Atherosclerosis 224 (2012) 213–217

Contents lists available at SciVerse ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Prognostic markers in young patients with premature coronary heart disease

Janine E. van Loon [a], Moniek P.M. de Maat [a], Jaap W. Deckers [b], Ron T. van Domburg [b], Frank W.G. Leebeek [a,*]

[a] Department of Haematology, Erasmus University Medical Center, Rotterdam, the Netherlands
[b] Department of Cardiology, Erasmus University Medical Center, Rotterdam, the Netherlands

ARTICLE INFO

Article history:
Received 3 April 2012
Received in revised form
27 June 2012
Accepted 28 June 2012
Available online 7 July 2012

Keywords:
Premature coronary heart disease
recurrent events
Prognosis
Risk factors
C-reactive protein
Von Willebrand factor
Fibrinogen
Prognostic markers

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

* Corresponding author. Dept. of Hematology (Room L-435), Erasmus University Medical Centre, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands. Tel.: +31 10 7033133; fax: +31 10 7035814.
E-mail address: f.leebeek@erasmusmc.nl (F.W.G. Leebeek).

0021-9150/
http://dx.doi.org/10.1016/j.atherosclerosis.2012.06.067

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