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Patients with premature cardiovascular disease and a positive family history for cardiovascular disease are prone to recurrent events

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ABSTRACT

Background: Premature cardiovascular disease (CVD) is treated in the same way as CVD of advanced age. However, in patients with premature CVD and a family history of CVD, different —possibly genetic— mechanisms may underlie this disease, which current medical treatment is not targeted to. This suggests that subjects with a genetic predisposition to CVD are more likely to have recurrent cardiovascular events.
Methods: We retrospectively investigated 291 patients with premature CVD and assessed the amount of recurrent events according to family history in a follow-up period of 31 years. Premature CVD was defined as an event <51 years for men or <56 for women. We used a Cox proportional hazards model to estimate the relationship between a positive family history and recurrence of cardiovascular events.
Results: Patients with recurrent events had more often a positive family history (60.0% vs. 47.1%; $p<0.05$), were more often smokers (85.2% vs. 70.7%; $p<0.05$), had more often hypertension (36.3% vs. 23.6%; $p<0.05$) and had a longer follow-up period (10.0 years vs. 5.4 years; $p<0.001$) than patients without recurrent events. After adjusting for these differences and modelling time to events, a positive family history was independently associated with recurrent events (Hazard ratio 1.31 (95% confidence intervals (CI) 1.01-1.72; $p<0.05$)).
Conclusions: Patients with a genetic predisposition for CVD are at risk for recurrent events, after adjusting for risk factors and other confounders. This might imply that in subjects with a genetic predisposition for CVD different pathophysiological mechanisms are active, leading to recurrent events.

1. Introduction

Cardiovascular disease is one of the biggest health problems in the world [1]. It is even a bigger issue among subjects with cardiovascular disease at a very young age (premature cardiovascular disease), because of the social and economical burden associated with it.

Premature cardiovascular disease is nowadays treated in the same way as cardiovascular disease of advanced age, with the idea to prevent recurrent events. However, one might question whether the underlying mechanisms responsible for cardiovascular disease in the young are similar to those in the elderly. This especially applies to patients with a genetic predisposition for cardiovascular disease, identified by a family history of premature cardiovascular disease.

The fact that a genetic predisposition is responsible for the development of cardiovascular disease in young patients has also been suggested in the literature [2–4]. For instance, the risk of developing cardiovascular disease in a sibling of a patient with premature cardiovascular disease is much higher than might be expected by the shared environmental risk factors within a family [5]. Furthermore, the expression of cardiovascular disease differs between young and elderly patients. Myocardial infarction without diffuse multi vessel disease accounts for approximately 16% of cases in patients under the age of 35 years [6], whereas the same study found it to be rather uncommon in elder patients (2%).

Therefore, it is believed that different mechanisms may underlie premature cardiovascular disease, for which current medical treatment might not be targeted to.

The Dutch guidelines, recommend that premature cardiovascular disease is treated in the same way as cardiovascular disease at

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advanced age [7]. Hereby, a possible different underlying mechanism is not taken into account. This suggests that, particularly in families with premature cardiovascular disease, standard medical treatment may be insufficient to prevent recurrent events.

We therefore hypothesize that patients with premature cardiovascular disease and a positive family history for cardiovascular disease are more likely to have recurrent cardiovascular events. To test this hypothesis we retrospectively investigated the association of a positive family history for cardiovascular disease in 291 patients with premature cardiovascular disease and the recurrence of cardiovascular events.

2. Methods

2.1. Study design

All patients who were referred to our specialized out-patient clinic for premature cardiovascular disease in the city of Maastricht, the Netherlands, by cardiologists, neurologists or vascular surgeons between January 2001 and January 2008, were identified and retrospectively analyzed. From our patient records we were able to identify 291 patients with premature cardiovascular disease. Of these patients complete data of the type of first cardiovascular event, follow-up data of the type of recurrent cardiovascular events, family history and the presence of traditional risk factors at the time of the first event were available from the patient records. Since referral and routine medical care of the city of Maastricht is directed to our hospital, all of the 291 patients with premature cardiovascular were diagnosed and seen on a regular basis. Therefore, follow-up data was present in the patients' records and was assessed retrospectively at the start of the analyses at January 2008.

Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

If there were blanks in the records, we contacted the general practitioner or patients themselves to obtain the missing information. Finally, 16 patients were excluded because their family history and their medication use could not be retrieved. Therefore, 275 patients remained for the analyses.

2.2. Patients

Premature cardiovascular disease was defined as a cardiovascular event occurring before the age of 51 years in men and 56 years in women, consistent with the literature on identifying a genetic predisposition [5]. A positive family history was defined as ≥ 1 first degree and/or ≥ 2 second degree family members with cardiovascular disease before the age of 55 years in men and 60 years in women.

Cardiovascular disease consisted of cardiac, peripheral artery and cerebrovascular disease. Cardiac disease was defined as a myocardial infarction or an acute coronary syndrome, as diagnosed by a cardiologist, a coronary artery bypass graft (CABG) or cardiac catheterization with or without percutaneous transluminal coronary angiography (PTCA). Cerebral disease was defined as a stroke or transient ischemic attack (TIA), as diagnosed by a neurologist. Peripheral artery disease was defined as intermittent claudication, as diagnosed by a vascular surgeon, percutaneous transluminal angiography, endarteriectomy, amputation of an extremity or bypass surgery.

We analyzed our data by dividing the patients into two groups: a group with recurrent events and a group without recurrent events. We registered adequate medical treatment before the first event and at the end of the follow-up period. We used the time since diagnosis as treatment time.

We defined the traditional risk factors as follows. Body mass index is the ratio between weight (kg) and the squared of height (m) (kg/m^2), hypertension, hypercholesterolemia and diabetes as the use of antihypertensive, anti-diabetic or cholesterol lowering medication *before* the start of the first event. We chose this definition because blood pressure data and cholesterol and glucose levels *before* the start of the first event could not reliably be extracted from the patients' records. We considered patients as smokers when they were smoking or had quit smoking less than 5 years *before* the first event and non-smokers when they had never smoked or quit smoking more than 5 years *before* the first event. The definition of 5 years was based on studies showing a normalization of risk after 5 years of smoking cessation [8,9].

2.3. Data analysis

We assessed differences in baseline characteristics between the group with recurrent events and the group without recurrent events, by using chi-square tests (in case of proportions), or Student's T-tests (in case of continuous data).

To analyze the association of a positive family history with the recurrence of cardiovascular events and to be able to model repeated events within one subject, we used both a frailty model (random effects model), and a generalized estimation equation model. These models provide a powerful tool to analyze clustered survival data and are a statistical modeling concept, which aims to account for heterogeneity, such as recurrence of events in the same individual [10]. In statistical terms, these models are random effect models for time-to-event data, where the random effect (the frailty) has a multiplicative effect on the baseline hazard function.

We first modeled univariate hazard ratios (HR) (model 1). This model was then further adjusted for age and sex (model 2) and finally, the model was also adjusted for hypertension, diabetes, hypercholesterolemia, smoking, body mass index and medication use (model 3). We only adjusted for the use of aspirin and a statin at the end of the follow-up period, since this was the only medication, which all different cardiovascular patients groups were supposed to use, regarding secondary prevention guidelines.

For all analyses, except for the modeling of the frailty, the Cox proportional hazard and the generalized estimation equation model, we used SPSS software, version 15.0 (SPSS, Inc., Chicago, Illinois). For the frailty, the Cox proportional hazards — and the generalized estimation equation model we used R, version 2.9.0. Continuous data are reported as means ± standard deviation (SD). All p-values are two-tailed, and values below 0.05 were considered statistically significant.

3. Results

The mean follow up of the entire cohort was 6.96 ± 5.51 years, patients with a positive family history had a mean follow up of 7.05 ± 5.27 years and patients with negative family history had a mean follow up of 6.81 ± 5.74 years.

Table 1 describes the population characteristics according to recurrent events. We found that 140 patients had no recurrent events and 135 patients had ≥1 recurrent event. Patients with recurrent events were more often smokers (85.2% vs. 70.7%; $p<0.05$), had more often hypertension (36.3% vs. 23.6%; $p<0.05$) and had a longer follow-up period (10.0 years vs. 5.4 years; $p<0.001$) and used more ACE inhibitors (43.9% vs. 32.1%; $p<0.05$) and calcium antagonists (35.6% vs. 11.8%; $p<0.001$) as compared to patients without recurrent events. Patients with recurrent events also had more often a positive family history for cardiovascular disease (60.0% vs. 47.1%; $p<0.05$) as compared to patients without recurrent events. Furthermore, patients with recurrent events had less often hypercholesterolemia, had more often diabetes, used more beta blockers, more ACE inhibitors, angiotensin II antagonists and used less often aspirin, but this did not reach statistical significance.

Since patients with recurrent events were more often smokers, had more often hypertension, used less often aspirin and had a longer follow-up time, we adjusted for these possible confounders in our analyses.

The frailty, generalized estimation equation and the standard Cox proportional hazards model all showed similar results. Because we did not observe any correlations between the repeated event periods within the same individual, we use a standard (unclustered) Cox proportional hazards model, modelling each event period as if it was obtained from a separate individual. We found that patients with a positive family history were at risk for recurrent events, with a hazard ratio of 1.30 (95% confidence intervals (CI)) ((1.02–1.66); $p<0.05$) (Table 2), as compared to patients with a negative family history (Table 2, model 1). This

Table 1
Population characteristics according to recurrent events.

	No recurrent events ($n=140$)	Recurrent events ($n=135$)
Age at first event	43.2 ± 6.0	41.9 ± 5.9
Male sex	80 (57.1)	77 (57.0)
Time since diagnosis in years	5.4 ± 3.5	10.0 ± 6.2*
Positive family history	66 (47.1)	81 (60.0)**
Smoking	99 (70.7)	115 (85.2)**
Hypertension	33 (23.6)	49 (36.3)**
Hypercholesterolemia	49 (35.0)	37 (27.4)
Diabetes	6 (4.3)	9 (6.7)
Body mass index (kg/m^2)	26.2 ± 4.0	27.0 ± 4.7
Aspirin use	128 (92.8)	111 (85.4)
Statin use	125 (90.6)	120 (91.6)
Beta blocker use	91 (66.4)	91 (68.9)
ACE inhibitor use	44 (32.1)	58 (43.9)**
Angiotensin II inhibitor use	23 (16.8)	26 (19.7)
Calcium antagonist use	16 (11.8)	47 (35.6)*

Continuous data are expressed as mean ± standard deviation, dichotomous data as absolute numbers with (percentages).
* $p<0.001$.
** $p<0.05$.

Table 2
Hazard ratio for recurrent events according to a positive family history.

Risk of a recurrent event	Model	HR	95% CI
Positive family history	1	1.30*	1.02–1.66
	2	1.30*	1.01–1.66
	3	1.31*	1.01–1.72

HR = Hazard Ratio.
Model 1: crude model.
Model 2: adjusted for sex and age.
Model 3: additionally adjusted for hypertension, diabetes, hypercholesterolemia, body mass index, smoking status and use of aspirin and statins.
* $p<0.05$.

Table 3
Hazard ratio for recurrent events for all covariates of model 3.

	HR	95% CI
Positive family history	1.31	1.01–1.72*
Age	0.99	0.97–1.01
Sex (male)	0.94	0.71–1.25
Smoking	1.34	0.87–2.06
Hypertension	1.03	0.77–1.37
Hypercholesterolemia	0.93	0.70–1.25
Diabetes	1.40	0.80–2.44
BMI	1.03	1.01–1.06*
Aspirin use	0.88	0.64–1.23
Statin use	1.05	0.58–1.90

HR = Hazard Ratio.
* $p<0.05$.

association remained after adjusting for age and sex (HR 1.30 (1.01–1.66); $p<0.05$, model 2) and all other possible confounders (HR 1.31 (1.01–1.72); $p<0.05$, model 3). We also show this relation in Fig. 1, where the cumulative hazard for recurrent events is plotted against family history.

The effect of the other confounders on recurrent events is shown in Table 3. Only BMI was also independently associated with recurrent events (HR 1.03 (1.01–1.06); $p<0.05$, Table 3).

4. Discussion

This study shows that the patients with premature cardiovascular disease and a positive family history for cardiovascular disease are more likely to have recurrent cardiovascular events, independent of traditional cardiovascular risk factors.

It is already known that a positive family history for premature cardiovascular disease is a major risk factor for the development of cardiovascular disease [2,11–13]. This risk even increases whenever the affected subject is younger of age at onset of cardiovascular disease, from an Odds ratio (OR) of 1.3 in patients affected at 51–55 years, to an OR of 8.3 in patients affected at 46–50 years, to an OR of 11.4 in patients affected <46 years [14]. Besides, cardiovascular mortality risk in a male monozygotic twin is 8 times higher if the other twin has died of cardiovascular disease before the age of 55 years [2].

On the other hand, as far as we know, it has never been shown that a positive family history for cardiovascular disease in patients with premature cardiovascular disease is a risk for *recurrent* cardiovascular events, while it is believed that standard treatment should prevent these recurrent events.

Interestingly, we also observed that there was an independent relationship between increasing BMI and the occurrence of recurrent events, underscoring the health issue related to obesity. The mechanisms responsible for the development of cardiovascular disease at advanced age are related to the classic risk factors such as smoking, obesity, diabetes, hypertension, dyslipidemia, male sex and older age [15–17]. Therefore, the treatment is targeted towards these risk factors. However, patients who develop cardiovascular disease at a very young age often have different risk profiles as compared to older patients [18–21]. In these young patients, especially if multiple family members are affected, there might be specific inherited mechanism involved, which current treatment is not targeted to. It has been suggested that these mechanisms included either thrombotic or certain inflammatory processes. Indeed, it is shown that both a first premature as recurrent cardiovascular events are associated with high levels of CRP [22,23]. Also, premature cardiovascular disease is associated with increased levels of prothrombotic proteins [24] and the factor V Leiden mutation shows a relation with cardiovascular disease in the young [25], whereas it does not in the elderly [26]. One could speculate that inflammatory processes could be targeted with low doses corticosteroids or methotrexate, while thrombotic processes could be targeted with vitamin K antagonist or the even more safe new anti-coagulant drugs such as thrombin inhibitors or factor Xa inhibitors.

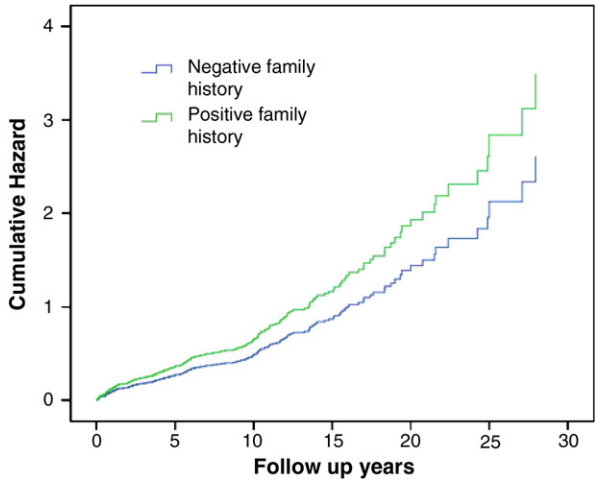

Fig. 1. Cumulative hazard for recurrent events, according to family history.

This study has some potential weaknesses. First of all, it has a retrospective study design. Most retrospective studies are limited because of lack of availability and accuracy level of data that can be retrieved from patients' records. We have limited our analyses to data which were robust, such as diagnoses made by the referring cardiologist, neurologist or vascular surgeon, instead of self reported diagnoses. Concerning family history, complete information on the specific age at which the first event in each family member took place was available from the patients' records for almost all patients. In only 16 patients this could not be ascertained and they were excluded from the analyses. On the other hand, the retrospective nature of our study gave us the opportunity to analyze patients over a longer time of follow-up, without the costs and infrastructure necessary for prospective cohort studies. Besides, the rare occurrence of premature cardiovascular disease makes prospective studying difficult.

Secondly, subjects with recurrent events had several obvious confounders such as a longer follow-up period and more classic risk factors. One might argue that the observed association between a positive family history and recurrent events might be due to these differences. On the other hand, after adjusting for these confounders the association remained. This suggests that subjects with a positive family history are at risk for recurrent events, independent of these classic risk factors. Also, a higher percentage of patients with recurrent events used additional medication, such as ACE inhibitors and calcium antagonists. This could be due to the higher percentage hypertensives in this group, but this seems to have no influence on the number of recurrent events.

Thirdly, our cohort has a rather small sample size, although premature atherosclerosis is rare. From that, we were not able to perform certain sub-analyses, such as investigating the effect on the different cardiovascular disease types (cardiac, peripheral artery and cerebrovascular disease) and the effect on gender. We did observe

however, a similar percentage of males and females with a positive family history for cardiovascular disease (52.8% vs. 53.2%), despite the fact that in the literature it has been suggested that gender might play a role in the predictive value of family history of cardiovascular disease [27,28].

One of the strengths of our study is the fact that we analyzed our data in different statistical models, to be able to handle repeated measurements within one individual. All these different models gave similar results, therefore underscoring the robustness of the data.

In conclusion, patients with premature cardiovascular disease and a positive family history for cardiovascular disease are at independent increased risk for recurrent cardiovascular events. This implies that specific pathophysiological mechanisms are of importance in these young patients with cardiovascular disease in which standard medical treatment is currently not targeted for.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [29].

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