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Outcomes with revascularization and medical therapy in patients with coronary disease and chronic kidney disease: A meta-analysis

Alexandre Leszek [a,1], Lauriane Poli [a,1], Stephanie Zbinden [a], Lucas C. Godoy [b,c], Jean-Luc Reny [a], Michael E. Farkouh [b], David M. Charytan [d], Thomas A. Mavrakanas [e,f,*]

[a] Department of Medicine, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland
[b] Peter Munk Cardiac Centre, And Heart and Stroke Richard Lewar Centre, University of Toronto, Toronto, ON, Canada
[c] Instituto do Coracao (InCor), Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, Brazil
[d] Department of Medicine, New York University Langone Medical Center & New York University Grossman School of Medicine, New York, NY, United States
[e] Department of Medicine, McGill University Health Centre, Montreal, QC, Canada
[f] Research Institute of the McGill University Health Centre, Montreal, QC, Canada

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ABSTRACT

Background and aims: Chronic kidney disease (CKD) confers a high risk for poor cardiovascular outcomes. We conducted a systematic review and meta-analysis to estimate the effects of revascularization as the initial management strategy compared with medical therapy among patients with CKD and coronary artery disease.
Methods: A Medline/PubMed literature research was conducted to identify randomized studies comparing early coronary revascularization with optimal medical therapy or medical therapy alone in patients with CKD (estimated glomerular filtration rate <60 mL/min/1.73 m^2 or maintenance dialysis). The primary outcome was myocardial infarction. The secondary outcomes were all-cause mortality or progression to kidney failure. The risk ratio (RR) was estimated using a random-effects model.
Results: Eleven randomized trials were included (3422 patients). Revascularization was associated with lower incidence of myocardial infarction compared with medical therapy in patients with CKD: RR 0.71 (95% confidence interval [CI] 0.54–0.94; p=0.02). This result was mainly driven from a significantly lower incidence of myocardial infarction with early revascularization among patients with stable coronary artery disease: RR 0.59; 95% CI 0.37–0.93. A similar incidence of all-cause mortality was observed with both treatment strategies: RR 0.88 (95% CI 0.72–1.08; p=0.22). A trend towards lower incidence of all-cause mortality was observed with revascularization in the subgroup of patients presenting with NSTE-ACS: RR 0.73 (95% CI 0.51–1.04; p=0.08) but not among patients with stable coronary disease. There was no difference in progression to kidney failure between the two strategies.
Conclusions: Coronary revascularization may be superior to medical therapy among patients with CKD and coronary disease.

1. Introduction

Chronic kidney disease (CKD) is known to confer a high risk for poor cardiovascular outcomes or death [1]. This risk increases with worsening estimated glomerular filtration rate (eGFR) or higher albuminuria [2]. Despite this observation, patients with CKD are less likely than patients with preserved kidney function to undergo coronary revascularization or to receive recommended medical treatment after an acute coronary event [3]. For patients with CKD and stable coronary artery disease (CAD), whether revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) as an initial management strategy can improve cardiovascular outcomes is uncertain. Potential benefits from coronary revascularization have to be balanced against a higher risk of peri-procedural complications or contrast-associated acute kidney injury (AKI) [4,5]. In addition, most randomized controlled trials (RCTs) in CAD have excluded patients with CKD or included a very small percentage of these patients [6,7]. Therefore, there is a lack of evidence for the optimal management of

* Corresponding author. McGill University Health Centre,1650 Cedar avenue, L04.520, Montreal, QC, H3G 1A4,Canada.
E-mail address: thomas.mavrakanas@mcgill.ca (T.A. Mavrakanas).
[1] These authors equally contributed to this work.

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CAD in this population.

Two recent meta-analyses showed that early coronary revascularization was associated with lower all-cause mortality compared with medical therapy in patients with CKD and CAD [8,9]. However, either no data from RCTs or no data on other relevant clinical outcomes were reported. Therefore, we conducted a systematic review and meta-analysis of randomized and observational studies to estimate the effects of coronary revascularization compared with medical therapy alone among patients with CKD and CAD on the incidence of major adverse cardiovascular and renal events.

2. Materials and methods

The protocol for this meta-analysis was registered in PROSPERO (CRD42018109247). Results are reported using the PRISMA checklist. Ethics approval or informed consent was not required as this is a meta-analysis of published data.

2.1. Search strategy

A literature research was conducted in PubMed from January 1960 to November 2019, inclusive. The following search terms were used: "Coronary Artery Disease/therapy"(Mesh)) AND "Renal Insufficiency"(Mesh). An alternative search strategy, using the following terms was also used: ((((("Renal Insufficiency, Chronic"(Mesh)) OR chronic kidney disease)) AND (((((((("Myocardial Revascularization"(Mesh)) OR "Angiography"(Mesh)) OR "Percutaneous Coronary Intervention"(Mesh)) OR "Catheterization"(Mesh))) OR revascularization) OR coronary angiography) OR percutaneous coronary intervention) OR cardiac catheterization)). The search was limited to English language articles.

2.2. Eligibility

The following criteria were required for inclusion: 1) study population: adult patients with CAD, including stable coronary disease or presenting with acute coronary syndrome (ACS), and CKD, defined as an eGFR <60 mL/min/1.73 m^2 (CKD Epidemiology Collaboration Equation); 2) intervention: early coronary revascularization with PCI or CABG *versus* optimal medical therapy in patients with or without known coronary anatomy (patients could have been randomized to either arm before or after a coronary angiogram, according to the study protocol); 3) study design: RCTs or observational cohort studies, published in the form of an article. Relevant published reviews and meta-analyses were also reviewed to potentially identify other eligible studies; 4) outcomes reported (at least one of these outcomes had to be reported): myocardial infarction (MI), all-cause mortality, CKD progression, AKI.

2.3. Study outcomes

The primary outcome was MI. The secondary outcomes were all-cause mortality, AKI, or CKD progression to end-stage renal disease (ESRD). Outcome definitions in each trial are shown in Table 1.

Table 1
Randomized controlled trials included in the meta-analysis: study characteristics and outcome definitions.

		Trial								
CHARACTERISTICS AND OUTCOMES		Manske et al. [15]	TIMI IIIB [14]	FRISC II [14]	TACTICS-TIMI 18 [14]	VINO [14]	ICTUS [14]	Italian Elderly ACS [17]	Farkouh et al. [13]	ISCHEMIA-CKD [16]
COUNTRY		USA	USA	Int.	Int.	CZE	NLD	ITA	CAN	Int.
PUBLICATION YEAR		1992	1994	2001	2001	2002	2005	2015	2019	2020
CKD DEFINITION		Transplant candidates	GFR[a]<60	GFR<60	GFR<60	GFR<60	GFR<60	GFR<45	GFR<60	GFR<30
SETTING		Stable CAD	NSTE- ACS	NSTE-ACS	NSTE-ACS	NSTE-ACS	NSTE-ACS	NSTE-ACS	Stable CAD	Stable CAD
DIABETES (%)		100%	8%	12%	28%	25%	14%	36%	100%	57%
RANDOMIZATION		Pre-angio	Pre-angio	Pre-angio	Pre-angio	Pre-angio	Pre-angio	Pre-angio	Post-angio	Pre-angio
PATIENTS PER ARM		13/13	221/228	211/218	216/213	12/17	58/59	38/70	719/339	388/389
MEDICAL THERAPY	ASA	X	X	X	X	X	X	ASA-clopidogrel	ASA-P_2Y_{12}	X
	Heparin		X	X	X	X	Enoxaparin	X		
	CCB	X	X	(X)	X			X		X
	β-blocker		X	X	X	X		X	X	X
	Statin			X	X		X	X	X	X
	ACEi			X					X	X
	Nitrates		X	(X)	X			X		X
REVASCULARIZATION DURING FOLLOW-UP		2/7	147/144	158/101	123/90	6/7	38/27	NA	140/117	195/76
MI DEFINITION		At 30 months	Non-fatal MI at 1-y					At 1-y	At 5-y	Non-fatal MI at 3-y
MORTALITY DEFINITION		All-cause at 30 months	All-cause mortality at 1-y					All-cause at 1y	All-cause at 5y	All-cause at 3y
JADAD SCORE		2	2	2	1	2	2	2	2[b]	3
RISK OF BIAS		Serious	Serious	Serious	Serious	Serious	Serious	Serious	Serious	Not serious

ACEi, angiotensin converting enzyme inhibitor; ACS, Acute Coronary Syndrome; Angio, angiography; ASA, aspirin; CAD, Coronary Artery Disease; CAN, Canada; CCB, calcium channel blocker; CKD, Chronic Kidney Disease; CZE, Czech Republic; FRISC, FRagmin and fast revascularization during InStability in Coronary artery disease; GFR, Glomerular Filtration Rate; ICTUS, Invasive versus Conservative Treatment in Unstable coronary Syndromes; Int, international; ISCHEMIA-CKD, International Study of Comparative Health Effectiveness with Medical and Invasive Approaches–Chronic Kidney Disease; ITA, Italy; MI, myocardial infarction; N, number; NA, not available; NLD, Netherlands; NSTE-ACS, Non-ST-segment Elevation Acute Coronary Syndrome; OMT, Optimal Medical Therapy; P_2Y_{12}, P_2Y_{12} receptor antagonist; Rev, revascularization; TACTICS, Thrombolysis And Counterpulsation To Improve Cardiogenic Shock survival; TIMI, Thrombolysis In Myocardial Infarction; USA, United States of America; VINO, Value of first day angiography/angioplasty In evolving Non-ST segment elevation myocardial infarction, an open multicenter randomized trial; y, year.

[a] GFR was calculated with the MDRD equation (in ml/min/1.73 m^2) except for the Italian Elderly ACS study (Cockcroft-Gault formula, in ml/min).

[b] The same Jadad score of 2 applied to all three randomized trials included in this meta-analysis.

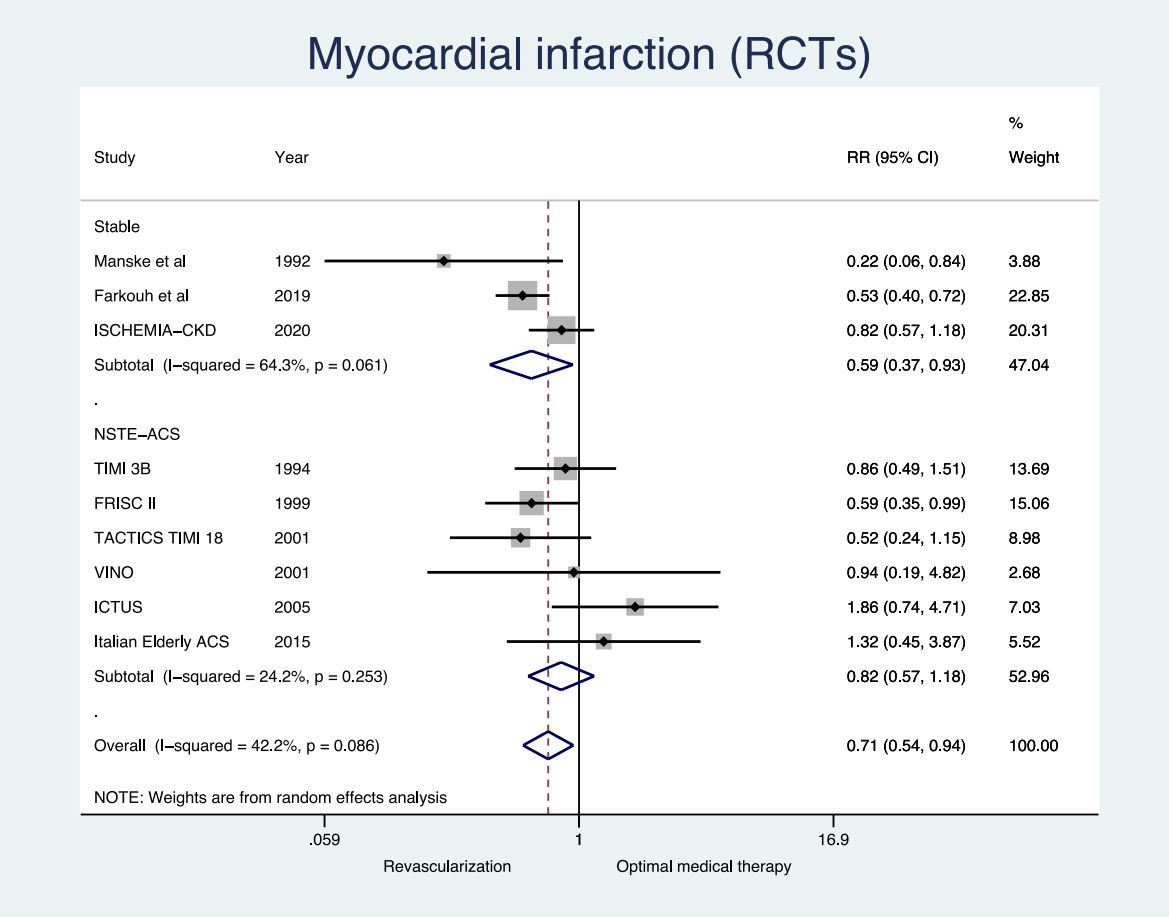

Fig. 1. Forest plot showing the incidence of myocardial infarction with revascularization as the initial management strategy compared with optimal medical therapy in patients with chronic kidney disease.
Results are stratified by the intervention setting: stable coronary disease *versus* NSTE-ACS (non-ST segment elevation acute coronary syndrome). Only results from the RCTs (randomized controlled trials) are presented in this Forest plot. Data are presented as risk ratios (RR) with 95% confidence intervals (95% CI). A lower incidence of myocardial infarction is identified with revascularization compared with optimal medical therapy in patients with stable coronary disease. A similar incidence of myocardial infarction is observed with revascularization compared with optimal medical therapy in patients with NSTE-ACS. A random effects model is used. ACS, Aacute Coronary Syndrome; FRISC, FRagmin and fast revascularization during InStability in Coronary artery disease; ICTUS, Invasive versus Conservative Treatment in Unstable coronary Syndromes; ISCHEMIA-CKD, International Study of Comparative Health Effectiveness with Medical and Invasive Approaches–Chronic Kidney Disease; TACTICS, Thrombolysis And Counterpulsation To Improve Cardiogenic Shock survival; TIMI, Thrombolysis In Myocardial Infarction; VINO, Value of first day angiography/angioplasty In evolving Non-ST segment elevation myocardial infarction, an open multicenter randomized trial.

2.4. Study selection and quality assessment

Two authors (LP & AL) independently reviewed the literature and selected the studies to be included in the meta-analysis. Any discrepancies were resolved by the senior author (TM). Data extraction was independently performed by two authors (LP & SZ) using digital spreadsheets. Data extracted included relevant baseline characteristics, eligibility criteria, and clinical outcomes.

To assess the quality of included studies, the Jadad score was used for RCTs and the Newcastle-Ottawa Scale for observational studies [10,11].

2.5. Statistical analysis

The relative risk (RR) was the principal summary measure. For the main analysis, only results from RCTs were included. A secondary analysis included data from observational studies or from RCTs and observational studies examined together.

The pooled RR for each outcome was estimated using a random-effects model. The I^2 index was used to assess heterogeneity. A funnel plot was used to assess publication bias. The total number of patients and events and the 95% confidence interval (CI) for the pooled RR were used to calculate the absolute effect estimate.

To explore heterogeneity, the following analyses were pre-specified [1]: type of study: RCTs or observational (cohort) studies [2]; setting: patients with non-ST segment elevation acute coronary syndromes (NSTE-ACS) or patients with stable CAD. In an attempt to explain the potential effect of CKD on clinical outcomes by treatment group, a post-hoc secondary analysis examined the effect of revascularization versus medical therapy in three different study populations: patients with advanced CKD (eGFR<30 mL/min/1.73 m^2 or maintenance dialysis), patients with CKD (eGFR<60 mL/min/1.73 m^2), and the whole study population of the included RCTs (with or without CKD). We also performed a meta-regression analysis for older versus newer studies (before and after 2002 or 2009) and studies with high (≥50%) and low (<50%) prevalence of diabetes mellitus among participants.

We used the GRADE approach to rate confidence in effect estimates [12].

Statistical analyses were performed in Stata (version 14 IC, College Station, TX). P values < 0.05 were considered statistically significant.

Table 2
Clinical outcomes by treatment strategy and certainty of evidence.

Outcome	Study group	Revascularization *vs.* OMT	Absolute effect estimate	Quality of evidence
Myocardial infarction	RCTs (all) – CKD	RR 0.71 (95% CI 0.54–0.94)	42 fewer per 1000 (95% CI 67 fewer – 9 fewer)	MODERATE Serious imprecision
	RCTs – stable CAD – CKD	RR 0.59 (95% CI 0.37–0.93)	74 fewer per 1000 (95% CI 113 fewer – 13 fewer)	LOW Serious inconsistency & imprecision
	RCTs – NSTE-ACS – CKD	RR 0.82 (95% CI 0.57–1.18)	21 fewer per 1000 (95% CI 49 fewer – 21 more)	MODERATE Serious imprecision
	Observational studies – CKD	RR 1.19 (95% CI 0.48–2.93)	6 more per 1000 (95% CI 15 fewer – 57 more)	VERY LOW Serious inconsistency & imprecision
All-cause mortality	RCTs (all) – CKD	RR 0.88 (95% CI 0.72–1.08)	19 fewer per 1000 (95% CI 44 fewer – 13 more)	MODERATE Serious imprecision
	RCTs – stable CAD – CKD	RR 0.96 (95% CI 0.77–1.18)	9 fewer per 1000 (95% CI 52 fewer – 41 more)	MODERATE Serious imprecision
	RCTs – NSTE-ACS – CKD	RR 0.73 (95% CI 0.51–1.04)	25 fewer per 1000 (95% CI 46 fewer – 4 more)	MODERATE Serious imprecision
	Observational studies – CKD	RR 0.59 (95% CI 0.49–0.71)	70 fewer per 1000 (95% CI 87 fewer – 50 fewer)	VERY LOW Large effect but very serious inconsistency
AKI	Observational studies – CKD	RR 1.02 (95% CI 0.74–1.41)	1 more per 1000 (95% CI 11 fewer – 17 more)	VERY LOW Very serious inconsistency
ESRD	Observational & RCT – CKD	RR 1.02 (95% CI 0.74–1.41)	1 more per 1000 (95% CI 18 fewer – 27 more)	VERY LOW Very serious inconsistency

OMT, optimal medical therapy; RCTs, randomized controlled trials; CKD, Chronic Kidney Disease; RR, relative risk; CI, confidence interval; CAD, Coronary Artery Disease; NSTE-ACS, Non-ST Segment Elevation Acute Coronary Syndrome; AKI, Acute Kidney Injury; ESRD, End-Stage Renal Disease.

3. Results

3.1. Study and patient characteristics

We identified and screened a total of 5643 references. Thirty-eight articles were retrieved for full-text review. Seven articles were identified from the references of these studies. After full text review, we excluded 19 studies: two meta-analyses, one trial that was a subgroup analysis of a larger study, one article that did not study the exposure of interest, seven studies that did not report the outcome per group of intervention, six studies that did not report the number of events per group of intervention and two studies that did not report the outcomes of interest in patients with CKD. Our meta-analysis included 26 published articles (Supplemental Fig. 1). One study was a patient level meta-analysis including individuals with diabetes and CKD from three RCTs (COURAGE, BARI 2D, FREEDOM); this study presents data as a single study and was treated as one study in this meta-analysis [13]. A second study was a meta-analysis of unpublished data from the CKD subgroup of five RCTs (TIMI IIIB, FRISC II, TACTICS TIMI 18, VINO, ICTUS); the principal investigator of this study provided relevant study-level data using a standardized digital spreadsheet [14]. We also included two RCTs in patients with CKD [15,16] and one RCT that provided the clinical outcomes in the CKD subgroup [17]. In addition, we included 21 observational studies for our secondary analyses [4,18–37].

Baseline characteristics of selected RCTs are shown in Table 1 and Supplemental Table 1. CKD definition was variable across the included studies. Six of them enrolled patients with NSTE-ACS [14,17], while three studies enrolled patients with stable CAD [13,15,16]. In most studies, there were more male than female participants. One trial included younger patients [15], whereas one trial included only elderly patients [17]. There was significant variability in the prevalence of diabetes mellitus and prior MI upon randomization across the included studies. Only one study randomized patients with known coronary anatomy (post-angiography) [13]. Based on the Jadad scale, the risk of bias was considered to be high in most trials, mainly due to the absence of blinding, as expected for this type of studies. However, all trials assessed hard outcomes that should not be considerably influenced by the open label design. Baseline characteristics of selected observational trials are shown in Supplemental Tables 2 and 3 Most observational studies were of optimal quality as assessed by the Newcastle-Ottawa scale.

3.2. Primary outcome

Revascularization as the initial management strategy was associated with a lower incidence of MI compared with optimal medical therapy in patients with CKD: RR 0.71 (95% CI 0.54–0.94; p=0.02) (Fig. 1 and Table 2). This result was mainly driven from a significantly lower incidence of MI with revascularization among patients with stable CAD and CKD: RR 0.59 (95% CI 0.37–0.93; p=0.03). A similar incidence of MI was observed with revascularization compared with optimal medical therapy among patients with NSTE-ACS and CKD: RR 0.82 (95% CI 0.57–1.18; p=0.29). Heterogeneity was low for studies in patients with NSTE-ACS (I^2 = 24%) but substantial for studies in patients with stable CAD (I^2 = 64%). There was no major publication bias identified at the inspection of the funnel plot (Supplemental Fig. 2). On a meta-regression analysis, the time period each study was conducted did not have an impact on the effect size (before or after 2002: p=0.35; before or after 2009: p=0.98). In addition, high (≥50%) or low (<50%) prevalence of diabetes among study participants did not have an impact on the effect size (p=0.31).

3.3. All-cause mortality

A similar incidence of all-cause mortality was observed with revascularization as the initial management strategy or optimal medical therapy in patients with CKD: RR 0.88 (95% CI 0.72–1.08; p=0.22) (Fig. 2 and Table 2). Although a trend towards lower all-cause mortality was seen in RCTs in patients with NSTE-ACS and CKD (RR 0.73; 95% CI 0.51–1.04; p=0.08), this was offset by a similar incidence of all-cause mortality in RCTs in patients with stable CAD and CKD (RR 0.96; 95% CI 0.77–1.18; p=0.68). No significant heterogeneity was identified in RCTs from patients with stable CAD (I^2 = 17%) or in RCTs from patients with NSTE-ACS (I^2 = 0%). On a meta-regression analysis, the time period each study was conducted did not have an impact on the effect size (before or after 2002: p=0.11; before or after 2009: p=0.25). In addition, high (≥50%) or low (<50%) prevalence of diabetes among study participants did not have an impact on the effect size (p=0.22).

3.4. Observational studies

Five observational studies provided results on recurring MI in patients with CKD undergoing revascularization or treated with optimal

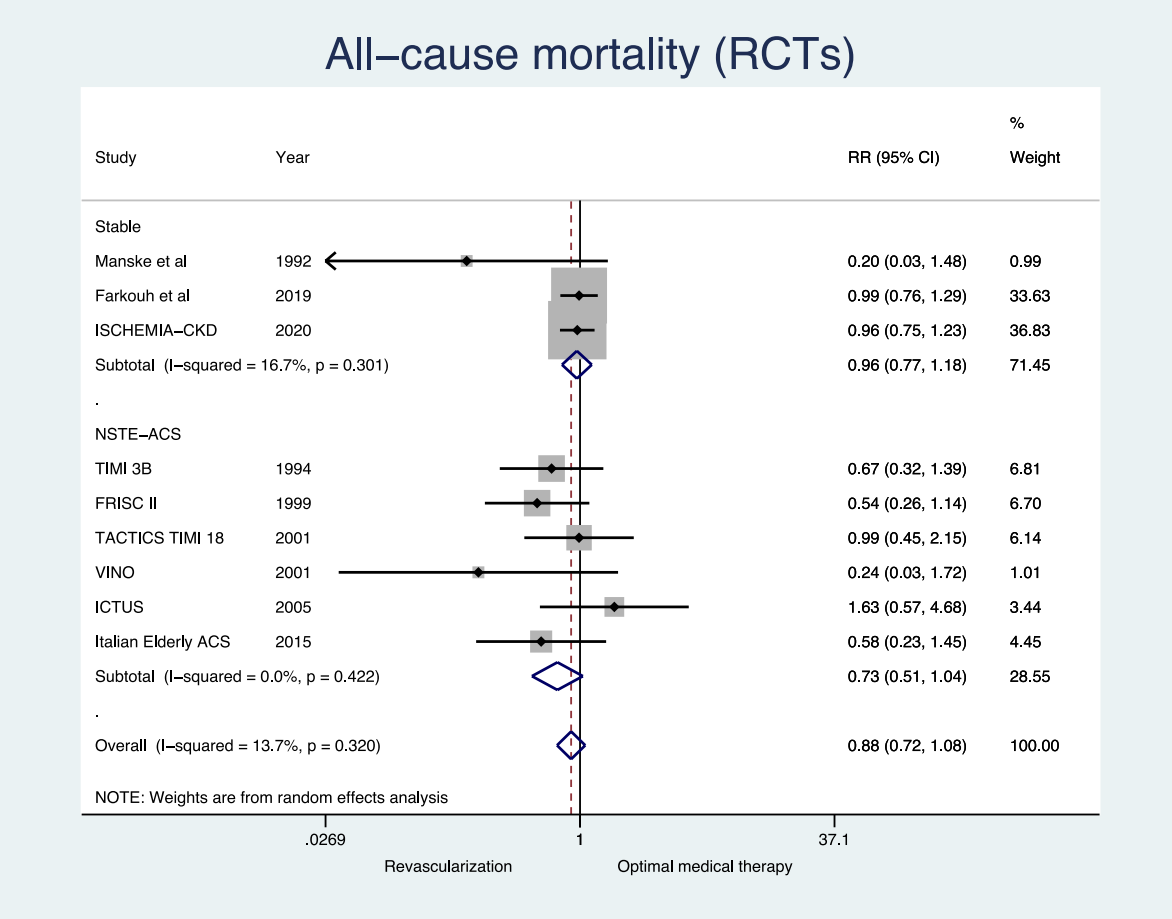

Fig. 2. Forest plot showing the incidence of all-cause mortality with revascularization as the initial management strategy compared with optimal medical therapy in patients with chronic kidney disease.
Results are stratified by the intervention setting: stable coronary disease versus NSTE-ACS (non ST-segment elevation acute coronary syndrome). Only results from the RCTs (randomized controlled trials) are presented in this Forest plot. Data are presented as risk ratios (RR) with 95% confidence intervals (95% CI). A similar incidence of all-cause mortality was seen with both treatment strategies in patients with stable coronary disease. A numerically lower incidence of mortality is observed with revascularization compared with optimal medical therapy in patients with NSTE-ACS. A random effects model is used. ACS, acute coronary syndrome; FRISC, FRagmin and fast revascularization during InStability in Coronary artery disease; ICTUS, Invasive versus Conservative Treatment in Unstable coronary Syndromes; ISCHEMIA-CKD, International Study of Comparative Health Effectiveness with Medical and Invasive Approaches–Chronic Kidney Disease; TACTICS, Thrombolysis And Counterpulsation To Improve Cardiogenic Shock survival; TIMI, Thrombolysis In Myocardial Infarction; VINO, Value of first day angiography/angioplasty In evolving Non-ST segment elevation myocardial infarction, an open multicenter randomized trial.

medical therapy [22,26,28,30,36]. There was no difference in the incidence of MI between the two treatment groups in these studies (Table 2 and Supplemental Fig. 3) but heterogeneity was very high ($I^2 = 79\%$).

Twenty-one observational studies provided data on all-cause mortality in patients with CKD undergoing revascularization or treated with medical therapy [4,18–37]. A significantly lower risk of mortality was observed with revascularization compared with optimal medical therapy: RR 0.59 (95% CI 0.49–0.71; $p < 0.001$) (Supplemental Figs. 4 and 5). Despite a large treatment effect, especially among patients with NSTE-ACS, our confidence on this estimate remains very low because of the observational nature and the significant heterogeneity of the included studies ($I^2 = 97\%$, Table 2).

3.5. Renal outcomes

The single RCT that assessed progression to ESRD did not identify any significant difference between the two treatment strategies for this outcome [16]. When this trial and the three available observational studies [4,27,33] were examined together, there was no difference in progression to ESRD between early revascularization and medical therapy: RR 1.02 (95% CI 0.73–1.41; p=0.93) (Table 2 and Fig. 3). Very high heterogeneity was identified ($I^2 = 90\%$).

Three observational studies provided the incidence of AKI per treatment group [26,27,34]. AKI definition was highly variable. There was no difference in the incidence of AKI between revascularization and medical therapy: RR 1.02 (95% CI 0.74–1.41; p=0.90) (Table 2 and Fig. 3). Heterogeneity was very high ($I^2 = 86\%$).

3.6. Advanced CKD and general population

For this analysis, we examined the CKD stage 4–5 subgroup (eGFR<30 ml/min/1.73 m^2), as well as the whole population of the included trials, with and without CKD [17,38–44]. We also included the ISCHEMIA trial that had a similar design with ISCHEMIA-CKD but was conducted in a population with an eGFR >30 ml/min/1.73 m^2 [45]. A lower incidence of MI was seen with revascularization compared with medical therapy in patients with CKD stage ≥3 (and a trend towards fewer MIs in patients with CKD stage 4–5) but not in the whole population of these trials (Supplemental Fig. 6). On the contrary, there was no difference of the treatment effect on all-cause mortality across the

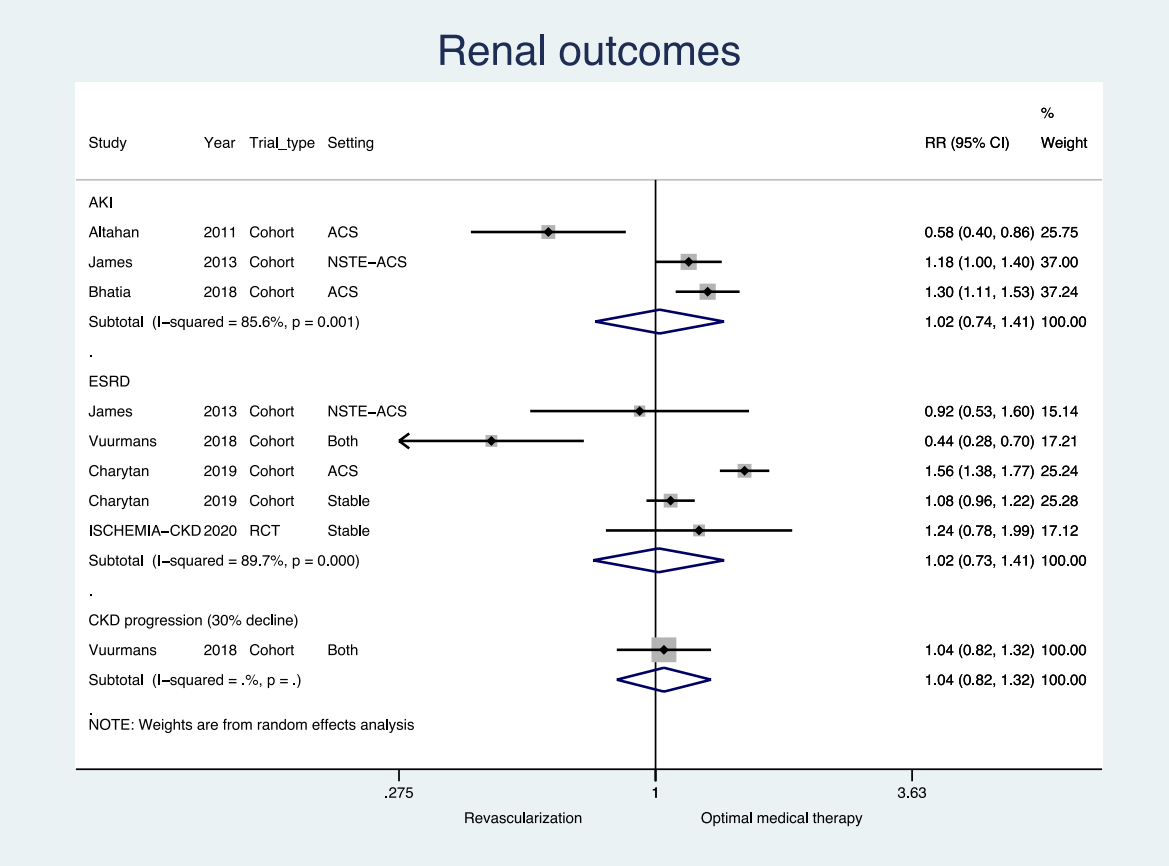

Fig. 3. Forest plot showing the incidence of renal outcomes with revascularization compared with optimal medical therapy in patients with chronic kidney disease. Results are stratified by the outcome of interest: acute kidney injury (AKI), progression to end-stage renal disease (ESRD), or progression of chronic kidney disease (CKD) defined as a persistent 30% drop in glomerular filtration rate. Data are presented as risk ratios (RR) with 95% confidence intervals (95% CI). A similar incidence for all renal outcomes is identified with revascularization compared with optimal medical therapy. A random effects model is used. ACS, Acute Coronary Syndrome; ISCHEMIA-CKD, International Study of Comparative Health Effectiveness with Medical and Invasive Approaches–Chronic Kidney Disease; NSTE-ACS, Non ST-Segment Elevation Acute Coronary Syndrome; RCT, randomized controlled trial.

kidney function subgroups and the whole study population (Supplemental Fig. 7).

4. Discussion

To our knowledge, this is the first meta-analysis of RCTs in patients with CKD and NSTE-ACS or stable CAD. Our study examines the effect of revascularization as the initial management strategy compared with medical therapy and includes 3422 patients from 11 RCTs. We show that coronary revascularization is associated with lower incidence of MI compared with medical therapy. This result seems to be driven by a lower incidence of MI with early coronary revascularization among patients with stable CAD and CKD, whereas no significant difference between the two treatment strategies is detected among patients with NSTE-ACS. In addition, a trend towards lower incidence of all-cause mortality with revascularization compared with medical therapy was observed in patients with NSTE-ACS and CKD but not among patients with stable CAD and CKD. Finally, data derived mostly from observational studies show a similar rate of AKI or CKD progression in patients treated with PCI/CABG and those who received medical therapy alone.

Half of the patients with NSTE-ACS and CKD who were initially randomized in the conservative arm of the trials included in this analysis were eventually treated with revascularization during the follow-up period, as guided by recurrence of symptoms or a positive stress test, according to each study protocol. The relatively high incidence of subsequent revascularization in the conservative arm may explain the lack of difference between the two treatment strategies for the outcome of MI in patients with NSTE-ACS and CKD. However, our study identifies the same trend towards fewer MIs with revascularization that has been observed in a recent meta-analysis in patients with NSTE-ACS irrespective of their kidney function [46].

We identified a lower incidence of MI with early revascularization compared with medical therapy among patients with stable CAD. This finding was confirmed in patients with advanced CKD but was not observed when the whole population of the same trials (with or without CKD) was examined. A meta-analysis of randomized trials in the general population showed similar results [47]. Therefore, it is possible that patients with moderate or advanced CKD and stable CAD may benefit more from revascularization as the initial management strategy compared with patients with preserved renal function. It has been hypothesized that the higher the atherosclerotic plaque burden the greater the probability that one of the plaques triggers vessel thrombosis with a subsequent clinical event [48]. A higher plaque burden among CKD patients could potentially explain the beneficial effect of revascularization in the incidence of MI [49,50]. However, medical therapy may not include all indicated agents or not be prescribed at the target dose in patients with CKD [3]. Therefore, suboptimal medical therapy may also explain why clinical outcomes seem to be better with an early invasive strategy in CKD.

We observe a numerically lower incidence of all-cause mortality with revascularization compared with medical therapy in patients with NSTE-ACS and CKD but an identical incidence of all-cause mortality with both treatment strategies in patients with stable CAD and CKD. Patients with NSTE-ACS treated with early revascularization may have a

lower incidence of acute complications, such as hemodynamic instability, heart failure, or ventricular arrhythmias, accounting for the numerically lower mortality rates with early revascularization in this subgroup.

We also report results from observational studies on MI and mortality with both treatment strategies. It is remarkable that results from these studies, that were until recently the only available evidence in patients with CKD and CAD [8,9], are qualitatively very different from results from RCTs. Very serious inconsistency and underlying selection bias preclude any meaningful conclusion from these studies. However, it is also possible that the differences are explained by the broader inclusion criteria in observational studies that have better generalizability compared with RCTs with highly selective criteria.

From a renal standpoint, no significant difference was identified between the two treatment strategies with respect to AKI incidence or progression to ESRD. However, heterogeneity of the included studies was very high and our confidence on this estimate remains very low. The only RCT that assessed progression to ESRD (ISCHEMIA-CKD) did not demonstrate any difference between revascularization or medical therapy for this outcome [16]. In conclusion, according to available evidence, clinicians may proceed with revascularization in patients with a clinical indication and not withhold this intervention for fear of adverse renal outcomes.

Our analysis has significant limitations. Coronary revascularization or invasive approach and medical therapy or conservative approach were not homogeneous across the selected studies, particularly when comparing trials enrolling patients with NSTE-ACS *versus* those in patients with stable CAD. The conservative arm (medical therapy) was not directly comparable across included studies reflecting changing patterns in the management of CAD during the last three decades. Most included studies were subgroup analyses from large RCTs without randomization stratification per CKD status. One of the included studies reported outcomes only in patients with CKD who also had diabetes [13]. This study provided pooled data from three clinical trials; primary data from each of the trials were unfortunately not available. In addition, this study included patients from the FREEDOM trial in the intervention arm (PCI or CABG), although there was no medical therapy arm in this study [51]. Patients with reduced left ventricular ejection fraction, refractory angina, or unprotected left main coronary artery stenosis have been excluded from most trials. Moreover, heterogeneity was not negligible, especially for studies in patients with stable CAD, with variable definitions of CKD, advanced CKD, or MI, and different study designs (randomization pre-versus post-angiography) accounting, at least in part, for between-study differences. Furthermore, we did not have access to patient-level data and interaction terms by CKD status could not be provided. Nevertheless, inclusion of 3422 patients from 11 RCTs in different clinical settings, enrollment of patients across various CKD stages including at least 411 patients on maintenance dialysis, non-significant inconsistency for the majority of clinical outcomes, and similar results on most analyses represent unique strengths of our study.

In this meta-analysis of RCTs in patients with CKD and CAD, we showed that coronary revascularization including PCI or CABG as the initial management strategy may be superior to medical therapy for the prevention of MI and, possibly, for the prevention of all-cause mortality among patients with NSTE-ACS and CKD. The incidence of adverse renal outcomes may be similar with both treatment strategies. A meta-analysis with patient-level data from all RCTs comparing early revascularization with optimal medical therapy in CAD across all CKD stages is needed to accurately identify the optimal management strategy in this population. Awaiting more precise results, an individualized approach is suggested: some patients may risk any future event to avoid current procedures, whereas others would do anything to eliminate risk. The presence of CKD of any stage should not be considered a contra-indication for revascularization when this is clinically indicated.

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CRediT authorship contribution statement

Alexandre Leszek: independently reviewed the literature and selected the studies to be included in the meta-analysis, drafted the manuscript. **Lauriane Poli:** independently reviewed the literature and selected the studies to be included in the meta-analysis, independently extracted available data, drafted the manuscript. **Stephanie Zbinden:** independently extracted available data, critically revised the paper. **Lucas C. Godoy:** provided non-published randomized data, interpreted the data, critically revised the paper. **Jean-Luc Reny:** interpreted the data, critically revised the paper. **Michael E. Farkouh:** provided non-published randomized data, interpreted the data, critically revised the paper. **David M. Charytan:** provided non-published randomized data, interpreted the data, critically revised the paper. **Thomas A. Mavrakanas:** designed the study, performed statistical analyses, interpreted the data, drafted the manuscript. All authors approved the final version of the manuscript.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Dr. Mavrakanas reports honoraria from Daiichi Sankyo, BMS Canada, Janssen, and Pfizer and served on advisory boards for Boehringer Ingelheim, outside the submitted work.

Drs. Leszek, Poli, Zbinden, Godoy, and Reny have nothing to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2022.02.023.

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