

Absence of Coronary Artery Disease is a Strong Negative Predictor of Major Adverse Cardiovascular Events in Patients with Chronic Kidney Disease

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Purpose: To investigate the interplay between chronic kidney disease (CKD) and coronary artery disease (CAD) on the incidence of cardiovascular events in patients with suspected chronic coronary syndrome (CCS).

Patients and Methods: Patients with suspected CCS who underwent first-time coronary angiography in Western Denmark between 2003 and 2016 were included in this cohort study. Moreover, an age- and sex-matched general population cohort was established. Patients were stratified according to estimated glomerular filtration rate (eGFR). Presence of CAD was defined as ≥ 1 obstructive stenosis or non-obstructive diffuse disease. Major adverse cardiovascular events (MACE) were defined as a composite of myocardial infarction, ischemic stroke, and cardiac death.

Results: A total of 42,611 patients were included with a median follow-up of 7.3 years. Patients without and with CAD had MACE rates per 100 person-years that were 0.52 and 1.67 for eGFR ≥ 90 mL/min/1.73 m², 0.68 and 2.09 for eGFR 60–89 mL/min/1.73 m², 1.27 and 3.85 for eGFR 30–59 mL/min/1.73 m², and 2.27 and 6.92 for eGFR < 30 mL/min/1.73 m². Comparing to eGFR ≥ 90 mL/min/1.73 m², the adjusted incidence rate ratios for MACE were 1.29 (1.10–1.51) for eGFR 60–89 mL/min/1.73 m², 1.86 (1.49–2.33) for eGFR 30–59 mL/min/1.73 m², and 3.57 (1.92–6.67) for eGFR < 30 mL/min/1.73 m² in patients without CAD, and 1.11 (1.03–1.20), 1.71 (1.55–1.90), and 2.46 (1.96–3.09) in patients with CAD. The inverse relationship between kidney function and risk of MACE was confirmed when comparing patients with and without CAD to matched individuals in the general population.

Conclusion: Absence of CAD is a strong negative predictor of major adverse cardiovascular events in patients with CKD.

Keywords: coronary artery disease, coronary angiography, kidney function, renal insufficiency, chronic kidney disease, chronic coronary syndrome

Introduction

Chronic kidney disease (CKD) is highly prevalent worldwide, it affects 8–16% of the population,¹ and CKD is the third fastest growing cause of death globally.² In high-income countries, CKD is mainly caused by diabetes or hypertension,³ which also represent central risk factors for development of cardiovascular diseases, both individually and synergistically.^{4,5}

Cardiovascular disease and CKD frequently coexist in patients.¹ Consequently, the current European Society of Cardiology (ESC) guidelines for chronic coronary syndrome (CCS) recommend that patients with CKD are treated to target values for cardiovascular risk factors such as hyperlipidemia, hypertension, and hyperglycemia.⁶ Moreover, CKD has previously been established as an important predictor of clinical cardiovascular outcomes, although data are sparse in patients with CCS.^{7,8} However, strong associations between impaired kidney function and long-term cardiovascular outcomes (risk of death, heart failure and myocardial infarction (MI)) in patients with CCS were recently reported in a Swedish cohort.⁹

We have previously shown that the absence of CAD eliminates the excess MI risk in patients with diabetes,^{10–13} reduces the excess risk of stroke and limb amputations in patients with diabetes,^{14,15} and reduces the risk of stroke in patients with atrial fibrillation.¹⁶ In the current study we aimed to investigate if CAD is also a strong negative predictor across different stages of CKD. To answer this question, we used a cohort of CCS patients undergoing coronary angiography (CAG) in Western Denmark and a matched general population comparison cohort.

Methods

Data Collection

Patients were identified from the Western Denmark Heart Registry (WDHR), where patient and procedure data from all cardiac procedures in Western Denmark are prospectively recorded, including CAGs since 1999.¹⁷ The WDHR was linked with other registries using the unique, individual Civil Person Register number, assigned to all Danish citizens, and recorded in the Danish Civil Registration System.¹⁸ This system allows us to collect long-term follow-up on patients by providing information on emigration and vital status.¹⁸

Several registries were used in this study; the Danish National Patient Registry (DNPR),¹⁹ the Danish National Prescription Registry,²⁰ and the Danish Register of Causes of Death.²¹ The DNPR collects primary and secondary discharge diagnoses after patient admissions. These diagnoses are registered in accordance with the International Classification of Diseases, 10th revision.

Patient Selection

We identified all patients undergoing CAG in Western Denmark from January 1, 2003 – December 31, 2016 (Figure 1). Patients below 18 years were excluded. Patients with CAG performed due to acute coronary syndromes or other indications than stable angina pectoris were excluded. We excluded all patients with missing CAD status and estimated glomerular filtration rate (eGFR) data and follow-up <30 days. Patients undergoing dialysis were excluded. Thereby, patients undergoing CAG due to suspicion of CCS were included and stratified on presence of CAD and kidney function.

Exposure

Kidney function was assessed by eGFR, which was estimated according to the most recent plasma creatinine measured before CAG. eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and adjusted to body surface area (BSA) as calculated by the Du Bois formula.²² The CKD-EPI equation is validated in a US population.²³ Kidney function was classified in CKD stages based on eGFR: eGFR ≥ 90 mL/min/1.73 m² as normal or high function; 60–89 mL/min/1.73 m² as mildly decreased; 30–59 mL/min/1.73 m² as moderately decreased; and <30 mL/min/1.73 m² as severely decreased/kidney failure.²⁴

CAD status was evaluated by CAG and recorded in the WDHR. CAD was defined as ≥ 1 coronary vessel(s) with obstructive stenosis ($\geq 50\%$ lumen narrowing and/or a fractional flow reserve ≤ 0.80 , the latter officially included in the definition in 2014) or diffuse non-significant vessel disease.

Baseline Characteristics

Information on age and sex were collected from the Civil Registration System. The WDHR and the DNPR were used to obtain patient data and information on comorbidities. Diabetes was defined as (1) being in dietary treatment, insulin treatment with or without oral glucose lowering treatment, or oral glucose lowering treatment according to the WDHR, (2) a diabetes diagnosis registered in the DNPR before CAG or within 30 days after CAG, (3) redemption of diabetes medication (being either insulin or non-insulin glucose lowering treatment) within 6 months before CAG to 30 days after as recorded in the Danish National Prescription Registry. Hypertension was defined as a combination of treatment for hypertension in the WDHR and a previous hypertension diagnosis registered in the DNPR. Heart failure with reduced ejection fraction (HFrEF) was characterized as an ejection fraction $\leq 40\%$ registered in the WDHR or a diagnosis of heart failure in the DNPR, before CAG or within 30 days after CAG. Prescription records on medications (within 6 months

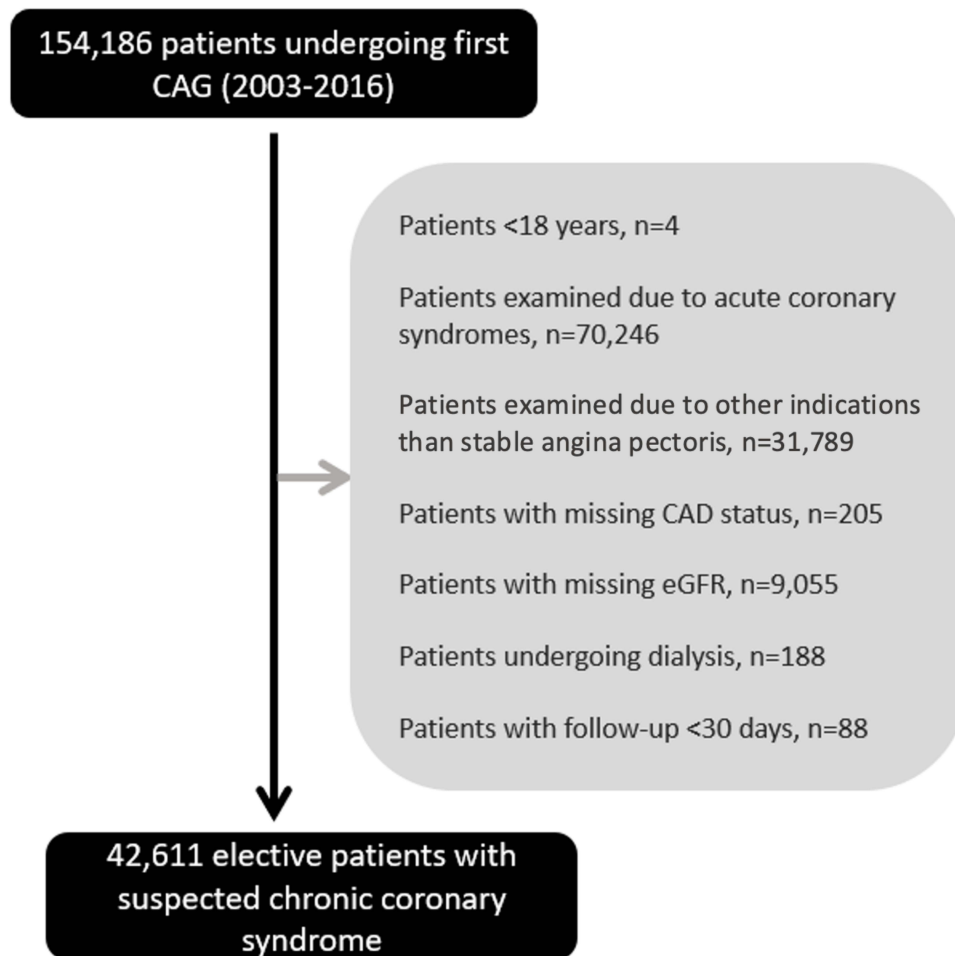


Figure 1 Patient selection. Flowchart displaying selection of patients with chronic coronary syndrome.

Abbreviations: CAG, coronary angiography; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate.

before CAG until 30 days after CAG) were obtained from the Danish National Prescription Registry. Charlson Comorbidity Index (CCI) was modified to exclude moderate-to-severe kidney disease.²⁵

Outcomes

Major adverse cardiac events (MACE) were defined as a composite of MI, ischemic stroke, and cardiac death. Data on MI and ischemic stroke were obtained by the primary and secondary discharge diagnoses from hospital admissions in the DNPR ([Supplementary Table 1](#)). Information on cardiac death is registered in the Danish Register of Causes of Death. All-cause mortality was determined from the Danish Civil Registration System. Follow-up and registration of events were initiated 30 days after CAG to avoid double recording of procedure-related events.

Statistical Analyses

Follow-up began 30 days after the CAG procedure and end of follow-up was defined as outcome, death, emigration, maximum 10-year follow-up, or at the date of last available data (December 31, 2018). Event rates were estimated per 100 person-years at risk. Information on smoking status was missing in 4% of patients and BMI in 0.1% of patients. These missing data were handled by imputation of 5 datasets using chained equations.²⁶ A modified Poisson regression with a robust variance-covariance estimator was used to compute unadjusted and adjusted incidence rate ratio (IRR), with the eGFR ≥ 90 mL/min/1.73 m² stratum as reference.²⁷ Analyses of event rates and IRRs were repeated for patients stratified by CAD status at CAG. IRR was adjusted to potential confounders based on clinical assessment. For MI, IRR

were adjusted for age category (<65 years, 65–74 years, and ≥ 75 years), sex, BMI category (<18.5 kg/m², 18.5–24 kg/m², 25–29 kg/m², and ≥ 30 kg/m²) (imputed), active smoking (imputed), hypertension, peripheral artery disease (PAD), previous ischemic stroke, diabetes, CAD severity, antiplatelet treatment (aspirin and adenosine-diphosphate receptor inhibitors), oral anticoagulant treatment (vitamin K-antagonists and direct oral anticoagulants), and statin treatment. For the ischemic stroke and MACE outcomes, data were additionally adjusted for HFrEF and atrial fibrillation. For all-cause mortality, data were adjusted for age category (18–64 years, 65–74 years, and ≥ 75 years), sex, BMI category (<18.5 kg/m², 18.5–24 kg/m², 25–29 kg/m², and ≥ 30 kg/m²) (imputed), active smoking (imputed), hypertension, CAD severity, modified CCI group, oral anticoagulant treatment, antiplatelet treatment, and statin treatment. We performed Log rank tests for trend to examine the trend between eGFR and any outcome, both with and without stratification for CAD. CAG patients were compared to an age- and sex-matched background population with respect to 10-years MACE using conditional, fixed-effect Poisson regression. Stratified analyses were performed for CAD and eGFR. Stata software, version 16.0 (StataCorp LLC, Texas, USA), was used for statistical analyses.

Ethical Considerations

The study was registered with the Danish Data Protection Agency (record no. 1-16-02-193-18). According to Danish regulation, observational, noninterventional registry-based studies require neither approval from ethics committees nor informed consent from patients.

Results

A total of 42,611 patients were included in the analyses. At the time of CAG, 16,084 (37.7%) had no CAD, while 26,527 (62.3%) patients had obstructive CAD or diffuse non-obstructive vessel disease. Median eGFR was 88 mL/min/1.73 m² (Q1-Q3: 72–104 mL/min/1.73 m²) and 5014 patients (11.5%) had an eGFR <60 mL/min/1.73 m². Median follow-up was 7.3 years (Q1-Q3: 4.4–10.0 years) and within this period 4266 MACE were observed.

Baseline Characteristics

Baseline characteristics are presented in Table 1. Overall, declining kidney function was associated with higher prevalence of important risk factors. For example, patients in the lowest eGFR strata <30 mL/min/1.73 m² were older

Table 1 Baseline Characteristics of Chronic Coronary Syndrome Patients Undergoing Coronary Angiography in Western Denmark

eGFR (mL/min/1.73 m ²)	<30 n=298	30–59 n=4716	60–89 n=17,462	≥ 90 n=20,145
Age mean (years) (SD)	71 (11.3)	73 (8.2)	68 (8.9)	59 (9.6)
Male	157 (52.7)	1763 (37.4)	8826 (50.6)	14,996 (74.4)
Body mass index median (kg/m ²) (IQR)	26.5 (24.0–29.0)	26.0 (23.0–29.0)	26.0 (24.0–29.0)	28.0 (25.0–32.0)
Systolic blood pressure mean (mmHg) (SD)	146 (24)	146 (22)	145 (21)	143 (20)
Diastolic blood pressure mean (mmHg) (SD)	76 (13)	77 (12)	80 (12)	82 (11)
Smoking				
Active	41 (13.8)	733 (15.5)	3072 (17.6)	5769 (28.6)
Former/never	231 (77.5)	3723 (78.9)	13,653 (78.2)	13,743 (68.2)
Missing	26 (8.7)	260 (5.5)	727 (4.2)	633 (3.1)
Comorbidities				
Ischemic stroke	21 (7.0)	194 (4.1)	351 (2.0)	275 (1.4)

(Continued)

Table 1 (Continued).

eGFR (mL/min/1.73 m ²)	<30 n=298	30–59 n=4716	60–89 n=17,462	≥90 n=20,145
Hemorrhagic stroke	1 (0.3)	11 (0.2)	31 (0.2)	23 (0.1)
TIA	13 (4.4)	201 (4.3)	525 (3.0)	477 (2.4)
AFib	48 (16.1)	760 (16.1)	1943 (11.1)	1611 (8.0)
PAD	37 (12.4)	472 (10.0)	975 (5.6)	822 (4.1)
Diabetes	100 (33.6)	1013 (21.5)	2662 (15.3)	3970 (19.7)
Hypertension	264 (88.6)	3763 (79.8)	11,726 (67.2)	12,391 (61.5)
HFrEF	60 (20.1)	656 (13.9)	1139 (6.5)	922 (4.6)
MI before CAG	15 (5.0)	155 (3.3)	342 (2.0)	358 (1.8)
MI <30 days after CAG	4 (1.3)	32 (0.7)	100 (0.6)	82 (0.4)
Previous PCI	7 (2.3)	87 (1.8)	271 (1.6)	331 (1.6)
Previous CABG	4 (1.3)	26 (0.6)	77 (0.4)	76 (0.4)
Cancer (any tumor)	35 (11.7)	438 (9.3)	1154 (6.6)	901 (4.5)
Dementia	0 (0.0)	27 (0.6)	34 (0.2)	32 (0.2)
Chronic obstructive pulmonary disease	29 (9.7)	466 (9.9)	1336 (7.7)	1320 (6.6)
Previous nephropathy	57 (19.1)	165 (3.5)	130 (0.7)	128 (0.6)
Previous retinopathy	37 (12.4)	187 (4.0)	372 (2.1)	592 (2.9)
Previous peripheral polyneuropathy	15 (5.0)	89 (1.9)	182 (1.0)	223 (1.1)
CAD status at CAG				
0 VD	63 (21.1)	1413 (30.0)	6474 (37.1)	8134 (40.4)
1 VD	73 (24.5)	1044 (22.1)	3894 (22.3)	4560 (22.6)
2 VD	44 (14.8)	726 (15.4)	2466 (14.1)	2645 (13.1)
3 VD	85 (28.5)	966 (20.5)	2559 (14.7)	2366 (11.7)
Diffuse VD	33 (11.1)	567 (12.0)	2059 (11.8)	2440 (12.1)
Medical treatment				
Aspirin	229 (76.8)	3797 (80.5)	13,811 (79.1)	15,606 (77.5)
ADP-inhibitors	106 (35.6)	1274 (27.0)	4258 (24.4)	4899 (24.3)
Vitamin K-antagonists	47 (15.8)	592 (12.6)	1469 (8.4)	1118 (5.5)
NOAC	9 (3.0)	101 (2.1)	315 (1.8)	262 (1.3)
Thiazide	56 (18.8)	1238 (26.3)	3416 (19.6)	2975 (14.8)
Statins	240 (80.5)	3747 (79.5)	13,776 (78.9)	15,592 (77.4)
Calcium channel blockers	169 (65.7)	2121 (45.0)	6606 (37.9)	6825 (33.9)
Beta blockers	220 (73.8)	3269 (69.3)	10,744 (61.6)	11,322 (56.2)

(Continued)

Table I (Continued).

eGFR (mL/min/1.73 m ²)	<30 n=298	30–59 n=4716	60–89 n=17,462	≥90 n=20,145
ARBs	117 (39.3)	1328 (28.2)	3495 (20.0)	3552 (17.6)
ACE-inhibitors	134 (45.0)	1769 (37.5)	5109 (29.3)	5660 (28.1)
Insulin	61 (20.5)	371 (7.9)	805 (4.6)	1,168 (5.8)
Non-insulin	36 (12.1)	570 (12.1)	1759 (10.1)	2882 (14.3)
CCS Scale				
Grade I	51 (17.1)	901 (19.1)	4086 (23.4)	4985 (24.7)
Grade II	178 (59.7)	2922 (62.0)	10,873 (62.3)	12,456 (61.8)
Grade III	58 (19.5)	708 (15.0)	1809 (10.4)	1841 (9.1)
Grade IV	1 (0.3)	23 (0.5)	58 (0.3)	74 (0.4)
Missing	10 (3.4)	162 (3.4)	626 (3.6)	789 (3.9)
CCI Group				
CCI 0	115 (38.6)	2443 (51.8)	11,675 (66.9)	13,954 (69.3)
CCI 1	60 (20.1)	1033 (21.9)	3089 (17.7)	3575 (17.7)
CCI 2	43 (14.4)	617 (13.1)	1527 (8.7)	1,424 (7.1)
CCI >2	80 (26.8)	623 (13.2)	1161 (6.7)	1192 (5.9)

Note: Values are indicated as number (%), unless otherwise stated.

Abbreviations: eGFR, estimated glomerular filtration rate; SD, standard deviation; IQR, interquartile range; TIA, transient ischemic attack; AFib, atrial fibrillation; PAD, peripheral artery disease; HFrEF, heart failure with reduced ejection fraction; MI, myocardial infarction; CAG, coronary angiography; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CAD, coronary artery disease; VD, vessel disease; ADP, adenosine diphosphate receptor; NOAC, non-vitamin K antagonist oral anticoagulants; ARBs, angiotensin receptor blockers; ACE, angiotensin-converting enzyme; CCS, Canadian Cardiovascular Society; CCI, Charlson Comorbidity Index.

and had a higher prevalence of previous ischemic stroke, atrial fibrillation, PAD, hypertension, HFrEF, previous MI, microvascular diseases, and diabetes. Additionally, presence and extent of CAD was inversely associated with kidney function. [Supplementary Tables 2](#) and [3](#) provide baseline characteristics of patients with and without CAD, respectively.

Clinical Outcomes

MACE rates are presented in [Table 2](#), further stratification for absence versus presence of CAD is shown in [Table 3](#), and the results are illustrated in [Figure 2](#). The rate of MACE was inversely related to kidney function. When comparing the eGFR <30 mL/min/1.73 m² stratum (5.73 events per 100 person-years [95% CI, 4.60–7.14]) to the eGFR ≥90 mL/min/1.73 m² stratum (1.16 events per 100 person-years [95% CI, 1.11–1.22]), the 10-year risk increased with a factor 4.92 [95% CI, (3.92–6.18)] for the overall cohort. Accordingly, [Figure 3](#) displays an increased cumulative incidence proportion of MACE with decreasing eGFR stratum. When stratifying for CAD status, only the eGFR <30 mL/min/1.73 m² stratum among patients without CAD resulted in an event rate (2.27 [95% CI, 1.13–4.53]) exceeding that of the eGFR ≥90 mL/min/1.73 m² stratum in patients with CAD (1.67 [95% CI, 1.58–1.76]). After adjustment for potential confounders, the risk of MACE remained incrementally associated with reduced kidney function regardless of CAD status.

After stratification for kidney function according to eGFR categories G1–G5, the resulting risk of MACE overall supported our previously reported results for patients with and without CAD ([Supplementary Table 4](#)). We additionally found a significantly increased risk of MACE for patients with CAD and eGFR 30–44 mL/min/1.73 m² (1.93 [95% CI, 1.65–2.27]) compared to the eGFR 45–59 mL/min/1.73 m² stratum (1.42 [95% CI, 1.25–1.60]). However, our data set

Table 2 Incidence Rate Ratios of Major Adverse Cardiovascular Events

eGFR (mL/min/1.73 m ²)	Person-Years	Events	Events per 100 Person-Years (95% CI)	Unadjusted IRR (95% CI)	Adjusted IRR* (95% CI)	P for Trend
Major Adverse Cardiovascular Events						
≥90	135,658	1579	1.16 (1.11–1.22)	Reference	Reference	p<0.001
60–89	116,791	1774	1.52 (1.45–1.59)	1.30 (1.22–1.40)	1.12 (1.04–1.20)	
30–59	28,056	834	2.97 (2.78–3.18)	2.55 (2.35–2.78)	1.66 (1.51–1.82)	
<30	1379	79	5.73 (4.60–7.14)	4.92 (3.92–6.18)	2.55 (2.07–3.13)	

Notes: Risk of major adverse cardiovascular events after coronary angiography stratified by kidney function strata. *We adjusted for age category (<65, 65–74, and ≥75), sex, BMI category (<18.5, 18.5–24, 25–29, and ≥30) (imputed), active smoking (imputed), hypertension, peripheral artery disease, previous ischemic stroke, Diabetes Mellitus, coronary artery disease category, oral anticoagulant treatment, antiplatelet treatment, statin treatment, heart failure with reduced ejection fraction, and atrial fibrillation.

Abbreviations: IRR, incidence rate ratio; eGFR, estimated glomerular filtration rate.

Table 3 Major Adverse Cardiovascular Events Stratified by Coronary Artery Disease

eGFR (mL/min/1.73 m ²)	Person-Years	Events	Events per 100 Person-Years (95% CI)	Unadjusted IRR (95% CI)	Adjusted IRR* (95% CI)	P for Trend
Major Adverse Cardiovascular Events						
No CAD						
≥90	59,341	307	0.52 (0.46–0.58)	Reference	Reference	p<0.001
60–89	47,334	324	0.68 (0.61–0.76)	1.32 (1.13–1.55)	1.29 (1.10–1.51)	
30–59	9576	122	1.27 (1.07–1.52)	2.46 (2.00–3.03)	1.86 (1.49–2.33)	
<30	353	8	2.27 (1.13–4.53)	4.38 (2.16–8.87)	3.57 (1.92–6.67)	
CAD						
≥90	76,317	1272	1.67 (1.58–1.76)	Reference	Reference	p<0.001
60–89	69,457	1450	2.09 (1.98–2.20)	1.25 (1.16–1.35)	1.08 (0.99–1.17)	
30–59	18,480	712	3.85 (3.58–4.15)	2.31 (2.11–2.53)	1.55 (1.38–1.73)	
<30	1026	71	6.92 (5.48–8.73)	4.15 (3.27–5.28)	2.58 (2.03–3.30)	

Notes: Risk of major adverse cardiovascular events after coronary angiography stratified by kidney function strata and presence/absence of coronary artery disease. *We adjusted for age category (<65, 65–74, and ≥75), sex, BMI category (<18.5, 18.5–24, 25–29, and ≥30) (imputed), active smoking (imputed), hypertension, peripheral artery disease, previous ischemic stroke, diabetes mellitus, coronary artery disease category, oral anticoagulant treatment, antiplatelet treatment, statin treatment, heart failure with reduced ejection fraction, and atrial fibrillation.

Abbreviations: IRR, incidence rate ratio; eGFR, estimated glomerular filtration rate; CAD, coronary artery disease.

contains few patients without CAD and eGFR <45 mL/min/1.73 m² (n=338) as well as patients with CAD and eGFR <30 mL/min/1.73 m² (n=235), making further interpretation of the sub-analysis challenging. Categorizing patients according to CAD status as diffuse, non-significant CAD, obstructive single-vessel CAD, and obstructive multivessel CAD, we confirmed the inverse relationship between kidney function and risk of MACE for each eGFR stratum ([Supplementary Table 5](#)). Additionally, we found that with increased extent of CAD, the rate of MACE overall worsened within equal eGFR strata. Likewise, we confirmed the inverse relationship when stratifying for LVEF>40% or LVEF≤40% within patients with CAD ([Supplementary Table 6](#)). Further, we found that patients with CAD, LVEF≤40%, and eGFR <30 mL/min/1.73 m² had the highest risk of MACE.

[Table 4](#) shows the comparison between patients and their age- and sex-matched individuals from the general population. For patients without CAD and eGFR ≥60 mL/min/1.73 m², the risk of MACE was comparable to that of the general population, whereas eGFR in the 30–59 mL/min/1.73 m² range was associated with a 31% (IRR 1.31 (1.04–1.66)) increased relative risk, and eGFR <30 mL/min/1.73 m² with a >3-fold (IRR 3.11 (0.96–10.05)) increased relative risk when compared with the age- and sex-matched background population. This becomes visible in [Figure 4](#) depicting the cumulative incidence proportions of MACE, which is similar to that of the matched background populations for patients without CAD and eGFR ≥30 mL/min/1.73 m². Concerning patients with CAD, the cumulative incidence

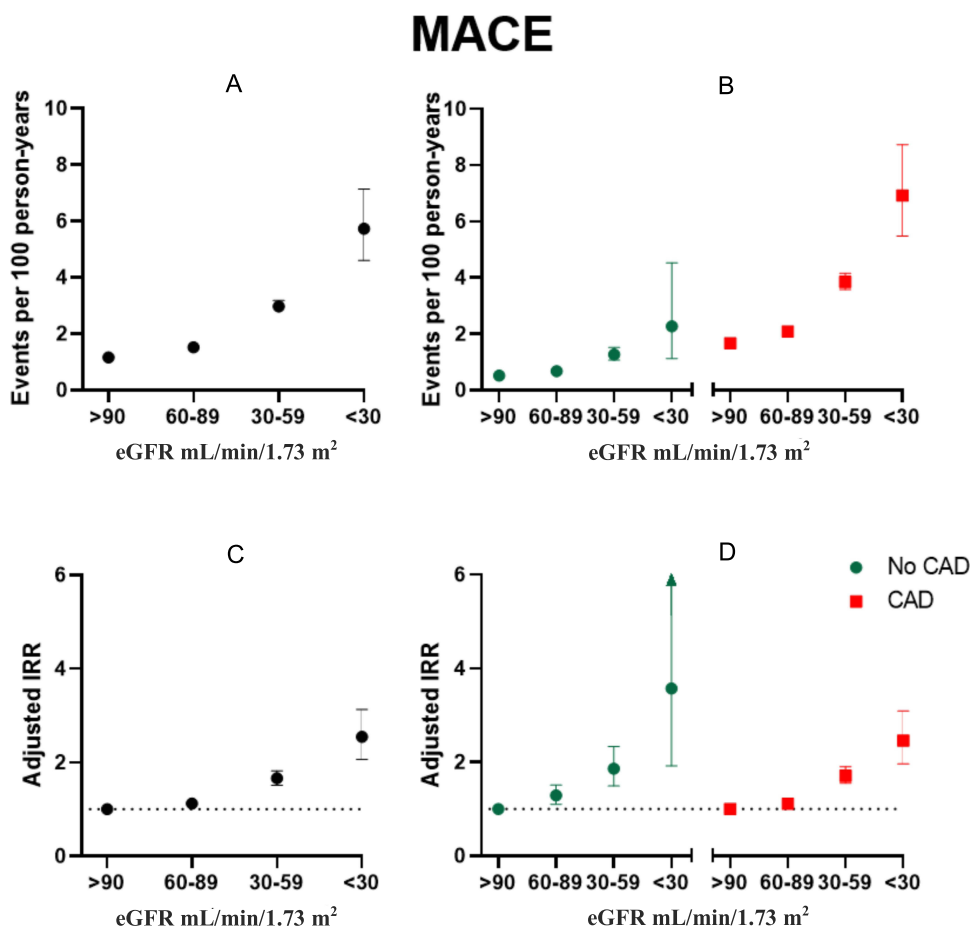


Figure 2 Outcome graph displaying major adverse cardiovascular event rates and adjusted incidence rate ratios. (A) MACE for different eGFR strata without stratification for coronary artery disease. (B) MACE for different eGFR strata with stratification for coronary artery disease. (C) Adjusted IRR for different eGFR strata without stratification for coronary artery disease. (D) Adjusted IRR for different eGFR strata with stratification for coronary artery disease.

Abbreviations: eGFR, estimated glomerular filtration rate; MACE, major adverse cardiovascular events; IRR, incidence rate ratio; CAD, coronary artery disease.

proportions of MACE were increased when comparing to the general population across all eGFR strata (Figure 4). Correspondingly, patients with CAD all had an increased risk of MACE being 2-3-fold higher for eGFR >90 mL/min/1.73 m², 60–89 mL/min/1.73 m², and 30–59 mL/min/1.73 m² than observed in the general population, while a substantial 7.42-fold (IRR 7.42 (4.67–11.81)) increased risk of MACE was observed for patients with eGFR <30 mL/min/1.73 m² (Table 4). Patients with eGFR <30 mL/min/1.73 m² had an increased incidence of MACE compared to the respective matched background population regardless of CAD status.

For all other clinical outcomes assessed in the current study (including MI, ischemic stroke and all-cause mortality), we found the same trend towards increased incidence across decreasing eGFR strata ($p < 0.001$) (Supplementary Table 7, Supplementary Figures 1 and 2). This was also the case after stratification for presence of CAD (Supplementary Table 8). Supplementary Table 9 displays that risk of MACE was similar irrespectively of using BSA or non-BSA adjusted eGFR. Finally, Supplementary Table 10 shows the risk of MACE without correction for BMI, which was comparable to the results adjusted for BMI.

Discussion

In the current study, we found that the absence of CAD is also a strong negative predictor of MACE in patients with CKD. Even though we observed a similar relative inverse relationship between CKD and risk of MACE in patients with and without CAD, the absence of CAD was associated with a substantially lower absolute risk of events when comparing equal eGFR strata. Moreover, the relationship between CKD and MACE in patients without CAD became more complex

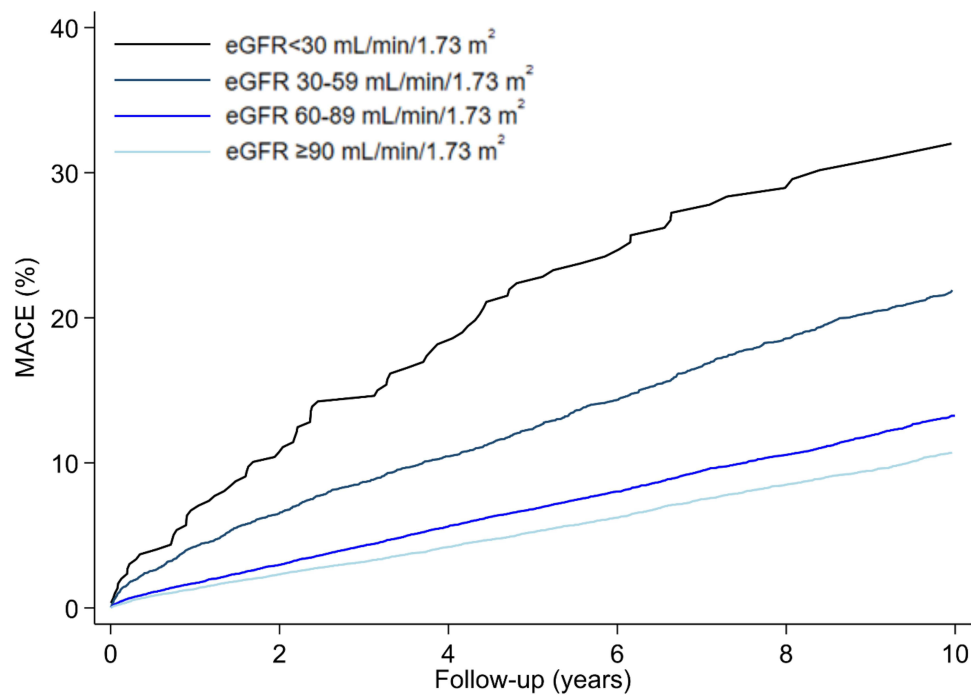


Figure 3 Cumulative incidence proportions.
Abbreviation: MACE, major adverse cardiovascular events.

when we additionally compared these patients with an age- and sex-matched general population. In the latter comparison, our results revealed no or only a negligible excess risk of MACE for patients without evident CAD and $eGFR \geq 30 \text{ mL/min/1.73 m}^2$ when compared to their matched general population individuals, whilst patients with severely reduced kidney function ($eGFR < 30 \text{ mL/min/1.73 m}^2$) were at increased risk of MACE irrespectively of CAD status. Thus, the

Table 4 Risk of Major Adverse Cardiovascular Events for Patients Compared to a Matched General Population

eGFR (mL/min/1.73 m ²)	Individuals	Events	Events per 100 Person-Years (95% CI)	Age- and Sex-Matched IRR (95% CI)
No CAD				
≥90				
General population	40,510	1302	0.44 (0.42–0.46)	Reference
CAG patients	8102	304	0.51 (0.46–0.58)	1.17 (1.01–1.35)
60–89				
General population	32,195	1539	0.67 (0.64–0.70)	Reference
CAG patients	6439	323	0.69 (0.62–0.77)	1.01 (0.88–1.16)
30–59				
General population	6970	461	0.98 (0.89–1.07)	Reference
CAG patients	1394	121	1.28 (1.07–1.53)	1.31 (1.04–1.66)
<30				
General population	315	19	0.97 (0.62–1.53)	Reference
CAG patients	63	8	2.27 (1.13–4.53)	3.11 (0.96–10.05)
CAD				
≥90				
General population	59,760	2793	0.71 (0.68–0.74)	Reference
CAG patients	11,952	1263	1.66 (1.57–1.76)	2.70 (2.48–2.93)

(Continued)

Table 4 (Continued).

eGFR (mL/min/1.73 m ²)	Individuals	Events	Events per 100 Person-Years (95% CI)	Age- and Sex-Matched IRR (95% CI)
60–89				
General population	54,390	3709	1.06 (1.03–1.10)	Reference
CAG patients	10,878	1439	2.09 (1.98–2.20)	2.15 (1.99–2.32)
30–59				
General population	16,235	1491	1.51 (1.43–1.58)	Reference
CAG patients	3247	696	3.83 (3.56–4.13)	3.04 (2.69–3.44)
<30				
General population	1155	96	1.38 (1.13–1.69)	Reference
CAG patients	231	70	6.96 (5.51–8.80)	7.42 (4.67–11.81)

Note: Comparing risk of 10-year major adverse cardiovascular events for patients with suspected chronic coronary syndrome to an age- and sex-matched background population.

Abbreviations: IRR, incidence rate ratio; eGFR, estimated glomerular filtration rate; CAD, coronary artery disease.

absence of CAD is a strong negative predictor of major adverse cardiovascular events in patients with CKD, while severely reduced kidney function is a strong positive predictor irrespectively of CAD status. Contrarily, among patients with either diffuse, single-vessel or multi-vessel CAD, we confirmed the reported inverse relationship between CKD and risk of MACE regardless of extent of CAD and presence or absence of HF_rEF.

Our finding is concordant with our previous publications regarding MI in patients with diabetes,^{10–13} stroke and limb amputations in patients with diabetes,^{14,15} and stroke in patients with atrial fibrillation.¹⁶ There is a paucity of studies examining the association between the presence of CAD, kidney function, and cardiovascular risk. A Swedish cohort study has previously investigated the significance of CAD and CKD in patients with stable CAD and found a similar reverse association between kidney function and risk of MI or all-cause mortality.⁹ In both the Swedish cohort and the Western Danish patients, the absence of CAD was a strong negative predictor of cardiovascular outcomes when comparing patients within the same kidney function group. Moreover, both studies show an inverse relationship between CKD stage and MACE in patients without CAD. However, this inverse relationship was less evident when we compared CCS patients with age- and sex-matched general population individuals where only those with severe CKD (eGFR <30 mL/min/1.73 m²) had a clinically relevant increased risk of MACE.

In patients with suspected CCS, we found that decreased kidney function was associated with increased presence of HF_rEF and extent of CAD at baseline. This is in accordance with previous studies describing the cardio-renal syndrome, constituting a pathophysiologic disorder of the heart and kidneys, where chronic dysfunction in one organ may induce acute or chronic dysfunction in the other.²⁸ Smoking, diabetes, hypertension, dyslipidemia, and obesity are shared risk factors by CAD and CKD.²⁹ Decreased eGFR has also previously been associated with the severity of CAD independently of traditional risk factors for CAD.³⁰ Major non-traditional risk factors include proteinuria, vascular calcification, neurohormonal dysregulation, impaired endothelium-dependent vasodilation, low-grade chronic inflammation, anemia, volume overload, and disturbances in the calcium-phosphate metabolism. The accumulated effect of these factors is often described as early or accelerated vascular aging, and affects most patients progressing to end-stage renal disease.³¹ The extensive comorbidities of patients with reduced eGFR are also recognized in the high risk of major adverse cardiovascular events found in this study.

CKD causes increased coronary artery calcification even in patients without common cardiovascular risk factors such as dyslipidemia and hypertension, thereby generating reduced coronary flow reserve and increased cardiovascular events.³¹ Coronary flow reserve is a marker of the coronary microvascular function and has been found significantly lower in patients with CKD compared to patients with eGFR >60 mL/min/1.73 m² in a cohort of patients without known CAD.³² Therefore, CKD-associated coronary microvascular dysfunction is suggested as a possible explanation for the

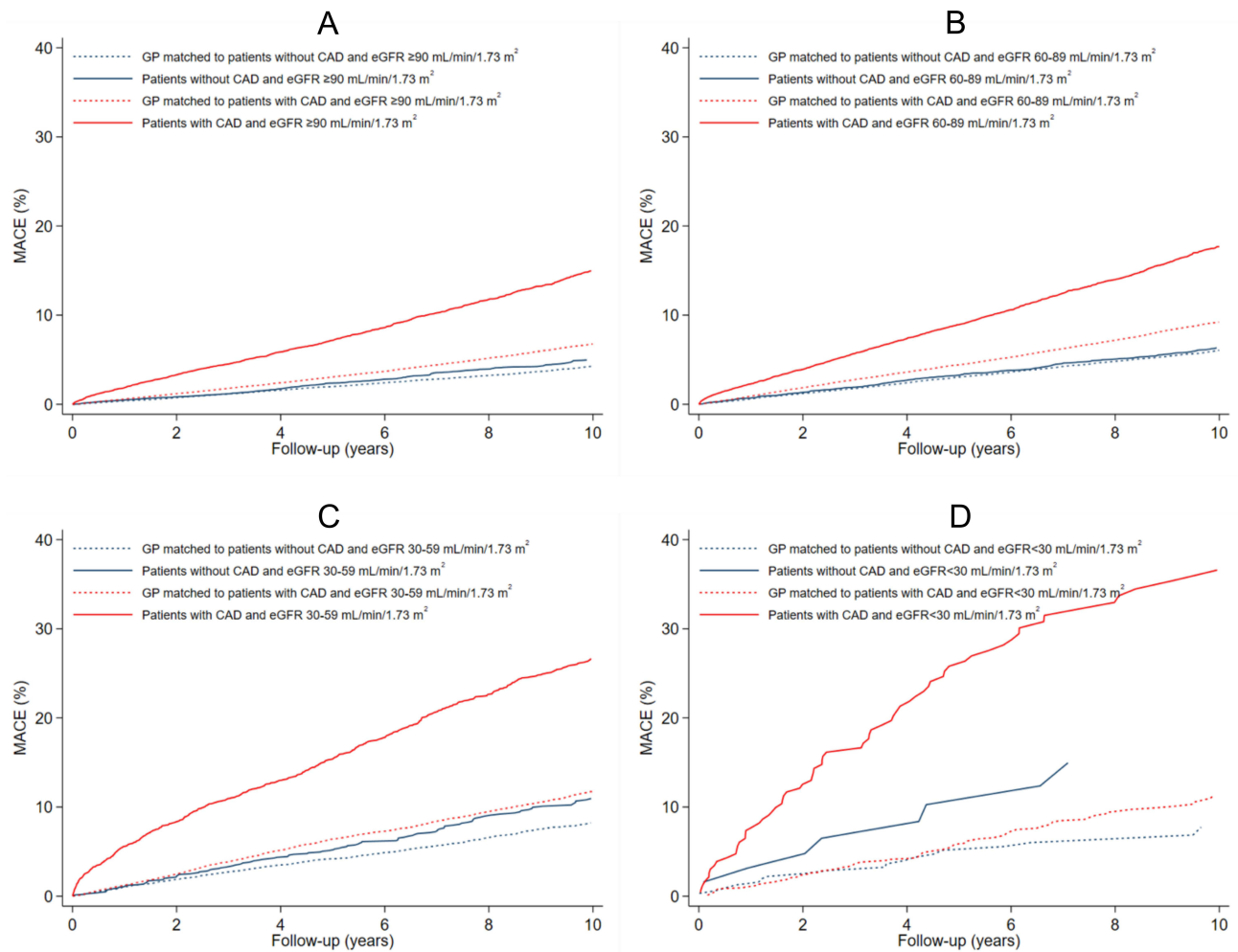


Figure 4 Cumulative incidence proportions for different kidney function strata. Patients with and without CAD on coronary angiography compared to their respective age- and sex-matched general population (GP). **(A)** Patients with eGFR ≥ 90 mL/min/1.73 m² with or without CAD and their corresponding matched GPs. **(B)** Patients with eGFR 60–89 mL/min/1.73 m² with or without CAD and their corresponding matched GPs. **(C)** Patients with eGFR 30–59 mL/min/1.73 m² with or without CAD and their corresponding matched GPs. **(D)** Patients with eGFR < 30 mL/min/1.73 m² with or without CAD and their corresponding matched GPs. **Abbreviations:** MACE, major adverse cardiovascular events; eGFR, estimated glomerular filtration rate; CAD, coronary artery disease.

increased risk of cardiovascular events in patients without evident CAD,^{31,32} which may explain why patients with eGFR < 30 mL/min/1.73 m² were at the highest risk of MACE irrespectively of CAD status in our dataset.

At baseline, the prevalence of hypertension differed from 62% in the eGFR ≥ 90 mL/min/1.73 m² stratum to 89% in the eGFR < 30 mL/min/1.73 m² stratum. Accordingly, patients with eGFR < 30 mL/min/1.73 m² tended to be more likely to receive antihypertensive treatment. Diabetes was also more common in patients with eGFR < 30 mL/min/1.73 m², confirming the known association between CKD and diabetes. The current ESC guidelines recommend that cardiovascular risk factors (hypertension, hyperlipidemia, and hyperglycemia) are medically treated to target values in patients with CCS and concomitant CKD,⁶ although blood pressure and hemoglobin A1c target values vary depending on severity of CKD and the presence of other cardiovascular risk factors and comorbidities.^{33,34} The guidelines are, however, not based on studies of patients with established CCS. Instead, they are based on studies either examining the risk of CKD or the risk of cardiovascular outcomes in patients with CKD.

Limitations

The study was conducted in a country with a tax-based health-care system, reducing selection bias caused by selective inclusion of specific hospitals, health insurance systems, or age groups. Follow-up and outcome ascertainment were standardized through high-quality registers, and patients were followed until death, emigration, or end of follow-up.

Information bias or differential outcome misclassification are therefore unlikely to have affected our results. The study population consisted of patients referred for elective CAG on suspicion of CAD. Thus, our results may not be directly applicable to patients in the general population, although additional comparison with a matched general population suggest that such a generalization is reasonable. We estimated eGFR based on a single value at the time of CAG, and classified patients in CKD groups accordingly. This could lead to misclassification over time due to deterioration of renal function (CKD progression), which we tried to minimize by excluding patients receiving dialysis and by terminating follow-up after a maximum of 10 years.

Conclusions

The absence of CAD is a strong negative predictor of major adverse cardiovascular events in patients with chronic kidney disease, while severely reduced kidney function is a strong positive predictor irrespectively of CAD status.

Abbreviations

BMI, body mass index; BSA, body surface area; CAD, coronary artery disease; CAG, coronary angiography; CCI, Charlson Comorbidity Index; CCS, chronic coronary syndrome; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DNPR, Danish National Patient Registry; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; HFREF, Heart failure with reduced ejection fraction; IRR, Incidence rate ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; PAD, peripheral artery disease; WDHR, Western Denmark Heart Registry.

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