

Aspirin and Statin Therapy for Nonobstructive Coronary Artery Disease: Five-year Outcomes from the CONFIRM Registry

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Purpose: In this cohort study, 5-year data from the Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry (ie, CONFIRM) were examined to identify associations of baseline aspirin and statin use with mortality, major adverse cardiovascular events (MACE), and myocardial infarction (MI) in individuals without substantial ($\geq 50\%$) stenosis.

Materials and Methods: In this prospective cohort study, all participants in the registry underwent coronary CT angiography and were classified as having no detectable coronary plaque or having nonobstructive coronary artery disease (CAD) (1%–49% stenosis). Participants with obstructive ($\geq 50\%$) stenosis were excluded from analysis. The study commenced in June 2003 and was completed in March 2016. All unadjusted and risk-adjusted analyses utilized the Cox proportional hazard model with hospital sites modeled using shared frailty.

Results: A total of 6386 participants with no detectable plaque or with nonobstructive CAD were included (mean age, 56.0 years \pm 13.3 [SD], 52% men). The mean follow-up period was 5.66 years \pm 1.10. Nonobstructive CAD ($n = 3571$, 56% of all participants included in the study) was associated with a greater risk of all-cause mortality (10.6% [298 of 2815] vs 4.8% [170 of 3571], $P < .001$) compared with those without CAD ($n = 2815$, 44%). Baseline aspirin and statin use was documented for 1415 and 1429 participants, respectively, with nonobstructive CAD, and for 1560 and 1565 participants without detectable plaque, respectively. In individuals with nonobstructive CAD, baseline aspirin use was not associated with a reduction in MACE (10.9% [102 of 936] vs 14.7% [52 of 355], $P = .06$), all-cause mortality (9.6% [95 of 991] vs 10.9% [46 of 424], $P = .468$), or MI (4.4% [41 of 936] vs 6.2% [22 of 355], $P = .18$). On multivariate risk-adjusted analysis, baseline statin use was associated with a lower rate of MACE (hazard ratio, 0.59; 95% CI: 0.40, 0.87; $P = .007$). Neither therapy improved clinical outcomes for participants with no detectable plaque.

Conclusion: In participants with nonobstructive CAD, baseline use of statins, but not of aspirin, was associated with improved clinical outcomes. Neither therapy was associated with benefit in participants without plaque.

Clinical trial registration no. NCT01443637

Supplemental material is available for this article.

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Abbreviations

CAD = coronary artery disease, CCTA = coronary CT angiography, CONFIRM = Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry, HR = hazard ratio, MACE = major adverse cardiovascular event, MI = myocardial infarction, SIS = segment involvement score

Summary

In participants with nonobstructive coronary artery disease at coronary CT angiography, baseline statin use was associated with fewer major adverse cardiovascular events over a mean follow-up of 5.7 years.

Key Points

- Baseline statin therapy was associated with reduction in major cardiovascular events in participants with nonobstructive coronary artery disease (CAD) (hazard ratio, 0.77; 95% CI: 0.48, 1.23; $P = .016$).
- The presence of nonobstructive CAD was associated with a greater risk of all-cause mortality (10.6% [298 of 2815] vs 4.8% [170 of 3571], $P < .001$) compared to those without CAD ($n = 2815$, 44%).

Keywords

Aspirin, Statin, Coronary Artery Disease, CT Angiography, Nonobstructive Coronary Artery Disease

Participants presenting with possible symptoms of myocardial ischemia are often investigated with coronary CT angiography (CCTA), which is now recommended as a first-line test by several authorities including the European Society of Cardiology (1), the National Institute for Health and Care Excellence (2), and most recently, by the American College of Cardiology/American Heart Association joint committee in the 2021 guideline for the evaluation and diagnosis of chest pain (3). Unlike functional testing (stress electrocardiography, stress echocardiography, myocardial perfusion imaging, and stress MRI), CCTA is able to detect nonobstructive coronary artery disease (CAD), which is associated with an increased risk of cardiovascular events (4). Statin therapy for nonobstructive CAD, defined variably as plaque causing either less than 50% or 70% luminal stenosis, has been shown to reduce adverse outcomes such as myocardial infarction (MI) and mortality in observational studies (5,6). The role of aspirin in nonobstructive CAD, however, remains unclear. Large, randomized trials have demonstrated a lack of benefit in primary prevention, although participants in these trials were recruited primarily based on Framingham risk factors and not on the presence or absence of nonobstructive CAD (7,8).

Using the 5-year outcome data from participants in the Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry (CONFIRM), the objectives of this study were as follows: (a) to analyze the impact of baseline aspirin therapy at the time of CCTA on major adverse cardiovascular events (MACE), MI, and mortality in participants with nonobstructive CAD and participants without detectable coronary plaque; (b) to analyze the impact of baseline statin therapy at the time of CCTA on MACE, MI, and mortality in those with nonobstructive CAD and participants without detectable coronary plaque; and (c) to characterize the risk of MI, MACE,

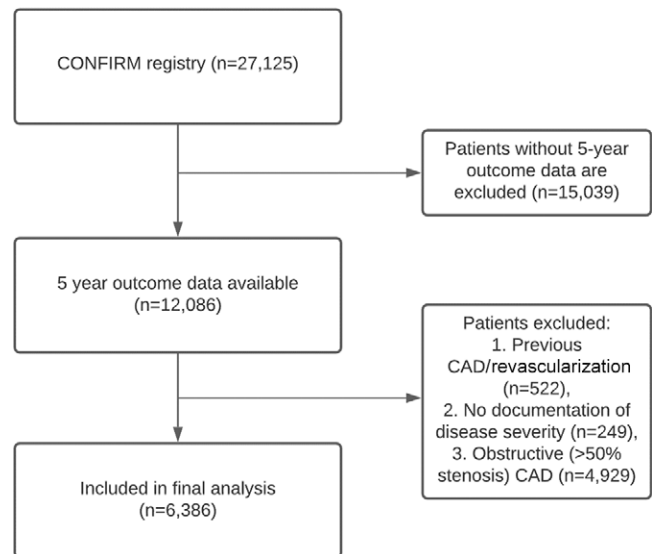


Figure 1: Flowchart of participant selection for analysis in the present study. CONFIRM = Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry, CAD = coronary artery disease.

and mortality in participants with nonobstructive CAD and participants without detectable coronary plaque.

Materials and Methods

CONFIRM Registry Participants

The methods of the CONFIRM study (ClinicalTrials.gov identifier: NCT01443637) have been previously described (9). In brief, the CONFIRM registry includes 27 125 consecutive participants from 12 cluster sites in six countries throughout North America, Europe, and Asia. Participants were enrolled, and medical history was prospectively gathered. The study commenced in June 2003 and was completed in March 2016. Health Insurance Portability and Accountability Act approval was obtained for all participating sites in the United States. A flowchart of participant selection is presented in Figure 1. Participants with previously treated CAD or revascularization, those with no documentation of disease severity, or those with obstructive coronary artery disease were excluded.

Imaging Protocol

Data were acquired using single- or dual-source 64-section CT scanners. Contrast-enhanced studies were used in all cases, and a noncontrast study was performed according to local institutional protocol or physician preference. Reporting occurred in line with standards defined by the Society of Cardiovascular Computed Tomography (10). Coronary segments were classified as either no CT detectable plaque, showing nonobstructive CAD (1%–49% luminal stenosis), or obstructive CAD (50% or more luminal stenosis in one or more arteries). The segment involvement score (SIS) was calculated by summation of the number of coronary segments with any plaque. Participants were grouped into SIS = 1, SIS = 2 or 3, and SIS = 4 or more.

Table 1: Baseline Characteristics and Clinical Outcomes of Participants

Parameter	All Participants (<i>n</i> = 6386)	No Plaque (<i>n</i> = 3571)	Nonobstructive CAD (<i>n</i> = 2815)	<i>P</i> Value
Age (y)	56.0 ± 13.3	51.7 ± 13.1	61.3 ± 11.4	<.001
No. of women	3064 (48%)	1920 (54%)	1144 (41%)	<.001
BMI (kg/m ²)	27.3 ± 5.17	27.1 ± 5.03	27.5 ± 5.29	.046
Persons currently smoking	1424 (22%)	822 (23%)	602 (21%)	.10
Hypertension	3145 (49%)	1582 (44%)	1563 (56%)	<.001
Dyslipidemia	3094 (49%)	1500 (42%)	1594 (57%)	<.001
Diabetes mellitus	868 (14%)	443 (12%)	425 (15%)	<.001
Family history of premature CAD	2473 (39%)	1473 (42%)	1000 (36%)	<.001
Aspirin therapy at baseline	748/2975 (25%)	324/1560 (21%)	424/1415 (30%)	<.001
Statin therapy at baseline	842/2994 (28%)	357/1565 (23%)	485/1429 (34%)	<.001
Death	468 (7.33%)	170 (4.76%)	298 (10.59%)	<.001
MACE	380/3546 (10.7%)	130/1848 (7.03%)	250/1698 (14.8%)	<.001
MI	189/3546 (5.33%)	71/1848 (3.84%)	118/1698 (6.95%)	<.001

Note.—Data are shown as means ± SDs or numbers with percentages in parentheses. Of the 6386 participants, MACE and MI data were available for 3546 (55.5%). BMI = body mass index, CAD = coronary artery disease, MACE = major adverse cardiovascular event, MI = myocardial infarction.

Primary Outcomes

Patient follow-up occurred via telephone and was institution dependent. Data from all 12 sites were included in the analysis. MACE was defined as all-cause death, MI, or unstable angina. Follow-up procedures were approved by all study centers' institutional review boards. Death status for non-U.S. centers was gathered by using clinical visits, telephone contacts, and questionnaires sent by mail; all reported events were verified by hospital records or direct contact with a patient's attending physician. Death status for U.S. centers was ascertained either by query of the Social Security Death Index or by direct physician and/or patient contact.

For the present study, only participants with documentation of CAD severity were included. For analyses relating to baseline aspirin and statin use, analysis was limited to participants for whom these data were available.

Statistical Analysis

Continuous variables are presented as means ± SDs if normally distributed and medians and interquartile ranges if not. Categorical variables are reported as frequencies and percentages. The independent two-sample *t* test or Wilcoxon rank sum test was used for comparison of continuous baseline characteristics, as appropriate, and the Pearson χ^2 test or Fisher exact test for cell counts less than six for categorical variables. All unadjusted and risk-adjusted analyses utilized the Cox proportional hazard model with hospital sites modeled using shared frailty. Aspirin and statin use was coded as either present or absent. Models were adjusted for aspirin or statin use, age, sex, hypertension, dyslipidemia, diabetes, and family history of CAD. The proportionality of hazards assumption was tested and verified using Schoenfeld residuals. A two-tailed *P* value of less than .05 was considered significant. Statistical analysis was performed using statistical software (Stata, release 16).

Results

Five-year extended follow-up outcome data from the CONFIRM registry were available for 12086 individuals. After excluding participants with previously treated CAD or revascularization, those with no documentation of disease severity, or those with obstructive CAD, the extent of coronary atherosclerosis as defined with CCTA was available for 6386 participants (5700 participants were excluded, see Fig 1). The mean age was 56.0 years ± 13.3 (SD). A total of 48% of participants were female. Demographic data are presented in Table 1. Baseline aspirin use was documented for 2975 participants, and statin use for 2994 participants. The mean follow-up time was 5.66 years ± 1.10.

Baseline Aspirin Use

Aspirin use at the time of initial CCTA was documented for 1415 participants with nonobstructive CAD. A total of 991 (70%) participants with nonobstructive CAD were not receiving aspirin therapy, while 424 (30%) were. Participants with nonobstructive CAD taking aspirin tended to be older and had higher rates of hypertension, dyslipidemia, and diabetes mellitus compared with participants with nonobstructive CAD who were not taking aspirin (Table 2). There was no evidence of a significant difference in unadjusted or multivariate risk-adjusted event rates for mortality, MACE, and MI for participants with nonobstructive CAD (Table 3). Aspirin therapy was not associated with a net clinical benefit on risk-adjusted analysis for participants with no plaque (*n* = 1686, Table E1 [supplement]). Baseline aspirin therapy was not shown to have any benefit for MACE, mortality, or MI across different SIS strata (see Table E2 [supplement]).

Baseline Statin Use

Documentation of statin use was available for 1429 participants with nonobstructive CAD. Participants with nonobstructive CAD taking statins tended to be older and had higher

Table 2: Baseline Characteristics and Clinical Outcomes of Participants with Nonobstructive CAD for Whom Aspirin Use Was Documented at the Time of Initial CCTA

Parameter	No Aspirin (n = 991)	Aspirin (n = 424)	P Value
Age (y)	62.4 ± 10.5	64.0 ± 10	.01
No. of women	366 (36.9%)	144 (34.0%)	.28
BMI (kg/m ²)	27.0 ± 5.1	27.4 ± 5.4	.18
Persons currently smoking	199 (20.1%)	95 (22.4%)	.33
Hypertension	523 (52.8%)	273 (64.4%)	<.001
Dyslipidemia	541 (54.6%)	278 (65.6%)	<.001
Diabetes mellitus	119 (12.0%)	73 (17.2%)	.009
Family history of premature CAD	310 (31.3%)	124 (29.3%)	.45
Death	95 (9.59%)	46 (10.85%)	.468
MACE	102/936 (10.9%)	52/355 (14.7%)	.06
MI	41/936 (4.38%)	22/355 (6.20%)	.18

Note.—Data are shown as means ± SDs or numbers with percentages in parentheses. Participants not taking aspirin were not excluded from taking statin or other therapy. Sixty-five patients in the no aspirin group lacked MACE/MI data. Sixty-nine patients in the aspirin group lacked MACE/MI data. BMI = body mass index, CAD = coronary artery disease, CCTA = coronary CT angiography, MACE = major adverse cardiovascular event, MI = myocardial infarction.

Table 3: Mortality, MI, and MACE for Statin and Aspirin Therapy at Baseline for Participants with Nonobstructive CAD

Endpoint	Mortality	MI	MACE
Risk-adjusted values*			
Aspirin at baseline	HR 0.77 (0.52, 1.15) P = .20	HR 1.03 (0.57, 1.85) P = .92	HR 1.06 (0.72, 1.54) P = .78
Statin at baseline	HR 0.77 (0.48, 1.23) P = .27	HR 0.54 (0.28, 1.05) P = .07	HR 0.59 (0.39, 0.91) P = .016
Nonadjusted values*			
Aspirin at baseline	HR 0.78 (0.53, 1.15) P = .217	HR 1.02 (0.57, 1.81) P = .95	HR 1.12 (0.78, 1.62) P = .542
Statin at baseline	HR 0.58 (0.40, 0.85) P = .005	HR 0.63 (0.34, 1.15) P = .133	HR 0.59 (0.40, 0.87) P = .007

Note.—Data are shown as hazard ratios (HRs), 95% CIs, P values. CAD = coronary artery disease, MACE = major adverse cardiovascular event, MI = myocardial infarction.

* Adjusted for age, sex, hypertension, dyslipidemia, diabetes, and family history of CAD.

rates of dyslipidemia, diabetes, and family history of premature CAD (Table 4). Among participants with nonobstructive CAD, baseline statin therapy was associated with a reduction in MACE on both nonadjusted (hazard ratio [HR], 0.59; 95% CI: 0.40, 0.87; *P* = .007) and risk-adjusted multivariate (HR, 0.59; 95% CI: 0.39, 0.91; *P* = .016) analyses, as shown in Table 3. A Kaplan-Meier survival analysis is presented in Figure 2. Baseline statin therapy was also associated with a reduction in all-cause mortality on nonadjusted analysis (HR, 0.58; 95% CI: 0.40, 0.85; *P* = .005). In the risk-adjusted analysis, there was a reduced incidence of MI, although this difference was of borderline statistical significance (4.28% [18 of 421] vs 5.1% [45 of 884], *P* = .07) (Table 3). Baseline statin therapy was not associated with improved clinical outcomes in participants with no detectable plaque (*n* = 1565, Table E2 [supplement]) or in participants with SIS of 1. However, on risk-adjusted

analysis, in participants with SIS score of 2–3, statin use was associated with a statistically significant reduction in MACE (9.4% vs 15.1%; HR, 0.43; 95% CI: 0.22, 0.83; *P* = .012) (Fig 3) and MI (4.4% vs 8.1%; HR, 0.30; 95% CI: 0.11, 0.82; *P* = .018). There was no statistically significant difference in mortality. In participants with SIS greater than or equal to 4, no statistically significant reductions in adverse events were noted, although fewer participants were present in this group. Clinical outcomes for baseline statin therapy stratified according to SIS are available in Table E3 (supplement).

Participants with No Detectable Plaque versus Nonobstructive CAD

Participants with nonobstructive CAD tended to be older and had higher prevalence of cardiovascular risk factors including hypertension, dyslipidemia, and diabetes mellitus.

Table 4: Baseline Characteristics and Clinical Outcomes of Participants with Nonobstructive CAD for Whom Statin Use Was Documented at the Time of Initial CCTA

Parameter	No Statin (<i>n</i> = 944)	Statin (<i>n</i> = 485)	<i>P</i> Value
Age (y)	62.3 ± 10.6	64.0 ± 10.1	.004
No. of women	316 (33.5%)	200 (41.2%)	.004
BMI (kg/m ²)	27.0 ± 4.9	27.5 ± 5.7	.10
Persons currently smoking	198 (21.0%)	102 (21.1%)	.981
Hypertension	521 (55.3%)	282 (58.1%)	.296
Dyslipidemia	395 (41.9%)	434 (89.5%)	<.001
Diabetes mellitus	111 (11.8%)	83 (17.1%)	.005
Family history of premature CAD	271 (28.7%)	170 (35.1%)	.014
Death	102 (10.8%)	40 (8.25%)	.126
MACE	115/884 (13.0%)	40/421 (9.5%)	.067
MI	45/884 (5.1%)	18/421 (4.28%)	.521

Note.—Data are shown as means ± SDs or numbers with percentages in parentheses. Participants not taking statins were not excluded from taking aspirin or other therapy. One hundred patients in the no statin group had no MACE/MI data collected. Sixty-four patients in the statin group had these data missing. BMI = body mass index, CAD = coronary artery disease, CCTA = coronary CT angiography, MACE = major adverse cardiovascular event, MI = myocardial infarction.

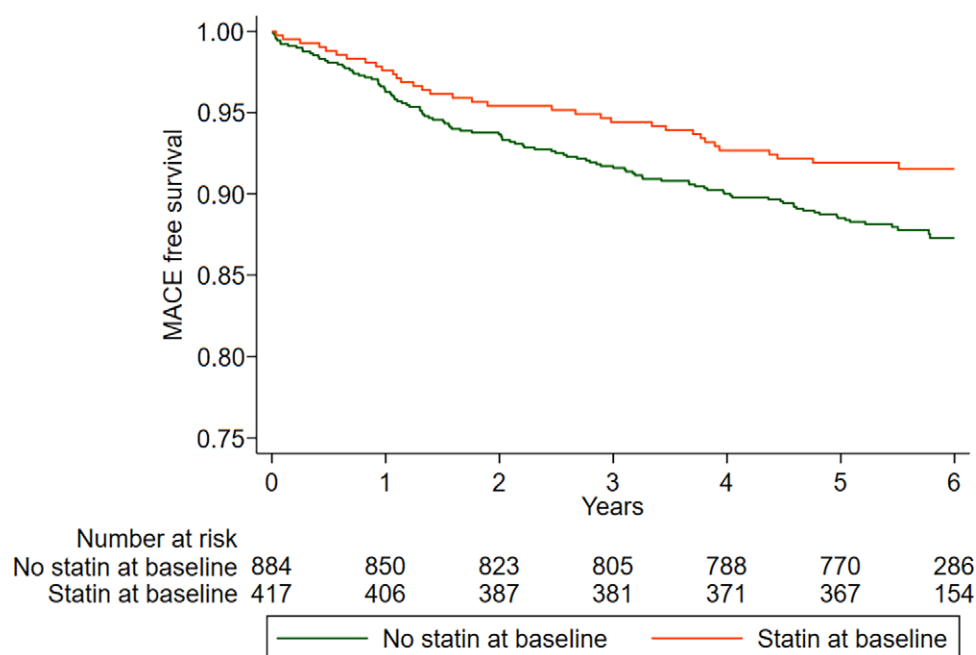


Figure 2: Kaplan-Meier analysis of MACE-free survival for participants with nonobstructive CAD who received baseline statin therapy versus those who did not. CAD = coronary artery disease, MACE = major adverse cardiovascular event.

Compared with participants with no plaque, participants with nonobstructive CAD were more likely to experience death (HR, 1.41; 95% CI: 1.03, 1.93; *P* = .03), MACE (HR, 1.91; 95% CI: 1.39, 2.63; *P* < .001) (see Fig 4), and MI (HR, 2.84; 95% CI: 1.70, 4.74; *P* < .001) on multivariate analysis, after adjusting for age, sex, smoking status, hypertension, dyslipidemia, diabetes mellitus, and family history of premature CAD.

Outcomes according to SIS

SIS was analyzed according to four groups: SIS = 0 (*n* = 3571), SIS = 1 (*n* = 1004), SIS = 2 or 3 (*n* = 1175), and SIS

greater than or equal to 4 (*n* = 636). Clinical outcomes are displayed in Table E6 (supplement).

A higher SIS was associated with an increase in the incidence of MACE (see Fig 5), mortality, and MI. Compared with those with no detectable plaque (SIS = 0), participants with a SIS of 1 were more likely to experience MACE (10.6% vs 7.0%; HR, 1.49; 95% CI: 1.00, 2.23; *P* = .05) and MI (5.2% vs 3.8%; HR, 1.91; 95% CI: 1.02, 3.58; *P* = .045) (Table E6 [supplement]), although after adjustment for demographic risk factors, as well as statin and aspirin therapy at baseline, the differences were of borderline

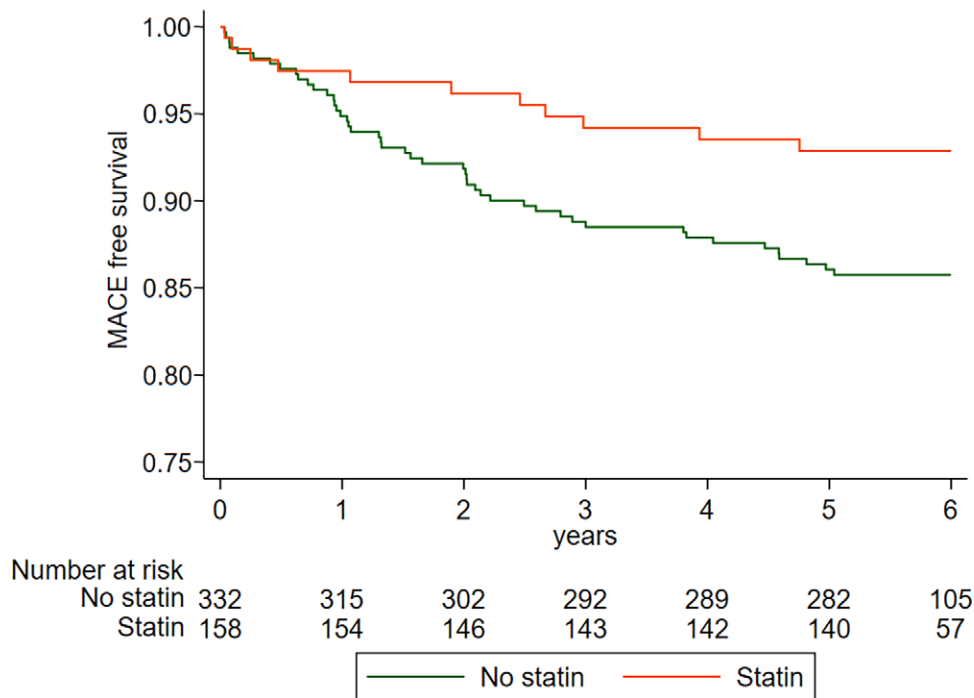


Figure 3: Kaplan-Meier analysis of MACE-free survival for participants with a SIS of 2 or 3 who received baseline statin therapy versus those who did not. MACE = major adverse cardiovascular event, SIS = segment involvement score.

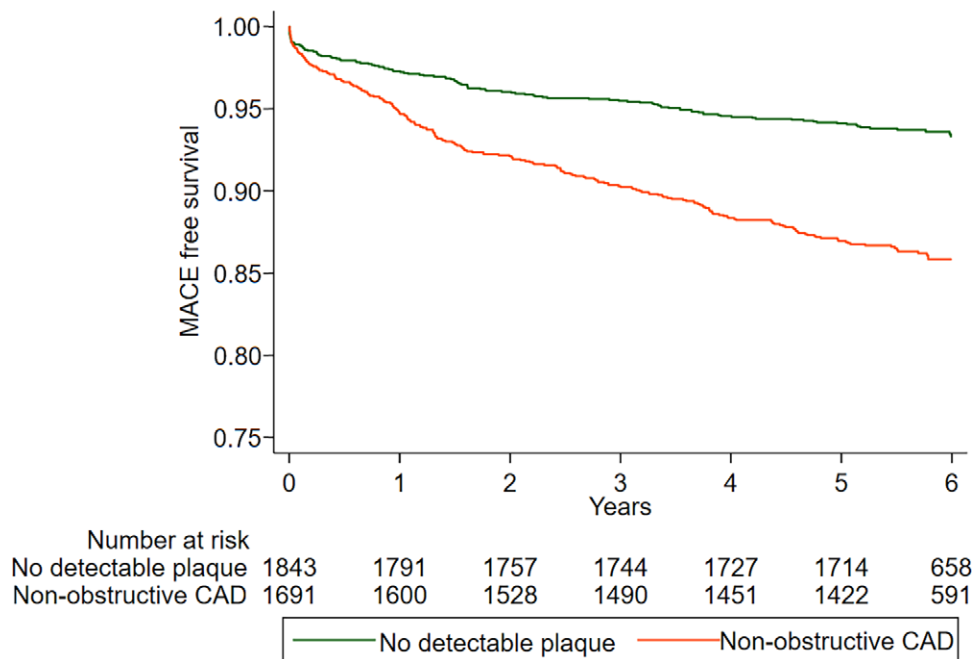


Figure 4: Kaplan-Meier analysis of MACE-free survival for all participants with nonobstructive CAD compared with those who had no detectable plaque. CAD = coronary artery disease, MACE = major adverse cardiovascular event.

statistical significance. Participants with a SIS of 2 or 3, or with a SIS of 4 and above, were more likely to experience MACE and mortality on multivariate risk-adjusted analysis (see Table E4 [supplement]).

Upon risk-adjusted analysis, participants with a SIS of 2 or 3 were more likely to experience MACE than those with a SIS of 1 (15.7% vs 10.6%; HR, 1.71; 95% CI: 1.15, 2.55;

$P = .008$). Mortality and MI were also more common (see Table E5 [supplement]). Similar results were observed for participants with SIS greater than or equal to 4 compared with those with SIS of 1.

Compared with those with SIS of 2–3, participants with a SIS of 4 or above were not statistically more likely to experience any adverse events.

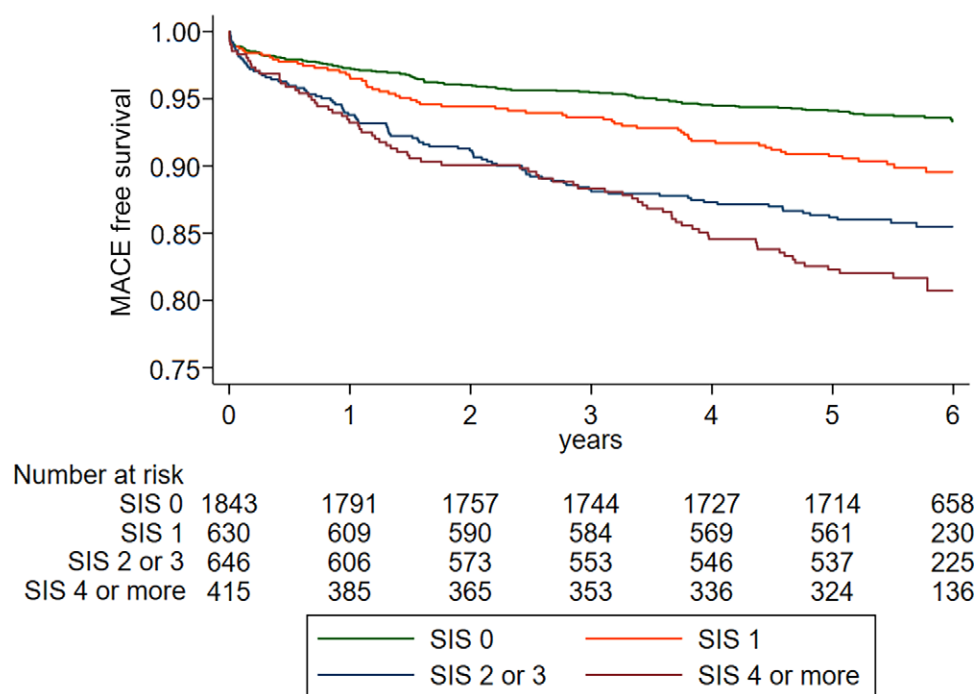


Figure 5: Kaplan-Meier analysis of MACE-free survival for participants as stratified by SIS. MACE = major adverse cardiovascular event, SIS = segment involvement score.

Discussion

This analysis of long-term outcome data from the large CONFIRM registry found that after adjustment for confounding factors, aspirin therapy at the time of baseline CCTA in participants with nonobstructive CAD was not associated with a reduction in MACE, mortality, or MI. By contrast, statin use was associated with a significant reduction of MACE, particularly in participants with a SIS of 2 or 3. Importantly, neither aspirin nor statins were associated with any benefit in participants with no detectable plaque. Additionally, the analysis confirmed the presence of nonobstructive CAD as an independent risk factor for mortality, MACE, and MI. These findings are similar to the intermediate-term results of the original CONFIRM analysis and have incremental value as the results are sustained over a 5-year follow-up period (11). Additionally, the analysis demonstrated the potential value of SIS as a marker of plaque burden, as higher SIS was associated with a higher incidence of MACE.

While previously used as a common primary prevention to reduce cardiovascular events, aspirin therapy is no longer recommended in this context. Multiple trials and a meta-analysis of more than 160 000 individuals have demonstrated a lack of net benefit for aspirin, particularly as the risk of gastrointestinal and major bleeding may obviate or outweigh any potential reduction in ischemic risk (7,8,12). As aspirin is clearly indicated for secondary prevention, it has been surmised that in cases of high plaque burden (or elevated calcium scores, eg, >100), aspirin may be of benefit, although these data are based on observational, nonrandomized studies (13). Analysis was performed in the present study to examine for benefit with aspirin in association with SIS, but no difference was found, although these analyses were possibly underpowered. There is a need to examine

the utility of aspirin in primary prevention in individuals with high-risk plaque or high plaque burden.

Prior to the CCTA era, the prognostic significance of nonobstructive CAD was underestimated. Analyses of large CCTA registries and trials have demonstrated that nonobstructive CAD is associated with adverse outcomes, particularly in the context of vulnerable plaque features (14) or a high overall plaque burden (15,16). MI occurs as a result of plaque rupture, erosion, and thrombosis, and nonobstructive plaques may rupture spontaneously, often as a result of rapid progression (17). While obstructive plaques are more likely to rupture on a per-plaque basis, nonobstructive plaques are far more common and thus may account for the majority of MIs (18).

The clinical significance of nonobstructive CAD may not always be clear. While it is often assumed that lesions causing less than 50% stenosis are incapable of causing myocardial ischemia under stable conditions, fractional flow reserve testing has demonstrated that such lesions can be physiologically important (19), particularly in the context of high-risk plaque features, which may be a surrogate for poor endothelial vaso-reactivity (20). The majority of these lesions are likely to be clinically silent until they progress or undergo an acute plaque change. Thus, many of these lesions may be undetected with stress echocardiography, MRI, or myocardial perfusion scanning. The use of CCTA thus has an obvious advantage, by detecting a potentially life-threatening condition early, where a well-defined treatment paradigm exists (statin therapy and lifestyle modification). CCTA has been shown to portend a mortality benefit when used in the investigation of chest pain compared with functional testing, the mechanism likely being due to increased use of primary prevention therapy (21).

Our findings are consistent with prior analyses from the same registry as well as other studies over shorter follow-up and highlight the benefit of statin therapy among those with nonobstructive CAD diagnosed at CCTA. Statins act by reducing levels of low-density lipoprotein cholesterol, thus reducing the substrate for plaque formation, but also can stabilize plaques by favorably changing the plaque pathophysiology; the change in pathophysiology is due to reduced inflammation, improved endothelial function, and increased calcification (22), which increases the structural integrity and reduces the risk of plaque rupture. Although loss of participants to extended follow-up may have caused the present study to be underpowered to detect a difference in mortality and MI compared with an earlier analysis (11), a clear reduction in MACE was identified. Many authorities suggest prescription of statin therapy in individuals with elevated cardiovascular risk calculated using traditional risk factors (23), but the use of statin therapy can also be guided by the presence and burden of nonobstructive CAD at CCTA. However, data from the PROMISE registry demonstrated that only a minority of patients with nonobstructive CAD were receiving statin therapy, suggesting the more widespread adoption of this strategy of treatment with statins when plaque is identified (6). In the present study, only 30% of participants with nonobstructive CAD were taking a statin at baseline, suggesting that traditional assessments may underestimate cardiovascular risk. It should be noted, however, that blanket prescription of statin therapy to all patients with nonobstructive CAD is not advised, particularly in older persons where the prevalence of nonobstructive CAD is very high. Given the lack of evidence of efficacy of statins in participants with no coronary plaque in the present study, it could be argued that statin therapy is not required for these patients, regardless of risk score. The concern of this, however, is that without serial CCTA or calcium score testing, the onset of plaque development may be missed, although this process is likely to take several years.

The strengths of the study included the large cohort size and long follow-up period. Apart from the observational nature of the registry, there were several limitations to the present study. While the use of aspirin and statin therapy at baseline was defined as the dependent variable, this was done as the use of these medications at follow-up was only recorded for 8.5% of participants. Thus, it is not known whether these medications were added or subtracted during the 5-year follow-up period in response to the CCTA findings, a changing risk profile, or ischemic events. Less than 50% of the participants originally enrolled were followed-up at 5 years. The use of statin and aspirin therapy at baseline was only available for 49% of participants, and doses, or the type and intensity of statin, were not recorded. MACE and MI outcomes were available only for 55.5% of participants. Calcium scoring and low-density lipoprotein cholesterol levels were only available for 47% and 29% of participants, respectively, thus analysis of baseline therapy in participants with high calcium scores or low-density lipoprotein cholesterol was not undertaken. No data were available for hemorrhagic events. A strategy of empirical aspirin prescription for patients with nonobstructive CAD does not appear to be supported by these data. Ultimately, further research is

required to determine whether, and at what threshold, clinicians should consider prescribing aspirin for patients on the identification of nonobstructive CAD at CCTA.

In this 5-year follow-up analysis of the CONFIRM registry, it is demonstrated that use of aspirin at the time of the initial CCTA was not associated with any clinical benefit in participants with nonobstructive CAD, even in participants with a high plaque burden. Baseline statin therapy was associated with a reduction in MACE in participants with nonobstructive CAD, suggesting a critical role for these medications in this population, although not in those with no coronary plaque.

Data sharing: Data generated or analyzed during the study are available from the corresponding author by request.

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