TITLE PAGE

Asymptomatic individuals with a positive family history for premature coronary artery disease and elevated coronary calcium scores benefit from statin treatment: *A post-hoc analysis from the St. Francis Heart Study Randomized Clinical Trial*

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ABSTRACT

Objectives

To evaluate whether of individuals with a positive family history for premature coronary artery disease (CAD) and elevated coronary calcium scoring (CCS), might be exposed to such an increased risk for cardiovascular disease (CVD), that preventive treatment might be effective.

Background

First degree relatives of patients with premature CAD have an increased risk for CVD. Traditional risk algorithms, however, poorly predict event rates in these individuals. It is assumed that surrogate markers, such as CCS, might refine risk scoring.

Nevertheless, the primary outcome of the St. Francis Heart study, which was designed to investigate the effect of treatment with atorvastatin in individuals with elevated CCS, did not reach statistical significance.

Methods

We questioned the database of the St. Francis trial in a post-hoc analysis to assess efficacy of treatment in those with both elevated calcium scores and the presence (n=546) or absence (n=464) of a positive family history for premature CAD. Primary outcomes included all cardiovascular events.

Results

After a follow-up of 4.3 years, the event rate for individuals with a positive family history was 7.2% in the treated group versus 12.5% in the placebo group (hazard ratio (HR) 0.55;(95% confidence intervals (CI); (0.31-0.97;p=0.040). In individuals with no family history, event rates were minimally reduced: 6.6% in the treated versus 6.8% in the placebo group (HR 1.04;(95% CI 0.51-2.13;p=0.912).

Conclusions

The combination of a positive family history and elevated CCS might identify a subgroup within the primary prevention population, which receives greater benefit from statin treatment than the population at large.

KEYWORDS: Coronary calcium score, family history, premature coronary artery disease

ABBREVEATIONS:

CAD = coronary artery disease

OR = odd's ratio

CVD = cardiovascular disease

CCS = coronary calcium score

RCT = randomized controlled trial

LDL = low density lipoprotein

HR = hazard ratio

CRP = c reactive protein

TEXT

INTRODUCTION

A positive family history for premature coronary artery disease (CAD) is an important risk factor for atherosclerotic vascular disease and is, in fact, independent from other risk factors (1-4). The associated risk increases further when relatives are affected at a younger age, with an odds ratio (OR) of 1.3 in individuals with relatives affected below 55 years, to OR's of 10 and higher in individuals with relatives affected below 45 years of age (5-7).

However, if we assume an important and (co)dominant hereditary component, not all relatives will be exposed to the same risk. This emphasizes the need to further refine the risk among siblings in these families. Traditional risk score algorithms poorly predict cardiovascular risk in general, but even more so in relatives of patients with premature CAD (8). This is mainly due to the fact that the question of risk in affected kindreds arises at a time when individuals are still young, while age is the most important risk predictor for cardiovascular disease (CVD) per sé.

Therefore, novel biomarkers are continuously developed to better indentify subclinical disease in asymptomatic but high risk individuals. Coronary calcium score (CCS) is considered such a marker that can investigate subclinical atherosclerosis in asymptomatic individuals and can predict cardiovascular events, independent of other risk factors (9-12).

In the 2010 American Heart Association Guidelines for Assessment of Cardiovascular Risk in Asymptomatic Adults, it was noted that *"measurement of CCS is a reasonable method for cardiovascular risk assessment in asymptomatic adults at intermediate risk"*(13). However, there is no evidence that treatment of such in individuals with high CCS has any benefit in a primary prevention setting. In fact, the only randomized controlled trial (RCT), the St. Francis Heart study, comparing aspirin, atorvastatin, vitamin C, and E with aspirin and matching placebo in 1,005 asymptomatic individuals with CCS above the 80th percentile, showed a 33% reduction in events, which failed to meet accepted levels of statistical significance (14).

In view of the clear predictive value of a positive family history for CAD, we hypothesized that individuals with both a positive family history for premature CAD and elevated CCS in the St. Francis Heart study might have benefited from treatment.

To test this hypothesis, we performed a post-hoc analysis in the database of the St. Francis Heart study and we compared treatment with atorvastatin 20 mg, aspirin 81 mg, vitamin C 1 g, and vitamin E 1,000 U with aspirin

81 mg and matching placebo in individuals with a CCS score above the 80th percentile, but then stratified those individuals into either presence or absence of a positive family history for premature CAD.

Here we present our results.

METHODS

Study individuals and design

The study design of the St. Francis Heart Study RCT was previously reported (15). In brief; men and women aged 50 to 70 years were considered eligible for CCS, provided they had no history, symptoms (Rose questionnaire) (16), or signs of CVD. Other exclusion criteria included insulin-dependent diabetes and lipid levels already requiring treatment. A lower limit for low density lipoprotein (LDL) cholesterol (<1.55 mmol/L) was chosen out of concern that local primary care physicians would become alarmed and withdraw patients from the study.

Electron beam CT scanning was performed at enrollment and repeated after two and four years with reconstruction to a 26-cm field of view. Forty contiguous 3-mm slices were scanned during a single breath hold. Scan time was 100 ms/slice, synchronized to 80% of the RR interval. At least two adjacent pixels with an attenuation coefficient >130 Hounsfield units defined a calcified lesion, and CCS was calculated according to Agatston (17). Individuals with CCS above the 80th percentile for age and gender, as defined by an internal database comprising more than 5,000 asymptomatic persons, were invited to participate in the RCT.

Individuals were randomized in two parallel groups, the first receiving atorvastatin 20 mg daily, vitamin C 1 g daily, and vitamin E (alpha tocopherol) 1,000 U daily (from now on called *treated group*) versus matching placebos (from now on called *placebo group*), administered in double-blind fashion. In addition, all participants were given 81 mg of aspirin daily. Study participants experiencing nonfatal coronary end points who met either Scandinavian Simvastatin Survival Study (4S) (18) or Cholesterol and Recurrent Events (CARE) (19) criteria were placed on open-label atorvastatin 20 mg daily.

Primary outcomes included all cardiovascular events, which were verified by an independent committee of current or former coronary care unit directors at academic medical centers, blinded to the CCS and treatment assignment. Cardiovascular events included coronary death, nonfatal myocardial infarction, surgical, or percutaneous coronary revascularization procedures, non-hemorrhagic stroke, and peripheral vascular (i.e. arterial) surgery. Only the first event experienced by a patient was recorded. Secondary outcomes included all

coronary events, which included both nonfatal myocardial infarction and coronary death, and all events occurring more than 90 days after randomization.

This study was approved by the St. Francis Hospital Institutional Review Board and all participants provided written informed consent.

Post-hoc analysis

We analyzed the initial cohort stratified to family history. There were 546 individuals with a positive family history for premature CAD. This was defined as ≥1 first degree relative with premature CAD: men before the age of 55 years and women before the age of 65 years. We then assessed whether the differences in treatment modalities led to a difference in cardiovascular outcome in individuals depending of the presence or absence of a positive family history for premature CAD.

Statistical analysis

We assessed differences in baseline characteristics between individuals with presence or absence of a positive family history for premature CAD by using chi-square tests (in case of proportions), or Student's T-tests (in case of continuous normally distributed data), or Wilcoxon signed-rank test (in case of continuous not-normally distributed data).

Kaplan-Meier curves were used to estimate the probability of experiencing a clinical event for either individuals receiving active treatment or placebo and tested differences between curves with Log-rank test. Cox proportional-hazards analyses were used to correct for differences between the treatment and the placebo groups were appropriate.

All hypothesis tests were conducted with an alpha level of 0.05 and were two tailed, and all end points were analyzed on the basis of intention to treat.

RESULTS

The flow of participants in this trial has been described in detail elsewhere (14). Table 1 shows the baseline characteristics of all randomized participants. We compared baseline characteristics of the treated group with the placebo group, stratified for either presence or absence of a positive family history for premature CAD. Within both strata of individuals with either a positive or a negative family history, all variables were well matched. Only in the stratum of individuals with a positive family history, triglyceride levels were lower at baseline in the treated group compared with the placebo group (1.5 ± 0.9 mmol/L vs. 1.8 ± 1.2 mmol/L; p=0.010)

Furthermore, individuals with a positive family history had a higher incidence of hypertension (34.4% (n=188) vs. 26.9% (n=125); p=0.010), total cholesterol levels (5.9 ± 0.9 mmol/L vs. 5.7 ± 0.9 mmol/L; p<0.0001) and LDL cholesterol levels (3.9 ± 0.8 mmol/L vs. 3.7 ± 0.8 mmol/L; p<0.0001) as compared to individuals with a negative family history.

Concerning the primary outcome, after a median follow-up of 4.3 years, in the stratum of individuals with a positive family history for premature CAD, the event rate was 7.2% (n=19) in the treated group versus 12.5% (n=35) in the placebo group (p=0.039) (table 2). In the stratum of individuals with a negative family history for premature CAD, the event rate was 6.6% (n=15) in the treated group versus 6.8% (n=15) in the placebo group (p=0.95) (table 2).

Concerning the secondary outcome of coronary events, in the stratum of individuals with a positive family history the event rate was 6.8% (n=18) in the treated group versus 10.7% (n=30) in the placebo group (p=0.11) (table 2), whereas, in the stratum of individuals with a negative family history the event rate was 5.7% (n=13) in the treated group versus 5.5% (n=13) in the placebo group (p=0.91) (table 2). Regarding the other secondary outcome, cardiovascular events after more than 90 days, in the stratum of individuals with a positive family history the event rate was 6.8% (n=18) in the treated group versus 11.0% (n=31) in the placebo group (p=0.048) (table 2). In the stratum of individuals with a negative family history, the event rate was 5.7% (n=13) in the treated group versus 5.9% (n=14) in the placebo group (p=0.93) (table 2).

Furthermore, Kaplan-Meier survival curves of the primary outcome showed that individuals with a positive family history had a 45% reduction in cardiovascular events (Hazard Ratio (HR)) 0.55; 95% CI 0.31-0.97; p=0.040) (Log Rank = 0.037, figure 1), whereas this was not observed in individuals with a negative family history (HR 1.04; 95% CI 0.51-2.13; p=0.912) (Log Rank = 0.912, figure 2). Correction for triglycerides at baseline, which was the only significantly different variable between the treatment and placebo group for individuals with a positive family history did not change the results (HR 0.56; 95% CI 0.32-0.99; p=0.045). No gender-based differences were present.

DISCUSSION

In this post-hoc analysis, we show that treatment with atorvastatin 20 mg, vitamin C 1 g, and vitamin E 1,000 U in asymptomatic individuals with a positive family history for premature CAD *and* a high CCS resulted in a 45% reduction in cardiovascular events. These data suggest that individuals with a positive family history for premature CAD and a high CCS do benefit from preventive treatment.

Preventive treatment in these individuals is still a matter of debate (20). If we assume an important hereditary component, not all relatives will be at risk to the same extent. Therefore, treatment should be tailored to those individuals with the highest chance of future clinical manifestations of CVD. In this post-hoc analysis this proved to be those with elevated CCS, which might reflect subclinical atherosclerotic vascular disease.

So far, no randomized controlled study has shown any beneficial effect of preventive treatment in individuals with elevated CCS. Yet, the latest American Heart Association guidelines on cardiovascular risk state that measuring CCS is reasonable for cardiovascular risk assessment in asymptomatic individuals (13). Surprisingly, although measuring CCS is recommended, no evidence existed that treatment of individuals with elevated CCS reduces cardiovascular risk.

The only RCT investigating the treatment of such a population is St. Francis Heart study (14), in which we have performed a post-hoc analysis. The St. Francis Heart study showed a 33% reduction in events after treatment, but this did not reach statistical significance (p=0.08). According to the authors, this might have been due to lack of power. On the other hand, a subgroup analysis of this study showed that treatment of individuals with CCS above 400 Agatston Units was significantly beneficial. In this subgroup analysis, the event rate in the treated group was 8.7% (n=20) vs. 15.0% (n=36) in the placebo group, which represents an event reduction of more than 40% (p=0.046) (15).

Other studies investigating this issue have only focused on progression of CCS and have shown conflicting results (21-24). These inconsistencies have been addressed by Henein et al. in a recent meta-analysis (25). These authors concluded that statin therapy did not reduce CCS progression, but did attenuate luminal CAD narrowing. A possible explanation lies in the fact that luminal narrowing represents soft tissue inflammatory pathology, whereas increased CCS represents tissue mineralization which is unlikely to regress with statins.

Our findings are in line with those recently obtained in the JUPITER trial. In this study, asymptomatic individuals with elevated hs-CRP levels were treated with rosuvastatin or placebo. Rosuvastatin therapy resulted in a significant reduction of cardiovascular events, which was, according to a subgroup analysis, most evident in those with a positive family history (26).

The strengths and the limitations of our study merit discussion. Strengths include the randomised double-blind trial design, the specific study population and the adjudication of cardiovascular outcomes. On the other hand, this study encompasses all inherent limitations of a post-hoc analysis, most importantly, the loss of randomization. Fortunately, in this post-hoc analysis, randomization was maintained, to some extent. In those with a positive family history, only triglyceride levels were significantly higher in the placebo group compared

to the treated group. However, this must have been due to chance, since randomization was done by concealment of allocation and information on family history or triglyceride levels could not have influenced this. Also, after correction for triglyceride levels results remained essentially the same.

Recent studies have shown no additional effects of vitamin supplementation on cardiovascular events (27,28). Therefore, we conclude that the difference in cardiovascular events in the St. Francis Heart Study RCT must have been based on the effect of atorvastatin.

In conclusion, preventive treatment of asymptomatic individuals with a positive family history for premature CAD and elevated CCS might reduce cardiovascular events. Although much controversy exists with regard to treatment of those with elevated CCS in primary prevention, we hypothesize that preventive treatment of individuals with a positive family history for premature CAD and a high CCS is beneficial in terms of cardiovascular outcome. This hypothesis will require testing in prospective controlled studies before implementation in the clinics.

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FIGURE TITLES AND LEGENDS

Figure 1. Kaplan-Meier survival curves for all cardiovascular events in individuals with a positive family history for premature CAD

Figure 2. Kaplan-Meier survival curves for all cardiovascular events in individuals with a negative family history for premature CAD

Figure 3. Kaplan-Meier survival curves for all coronary events in individuals with a positive family history for premature CAD

Figure 4. Kaplan-Meier survival curves for all coronary events in individuals with a negative family history for premature CAD

Figure 5. Kaplan-Meier survival curves for all cardiovascular events after 90 days in individuals with a positive family history for premature CAD

Figure 6. Kaplan-Meier survival curves for all cardiovascular events after 90 days in individuals with a negative family history for premature CAD

TABLES

Table 1. Patient characteristics of individuals with a positive and a negative family history for premature CAD, divided by treatment

	Positive family history			Negative family history		
	Placebo (n=281)	Treated (n=265)	*All (n=546)*	Placebo (n=237)	Treated (n=227)	*All (n=464)*
Age (years)	58.4 ± 5.9	58.9 ± 5.8	*58.7 ± 5.9*	59.5 ± 6.1	59.2 ± 6.0	*59.4 ± 6.0*
Sex (male)	206 (73.3)	183 (69.1)	*389 (71.2)*	177 (74.7)	177 (78.0)	*354 (76.3)*
History of smoking	188 (66.9)	167 (63.0)	*355 (65.0)*	159 (67.1)	165 (72.7)	*324 (69.8)*
History of hypertension	96 (34.2)	92 (34.7)	*188 (34.4) **	68 (28.7)	57 (25.1)	*125 (26.9)*
BMI (kg/m^2)	29.3 ± 5.0	29.1 ± 5.0	*29.3 ± 5.0*	29.2 ± 5.1	29.9 ± 4.9	*29.5 ± 5.0*
SBP (mm Hg)	137.4 ± 19.0	135.9 ± 20.9	*136.7 ± 19.9*	136.1 ± 19.1	136.0 ± 16.7	*136.0 ± 17.9*
DBP (mm Hg)	79.6 ± 9.3	79.0 ± 9.9	*79.3 ± 9.6*	79.0 ± 9.0	78.9 ± 8.4	*78.9 ± 8.7*
Total cholesterol (mmol/L)	5.9 ± 0.9	6.0 ± 0.9	*5.9 ± 0.9 **	5.8 ± 0.9	5.6 ± 0.9	*5.7 ± 0.9*
LDL cholesterol (mmol/L)	3.9 ± 0.8	3.9 ± 0.8	*3.9 ± 0.8 **	3.8 ± 0.7	3.6 ± 0.8	*3.7 ± 0.8*
HDL cholesterol (mmol/L)	1.3 ± 0.4	1.3 ± 0.4	*1.3 ± 0.4*	1.3 ± 0.4	1.3 ± 0.4	*1.3 ± 0.4*
Triglycerides (mmol/L)	1.8 ± 1.2 †	1.5 ± 0.9	*1.8 ± 1.2*	1.6 ± 1.0	1.5 ± 1.0	*1.6 ± 1.0*
Glucose (mmol/L)	6.2 ± 1.8	6.1 ± 1.5	*6.2 ± 1.8*	6.2 ± 1.4	6.2 ± 1.9	*6.2 ± 1.7*

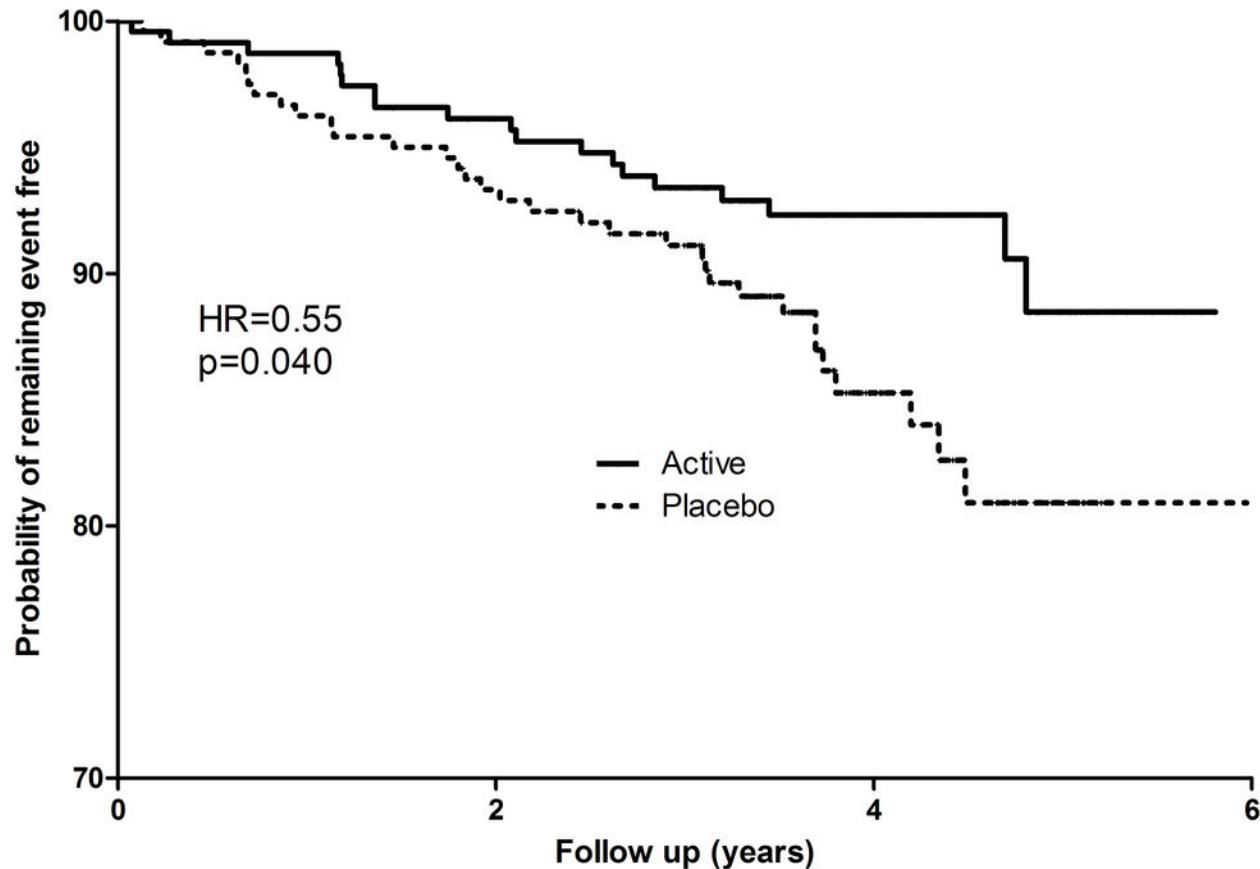|						
C-reactive protein (mg/l)	2.12 (1.08; 4.07)	1.74 (0.94; 3.96)	*1.90 (0.98; 3.98)*	2.10 (0.87; 5.02)	2.63 (0.98; 4.47)	*2.26 (0.93; 4.61)*
Framingham risk score	11.9 (7.6; 16.9)	11.0 (7.2; 16.2)	*11.3 (7.4; 16.6)*	10.5 (7.1; 17.0)	10.6 (7.3; 15.7)	*10.6 (7.2; 16.2)*
Baseline calcium score	360.5 (177.1; 627.0)	354.8 (179.5; 626.6)	*358.7 (178.7; 626.4)*	395.7 (188.3; 747.7)	396.8 (186.2; 659.1)	*396.3 (187.5; 690.7)*

Continuous data are expressed as mean ± standard deviation except for CRP, Framingham score and Calcium score, which are expressed as median (25th; 75th percentiles), categorical data are expressed as absolute numbers with (percentages); BMI= body mass index, LDL= low density lipoprotein, HDL= high density lipoprotein, SBP= systolic blood pressure, DBP= diastolic blood pressure; *p<0.05 versus all patients with a negative family history, † p<0.05 versus treated

Table 2. Cardiovascular event rate in individuals with a positive and

a negative family history for premature CAD, divided by treatment

|	Positive family history		Negative family history	
	Placebo (n=281)	Treated (n=265)	Placebo (n=237)	Treated (n=227)
Primary end point				
All CV events, n (%)	35 (12.5)	19 (7.2) *	16 (6.8)	15 (6.6)
Secondary end points				
All coronary events, n (%)	30 (10.7)	18 (6.8)	13 (5.5)	13 (5.7)
CV events after 90 days, n (%)	31 (11.0)	18 (6.8) *	14 (5.9)	13 (5.7)

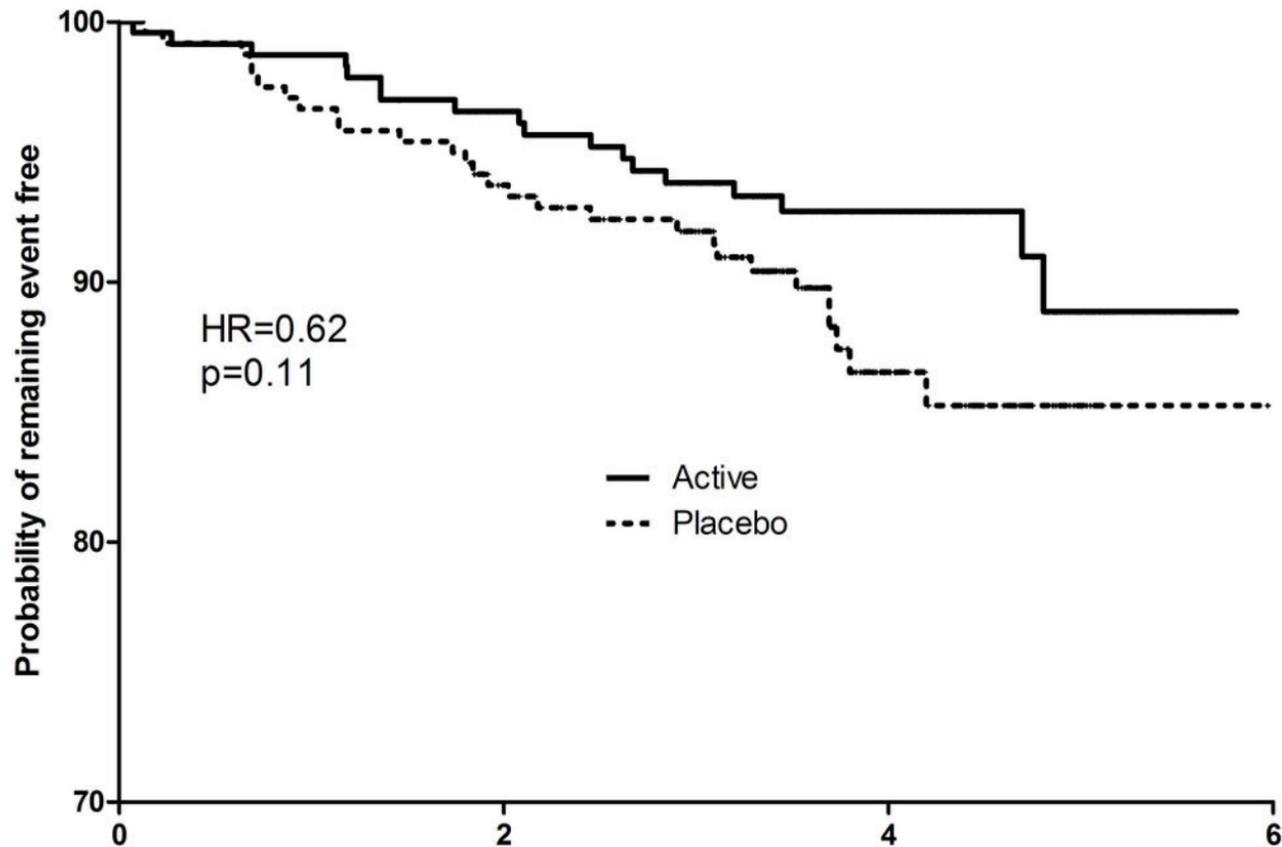Categorical data are expressed as absolute numbers with (percentages); CV= cardiovascular;

*p<0.05

HR=0.55
p=0.040

Active
Placebo

Number at risk						
Active	265	232	214	195	111	25
Placebo	281	232	219	192	84	17

HR=1.04
p=0.91
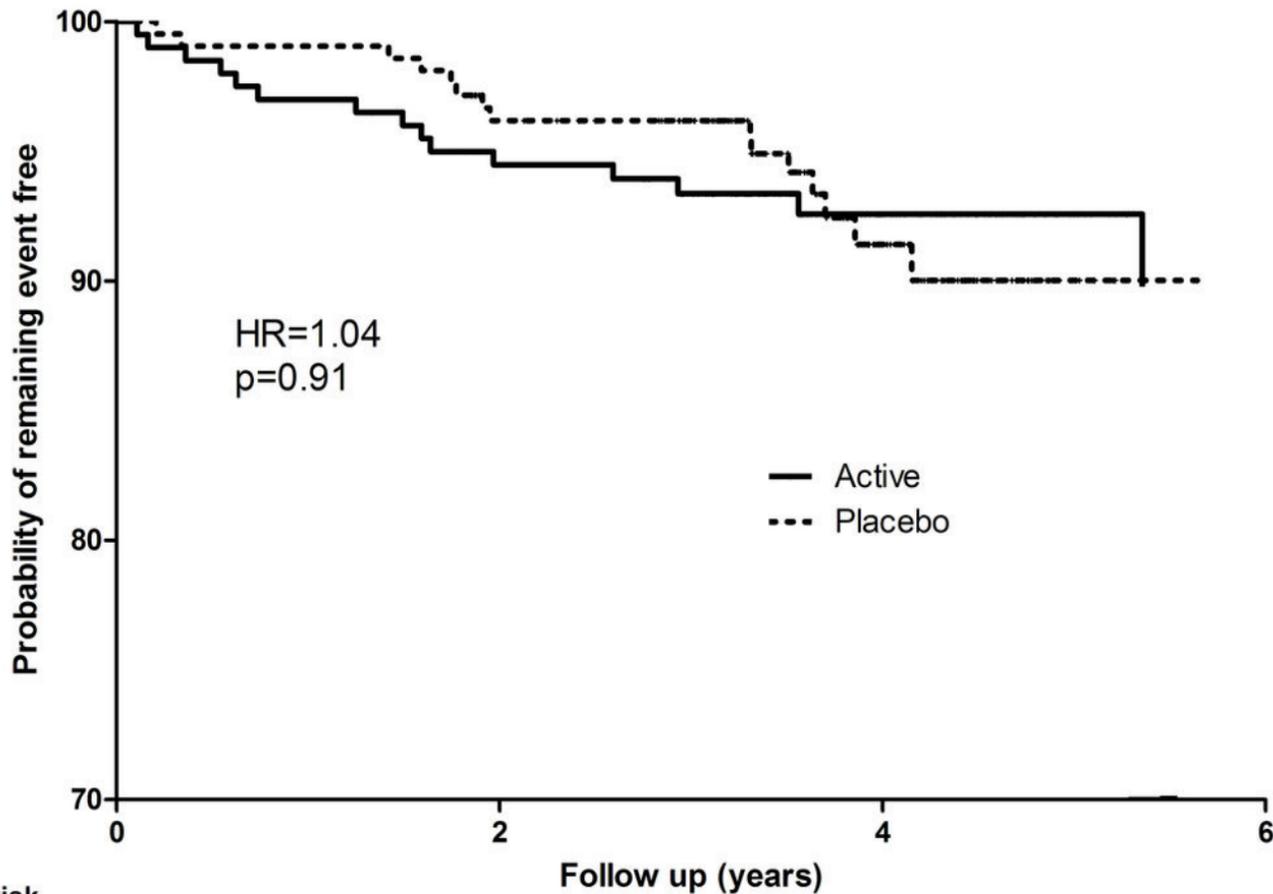
— Active
- - - Placebo

Number at risk						
Active	227	195	184	163	76	9
Placebo	237	211	196	175	74	11
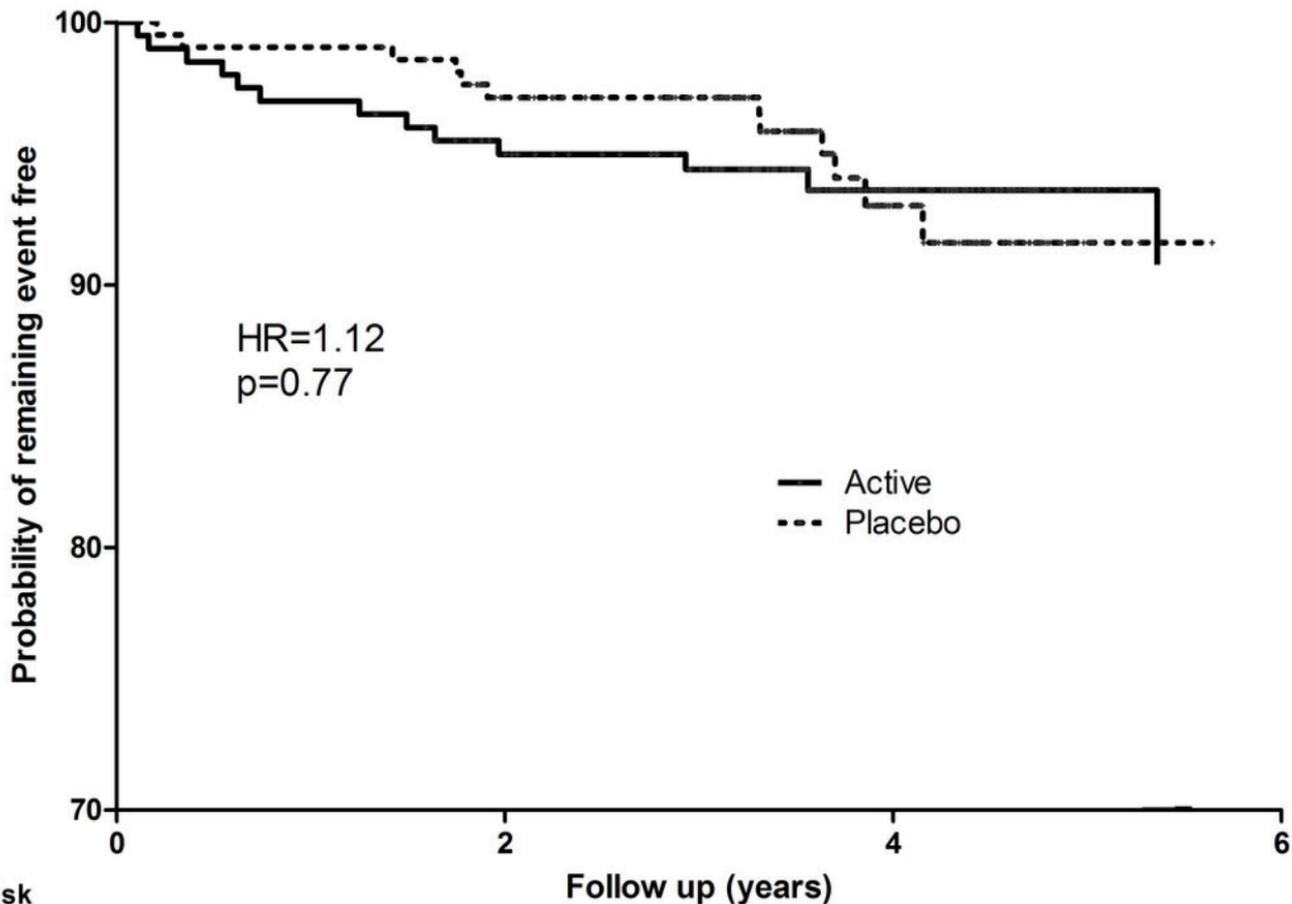
HR=0.62
p=0.11

— Active
---- Placebo

Number at risk

Active	265	232	214	195	111	25
Placebo	281	232	219	192	84	17

Number at risk

Active	227	195	184	161	77	11
Placebo	237	211	196	175	74	9

HR=0.56
p=0.04
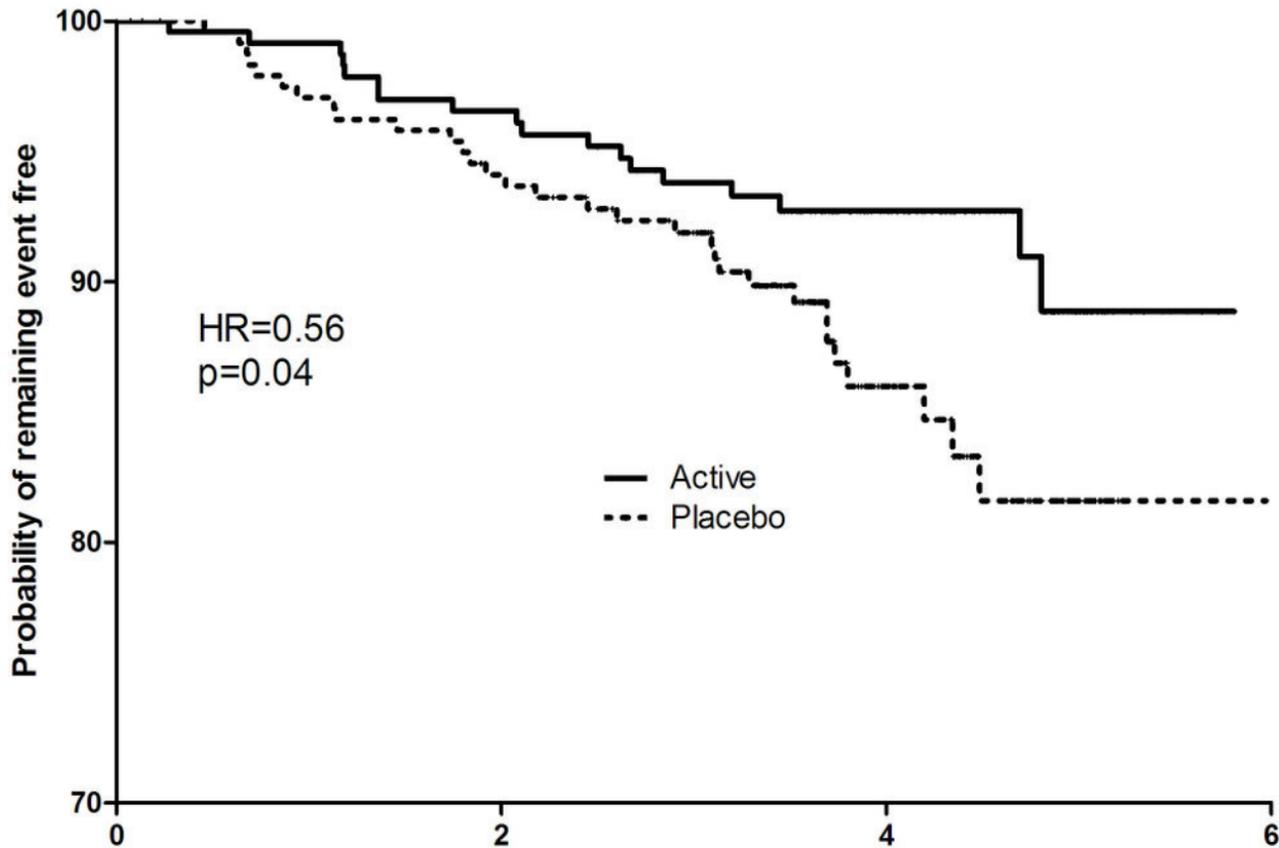
— Active
--- Placebo

Number at risk						
Active	265	232	214	195	111	25
Placebo	281	231	219	192	84	17

Follow up (years)

Probability of remaining event free

HR=0.96
p=0.93

Number at risk

Active	227	195	184	161	77	11
Placebo	237	211	196	175	74	9