Nonobstructive Coronary Artery Disease by Coronary CT Angiography Improves Risk Stratification and Allocation of Statin Therapy

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ABSTRACT

OBJECTIVES This study sought to determine prognostic value of nonobstructive coronary artery disease (CAD) for atherosclerotic cardiovascular disease (ASCVD) events and to determine whether incorporation of this information into the pooled cohort equation reclassifies recommendations for statin therapy as defined by the 2013 guidelines for cholesterol management of the American College of Cardiology and American Heart Association (ACC/AHA).

BACKGROUND Detection of nonobstructive CAD by coronary computed tomography angiography may improve risk stratification and permit individualized and more appropriate allocation of statin therapy.

METHODS This study determined the pooled hazard ratio of nonobstructive CAD for ASCVD events from published studies and incorporated this information into the ACC/AHA pooled cohort equation. The study calculated revised sex- and ethnicity-based 10-year ASCVD risk and determined boundaries corresponding to the original 7.5% risk for ASCVD events. It also assessed reclassification for statin eligibility by incorporating the results from meta-analysis to individual patients from a separate cohort.

RESULTS This study included 2 studies (2,295 subjects; 66% male; prevalence of nonobstructive CAD, 47%; median follow-up, 49 months; 67 ASCVD events). The hazard ratio of nonobstructive CAD for ASCVD events was 3.2 (95% confidence interval: 1.5 to 6.7). Incorporation of this information into the pooled cohort equation resulted in reclassification toward statin eligibility in individuals with nonobstructive CAD, with an original ASCVD score of 3.0% and 5.9% or higher in African-American women and men and a score of 4.4% and 4.6% or higher in Caucasian women and men, respectively. The absence of nonobstructive CAD resulted in reclassification toward statin ineligibility if the original ASCVD score was as 10.0% and 17.9% or lower in African-American women and men and 13.7% and 14.3% or lower in Caucasian women and men, respectively. Reclassification is observed in 14% of patients.

CONCLUSIONS Detection of nonobstructive CAD by coronary computed tomography angiography improves risk stratification and permits individualized and more appropriate allocation of statin therapy across sex and ethnicity groups. (J Am Coll Cardiol Img 2017;:–) © 2017 by the American College of Cardiology Foundation.
The 2013 guidelines of the American College of Cardiology and American Heart Association (ACC/AHA) (1) introduced the 10-year event risk for atherosclerotic cardiovascular disease (ASCVD) as a benchmark for recommendations for statin therapy. These estimated event risks and thresholds were determined on the basis of the pooled cohort risk calculator of ASCVD, which uses the demographic and clinical risk factors from observational cohorts to calculate the 10-year event risk.

Following the release of the 2013 ACC/AHA guidelines, it has been demonstrated that these guidelines significantly improve the alignment of statin eligibility (defined as ≥7.5% 10-year ASCVD risk) and the presence of coronary artery disease (CAD); for example, Pursnani et al. (2) showed that alignment of the presence of coronary artery calcification (CAC) and statin eligibility in asymptomatic patients was improved from 23% to 63% as compared with the 2004 Adult Treatment Panel III guidelines of the National Cholesterol Education Program. Furthermore, studies suggest that assessment of CAD can reclassify statin eligibility in up to 50% of patients (3,4). For example, the absence of CAC identifies a large group (33%) of statin-eligible individuals who are at a similarly low risk as non-statin-eligible individuals (1.0% vs. 1.1% 10-year ASCVD risk, respectively) (2). Thus, although the newer guidelines improve detection of patients with CAD, cardiovascular imaging has demonstrated promising results to improve the statin allocation further.

Symptomatic patients undergo coronary computed tomography angiography (CTA) for the assessment of obstructive CAD but few (<15%) of these patients are diagnosed with obstructive CAD (5,6). However, the benefit of coronary CTA extends to the remaining 85% of patients because either CAD can be accurately excluded (30% to 40%) or nonobstructive CAD can be detected (approximately 50%) (5,7), both of which provide tremendous prognostic information beyond traditional risk assessment in both asymptomatic and symptomatic patients (8). Nevertheless, neither current primary prevention nor secondary prevention guidelines contain recommendations for medical therapy in patients with nonobstructive CAD beyond traditional cardiovascular risk factors. However, detailed knowledge of presence or absence of nonobstructive CAD may improve risk stratification and permit individualized and more appropriate allocation of statin therapy.

In this study, we used published data on the prognostic value of nonobstructive CAD to determine whether incorporation of this information into the pooled cohort equation reclassifies recommendations for statin therapy as defined by the 2013 ACC/AHA guidelines for cholesterol management. To do so, we performed a meta-analysis, used the results to modify the ASCVD risk calculator, and applied it to a separate population to assess the reclassification.

METHODS

SYSTEMATIC LITERATURE REVIEW AND DATA COLLECTION. A meta-analysis was conducted in adherence to the MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines for meta-analyses and systematic reviews of observational studies (9). Two physician scientists (H.E. and R.A.P.T) searched PubMed for eligible studies using pre-defined selection criteria (Figure 1) and pre-defined search syntax for selection of studies that had assessed the prognostic value of coronary CTA published up to May 2016 (Online Appendix). No search restrictions were used, and references of included studies were manually checked to identify eligible studies missed by the primary search strategy. We included the eligible articles on the basis of the following criteria: study domain (patients with suspected CAD without a previous history of CAD); and index test (coronary CTA: obstructive CAD, nonobstructive CAD). If there was an overlap in study populations, the study with the largest population was included. We excluded animal studies, phantom studies, case reports (N < 10), and studies that did not report hazard ratios (HRs) for ASCVD events. Abstracts and unpublished studies were not included, and no contact was made with publication authors.

The characteristics of study subjects at baseline and outcomes were collected in consensus by 2 physician scientists (H.E. and R.A.P.T) for all selected studies. All the selected studies defined obstructive CAD as >50% luminal stenosis and nonobstructive CAD as any CAD with <50% luminal narrowing in at least 1 coronary artery segment. Study quality was assessed in consensus (H.E. and R.A.P.T) by using a modified version of the Quality In Prognosis Studies (QUIPS) tool (10). Our primary outcome of interest was ASCVD defined as cardiovascular death, nonfatal myocardial infarction, and stroke. The annualized ASCVD event risk in each study (if not reported) is calculated by using the median follow-up period. The average annual ASCVD risk of selected studies is calculated as mean of reported or calculated annualized event rates of the individual studies.

META-ANALYSIS: PROGNOSTIC VALUE OF NONOBSTRUCTIVE CORONARY ARTERY DISEASE. We identified studies that reported HRs of nonobstructive
CAD for ASCVD events. The types of events, as well as observed overall event rates, annualized event rates, and HRs with their corresponding 95% confidence intervals (CIs) for ASCVD events, were collected. We calculated log HRs and their standard errors, as to perform a random effects generic inverse variance method for ascertaining pooled log-HR. Forest plots were generated for graphic display of the results. The I² statistic was calculated to determine heterogeneity. For the meta-analysis, we used RevMan version 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark).

REVISION OF ASCVD RISK USING INFORMATION ON THE PROGNOSTIC VALUE OF PRESENCE OR ABSENCE OF NONOBSTRUCTIVE CORONARY ARTERY DISEASE. The 10-year risk for ASCVD was derived from the pooled cohort equation as described by Goff et al. (1). We incorporated the study level pooled log-HR of nonobstructive CAD for ASCVD events into the original pooled cohort equation and calculated a revised ASCVD score including the 95% CIs for the revised risk thresholds by using the lower and upper bounds of the CIs of the pooled HR. As the equation contains coefficients for sex and ethnicity, we calculated 8 revised ASCVD scores for patients with and 8 for patients without nonobstructive CAD. In patients without CAD, the calculation determined the highest original score that, in consideration of the prognostic value of absence of CAD, would correspond to a revised score of 7.5%. In patients with nonobstructive CAD, the calculation determined the lowest original score that, in consideration of the prognostic value of presence of nonobstructive CAD, would correspond to a revised score of 7.5%.
TABLE 1 Selected Studies

<table>
<thead>
<tr>
<th>First Author, Yr (Ref. #)</th>
<th>Study Design</th>
<th>Median Follow-Up (months)</th>
<th>Total Number of Events</th>
<th>Event Rate (%)</th>
<th>Annualized Event Rate (%)</th>
<th>ASCVD Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hadamitzky, 2013 (13)</td>
<td>Prospective Cohort (n = 1,584)</td>
<td>67</td>
<td>61</td>
<td>3.9</td>
<td>0.7</td>
<td>61</td>
</tr>
<tr>
<td>Plank, 2014 (14)</td>
<td>Prospective cohort (n = 711)</td>
<td>32</td>
<td>6</td>
<td>0.8</td>
<td>0.3</td>
<td>6</td>
</tr>
</tbody>
</table>

TABLE 1 Continued

<table>
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<tr>
<th>First Author, Yr (Ref. #)</th>
<th>Characteristics of Study Population</th>
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<tr>
<td></td>
<td>Age</td>
</tr>
<tr>
<td>Hadamitzky, 2013 (13)</td>
<td>58 ± 11</td>
</tr>
<tr>
<td>Plank, 2014 (14)</td>
<td>62</td>
</tr>
</tbody>
</table>

Values are mean ± SD or n (%). *The status of included subjects in regards to their symptoms in the studies.

ASCVD = atherosclerotic cardiovascular disease; CAD = coronary artery disease; DLP = dyslipidemia; DM = diabetes mellitus; HTN = hypertension.

**RECLASSIFICATION OF INDIVIDUALS FOR STATIN ELIGIBILITY.** To determine the number of patients who would have reclassified statin eligibility on the basis of the knowledge of the presence or absence of nonobstructive CAD, we applied the modified risk calculator in patients with acute chest pain without acute coronary syndrome who had undergone coronary CTA (11). Please see the Online Appendix for the details of selection of this patient population.

The 2013 ACC/AHA guidelines were used to determine statin eligibility as follows: 1) clinical ASCVD (not applicable to this patient population); 2) low-density lipoprotein $\geq$ 190 mg/dl; 3) diabetes at 40 to 75 years-of-age and low-density lipoprotein of 70 to 189 mg/dl; or 4) without clinical ASCVD or diabetes, low-density lipoprotein of 70 to 189 mg/dl, and estimated ASCVD risk $\geq$ 7.5%. Individual ASCVD risk was determined with and without knowledge of CAD status. Individuals with nonobstructive CAD could be reclassified to be newly statin eligible only if their original ASCVD score was $<$ 7.5% and their newly modified (after incorporating HR of nonobstructive CAD) ASCVD risk was $\geq$ 7.5%. Individuals without nonobstructive CAD could be reclassified to be not statin eligible, only if their original ASCVD score was $\geq$ 7.5% and their newly modified (after incorporating HR of absence of nonobstructive CAD) ASCVD risk was $<$ 7.5%. McNemar’s test was used to determine whether a significant proportion of patients was reclassified.

Stata software version 13.1 (StataCorp, College Station, Texas) was used for all calculations regarding the modification and application of the ASCVD risk.

**RESULTS**

**PROGNOSTIC VALUE OF NONOBSTRUCTIVE CORONARY ARTERY DISEASE.** We identified 2 studies reporting on ASCVD event HRs for nonobstructive CAD; these studies included symptomatic individual patients without known CAD who had noncardiac chest pain or were asymptomatic individuals with a high lifetime risk of a cardiovascular disease profile (12). These studies included 2,295 subjects (66% male; 55% with hypertension; 51% with dyslipidemia; 8% with diabetes; prevalence of nonobstructive CAD, 46% [n = 1,075 of 2,295], a median follow-up period of 50 months, and 67 ASCVD events). The average annual ASCVD event rate was 0.5% (Table 1). The presence of nonobstructive CAD as determined by coronary CTA was associated with a significantly increased risk of future ASCVD events (pooled unadjusted HR = 3.20 [1.53, 6.70]) (Figure 2). The I^2 statistic was 0%.

**REVISION OF ASCVD RISK USING INFORMATION ON THE PROGNOSTIC VALUE OF PRESENCE OR ABSENCE OF NONOBSTRUCTIVE CORONARY ARTERY DISEASE.** In patients without CAD, the highest original ASCVD score that, in consideration of the prognostic value of the absence of CAD would correspond to a revised score of 7.5%, ranged from 10.0% to 17.9% in African-American women and men and from 13.7% to 14.3% in Caucasian women and men, respectively.

In patients with nonobstructive CAD, the lowest original ASCVD score that, in consideration of the prognostic value of presence of nonobstructive CAD would correspond to a revised score of 7.5%, ranged from 3.0% to 5.9% in African-American women and men and from 4.4% to 4.6% in Caucasian women and men, respectively (Figure 3). The degree of revision was more prominent in African Americans than in Caucasians and more prominent in men as compared with women.
RECLASSIFICATION OF INDIVIDUALS FOR STATIN ELIGIBILITY. To determine the number of patients with coronary CTA who would have reclassified statin eligibility on the basis of the knowledge of the presence or absence of nonobstructive CAD, the modified risk scores were calculated in 169 patients with acute chest pain without acute coronary syndrome (age 53 ± 9 years, 56% male) (11). The mean

![Figure 2: Risk Estimates of ASCVD Events for Presence of Nonobstructive CAD](image)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
<th>Hazard Ratio IV Random 95% CI</th>
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<tbody>
<tr>
<td>Hadamitzky, 2013</td>
<td>73.1%</td>
<td>3.33 [1.40, 7.91]</td>
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<tr>
<td>Plank, 2014</td>
<td>26.9%</td>
<td>2.87 [0.69, 11.93]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>100.0%</td>
<td>3.20 [1.53, 6.70]</td>
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Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%
Test for overall effect: Z = 3.08 (P = 0.002)

We identified 2 studies that reported on the atherosclerotic cardiovascular disease (ASCVD) event hazard ratio for nonobstructive coronary artery disease (CAD). The presence of nonobstructive coronary artery disease by coronary computed tomography angiography was associated with a significantly increased risk of future atherosclerotic cardiovascular disease events (pooled unadjusted hazard ratio: 3.20 [1.53, 6.70]). The I² statistic was 0%. CI = confidence interval.

![Figure 3: Reclassification Thresholds (Including 95% Confidence Intervals) of Original ASCVD Risk Calculator to Determine Statin Eligibility on the Basis of Coronary CTA Findings](image)

Reclassification of patients on the basis of the presence or absence of nonobstructive coronary artery disease (CAD) demonstrated that in patients without coronary artery disease, the highest original atherosclerotic cardiovascular disease (ASCVD) score that, in consideration of the prognostic value of the absence of coronary artery disease that would correspond to a revised score of 7.5%, ranged from 10.0% to 17.9% in African-American women and men and from 13.7% to 14.3% in Caucasian women and men, respectively. In patients with nonobstructive coronary artery disease, the lowest original atherosclerotic cardiovascular disease score that, in consideration of the prognostic value of the presence of nonobstructive coronary artery disease that would correspond to a revised score of 7.5%, ranged from 3.0% to 5.9% in African-American women and men and from 4.4% to 4.6% in Caucasian women and men, respectively. CTA — computed tomography angiography.
original 10-year ASCVD risk in this population was \( 7.2 \pm 7.7\% \), 101 (60%) were without CAD, and 68 (40%) had nonobstructive CAD. After including the pooled log-HR for nonobstructive CAD, statin eligibility was revised in 14% of the population (\( n = 24 \) of 169).

Specifically, 12 of 101 patients (12%) who had an original ASCVD score of \( \geq 7.5\% \) and who had no CAD were reclassified as non–statin eligible, whereas 12 of 68 patients (18%) who had nonobstructive CAD but an original ASCVD score < 7.5% were reclassified as statin eligible (Online Figure 1).

For example, on the basis of the original ASCVD risk calculation, a 49-year-old nonsmoker Caucasian man with a total cholesterol level of 212 mg/dl, a high-density lipoprotein cholesterol level of 40 mg/dl, and systolic blood pressure of 136 mmHg had a 5.5% 10-year event risk and was not statin eligible. However, this patient had nonobstructive CAD on coronary CTA. Incorporation of this information into the pooled cohort equation resulted in a revised 10-year ASCVD risk of 9%, thus making him eligible for statin therapy. Other examples of individual patients from our cohort with both upward and downward reclassification are shown in Figure 4.

**DISCUSSION**

We demonstrated that nonobstructive CAD carries a 3 times higher risk for incident ASCVD events as compared with no CAD. More importantly, by incorporating this information into the AHA/ACC pooled cohort equation, we demonstrated that patients with nonobstructive CAD with an original score as low as 3.0% would be reclassified as statin eligible, whereas patients without CAD with an original ASCVD score as high as 17.9% would be reclassified as not statin eligible. In a separate cohort of patients with acute chest pain but without acute coronary syndrome, this would result in reclassification of statin eligibility in 14% of patients.

The 2013 ACC/AHA guidelines for cholesterol management are estimated to identify almost 12 million more individuals as statin eligible (15). However, they accurately identify patients as statin eligible who are at a relatively higher risk as compared with patients who are not statin eligible in regard to the following: 1) ASCVD: HR 6.8 (95% CI: 3.8 to 11.9) versus 3.1 (95% CI: 1.9 to 5.0) (2); 2) CAC score > 300: 85% versus 34% (2); and 3) obstructive CAD: 90% versus 60% as compared with the Adult Treatment Panel III guidelines (16). In addition, the absence of CAC identifies a large group of patients who are at very low risk for ASCVD events despite being statin eligible by pooled cohort equation (33% in the Framingham Heart Study [2] and 40% in the MESA study [Multi-Ethnic Study of Atherosclerosis] [4]) (1.0% vs. 1.1% 10-year ASCVD risk, respectively). However, the caveat with the absence of CAC is that it does not necessarily exclude the presence of other ASCVDs such as stroke.

Our study goes 1 step farther and directly determines how prognostic information on nonobstructive CAD can revise ASCVD risk and subsequent statin eligibility in symptomatic patients undergoing coronary CTA who have no obstructive CAD. It is indeed a challenge to determine whether

<table>
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<th>FIGURE 4 Application of Original and Modified ASCVD Risk Calculators in a Primary Prevention Patient Population</th>
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<tr>
<td>Age</td>
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<tr>
<td>49</td>
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Real-life examples from a cohort of patients are demonstrated with upward and downward reclassification of statin eligibility on the basis of the presence or absence of nonobstructive coronary artery disease (CAD), respectively. ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; SBP = systolic blood pressure.
patients with chest pain who have nonobstructive CAD should be treated by primary or secondary prevention guidelines. One could argue that they represent an intermediate group because they are not asymptomatic but do have CAD associated with an increased risk for future cardiovascular events. As a result of the lack of guidelines and the uncertainty of benefits of modifications in preventive medical therapy beyond traditional risk factors, approximately one-half of the patients with nonobstructive CAD are currently not receiving statin treatment (2,17–19). It is worth mentioning that in this study we did not include the patients with obstructive CAD because in current clinical practice these patients would be treated with statins as part of optimal medical management.

Our data suggest that approximately 14% of these patients would benefit from incorporation of nonobstructive CAD into the pooled cohort equation. The effect reaches across sex and ethnicity but was more prominent in men as compared with women and more prominent in African Americans as compared with Caucasians. Reclassification of statin eligibility on the basis of the absence of CAD constitutes a relatively new concept but is supported by many studies demonstrating the excellent negative predictive value. This option may be especially important for patients who are at higher risk for adverse effects of medical therapy such as pre-diabetic patients. Nevertheless, the final decision for initiation of statin therapy is made after a clinician-patient discussion with all the risk factors considered.

STUDY LIMITATIONS. The main limitation of our study is the small number of eligible studies because the selection process resulted in 2 studies. Additionally, our results are limited by the small number of events, as well as short follow-up period (4.2 years). The results of this study such as the prognostic value of nonobstructive CAD and the modification of the ASCVD score are derived from study-level data because we did not have access to individual-level data. However, the 95% CIs for the revision of the original ASCVD risk did not overlap with 7.5% threshold in both directions, thus indicating the robustness of our estimates. In addition, we acknowledge that according to AHA/ACC guidelines, even patients with a 5% to 7.5% ASCVD risk are considered for statin therapy by level II evidence and that the concept of statin eligibility on the basis of ASCVD risk is a recommendation rather than an absolute measure for therapy, as a result of personal preferences and variable risk profiles of patients. Additionally, the risk thresholds are used for risk quantification, and patients with lower ASCVD risk may also benefit from statin therapy if they are deemed at high risk on the basis of a discussion with their clinicians.

CONCLUSIONS

Detection of nonobstructive CAD by coronary CTA improves risk stratification and permits individualized and more appropriate allocation of statin therapy across sex and ethnicity groups.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Nonobstructive CAD is associated with increased risk of ASCVD events. Furthermore, in patients who have undergone coronary CTA for clinical indications, the presence or absence of nonobstructive CAD is valuable for reclassification of statin eligibility.

TRANSLATIONAL OUTLOOK: Additional studies are required to validate the findings and test whether using the modified thresholds for statin therapy would improve outcomes.

REFERENCES


KEY WORDS 2013 American College of Cardiology and American Heart Association prevention guidelines, coronary artery disease, prognosis, risk factors

APPENDIX For supplemental search syntax and patient eligibility criteria information and for supplemental figures, please see the online version of this paper.