aging. A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org.

Disclosures
None.

References
Significance

This large individual patient data meta-analyses on >30 000 subjects explored the association between the metabolic syndrome and its individual components and venous thromboembolism. The study provides some important confirmation on the role of obesity and visceral obesity as risk factors for venous thrombosis, with important clinical implications for both the primary and the secondary prevention. The results of this meta-analysis do not fully support the role of the metabolic syndrome, given the discrepancy between the results of case–control studies and prospective cohort studies. The modifiable nature of the individual components of the metabolic syndrome, but also bias that are intrinsic in the design of case–control studies, may explain this discrepancy and suggest the need for additional studies that are specifically designed to address this clinical question.
Association Between the Metabolic Syndrome, Its Individual Components, and Unprovoked Venous Thromboembolism: Results of a Patient-Level Meta-Analysis

Walter Ageno, Matteo N.D. Di Minno, Cihan Ay, Moon Ju Jang, John-Bjarne Hansen, Lyn M. Steffen, Amparo Vayà, Marcello Rattazzi, Ingrid Pabinger, Doyeun Oh, Giovanni Di Minno, Sigrid K. Braekkan, Mary Cushman, Elena Bonet, Paolo Pauletto, Alessandro Squizzato and Francesco Dentali

Arterioscler Thromb Vasc Biol. 2014;34:2478-2485; originally published online September 11, 2014;
doi: 10.1161/ATVBAHA.114.304085

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/34/11/2478

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/
Search Strategy:

1. metabolic syndrome X/ (18235)
2. venous thrombosis/ (17390)
3. Venous thromboembolism/ (4233)
4. pulmonary embolism/ (30745)
5. 2 or 3 or 4 (48151)
6. 1 and 5 (37)
MATERIALS AND METHODS

The main aims of our study were to provide an accurate estimate of the association between VTE and metabolic syndrome in different subgroups of patients and an accurate estimate of the association between VTE and the components of the metabolic syndrome, taken individually and then progressively clustered. Because a meta-analysis of aggregate data does not allow study of questions pertinent to patient subgroups and adjustment for potential confounders (1), we performed an individual patient data meta-analysis. Since we considered the role of the metabolic syndrome and of its components of greatest interest for the understanding of the pathogenesis of unprovoked VTE, we restricted our study to consideration of unprovoked VTE.

A protocol was prospectively developed. Specific objectives, criteria for study selection, approach to assess study quality, outcomes, and statistical methods were defined a priori (2).

Study Identification

We identified all published studies that evaluated the role of the metabolic syndrome as a risk factor for VTE using Medline (1946 to February week 1 2014) and EMBASE (1980 to February week 1 2014) databases. The search strategy used the keywords and medical subject headings presented in Appendix 1. We supplemented our search by reviewing the International Society of Thrombosis and Haemostasis and American Society of Hematology scientific meeting abstracts from 2003 to 2013 using metabolic syndrome, and venous thrombosis or pulmonary embolism as search terms and by manually reviewing the reference list of all articles retrieved for additional published or unpublished trials.

Study Selection

Study selection was performed independently by 2 reviewers (FD, WA), with disagreements resolved through discussion and by the opinion of a third reviewer (AS), if necessary.
Studies were included if they met the following criteria: 1) diagnosis of VTE was objectively confirmed according to established criteria (i.e. ultrasound of the lower limbs or CT scan for deep vein thrombosis and CT scan or high probability V/Q scan for pulmonary embolism); 2) Patients with unprovoked VTE were included, 3) Availability of quantitative data to adjudicate all individual components of the metabolic syndrome according to international definitions (see below).

To assess the agreement between reviewers for study selection, we used the $\kappa$ statistic, which measures agreement beyond chance (3). According to Maclure and Willett, $K$ values higher than 0.6 are considered to represent a substantial agreement and values higher than 0.8 an almost perfect agreement (4).

**Study Validity Assessment**

The same two investigators independently completed the assessment of study validity. Disagreement was resolved by consensus and by the opinion of a third reviewer, if necessary.

Although the use of quality scoring systems or quality scales in observational studies is controversial (2), we adapted the Newcastle-Ottawa Scale for assessing quality of non-randomized studies (25). This assesses the three broad areas of selection, comparability, and outcome or exposure, for case-control or cohort studies. The main items for case-control studies were the following: 1) definition of VTE (objective diagnosis); 2) consecutive selection of patients; 3) definition of control group (representativeness of the general population); 4) selection of control group (no previous history of VTE); 5) comparability on the basis of the design or analysis (age and sex matched or an adequate adjustment for age and sex in the statistical analysis); and 6) objective ascertainment of exposure (i.e. metabolic syndrome). The main items for the cohort studies were as follows: 1) representativeness of the exposed cohort; 2) objective ascertainment of exposure (i.e. metabolic syndrome); 3) selection of the non-exposed subjects; 4) comparability on the basis of the design or analysis (either exposed and non-exposed individuals must be matched in the design
and/or confounders must be adjusted for in the analysis); 5) objective definition of VTE as an outcome; 6) adequacy of follow-up of cohorts. The scoring system defined three quality categories as follows: a total of 6 points defined high-quality study; 4 and 5 points defined medium-quality studies; and 3 or less points defined low-quality studies. No attempts to mask for authorship, journal name, or institution were made.

**Development of Individual Patient Database**

We contacted the principal investigator of each eligible study to explain our meta-analysis objectives and analysis plan. After all investigators agreed to share their databases, the databases were transferred to a central location under the auspices of 2 reviewers (FD, WA). Data were checked, explanations for coding and uncertain or missing data were clarified, and a single pooled database was developed.

**Data Extraction**

Two reviewers (FD, WA) independently completed data extraction. Disagreement was resolved by consensus or by the opinion of a third reviewer (AS), if necessary. The following data were collected from each database: age, sex, body weight, height, body mass index (BMI), waist circumference, presence of hypertension, presence of diabetes mellitus or impaired glucose tolerance, hyperlipidemia, and concomitant drugs. In addition, total cholesterol, HDL cholesterol and triglycerides values were obtained, and LDL values were calculated using the Friedewald formula with the exception of subjects with plasma triglycerides above 400 mg/dL. The metabolic syndrome was defined by the presence of three or more of the following risk factors according to the revised National Cholesterol Education Program (NCEP) guidelines (6): abdominal obesity (i.e. waist circumference of greater than 102 cm for men and of greater than 88 cm for women); triglycerides levels equal to or greater than 150 mg dL⁻¹; HDL cholesterol of lower than 40 mg dL⁻¹ for men and of lower than 50 mg dL⁻¹ for women, blood pressure of equal to or greater than 130
mmHg for systolic and/or 85 mmHg for diastolic blood pressure, and fasting glucose levels equal to or greater than 100 mg dL$^{-1}$. Patients currently receiving drug therapy for hypertension, diabetes, or dyslipidemia (only statins) were defined as having those disorders. Obesity was considered as a BMI greater than 30 kg/m$^2$. According to the Asia–Pacific criteria (7), obesity in Asians was considered as a BMI greater than 25 kg/m$^2$ and abdominal obesity as a waist circumference of greater than 90 cm for men and of greater than 80 cm for women.

**Statistical Analysis**

Separate analysis was carried out for case-control studies and for cohort studies. Descriptive statistics were used for variables in the pooled database. For continuous variables, we used mean and standard deviation (SD) for data with a normal distribution (Kolmogorov-Smirnov test) or median and inter-quartile range (IQR) for data with a non-normal distribution. For categorical data, we used frequencies and proportions.

We first calculated pooled odds ratios (OR) and 95% confidence intervals (CIs) of the aggregate data of the association between VTE and the metabolic syndrome for both case-control and cohort studies using a random-effects model (DerSimonian and Laird method) (8). The use of OR for cohort studies is due to the fact that in a study level meta-analysis differences in follow-up time cannot be considered. Statistical heterogeneity was evaluated using the I$^2$ statistic, which assesses the appropriateness of pooling the individual study results (9).

The association between metabolic syndrome and VTE was subsequently calculated on an individual patient level using a study-stratified approach.

*Analysis of case-control studies*

Pooled results were reported as odds ratio (OR) with 95% confidence intervals (CI) and with 2-sided probability values. We analysed two pre-specified subgroups: male and female patients, and young and old patients using the median age of the entire group (i.e. 50 years) as the cut off. The presence of heterogeneity among the pre-specified subgroups was evaluated using the chi-square
for heterogeneity (Mantel–Haenszel method). Logistic regression analysis was used to evaluate the influence of individual components of the metabolic syndrome on the odds of VTE. We defined age, BMI, sex, and the metabolic syndrome as potential confounding variables a priori, and included them in our regression analysis. Obesity was categorized as a dichotomous variable. Age was expressed as a continuous variable. To further explore if the association between the metabolic syndrome and VTE depends on the presence of abdominal obesity, we repeated the multivariate analysis after the exclusion of all patients with an elevated waist circumference. Multivariate analysis was subsequently performed including all previous variables and the individual components of the metabolic syndrome in the place of the metabolic syndrome.

*Analysis of cohort studies*

Kaplan-Meier analysis was used to calculate the cumulative incidence of VTE, with associated 95% confidence intervals. Follow-up was calculated as time from baseline to time when one of the following events occurred: the subjects developed VTE, the subject died from another cause, the date an individual moved out of the VTE catchment area or the last follow-up occurred. The HR and 95% confidence intervals of VTE were calculated for the metabolic syndrome using multivariable Cox regression. We allowed for across study heterogeneity by initially running a Cox model with random effect (“shared frailty” \( \gamma \) distributed) for the study variable. A study stratified Cox model under the fixed effect assumption was planned if no significant variance of \( \gamma \) distribution was found. Other variables a priori defined in the regression model were age, BMI, and sex as potential confounding variables. Subjects age was handled as a continuous variable and as a dichotomous variable using the median age as the cut off and obesity was categorized as a dichotomous variable using the ethnic specific definitions previously reported. All variables were retained if the p value was less than 0.10 or if they significantly affected the regression coefficients of other variables. The proportional hazards assumption was assessed by analysis of Schoenfeld residuals and a sensitivity analysis around the primary diagnosis was performed. Subsequently, we carried out the analysis including all previous variables and the individual components of the
metabolic syndrome in the place of the metabolic syndrome. Furthermore, if an association between the metabolic syndrome and VTE was found, hazard regression models were to be used to investigate the impact of increasing number of individual components of the metabolic syndrome on the risk of VTE, and to explore the influence of abdominal obesity on this relationship using subjects with no components of the metabolic syndrome were as a reference population.

All the analyses were performed using Minitab and SPSS 18 (SPSS Inc., Chicago, IL, USA).

REFERENCES


