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Prognostic markers in young patients with premature coronary heart disease

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ABSTRACT

Objectives: To evaluate the survival and prognostic implications of cardiovascular, inflammatory and prothrombotic risk factors in young patients with premature coronary heart disease (CHD).
Methods: Follow-up data were obtained from 353 young patients with a first cardiac event (men ≤45 years and women ≤55 years). Baseline characteristics on traditional risk factors were collected at the time of the first event, and plasma levels of C-reactive protein (CRP), von Willebrand Factor (VWF), and fibrinogen were measured one to three months after the first event to exclude an acute phase response. We performed age and sex adjusted Cox regression analyses to assess the relationship between these factors and recurrent events with three different endpoints: all cause mortality, recurrent cardiac event (myocardial infarction or revascularisation procedure), and any recurrent event (cardiac event, cerebrovascular event or all cause mortality).
Results: During a total follow-up time of 1483 person years (mean 4.2 years), 11 patients died (3%), 42 patients had a recurrent cardiac event (12%), and 53 patients had any recurrent event (15%). CRP was associated with an increased risk of any recurrent event (HR 1.28[95% CI = 1.02–1.59] per unit increase in lnCRP). Also, both CRP (5.00[1.04–24.04]) and fibrinogen (5.04[1.05–24.23]) were associated with all cause mortality when levels were above the 50th percentile.
Conclusions: Fifteen percent of young patients with a first cardiac event have a recurrent event or die within a median follow-up of 4.2 years. In these young patients we have shown that, independently of cardiovascular risk factors, high CRP levels contribute to the risk of recurrent events, including all cause mortality, and high fibrinogen levels are associated with all cause mortality.

1. Introduction

Despite many improvements in medical treatment, coronary heart disease (CHD) is still a major health concern in today's clinical practice. Only a very small percentage (<10%) of all patients with myocardial infarction is below the age of 45 years [1,2]. However, the number of young individuals with coronary atherosclerosis is probably much larger than can be currently estimated. Autopsies have shown that about 50% of young individuals have coronary atherosclerosis [3]. Few studies have accomplished to include sufficiently large groups of young CHD patients to investigate their risk profiles and prognosis. However, there is a growing need to identify those at risk for recurrent events, since especially young CHD patients comprise an interesting group for preventive cardiology.

Generally, young subjects with CHD have multiple traditional risk factors and have a different risk profile than older patients [4,5]. Also, the occurrence of recurrent symptoms and events is surprisingly common. Reported long-term event rates including mortality are as high as 50% [6,7]. The main predictors of long-term recurrent events and mortality in young subjects that have been established over the years are diabetes, a low ejection fraction, atrial fibrillation, use of antiarrhythmic drugs, continued smoking, and plasma plasminogen activator inhibitor (PAI-1) concentration [5–7]. Moreover, there is a growing believe that prognostic risk factors differ between men and women.

In the last few decades novel risk factors for CHD have been identified in previously healthy subjects. Examples of these are inflammatory markers, such as C-reactive protein (CRP), and prothrombotic markers, including von Willebrand Factor (VWF) and fibrinogen [8–11]. However, information on their predictive value

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for recurrent cardiovascular events in especially young patients is very scarce.

Considering the necessity to recognize young CHD patients at risk for a recurrent event and to improve prevention strategies in this special group of patients, we aimed to evaluate the prognostic implications of traditional risk factor, CRP, VWF, and fibrinogen in a unique and relatively large cohort of young patients with a first acute coronary syndrome.

2. Methods

2.1. Patients

This follow-up study is a sub-study of the 'Genetic risk factors for Arterial Thrombosis at young age: the role of TAFI and other Coagulation factors' (ATTAC) study. The ATTAC study is a single-center, case-control study, described in more detail previously [12]. For this sub-study we obtained follow-up data from all cardiac patients ($N = 385$), who were consecutively recruited one to three months after their first event (acute myocardial infarction or unstable angina pectoris) at the department of Cardiology at the Erasmus Medical Center Rotterdam between 2001 and 2010. Patients were eligible for inclusion when they were 18–45 years for males and 18–55 years for females at the time of diagnosis. The follow-up study was approved by the medical research board at Erasmus University Medical Center and written informed consent was obtained from all participants at inclusion.

After all cardiac patients were asked to participate in the follow-up study, data on their current health status were obtained via a telephone interview and verified in medical records. We used three different endpoints: all cause mortality, recurrent cardiac event, which was defined as a myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft surgery, and any recurrent event, including a cardiac event (myocardial infarction or revascularisation procedure), cerebrovascular event (CVA or TIA) or all cause mortality.

Of all cardiac patients, 22 patients were lost to follow-up, mainly because of emigration or because their contact information had changed and could not be traced down. Ten patients gave no permission for the follow-up study. We could include 353 cardiac patients in our analyses. Between the first event and the start of the follow-up study eleven patients died. Since we could not obtain informed consent of these patients to investigate their cause of death, we classified these patients as deaths of any cause.

2.2. Blood sampling

Blood was drawn one to three months after the first ischemic event by venipuncture in the antecubital vein using the Vacutainer system (Becton–Dickinson, Plymouth, UK). Blood for coagulation measurements was collected in 3.2% trisodium citrate (9:1 vol/vol). Citrated blood was centrifuged within 1 h at 2000 × g for 10 min at 4 °C. Plasma was additionally centrifuged at 14,000 × g for 10 min at 4 °C and stored in aliquots at −80 °C.

2.3. Laboratory measurements

CRP was determined in serum using Rate Near Infrared Particle Immunoassay (Immage Immunochemistry System, Beckman Coulter, USA). This system measures concentrations ranging from 0.2 to 1440 mg/L, with a within-run precision <5.0%, a total precision <7.5%, and a reliability coefficient of 0.995.

VWF antigen (VWF:Ag) was determined at baseline with an in-house ELISA with polyclonal rabbit anti-human VWF antibodies and horseradish peroxidase conjugated anti-human VWF antibodies (DakoCytomation, Glostrop, Denmark) for catching and tagging, respectively. The intra-assay coefficient of variation was 5.7%, and the interassay coefficient of variation was 7.8%.

Plasma fibrinogen was measured as described by von Clauss [13] on the Sysmex CA 1500 coagulation analyzer (Dade Behring, Leusden, Netherlands). The within-day variation was 1.7% and the between-day variation 6.3%.

Cholesterol and HDL were determined on Modular Analytics® (Roche Diagnostics, Mannheim, Germany). The total assay variation was 3% and 2% for cholesterol and HDL, respectively.

2.4. Statistical analysis

Data on population characteristics are presented as means and standard deviations for continuous variables and as counts and percentages for categorical data. Since CRP and VWF:Ag levels were skewed, these data were natural logarithmically transformed (lnCRP and lnVWF:Ag, respectively) and presented as geometric mean and standard deviation. We used Cox regression analyses adjusted for age and sex to assess the relationship between the selected markers and the risk of recurrent events. For the association between traditional cardiovascular risk factors and the risk of recurrent events a sex-specific analysis was performed additionally. Since CRP, VWF, and fibrinogen are associated with cardiovascular risk factors, all associations were adjusted additionally for cardiovascular risk factors present at inclusion (family history of cardiovascular disease, hypertension, diabetes, cholesterol, high-density lipoprotein, hypercholesterolemia, BMI and smoking). The analyses with all cause mortality as endpoint were not adjusted for sex or diabetes, since only one of all deaths was female and none had diabetes. Levels of CRP, VWF and fibrinogen were divided into two groups: below and above the 50th percentile. Cut-off level for CRP was 0.87 mg/L, for VWF 1.23 IU/mL, and 3.4 g/L for fibrinogen.

Cumulative survival curves and cumulative event-free survival curves were constructed using the Kaplan–Meier (KM) method. In order to compare the KM-curves we used a Log-rank test.

Statistical analyses were performed with SPSS for Windows, version 17.0 (SPSS Inc, Chicago, USA). A two-sided value of $p < 0.05$ was considered statistically significant.

3. Results

Our study population consists of 353 patients with a total follow-up of 1483 person years (mean ± SD, 4.2 ± 2.6 years). Baseline characteristics are shown in Table 1, as well as the reference values and the baseline characteristics of 487 control subjects that were included in the ATTAC study. Of all cardiac patients, 299 had a myocardial infarction as first event and 54 had unstable angina pectoris as first event. Most patients received a drug-eluting stent (91%) and had single vessel disease (76%). Left ventricular ejection fraction was available in 109 subjects: good (>55%) in 73 subjects, moderate (40–55%) in 32 subjects, and poor (<40%) in 4 subjects.

During follow-up, 11 patients died of any cause (3%), 42 patients had a recurrent cardiac event (12%), and two patients had a cerebrovascular event (<1%). The mean age of the total follow-up cohort was 43.8 years and 156 (44%) patients were female. Of all patients, 98% was on anti-platelet therapy (aspirin and/or clopidogrel), 95% used statins, and 94% used any blood pressure lowering drugs, including bèta-blockers, ACE-inhibitors, calcium antagonists, diuretics or angiotensin-II receptor antagonists. In the total group, both age and sex did not differ between patients who had a recurrent event and patients without reinfarction.

Classical cardiovascular risk factors were not associated with recurrent cardiac events (Table 2). However, in a sex-specific

Table 1
Baseline characteristics.

	Cardiac patients $N = 353$	Controls ATTAC study $N = 487$	Reference values
Age (years)	43.8 ± 5.9	38.8 ± 7.8	
Female sex, *N* (%)	156 (44%)	293 (63%)	
First event			
Myocardial infarction	299 (85%)		
NSTEMI	232 (89%)		
STEMI	30 (11%)		
Unstable angina pectoris	54 (15%)		
Family history of cardiovascular disease, *N* (%)	173 (49%)	112 (23%)	
Hypertension, *N* (%)	88 (25%)	30 (7%)	
Diabetes, *N* (%)	35 (10%)	8 (2%)	
Smoking, current, *N* (%)	133 (38%)	123 (25%)	
Smoking, former, *N* (%)	165 (47%)	129 (27%)	
Total cholesterol (μmol/L)	4.2 ± 0.9	5.0 ± 0.9	2.9–6.5
HDL (μmol/L)	1.2 ± 0.4	1.5 ± 0.4	>1.55
Hypercholesterolemia, *N* (%)	172 (49%)	167 (42%)	
BMI (kg/m^2)	27 ± 5	25 ± 4	
Bèta-blockers, *N* (%)	291 (82%)	14 (3%)	
ACE-inhibitors, *N* (%)	210 (60%)	4 (1%)	
Diuretics, *N* (%)	22 (6%)	8 (2%)	
Calcium antagonists, *N* (%)	31 (9%)	2 (0.4%)	
Angiotensin-II receptor antagonists, *N* (%)	14 (4%)	7 (2%)	
Statins, *N* (%)	336 (95%)	8 (2%)	
Anti-platelet drugs, *N* (%)	347 (98%)	6 (1%)	
CRP (mg/L)	0.78 ± 2.1	0.65 ± 1.9	0.2–7.3
VWF:Ag (IU/mL)	1.19 ± 0.7	1.04 ± 0.4	0.60–1.40
Fibrinogen (g/L)	3.45 ± 0.7	ND	1.5–3.6

Summary statistics for continuous variables are presented as mean ± standard deviation. Categorical data are summarized as percentages.
ND = not determined.

analyses diabetes was associated with any recurrent event (2.66 [95% CI = 1.02–6.94]) and a recurrent cardiac event (4.11 [95% CI = 1.50–11.27]) in men. In women, current smoking and former smoking were significantly associated with both recurrent cardiac event and any recurrent event. Current smoking had an HR of 6.61 [95% CI = 1.52–28.78] for any recurrent event and an HR of 12.3 [95% CI = 1.63–93.45] for a recurrent cardiac event. Former smoking had an HR of 5.96 [95% CI = 1.16–30.71] for any recurrent event and an HR of 9.82 [95% CI = 1.10–87.88] for a recurrent cardiac event.

CRP levels were higher in patients who died of any cause (1.04 mg/L), in patients with a recurrent cardiac event (1.02 mg/L), and in patients with any recurrent event (1.06 mg/L) than in patients without reinfarction (0.73 mg/L). The age and sex adjusted hazard ratios per unit increase in lnCRP levels were 1.56 [95% CI = 0.92–2.63] for all cause mortality, 1.23 [95% CI = 0.96–1.59] for a recurrent cardiac event, and 1.28 [95% CI = 1.02–1.59] for any recurrent event (Table 3). In a multivariate model including all traditional risk factors the hazard ratios per unit increase in lnCRP levels were 1.80 [95% CI = 0.95–3.39] for all cause mortality, 1.21 [95% CI = 0.90–1.63] for a recurrent cardiac event, and 1.35 [95% CI = 1.03–1.77] for any recurrent event. Patients with CRP levels above the 50th percentile had a 5-fold increased risk of all cause mortality (HR 5.00 [95% CI = 1.04–24.04]). Moreover, it is clearly shown that subjects with the highest CRP levels have a lower cumulative survival (93%) than subjects with the lowest CRP levels (99%, log-rank test $p < 0.05$) (Fig. 1A). Also, the cumulative event-free survival was lower in subjects with the highest CRP levels (78%) than in subjects with the lowest CRP levels (81%, log-rank test $p = 0.13$), though just below the statistical significance level (Fig. 1B).

The mean fibrinogen levels were 3.8 ± 0.7 g/L in patients who died of any cause, 3.4 ± 0.9 g/L in patients with a recurrent cardiac event, 3.4 ± 0.9 g/L in patients with any recurrent event, and 3.5 ± 0.7 g/L in patients without reinfarction. High fibrinogen levels were weakly correlated with an increased risk of all cause mortality only (Table 3). Subjects with fibrinogen levels above the 50th percentile had a significantly increased risk of all cause mortality (HR 5.04 [95% CI = 1.05–24.23]), also after adjustment for classical cardiovascular risk factors (HR 10.41 [95% CI = 1.18–91.80]). The cumulative survival of patients with the highest fibrinogen levels was 94% compared to 98% in patients with the lowest fibrinogen levels (Log-rank test $p = 0.05$) (Fig. 2A).

The mean VWF:Ag levels were 1.1 ± 1.0 IU/mL in patients who died of any cause, 1.2 ± 0.5 IU/mL in patients with a recurrent cardiac event, 1.2 ± 0.6 IU/mL in patients with any recurrent event, and 1.2 ± 0.7 IU/mL in patients without reinfarction. VWF:Ag levels were not associated with recurrent events (Table 3).

Table 2
Association between traditional cardiovascular risk factors and the risk of recurrent events.

	All cause mortality HR (95% CI)	Recurrent cardiac event HR (95% CI)	Any recurrent event HR (95% CI)
Age	0.98 (0.89–1.08)	0.98 (0.93–1.03)	0.99 (0.94–1.03)
Female sex	–	1.26 (0.68–2.33)	0.98 (0.57–1.67)
Family history of cardiovascular disease	0.69 (0.19–2.43)	0.96 (0.52–1.78)	0.91 (0.53–1.56)
Hypertension	0.26 (0.03–2.04)	0.59 (0.26–1.34)	0.56 (0.27–1.14)
Diabetes	–	1.88 (0.84–4.25)	1.39 (0.63–3.07)
Smoking, current	0.40 (0.09–1.67)	2.07 (0.96–4.43)	1.42 (0.76–2.66)
Smoking, former	1.34 (0.32–5.60)	1.96 (0.73–5.28)	1.66 (0.74–3.69)
Total cholesterol	1.47 (0.77–2.81)	1.11 (0.79–1.56)	1.17 (0.88–1.57)
HDL	1.31 (0.29–6.01)	1.20 (0.55–2.59)	1.29 (0.66–2.51)
Hypercholesterolemia	1.72 (0.44–6.68)	1.01 (0.54–1.91)	1.10 (0.63–1.92)
BMI	0.94 (0.82–1.08)	0.99 (0.93–1.06)	0.98 (0.93–1.04)

Cox regression analysis to assess the relationship between traditional cardiovascular risk factors and the risk of recurrent events. Recurrent cardiac event was defined as a myocardial infarction or revascularisation procedure. Any recurrent event was defined as a cardiac event, a cerebrovascular event or all cause mortality. Data are presented as hazard ratios with 95% confidence intervals. Analyses with the endpoint all cause mortality were not performed for female sex (number of event = 1) and diabetes (number of event = 0).

Table 3
Adjusted association between inflammatory and prothrombotic markers and the risk of recurrent events.

Variable	Model 1 HR (95% CI)	Model 2 HR (95% CI)
All cause mortality		
lnCRP	1.56 (0.92–2.63)	1.80 (0.95–3.39)
lnVWF:Ag	0.90 (0.22–3.64)	1.33 (0.21–8.23)
Fibrinogen	1.85 (0.91–3.80)	1.79 (0.80–3.97)
Recurrent cardiac event		
lnCRP	1.23 (0.96–1.59)	1.21 (0.90–1.63)
lnVWF:Ag	1.12 (0.53–2.36)	1.10 (0.48–2.56)
Fibrinogen	0.87 (0.53–1.40)	0.88 (0.52–1.50)
Any recurrent event		
lnCRP	1.28 (1.02–1.59)	1.35 (1.03–1.77)
lnVWF:Ag	1.06 (0.54–2.05)	1.20 (0.55–2.62)
Fibrinogen	1.05 (0.70–1.57)	1.15 (0.74–1.77)

Cox regression analysis to assess the relationship between selected biomarkers (CRP, von Willebrand Factor, and fibrinogen) and the risk of a recurrent event. lnCRP and lnVWF:Ag are the natural logarithmically transformed CRP and vWF:Ag levels. Recurrent cardiac event was defined as a myocardial infarction or revascularisation procedure. Any recurrent event was defined as a cardiac event, a cerebrovascular event or all cause mortality. Data are presented as hazard ratios with 95% confidence intervals per unit increase in lnCRP, lnVWF, and fibrinogen, respectively. Model 1 is adjusted for age and sex. Model 2 is additionally adjusted for family history of cardiovascular disease, hypertension, diabetes, cholesterol, high-density lipoprotein, hypercholesterolemia, BMI and smoking. The analyses with all cause mortality as endpoint were not adjusted for sex or diabetes.

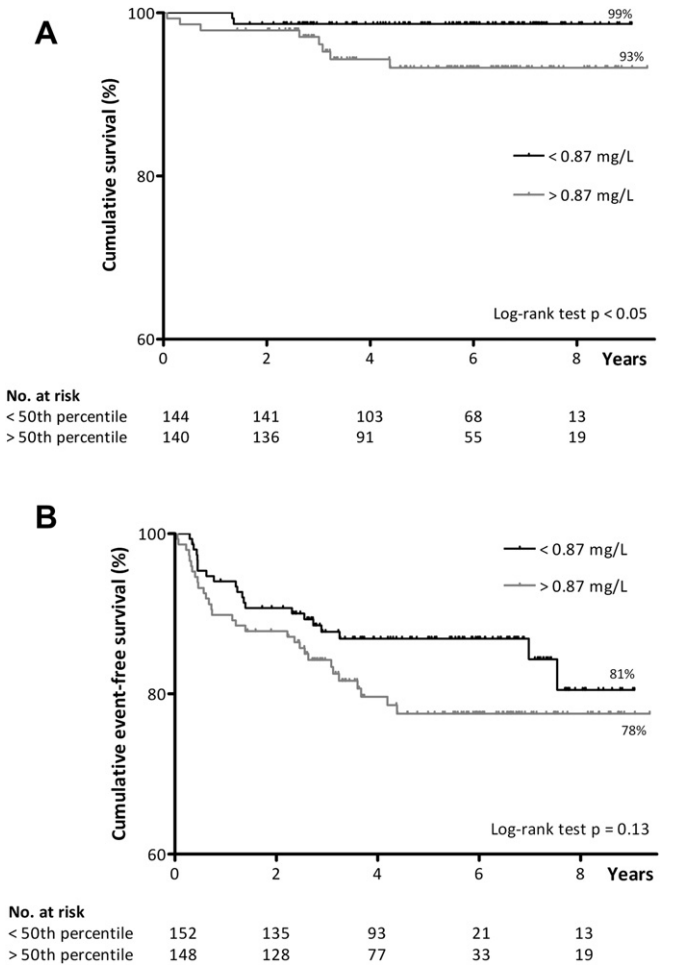

Fig. 1. Cumulative survival for CRP levels below and above the 50th percentile Kaplan–Meier curve for cumulative survival (A) and cumulative event-free survival (B) For CRP levels above and below the 50th percentile. The cut-off value was 0.87 mg/L.

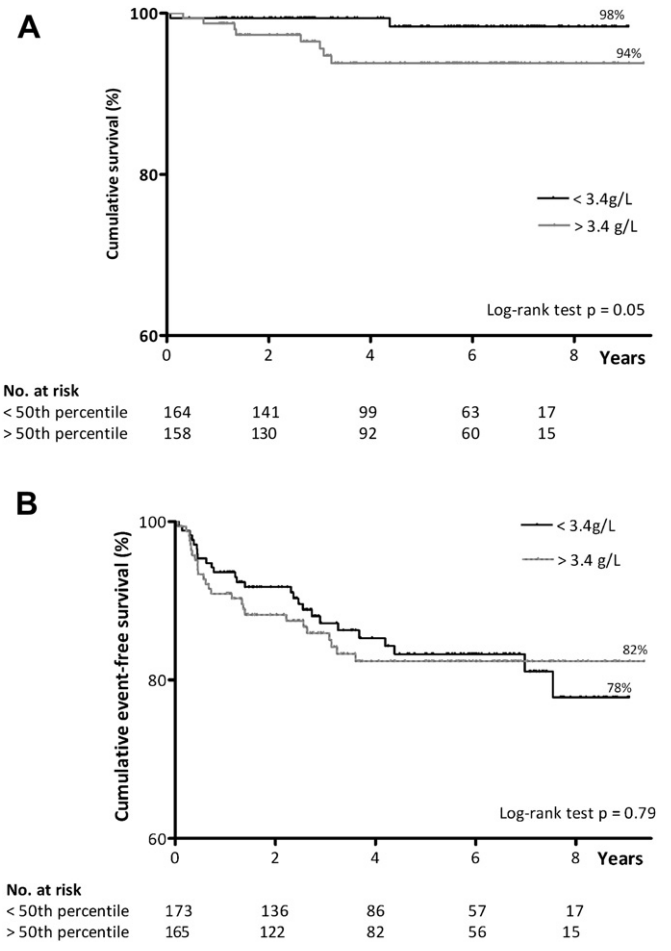

Fig. 2. Cumulative survival for fibrinogen levels below and above the 50th percentile Kaplan–Meier curve for cumulative survival (A) and cumulative event-free survival (B) For fibrinogen levels above and below the 50th percentile. The cut-off value was 3.4 g/L.

4. Discussion

In this follow-up study of young patients with premature CHD fifteen percent had a recurrent cardiac event or died of any cause within a median follow-up period of 4.2 years. In addition, high CRP levels contributed to the risk of recurrent events and all cause mortality. High fibrinogen levels were associated with all cause mortality only.

The independent relationship between CRP levels and all cause mortality or any recurrent event was yet unknown in young patients with CHD. Since we measured CRP levels one to three months after the first event, our findings are less influenced by an acute phase response that follows infarction. This is in contrast to many other studies that measured CRP levels at the onset of a first myocardial infarction. Some studies showed that CRP levels during acute myocardial infarction predict 30-day and long-term mortality [14,15], whereas other studies did not show this relationship [16–18]. CRP levels measured at the time of an acute myocardial infarction may reflect the severity of disease at that time point and may therefore not be useful for long-term cardiovascular assessment. Harb et al. measured CRP levels two months after a myocardial infarction. Although they showed that CRP levels tended to be higher in patients with recurrent events, CRP was not an independent marker for recurrent events in a multivariate model [19].

In addition, we found a significant association between high fibrinogen levels and all cause mortality, even after adjustment for cardiovascular risk factors. Studies on the predictive value of fibrinogen for recurrent cardiovascular events are scarce. One study reported an association between fibrinogen levels and the risk of coronary events in patients with stable coronary artery disease [20]. Also, a study of Pineda et al. in young subjects with coronary artery disease (median age 41 years) showed that fibrinogen was predictive for cardiovascular events, though only in the unadjusted analysis [21].

No relation was found between VWF levels and the risk of recurrent events. VWF:Ag levels have been associated with reinfarction and/or mortality risk in patients with CHD by numerous studies [22]. However, these patients were generally much older than our current study population. Pineda et al. investigated the prognostic implications of VWF:Ag levels in young patients with a first myocardial infarction [21]. In the current study there was also no association between VWF:Ag levels and cardiovascular events observed.

Since the inflammatory markers CRP and fibrinogen, but not VWF, were associated with recurrent events or all cause mortality, our results suggest that inflammation is an important determinant of prognosis. Indeed, there is a strong cross-talk between inflammation and thrombosis [23]. Inflammation has been associated with the occurrence of myocardial infarction [24,25]. The absence of an association in young CHD patients between VWF:Ag levels and recurrent events in our study and in previous studies is an

interesting and unexpected finding, since VWF is a well established risk factor for CHD in older subjects. Levels of VWF:Ag mirror the extent of endothelial dysfunction and thereby the atherosclerosis burden in the body. Since CRP and fibrinogen, but not VWF, were associated with recurrent events or all cause mortality, we hypothesize that at young age inflammation, as reflected by the CRP and fibrinogen levels, is more important than the extent of atherosclerosis for prognosis. However, considering the number of recurrent events in our study our results should be interpreted with care.

Surprisingly, traditional cardiovascular risk factors were not associated with recurrent events in the total group. However, since it is suspected that there are strong gender differences in prognostic markers we performed a sex-specific analysis. In this analysis diabetes was associated with recurrent events in men. In women both former smoking and current smoking were associated with recurrent events. However, considering the small numbers in this subanalysis larger studies are required to investigate this in more detail.

In our study, 98% of all cardiac patients were on anti-platelet therapy, 95% used statins, and 94% used any blood pressure lowering drug. It is interesting that despite optimal medical therapy these young patients experience this many recurrent events (15%), although the survival after a first cardiac event is excellent (97%). Recently, in a large group of young patients ($\leq$50 years) undergoing PCI it has been shown that the long-term outcome has not changed in the last 30 years despite improved secondary prevention [26]. These findings imply a negative trend in risk profiles of young individuals or that current treatment strategies are possibly still not adequate.

Although our study comprises a considerable large group of young subjects with premature CHD followed in time, our study was still limited by the number of patients and the number of recurrent events. Also, since we included patients after one to three months, we possibly missed patients who had a recurrent event before inclusion or patients who died shortly after the first event. Finally, CRP and fibrinogen were significantly associated with respectively a recurrent event and all cause mortality, though their effect sizes were modest. Nevertheless, the findings of the current study clearly illustrate that the risk profiles in young CHD patients are different than the risk profiles at older age and that the prevention strategies should be adapted to this.

In conclusion, we show that although the survival after a first cardiac event in young patients is good, the recurrent event rate is quite high despite optimal medical therapy. In addition, in these young patients high CRP levels contribute to the risk of recurrent events and high fibrinogen levels are associated with all cause mortality independently of cardiovascular risk factors.

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Conflicts of interest

We have no disclosures to declare.

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