Thrombomodulin Gene Polymorphisms and Haplotypes and the Risk of Cardiovascular Events

A Prospective Follow-Up Study

K. Auro, K. Komulainen, M. Alanne, K. Silander, L. Peltonen, M. Perola, V. Salomaa

Background—Thrombomodulin is an anticoagulant expressed during endothelial activation and damage. To address the potential role of allelic variants of thrombomodulin gene in the pathogenesis of cardiovascular diseases, we analyzed in a prospective follow-up study 8 single-nucleotide polymorphisms (SNPs) across the thrombomodulin locus, covering all common (>5%) haplotypes.

Methods and Results—Two separate, stratified random samples of men and women 25 to 74 years of age were examined in Finland in 1992 and 1997. The total sample size was 14 140 individuals, with 7 (1997 cohort) to 10 (1992 cohort) years of follow-up. Altogether, 662 individuals had a history of cardiovascular events already at baseline. During the follow-up, 401 incident coronary events and 148 incident ischemic strokes were observed. The alleles and common haplotypes of 8 SNPs were tested in Cox proportional hazards models using incident coronary events, incident ischemic strokes, and total mortality as end points. None of the SNPs or major SNP haplotypes showed consistent association with the end points analyzed in the combined data.

Conclusions—Results from this prospective, population-based study suggest that common allelic variants of the thrombomodulin gene may not significantly contribute to the risk of cardiovascular events at the population level. (Arterioscler Thromb Vasc Biol. 2006;26:942-947.)

Key Words: coronary artery disease ■ stroke ■ thrombosis ■ genetic mutations ■ epidemiology

Thrombomodulin (THBD) is an important endothelial anticoagulant protein that activates protein C, resulting in inactivation of factor Va and factor VIII, and reduction of thrombin formation. The protein, encoded by a single exon, is an endothelial-specific type I membrane receptor that binds thrombin. THBD is also independently involved in anti-inflammatory responses. The expression of THBD gene reflects endothelial activation and damage.

Previous studies of the role of soluble THBD in the risk of coronary heart disease (CHD) have been controversial. A recent report suggested that soluble THBD may not represent an independent risk marker. However, other studies have suggested that soluble THBD would contribute to the risk of cardiovascular events together with other coagulation markers. In the Atherosclerosis Risk in Communities study, soluble THBD was found to be a strong predictor of incident CHD depending on the concentration of factor VIII. Lowered THBD concentration combined with elevated intercellular adhesion molecule-1 concentration appeared to increase the CHD risk. Further, several genetic studies have implied that variations in the THBD gene predict cardiovascular events; decreased function or expression of THBD could increase the risk of CHD and myocardial infarction. In all these studies, only 1 or 2 variants of the THBD gene have been analyzed, without capturing the full allelic diversity.

We aimed to test the significance of various THBD gene alleles for cardiovascular disease (CVD) in a prospective case-cohort study by analyzing 8 common (minor allele frequency >5%) SNPs that capture the common haplotype variants. To confirm any potential findings, 2 independent cohorts of the same population were used.

Methods

Study Setting

FINRISK is a study in which an independent population sample is collected every 5 years in Finland with an aim to evaluate population-wide risk factors for CVD and related disorders. Our study used 2 cohorts. FINRISK-92 is a sample with 5999 participants 25 to 64 years of age from 4 different regions of Finland: Helsinki and Kuopio regions, southwestern Finland, and North Karelia. The response rate was 76%. FINRISK-97 has 8141 participants 25 to 74 years of age with a 73% response rate, and also a fifth geographic region, Oulu province, was included. Both samples were drawn from the National Population Register and stratified by age, sex, and geographic area according to the principles of the World Health Organization Monitoring Trends Determinants in Cardiovascular
Disease Project. The cohorts were followed up for 10 years (1992 to 2001) and for 7 years (1997 to 2003) for fatal and nonfatal coronary and stroke events and total mortality. A combination of specific myocardial infarction and stroke registers, the National coronary and stroke events and total mortality. A combination of specific myocardial infarction and stroke registers, the National Hospital Discharge Register, and the National Causes of Death Register was used to identify these events during the follow-up. These registers cover every hospitalization in Finland and every death of a permanent resident of Finland, yielding in practice 100% coverage for the follow-up.

FINRISK belongs to a larger consortium of cohort studies: MORGAM. The present analyses have been performed following the procedures and infrastructure of the study consortium. A more detailed description of the cohorts, methodology, follow-up, and quality checks is presented at the MORGAM web site. The study was approved by the ethics committee of the National Public Health Institute of Finland.

The Case-Cohort Design
To use the case-cohort design, we first classified all individuals with cardiovascular (coronary or ischemic stroke) events at the baseline as baseline cases (n=11005662) and individuals with an incident coronary cardiovascular (coronary or ischemic stroke) events at the baseline as follow-up cases. These groups cover every hospitalization in Finland and every death of a permanent resident of Finland, yielding in practice 100% coverage for the follow-up.

Biological Measurements and DNA Extraction
A physical examination with blood pressure and anthropometric measurements was performed at baseline together with a questionnaire for phenotypic data concerning cardiovascular risk factors, such as hypertension, smoking, family history, medication, and previous cardiovascular events. Serum lipids were measured at semifasting state using an enzymatic method (CHOD-PAP; Boehringer-Mannheim). For FINRISK-92, concentrations of C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) were measured from frozen samples by solid-phase chemiluminescent immunometric assay (Immulite; Diagnostic Products Corporation). Whole blood samples for DNA extraction were stored at −20°C. DNA was extracted using standard protocols. Additionally, 100 samples did not contain enough genomic DNA, and 10 ng of DNA was amplified with GenomePher DNA amplification kit (GE Healthcare) before genotyping, as described previously.

Genetic Markers
To capture the major haplotypes and to form a tight locus map throughout the gene, 15 single-nucleotide polymorphisms (SNPs) relatively evenly spaced over the region were selected for genotyping. These SNPs cover all bins >2% of the Seattle SNP database. In addition to the haplotype tagging polymorphisms, other SNPs were selected in the 3’ end, promoter region, and in the coding exon and its close vicinity (Figure). Six of the initially chosen SNPs, including the majority of exonal SNPs, were monomorphic (frequency <0.5%) in the Finnish population when examined in 370 samples and were excluded from further analyses (rs3176122, rs3176121, rs1800578, rs1800579, rs1800577, and rs1800576). In addition, rs1042579, a SNP previously shown to associate with CVD, was in perfect linkage disequilibrium (LD; r²=1) with another SNP (rs3176123) and was left out because of technical reasons because the other one provided the same information. Based on the analysis with 60 Finnish trios, rs6113909, rs6082986, and rs1042580 were in relatively strong LD (r²=0.73 to 0.83; Table 2). To assure the coverage, we compared our SNP selection with the HapMap database. The HapMap shows 3 polymorphic SNPs in the

| TABLE 1. Numbers of Participants in Case-Cohort Samples by the Type of Event |
|---------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                           | Baseline CVD    | Incident CHD    | Incident Stroke| Death (any cause) | No Events† |
|                           | Men | Women | Men | Women | Men | Women | Men | Women | Men | Women | Men | Women |
| FINRISK-92                |     |       |     |       |     |       |     |       |     |       |     |       |
| Genotyping sample (n=1002) | 159 | 63    | 143 | 53    | 35  | 33    | 188 | 94    | 206 | 99   |     |       |
| Subcohort* (n=400)       | 29  | 3     | 30  | 4     | 8   | 3     | 34  | 9     | 206 | 99   |     |       |
| FINRISK-97                |     |       |     |       |     |       |     |       |     |       |     |       |
| Genotyping sample (n=1223)| 322 | 118   | 156 | 49    | 59  | 21    | 242 | 86    | 213 | 68   |     |       |
| Subcohort* (n=386)       | 50  | 6     | 14  | 3     | 10  | 2     | 35  | 8     | 213 | 68   |     |       |
| All                      | 481 | 181   | 299 | 102   | 94  | 54    | 430 | 180   | 419 | 167  |     |       |

*Subcohort is a part of the genotyping sample; †individuals with no cardiovascular events of any kind and alive at the end of the follow-up.

rs6113909
rs1962
rs1042580
rs3176121
rs1800578
rs1800577
rs3176119
rs6048519
rs6082986
rs3176123
rs3176122
rs1800579
rs1042579
rs1800576
rs3216183

The THBD gene on chromosome 20q11.21 and the SNPs initially chosen for genotyping.
testing between the genotypes and phenotypic data. The subcohorts were used as control groups for \( \chi^2 \) testing after excluding the CVD cases. Hazard ratios (HRs) were computed using a weighted Cox proportional hazards model, modified for the case-cohort design.21,22 Four different end points were used in all time-to-event analyses performed: incident coronary events, incident ischemic stroke events, incident cardiovascular events (the sum of incident coronary and ischemic stroke events), and total mortality. Both univariate and multivariate models were calculated for all genetic variants and common haplotypes (frequency >5%). The multivariate models were adjusted for traditional CVD risk factors: age, sex, total cholesterol to high-density lipoprotein (HDL) cholesterol ratio, smoking, diabetes, hypertension (RR \( \geq 140/90 \) mm Hg or antihypertensive medication), serum CRP (FINRISK-92), and body mass index, and also for cohort when using the combined data set. To analyze gene–environment interaction with smoking, a separate interaction term was created with smoking and each SNP and each common haplotype.

**Results**

Our study consisted of 112,436 person years of follow-up for total mortality and only slightly less for CVD events. The distributions of case-cohort samples by the event type are presented in Table 1. The subcohort members had a better lipid profile (lower total cholesterol and total to HDL cholesterol ratio, and higher HDL cholesterol) than the cases in both cohorts and both sexes. Diabetes and smoking were more common among the CVD cases than the subcohort members free of CVD (Table 3). The genotype distribution followed Hardy–Weinberg equilibrium in the subcohort for all SNPs (significance level 0.05). The

**Statistical Analyses**

The 2 cohorts were first analyzed separately and then combined. The PHASE2.1.1 program was used for haplotype estimation.18–20 Statistical analyses were performed using SAS v.8.2. General linear models procedures and \( \chi^2 \) tests were used for basic association
SNP allelic frequencies did not differ significantly between the incident cases and members of the subcohort (supplemental Table 1, available online at http://atvb.ahajournals.org). The majority of the altogether 35 haplotypes observed in the data sets (25 in the FINRISK-92 and 30 in the FINRISK-97) were rare: only 7 haplotypes had a frequency >5% (Table 4). No consistent association to the traditional CVD risk factors or to the serum inflammation markers (CRP, IL-6, and TNF-α) was observed with any of the individual SNPs or the 7 major haplotypes (data not shown).

In the FINRISK-92 cohort, all CVD events and baseline CVDs were significantly less common among the carriers of haplotype 6 (AAGGTG(-TT)G) than among the noncarriers (19.9% in the subcohort versus 14.6% in all CVD cases and 12.8% in baseline CVD cases; \( P = 0.0054 \) and \( P = 0.005 \), respectively). However, in the FINRISK-97, this haplotype was more common among the CVD cases (15.1%) than in the subcohort (12.7%). A similar situation was seen with other haplotypes: haplotype 4 (AAGTTG(+TT)T) associated to baseline CVD in the FINRISK-92 data (10.8% in the subcohort versus 14.6% among the baseline CVD cases; \( P = 0.0386 \)), whereas in FINRISK-97, no differences between the CVD cases and the subcohort were seen. The carriers of haplotype 2 (GGGTGC(+TT)T) had significantly more all-CVD events and baseline CVD in FINRISK-92 data (13.1% in the subcohort versus 18.1% in all CVD cases, \( P = 0.0369 \), and 18.9% in baseline CVD cases, \( P = 0.0089 \)), but again, no consistent association was seen in the other cohort. Instead, in FINRISK-97, this haplotype appeared to be more common in the subcohort (12.7%). A similar situation was observed for other haplotypes: haplotype 4 (AAGTTG(+TT)T) associated to baseline CVD in the FINRISK-92 data (10.8% in the subcohort versus 14.6% among the baseline CVD cases; \( P = 0.0386 \)), whereas in FINRISK-97, no differences between the CVD cases and the subcohort were seen. The carriers of haplotype 2 (GGGTGC(+TT)T) had significantly more all-CVD events and baseline CVD in FINRISK-92 data (13.1% in the subcohort versus 18.1% in all CVD cases, \( P = 0.0369 \), and 18.9% in baseline CVD cases, \( P = 0.0089 \)), but again, no consistent association was seen in the other cohort. Instead, in FINRISK-97, this haplotype seemed to be protective for total mortality (18.9% in the subcohort versus 12.7% in total mortality group; \( P = 0.0041 \)), an association not observed in the FINRISK-92 data, the findings were not statistically significant, and the HR of 0.76 suggested a protective rather than predisposing role.

With the end point total mortality, again a predisposing effect of GGGTCG(+TT)T was observed in the FINRISK-92 data (HR, 1.57; 95% CI, 1.06 to 2.33: \( P = 0.024 \)), but in the FINRISK-97 data, the role of this haplotype seemed to be protective (HR, 0.58; 95% CI, 0.39 to 0.87: \( P = 0.007 \)). When combining the cohorts, no association to CHD events or to total mortality was seen. (Table 5). No significant interaction could be detected between smoking and THBD genotypes or haplotypes (data not shown).

**Discussion**

We found in a prospective study setting that neither SNPs nor major haplotypes of the THBD gene showed any consistent association to the risk of cardiovascular events or total mortality. In the FINRISK-92 sample, the haplotype 2 (GGGTGC(+TT)T; Table 4) predisposed to coronary events in time-to-event analyses. However, in the FINRISK-97 data, this haplotype appeared to be more common in the subcohort and did not predispose to cardiovascular events. Instead, it seemed to have a protective role for total mortality in the whole cohort and in men, whereas the FINRISK-92 data suggested a predisposing role for total mortality. Previously, rs1042579 and rs3216183 have been reported to associate to CVD events, but these findings were not replicated in our study. rs1042579 was in perfect LD with rs3176123 in our data, and for technical reasons, the latter was chosen for genotyping because the information they provide is the same. Another SNP reported previously to associate with CVD, rs1800576, turned out to be monomorphic in our population. Previous literature has also suggested an interaction between smoking and THBD genotypes. Our present analysis of common allelic variants of the THBD gene did not provide support for such an interaction. Our results were not corrected for multiple testing. However, all the findings were
than individual SNPs alone, would be more relevant for haplotypes, providing more information on allelic diversity. Some recent studies have shown that estimation of haplotypes from population-based, nonfamily data with no phase information is always a potential source of error. Although the algorithm applied here with the PHASE2 program has been suggested to outperform many of the existing alternatives, it is probable that some errors still remain. We looked into this potential source of error by repeating the PHASE2 runs 40 times to assess the reliability of the estimations by noting any variations between the separate runs (data not shown). These haplotypes were rare and were excluded from all our analyses. We analyzed the THBD gene locus by applying the common disease–common variant hypothesis and selecting a highly informative set of SNPs covering the haplotype structures, using the Seattle SNP database and the haplotype blocks of the HapMap. The Seattle SNP database provides information on gene variation produced by complete resequencing of the full gene region in 23 individuals of European descent. Thus, the SNPs in this study were selected based on extensive knowledge of the common genetic variation and haplotype structure in this gene.28 Our SNPs produce a much denser map over the region than, for example, the 100K commercially available SNP set suggested to be used for genome-wide association would produce on average. Some recent studies have shown that haplotypes, providing more information on allelic diversity than individual SNPs alone, would be more relevant for statistical analysis of population-based studies. This is relatively obvious for multiple reasons: Haplotypes determine the genetic variance of a locus more accurately than individual SNPs. Furthermore, haplotypes could guide even to more rare variants embedded on the background of a relatively common haplotype and lead to identification of the real “causative” variant. A probably less common reason for haplotype association would be that all or the majority of selected variants would jointly contribute to the genetic risk, for example by interfering with multiple functional DNA domains (eg, protein-binding sites). However, the haplotype analyses here did not show consistent association to CVD. The strengths of the present study include its prospective, population-based design, large sample size, and a complete follow-up, producing a total of 112,436 follow-up years for the combined study sample. Additional power of our study design emerges from 2 independent cohorts of the same population with altogether 401 incident coronary and 148 incident stroke events, plus 662 prevalent CVD cases at baseline. This design enabled us to look for consistency of the findings and provided some safeguards against chance findings, which otherwise are common in genetic association studies. Finally, our study is a thorough analysis of the findings and provided some safeguards against chance findings, which otherwise are common in genetic association studies. The strengths of the present study include its prospective, population-based design, large sample size, and a complete follow-up, producing a total of 112,436 follow-up years for the combined study sample. Additional power of our study design emerges from 2 independent cohorts of the same population with altogether 401 incident coronary and 148 incident stroke events, plus 662 prevalent CVD cases at baseline. This design enabled us to look for consistency of the findings and provided some safeguards against chance findings, which otherwise are common in genetic association studies. Finally, our study is a thorough analysis of the common variations present in the THBD gene. A limitation of the study was that we could only examine the allelic diversity of the gene and did not have data on the plasma concentrations of soluble THBD. Neither did we have functional studies on the potential biological or biochemical effects of the SNPs analyzed. Despite these limitations, our data suggest that common genetic variants of the THBD gene may not contribute to the risk of cardiovascular events.

### Table 5: Association of the THBD Haplotype GGGTCG(+-TT)T With the End Points Studied

<table>
<thead>
<tr>
<th></th>
<th>FINRISK – 92(^*)</th>
<th>FINRISK – 97(^†)</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR 95% CI</td>
<td>P</td>
<td>HR 95% CI</td>
</tr>
<tr>
<td>CHD‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1.73 0.97–3.10 0.064</td>
<td>0.86 0.49–1.51 0.603</td>
<td>1.11 0.75–1.67 0.594</td>
</tr>
<tr>
<td>Women</td>
<td>1.61 0.40–6.44 0.502</td>
<td>0.62 0.16–2.43 0.495</td>
<td>1.03 0.41–2.55 0.953</td>
</tr>
<tr>
<td>All</td>
<td>1.79 1.10–2.91 0.018</td>
<td>0.76 0.47–1.23 0.259</td>
<td>1.07 0.76–1.52 0.686</td>
</tr>
<tr>
<td>Stroke§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>0.41 0.09–1.86 0.244</td>
<td>1.44 0.67–3.10 0.353</td>
<td>1.31 0.67–2.55 0.426</td>
</tr>
<tr>
<td>Women</td>
<td>1.35 0.32–5.58 0.683</td>
<td>0.36 0.05–2.39 0.290</td>
<td>0.27 0.03–2.40 0.239</td>
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<tr>
<td>All</td>
<td>0.63 0.27–1.45 0.277</td>
<td>0.95 0.50–1.80 0.878</td>
<td>0.76 0.46–1.42 0.391</td>
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<tr>
<td>CVD</td>
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</tr>
<tr>
<td>Men</td>
<td>1.45 0.83–2.54 0.197</td>
<td>1.06 0.64–1.73 0.829</td>
<td>1.15 0.79–1.66 0.467</td>
</tr>
<tr>
<td>Women</td>
<td>1.56 0.54–4.52 0.414</td>
<td>0.52 0.15–1.73 0.285</td>
<td>0.93 0.43–2.01 0.863</td>
</tr>
<tr>
<td>All</td>
<td>1.45 0.91–2.23 0.121</td>
<td>0.85 0.55–1.30 0.846</td>
<td>1.03 0.75–1.40 0.887</td>
</tr>
<tr>
<td>Total mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1.56 0.96–2.55 0.073</td>
<td>0.57 0.31–0.82 0.0056</td>
<td>0.83 0.59–1.17 0.283</td>
</tr>
<tr>
<td>Women</td>
<td>1.75 0.80–3.81 0.167</td>
<td>0.84 0.29–2.45 0.836</td>
<td>1.25 0.67–2.34 0.492</td>
</tr>
<tr>
<td>All</td>
<td>1.57 1.06–2.33 0.024</td>
<td>0.58 0.39–0.87 0.007</td>
<td>0.91 0.69–1.20 0.521</td>
</tr>
</tbody>
</table>

\(^*\) Adjusted for age, sex when relevant, smoking, hypertension, total cholesterol/HDL ratio, diabetes, and BMI. Also adjusted for CRP in CHD and CVD analyses.

\(^†\) Adjusted for age, and sex when relevant, smoking, hypertension, total cholesterol/HDL ratio, diabetes, and BMI.

‡CHD, first coronary event during follow-up; §Stroke, first ischemic stroke during follow-up; ||CVD, first coronary event or ischemic stroke during follow-up.
Acknowledgments

This work was supported by the Center of Excellence of Disease Genetics by the Academy of Finland, Biocentrum Helsinki, Sigrid Juselius Foundation, Jenny and Antti Wihuri Foundation, the Finnish Heart Foundation, the Finnish Academy (grant 53646), and a grant from the NIH/NHLBI 1R01HL70150-01A1. MORGAM is a part of the GenomeEuwin project, which is supported by the European Commission under the program “Quality of Life and Management of the Living Resources” of Fifth Framework Programme (QLG2-CT-2002-01254). We thank the participants of the FINRISK-92 and FINRISK-97 studies. We thank Susanna Anjala, Pekka Ellonen, Minttu Jussila, Siv Kaapinlaa, Minna Levander, and Anne Nyberg for excellent technical assistance, Tero Hiekkinen and Zygmantas Cepaitis for assistance in the data management, and Dr Sangita Kulathinal and Olli Saarela for statistical assistance.

References


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Arterioscler Thromb Vasc Biol. 2006;26:942-947; originally published online February 2, 2006; doi: 10.1161/01.ATV.0000208365.45200.41

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

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Supplementary Table I: Minor Allele Frequencies for 8 SNPs of the Thrombomodulin Gene.

<table>
<thead>
<tr>
<th>SNP</th>
<th>FINRISK-92 Males</th>
<th>FINRISK-92 Females</th>
<th>FINRISK-97 Males</th>
<th>FINRISK-97 Females</th>
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<tr>
<td></td>
<td>CVD1*</td>
<td>CVD2 †</td>
<td>Subcoh‡</td>
<td>CVD1</td>
</tr>
<tr>
<td></td>
<td>(n=170)</td>
<td>(n=159)</td>
<td>(n=220)</td>
<td>(n=86)</td>
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<td>0.37</td>
<td>0.46</td>
<td>0.38</td>
<td>0.40</td>
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<td>0.37</td>
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<td>0.14</td>
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<td>rs6048519</td>
<td>0.44</td>
<td>0.48</td>
<td>0.43</td>
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</tr>
</tbody>
</table>

* CVD1: Individuals with first coronary or ischemic stroke event during the follow-up
† CVD2: Individuals with baseline CVD
‡ Individuals with a history of cardiovascular event at baseline or during follow-up excluded from the subcohort