# Risk Reclassification With Coronary Computed Tomography Angiography-Visualized Nonobstructive Coronary Artery Disease According to 2018 American College of Cardiology/American Heart Association Cholesterol Guidelines (from the Coronary Computed Tomography Angiography Evaluation for Clinical Outcomes : An International Multicenter Registry [CONFIRM])

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**The 2018 American College of Cardiology (ACC)/American Heart Association (AHA) cholesterol management guideline recommends risk enhancers in the borderline-risk and statin recommended/intermediate-risk groups. We determined the risk reclassification by the presence and severity of coronary computed tomography angiography (CCTA)-visualized coronary artery disease (CAD) according to statin eligibility groups. Of 35,281 individuals who underwent CCTA, 1,303 asymptomatic patients (age 59, 65% male) were identified. Patients were categorized as low risk, borderline risk, statin recommended/intermediate risk or statin recommended/high risk according to the**

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See page 1403 for disclosure information.

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**guideline. CCTA-visualized CAD was categorized as no CAD, nonobstructive, or obstructive. Major adverse cardiovascular events (MACE) were defined as a composite outcome of all-cause mortality, nonfatal myocardial infarction, and late coronary revascularization (>90 days). We tested a reclassification wherein no CAD reclassifies downward, and the presence of any CAD reclassifies upward. During a median follow-up of 2.9 years, 93 MACE events (7.1%) were observed. Among the borderline-risk and statin-recommended/intermediate-risk groups eligible for risk enhancers, the presence or absence of any CCTA-visualized CAD led to a net increase of 2.3% of cases and 22.4% of controls correctly classified (net reclassification index [NRI] 0.27, 95% CI 0.13 to 0.41, p = 0.0002). The NRI was not significant among low- or statin-recommended/high-risk patients (all p >0.05). The presence or absence of CCTA-visualized CAD, including both obstructive and nonobstructive CAD, significantly improves reclassification in patients eligible for risk enhancers in 2018 ACC/AHA guidelines. Patients in low- and high-risk groups derive no significant improvement in risk reclassification from CCTA.** © 2019 Published by Elsevier Inc. (Am J Cardiol 2019;124:1397−1405)

Categorization of cardiovascular risk forms the backbone of primary prevention with statins and other cholesterol-lowering drugs.[1,2] The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines outlined borderline- and intermediate- to high-risk categories for statin therapy that dramatically increased the number of older adults in the US receiving or eligible for statin therapy from 43.2 million (37.5%) to 56.0 million (48.6%).[3] The 2018 updated guidelines may reduce overprescription of statins by recommending shared decision making and use of risk enhancers in patients at borderline or intermediate risk.[4] Coronary computed tomographic angiography (CCTA) has demonstrated prognostic value for obstructive and nonobstructive coronary artery disease (CAD) for major adverse cardiac events (MACE), and the absence of coronary plaque portends an extremely low risk of death in asymptomatic patients.[5,6] Although CCTA is not considered appropriate for asymptomatic patients, some may obtain CCTA imaging as a risk enhancer outside of guidelines.[7] Once obtained, it is unclear how to interpret CCTA findings, including nonobstructive and obstructive CAD, in conjunction with statin eligibility groups for therapeutic decisions. In the multicenter COroNary CT Angiography Evaluation For Clinical Outcomes: An InteRnational Multicenter (CONFIRM) registry of CCTA, we evaluated the value of CCTA to risk reclassify asymptomatic patients evaluated for statin therapy according to 2018 cholesterol lowering guidelines, using intermediate-term MACE events.

## Methods

The CONFIRM registry is a prospective, open-label, multicenter dynamic observational registry designed to identify correlates between CCTA and clinical presentation. The complete rationale, study design, objectives, endpoints, patient/site selection criteria, and follow-up periods have been previously described by the investigators.[8] Overall, 35,281 patients underwent CCTA between December 2002 date and May 2011 date at 20 centers in 9 countries (Austria, Canada, Germany, Israel, Italy, Portugal, South Korea, Switzerland, and United State). Of these 20 sites, 15 hospitals collected MACE follow-up, leaving 24,696 eligible patients.

We excluded individuals according to the following criteria: loss to follow-up (n = 125), symptoms of chest pain or shortness of breath (n = 18277), previous revascularization (CABG or PCI) or myocardial infarction (n = 987), an absence of the information for calculating 10-year risk of atherosclerotic cardiovascular disease (ASCVD) risk score (n = 3759), absence of lipid values for ASCVD (n = 129) or CCTA plaque severity data (n = 2), and early revascularization <90 days from index CCTA (n = 109), and patients not eligible for consideration of statins (low-density lipoprotein [LDL] <70 without previously taking statins and nondiabetic, n = 5) (Figure 1). A total of 1,303 patients from 7 centers in 4 countries (Germany, USA, Canada, and Italy) were included in the current analysis. All sites had approval of respective institutional review boards, and were compliant with the Health Insurance Portability and Accountability Act, where applicable. Patient consent or a waiver of informed consent was obtained at each site in keeping with site-specific regulations. The study was consistent with the principles of the Declaration of Helsinki.

Baseline demographics, risk factors, CCTA acquisition, and interpretation were performed as previously described.[8] Experienced level III (or equivalent) readers evaluated patient scans for the presence of coronary atherosclerotic plaque using a 16-segment modified Society of Cardiovascular Computed Tomography coronary artery model.[9] The severity of CAD was defined on a per-patient basis as No CAD (0% intraluminal stenosis), Nonobstructive CAD (1% to 49%, presence of coronary artery calcification [CAC], or plaque with outward remodeling), or Obstructive CAD (≥50%). The nonobstructive patients were further classified into 2 categories: extensive, with either 3 vessels or >4 segments involved; or minimal, for lesser degrees of nonobstructive CAD.[10-13]

Patients were assigned to 1 of 4 statin eligibility groups using the 2018 ACC/AHA criteria: Low risk, borderline risk, statin recommended/intermediate risk, and statin recommended/high risk. The statin-recommended group was comprised of patients on statin therapy before CCTA, LDL-C ≥190, diabetics age >40, or nondiabetics with LDL 70 to 189 with ASCVD risk ≥7.5%.[1] Congruent to the updated guidelines, the statin-recommended group was further divided into intermediate-risk (ASCVD <20%) and

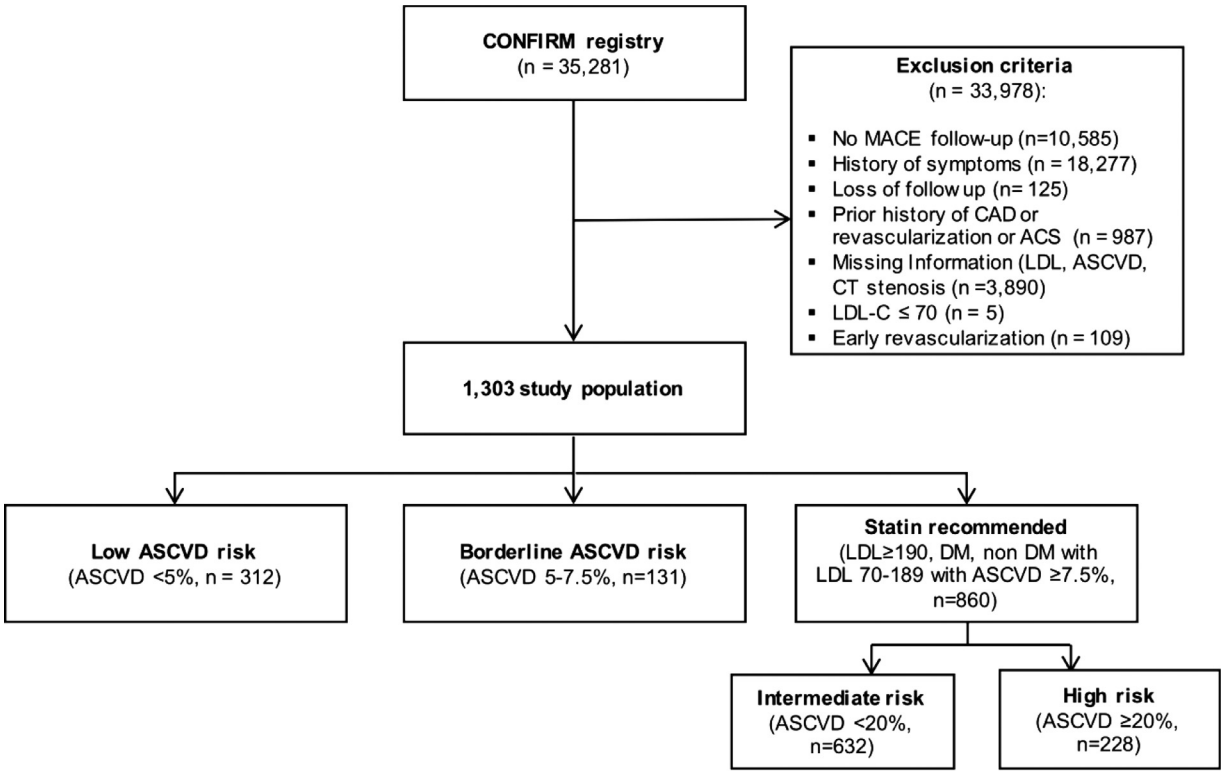


Figure 1. Study flow chart.
Abbreviations: CAD = coronary artery disease; MACE = major adverse cardiovascular event; ACS = acute coronary syndrome; LDL-C = low density lipoprotein cholesterol; ASCVD = 10-year risk of atherosclerotic cardiovascular disease.

high-risk (≥20%) groups. The remaining patients were divided into borderline risk (ASCVD risk score from 5 to ≤7.5), and low risk (ASCVD risk score <5%). The primary comparison was made among the borderline and statin recommended/intermediate-risk patients for whom risk enhancers are guideline accepted.

The primary endpoint of this study was MACE, defined as a composite outcome of all-cause death, non-fatal myocardial infarction, and late coronary revascularization (>90 days). Patients with a diagnosis of ischemic/hemorrhagic stroke or transient ischemic attack were not included in the MACE. The study procedures for follow-up have been previously described in detail.[8] Briefly, ascertainment of death and myocardial infarction events were determined by direct/telephone interview, as well as review of medical charts, and/or query of the national medical database at each institution by a dedicated physician and/or research nurse.

We tested a reclassification wherein the absence of CAD reclassifies downward, and the presence of any CAD, whether obstructive or nonobstructive, reclassifies upward as a primary strategy. Within the nonobstructive patients, we further tested a second strategy, wherein nonobstructive CAD does not risk reclassify, and a third strategy, wherein only extensive nonobstructive CAD reclassifies upward and minimal nonobstructive CAD reclassifies downward.

Frequencies and proportions were calculated for categorical variables, and means with standard deviations were calculated for continuous variables. Tests for trend and Chi-square tests were used for comparison of clinical and CAD between statin eligibility groups. Kaplan-Meier cumulative MACE rates in events/1000 person-years were estimated according to statin eligibility groups and CAD severity. Because the primary MACE endpoint did not include stroke and likely underestimates ASCVD events, one-tailed comparisons were performed for MACE event rates ≥7.5% over 10 years. Among the borderline and statin-recommended/intermediate-risk patients for whom risk enhancers are guideline accepted, we calculated the net reclassification index (NRI) of the absence or presence of CAD by CCTA compared with the statin eligibility groups alone.[14,15] A sensitivity analysis was performed, restricted only to primary prevention patients in the borderline- and statin-recommended/intermediate-risk patients, excluding those with diabetes and LDL ≥190. Subgroup analyses were performed in each statin eligibility group and overall. All statistical analyses were performed using STATA version 14 (StataCorp LP, College Station, TX). A two-tailed p-value <0.05 was considered significant except as noted.

## Results

Of the 1,303 patients, the mean age of the study population was 59.0 ± 9.2 years and 64.9% were male, with an ASCVD risk of 11.5 ± 9.9 (Table 1). As defined by 2018 ACC/AHA guidelines, the low-risk group included 312 patients; the borderline-risk group included 131 patients; and the statin-recommended group of 860 patients included 154 diabetes patients. Of the statin-recommended group, 632 patients were intermediate risk and 228 were high risk. As may be expected by guidelines, clinical risk

Table 1
Baseline characteristics of study population according to statin eligibility group

| N = 1303 | Low risk (n = 312) N (%) or mean ± SD | Borderline risk (n = 131) N (%) or mean ± SD | Statin recommended (n = 860) N (%) or mean ± SD | p for trend |
|---|---|---|---|---|
| Age (years) | 50.5 ± 5.6 | 56.2 ± 6.4 | 62.5 ± 8.4 | <0.001 |
| Male | 147 (47.1) | 79 (60.3) | 620 (72.1) | <0.001 |
| BMI | 26.4 ± 4.9 | 26.6 ± 4.7 | 27.5 ± 4.8 | <0.001 |
| Hypertension | 123 (39.4) | 72 (55.0) | 636 (74.0) | <0.001 |
| Diabetes | 0 (0) | 0 (0) | 154 (17.9) | NA |
| Dyslipidemia | 128 (41.0) | 68 (51.9) | 597 (69.4) | <0.001 |
| Current smoking | 10 (3.2) | 22 (16.8) | 125 (14.5) | <0.001 |
| Total cholesterol | 208.6 ± 34.7 | 213.2 ± 35.8 | 209.2 ± 40.0 | 0.756 |
| HDL cholesterol | 59.9 ± 15.1 | 56.0 ± 14.2 | 54.6 ± 14.6 | <0.001 |
| LDL cholesterol | 125.1 ± 28.1 | 129.8 ± 31.1 | 126.5 ± 36.0 | 0.787 |
| Taking statin | 0 (0) | 0 (0) | 325 (42.1) | NA |
| CAD by CCTA: | | | | |
| No CAD | 185 (59.3) | 59 (45.0) | 207 (24.1) | <0.001 |
| Nonobstructive: | 104 (33.3) | 56 (42.8) | 456 (53.0) | <0.001 |
| Minimal | 88 (28.2) | 41 (31.3) | 312 (36.3) | 0.008 |
| Extensive | 16 (5.1) | 15 (11.5) | 144 (16.7) | <0.001 |
| Obstructive ( ≥50%) | 23 (7.4) | 16 (12.2) | 197 (22.9) | <0.001 |

factors increased with statin eligibility (Table 1). Obstructive CAD, nonobstructive CAD, and no CAD by CCTA was observed in 18.1%, 47.3%, and 34.6% of patients overall, and 17.4%, 3.1%, and 0.9% of those patients underwent invasive coronary angiography within 30 days after CCTA scanning, respectively. Statin eligibility was associated with increasing severity of CAD (p <0.001). The proportion of both nonobstructive disease and obstructive disease tended to increase with the statin-recommended group (intermediate risk: 72.6%, high risk: 85.1%), as compared with low-risk (40.7%), and borderline-risk group (55%) (p for trend <0.001, Figure 2).

During a median follow-up of 2.9 years (interquartile range 1.4 to 5.3), 93 (7.1%) MACE over 4,086 person-years occurred in the study population. The MACE event rate among the low-risk, borderline-risk, and statin-recommended groups was 6.64/1000 (95% confidence interval [CI] 2.98 to 14.78), 8.94/1000 (95% CI 3.36 to 23.83), and 30.34/1000 (95% CI 24.47 to 37.63) person-years, respectively (Figure 3). Low-risk patients with obstructive CAD had an elevated event rate, significantly above the threshold of 7.5% over 10 years (one-way p <0.0001). Among borderline-risk patients, only patients with obstructive CAD significantly exceeded the threshold of 7.5% over 10 years (p <0.001). Intermediate-risk patients with obstructive CAD and all high-risk patients including those with no CAD, significantly exceeded the threshold of 7.5% over 10 years (p <0.05 for all).

In the borderline- and intermediate-risk groups, the presence or absence of any CAD resulted in a net increase of 2.3% in cases and 22.4% in controls correctly classified, with an overall overall net reclassification index of 0.25 (95% CI 0.12 to 0.38, p = 0.001, Table 2 and Figure 4). Excluding patients with diabetes and LDL ≥190 as a sensitivity analysis, the presence or absence of any CAD still displayed significant NRI, resulted in a 5.6% net increase in cases and 21.7% in controls correctly classified, with an NRI of 0.27(95% CI 0.13 to 0.41, p <0.001). There was no significant improvement in reclassification in the low-risk or statin-recommended/high-risk groups, with NRI of 0.26 (95% CI −0.12to 0.65, p = 0.42) and 0.04 (−0.06 to 0.15, p = 0.50), respectively (Table 2). Specifically, in the low-risk group, although the presence or absence of any CAD correctly reclassified cases (66.7%, p = 0.046), it incorrectly reclassified a substantial number of controls (40.2%, p = 0.001). In contrast, in the statin-recommended/high-risk patients, the presence or absence of any CAD significantly improved reclassification of controls (15.7%, p <0.001), but incorrectly reclassified cases (11.6%, p = 0.025). In the borderline-risk group, the presence or absence of any CAD resulted in a 100% net increase in cases and 7.1% net loss in controls correctly classified (Figure 4), with an NRI of 0.93 (95% CI 0.76 to 1.10, p = 0.07). In the statin-recommended/intermediate-risk group, the presence or absence of any CAD resulted in a 7.5% net loss in cases and 28.7% net increase in controls correctly classified (Table 2), with an NRI of 0.21 (95% CI 0.12 to 0.30, p <0.001).

Restricted to 387 nonobstructive patients in the borderline-risk and statin-recommended/intermediate-risk groups, we compared alternative thresholds of reclassification the primary strategy by the presence or absence of CAD. A second strategy, wherein nonobstructive CAD does not risk reclassify, resulted in a net decrease of 16.7% of cases and net increase of 14.0% of controls correctly classified, with an overall net reclassification index of −0.03 (−0.24 to 0.19, p = 0.82) (Table 2). A third strategy, using a threshold of significant versus minimal nonobstructive CAD, resulted in a net loss of 66.7% of cases and net increase of 70.0% of controls correctly classified, with an overall NRI of 0.03 (−0.24 to 0.30, p = 0.89).

## Discussion

We observed in a large, international referral cohort that CCTA added significant risk reclassification in patients with borderline risk and intermediate risk who are currently recommended for consideration of risk enhancers for future ASCVD risk estimation. A strategy that reclassified the

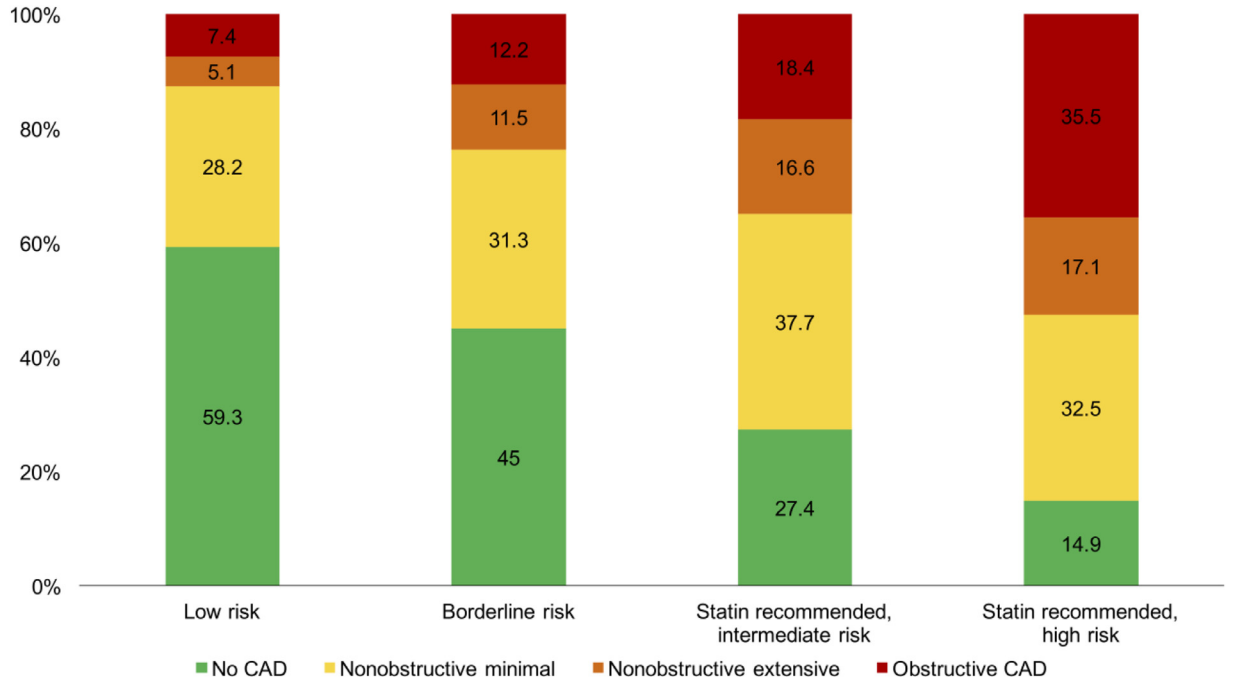


Figure 2. Prevalence of CCTA-visualized CAD across statin eligibility group.
Abbreviation: CAD = coronary artery disease.

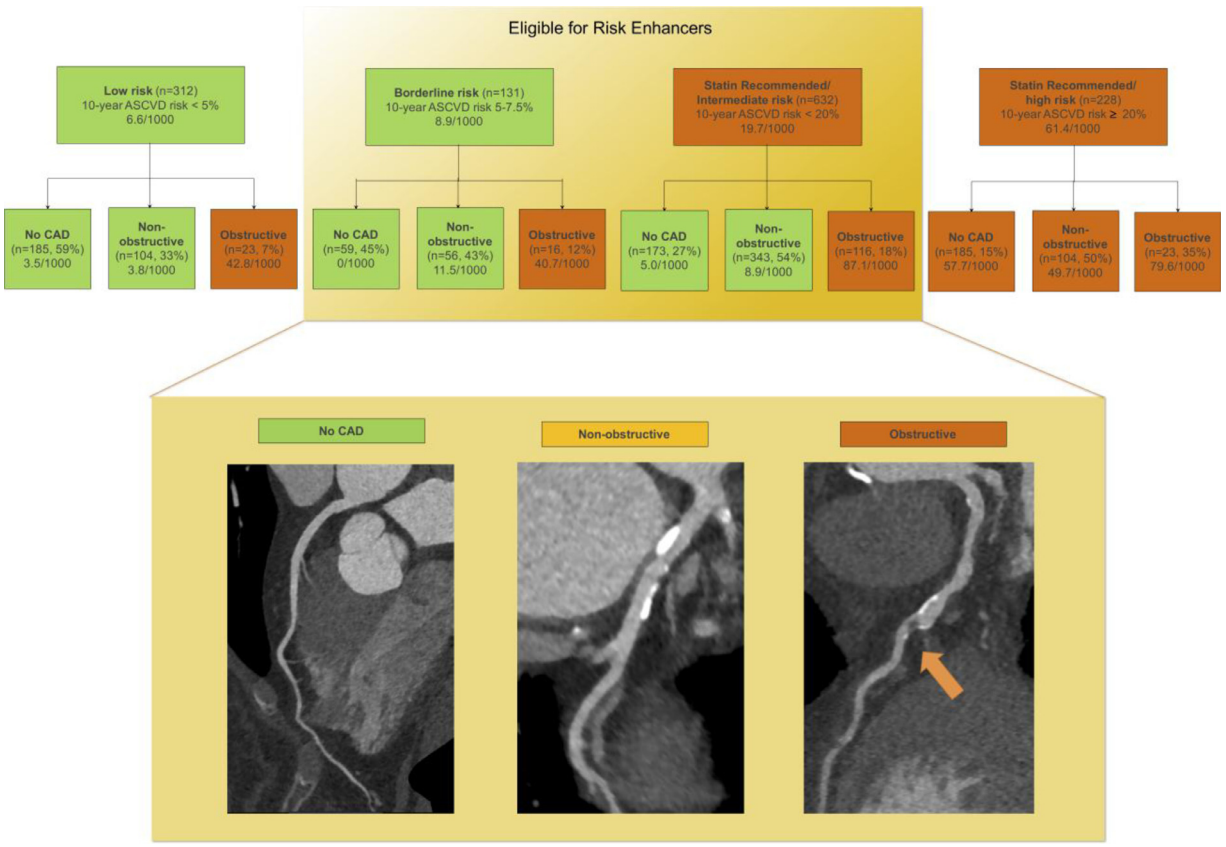


Figure 3. Major adverse cardiac event rates (event per 1,000 person-years) by statin eligibility and CCTA-visualized CAD.
In borderline-risk and statin-recommended/intermediate-risk patients who are eligible for risk enhancers, the presence of obstructive or nonobstructive CAD significantly improved risk reclassification (net reclassification index $p = 0.0002$). In low-risk and statin-recommended/high-risk patients, the presence or absence of CAD does not improve risk reclassification ($p > 0.05$ for both). The event rate significantly exceeds 7.5/1000 person years (one-tailed $p < 0.05$, highlighted in red) in low-risk, borderline-risk, and statin-recommended/intermediate-risk patients with obstructive CAD, and in statin-recommended/high-risk patients with any CCTA finding, including absence of CAD. Abbreviations: CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CI = Confidence Interval.

Table 2
Risk reclassification by CCTA visualized nonobstructive stenosis

| | Net cases | | Net controls | | NRI | | |
|---|---|---|---|---|---|---|---|
| | % reclassified | p-value | % reclassified | p-value | NRI | 95% CI | p-value |
| **A. By statin eligibility categories** | | | | | | | |
| Low risk | 66.7% | 0.046 | −40.2% | <0.001 | 0.26 | −0.11-0.65 | 0.429 |
| Borderline risk | 100% | 0.046 | −7.1% | 0.425 | 0.93 | 0.76-1.10 | 0.067 |
| Statin recommended, intermediate risk | −7.5% | 0.083 | 28.7% | <0.001 | 0.21 | 0.12-0.30 | <0.001 |
| Statin recommended, high risk | −11.6 | 0.025 | 15.7% | <0.001 | 0.04 | −0.07-0.15 | 0.497 |
| | Net cases | | Net controls | | NRI | | |
| | % reclassified | p-value | % reclassified | p-value | NRI | 95% CI | p-value |
| **B. In patients eligible for risk enhancers** | | | | | | | |
| Any nonobstructive stenosis (primary strategy) | 2.3% | 0.705 | 22.4% | <0.001 | 0.25 | 0.12-0.37 | <0.001 |
| Additional reclassification by 2nd strategy over primary strategy | −16.7% | 0.157 | 14.0% | <0.001 | −0.03 | −0.24-0.19 | 0.820 |

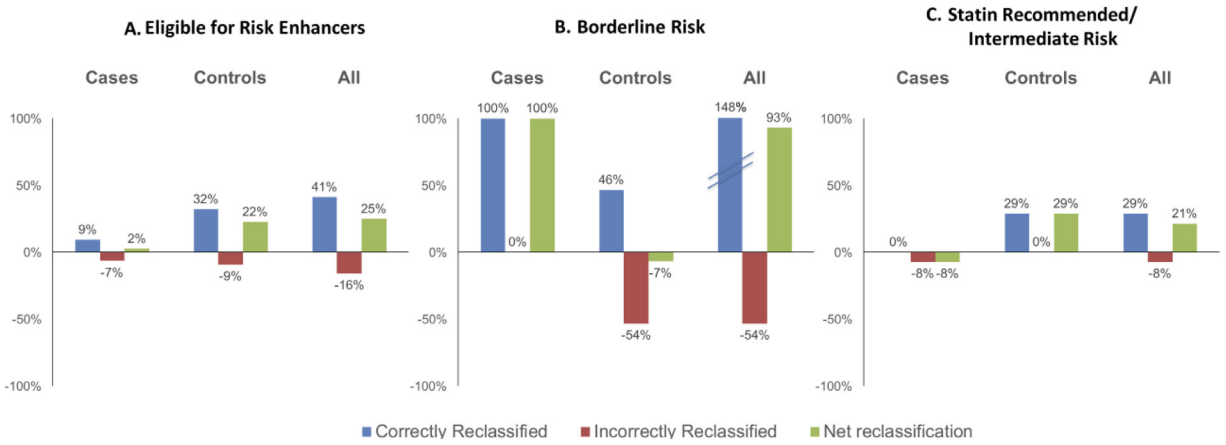


Figure 4. Reclassification by presence or absence of CCTA-visualized CAD. *(A)* Among patients eligible for risk enhancement, the presence or absence of CCTA-visualized CAD led to a net increase of 2.3% of cases and 22.4% of controls correctly classified (net reclassification index 0.25, 95% CI 0.13 to 0.41). *(B)* In the borderline-risk group, the net increase in cases exceeded the net loss in controls, with an NRI of 0.93 (95% CI 0.76, 1.10, p = 0.07). C) In the statin-recommended/intermediate-risk group, the increase in controls exceeded the net loss in cases, with an NRI of 0.21 (95% CI 0.12, 0.30, p = 0.00001). Abbreviations: CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CI = Confidence Interval.

absence of CAD downward, and the presence of any CAD upward, led to a net increase of 2.3% of cases and 22.4% of controls correctly classified. CCTA did not provide significant risk reclassification among low- or high-risk patients. Among high-risk patients, the event rate exceeded the 7.5% threshold even among those with no CAD.

Risk reclassification by CCTA has not been previously evaluated with the current 2018 ACC/AHA guidelines for primary prevention. In a recent study, Emami et al modeled the effect of incorporation of any nonobstructive CAD into risk stratification with the 2013 ACC/AHA guidelines. Although this investigation provided some insight of risk reclassification by CCTA, it should be noted that they tested the model in ED patients and lacked outcomes to validate their modeling results.[16] In contrast, our study evaluates NRI in the outpatient population that is most similar to clinical practice with intermediate-term MACE outcomes.

The primary benefit we observed is in correct reclassification of controls among borderline to intermediate risk patients, sparing patients who would otherwise have been assigned or considered for statins. In addition, CCTA does not contribute to clinical decision making for statin use in high-risk patients. These current findings are consistent with the CAC literature, demonstrating improved classification of nonevents in CAC primarily in the intermediate-risk population.[17,18] Conservatively estimating that the incidence of our MACE outcome is lower than for ASCVD, the event rate of statin-recommended/high-risk patients with no CAD significantly exceed the statin recommended threshold of 7.5 events/1000 person years (7.5% over 10 years), and statins should not be discontinued because of the CCTA alone. Among low-risk patients, although the NRI is nonsignificant, those with obstructive CAD do exhibit an elevated event rate significantly above 7.5% that may merit consideration of statin therapy.

The optimal threshold of reclassification for nonobstructive CAD has not been well explored. Previous observational cohorts have focused on the risks of extensive

nonobstructive CAD, such as three-vessel or >4 segments involvement.[10,13] Our group observed in early observational cohorts a nonlinear dose-response of nonobstructive plaque for all-cause mortality with an inflection point at 5 segments of plaque.[11] However, previous studies are difficult to generalize to current ACC/AHA guidelines as they included both very high and very low-risk patients. In this study, among the borderline- and statin-recommended/intermediate-risk patients where risk enhancers are deemed appropriate, more complex categorization of nonobstructive CAD did not improve risk reclassification compared to the primary strategy, resulting in similar losses in cases as gains in controls. The simple presence or absence of any CAD is sufficient as a risk enhancer.

Current guidelines recommend CAC as a risk enhancer, due to its population-based evidence base and lower radiation dose than traditional CCTA.[4] As more recent CCTA protocols approach radiation doses lower than those of CAC,[19,20] use of CCTA as a risk enhancer is appealing as a means to visualize noncalcified plaque and detect earlier stages of subclinical CAD. The forthcoming Scottish COmputed Tomography of the HEART 2 (SCOT-HEART 2) randomized controlled trial of CCTA and CAC (NCT03920176) will compare the outcomes of the 2 screening strategies, and our data will be useful context for interpretation of those study results. At the current time, our study provides insight to interpret CCTA as a risk enhancer when patients have already obtained CCTA outside of guidelines by referring physicians, or in the course of evaluations for structural heart disease or electrophysiology intervention.

Consideration of nonobstructive CAD matters because treatment improves clinical outcomes. In previous studies from the CONFIRM registry, Chow et al observed that statins reduced mortality in nonobstructive CAD, with no effect in patients with no CAD.[21] More recently, Cho et al additionally demonstrated that baseline statin therapy in patients with nonobstructive CAD attenuated the increase in mortality risk.[22] Finally, long-term follow-up in the SCOT-HEART study demonstrates significant MACE reductions in the CCTA randomized arm, coupled with increased prescription of statin and aspirin for CCTA-visualized nonobstructive disease.[23] Risk reclassification may be important not just for statins, but also for other preventive medications such as aspirin. The recent A Study of Cardiovascular Event iN Diabetes (ASCEND) and the Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE) trials observed absence of net benefit for aspirin in diabetic and older patients, respectively, highlighting the weakness of risk equivalent categories for primary prevention.[24,25] CCTA-visualized presence or absence of CAD may be useful to target individuals among intermediate risk groups who may obtain lesser benefit and could be spared preventive therapy.

Of note, the 18% prevalence of obstructive CAD was elevated for an asymptomatic group, consistent with earlier CONFIRM analyses demonstrating incremental prognostic value of CCTA over CAC in asymptomatic diabetics and older patients.[26,27] Because diabetes and most older patients are statin-recommended, the detection of obstructive disease by CCTA does not translate into reclassification of statin recommendations for primary prevention reclassification for statins. We lacked sufficient numbers within each strata of statin eligibility and CAD to perform further subgroup analyses of diabetics and older patients. However, it is possible that in high-risk asymptomatic groups, CCTA may be useful to reclassify patients for aggressive secondary prevention and nonstatin lipid-lowering therapy.

The current study is not without limitations. Because CCTA is considered inappropriate for asymptomatic patients, the referral bias of our study is unknown.[28] The acquisition of information on downstream changes in medical therapy after CCTA was unavailable. Therefore, the potential impact of CCTA result for treatment choice and downstream events remains unknown. In addition, our median observation period of 2.8 years may be insufficient to extrapolate 10-year risk. However, we have previously shown a 7-year "warranty period" for a normal CCTA with no CAD.[13] Only 445 patients in our cohort underwent CAC, so we could not examine the reclassification of CCTA beyond CAC in current investigation. Finally, we used intermediate term MACE events and lacked information on stroke; studies with ASCVD events are needed to further evaluate risk reclassification strategies of CCTA for primary prevention.

Among borderline- and statin-recommended/intermediate-risk patients that are eligible for risk enhancers in 2018 ACC/AHA guidelines, the presence or absence of any plaque by CCTA has clinical utility for risk reclassification. CCTA findings may be incorporated with ASCVD guidelines for shared decision making in cholesterol lowering treatment.

## Disclosures

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## Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.07.045.

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