# Risk of Myocardial Infarction in Patients Without Angiographic Coronary Artery Disease Compared With the General Population

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**We examined the 10-year risk of myocardial infarction (MI) and death in patients without obstructive coronary artery disease (CAD) compared with the general population. We conducted a cohort study of every patient without obstructive CAD by coronary angiography (CAG) between 2003 and 2016 in Western Denmark. Patients were matched by gender and age with individuals from the general population of Western Denmark with no history of CAD. End points were MI and death. Ten-year risk differences in cumulative incidence proportions were computed, accounting for the competing risk of death in the case of MI. Unadjusted and adjusted incidence rate ratios (aIRRs) were estimated using conditional Poisson regression. We included 46,467 patients and 234,654 individuals from the general population. Median follow-up was 7.7 years. The 10-year cumulative incidence of MI was 2.40% (95% confidence interval [CI] 2.24 to 2.57) in patients without obstructive CAD in the CAG and 2.70% (95% CI 2.62 to 2.78) in the general population, with a reduced absolute 10-year risk (risk difference −0.30%, 95% CI −0.49 to -0.12) and a reduced aIRR (aIRR 0.70, 95% CI 0.63 to 0.77). Ten-year mortality was higher in patients without obstructive CAD in the CAG (21.44%, 95% CI 20.99 to 21.89) compared with the general population (17.25%, 95% CI 17.06 to 17.44). However, mortality rates were similar after adjustment (aIRR 1.00, 95% CI 0.96 to 1.02).**

**In conclusion, the absence of obstructive CAD according to CAG is associated with a lower risk of MI than in the general population, and similar 10-year mortality.**  **(Am J Cardiol 2020;132:8−14)**

Despite recent advances in non-invasive modalities for diagnosing coronary artery disease (CAD), invasive coronary angiography (CAG) remains the reference standard for evaluating CAD.[1] Many patients referred for CAG do not have obstructive CAD, despite symptoms suggestive of coronary stenosis.[2,3] However, a normal CAG or mild CAD according to CAG reflects only luminal changes and may be a poor indicator of both the magnitude of CAD and future ischemic events. Conflicting reports about the long-term prognosis of such patients challenge cardiovascular risk assessment and subsequent management.[2−8] We therefore examined risks of myocardial infarction (MI) and all-cause death in patients registered in the Western Denmark Heart Registry for whom CAG did not show obstructive CAD (i.e., no coronary arteries with ≥50% stenosis). We also compared the risk of MI and all-cause death in these patients with that in an age- and gender-matched general comparison cohort with no history of MI or coronary revascularization.

## Methods

We conducted a registry-based cohort study. The Western Denmark Heart Registry has collected information on every invasive cardiac procedure, including CAG, performed in Western Denmark since January 1999.[9] Each interventional cardiologist is required to report patient characteristics and the quality of each procedure to the Western Denmark Heart Registry to guarantee that basic standards of care are met. Variables include medical history, a physician's report tailored to a given procedure, pre- and post-operative circumstances, information concerning referral, admission, and discharge, and any procedural complications.[9] Completion of registration in the Western Denmark Heart Registry remains high, reaching 98% for CAG.[9] Data from the Western Denmark Heart Registry was cross-linked with other national health care registries, including the Danish Civil Registration System, the Danish National Patient Registry, and the Danish National Prescription Registry.[10−12]

In case of multiple CAG examinations in the same patient during the inclusion period, the first CAG was considered the index procedure and basis for inclusion. Our

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study included every patient ≥18 years with residence in Denmark, who underwent CAG in Western Denmark between January 1, 2003 and December 31, 2016 (Figure 1). Patients with obstructive CAD (defined as ≥1 coronary vessel with ≥50% coronary stenosis) were excluded. Patients with diffuse CAD, defined as non-obstructive CAD in ≥2 coronary vessels, or missing coronary status were excluded. Thus, we only included patients with no angiographical sign of CAD or non-obstructive CAD (1% to 49% stenosis) in a single vessel. In addition, patients with a history of MI, percutaneous coronary intervention, or coronary artery bypass grafting surgery recorded in the Western Denmark Heart Registry or the Danish National Patient Registry before CAG were excluded (Table S1).

CAG patients with no CAD were matched by gender and age in 1:5 ratio with individuals from the general population of Western Denmark, who had no history of MI, percutaneous coronary intervention, or coronary artery bypass grafting recorded in the Danish National Patient Registry at the time of matching.

The Charlson Comorbidity Index (CCI) score was computed for members of the CAG population and the general population cohort upon study inclusion. The CCI score was based on data in the Danish National Patient Registry using a full look-back period (Table S2).[13,14]

Treatment with statins, aspirin, adenosine diphosphate-inhibitors, oral anticoagulants, beta-blockers, angiotensin converting enzyme-inhibitors, angiotensin-II receptor blockers, insulin, and non-insulin anti-diabetes medications was defined as redeeming ≥1 prescription(s), as registered in the Danish National Prescription Registry, during the 6 months before or 30 days after the study inclusion date.[12] Changes in prescription dispensation frequencies 6 months before and 6 months following CAG were evaluated in CAG patients, who had ≥6 months of follow-up (n = 45,821).

MI was defined as a primary or secondary discharge diagnosis of MI associated with an acute hospitalization, as recorded in the Danish National Patient Registry (Table S1).[15] All-cause death was ascertained through the Danish Civil Registration System.

Follow-up started 30 days after study inclusion to avoid the risk of double-registration of any procedure-related MI. Persons who either died or emigrated <30 days after inclusion were excluded from the analysis. Follow-up continued until the end points of death or MI, emigration, or end of follow-up (December 31, 2018). Maximum follow-up was 10 years. Cumulative incidence proportion curves were constructed, and the competing risk of death was taken into account for MI. The 10-year cumulative incidence proportion and risk difference of MI and death were estimated. Conditional fixed-effect Poisson regression was used to estimate incidence rate ratios (IRRs) using a robust variance estimator.[16] We adjusted for statin treatment, antiplatelet treatment (aspirin and/or adenosine diphosphate-inhibitor treatment), oral anticoagulant treatment (vitamin K antagonists or direct oral anticoagulants), and MI within 30 days after study inclusion, hypertension, peripheral artery disease, chronic obstructive pulmonary disease, diabetes, previous stroke, atrial fibrillation, moderate-to-severe renal disease, and heart failure. A subgroup analysis was restricted to patients who underwent elective CAG and their references. We performed a stratified analysis according to the CCI scores (0 points, 1 point, 2 points, and ≥3 points) and a stratified analysis by procedural indication (acute coronary syndrome [ACS] and non-ACS). We adjusted for age, gender, year of inclusion, hypertension, statin treatment, antiplatelet treatment, and oral anticoagulant treatment in the stratified analyses. We also compared CAG patients and individuals from the general population who were not in antithrombotic, anticoagulant, or statin treatment. Lastly, we performed a stratified analysis based on statin use, oral anticoagulant treatment, and antiplatelet treatment. The general population cohort was the reference in the comparative analyses. Stata/MP 15.1 (StataCorp LLC, College Station, TX, USA) was used for all analyses.

This study was approved by the Danish Data Protection Agency (record no. 1-16-02-193-18). According to Danish regulations, observational registry-based studies do not require approval from ethics committees or informed consent from participants.

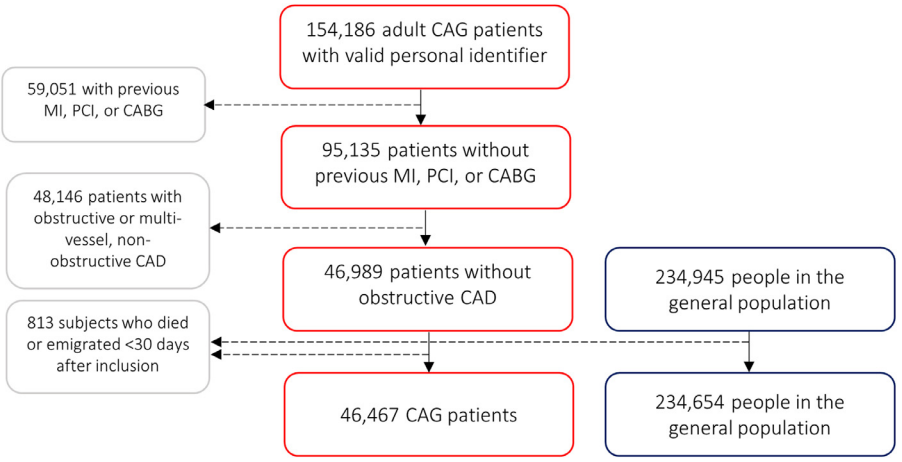


Figure 1. Flowchart showing selection of patients who underwent first-time coronary angiography in Western Denmark between January 1, 2003 and December 31, 2016.

## Results

The final CAG cohort consisted of 46,467 patients without obstructive CAD observed on the index CAG (Figure 1). The comparison cohort comprised 234,654 persons from the general population. Median follow-up time was 7.7 years.

Men and women were equally represented in both cohorts, and median age was 61 years (Table 1). The majority of CAG patients underwent elective procedures, primarily with an indication of stable angina pectoris and valvular heart disease. Compared with the general population, CAG patients more often had diabetes, hypertension, heart ff, and atrial fibrillation, as well as higher CCI scores. Overall, CAG patients were treated with cardioprotective agents and diabetes medications more frequently than matched members of the general population.

In CAG patients without CAD, we observed an absolute decrease of 4.3% in aspirin treatment after CAG (Table 2), that is, 16.6% of CAG patients discontinued aspirin treatment after CAG and 12.2% initiated treatment after CAG, despite the absence of CAD. A 3.9% net increase in statin treatment also was observed after CAG.

CAG patients had a lower 10-year risk (Table 3). In adjusted analyses, CAG patients retained a lower rate of MI. Ten-year cumulative incidence proportion curves showing MI after study inclusion are displayed in Figure 2.

Figure 2 shows that patients without CAD according to CAG had higher mortality than the general population cohort. When adjusting for comorbidity and medication, CAG patients had the same rate of death compared with the general population cohort.

When we restricted our analysis to elective CAG patients without CAD, MI results were similar to those of the main analysis, and mortality was reduced compared with the general population (Table S3). MI risk was consistently reduced in CAG patients without CAD compared with individuals from the general population with similar level of comorbidity (Figure 3 and Table S4). Mortality was similar between groups, except that CAG patients without CAD had lower mortality if CCI score ≥3 points. Stratification of patients according to procedural referral indication found that non-ACS patients had reduced risk of MI and similar mortality as observed in the general population, whereas patients with an ACS referral indication had similar risk of MI and increased mortality compared with the general population (Table S5). ACS patients had an increased risk of MI (aIRR 1.54, 95% CI 1.27 to 1.87) and death (aIRR 1.09, 95% CI 1.01 to 1.17) compared with non-ACS patients. Excluding persons treated with oral anticoagulants, anti-platelet drugs, and statins, showed that the risk of MI remained lower in CAG patients, but mortality was higher (Table S6 and Table S7).

## Discussion

Our main finding was that patients without obstructive CAD according to CAG had a lower risk of MI compared with an age- and gender-matched general population cohort without a diagnosed of CAD. Thus, absence of obstructive CAD was associated with a favorable MI risk despite an a

Table 1
Baseline characteristics

| Variable | CAG population (n = 46,467) n (%) | General population (n = 234,654) n (%) |
|---|---|---|
| Men | 23,517 (51%) | 118,826 (51%) |
| Median age, years (IQR) | 61 (52−70) | 61 (52−70) |
| Family history of ischemic heart disease* | | |
| Yes | 17,020 (37%) | |
| Missing | 4,464 (10%) | |
| Smoker* | | |
| Active | 9,647 (21%) | |
| Former | 16,776 (36%) | |
| Never | 15,104 (33%) | |
| Missing | 4,940 (11%) | |
| Body mass index* | | |
| <18.5 kg/m$^2$ | 699 (2%) | |
| 18.5−24.9 kg/m$^2$ | 11,853 (26%) | |
| 25.0−29.9 kg/m$^2$ | 15,949 (34%) | |
| ≥30 kg/m$^2$ | 11,363 (25%) | |
| Missing | 6,603 (14%) | |
| CAG priority* | | |
| Acute/subacute | 12,175 (26%) | |
| Elective | 34,292 (74%) | |
| CAG indication* | | |
| STEMI | 1,296 (3%) | |
| NSTEMI | 2,378 (5%) | |
| Unstable angina pectoris | 1,551 (3%) | |
| Stable angina pectoris | 20,380 (44%) | |
| Arrhythmia | 2,234 (5%) | |
| Valvular disease | 6,176 (13%) | |
| Cardiomyopathy | 4,524 (10%) | |
| Other | 6,989 (15%) | |
| Missing | 939 (2%) | |
| Diabetes mellitus | 4,625 (10%) | 10,010 (4%) |
| Chronic pulmonary disease | 3,923 (8%) | 8,584 (4%) |
| Hypertension | 16,770 (36%) | 23,607 (10%) |
| Peripheral artery disease | 1,151 (3%) | 3,512 (2%) |
| Heart failure | 6,078 (13%) | 2,468 (1%) |
| Atrial fibrillation | 7,567 (16%) | 7,522 (3%) |
| Ischemic stroke | 785 (2%) | 2,280 (1%) |
| Hemorrhagic stroke | 76 (0%) | 415 (0%) |
| MI <30 days after CAG | 36 (0%) | 43 (0%) |
| Charlson Comorbidity Index score | | |
| 0 | 30,932 (67%) | 192,925 (82%) |
| 1 | 8,451 (18%) | 19,814 (8%) |
| 2 | 3,970 (9%) | 13,479 (6%) |
| ≥3 | 3,114 (7%) | 8,436 (4%) |
| Medications | | |
| Aspirin | 24,017 (52%) | 27,218 (12%) |
| ADP-inhibitor | 1,641 (4%) | 2,150 (1%) |
| Vitamin K-antagonist | 6,518 (14%) | 6,318 (3%) |
| Direct oral anticoagulant | 1,184 (3%) | 1,050 (0%) |
| Statin | 21,114 (45%) | 40,566 (17%) |
| Beta-blocker | 23,118 (50%) | 25,274 (11%) |
| ACE-inhibitor | 14,056 (30%) | 29,450 (13%) |
| ARB | 7,526 (16%) | 21,781 (9%) |
| Thiazide | 7,704 (16%) | 23,387 (10%) |
| Calcium-blocker | 12,129 (26%) | 27,938 (12%) |
| Insulin | 1,637 (4%) | 4,336 (2%) |
| Non-insulin anti-diabetes agent | 3,674 (8%) | 11,160 (5%) |

Abbreviations: ACE= angiotensin converting enzyme; ADP= adenosine diphosphate; ARB = angiotensin-II receptor blocker; CAG = coronary angiography; IQR = inter-quartile range; MI = myocardial infarction; NSTEMI = non ST-elevation myocardial infarction; SD = standard deviation; STEMI = ST-elevation myocardial infarction.

* Data from the Western Denmark Heart Registry. Unavailable for the general population.

Table 2
Changes in medical treatment from 6 months before 6 months following coronary angiography in patients without coronary artery disease who had >6 months of follow-up (n = 45,821)

| | Before CAG | After CAG | New users | Former users | Net change (+/-) |
|---|---|---|---|---|---|
| Aspirin | 44.6% | 40.4% | 12.3% | 16.6% | -4.3% |
| Statin | 38.4% | 42.3% | 10.0% | 6.1% | +3.9% |
| ADP-inhibitor | 2.5% | 3.6% | 2.2% | 1.1% | +1.1% |
| Vitamin-K antagonist | 10.7% | 18.9% | 9.1% | 0.9% | +8.2% |
| DOAC | 1.8% | 2.9% | 1.4% | 0.3% | +1.1% |
| Beta-blocker | 40.4% | 45.7% | 14.4% | 9.1% | +5.3% |
| ACE-inhibitor | 24.7% | 29.6% | 8.4% | 3.5% | +4.9% |
| ARB | 15.0% | 17.0% | 3.8% | 1.8% | +2.0% |
| Thiazide | 15.0% | 14.6% | 4.0% | 4.4% | -0.4% |
| Calcium-blocker | 21.2% | 24.9% | 8.5% | 4.8% | +3.7% |
| Insulin | 3.3% | 3.7% | 0.5% | 0.1% | +0.4% |
| Non-insulin anti-diabetic agent | 7.6% | 8.0% | 0.9% | 0.5% | +0.4% |

Abbreviations: ACE: angiotensin converting enzyme; ADP, adenosine diphosphate; ARB, angiotensin-II receptor blocker; DOAC, direct oral anticoagulants.

Before: redeemed ≥1 prescription within 6 months before CAG.

After: redeemed ≥1 prescription within 6 months following CAG.

New user: redeemed ≥1 prescription within 6 months following CAG, but not during previous 6 months.

Former user: redeemed ≥1 prescription within 6 months before CAG, but not during following 6 months.

Net change: overall change in prescriptions in the period 6 months before CAG to 6 months after CAG.

Table 3
Risk of myocardial infarction and all-cause death

| | Individuals (n) | Events (n) | 10-year CIP* (95% CI) | 10-year risk difference* (95% CI) | Unadjusted IRR (95% CI) | Adjusted IRR† (95% CI) |
|---|---|---|---|---|---|---|
| Myocardial infarction | | | | | | |
| General population | 234,654 | 4,853 | 2.70% (2.62−2.78) | reference | reference | reference |
| CAG population | 46,467 | 841 | 2.40% (2.24−2.57) | -0.30% (−0.49 − −0.12) | 0.88 (0.81−0.96) | 0.70 (0.63−0.77) |
| All-cause death | | | | | | |
| General population | 234,654 | 30,322 | 17.25% (17.06−17.44) | reference | reference | reference |
| CAG population | 46,467 | 7,572 | 21.44% (20.99−21.89) | 4.19% (3.70−4.68) | 1.35 (1.31−1.38) | 1.00 (0.96−1.03) |

Abbreviations: CAG = coronary angiography; CI = confidence interval; CIP = cumulative incidence proportion; IRR = incidence rate ratio.

* Adjusted for the competing risk of death in case of myocardial infarction.

† Adjusted for peripheral artery disease, hypertension, diabetes, chronic pulmonary disease, previous stroke, renal disease, atrial fibrillation, heart failure, statin treatment, antiplatelet treatment, oral anticoagulant treatment, examination years, and myocardial infarction within 30 days after inclusion.

priori higher risk based on the clinical risk profile at baseline. However, as our results also documented that the risk is low in patients with stable CAD with an absolute 10-year difference of 0.3%, the relative differences in MI risk may not represent clinically meaningful differences.

Although no individuals from the general population had a history of ischemic heart disease at the time of matching, their coronary status was unknown. CAD is common in patients dying from non-cardiac causes based on autopsy findings.[17−19] It is likely that the increased MI risk in the general population is caused by presence of undiagnosed CAD. However, the low MI risk in CAG patients without obstructive CAD may also reflect their higher use of prophylactic cardiovascular treatment. About half of CAG patients without CAD were treated with aspirin, statins, or beta-blockers. CAG patients were also treated with oral anticoagulants, reflecting the higher prevalence of atrial fibrillation, and anti-hypertensive drugs more frequently used than the in the general population. Prophylactic cardiovascular treatment was widely prescribed in the CAG cohort despite no previous MI or revascularization and a low baseline rate of cerebrovascular disease and peripheral artery disease. Use of prophylactic drugs may reflect increased overall comorbidity levels in CAG patients and in turn may have contributed to a persistently low 10-year risk of MI. When we excluded individuals treated with statins, antiplatelet agents, or anticoagulants, CAG patients maintained a lower MI risk, but mortality was increased. About 4 in 10 patients continued aspirin treatment after CAG although their examination did not show obstructive CAD. The role of aspirin in primary cardiovascular prevention is disputed and differs in European and American guidelines.[20,21] A meta-analysis on 164,225 patients without previous cardiovascular disease, who were randomized to either aspirin or placebo, reported an absolute MI risk reduction of 0.28% (95% CI 0.05 to 0.47) after median 5-year follow-up, with similar results in low-risk and high-risk patients.[22] However, this modest protective effect was offset by an increased risk of major bleeding (risk difference 0.47%, 95% CI 0.34 to 0.62), which was even higher in high-risk patients. Thus, in the absence of obstructive CAD our CAG cohort with much higher rates of risk factors

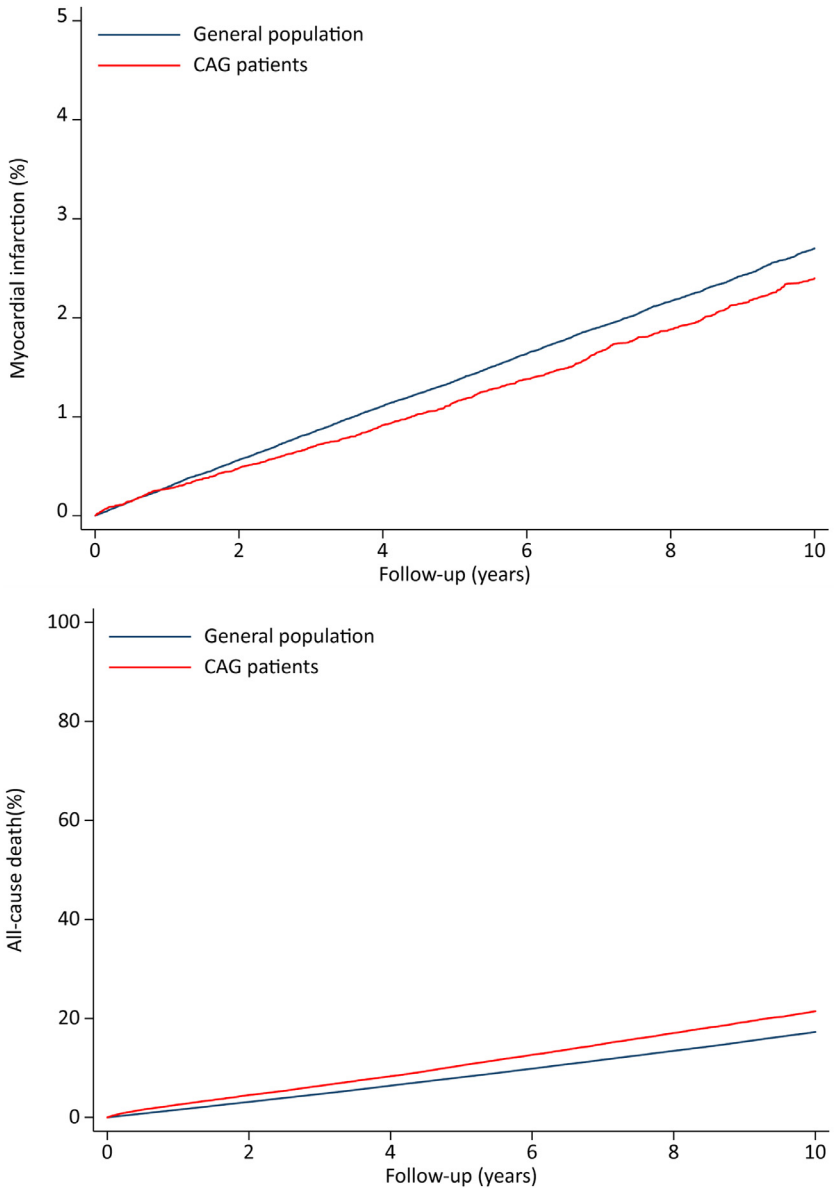


Figure 2. Cumulative incidence proportion of myocardial infarction (top) and all-cause death (bottom).

for MI had a lower MI risk than the matched general population cohort.

Despite absence of obstructive CAD and low MI risk, our study demonstrated >4% absolute increase in 10-year mortality in the CAG cohort. However, CAG patients were more often diagnosed with other comorbidities (e.g., hypertension, diabetes, and peripheral artery disease). When we either adjusted for or stratified by comorbidity, mortality was similar between groups. Other studies have reported low mortality in patients without obstructive CAD compared with patients with obstructive CAD.[23–27] However, they did not explore MI risk and mortality compared with a general population cohort. Moreover, the reference group used in these studies often consisted of other high-risk patients with suspected cardiovascular disease, and such comparison groups do not reflect MI risk or mortality in the general population. Furthermore, earlier studies examined significantly smaller cohorts, and many were published >25 years ago thus not reflecting the improved procedural practices and medical therapies of today.

Our data are consistent with an American study that examined 1-year MI and mortality rates in U.S. veterans underwent first-time elective CAG.[28] This study reported a low 1-year risk of MI and mortality in patients with both normal coronary arteries and non-obstructive CAD according to CAG. However, a higher risk of death and MI was found in patients with non-obstructive multivessel disease, compared with patients with no sign of CAD. Maddox and colleagues argue against a dichotomous view of CAD as being either non-obstructive or obstructive (< or ≥50% coronary stenosis). They propose that the extent of CAD rather than the severity of the coronary stenosis should determine subsequent patient management. In the present study, we were unable to distinguish between normal coronary

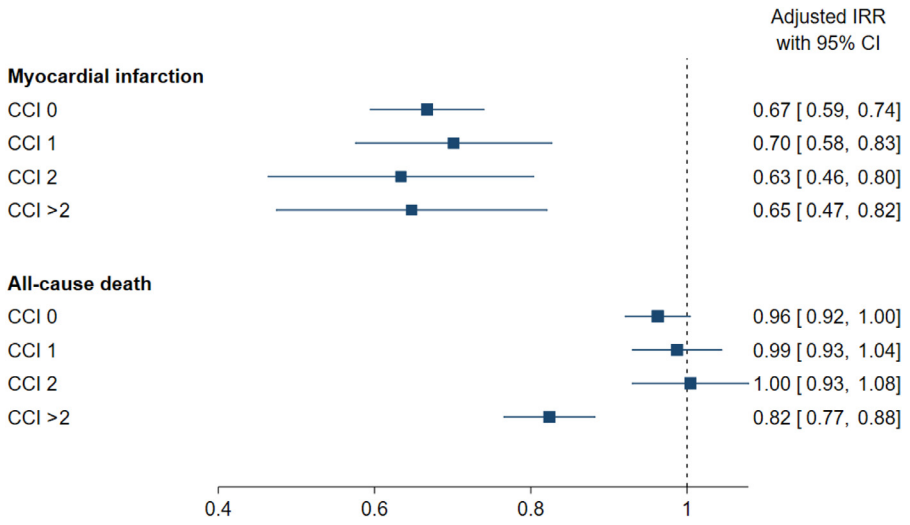


Figure 3. Adjusted incidence rate ratio of myocardial infarction and all-cause death by Charlson Comorbidity Index score.

arteries and non-obstructive CAD based on data recorded in the Western Denmark Heart Registry. However, such differentiation based on angiography has limitations since "normal" looking coronary arteries may have significant CAD, when assessed using high-resolution imaging modalities such as intravascular ultrasound or optical coherence tomography as well as non-invasive coronary computed tomography angiography (CTA).[29] Non-obstructive stenosis and increased calcium scores assessed by coronary CTA are associated with cardiovascular risk.[30–32] We have found similar results in symptomatic, routine clinical care, coronary CTA patients from Western Denmark.[33]

Our study has some limitations. We are unable to distinguish patients with no apparent CAD from patients with a non-obstructive stenosis in a single vessel. As CAD severity represent a continuum, within the cohort of patients without obstructive CAD, risk of MI and death may vary. However, at a cohort level, absence of obstructive CAD was associated with a favorable cardiovascular risk. For the general population cohort, we did not have access to lifestyle risk factors, such as smoking and obesity, associated with both MI and death. The CAG cohort was more often diagnosed with chronic obstructive pulmonary disease, indicating greater likelihood of smoking in this group. The CAG cohort also had a higher prevalence of diabetes, which may indicate a higher prevalence of obesity. Although both chronic obstructive pulmonary disease and diabetes were included in the adjusted regression models, and serve as proxies for smoking and obesity, we cannot rule out the risk of residual confounding.

In conclusion, our data showed that assessment of CAD in relatively high-risk patients could identify a low-risk cohort, in which the 10-year risk of MI was lower and the mortality was similar to an age- and gender-matched general population cohort without known CAD. Future research is needed to assess whether assessment of CAD, for example, by coronary computed tomography angiography, is a clinically superior and cost-effective strategy to guide prophylactic treatment as compared with risk assessment based on traditional risk factors.

## Author contributions

Kevin Kris Warnakula Olesen: Conceptualization, Methodology, Data Curation Writing- Original draft preparation, Morten Madsen: Methodology, Writing- Reviewing and Editing. Morten Würtz: Writing- Reviewing and Editing. Troels Thim: Writing- Reviewing and Editing. Lisette Okkels Jensen: Writing- Reviewing and Editing. Bent Raungaard: Writing- Reviewing and Editing. Hans Erik Bøtker: Methodology, Writing- Reviewing and Editing. Henrik Toft Sørensen: Methodology, Writing- Reviewing and Editing. Michael Maeng: Conceptualization, Supervision, Methodology, Writing- Original draft preparation.

## Disclosures

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.06.068.

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