Venous thromboembolism in association with features of the metabolic syndrome

J.G. Ray1,2,3, E. Lonn4,6, Q. Yi4, A. Rathe4, P. Sheridan4 and C. Kearon5,7 on behalf of the HOPE-2 investigators*

From the 1Departments of Medicine, 2Obstetrics and Gynecology, and 3Health Policy Management and Evaluation, St Michael’s Hospital, University of Toronto, Toronto, 4Population Health Research Institute, and 5Department of Medicine, Hamilton General Hospital, McMaster University, 6Department of Medicine, Division of Cardiology, Hamilton Health Sciences, and 7Henderson Research Center, Hamilton, Ontario, Canada

Received 23 May 2007 and in revised form 29 June 2007

Summary

Background: Central obesity, diabetes mellitus, dyslipidaemia and chronic hypertension—features of the metabolic syndrome—have been individually associated with venous thromboembolism (VTE). However, whether each of these factors additively increases the risk of VTE is uncertain.

Aim: To determine whether features of the metabolic syndrome independently increase the risk of VTE.

Design: Prospective cohort study derived from the Heart Outcomes Prevention Evaluation 2 (HOPE-2) randomized clinical trial.

Setting: One hundred and forty-five clinical centres in 13 countries.

Methods: We studied 5522 adults aged ≥55 years with cardiovascular disease or diabetes mellitus. At enrolment, 35% had 0–1 features of the metabolic syndrome, 30% had two, 24% had three and 11% had four. We defined symptomatic VTE as an objectively confirmed new episode of deep-vein thrombosis or pulmonary embolism.

Results: VTE occurred in 88 individuals during a median 5.0 years of follow-up. The incidence rate of VTE (per 100 person-years) was 0.30 with 0–1 features, 0.36 with two features, 0.38 with three features and 0.40 with four features of the metabolic syndrome (trend \( p = 0.43 \)). Relative to the presence of 0–1 features of the metabolic syndrome, the adjusted hazard ratio (95%CI) for VTE was 1.22 (0.71–2.08) with two features, 1.25 (0.70–2.24) with three features, and 1.26 (0.59–2.69) with four features.

Discussion: The number of features of the metabolic syndrome present was not a clinically important risk factor for VTE in older adults with vascular arterial disease.

Introduction

The metabolic syndrome—characterized by the presence of central obesity, dyslipidaemia, impaired handling of glucose and chronic hypertension—¹ is associated with an increased risk of
atherothrombosis, endothelial dysfunction and activation of the coagulation system. Obesity, type 2 diabetes mellitus and dyslipidemia have all been associated with venous thromboembolism (VTE). Ageno and colleagues recently reported a doubling of the risk of deep vein thrombosis (DVT) in association with the metabolic syndrome. However, it remains to be determined whether the risk of VTE increases in proportion to the number of features of the metabolic syndrome that are present.

Methods

We completed a prospective cohort study of VTE occurrence among the HOPE-2 study participants. As described elsewhere, HOPE-2 was a large randomized, placebo-controlled clinical trial that enrolled 5522 persons aged 55 years of age or older with a history of symptomatic cardiovascular disease, or who had diabetes mellitus and at least one additional risk factor for atherosclerosis. Participants from 145 clinical centres were randomized to receive a once-daily supplement containing 2.5 mg folic acid, 50 mg vitamin B6 and 1 mg vitamin B12, or matching placebo, and were followed for a median of 5 years. Written informed consent was obtained from all trial participants, and the trial was approved by the research ethics review board of each participating centre.

The prevalence of features of the metabolic syndrome was recorded at baseline, using the original inclusion criteria definitions in the HOPE-2 study, as follows: (i) central obesity, defined as a waist circumference >102 cm in men and >88 cm in women; (ii) diabetes mellitus, defined as a confirmed history of diabetes; (iii) pre-existing hypertension, defined as a systolic blood pressure >160 mmHg, diastolic blood pressure >90 mmHg, or treatment with antihypertensive medication(s); and (iv) dyslipidaemia, defined as a fasting serum total cholesterol >5.2 mmol/l or a high-density lipoprotein cholesterol (HDL-C) <0.9 mmol/l. Serum triglycerides were not measured.

VTE during follow-up included symptomatic, objectively diagnosed DVT or pulmonary embolism. DVT was confirmed by duplex leg ultrasonography or venography, and pulmonary embolism confirmed by ventilation-perfusion lung scanning, CT pulmonary angiography or conventional pulmonary angiography. Only one episode of VTE was counted per participant during follow-up. VTE that occurred in participants who did not have cancer at baseline and that did not occur within 90 days of a lower limb fracture or within 30 days of being hospitalized, were subcategorized as episodes of unprovoked VTE.

Incidence rates were calculated for the presence of 0–1, 2, 3 or 4 features, and trends were analysed using the Cochran-Armitage test. A time-to-event analysis was done using Cox’s proportional hazards regression model. A hazard ratio (HR) and 95% CI expressed the risk of VTE in association with 2, 3 or 4 features of the metabolic syndrome, relative to 0–1 features. A priori, we chose having 0–1 characteristics as the reference group, as few participants had no metabolic syndrome features. The HR was adjusted for the 11 variables listed in the footnote of Table 2. Incidence rates of VTE were compared in the presence vs. absence of each individual metabolic syndrome feature using a χ² test. Statistical significance was set at two-sided p < 0.05 for all analyses.

Results

There were 5522 participants, with a total of 25 215 person-years of observation. The mean age at enrolment was 68.9 years, and 28% were female (Table 1). The prevalence of each metabolic syndrome feature is listed in Table 1.

There were 88 episodes of VTE during follow-up, equivalent to an overall incidence rate of 0.35 per 100 person-years. Three episodes that were considered episodes of VTE in the original report of HOPE-2 were not included in this analysis, as the method of diagnosis was not indicated, and initiation of anticoagulant therapy was not documented. DVT occurred in 61 cases, pulmonary embolism in 33, and six had both DVT and pulmonary embolism. Of the 88 VTE events, 42 were unprovoked.

About 35% of participants had 0–1 features of the metabolic syndrome (Table 2). The incidence rate of VTE increased somewhat according to the number of metabolic syndrome features, but not significantly so (trend p = 0.43) (Table 2). Relative to the reference group (0–1 features), there was a 22% higher adjusted risk with two features of the metabolic syndrome, a 25% higher relative risk with three features and a 26% higher risk with four features (Table 2).

The incidence rates of VTE (per 100 person-years), comparing the presence vs. absence of each individual metabolic syndrome feature, were as follows: 0.35 vs. 0.35 for chronic hypertension (p = 0.97), 0.36 vs. 0.34 for dyslipidaemia (p = 0.75), 0.34 vs. 0.36 for diabetes mellitus (p = 0.81) and 0.43 vs. 0.27 for elevated waist circumference (p = 0.03).
Discussion

In a cohort of adults with cardiovascular disease or diabetes and additional vascular risk factor(s), we failed to observe a significant association between presence of a greater number of metabolic syndrome features and the risk of VTE.

As a study limitation, the number of participants with an episode of VTE prior to study entry was not known, and more than half of all VTE episodes were provoked, occurring near the time of a hospitalization or lower limb fracture. We also defined dyslipidaemia based on an elevated serum total cholesterol level or a low HDL-C, while conventional definitions rely on elevated serum triglycerides or low HDL-C.\(^1\) At the same time, there is ongoing debate about the relative importance of triglycerides in vascular thrombosis.\(^2,8\) Abnormal glucose metabolism was based on a history of diabetes mellitus, but plasma glucose levels or other markers of insulin resistance were not measured. Hypertension was based on receipt of antihypertensive therapy at baseline (which was so for the majority of participants\(^10,11\)), or the presence of a systolic blood pressure \(>160\) mmHg or a diastolic blood pressure \(>90\) mmHg, a higher value than the threshold of \(140/90\) mmHg conventionally used in defining the metabolic syndrome.\(^1,2\) Hence, we may have misclassified some participants as being free of one or more features of the metabolic syndrome, which would attenuate any true relationship between metabolic syndrome and VTE, especially unprovoked VTE. The current study was also statistically underpowered to detect a small increase in risk of VTE with metabolic syndrome features: there was only a 34% power to detect the 0.10% observed difference in the incidence of VTE among persons with 4 vs. 0–1 features of the metabolic syndrome.

Ageno et al recently completed a case-control study of 93 persons with unprovoked DVT at a mean age of 65 years.\(^9\) The adjusted odds ratio in their study was 1.94 (95%CI 1.04–3.63) for DVT in association with the metabolic syndrome, but the authors did not adjust for concomitant medication use, and did not explore the association between the individual components of the metabolic syndrome and VTE risk. Rather than using their ‘all-or-nothing’ definition for the metabolic syndrome, we considered the additive effect of having more than one feature. However, central obesity alone appeared to be a contributing risk factor, a finding consistent with other studies.\(^5,6,12\)

Better epidemiological evidence is needed to establish whether the metabolic syndrome is a risk factor for VTE, and, if so, which features are most

### Table 1  Characteristics of 5522 persons enrolled in the HOPE-2 study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68.9 ± 7.0</td>
</tr>
<tr>
<td>Females</td>
<td>1559 (28.3%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3039 (55.0%)</td>
</tr>
<tr>
<td><strong>Dyslipidaemia (mmol/l)</strong></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (&gt;5.2)</td>
<td>2639 (47.8%)</td>
</tr>
<tr>
<td>HDL-cholesterol (&lt;0.9)</td>
<td>886 (16.0%)</td>
</tr>
<tr>
<td>Total cholesterol (&gt;5.2) or HDL-cholesterol (&lt;0.9)</td>
<td>3050 (55.2%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2209 (40.0%)</td>
</tr>
<tr>
<td>Elevated waist circumference (&gt;102 cm in men, &gt;88 cm in women)</td>
<td>2836 (51.4%)</td>
</tr>
<tr>
<td>Waist circumference in males/females (cm)</td>
<td>101.8 ± 11.7/96.9 ± 14.1</td>
</tr>
<tr>
<td>Waist–hip-ratio in males/females</td>
<td>0.97 ± 0.26/0.88 ± 0.12</td>
</tr>
<tr>
<td>Body mass index (kg/m(^2))</td>
<td>29.6 ± 18.9</td>
</tr>
<tr>
<td>Non-White ethnicity</td>
<td>215 (3.9%)</td>
</tr>
<tr>
<td>Stable and/or unstable angina</td>
<td>3725 (67.5%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2999 (54.3%)</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>1111 (20.1%)</td>
</tr>
<tr>
<td>Coronary artery bypass surgery</td>
<td>1501 (27.2%)</td>
</tr>
<tr>
<td>Stroke or transient ischemic attack</td>
<td>684 (12.4%)</td>
</tr>
<tr>
<td>Carotid endarterectomy</td>
<td>146 (2.6%)</td>
</tr>
<tr>
<td>Intermittent claudication</td>
<td>133 (2.4%)</td>
</tr>
<tr>
<td>Peripheral artery surgery or percutaneous transluminal angioplasty</td>
<td>276 (5.0%)</td>
</tr>
<tr>
<td>Hospitalized for heart failure during study period</td>
<td>375 (6.8%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>633 (11.5%)</td>
</tr>
<tr>
<td>Cancer at baseline or during study period(^b)</td>
<td>859 (15.6%)</td>
</tr>
<tr>
<td>Hip or lower-limb fracture during study period</td>
<td>262 (4.7%)</td>
</tr>
<tr>
<td>Anti-platelet therapy use at baseline or during study period</td>
<td>4984 (90.2%)</td>
</tr>
<tr>
<td>Oral anticoagulant use at baseline or during study period</td>
<td>854 (15.4%)</td>
</tr>
<tr>
<td>Cholesterol-lowering therapy use at baseline or during study period</td>
<td>4352 (78.8%)</td>
</tr>
<tr>
<td>Any oestrogen replacement therapy use at baseline or during study period(^c)</td>
<td>282 (18.1%)</td>
</tr>
</tbody>
</table>

Data are numbers (%) or means±SD, as appropriate. \(^a\)Describes a baseline characteristic, unless otherwise specified. \(^b\)All cancers, except for non-melanoma skin cancer. \(^c\)Among 1559 women.
influential. The optimal study should be restricted to persons with unprovoked VTE. Until then, the metabolic syndrome should not be viewed as a clinically useful indicator of VTE risk.

Acknowledgements

This study was supported by a Canadian Institutes of Health Research Grant (MT-15418) and in-kind contributions by Jamieson Laboratories, Canada. Drs Ray and Kearon are supported by awards from the Canadian Institutes for Health Research.

References


Appendix 1. Participants in the HOPE-2 study

Venous thromboembolism sub-study

J. Ray, C. Kearon, E. Lonn.

Main study writing group

Steering committee

Events adjudication committee

Substudies and publication-policy committee
J. Probstfield (chair), R. Davies, E. Lonn, M. McQueen, J. Ostergren, S. Yusuf.

Data and safety monitoring board
D. Sackett (chair), R. Collins, E. Davis, C. Furberg, C. Hennekens, B. Pitt, W. Taylor

Senior study statistician
J. Pogue

Junior study statistician
P. Sheridan

Study coordination

Principal investigators and co-investigators
Austria
M. Grisold, W. Klein.

Belgium
G. Heyndrickx.

Brazil

Canada

Denmark
H. Juhl.

Finland
T. Hämäläinen.
Germany

The Netherlands
L.G. van Doorn.

Slovak Republic
M. Kotrec, V. Krpčiar, J. Lietava.

Spain

Sweden

Switzerland
P. Gerber, T. Moccetti, E. Safwan, G. Spinas.

United States