The molecular basis of early onset cardiovascular disease

Sivapalaratnam, S.

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CHAPTER 5

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


Departments of Vascular Medicine (TM, SS, ES, JJP) and Clinical Epidemiology, Biostatistics and Bioinformatics (SJP), Academic Medical Centre, Amsterdam, the Netherlands; Department of Cardiology (AG), St. Francis Hospital, New York, USA.

ABSTRACT

Objective
To evaluate whether individuals with a positive family history for premature coronary artery disease (CAD) and coronary calcium scoring (CCS) >80th percentile might benefit from preventive treatment.

Background
First degree relatives of patients with premature CAD have an increased risk for cardiovascular disease (CVD), while events are poorly predicted in these individuals. Surrogate markers, such as CCS, might refine risk scoring. Nevertheless, the outcome of the St. Francis Heart trial, which investigated the effect of atorvastatin 20mg/d in asymptomatic individuals with CCS >80th percentile, did not reach statistical significance.

Methods
We performed a post-hoc analysis on the database of the St. Francis trial to assess efficacy of treatment with atorvastatin 20mg/d in those with CCS >80th percentile and presence (n=543) or absence (n=462) of a positive family history for premature CAD. All participants received aspirin 81mg/d. Primary outcome included coronary death, myocardial infarction, coronary revascularization, stroke and arterial surgery.

Results
In trial participated 1005 individuals; with a mean age 59.0±5.9 years and a median absolute CCS of 370 Agatston units (interquartile range 183-662). After a follow-up of 4.3 (interquartile range 3.5-4.5) years, 7.2% of the treated individuals with a positive family history had a cardiovascular event versus 12.5% of the placebo group (hazard ratio (HR) 0.55 ;(95% confidence intervals (CI) (0.31-0.97;p=0.040). This is comparable with a number needed to treat of 18.9. In individuals without a family history, events 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).

Conclusion
The combination of a positive family history and CCS >80th percentile identifies a subgroup within the primary prevention population, which receives greater benefit from statin treatment than the population at large. These results have important implications for future guidelines concerning individuals with a positive family history for premature CAD.
INTRODUCTION

A positive family history for premature coronary artery disease (CAD) is an independent risk factor for cardiovascular disease (CVD)\(^1\)\(^-\)\(^4\). 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 assessment among siblings in these families. Traditional risk 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 mostly arises at a time when individuals are still young, while age is the most important risk predictor for CVD per sé.

Therefore, novel tools are continuously developed to better identify subclinical disease in asymptomatic individuals.

Coronary calcium score (CCS) has emerged as an interesting tool in the cardiovascular arena, since it can measure the severity of subclinical coronary artery disease, correlates well with plaque burden in pathology studies and can predict cardiovascular events independent of other risk factors\(^9\)\(^-\)\(^13\).

In both the American College of Cardiology/American Heart Association 2010 Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults and the American College of Cardiology Appropriate Use Criteria for Cardiac Computed Tomography, it is expressed that measurement of CCS is a reasonable method for cardiovascular risk assessment in asymptomatic adults at intermediate risk\(^14\). In the Appropriate Use Criteria for Cardiac Computed Tomography it was even stated that it is appropriate for individuals at low risk in whom a family history of premature CAD is present\(^15\).

However, to date there is no evidence that treatment of such in individuals has any benefit in a primary prevention setting as recently mentioned by the Working Group on Nuclear Cardiology and Cardiac CT of the European Society of Cardiology\(^16\). In fact, the only randomized controlled trial (RCT), the St. Francis Heart Study, comparing treatment versus placebos in asymptomatic individuals with CCS above the 80\(^{th}\) percentile, showed a 33\% reduction in events, which failed to meet accepted levels of statistical significance\(^17\).

In view of the clear predictive value of a positive family history, we hypothesized that individuals with both a positive family history for premature CAD and elevated CCS in the St. Francis Heart Study, represent a high risk population which 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, stratified to either the presence or absence of a positive family history for premature CAD.

METHODS

Study individuals and design

The study design of the St. Francis Heart Study RCT was previously reported18. In brief, recruitment began in February 1996. Approximately 300,000 recruitment letters and questionnaires were sent to residents of Nassau and Queens counties in New York state. About 20,000 questionnaires were returned and screened for exclusion criteria. men and women aged 50 to 70 years were considered eligible for this study, provided they had no history, no symptoms (Rose questionnaire)19, or no signs of any cardiovascular disease. Furthermore, individuals were excluded if they had insulin-dependent diabetes mellitus or if they used any lipid-lowering drugs.

After this, 5582 subjects who met the inclusion criteria and signed informed consent were scanned with electron beam CT. CT scanning was performed at enrollment 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 20.

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 outcomes who met either Scandinavian Simvastatin Survival Study (4S)21 or Cholesterol and Recurrent Events (CARE)22 criteria were placed on open-label atorvastatin 20 mg daily. Compliance was defined as consumption of at least 85% of study medications, was assessed by pill counts every three months.

Primary outcome 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. We calculated the effect of all different composites of the primary outcome with Cox proportional-hazards analyses.

Secondary outcomes included all coronary events, which included nonfatal myocardial infarction, surgical or percutaneous coronary revascularization procedures, and all events occurring more than 90 days after randomization. The latter was chosen since early events (e.g. before 90 days) might not have been influenced by the treatment protocol.

Furthermore, we calculated the effect of treatment, excluding individuals with a high Framingham risk (>20%) or with diabetes mellitus, to ensure that the results were not driven by patients already recommended for statin therapy.

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), 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 where appropriate. Also, we performed an interaction test for family history and efficacy of treatment via Cox proportional-hazards analyses.

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

Population
The flow of participants in this trial has been described in detail elsewhere. 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. 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 (1.3 (interquartile range 0.9-2.0) mmol/L vs. 1.5 (interquartile range 1.0-2.1) mmol/L; p=0.010). In the stratum of individuals with a negative family history, in the treated group, more individuals had an intermediate Framingham risk (49.1% (n=111) vs. 36.0% (n=85); p=0.004) and fewer individuals had a high Framingham risk (8.0% (n=18) vs. 16.5% (n=39); p=0.005) compared to the placebo group. Medication use and risk factor presence were similar in all groups.

Furthermore, individuals with a positive family history had overall a higher incidence of hypertension (34.6% (n=188) vs. 27.1% (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) compared to individuals with a negative family history. No gender differences were present.

During the course of the trial, there were no significant differences between the treated group and the placebo group in both strata in blood pressure, body mass index and glucose levels. Total cholesterol and LDL cholesterol levels did differ between treated and untreated individuals in both strata. However, in the treated individuals those with a positive and a negative family history did not differ in terms of total cholesterol and LDL cholesterol levels. This also applied to the placebo treated individuals.

Compliance averaged 85% for atorvastatin or its matching placebo, 88% for vitamins C and E or their matching placebos, and 79% for aspirin. Conversely, under the direction of their private physicians, 14% of subjects assigned to the control arm were initiated on a statin without an antecedent cardiovascular event.
<table>
<thead>
<tr>
<th></th>
<th>Positive family history</th>
<th>Negative family history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=280)</td>
<td>Treated (n=263)</td>
<td>All (n=543)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.4 ± 5.9</td>
<td>58.9 ± 5.8</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>205 (73.2)</td>
<td>182 (69.2)</td>
</tr>
<tr>
<td>History of smoking</td>
<td>187 (66.8)</td>
<td>165 (62.7)</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
<td>24 (8.6)</td>
<td>19 (7.2)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>96 (34.2)</td>
<td>92 (35.0)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.3 ± 5.0</td>
<td>29.1 ± 5.0</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>137.4 ± 19.0</td>
<td>135.9 ± 20.9</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>79.6 ± 9.3</td>
<td>79.0 ± 9.9</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.9 ± 0.9</td>
<td>6.0 ± 0.9</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>3.9 ± 0.8</td>
<td>3.9 ± 0.8</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.3 ± 0.4</td>
<td>1.3 ± 0.4</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.5 (1.0; 2.1)</td>
<td>1.3 (0.9; 2.0)</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>6.2 ± 1.8</td>
<td>6.1 ± 1.5</td>
</tr>
<tr>
<td>C-reactive protein (mg/l)</td>
<td>2.12 (1.08; 4.07)</td>
<td>1.74 (0.94; 3.96)</td>
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<tr>
<td>Framingham risk score</td>
<td>Median 11.9 (7.6; 16.9)</td>
<td>11.0 (7.2; 16.2)</td>
</tr>
<tr>
<td>Baseline calcium score</td>
<td>360.5 (177.1; 627.0)</td>
<td>354.8 (179.5; 626.6)</td>
</tr>
<tr>
<td>Medication use</td>
<td>Betablocker 25 (8.9)</td>
<td>26 (9.9)</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>16 (5.7)</td>
<td>20 (7.6)</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>15 (5.4)</td>
<td>18 (6.8)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>22 (7.9)</td>
<td>13 (4.9)</td>
</tr>
<tr>
<td>Other BP lowering drugs</td>
<td>16 (5.7)</td>
<td>20 (7.6)</td>
</tr>
<tr>
<td>Oral anti diabetics</td>
<td>16 (5.7)</td>
<td>12 (4.5)</td>
</tr>
<tr>
<td>End of study visit</td>
<td>Total cholesterol (mmol/L)</td>
<td>5.33 ± 1.02 *</td>
</tr>
<tr>
<td></td>
<td>LDL cholesterol (mmol/L)</td>
<td>3.36 ± 0.76 *</td>
</tr>
</tbody>
</table>

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, BP= blood pressure, DBP= diastolic blood pressure, HDL= high density lipoprotein, IQR= interquartile ranges, LDL= low density lipoprotein, SBP= systolic blood pressure; *p<0.05 versus all patients with a negative family history, † p<0.05 versus treated
Primary outcome

After a median follow-up of 4.3 years, in the stratum of individuals with a positive family history for premature CAD, 7.2% (n=19) in the treated group versus 12.5% (n=35) in the placebo group had a cardiovascular event (p=0.039) (table 2). The events in both the treated and the placebo group consisted mostly of coronary revascularizations (n=13 and n=17, respectively) and myocardial infarctions (n=5 and n=13, respectively). In the stratum of individuals with a negative family history for premature CAD, 6.6% (n=15) in the treated group versus 6.8% (n=15) in the placebo group had a cardiovascular event (p=0.95) (table 2).

Coronary events

In the stratum of individuals with a positive family history, 6.8% (n=18) in the treated group versus 10.7% (n=30) in the placebo group had a coronary event (p=0.11) (table 2). Whereas, in the stratum of individuals with a negative family history, 5.7% (n=13) in the treated group versus 5.5% (n=13) in the placebo group had a coronary event (p=0.91) (table 2).

Table 2. Outcome rate in individuals with a positive and a negative family history for premature CAD, divided by treatment

<table>
<thead>
<tr>
<th></th>
<th>Positive family history</th>
<th>Negative family history</th>
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<tbody>
<tr>
<td></td>
<td>Placebo (n=280)</td>
<td>Treated (n=263)</td>
</tr>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All CV events, n (%)</td>
<td>35 (12.5)</td>
<td>19 (7.2) *</td>
</tr>
<tr>
<td>Myocardial infarction, n (%)</td>
<td>13 (4.6)</td>
<td>5 (1.9)</td>
</tr>
<tr>
<td>Coronary revascularization, n (%)</td>
<td>17 (6.0)</td>
<td>13 (4.9)</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>0 (0)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Peripheral vascular surgery, n (%)</td>
<td>5 (1.8)</td>
<td>0 (0) *</td>
</tr>
<tr>
<td>Secondary outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All coronary events, n (%)</td>
<td>30 (10.7)</td>
<td>18 (6.8)</td>
</tr>
<tr>
<td>CV events after 90 days, n (%)</td>
<td>31 (11.0)</td>
<td>18 (6.8) *</td>
</tr>
</tbody>
</table>

Categorical data are expressed as absolute numbers with (percentages); CV= cardiovascular; *p<0.05 versus placebo. All Coronary events included nonfatal myocardial infarction, coronary death and surgical or percutaneous coronary revascularization procedures.

Cardiovascular events after more than 90 days

In the stratum of individuals with a positive family history, 6.8% (n=18) in the treated group versus 11.0% (n=31) in the placebo group had a cardiovascular event after more than 90 days (p=0.048) (table 2). In the stratum of individuals with a negative family history, 5.7% (n=13) in the treated group versus 5.9% (n=14) in the placebo group had a cardiovascular event after more than 90 days (p=0.93) (table 2).
Furthermore, Cox proportional-hazards analyses 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). This reduction in cardiovascular events in individuals with a positive family history resulted in a number needed to treat of 18.9.

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

We assessed Cox proportional-hazards analyses to evaluate the different components of the primary outcome (figure 7). Figure 7 shows the treatment effect in individuals with a positive family history assessed by HR and 95% CI in the primary outcome, its components and the secondary outcomes. For the primary outcome, the components stroke and peripheral vascular surgery are not included in figure 7, since the low event rates resulted in erratic effect estimates. We found that the effect of treatment was mainly driven by the reduction in myocardial infarctions (HR 0.40; 95% CI 0.14-1.14; p=0.083). 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). Correction for other possible confounders did not change these results. Furthermore, excluding individuals already recommended for statin therapy (e.g. individuals with a high Framingham risk or diabetes mellitus) even increased the effect of treatment (HR 0.46; 95% CI 0.24-0.87; p=0.016). The results of the interaction test between treatment group and family history for the primary outcome showed similar results as for the stratified analysis. However, it did not reach statistical significance, possibly due to the low event rate (HR 0.42; 95% CI 0.17-1.04; p=0.06).

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

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<table>
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<th>Number at risk</th>
<th>Follow up (years)</th>
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<tr>
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</tr>
<tr>
<td>Active</td>
<td>227</td>
</tr>
<tr>
<td>Placebo</td>
<td>237</td>
</tr>
</tbody>
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HR= Hazard Ratio, CI= Confidence Interval
Figure 3. Survival curve - Kaplan-Meier survival curves for all coronary events in individuals with a positive family history for premature CAD.

HR (95% CI) = 0.61 (0.34-1.11)  
\( p = 0.11 \)

HR = Hazard Ratio, CI = Confidence Interval

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

HR (95% CI) = 1.12 (0.51-2.46)  
\( p = 0.77 \)
Figure 5. Survival curve - Kaplan-Meier survival curves for all cardiovascular events after 90 days in individuals with a positive family history for premature CAD.

HR (95% CI) = 0.56 (0.31-0.98)  
p = 0.04

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

HR (95% CI) = 0.96 (0.45-2.05)  
p = 0.93
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. Interestingly, excluding individuals already recommended for statin therapy even increased the effect of treatment.

Preventive treatment in these individuals is still a matter of debate. 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. This was extended by the American College of Cardiology Foundation, by stating that measuring CCS is also appropriate in low-risk patients in whom a family history of premature CAD was present.

Surprisingly, although measuring CCS is recommended, no evidence existed that treatment of individuals with elevated CCS reduces cardiovascular risk. In these guidelines, this lack of evidence was already recognized.

The only RCT investigating the treatment of such a population is St. Francis Heart study, in which we have performed a post-hoc analysis. The St. Francis Heart study
show a 33% reduction in events, 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 beneficial. In this subgroup analysis, the event rate in the treated group was 8.7% vs. 15.0% in the placebo group, which represents an event reduction of more than 40%.17

Other studies investigating this issue have only focused on progression of CCS and have shown conflicting results. These inconsistencies have been addressed by Henein et al. in a recent meta-analysis. 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 rosvastatin 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.29

The possible limitations of our study merit discussion. This study encompasses all inherent limitations of a post-hoc analysis, most importantly, the loss of randomization and power. 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. After correction for triglyceride levels results remained the same. In terms of the interaction test between family history and treatment, we found a similar effect as we did in the stratified analysis of individuals with a positive family history. The test for interaction was nearly significant (p=0.06), which we believe is due to lack of power, based on the rather low number of events. Also, the inclusion of revascularizations is a relative soft outcome, however the effect of treatment was more pronounced in reducing myocardial infarctions.

Furthermore, we emphasize that this population was selected as those with CCS above the 80th percentile. The results should not be extrapolated to patients with lower CCS; we believe that further study is needed in this area.

Recent studies have shown no additional effects of vitamin supplementation on cardiovascular events. 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. These results have important implications for future guidelines concerning primary prevention in individuals with a positive family history for premature CAD. Although much controversy exists with regard to treatment of those with elevated CCS in primary prevention, preventive treatment of individuals with a positive family history for premature CAD and a high CCS could indeed be beneficial in terms of cardiovascular outcome.

FUNDING

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