Clinical and Population Studies

Prognostic and Therapeutic Implications of Statin and Aspirin Therapy in Individuals With Nonobstructive Coronary Artery Disease

Results From the CONFIRM (Coronary CT Angiography Evaluation For Clinical Outcomes: An International Multicenter Registry) Registry


Objective—We sought to examine the risk of mortality associated with nonobstructive coronary artery disease (CAD) and to determine the impact of baseline statin and aspirin use on mortality.

Approach and Results—Coronary computed tomographic angiography permits direct visualization of nonobstructive CAD. To date, the prognostic implications of nonobstructive CAD and the potential benefit of directing therapy based on nonobstructive CAD have not been carefully examined. A total of 27,125 consecutive patients who underwent computed tomographic angiography (12 enrolling centers and 6 countries) were prospectively entered into the COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter (CONFIRM) registry. Patients, without history of previous CAD or obstructive CAD, for whom baseline statin and aspirin use was available were analyzed. Each coronary segment was classified as normal or nonobstructive CAD (1%–49% stenosis). Patients were followed up for a median of 27.2 months for all-cause mortality. The study comprised 10,418 patients (5712 normal and 4706 with nonobstructive CAD). In multivariable analyses, patients with nonobstructive CAD had a 6% (95% confidence interval, 1%–12%) higher risk of mortality for each additional segment with nonobstructive plaque ($P = 0.021$). Baseline statin use was associated with a reduced risk of mortality (hazard ratio, 0.44; 95% confidence interval, 0.28–0.68; $P = 0.0003$), a benefit that was present for individuals with nonobstructive CAD (hazard ratio, 0.32; 95% confidence interval, 0.19–0.55; $P < 0.001$) but not for those without plaque (hazard ratio, 0.66; 95% confidence interval, 0.30–1.43; $P = 0.287$). When stratified by National Cholesterol Education Program/Adult Treatment Program III, no mortality benefit was observed in individuals without plaque. Aspirin use was not associated with mortality benefit, irrespective of the status of plaque.

Conclusions—The presence and extent of nonobstructive CAD predicted mortality. Baseline statin therapy was associated with a significant reduction in mortality for individuals with nonobstructive CAD but not for individuals without CAD.
Coronary computed tomographic angiography (CTA) is a noninvasive angiographic modality that allows for direct visualization of obstructive and nonobstructive coronary artery disease (CAD). 1–7 Although several previous studies have carefully examined the prognostic implications of obstructive CAD for individuals undergoing coronary CTA, the relationship of nonobstructive CAD to future adverse events remains not completely understood.

Furthermore, the decisions on primary prevention for individuals with nonobstructive CAD remain unclear. Statin and aspirin treatment, for primary prevention, is recommended for patients at high risk of future cardiovascular events based on clinical or laboratory markers, such as those with diabetes mellitus, dyslipidemia, high Framingham or National Cholesterol Education Program/Adult Treatment Program III (NCEP/ATP III) risk scores, or intermediate Framingham Risk Score with clinical or laboratory markers, such as those with diabetes mellitus, dyslipidemia, high Framingham or National Cholesterol Education Program/Adult Treatment Program III (NCEP/ATP III) risk scores, or intermediate Framingham Risk Score with elevated high-sensitivity-C-reactive protein. 8,9 Several recent analyses have directly challenged the efficacy of statin or aspirin therapy in primary prevention. 10–12 Whether the use of coronary CTA to identify nonobstructive CAD offers a feasible method by which at-risk patients can be identified and effectively treated remains unknown.

Therefore, using a large prospective multicenter international registry, we examined the risk of mortality and the impact of baseline statin and aspirin use on mortality risk in individuals without obstructive CAD by coronary CTA.

Materials and Methods
Materials and Methods are available in the online-only Data Supplement.

Results
Study Population
Of the 27,125 CONFIRM registry patients, centers without medication data were excluded (3 centers with 7422 patients). An additional 6074 patients were excluded for incomplete coronary plaque information (836 patients), history of myocardial infarction or revascularization (1491 patients), congenital heart disease (119 patients), missing body mass index (449 patients), missing age (2 patient), and obstructive CAD diagnosed on coronary plaque information (836 patients). Of the remaining 13,629 patients, 3211 (23.6%) patients had missing statin or aspirin information. For those with numeric values of lipoproteins, total cholesterol was 191±43 mg/dL (n=7426), low-density lipoprotein cholesterol was 117.2±36.1 mg/dL (n=6831), and high-density lipoprotein cholesterol was 53.4±16.3 mg/dL (n=7263).

Follow-up (median, 27.2 [interquartile range, 17.7–40.8] months) was available for 99.3% of patients. Although few were lost to follow-up (77 [0.7%] patients), patients lost to follow-up were younger (48.7±11.5 years) and were less likely to be hypertensive (31.2%) or dyslipidemic (40.3%; P<0.01 for all).

A total of 10,418 patients (5712 with normal coronary arteries and 4706 with nonobstructive CAD) met the enrolment criteria and were analyzed (Table 1). There were observed differences between statin and nonstatin users for age (60.5 versus 55.6 years; P<0.001), and prevalence of hypertension (54.7% versus 42.3%; P<0.001), diabetes mellitus (18.5% versus 8.4%; P<0.001), dyslipidemia (85.0% versus 39.1%, P<0.001), but not smoking (24.7% versus 25.5%; P=0.38).

Important also clinical differences existed between aspirin users and nonaspirin users for measures of age (59.6 versus 55.8 years; P<0.001), hypertension (54.5% versus 51.6%; P<0.001), diabetes mellitus (15.5% versus 9.5%; P<0.001), dyslipidemia (62.3% versus 49.5%; P<0.001), but not smoking (25.0% versus 25.4%; P=0.67).

Compared with patients with normal coronary arteries, those with nonobstructive CAD were older, more often men, had more cardiac risk factors, and had higher NCEP/ATP III risk scores (P<0.001 for all). Patients with nonobstructive CAD by coronary CTA were more likely to be taking statins (43.2% versus 25.1%; P<0.001) and aspirin (46.2% versus 30.8%; P<0.001) at the time of coronary CTA when compared with patients without CAD by coronary CTA.

At follow-up, there were a total of 120 deaths. Seventy-nine deaths occurred in 4706 patients with nonobstructive coronary plaque (1.68%) and 41 deaths occurred in the 5712 individuals with normal coronary arteries (0.72%). Of the 3465 patients treated with statins, there were a total of 29 (0.76%) deaths, whereas of the 6953 patients without statin therapy, there were 91 (1.31%) deaths. The relationship of statin use and plaque as a function of mortality exhibited differences. Deaths occurred in 9 (0.6%) statin-using patients compared with 32 (0.8%) non–statin-using patients (P=0.64) with normal coronary arteries, whereas occurring in 20 (1.0%) statin-using patients and 59 (2.2%) non–statin-using patients (P=0.001) with nonobstructive CAD.

<table>
<thead>
<tr>
<th>Nonstandard Abbreviations and Acronyms</th>
<th>Description</th>
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<tbody>
<tr>
<td>CAD</td>
<td>coronary artery disease</td>
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<tr>
<td>CTA</td>
<td>computed tomographic angiography</td>
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<tr>
<td>HR</td>
<td>hazard ratio</td>
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<tr>
<td>NCEP/ATP III</td>
<td>National Cholesterol Education Program/Adult Treatment Program III</td>
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Univariable Analysis of Clinical Variables and Medications for All-Cause Mortality
In univariable analysis of the entire study cohort, age, cardiac risk factors, and NCEP/ATP III risk were associated with all-cause mortality (Table 2). Baseline statin therapy was associated with lower mortality in the entire study cohort (hazard ratio [HR], 0.65 [0.43–0.99]; P=0.046) and those with...
nonobstructive CAD (HR, 0.45 [0.27–0.75]; P=0.002), but not in patients with normal coronary arteries (HR, 0.84 [0.40–1.76]; P=0.646). Aspirin use at baseline was not associated with differences in survival in the overall study group (HR, 0.89 [0.61–1.3]; P=0.537) or in those with and without nonobstructive CAD (HR, 0.72 [0.46–1.14]; P=0.161) and (HR, 0.84 [0.40–1.76]; P=0.646, respectively).

**Nonobstructive CAD and All-Cause Mortality**

When compared with individuals with normal coronary arteries, patients with nonobstructive CAD in Coronary computed tomographic angiography (CCTA) experienced higher mortality and there was incremental risk both with the number of coronary vessels and the number of coronary segments involved (Table 3; Figure 1). The relationship between the summed total number of segments with nonobstructive CAD and mortality risk was assessed. All segment scores >0 were associated with increased mortality risk, and there was no lower threshold for the absence of mortality risk.

**Statin and Aspirin Primary Prevention and All-Cause Mortality**

Statin use at the time of CCTA was associated with lower mortality (0.76% versus 1.31%) and a lower annual death rate (0.33% versus 0.59%; P=0.032). In patients with nonobstructive CAD, the annual death rate was significantly lower in those (0.47% and 1.04%; P=0.002). Conversely, aspirin therapy was not (1.04% versus 1.22%; P=0.473) associated with an improvement in all-cause mortality. In multivariable risk-adjusted models, statin use was associated with a significant survival benefit (HR, 0.52; 95% confidence interval, 0.34–0.79; P=0.002); however, an interaction analysis between statin use and nonobstructive CAD showed the survival benefit of statin use without an obvious difference between those with plaque and those with normal coronary arteries (P=0.233). Further subgroup analysis showed that the effect of statin use was only observed for patients with nonobstructive CAD (HR, 0.39 [0.23–0.65]; P<0.001) and was not observed in patients with normal coronary arteries (HR, 0.64 [0.30–1.37]; P=0.252; Table 4). The lower HR for patients with nonobstructive CAD suggests that a larger study will be needed to identify an interaction (Figures 2 and 3).

When stratified by NCEP/ATP III risk, the beneficial effect of statins was observed in patients with nonobstructive CAD and in a subanalysis of these patients, a significant reduction in mortality was observed in those patients with coronary atherosclerosis and at intermediate NCEP/ATP III risk. A trend was observed in patients at high NCEP/ATP III risk (P=0.060; Table 5). Further subgroup analyses in the univariable models and also multivariable models adjusting for NCEP/ATP III risk, both showed that mortality reduction was also observed across many subgroups taking statins at baseline (Figure 4).

<table>
<thead>
<tr>
<th>Table 1. Patient Characteristics</th>
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<tbody>
<tr>
<td>All Patients</td>
</tr>
<tr>
<td>n=10418</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
</tr>
</tbody>
</table>

Cardiac risk factors:

- Smoker/ex-smoker      | 2626 (25.2%) | 1248 (21.8%) | 1378 (29.3%) | <0.001 |
- Hypertension          | 4837 (46.4%) | 2444 (42.8%) | 2393 (50.8%) | <0.001 |
- Dyslipidemia†         | 5662 (54.3%) | 2888 (50.6%) | 2774 (58.9%) | <0.001 |
- Diabetes mellitus     | 1226 (11.8%) | 525 (9.2%)   | 701 (14.9%)  | <0.001 |
- Family history of CAD | 2885 (27.7%) | 1501 (26.3%) | 1384 (29.4%) | <0.001 |

Indications for study:

- Chest pain            | 6012 (57.7%) | 3566 (62.4%) | 2446 (52.0%) | <0.001 |
- Typical angina        | 1094 (10.5%) | 625 (10.9%) | 469 (10.0%) | 0.109 |
- Dyspnea               | 784 (7.5%)   | 358 (6.3%) | 426 (9.1%)  | <0.001 |
- Chest pain+dyspnea    | 1127 (10.8%) | 586 (10.3%) | 541 (11.5%) | 0.043 |

NCEP/ATP III risk:

- Low risk              | 3240 (31.1%) | 2155 (37.7%) | 1085 (23.1%) | <0.001 |
- Intermediate risk     | 5699 (54.7%) | 2899 (50.8%) | 2800 (59.5%) | <0.001 |
- High risk             | 1479 (14.2%) | 658 (11.5%) | 821 (17.4%) | <0.001 |

Medications:

- Aspirin               | 3932 (37.7%) | 1758 (30.8%) | 2174 (46.2%) | <0.001 |
- Statin                | 3465 (33.3%) | 1432 (25.1%) | 2033 (43.2%) | <0.001 |

Values are given as mean±SD or n (%). CAD indicates coronary artery disease; and NCEP/ATP III, National Cholesterol Education Program/Adult Treatment Program III.

*Comparison of patients with no plaque and with nonobstructive CAD.
†Self-reported dyslipidemia.
particularly, there was a significant interaction between hyper-
tension and statins ($P = 0.013$) with statins therapy being more
effective in hypertensive patients versus normotensive patients
(HR, 0.35 [0.20–0.60] versus 1.13 [0.56–2.30]). There was
also weak interaction between diabetes mellitus and statin use
($P = 0.051$) such that patients with diabetes mellitus seemed to
have a greater benefit from statin therapy. Initial analysis of
suggested a trend toward benefit of statin therapy in patients
without dyslipidemia. Acknowledging that diabetics could be
categorized as without dyslipidemia, a post hoc analysis was
performed excluding diabetics. The HR for patients with dys-
lipidemia was 0.70 (0.28–1.77) and without dyslipidemia was
1.09 (0.55–2.15).

**Discussion**

The present study represents the first large prospective multi-
center international study to estimate the risk of mortality for
patients with nonobstructive CAD, and further determine the
therapeutic implications of statin and aspirin use in patients
with nonobstructive CAD, stratified by NCEP/ATP III risk.
In this intermediate-term follow-up, we identified a relation-
ship between increasing burden of nonobstructive CAD and
higher mortality rates and observed a reduction in mortality
risk associated with baseline statin therapy but not aspirin,
a finding that may be because of a statistical underpower-
ing because of the number of observed events (n=120). This
finding was accentuated for individuals with coronary

**Table 3. Univariable and Multivariable Hazard Ratios for All-Cause Mortality by Per-Segment, Per-Vessel and Location-Based
Coronary Computed Tomographic Angiography-Identified Nonobstructive CAD (Compared With Patients without Coronary Plaque)**

<table>
<thead>
<tr>
<th>Segment-based analysis</th>
<th>Unadjusted HR (95% CI)</th>
<th>P Value</th>
<th>NCEP/ATP III Adjusted HR (95% CI)</th>
<th>P Value</th>
<th>NCEP/ATP III and Statin Adjusted HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per additional segment</td>
<td>1.13 (1.08–1.18)</td>
<td>&lt;0.0001</td>
<td>1.12 (1.07–1.17)</td>
<td>&lt;0.0001</td>
<td>1.12 (1.07–1.17)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1–4 segments</td>
<td>4.02 (2.26–7.18)</td>
<td>&lt;0.0001</td>
<td>3.75 (2.10–6.69)</td>
<td>&lt;0.0001</td>
<td>3.92 (2.19–6.99)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥5 segments</td>
<td>7.30 (3.97–13.4)</td>
<td>&lt;0.0001</td>
<td>6.55 (3.56–12.1)</td>
<td>&lt;0.0001</td>
<td>6.82 (3.69–12.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vessel-based analysis</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1 vessel vs no coronary plaque</td>
<td>1.43 (0.79–2.58)</td>
<td>0.2407</td>
<td>1.25 (0.69–2.26)</td>
<td>0.462</td>
<td>1.33 (0.73–2.41)</td>
<td>0.3538</td>
</tr>
<tr>
<td>2 vessels vs no coronary plaque</td>
<td>2.98 (1.77–5.00)</td>
<td>&lt;0.0001</td>
<td>2.64 (1.57–4.45)</td>
<td>0.0003</td>
<td>2.84 (1.68–4.81)</td>
<td>0.0001</td>
</tr>
<tr>
<td>3 vessels vs no coronary plaque</td>
<td>2.99 (1.94–4.60)</td>
<td>&lt;0.0001</td>
<td>2.62 (1.70–4.05)</td>
<td>&lt;0.0001</td>
<td>2.76 (1.78–4.29)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; HR, hazard ratio; and NCEP/ATP III, National Cholesterol Education Program/Adult Treatment Panel.
CTA-identified nonobstructive CAD and intermediate NCEP/ATP III risk. Although underpowered, a trend was observed in those patients with high NCEP/ATP III risk and nonobstructive CAD. Importantly, we observed no significant mortality benefit of statins at baseline in those with normal coronary arteries by coronary CTA.

These findings in patients with nonobstructive CAD, extend those of previous studies that have focused primarily on the presence, extent, and severity of obstructive CAD, but confirm those recently observed with invasive coronary angiography. Because of the size of our cohort, we were able to examine the hazards of nonobstructive CAD as stratified by NCEP/ATP III risk, and observed a low mortality risk, over the follow-up period, of patients with nonobstructive CAD already considered low risk by clinical risk assessment. As well, during this follow-up period, we identified no mortality benefit associated with statin use in patients who were considered higher clinical risk but without evidence of coronary CTA-identified plaque.

Although it remains possible that some of the nonobstructive lesions (1%–49% diameter stenosis) could result in lesion-specific ischemia, it is likely that these were few in number, and more likely to be undetectable using traditional methods of CAD evaluation, such as exercise treadmill testing, stress echocardiography, and myocardial perfusion imaging. Previous investigations have shown that minor coronary stenoses are associated the majority of acute myocardial infarctions and sudden cardiac deaths. Thus, our analysis highlights a potential advantage of atherosclerosis imaging with coronary CTA and its potential to direct patient therapy.

In this regard, the present study findings also sought to examine the benefit of medical therapy for reduction of mortality in individuals with nonobstructive CAD. Although statin therapy is routinely advocated and prescribed for patients with documented cardiovascular disease, the evidence underlying the efficacy in primary prevention is less robust. The Cochrane meta-analysis and a meta-analysis by Kostis et al demonstrated a reduction in total mortality with statin use, whereas a meta-analysis by Ray et al showed a strong trend toward benefit but the confidence interval overlapped 1.0. The results of our study further lend support for

| Table 4. Cox Models for All-Cause Mortality in Patients With Nonobstructive CAD |
|-----------------------------|-----------------------------|-----------------------------|
| Models                      | Hazard Ratio* (95% CI)      | P Value                     |
| All patients (n=10,418)     |                             |                             |
| Statin therapy              | 0.52 (0.34–0.79)            | 0.002                       |
| ASA therapy                 | 0.77 (0.53–1.12)            | 0.173                       |
| Nonobstructive CAD (n=4706) |                             |                             |
| Statin therapy              | 0.39 (0.23–0.65)            | <0.001                      |
| ASA therapy                 | 0.66 (0.42–1.04)            | 0.070                       |
| No coronary plaque (n=5712) |                             |                             |
| Statin therapy              | 0.64 (0.30–1.37)            | 0.252                       |
| ASA therapy                 | 0.73 (0.37–1.47)            | 0.384                       |

*Adjusted for National Cholesterol Education Program/Adult Treatment Program III risk.
statin use in primary prevention, specifically in those with subclinical atherosclerosis.

Similarly, the benefit of aspirin therapy for primary prevention has also been questioned. At present, statin and aspirin treatment recommendations for primary prevention exist only for patients at high risk of future cardiovascular events. To date, these high-risk classifications have been restricted to definitions based on clinical or laboratory markers, and include diabetes mellitus, dyslipidemia, high Framingham or NCEP/ATP III risk scores, or intermediate Framingham Risk Score with elevated high-sensitivity C-reactive protein. At present, no uniform recommendation exists for primary prevention therapies based on imaging findings, and results of the present study challenge these recommendations, and suggest that the individual with intermediate or high NCEP/ATP III risk and nonobstructive CAD may derive significant benefit from statin therapy.

Table 5. Multivariable Hazard Ratios for All-Cause Mortality of Individuals Treated at Baseline With Statins as Stratified by NCEP/ATP III Risk

<table>
<thead>
<tr>
<th>Overall study group</th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCEP/ATP III risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>2.52</td>
<td>0.98–6.51</td>
<td>0.056</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>0.39</td>
<td>0.21–0.72</td>
<td>0.003</td>
</tr>
<tr>
<td>High risk</td>
<td>0.40</td>
<td>0.19–0.84</td>
<td>0.015</td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCEP/ATP III risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>2.55</td>
<td>0.64–10.22</td>
<td>0.637</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>0.69</td>
<td>0.23–2.07</td>
<td>0.503</td>
</tr>
<tr>
<td>High risk</td>
<td>0.25</td>
<td>0.06–1.11</td>
<td>0.068</td>
</tr>
<tr>
<td>Nonobstructive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCEP/ATP III risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>2.07</td>
<td>0.55–7.72</td>
<td>0.281</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>0.24</td>
<td>0.11–0.52</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High risk</td>
<td>0.45</td>
<td>0.19–1.06</td>
<td>0.068</td>
</tr>
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</table>

CI indicates confidence interval; HR, hazard ratio; and NCEP/ATP III, National Cholesterol Education Program/Adult Treatment Program III.

Attractive to clinicians and healthcare payers is the potential shift of primary prevention treatment from a population-based treat all patients paradigm to one of individualized tailoring of therapies to those who actually have disease and are actually at risk for incident adverse events. Our study results identified higher risk for patients who had both elevated clinical risk scores and nonobstructive CAD, with no increased risk in individuals who had either one or the other alone. Although it is currently unknown whether statin therapy in patients with subclinical atherosclerosis improves outcomes, the current study results suggest that statin therapy in patients with nonobstructive plaque may be of mortality benefit. Given several recent analyses that have failed to show efficacy of statin or aspirin therapy for primary prevention, proof that coronary CTA identifies patients who benefit from prevention strategies will require extensive corroboration in longer term follow-up studies and with additional nonfatal and fatal cardiovascular end points. In a collaborative meta-analysis of 6 primary prevention trials (95,000 patients), no apparent mortality benefit was observed with aspirin therapy. As such, current guidelines do not recommend aspirin to prevent ischemic vascular events in patients without evidence of manifest vascular disease. In daily coronary CTA practice, the identification of patients with nonobstructive CAD is common. Whether the presence of nonobstructive CAD by coronary CTA constitutes manifest vascular disease has remained a clinical challenge, and many clinicians have adopted a protocol of reflexive statin or aspirin use for these patients. However, the use of aspirin was not significantly associated with mortality reduction in our patient cohort, even if coronary atherosclerotic plaque was present. Given the wide confidence intervals associated with aspirin use, caution should be taken when interpreting these results. The HR ratios (0.64 and 0.75) associated with aspirin use may be clinically important but were not statistically significant in our study, which may be a function of power. Additional study is needed before definitive conclusions on aspirin therapy can be made.

Limitations

This study is not without limitations. We included information on statin use at baseline; however, 23% of patients did not have medication information, which could result in a bias in our population. As well, we do not have data on the initial statin dose, subsequent initiation, discontinuation, dose modification, or compliance changes that may have occurred after coronary CTA. Although longitudinal differences in statin use may significantly affect study outcomes, we think that patients already being treated with statins would have been less likely to discontinue therapy after documentation of nonobstructive CAD. Indeed, the initiation of statins after coronary CTA in individuals with nonobstructive CAD would serve to reduce the apparent difference in outcomes between the statin and no-statin groups and would have resulted in the underestimation rather than overestimation of the true benefit of statin therapy. Conversely patients with normal arteries may have discontinued statin therapy, thereby underestimating the benefit of statins in this subpopulation. Although a recommendation cannot be made on...
discontinuing statin therapy in those without coronary atherosclerosis on CCTA, Blaha et al33 have previously demonstrated that the absence of coronary calcification in the asymptomatic population portended an excellent prognosis with a 10-year mortality rate of ≈1%. Similarly, there is also a lack of data on pretherapy lipid profiles and subsequent changes in lipid profile, which could also affect our conclusions. Additional large-scale studies examining the impact of statin therapy on outcomes in individuals with nonobstructive CAD by CCTA now seem warranted. Finally, it is possible that the higher use of statins may be explained by factors beyond the scope of this study, such as better access to healthcare or healthier lifestyles.

We used all-cause mortality as the primary end point for our study, given its unparalleled clinical importance and freedom from ascertainment bias. However, as specific causes of death for each patient were not uniformly available at all sites, the true proportion of deaths that may have been attributable to cardiovascular events in the study population is unknown. Also germane to this limitation is that the NCEP/ATP III risk algorithms are aimed at prediction of future cardiovascular events and not all-cause mortality. Consequently, the present study may result in the underestimation of the prognostic power of clinical variables and overestimate those of coronary CTA and statin therapy. Although the capture of other major adverse cardiovascular events (eg, stroke) is desirable, one distinct advantage of using all-cause mortality as a primary outcome measure is its ability to capture adverse deaths that may have been related to medication use (eg, hemorrhagic stroke, liver failure, and rhabdomyolysis).

Figure 4. Forest plot of subgroup analyses, adjusted for National Cholesterol Education Program/Adult Treatment Program III Risk. BMI indicates body mass index; CAD, coronary artery disease; and CI, confidence interval.
This study is comprised a cohort of individuals who were clinically referred for coronary CTA for suspected CAD, with the majority being asymptomatic. Although our cohort’s symptoms are unlikely to be related to nonobstructive plaque, the generalized application of our study findings to asymptomatic individuals remains uncertain.

Conclusions
In this intermediate-term follow-up of individuals undergoing CCTA, the presence and extent of nonobstructive CAD are associated with increased mortality. Baseline statin therapy seems to be associated with a significant reduction in mortality for individuals with nonobstructive CAD. Future studies applying targeted therapies to patients with nonobstructive CAD should be considered. Whether statin therapy benefits those with normal coronary arteries remains uncertain and requires further investigation.

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Disclosures
Dr Min serves as a consultant to HeartFlow. The other authors report no conflicts.

References
8. National Cholesterol Education Program Expert Panel on Detection...
This study was to examine a large-scale population of patients with nonobstructive coronary artery disease—as diagnosed by coronary computed tomographic angiography—and to examine the prognosis of these findings in relation to treatment with statins and aspirin. This study found that statins, but not aspirin, was highly efficacious at reducing the rates of death for patients with nonobstructive plaque.
Prognostic and Therapeutic Implications of Statin and Aspirin Therapy in Individuals With Nonobstructive Coronary Artery Disease: Results From the CONFIRM (Coronary CT Angiography Evaluation For Clinical Outcomes: An International Multicenter Registry) Registry


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Materials and Methods

Clinical Predictors

A medical history was prospectively recorded for all patients (1-3) by a physician or research nurse, and each patient’s risk of future cardiac event was then estimated using National Cholesterol Education Program/Adult Treatment Panel (NCEP/ATP) III guidelines (4, 1). Dyslipidemia was defined as known but untreated dyslipidemia or current treatment with lipid-lowering medications based upon a diagnosis of dyslipidemia in direct accordance to societal guidelines.

Coronary CT Angiography Measures

Coronary CTA image acquisition was performed using single- or dual-source 64-slice CT scanners. All acquisitions and interpretations were performed in direct accordance with the Society of Cardiovascular Computed Tomography Guidelines (5, 6, 1). Using a segment model, each segment was classified as “normal” (no detectable plaque) or as having non-obstructive coronary atherosclerotic plaque (1-49% diameter stenosis). For each patient, the segment score (sum of the coronary segments with coronary atherosclerosis) was calculated (7,8).

Patient Follow-up

Patient follow-up (all-cause mortality) was performed by each local institution by telephone interview with validation of reported death through medical records whenever possible and/or a National death registry.

Statistical Analysis

Statistical analyses were performed using SAS (version 9.2, SAS Institute Inc., Cary, North Carolina), and p value <0.05 was considered statistically significant. Continuous variables were presented as means and standard deviations and if not normally distributed, presented as medians with interquartile range. Categorical variables were presented as frequencies with percentages. For baseline characteristics comparisons, the Wilcoxon rank-sum test was used for continuous variables, and the chi-squared statistic or Fisher’s exact test was used for categorical variables.

The prognostic value of non-obstructive CAD by coronary CTA, statin and aspirin therapy was assessed for univariable association as well as multivariable association
with all-cause mortality. Unadjusted comparisons of all-cause mortality according to presence and extent of non-obstructive CAD, NCEP/ATP III risk and therapy were performed on Kaplan-Meier survival curves using log-rank tests. Risk-adjusted analysis was performed using a multivariable Cox proportional hazard model to determine the effect of therapy (aspirin or statin) on incident mortality by controlling for age, gender, CAD pre-test risk (NCEP/ATP III). Cox proportional hazard models were also used to test for interactions between the therapy and CAD group and also in the various subgroups. Model overfitting was carefully considered and the proportional hazards assumption was met in all analyses.

REFERENCES:


