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## **Risk of arterial thrombosis in carriers of familial thrombophilia**

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overuse and underuse of thromboprophylaxis, thereby confirming and extending previously published data [7–9].

In conclusion, decision-making for thromboprophylaxis in current clinical practice seems too random in acutely ill medical patients. Our results point out to the need for developing and implementing explicit evidenced-based criteria and to standardize the indications for prevention of venous thromboembolism in these patients, as recently reminded [10]. Because the present heterogeneity and inadequacy of practice is probably large because of the lack of clear, immediately applicable guidelines, the simple score assessed in the present study might represent a promising step toward this necessary standardization of practice.

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## Risk of arterial thrombosis in carriers of familial thrombophilia

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Factor (F) V Leiden, the prothrombin G20210A mutation and inherited deficiencies in antithrombin, protein C, and protein S are established risk factors for venous thrombosis [1], but their impact on arterial disease is less evident because of a paucity of large studies [2–6]. Results appear contradictory [7–11], which may be explained by the presence or absence of additional

cardiovascular risk factors. The risk of arterial disease may stand out more in thrombophilic families, in which multiple risk factors interact in increasing the risk of thrombosis [12,13].

In 1993, the European Prospective Cohort on Thrombophilia (EPCOT) study was initiated. The primary aim of this study was to determine the risk of venous thrombosis in thrombophilic families. In addition, information was gathered on arterial events [e.g. myocardial infarction (MI), ischemic stroke (IS) and transient ischemic attacks (TIA)]. The design of the study has been described in detail previously [14,15]. All participants were enrolled between March 1994 and September 1997. The inherited defects studied were the FV Leiden mutation, deficiencies of protein C, protein S or antithrombin, or a combination of these defects. During follow-up, we

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**Table 1** Number and incidence per 1000 person years of a first MI or IS in thrombophilic individuals and controls without a VT history before inclusion in the EPCOT study

	Total ( <i>n</i> )	Total events ( <i>n</i> )	MI ( <i>n</i> )	IS ( <i>n</i> )	Mean age at event (range)	Incidence MI/IS per 1000 person years (95% CI)
Controls	1125	5	5	0	58 (41–77)	0.2 (0.1–0.4)
Men	588	4	4	0	58 (41–77)	0.3 (0.1–0.7)
Women	537	1	1	0	57	0.1 (0.0–0.4)
Thrombophilics	622	24	15	9	48 (24–67)	1.7 (1.1–2.6)
Men	220	19	12	7	48 (29–65)	3.8 (2.3–6.0)
Women	402	5	3	2	45 (24–67)	0.6 (0.2–1.3)
PC	150	5	2	3	48 (30–65)	1.5 (0.5–3.5)
PS	111	4	3	1	48 (41–58)	1.8 (0.5–4.5)
AT	92	3	0	3	39 (29–49)	1.5 (0.3–4.3)
FVL	208	10	9	1	52 (43–67)	2.1 (1.0–3.9)
> 1 defect	61*	2	1†	1‡	38 (24–53)	1.4 (0.2–5.1)

MI, Myocardial infarction; IS, ischemic stroke; CI, confidence interval; PC, protein C deficiency; PS, protein S deficiency; AT, antithrombin deficiency; FVL, factor V Leiden.

\*13 with PC-FVL, one with PC-PS, 15 with PS-FVL, four with AT-FVL, 15 with PT20210A-FVL, nine with PC-PT20210A, three with PS-PT20210A and one with AT-PT20210A.

†This person had PS deficiency and FVL.

‡This person had AT deficiency and FVL.

determined the presence of the prothrombin G20210A mutation as an additional defect in thrombophilic individuals. We calculated the absolute risk (incidence) of arterial events before study entry in participants older than 20 years at study inclusion. The incidence was calculated by dividing the number of arterial events by the total of observation-years, i.e. the number of years between the age of 20 and inclusion in the study or a first MI or IS, whichever occurred first. TIAs were not taken into account, as the diagnosis of a TIA is more difficult. The 95% confidence intervals (95% CI) were calculated according to the Poisson distribution for the number of events [16]. Hazard ratios as an estimation of the relative risk were calculated by Cox-regression for men and women separately. To minimize selection bias, we included in this analysis only individuals who were screened for thrombophilia because of a personal or family history of venous thrombosis and not for other reasons such as arterial thrombosis or family planning. To avoid any influence from the use of (long-term) anticoagulation on which we had no detailed information before study entry, we focused on participants who did not experience venous thrombotic events and we excluded all asymptomatic individuals on long-term anticoagulation during follow-up. Because of a small number of arterial events during follow-up ( $n = 6$ ) in thrombophilic individuals without a history of venous or arterial thrombosis and anticoagulant treatment, we did not calculate the incidence of arterial events during prospective follow-up.

In total, 622 individuals with thrombophilia (60 probands and 562 relatives) and 1125 controls (878 partners and 247 friends) fulfilled the eligibility criteria. The age at inclusion was 43 years (range 21–91) in thrombophilic individuals and 43 years (range 21–87) in controls. Table 1 shows the incidence per 1000 person years of a first MI and IS before study entry for the thrombophilic individuals and controls. The mean age at the first MI or IS was 58 years (range 41–77) in controls and 48 years (range 24–67) in thrombophilic individuals (Table 1).

The risk of developing a first MI or IS associated with thrombophilia was increased 12-fold in men (relative risk 12.1; 95% CI 4.1–35.7) and sevenfold in women (relative risk 7.1; 95% CI 0.8–61.2). The relative risk was 8.8 (95% CI 2.9–27.0) in men and 4.5 (95% CI 0.5–43.5) in women when we excluded the probands, i.e. the first of a family in whom thrombophilia was detected. The incidence ranged from 1.4 per 1000 person years in those with combined defects to 2.1 per 1000 person years in FV Leiden carriers (Table 1). MIs were more common than ISs in individuals with FV Leiden, whereas no MIs were present among individuals with antithrombin deficiency (Table 1).

Our results show an increased risk of arterial thrombosis in individuals with inherited thrombophilia. Unfortunately, this is a retrospective analysis and we lack information on additional cardiovascular risk factors such as smoking and hypertension to perform further risk stratification. The risk was lower than the risk found for venous thrombosis before study entry (4.4 per 1000 person years) [14]. The incidence of MI or IS in the controls was lower than the incidence in controls in a recent retrospective study (0.5 per 1000 for MI and 0.2 per 1000 for IS) [17]. However, they also included relatives from probands with premature atherosclerosis [17]. On the other hand, the incidences in our study could be underestimated as we focussed on participants who did not experience venous thrombotic events and did not use long-term anticoagulation treatment, who might have had the highest risk of developing arterial events. Incidences could also be overestimated because we did not have information on whether the arterial events were objectively confirmed and underestimated because we did not include those with fatal arterial events. Nevertheless, it is unlikely that any of these limitations would explain a difference between thrombophilic individuals and controls, and therefore, these findings indicate that familial coagulation defects do affect the risk of arterial disease and that venous and arterial events share common risk factors.

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# Alternatively spliced tissue factor in mice: induction by *Streptococcus pneumoniae*

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In the traditional view of blood coagulation, vascular injury leads to the exposure of extravascular membrane-bound tissue factor (TF) to the blood stream thereby initiating blood clot formation. Essential in this model of hemostasis is that TF is normally not in contact with blood as it resides in the adventitial lining of blood vessels. However, a soluble TF variant, which is derived by alternatively splicing of the TF