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Coronary angiography in patients with kidney dysfunction and myocardial injury: A retrospective cohort study on management of myocardial injury in hospitalized patients with kidney disease

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ABSTRACT

Background: Although kidney insufficiency has been shown to be associated with increased risk of myocardial injury, benefit of coronary angiography (CAG) and revascularization remains uncertain, with implications on management strategies and outcomes. We aimed to compare rates of CAG and revascularization and subsequent risk of cardiovascular and kidney outcomes in hospitalized patients with myocardial injury and kidney dysfunction.

Methods: Retrospective cohort study encompassing hospitalized patients with myocardial injury i.e. elevated troponin I or T and an eGFR ≤60 ml/min/1.73 m^2 identified between 2011 and 2021 in Danish national registers. 30-day odds for CAG were computed across granular eGFR-categories based on multiple logistic regression. Standardized one-year risks of cardiovascular and kidney outcomes including mortality were determined based on hazards obtained in multiple Cox regression.

Results: A total of 52,798 patients with myocardial injury were identified. CAG was performed in 14.3 % (n = 7549). 30-day odds ratios for CAG were 0.64 [0.60–0.68], 0.38 [0.34–0.42], 0.18 [0.14–0.22], and 0.35 [0.30–0.40] in patients with eGFR 31–45 ml/min/1.73 m^2, eGFR 15–30 ml/min/1.73 m^2 for eGFR<15 ml/min/1.73 m^2 and chronic dialysis, respectively (eGFR 46-60 ml/min/1.73 m^2 as reference). Median follow-up was 4.1 years. One-year mortality risk differences associated with CAG and revascularization (no CAG as reference) were −7.8 [−7.0; −8.7] and −9.1 [−8.4; −9.9] for eGFR 46-60 ml/min/1.73 m^2; −7.0 [−5.7;-8–3] and −8.0 [−6.6; −9.5] for eGFR 31-45 ml/min/1.73 m^2; −5.4 [−3.0; −7.2] and −5.2 [−2.2; −8.3] for eGFR 15-30 ml/min/1.73 m^2; −8.8 [−3.1; −13.7] and −5.4 [3.1; −13.4] for eGFR<15 ml/min/1.73 m^2; and −4.9 [−0.1; −9.7] and −4.2 [1.5; −9.2] for chronic dialysis, respectively.

Conclusion: Probability of CAG following myocardial injury declined with progressive kidney dysfunction. Overall, CAG was associated with lower mortality irrespective of kidney function and subsequent revascularization.

1. Introduction

Chronic kidney disease (CKD) affects >10 % of the general population, and global prevalence is growing [1–3], with consequent increasing recognition of CKD as a global health issue with substantial implications on patient health and outcomes. CKD is associated with increased progressive increase in risk of cardiovascular morbidity and mortality [4–6], with risk of cardiovascular death 10–20 times increased in patients on chronic dialysis compared with general populations [7]. Despite improvements in treatment and outcomes of cardiovascular diseases in general populations, prognosis in advanced CKD remains poor [8].

Management of cardiovascular disease in patients with advanced CKD is challenging. Symptoms are often understated and indefinite [9], and use of cardiac troponins for identification of myocardial injury is subject to interpretation [10,11]. Kidney insufficiency is associated with elevated troponin levels irrespective of myocardial injury [11,12], with implications

Abbreviations: CABG, coronary artery bypass grafting; CAG, coronary angiography; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; HR, hazard ratio; OR, odds ratio; PCI, percutaneous coronary intervention; SD, standard deviation.

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for provision of coronary angiography (CAG) and subsequent revascularization among patients with CKD [9,13–15]. Measurement of cardiac troponins is common in hospitalized patients with indeterminate symptoms to evaluate for myocardial injury [16]. Elevated levels denote myocardial injury [17,18], with associated increased risk of mortality [19], Guidelines remain ambiguous, with data pertaining to management and outcomes of myocardial injury in hospitalized patients beyond acute coronary syndrome largely unaddressed.

Myocardial injury without acute coronary syndrome remains common in hospitalized patients, with prevalence rates reported to be 20–40 % [20,21]. Management remains subject to interpretation, with further cardiac investigations reserved for selected patients only. The present study aims to evaluate the impact of kidney function on provision of CAG and revascularization in hospitalized patients with myocardial injury and to compare associated effects on cardiovascular and kidney outcomes including mortality.

2. Methods

2.1. Study data

A personal and unique civil registration number is afforded all Danish citizens at birth or immigration, enabling cross-referencing of data from a multitude of national administrative health care registers on an individual-level basis. The Danish National Patient Register holds information on all hospital contacts including outpatient and inpatient diagnoses, and in-hospital procedures including surgeries [22,23]. The Register of Pharmaceutical Sales contains individual-level data on all prescription medication sold in Danish pharmacies [24].The Clinical Laboratory Information Registry contains laboratory results from 4 of 5 administrative regions in Denmark covering >75 % of the population. The Danish Civil Registration System records vital status and date of death. An overview of all employed administrations codes is provided in the supplemental materials (supplemental Table s1).

2.2. Patient characteristics

All comorbidities were identified based on administrative diagnosis and procedure codes within five years prior to inclusion. Diabetes and hypertension were identified based on claimed prescriptions for antidiabetic medication (ATC A10) and antihypertensive medication (ATC C02). Baseline medication was identified based on prescriptions dispensed within 180 days prior to myocardial injury. Chronic dialysis was identified based on any procedure code denoting dialysis <90 days prior to myocardial injury. Kidney function was computed based on a validated algorithm entailing identification of the last plasma creatinine <2 years of the myocardial injury with calculation of estimated glomerular filtration rate (eGFR) based on the CKD Epidemiology Collaboration equation [25].

2.3. Study population

All hospitalized patients with an eGFR $\leq$60 ml/min/1.73 m^2 and myocardial injury were identified between January 1st 2011 and January 31st 2022. Myocardial injury was defined by troponin I or T elevation greater than the assay-specific threshold, with standardization of reported peak troponin levels based on the reported 99th percentile. Patients <18 years, patients diagnosed with myocardial infarction (ICD-10 DI21) <30 days before inclusion, and patients emigrating or dying <30 days following inclusion were excluded.

2.4. Study design

Based on a retrospective cohort design, rates of CAG within 30 days of myocardial injury were evaluated across granular eGFR in all 30-day survivors, with subsequent reporting of revascularization rates as defined by percutaneous coronary intervention (PCI) and coronary artery bypass-grafting (CABG) within 7 days of CAG.

Associated risks of cardiovascular and kidney outcomes including death were compared based on CAG referral and revascularization in survival analyses with follow-up from 30 days following myocardial injury (to enable classification of management based on referral for CAG) until emigration, death, or end of follow-up (January 31st 2022).

Study outcomes were defined as; (i) all-cause mortality; (ii) hospitalization with heart failure; (iii) kidney failure (eGFR decrease $\geq$50 %, eGFR <15 ml/min/1.73 m^2, or chronic dialysis); and (iv) myocardial re-infarction i.e. readmission with de novo acute myocardial infarction.

2.5. Statistical analyses

Patient characteristics were summarized as means with standard deviations or medians with interquartile range (IQR) for continuous variables, and as percentages for categorical variables. Kidney function was evaluated based on predefined strata of eGFR (60–46 ml/min/1.73 m^2; 45–31 ml/min/1.73 m^2; 30–15 ml/min/1.73 m^2; <15 ml/min/1.73 m^2; and chronic dialysis).

Odds ratios for CAG < 30 days following myocardial injury were computed across the strata of kidney function based on multiple logistic regression adjusted for age (categorized: $\leq$60 years; 61–80: >80 years), gender, comorbidity (diabetes, ischemic heart disease, prior heart failure, and stroke), concomitant medication (insulin and diuretics), and calendar time (categorized: 2011–2014; 2015–2018; 2019–2022) and standardized peak troponin (categorized: $\leq$5× elevated; 6-100× elevated; >100× elevated), with subsequent estimations of 30-day probability i.e. relative risk of CAG based on the computed odds ratios. Furthermore, log-odds for PCI and CABG $\leq$7 days following CAG were calculated in multinomial logistic regression models stratified on kidney function and adjusted for age (categorized: $\leq$60 years; 61–80: >80 years), gender, comorbidity (diabetes, ischemic heart disease, prior heart failure, and stroke), concomitant medication (insulin and diuretics), and calendar time (categorized: 2011–2014; 2015–2018; 2019–2022) and standardized peak troponin (categorized: $\leq$5× elevated; 6-100× elevated; >100× elevated), with subsequent calculation of probabilities of PCI and CABG $\leq$7 days based on the computed log-odds.

Median follow up was computed based on Kaplan-Meier estimates for censored times. Rates of subsequent death, hospitalization with heart failure, kidney failure (eGFR-decrease $\geq$50 %, eGFR <15 ml/min/1.73 m^2, or dialysis), and myocardial infarction were compared across strata of kidney function. Hazard ratios were calculated stratified on CAG and revascularization in multiple Cox regression models adjusted for age, gender, and comorbidity (diabetes, ischemic heart disease, prior heart failure, stroke, vascular disease), stratified on calendar time and standardized peak troponin. Based on results, one-year risks of outcomes were computed standardized to the distribution of covariates in the sample with bootstrapping of 95 % confidence intervals [26,27]. Likelihood of CAG and revascularization and subsequent outcomes were further tested in analyses comparing odds ratios and risk across gender, age-strata (age $\leq$ 60 years, 61–80, >80 years), period (2011–2014, 2015–2018, 2019–2022) and troponin-strata ($\leq$5× elevated, 6-100× elevated, >100× elevated). To address possible misclassification bias due to spurious measurement of troponin, principal analyses were retested in sensitivity analysis in patients with troponin I or troponin T elevation >20 %.

Statistical significance was set to $p < 0.05$. All statistical tests were 2-tailed. All analyses were performed using SAS statistical software [version 9.4; SAS Institute, Cary, NC, USA] and R [version 4.0.1; R Core Team (2019)].

2.6. Ethics

In Denmark, administrative health care data is considered public domain, and retrospective register-based studies do not require ethical approval. Use of study data was approved through the Danish Data Protection Agency (ref. P-2019-191). All pseudo-anonymized data were linked, stored, and analyzed securely within a research platform administered through Statistics Denmark. All code is shared openly for review and re-use under

Table 1
Baseline characteristics for patients with renal insufficiency stratified by kidney function.

Characteristics	eGFR (ml/min/1.73 m^2)				
	60–46	45–31	30–15	<15	Chronic dialysis
No. of patients	n = 25,898	n = 15,921	n = 7051	n = 1789	n = 2139
Women, n (%)	12,171 (47.0)	7972 (50.1)	3343 (47.4)	737 (41.2)	743 (34.7)
Age (years), median [IQR]	80 [73.6, 85.8]	82.2 [75.5, 87.8]	81.8 [74.3, 87.8]	76.3 [68.1, 83.7]	68.3 [57.4, 76.3]
Comorbidities					
Hypertension, n (%)	11,213 (43.3)	8007 (50.3)	3754 (53.2)	910 (50.9)	1063 (49.7)
Diabetes, n (%)	5661 (21.9)	4550 (28.6)	2450 (34.7)	670 (37.5)	761 (35.6)
IHD, n (%)	5832 (22.5)	3915 (24.6)	1787 (25.3)	369 (20.6)	593 (27.7)
Heart failure, n (%)	3741 (14.4)	3487 (21.9)	1845 (26.2)	322 (18.0)	531 (24.8)
Prior stroke, n (%)	1400 (5.4)	941 (5.9)	385 (5.5)	84 (4.7)	118 (5.5)
Prior cancer, n (%)	5835 (22.5)	3512 (22.1)	1627 (23.1)	452 (25.3)	449 (21.0)
Prior tromboembolism, n (%)	121 (0.5)	89 (0.6)	45 (0.6)	14 (0.8)	37 (1.7)
COPD, n (%)	3261 (12.6)	2230 (14.0)	1019 (14.5)	213 (11.9)	252 (11.8)
Medication					
Insulin, n (%)	1430 (5.5)	1556 (9.8)	1181 (16.7)	349 (19.5)	571 (26.7)
Loop diuretics, n (%)	9525 (36.8)	6.062 (38.1)	2311 (32.8)	426 (23.8)	170 (7.9)
Any anticoagulation, n (%)	15,465 (59.5)	10,327 (64.3)	4.725 (65.2)	1210 (49.8)	521 (48.9)
RAASi, n (%)	14,341 (55.4)	9194 (57.7)	3988 (56.6)	883 (49.4)	796 (37.2)
Lipid-lowering therapy, n (%)	11,692 (45.1)	7536 (47.3)	3414 (48.4)	832 (46.5)	835 (39.0)
Troponin value					
Ratio, median [IQR]	3.2 [1.7, 12.4]	3.4 [1.9, 10.2]	4.3 [2.2, 11.6]	6.1 [2.9, 16.7]	5.2 [2.5, 14.5]
TnT (n = 35,158), mean (SD)	197 (1140)	186 (814)	204 (739)	342 (2108)	262 (901)
TnI (n = 17,640), mean (SD)	1186 (5127)	1185 (5074)	1276 (5805)	1923 (9894)	1220 (5718)

eGFR: estimated glomerular filtration rate, IHD: ischemic heart disease, COPD: chronic, obstructive pulmonary disease, RAASi: renin-angiotensin-aldosterone system inhibitor, TnT: troponin T, TnI: Troponin I.

the Statistics Denmark license. As detailed patient data holds potential for re-identification, full data sharing is not possible.

3. Results

A total of 52,798 eligible patients were identified between January 1st 2011 and January 31st, 2022. Patients were predominantly male (52.7 %, n = 27,832), median age was 80.5 years (IQR 73.5–86.5), and median eGFR was 45 ml/min/1.73 m^2 (IQR 33–53) with a total of 2139 (4.1 %) of patients on chronic dialysis. Baseline characteristics according to renal function are shown in Table 1. A flow chart depicting study design is provided in Fig. 1.

CAG was performed in 14.3 % (n = 7549) of patients within 30 days of myocardial injury. PCI and CABG were performed in 49.4 % (n = 3732) and 15.0 % (n = 1129) of patients undergoing CAG, respectively. An overview of management strategies stratified on renal function is shown in

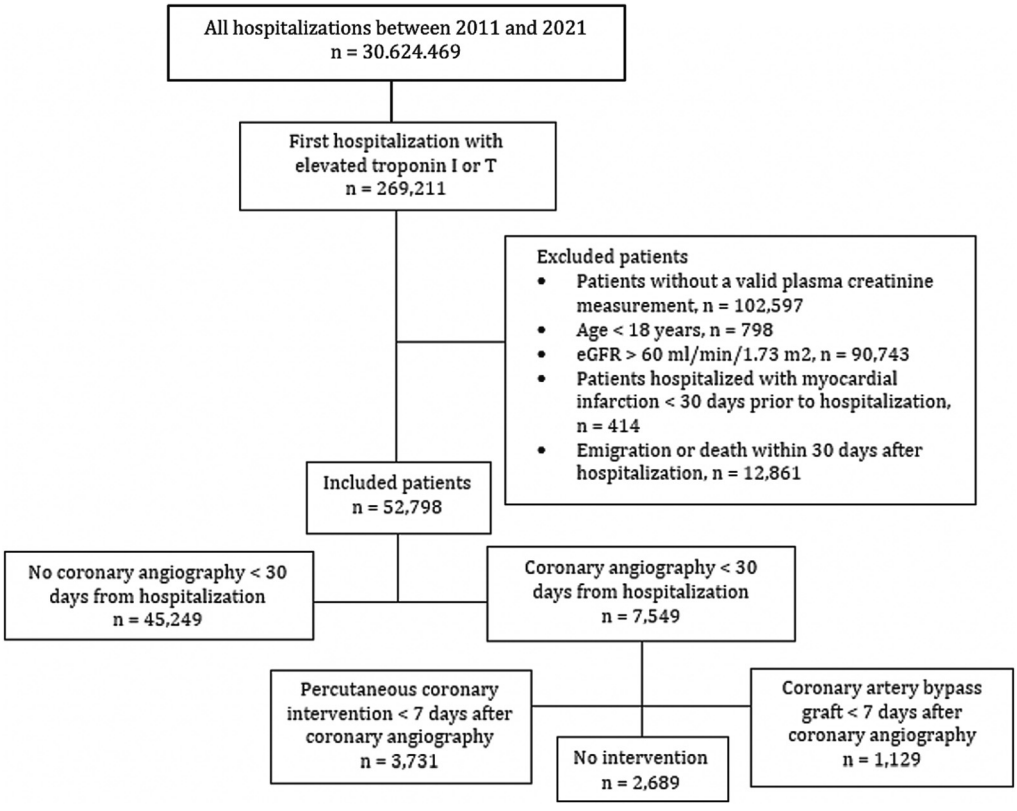

Fig. 1. Flow diagram of study population. eGFR: estimated glomerular filtration rate.

Table 2
a-d. Standardized one-year risks and hazard ratios of outcomes.

a. Standardized one-year risks and hazard ratios of mortality

eGFR (ml/min/1.73 m^2)	Intervention	n	One-year risk % (95 % CI)	HR (95 % CI)	*P*-value
eGFR 46–60	None	21,246	20.6 % (20.2;21.1)	REF	
	Coronary angiography	4652	12.9 % (12.0;13.4)	0.59 (0.56;0.63)	<0.001
	Revascularization	2413	11.6 % (10.7;12.2)	0.66 (0.61;0.71)	<0.001
eGFR 31–45	None	13,987	24.5 % (24.0;25.2)	REF	
	Coronary angiography	1934	17.5 % (16.4;18.8)	0.67 (0.63;0.73)	<0.001
	Revascularization	943	16.6 % (15.2;17.9)	0.64 (0.57;0.71)	<0.001
eGFR 15–30	None	6452	29.2 % (28.4;30.1)	REF	
	Coronary angiography	599	24.1 % (21.7;26.0)	0.78 (0.70;0.88)	<0.001
	Revascularization	316	24.2 % (21.2;26.7)	0.80 (0.69;0.92)	0.002
eGFR <15	None	1680	33.4 % (31.9;35.2)	REF	
	Coronary angiography	109	24.5 % (20.5;30.1)	0.67 (0.51;0.73)	0.003
	Revascularization	58	27.3 % (20.2;37.1)	0.78 (0.55;1.10)	0.159
Chronic dialysis	None	1884	34.6 % (33.0;36.2)	REF	
	Coronary angiography	255	29.8 % (25.1;36.2)	0.84 (0.69;1.01)	0.068
	Revascularization	131	30.5 % (25.0;35.7)	0.83 (0.64;1.07)	0.147

b. Standardized one-year risks and hazard ratios of heart failure

eGFR (ml/min/1.73 m^2)	Intervention	n	One-year risk % (95 % CI)	HR (95 % CI)	P-value
eGFR 46–60	None	21,246	25.2 % (24.7;25.6)	REF	
	Coronary angiography	4652	20.1 % (19.2;21.2)	0.77 (0.73;0.80)	<0.001
	Revascularization	2413	17.6 % (16.7;18.4)	0.67 (0.62;0.72)	<0.001
eGFR 31–45	None	13,987	29.1 % (28.5;29.9)	REF	
	Coronary angiography	1934	24.6 % (23.1;25.7)	0.81 (0.76;0.86)	<0.001
	Revascularization	943	22.2 % (20.8;24.3)	0.72 (0.66;0.79)	<0.001
eGFR 15–30	None	6452	33.2 % (32.2;34.2)	REF	
	Coronary angiography	599	31.9 % (28.2;33.0)	0.91 (0.82;1.01)	0.069
	Revascularization	316	30.4 % (27.8;33.9)	0.88 (0.76;1.01)	0.069
eGFR <15	None	1680	37.1 % (35.2;39.3)	REF	
	Coronary angiography	109	28.1 % (22.9;34.7)	0.69 (0.53;0.89)	0.004
	Revascularization	58	32.4 % (23.5;39.6)	0.82 (0.59;1.14)	0.243
Chronic dialysis	None	1884	36.8 % (35.2;39.2)	REF	
	Coronary angiography	255	37.1 % (34.1;41.7)	1.00 (0.85;1.18)	0.993
	Revascularization	131	36.9 % (32.9;44.3)	0.97 (0.77;1.23)	0.799

c. Standardized one-year risks and hazard ratios of kidney outcome

eGFR (ml/min/1.73 m^2)	Intervention	n	One-year risk % (95 % CI)	HR (95 % CI)	P-value
eGFR 46–60	None	21,246	24.8 % (24.3;25.3)	REF	
	Coronary angiography	4652	17.4 % (16.7;18.6)	0.67 (0.64;0.71)	<0.001
	Revascularization	2413	15.7 % (14.4;16.8)	0.59 (0.55;0.64)	<0.001
eGFR 31–45	None	13,987	28.6 % (27.9;29.3)	REF	
	Coronary angiography	1934	22.6 % (21.2;24.0)	0.75 (0.70;0.80)	<0.001
	Revascularization	943	21.2 % (19.5;22.9)	0.69 (0.62;0.76)	<0.001
eGFR 15–30	None	6452	33.5 % (32.6;34.4)	REF	
	Coronary angiography	599	30.8 % (28.1;33.8)	0.89 (0.80;0.99)	0.034
	Revascularization	316	31.2 % (28.1;35.0)	0.92 (0.80;1.05)	0.220
eGFR <15	None	1680	40.0 % (32.6;34.4)	REF	
	Coronary angiography	109	36.5 % (30.8;43.4)	0.85 (0.98;1.06)	0.141
	Revascularization	58	39.1 % (32.6;47.4)	0.91 (0.68;1.23)	0.536

d. Standardized one-year risks and hazard ratios of re-admission with myocardial infarction

eGFR (ml/min/1.73 m^2)	Intervention	n	One-year risk % (95 % CI)	HR (95 % CI)	P-value
eGFR 46–60	None	21,246	22.3 % (21.7;22.7)	Reference	
	Coronary angiography	4652	18.4 % (17.5;18.9)	0.80 (0.76;0.84)	<0.001
	Revascularization	2413	19.2 % (17.9;20.4)	0.77 (0.72;0.83)	<0.001
eGFR 31–45	None	13,987	26.3 % (25.6;26.9)	Reference	
	Coronary angiography	1934	22.0 % (26.1;31.1)	0.68 (0.63;0.74)	<0.001
	Revascularization	943	22.7 % (20.9;25.0)	0.59 (0.52;0.66)	<0.001
eGFR 15–30	None	6452	31.2 % (30.4;32.1)	Reference	
	Coronary angiography	599	29.0 % (26.1;31.1)	0.90 (0.81;1.00)	0.056
	Revascularization	316	29.5 % (25.7;33.2)	0.93 (0.81;1.07)	0.316
eGFR <15	None	1680	35.0 % (33.3;37.3)	Reference	
	Coronary angiography	109	30.5 % (24.9;37.0)	0.81 (0.63;1.04)	0.102
	Revascularization	58	35.8 % (29.1; 43.1)	0.92 (0.66;1.29)	0.630
Chronic dialysis	None	1884	36.3 % (34.5;38.3)	Reference	
	Coronary angiography	255	35.3 % (30.5;39.8)	0.96 (0.80;1.14)	0.608
	Revascularization	131	35.8 % (29.1;43.1)	0.99 (0.78;1.26)	0.957

eGFR: estimated glomerular filtration rate, HR: hazard ratio.

Supplemental Fig. s1. Cumulative incidence of CAG within 3 months is shown in Supplemental Fig. s2. Probability of CAG was associated with kidney dysfunction (p for trend <0.001). Odds ratios for 30-day likelihood of CAG were 0.64 (95 % IC 0.60–0.68) for eGFR 31–45 ml/min/1.73 m^2, 0.38 (95 % CI 0.34–0.42) for eGFR 15–30 ml/min/1.73 m2, 0.18 (95 % CI 0.14–0.22) for eGFR <15 ml/min/1.73m^2 and 0.35 (95 % CI 0.30–0.40) for chronic dialysis, using eGFR 46–60 ml/min/1.73m^2 as reference. Odds ratios for 30-day likelihood of CAG in subgroups are shown in supplemental Tables s2a-d. Probabilities of CAG were 39.1 % for eGFR 31–45 ml/min/1.73m^2, 27.4 % for eGFR 15–30 ml/min/1.73m^2, 14.9 % for eGFR <15 ml/min/1.73m^2 and 25.7 % for chronic dialysis, using eGFR 46–60 ml/min/1.73m^2 as reference.

Odds ratios for revascularization in patients undergoing CAG were 0.90 (95 % CI 0.80–1.02) for eGFR 31–45 ml/min/1.74m^2, 1.03 (95 % CI 0.85–1.24) for eGFR 15–30 ml/min/1.73 m^2, 0.68 (95 % CI 0.45–1.02) for eGFR <15 ml/min/1.73m^2 and 0.82 (95 % CI 0.62–1.09) for chronic dialysis, using eGFR 46–60 ml/min/1.73m^2 as reference. Probabilities of revascularization were 39.1 % and 47.5 % for eGFR 31–45 ml/min/1.73m^2, 30.2 % and 50.7 % for eGFR 15–30 ml/min/1.73m^2, 17.3 % and 40.3 % for eGFR <15 ml/min/1.73m^2, and 30.8 % and 45.1 % for chronic dialysis (eGFR 46–60 ml/min/1.73m^2 as reference), in all patients and patients undergoing CAG, respectively, with kidney dysfunction associated with lower likelihood of revascularization in both cohorts (p for trend in all patients: <0.001, and in patients undergoing CAG alone: 0.06). Probabilities of CAG and revascularization stratified by intervention across granular eGFR categories are shown in the Supplemental Fig. s3a-b.

Median follow-up was 4.1 years (95 % CI 1.9–6.0). Crude one-year mortality was 15 % (n = 7900). Kaplan-Meier curves stratified on kidney function and CAG are provided in Supplemental Fig. s4a-c. Standardized one-year risks including adjusted hazards from the multiple Cox regression models for all defined outcomes following CAG and revascularization are shown in Table 2a-d. Associated benefit of CAG and revascularization on standardized one-year mortality risk stratified by renal function are illustrated in Fig. 2-b. Hazard ratios and standardized one-year risks of all outcomes in subgroups are provided in Supplemental Tables s3–6.

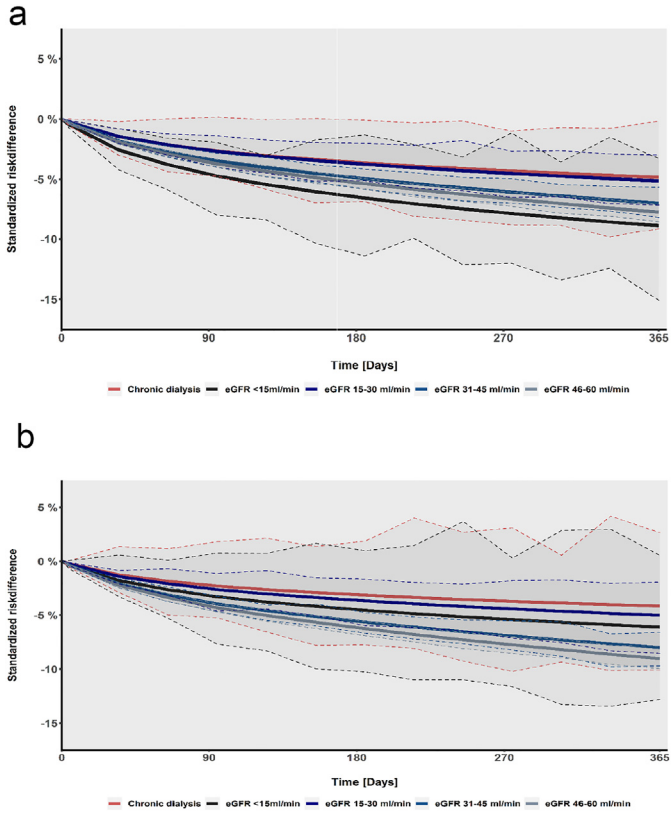

Fig. 2. a-b. One-year standardized mortality risk difference associated with CAG and revascularization compared with no intervention stratified on kidney function.

Results remained principally unchanged in sensitivity analysis with inclusion limited to patients with >20 % increase in troponin levels. Odds ratios of CAG and revascularization in patients with >20 % peak troponin elevation stratified on renal function are provided in Supplemental Table s7 and Fig. s5a-b. Hazard ratios and standardized one-year risks of outcomes in patients with >20 % troponin elevation are provided in Supplemental Tables s8a-d.

4. Discussion

Based on results from a nationwide retrospective cohort study encompassing >50.000 patients with eGFR ≤60 ml/min/1.73m^2 and myocardial injury, probability of CAG and subsequent revascularization declined with progressive kidney dysfunction. Overall >14 % of patients underwent CAG within 30 days of myocardial injury, with revascularization performed in >60 % of patients referred for CAG. Comparably, risks of adverse outcomes were lower in patients referred for CAG, with CAG associated with 5–10 % decrease in one-year risks of adverse outcomes, irrespective of subsequent revascularization across all strata of eGFR.

Referral rates for evaluation of cardiac ischemia in non-acute coronary syndrome remain underreported. Based on >12.000 patients in the Veteran Affairs database in the United States, referral rates are reported to be approximately 20 % [16]. Referral rate for CAG in our population was 14.3 % within 30 days (15.2 % within 90 days). Patients with kidney disease are however less likely to be referred for CAG following myocardial infarction, with associated probability of CAG reportedly 50 % lower in Medicare patients in the United States with kidney insufficiency [13,27]. Similar results have also been reported in general populations investigating utility of cardiac troponins in management of myocardial infarction in Scotland, with rates of CAG lowest in patients with eGFR <30 ml/min/1.73m^2 [14]. CAG utilization is however plausibly biased by patient-specific factors including comorbidity. As such, comparisons of referral rates between patients with and without kidney disease remain uncertain given the substantial increased burden of comorbidity prevalent in patients with kidney insufficiency.

Overall revascularization rates are increasing, however disparities persist for patients with kidney disease [28], with lower rates of revascularization reported in patients with CKD [3,14,28]. Outcomes following revascularization in patients with kidney disease are comparably worse, with notable increased risk of periprocedural stroke and postprocedural hemorrhage [29,30], poorer outcomes in patients with mild kidney dysfunction [31,32], poorer rates of stent delivery, increased occurrence of post-procedural residual stenosis [33,34], and suboptimal implementation of preventive therapies including statins, beta-blockers, and antiplatelet therapies [35–37]. Prior trials evaluating revascularization including the COURAGE, FAME2, and BARI2D trials have largely excluded patients with kidney disease, and results from the ISCHEMIA-CKD trial evaluating benefit of invasive management in patients with stable ischemia and CKD disappointed [38], with invasive management demonstrating no benefit (or harm) on a variety of cardiovascular and kidney outcomes. As such, although methodological limitations apply with regard to the generalizability of the ISCHEMIA-CKD trial, study results were overall consistent, benefit of invasive management compared with drug therapy alone in patients with CKD beyond overt myocardial infarction remains uncertain [15,38,39].

Our results demonstrate a 5–10 % decrease in one-year risk of adverse outcomes in patients referred for invasive management with CAG and/or revascularization. Of note, although the associated mortality risk reduction remained unchanged irrespective of kidney dysfunction, associated risk reduction on myocardial re-infarction was attenuated in patients with advanced CKD in alignment with results from the ISCHEMIA-CKD trial. Nonetheless, differences are to be expected when comparing observational and randomized data on CAG outcomes; particularly considering the plausible inherent differences between non-selected patients with myocardial injury and trial participants with reported low burden of symptoms (>50 % of trial

participants in ISCHEMIA-CKD were asymptomatic). Similar results have been reported previously in other observational studies, with CAG associated with a >10 % reduction in one-year risk of death in Medicare patients with CKD and myocardial infarction, benefit on cardiovascular outcomes in a Scottish population with CKD, and mortality benefit in a cohort of Swedish patients with myocardial infarction [13,14,40]. Results from observational studies are however subject to unmeasured confounding and inherent biases, and causality remains unlikely, particularly in light of the lack of benefit of invasive management in the ISCHEMIA-CKD trial. Management of myocardial injury in advanced CKD remains uncertain and plausibly prone to selection biases leading to spurious association of benefit. Overall, our results demonstrate comparably lower risk of death, and in part cardiovascular and renal outcomes, associated with invasive management of myocardial injury, with associated risk benefit comparable across strata and subgroups with differences attributable to expected variance. Conclusions are however uncertain, with plausible substantial positive and negative indication biases associated with selection of patients to be referred for coronary angiography as demonstrated by the greatest apparent benefit demonstrable for patients referred for CAG irrespective of subsequent revascularization.

Our study presents several strengths and limitations. The overall size of the cohort and the employment of excellently validated data from a multitude of nationwide registers lends strength to the observed results. Furthermore, our results address the coexistent likelihoods of CAG and revascularization, with emphasis on the overall impact of management choices on associated outcomes. Additionally, results remained robust across diverging sensitivity and subgroup analysis. Due to a nationwide availability of data, the structure of public health care in Denmark and the relative homogeneity of the general Danish populations, the impact of selection bias due to geographical demographic variation is minimized. Of note, the study attempts to evaluate the overall impact of myocardial injury in a heterogenous non-selected cohort with emphasis on markers of myocardial injury as opposed to diagnoses codes. Multiple important clinical parameters are however unaddressed including symptomatology during hospitalization, CAG findings and electrocardiogram-changes, and unmeasured residual confounding likely remains. Furthermore, both the notable apparent benefit of CAG irrespective of subsequent revascularization plausibly reflects inevitable unaddressed bias, and the overall inherent observational nature of the study precludes casual interpretation, whereby conclusions remain strictly exploratory. As such, interpretation of associated benefit should remain cautious. Moreover, the plasma creatinine measurement used to determine kidney function at inclusion may not reflect steady-state, and although the algorithm employed has been validated previously [23], the impact in this study remains unaddressed. Although information on plasma creatinine in >80 % of the Danish general population is available in Danish registers, accurate identification eGFR remains uncertain and subject to both general and specific limitations related to methodology. As such, although the algorithm for identification of baseline creatinine in our study has been validated with an intraclass correlation coefficient of 0.88 (95 % CI 0.85–0.91), variation remains perceptible between methods [41,42]. Finally, kidney insufficiency could be associated with greater likelihood of hospital admission due to troponin-elevation, leading to susceptibility of results to ascertainment bias; the effect hereof remains unaddressed.

5. Conclusions

Although invasive management as defined by CAG and revascularization declined with progressive kidney dysfunction, patients referred for CAG observed a comparable 5–10 % reduction in one-year risks of cardiovascular and kidney outcomes including death, irrespective of kidney function and subsequent revascularization.

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CRediT authorship contribution statement

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Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carrev.2024.01.001.

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