2-15-2022

Coronary Revascularization Versus Optimal Medical Therapy in Renal Transplant Candidates With Coronary Artery Disease: A Systematic Review and Meta-Analysis.

Muhammad U Siddiqui

Joey Junarta
Thomas Jefferson University

Gregary D. Marhefka
Thomas Jefferson University

Journal of the American Heart Association

SYSTEMATIC REVIEW AND META-ANALYSIS

Coronary Revascularization Versus Optimal Medical Therapy in Renal Transplant Candidates With Coronary Artery Disease: A Systematic Review and Meta-Analysis

Muhammad U. Siddiqui, MD, MS; Joey Junarta, MBBS; Gregary D. Marhefka, MD

BACKGROUND: Coronary artery disease (CAD) is highly prevalent in patients with chronic kidney disease and is a common cause of mortality in end-stage renal disease. Thus, patients with end-stage renal disease are routinely screened for CAD before renal transplantation. The usefulness of revascularization before transplantation remains unclear. We hypothesize that there is no difference in all-cause and cardiovascular mortality in waitlisted renal transplant candidates with CAD who underwent revascularization versus those treated with optimal medical therapy before transplantation.

METHODS AND RESULTS: This meta-analysis was reported according to the *Preferred Reporting Items for Systematic Review and Meta-Analyses* guidelines. MEDLINE, Scopus, and Cochrane Central Register of Controlled Trials were systematically searched to identify relevant studies. Risk of bias was assessed using the modified Newcastle-Ottawa Scale and Cochrane risk of bias tool. The primary outcome of interest was all-cause mortality. Eight studies comprising 945 patients were included (36% women, mean age 56 years). There was no difference in all-cause mortality (risk ratio [RR], 1.16 [95% CI, 0.63–2.12), cardiovascular mortality (RR, 0.75 [95% CI, 0.29–1.89]), or major adverse cardiovascular events (RR, 0.78 [95% CI, 0.30–2.07]) when comparing renal transplant candidates with CAD who underwent revascularization versus those who were on optimal medical therapy before renal transplant.

CONCLUSIONS: This meta-analysis demonstrates that revascularization is not superior to optimal medical therapy in reducing all-cause mortality, cardiovascular mortality, or major adverse cardiovascular events in waitlisted kidney transplant candidates with CAD who eventually underwent kidney transplantation.

Key Words: coronary artery disease ■ coronary revascularization ■ medical therapy ■ renal transplantation

Cardiovascular disease is a leading cause of morbidity and mortality among patients with end-stage renal disease. Kidney transplant candidates are at high risk for adverse cardiovascular events, despite already having undergone cardiovascular evaluation to be listed for transplantation.[1,2] The cumulative incidence of myocardial infarction (MI) has been shown to range from 9% to 17% by 3 years after transplant listing, and from 5% to 11% after kidney transplantation.[3,4] Cardiovascular disease is the most common cause of death in kidney transplant recipients with functioning allografts, accounting for 30% of overall mortality, with highest rates in the peritransplant period.[5]

Because of this, transplant candidates are routinely screened for asymptomatic coronary artery disease (CAD). The goal is to identify and correct undiagnosed CAD to prevent premature cardiovascular mortality at transplantation or soon after. Occasionally, investigated

Correspondence to: Muhammad U. Siddiqui, MD, MS, Department of Internal Medicine, Thomas Jefferson University Hospitals, 833 Chestnut Street, Suite 701, Philadelphia, PA 19107. E-mail: muhammad.siddiqui@jefferson.edu

For Sources of Funding and Disclosures, see page 10.

The results presented in this article have not been published previously in whole or part, except in abstract form. Presented at the Scientific Sessions of the American Heart Association, Boston, MA, November 13-15, 2021, and published in abstract form (Circulation. 2021;144:A11565).

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Our meta-analysis demonstrates that coronary revascularization is not superior to optimal medical therapy in reducing all-cause mortality, cardiovascular mortality, or major adverse cardiovascular events in waitlisted kidney transplant candidates with coronary artery disease who eventually underwent kidney transplantation.

What Are the Clinical Implications?

- Our findings suggest that asymptomatic kidney transplant candidates with coronary artery disease should not undergo routine coronary revascularization exclusively to reduce perioperative cardiovascular events.

Nonstandard Abbreviations and Acronyms

MACE	major adverse cardiovascular event
OMT	optimal medical therapy

patients are deemed unsuitable for transplant because of unmodifiable cardiac risk and poor prognosis. Such patients are subsequently removed from the waitlist. Currently, there is no established protocol to determine the optimal strategy to monitor and maintain cardiac fitness in waitlisted patients. Critically, whether abnormal screening results warrant further invasive investigation, such as coronary angiography and subsequent revascularization, is unclear.

The objective of this meta-analysis was to compare the usefulness of coronary revascularization versus medical management before transplantation in improving hard outcomes in renal transplant recipients with CAD. Our hypothesis is that there would be no difference in outcomes in transplant candidates with CAD who underwent revascularization versus those treated with optimal medical therapy (OMT) alone before transplantation.

METHODS

Data are safely kept in a password-protected security system at Thomas Jefferson University Hospital. The data sets used and/or analyzed during the current study are deidentified and available from the corresponding author on reasonable request.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was a meta-analysis that did not require approval from our institutional review board. This article does not contain any studies with animals performed by any of the authors.

Data Sources and Search Strategy

This systematic review and meta-analysis was reported according to the *Preferred Reporting Items for Systematic Review and Meta-Analyses* guidelines.[6] MEDLINE, Scopus, and Cochrane Central Register of Controlled Trials were searched from database inception through June 2021 using the following combination of keywords: coronary artery disease OR heart disease OR CAD OR coronary disease AND renal transplant OR kidney transplant. No time restriction was placed on the search. However, language was restricted to English. We also searched trial registries (eg, www.clinicaltrialresults.org, www.clinicaltrials.gov), abstracts, and presentations from major cardiovascular proceedings. All citations retrieved from the search were transferred to EndNote X7.5 (Thompson ISI ResearchSoft, Philadelphia, PA) Reference Manager, and duplicates were removed.

Study Selection

All citations were screened by one reviewer (M.U.S.). Eligible studies reported outcomes in renal transplant candidates who underwent revascularization for CAD versus medical therapy alone for CAD before transplant. We included randomized and nonrandomized studies. Exclusion criteria included studies that focused on screening for CAD in renal transplant candidates without studying the effects of treatment strategy on outcomes.

The main outcomes of interest were all-cause mortality, cardiovascular mortality, and major adverse cardiovascular events (MACEs), which included MI, acute coronary syndrome, heart failure, and ventricular arrythmias.

Data Extraction and Risk of Bias

Two independent reviewers (M.U.S. and J.J.) extracted the data on year of publication, study design, inclusion criteria, primary end points, and follow-up time using a standardized data extraction form. Risk of bias was assessed using the modified Newcastle-Ottawa Scale for observational studies, which assesses 3 domains: patient selection, comparability, and outcome assessment.[7] For randomized controlled trials, the Cochrane risk of bias tool was used.[8] The methodological quality of a study was graded as high or low based on whether the study had adequate adjustment for confounders,

which we judged to be the most critical domain affecting the main outcomes of interest.[9]

Statistical Analysis

We extracted or calculated a risk ratio (RR) and 95% CI from each study. RRs were pooled using a random-effects model to account for between-study variance.[10] The I^2 statistic was quantified to measure heterogeneity with values >25%, 50%, and 75% consistent with low, moderate, and high degrees of heterogeneity, respectively.[11] Review Manager software version 5.4 was used for analysis. $P<0.05$ was considered statistically significant. Certainty in the evidence (ie, confidence in the final estimates) was assessed using the Grades of Recommendation, Assessment, Development, and Evaluation approach based on the risk of bias, imprecision, indirectness, inconsistency, and publication bias.[12] The authors had full access to all the data in the study and take responsibility for its integrity and the data analysis.

RESULTS

Study Selection

Of 728 potential articles screened, 8 studies comprising 945 patients were included (Figure 1). Table 1 summarizes the characteristics of included studies.[13–20] Of these, 481 patients underwent revascularization for CAD before renal transplant, and 464 patients received OMT alone. All the studies were observational (nonrandomized), except for Herzog et al, which was a randomized controlled trial.[20] The studies did not report the medications used to provide OMT. Table 2 summarizes the baseline characteristics of included patients. Out of 945 patients included in this analysis, 339 were women (35.9%). The data on number of female patients participating in the studies performed by Lindley et al, Tita et al, and Eschertzhuber et al could not be obtained.[14,17,19] The mean age of patients who underwent revascularization was 56.5 years, whereas

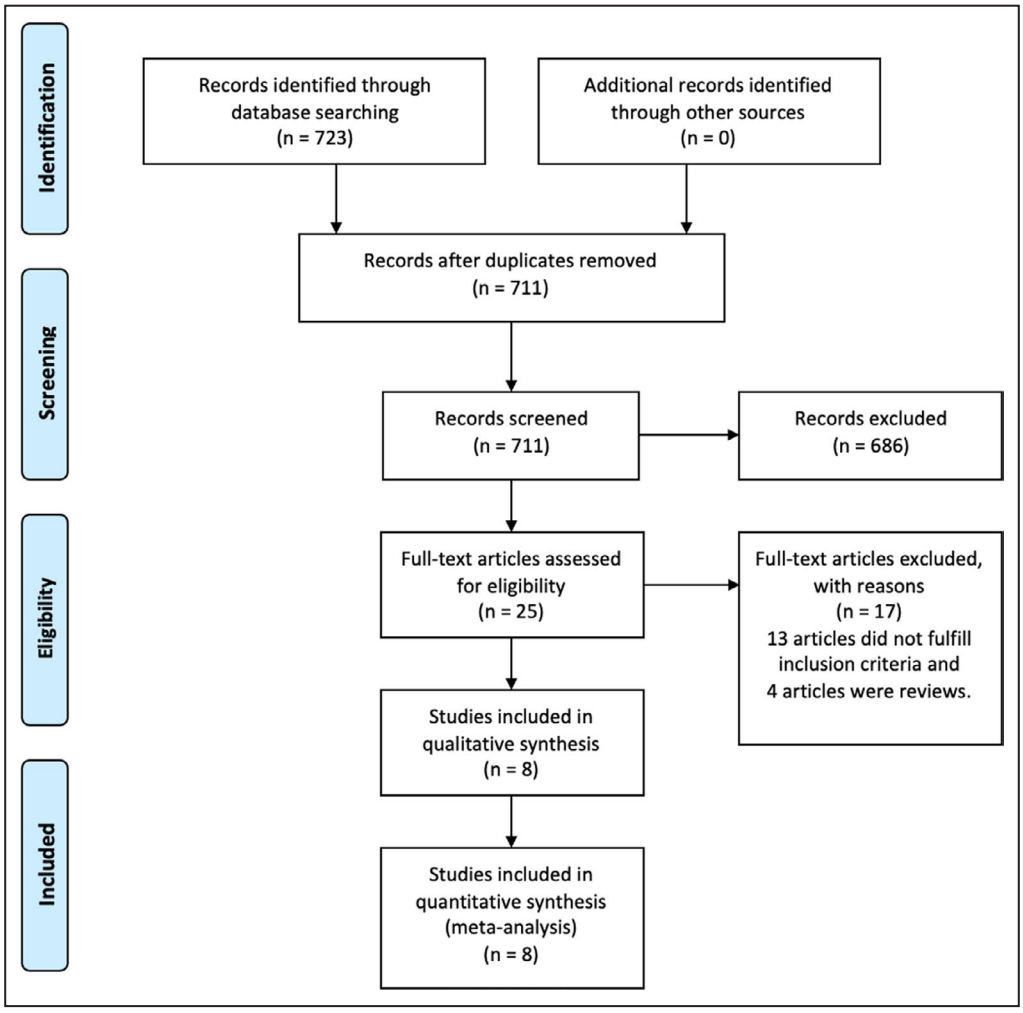

Figure 1. The *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* flow diagram of included studies.

Table 1. Characteristics of Included Studies

Study	Design	Population	Experimental arm	Control arm	End points	Follow-up duration
De Lima et al[13]	Prospective cohort study	Hemodialysis patients with ESRD waiting to receive their first kidney graft	Coronary revascularization before kidney transplantation (surgical or percutaneous) plus medical treatment	Medical treatment	Cardiac events (composite of myocardial infarction, unstable angina, sudden death) and all-cause mortality	Patients were followed up until death or a coronary event. There was no mention of the mean or median duration of follow-up.
Eschertzhuber et al[14]	Retrospective cohort study	Patients with ESRD who received kidney transplantation	Coronary revascularization before kidney transplantation (surgical or percutaneous) plus medical treatment	Medical treatment	Early or late postoperative death, myocardial infarction, other posttransplant cardiac event	3 y
Felix et al[15]	Retrospective cohort study	Dialysis and nondialysis patients with ESRD who received kidney transplantation	Coronary revascularization before kidney transplantation (surgical or percutaneous) plus medical treatment	Medical treatment	Primary outcome: composite of cardiovascular mortality, acute coronary syndrome, and coronary revascularization after renal transplantation; secondary outcome: components of the primary outcome, incident angina, incident heart failure, and all-cause mortality	5.6 y
Kahn et al[16]	Retrospective cohort study	Dialysis and nondialysis patients with ESRD who received kidney transplantation	Coronary revascularization before kidney transplantation (surgical or percutaneous) plus medical treatment	Medical treatment	All-cause mortality	5 y
Lindley et al[17]	Prospective cohort study	Patients with ESRD waiting to receive kidney graft	Coronary revascularization before kidney transplantation (surgical or percutaneous) plus medical treatment	Medical treatment	Graft failure, revascularization, nonfatal myocardial infarction, stroke, and all-cause mortality	1 y
Singh et al[18]	Retrospective cohort study	Patients with diabetes with ESRD who received kidney transplantation	Coronary revascularization before kidney transplantation (surgical or percutaneous) plus medical treatment	Medical treatment	Cardiac events (myocardial infarction, ventricular arrhythmia, heart failure), cardiovascular mortality, and all-cause mortality	1 y
Tita et al[19]	Retrospective cohort study	Dialysis and nondialysis patients with ESRD who received kidney transplantation	Coronary revascularization before kidney transplantation (percutaneous) plus medical treatment	Medical treatment	Cardiac events (coronary revascularization, nonfatal myocardial infarction, heart failure, cardiovascular mortality) and cerebrovascular events	2.85 y
Herzog et al[20]	Randomized controlled trial	Dialysis and nondialysis patients with ESRD waiting to receive kidney graft	Coronary revascularization before kidney transplantation (surgical or percutaneous) plus medical treatment	Medical treatment	Primary outcome: composite of nonfatal myocardial infarction and all-cause mortality; secondary outcomes: composite of death, nonfatal myocardial infarction, stroke, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest	3 y

ESRD indicates end-stage renal disease.

Table 2. Patient Baseline Characteristics

Study	De Lima et al[13]		Eschertzhuber et al[14]		Felix et al[15]		Herzog et al[20]		Kahn et al[16]		Lindley et al[17]*		Singh et al[18]		Tita et al[19]†	
	Revascul-arization	Medical	Revascul-arization	Medical	Revascul-arization	Medical	Revascul-arization	Medical	Revascul-arization	Medical‡	Revascul-arization	Medical	Revascul-arization	Medical	Revascul-arization	Medical
No. of patients	49	87	15	7	89	207	94	100	182	16	19	3	32	35	1	9
Age, y, mean (SD) or median (IQR)	56.8 (8.7)	59.1 (8.6)	NR	NR	58.1 (9.3)	56.0 (10.7)	59 (54–64)	61 (53–65)	64 (57–69)	62 (50–72)	48.0 (15.0)		57.0 (8.3)	54.0 (9.8)	53.4 (11.0)	
Women, n (%)	13 (27%)	26 (30%)	NR	NR	22 (25%)	65 (31%)	25 (27%)	24 (24%)	43 (24%)	9 (29%)	299 (44%)		13 (40%)	9 (26%)	70 (47%)	
Smoking history, n (%)	20 (41%)	32 (37%)	NR	NR	NR	NR	49 (52%)	54 (54%)	57 (31%)	9 (29%)	43 (6%)		6 (19%)	12 (34%)	NR	
Hypertension, n (%)	36 (73%)	77 (89%)	NR	NR	81 (91%)	176 (85%)	82 (92%)	92 (92%)	178 (98%)	27 (87%)	574 (84%)		30 (94%)	30 (86%)	143 (96%)	
Diabetes, n (%)	32 (65%)	56 (64%)	NR	NR	81 (91%)	181 (87%)	59 (63%)	55 (55%)	121 (66%)	22 (71%)	252 (37%)		32 (100%)	35 (100%)	97 (65%)	
Dyslipidemia, n (%)	21 (43%)	31 (36%)	NR	NR	77 (87%)	141 (68%)	NR	NR	120 (66%)	18 (58%)	280 (41%)		NR	NR	89 (60%)	
Coronary artery disease, n (%)	37 (76%)	39 (45%)	NR	NR	89 (100%)	207 (100%)	11 (12%)	14 (14%)	158 (87%)	17 (55%)	109 (16%)		23 (72%)	20 (57%)	16 (11%)	
LVEF %, mean (SD) or median (IQR)	57.0 (13.0)	60.0 (13.0)	NR	NR	NR	NR	58 (60–61)	60 (52–65)	NR	NR	NR		50.0 (15.2)	50.0 (12.8)	NR	
Time on dialysis, mo, mean (SD) or median (IQR)	22 (median)	29 (median)	NR	NR	NR	NR	24 (12–60)	24 (12–36)	109 (42–161)	116 (62–191)	NR		NR	NR	NR	
Statin use, n (%)	NR	NR	NR	NR	38 (43%)	62 (30%)	68 (73%)	76 (76%)	106 (58%)	10 (32%)	NR		23 (72%)	24 (67%)	NR	
β-Blocker use, n (%)	NR	NR	NR	NR	67 (75%)	134 (65%)	NR	NR	130 (71%)	15 (48%)	NR		27 (84%)	23 (66%)	NR	
ACEi or ARB, n (%)	NR	NR	NR	NR	NR	NR	50 (54%)	39 (39%)	75 (41%)	7 (23%)	NR		7 (22%)	11 (31%)	NR	
Antiplatelet agent, n (%)	NR	NR	NR	NR	NR	NR	78 (83%)	94 (94%)	132 (73%)	18 (58%)	NR		32 (100%)	35 (100%)	NR	

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; IQR, interquartile range; LVEF, left ventricular ejection fraction; and NR, not reported.

*Baseline characteristics of all included patients (n=685) at study recruitment, including those not transplanted. Baseline characteristics stratified by whether patients were revascularized vs medically managed alone before transplantation were not reported.

†Baseline characteristics of all included patients (n=149) at study recruitment. Baseline characteristics stratified by whether patients were revascularized vs medically managed alone before transplantation were not reported.

‡Baseline characteristics of all included patients (n=31) in the medical therapy group at study recruitment, including those not having significant coronary artery disease. Baseline characteristics of patients with significant coronary artery disease medically managed before transplantation were not separately reported.

Table 3. Risk of Bias Assessment of the Included Observational Studies

Modified Newcastle-Ottawa Scale	Studies						
	De Lima et al[13]	Eschertzhuber et al[14]	Felix et al[15]	Kahn et al[16]	Lindley et al[17]	Singh et al[18]	Tita et al[19]
Selection	4	4	4	4	4	4	4
Comparability	2	0	1	2	0	1	1
Adjustment	Adjusted	Unadjusted	Adjusted	Adjusted	Unadjusted	Adjusted	Adjusted
Outcome	2	3	3	3	2	2	3
Total, maximum score=9	8	7	7	9	6	7	8

For selection, the highest score was 4 based on the representativeness of the exposed cohort, selection of the nonexposed cohort, ascertainment of the exposure, and outcome of interest at the start of the study. For comparability, the highest score was 2 based on comparability of the cohort. For outcome, the highest score was 3 based on assessment of the outcome, follow-up period, and adequacy of the follow-up period.

the mean age of patients who received OMT alone was 56.1 years. Mean follow-up duration was 3.1 years.

Tables 3 and 4 show the risk of bias assessment. There was high risk of selection bias and performance bias in the 7 observational studies included because of lack of randomization and blinding. Overall, the risk of detection bias, reporting bias, and attrition bias was low among all studies. We were unable to statistically evaluate publication bias because of the small number of included studies.

Outcomes

Outcomes in renal transplant candidates with CAD who underwent revascularization versus those who received OMT alone before renal transplantation were compared. Five studies reported all-cause mortality, and pooled results found no difference between groups (RR, 1.16 [95% CI, 0.63–2.12]) (Figure 2). Four studies reported cardiovascular mortality and pooled results and found no difference between groups (RR, 0.75 [95% CI, 0.29–1.89]) (Figure 3). Six studies reported MACEs, and pooled results found no difference between groups (RR, 0.78 [95% CI, 0.30–2.07]) (Figure 4).

Sensitivity Analysis

The sensitivity analysis of the pooled findings after the exclusion of the unadjusted data from the studies by Eschertzhuber et al and Lindley et al showed results consistent with the overall risk of MACEs (RR, 1.23 [95% CI, 0.53–2.88]) (Figure 5).[14,17] The pooled results from the unadjusted studies favored revascularization, and the result was statistically significant (RR, 0.07 [95% CI, 0.01–0.55]). This contrasting result was likely because of the small sample size and increased confounding in the unadjusted studies. The χ^2 test for subgroup differences was significant (P=0.01).[6]

Certainty in the Estimates

All studies included were observational except the study by Herzog et al.[20] Thus, these studies had variable methodological quality and are at increased risk of selection and confounding bias. The estimates were not precise for the 3 reported outcomes because of a smaller number of events. There was no indirectness or evidence of publication bias. Heterogeneity was noted among the included studies. The quantified I^2 value for each individual outcome investigated are as follows: all-cause mortality 68% (moderate), cardiovascular mortality 35% (moderate), and MACEs 67% (moderate). Overall, the certainty in the estimates in all the outcomes was judged to be low.

DISCUSSION

Screening for cardiovascular disease in kidney transplant candidates may be important for 2 reasons. First, screening is important to identify those with asymptomatic CAD to enable revascularization or removal of the patient from the waitlist, with the end goal of preventing premature cardiovascular mortality at transplantation or soon after. Second, screening is also important to avoid the misallocation of scarce donor allografts into those who experience early mortality. It is unclear whether coronary revascularization is superior to medical therapy in correcting CAD in this patient population. This meta-analysis demonstrated no difference in all-cause mortality, cardiovascular mortality, or MACEs in renal transplant recipients with CAD who underwent

Table 4. Cochrane Risk of Bias Tool for Randomized Controlled Trials

Reference	Sequence generation	Allocation concealment	Blinding participants	Blinding assessors	Incomplete outcome data	Selective reporting	Other bias
Herzog et al[20]	Yes	Yes	Yes	Yes	All patients were accounted for	No	None

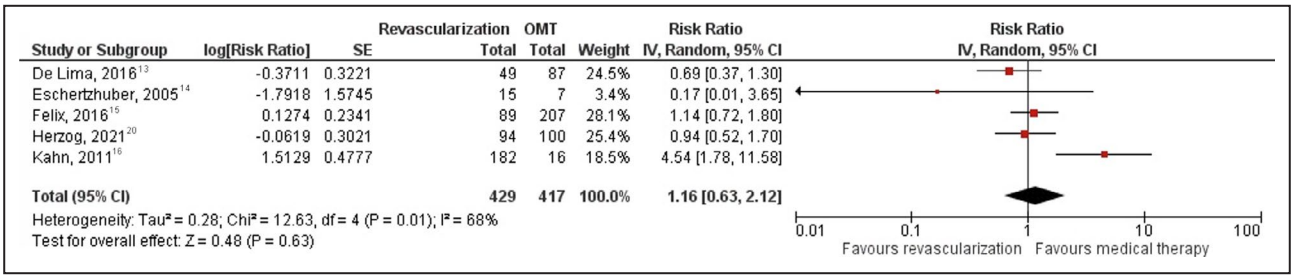

Figure 2. Forest plot for all-cause mortality comparing revascularization vs medical therapy.
The pooled risk ratio with 95% CI were calculated using a random-effects model. Weight refers to the contribution of each study to the pooled estimate. Squares and horizontal lines denote the point estimate and 95% CI for each study's risk ratio. The diamond signifies the pooled risk ratio, the diamond center denotes the point estimate, and the width denotes the 95% CI. IV indicates inverse; and OMT, optimal medical therapy.

revascularization versus patients who were on OMT alone before renal transplantation.

Our findings agree with the meta-analysis conducted by Kamran et al.[21] They found no difference in cardiovascular mortality in those treated with OMT versus coronary revascularization for CAD before transplantation. However, only 6 studies were included in their analysis, and notable outcomes such as all-cause mortality and MACEs were not assessed. Additionally, information on the risk of bias and certainty in the estimates of included studies were not reported. Finally, a sensitivity analysis after exclusion of the unadjusted data was not conducted. A separate meta-analysis consisting of 3 randomized controlled trials conducted by Farkouh et al also reported similar findings to our study.[22] In this study, strategies of coronary artery bypass graft surgery with OMT, percutaneous coronary intervention with OMT, or OMT alone were compared in a group of patients with chronic kidney disease (CKD) and concomitant diabetes and stable ischemic heart disease. There was no difference in the primary composite outcome of all-cause mortality, nonfatal MI, and nonfatal stroke when comparing OMT alone versus coronary artery bypass graft surgery with OMT or percutaneous coronary intervention with OMT. In contrast to our study, included patients all had diabetes and were not exclusively kidney transplant candidates. Thus, posttransplant outcomes were not investigated.

There are other notable studies that have investigated preemptive revascularization in kidney transplant candidates and those with end-stage renal disease. Kumar et al evaluated the usefulness of an aggressive approach to invasive cardiac investigations during transplant evaluation.[23] Their practice involved performing screening coronary angiography on all potential transplant recipients who were over the age of 50 years, those with diabetes, those with cardiac symptoms or disease, and those with an electrocardiogram showing changes suggestive of ischemia or previous MI. Subsequent revascularization was at the discretion of a single cardiologist. In that study, 168 of 657 patients underwent revascularization. Overall survival 3 years after revascularization was 83.5%, versus 91.5% in those who were not intervened. Cardiac event-free survival 3 years after revascularization was 86.8%, versus 95.1% in those who were not intervened. These comparisons were made regardless of whether patients were transplanted or not. Exclusive posttransplant outcomes between groups were not compared. In the study by Hemmelgarn et al, data on 41 786 patients were captured on all patients undergoing cardiac catheterization in Alberta, Canada

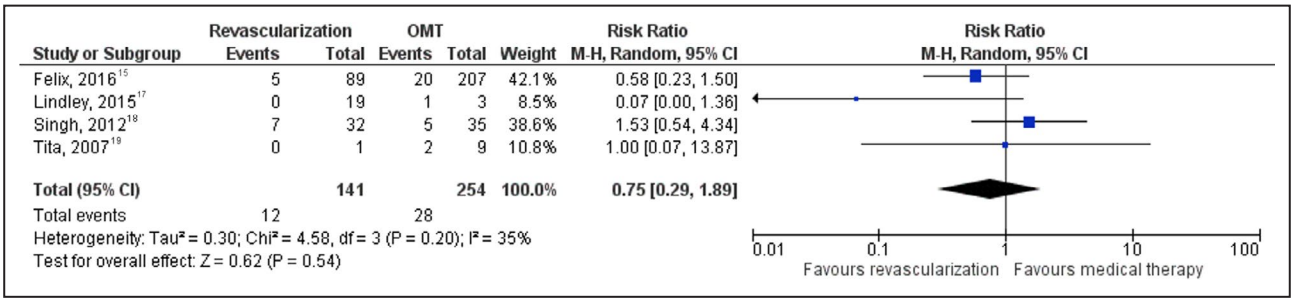

Figure 3. Forest plot for cardiovascular mortality comparing revascularization vs medical therapy.
The pooled risk ratio with 95% CI were calculated using a random-effects model. Weight refers to the contribution of each study to the pooled estimate. Squares and horizontal lines denote the point estimate and 95% CI for each study's risk ratio. The diamond signifies the pooled risk ratio, the diamond center denotes the point estimate, and the width denotes the 95% CI. M-H indicates Mantel-Haenszel; and OMT, optimal medical therapy.

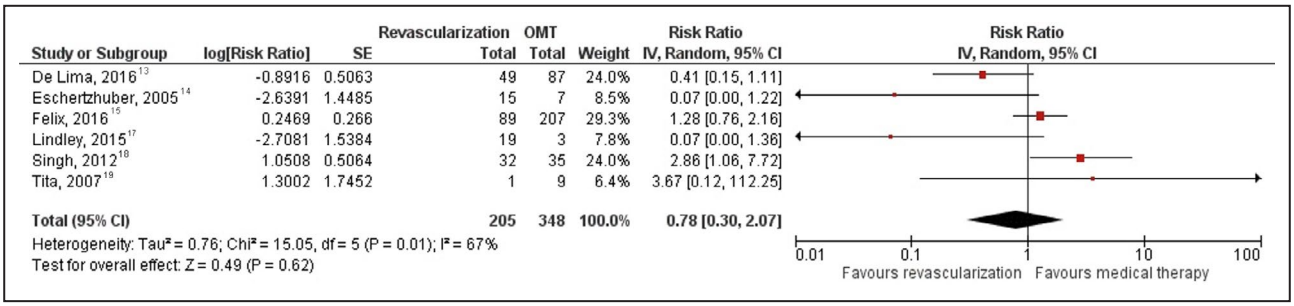

Figure 4. Forest plot for major adverse cardiac events comparing revascularization vs medical therapy.
The pooled risk ratio with 95% CI were calculated using a random-effects model. Weight refers to the contribution of each study to the pooled estimate. Squares and horizontal lines denote the point estimate and 95% CI for each study's risk ratio. The diamond signifies the pooled risk ratio, the diamond center denotes the point estimate, and the width denotes the 95% CI. IV indicates inverse; and OMT, optimal medical therapy.

from 1995 to 2001.[24] Revascularization with PCI was associated with a lower risk of death versus no revascularization in patients with end-stage renal disease, but not in patients who were non–dialysis-dependent with CKD. Patel et al studied 222 waitlisted transplant candidates who underwent pretransplant cardiac assessment.[25] Patients with a high index of suspicion of CAD underwent angiography and revascularization if indicated. There was no apparent survival difference in patients who underwent percutaneous coronary intervention or coronary artery bypass graft surgery compared with those who were not revascularized.

Ultimately, it is important to note that the support for preemptive revascularization to date have been based on observational studies such as these without a comparator group and 1 small randomized controlled trial performed in 1992.[26] At present, ISCHEMIA-CKD (International Study of Comparative Health Effectiveness of Medical and Invasive Approaches-Chronic Kidney Disease) is the only large randomized controlled trial to compare invasive revascularization with OMT versus OMT alone in patients with CKD and CAD.[20] In a post hoc analysis from ISCHEMIA-CKD, 194 of 777 patients were transplant candidates. An invasive strategy with preemptive revascularization compared with conservative OMT did not improve all-cause mortality or nonfatal MI in these patients.

There is general agreement among the kidney transplant community on the need to screen for asymptomatic CAD among transplant candidates who are at high risk. However, how to screen for asymptomatic CAD and whether subsequent revascularization is performed vary widely among different transplant centers. This is despite guidance available and endorsed by the American College of Cardiology, the American Heart Association, the National Kidney Foundation, and the

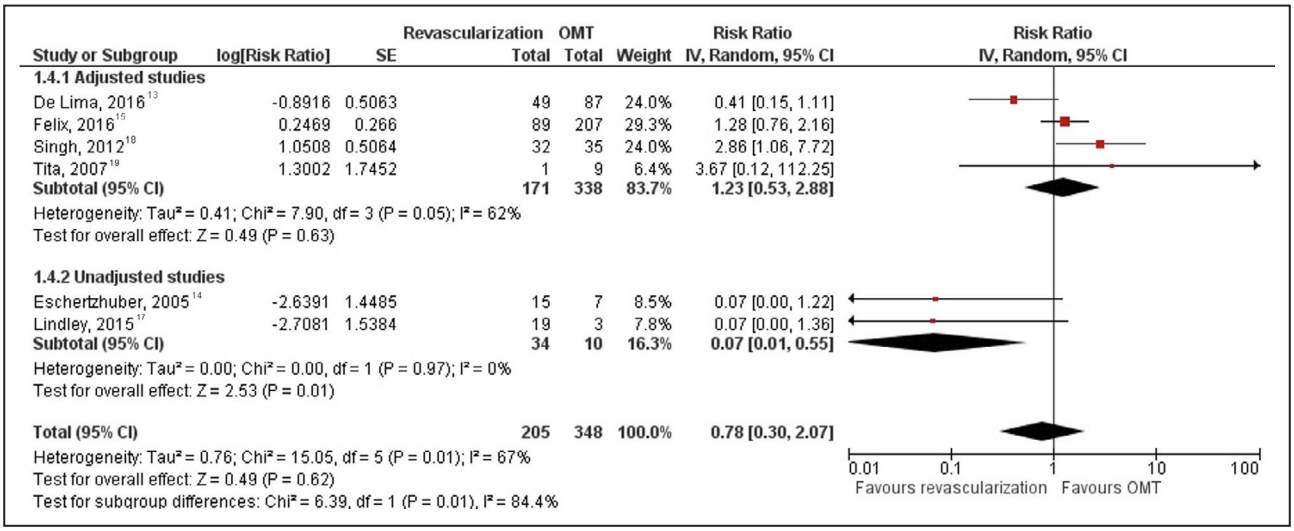

Figure 5. Subgroup sensitivity analysis for major adverse cardiac events.
The pooled risk ratio with 95% CI were calculated using a random-effects model. Weight refers to the contribution of each study to the pooled estimate. Squares and horizontal lines denote the point estimate and 95% CI for each study's risk ratio. The diamond signifies the pooled risk ratio, the diamond center denotes the point estimate, and the width denotes the 95% CI. IV indicates inverse; and OMT, optimal medical therapy.

American Society of Transplantation.[27] *The Kidney Disease: Improving Global Outcomes* clinical practice guidelines and the American Heart Association/American College of Cardiology recommend that asymptomatic kidney and liver transplant candidates with known CAD should not undergo routine coronary revascularization exclusively to reduce perioperative cardiac events. Rather, such therapy should be reserved for high-risk anatomic subsets where revascularization would allow improved survival.[28,29]

Two reasons may explain why revascularization practices are so varied despite the available guidance. First, there is a paucity of robust data on the optimal screening and subsequent appropriate management when CAD is found. This is unsurprising, because patients with CKD are often excluded from major cardiovascular disease trials. Second, waitlisted patients invariably fall into a no man's land, where the responsibility of cardiovascular risk ownership is unclear in the setting of a fragmented model of care consisting of the transplant nephrologist, the evaluating cardiologist, and the referring nephrologist.

The objective of this meta-analysis was to aid in further clarifying whether preemptive revascularization confers a benefit over OMT in transplant candidates with CAD. Our findings demonstrate that this is not the case. Coronary revascularization is not without its risks. Additionally, it may delay kidney transplantation and prolong waitlist times. Ultimately, patients may not survive long enough while on the waitlist to be transplanted. There are also patients who are denied a transplant if they are not revascularized, inevitably denying them the benefits of transplantation. Although the widespread use of OMT has progressed, including the use of guideline-based statins, β-blockers, and angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors, the use of it in practice is still suboptimal. In the ISCHEMIA-CKD trial, <50% of all participants were on angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors at recruitment.[20] In a separate study from the United Kingdom, the use of an interdisciplinary CKD heart failure clinic in managing patients with CKD and heart failure was conducted in a real-word cohort. At recruitment, 81% of patients were on β-blockers, but only 55% were on angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors, and only 17% were on mineralocorticoid receptor antagonists.[30] Less use of angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors in patients with established CKD is likely because of concern for worsening renal function and subsequent risk of developing hyperkalemia. Ultimately, future large randomized controlled trials such as ISCHEMIA-CKD, which includes patients with CKD on the transplant waitlist, and meta-analyses of studies such as these will help confirm the benefit of OMT over preemptive revascularization in this population. In turn, this may help improve the use of these guideline-based medications.

Limitations

This meta-analysis has limitations primarily because of limitations in the studies that were included. There was heterogeneity in the baseline characteristics of the patients included in each study. The mean follow-up duration was 3 years, and it is possible that longer follow-up would be required to detect differences in outcomes between the 2 groups. The specific OMT regimen used for CAD was not described within the individual studies; therefore, it is unclear what the composition and dosage of the medications used were. Additionally, except for one, most studies included were observational in design and lacked randomization, which increases the possibility of selection bias and confounding. Finally, meta-analyses are prone to reviewer selection bias. However, this was minimized by using the systematic *Preferred Reporting Items for Systematic Review and Meta-Analyses* guidelines to report this meta-analysis and having 2 independent reviewers extract the data.

CONCLUSIONS

At present, there is no established protocol to determine the optimal strategy to screen for CAD in kidney transplant candidates. Importantly, whether abnormal screening results warrant further invasive investigation, such as coronary angiography and subsequent revascularization, is unclear. More robust data are required before clear protocols can be established. This meta-analysis suggests that revascularization was not superior to OMT in reducing all-cause mortality, cardiovascular mortality, or MACEs in waitlisted kidney transplant candidates with asymptomatic CAD who eventually underwent kidney transplantation. These findings are not surprising. The cardiologist's approach to any preoperative ischemia evaluation is not to find asymptomatic disease and correct it, because it is clear that this approach does not make people feel better, live longer, or improve survival in noncardiac surgery. The goal is to uncover left main disease for which bypass surgery would be indicated, independent of planned noncardiac surgery. Therefore, initiating aggressive OMT and conducting vigorous cardiac risk stratification primarily to exclude left main disease, with close hemodynamic monitoring perioperatively, are essential for optimizing outcomes in this high-risk population.

ARTICLE INFORMATION

Received August 6, 2021; accepted November 29, 2021.

Affiliations

Department of Medicine (M.U.S., J.J.) and Jefferson Heart Institute, Thomas Jefferson University Hospitals, Philadelphia, PA (G.D.M.).

Acknowledgments

The results presented in this article have not been published previously in whole or part, except in abstract form. Publication made possible in part by support from the Thomas Jefferson University Open Access Fund.
Author Contributions Dr Siddiqui was involved with the study design, data collection, analysis, writing the article, and study supervision. Dr Junarta was involved with the data collection and analysis, and writing the article. Dr Marhefka was involved with writing the article and study supervision.

Sources of Funding

None.

Disclosures

None.

REFERENCES

1. Machnicki G, Pinsky B, Takemoto S, Balshaw R, Salvalaggio PR, Buchanan PM, Irish W, Bunnapradist S, Lentine KL, Burroughs TE, et al. Predictive ability of pretransplant comorbidities to predict long-term graft loss and death. *Am J Transplant*. 2009;9:494–505. doi: 10.1111/j.1600-6143.2008.02486.x
2. Sapir-Pichhadze R, Tinckam KJ, Laupacis A, Logan AG, Beyene J, Kim SJ. Immune sensitization and mortality in wait-listed kidney transplant candidates. *J Am Soc Nephrol*. 2016;27:570–578. doi: 10.1681/ASN.2014090894
3. Lentine KL, Brennan DC, Schnitzler MA. Incidence and predictors of myocardial infarction after kidney transplantation. *J Am Soc Nephrol*. 2005;16:496–506. doi: 10.1681/ASN.2004070580
4. Kasiske BL, Maclean JR, Snyder JJ. Acute myocardial infarction and kidney transplantation. *J Am Soc Nephrol*. 2006;17:900–907. doi: 10.1681/ASN.2005090984
5. Ramanathan V, Goral S, Tanriover B, Feurer ID, Kazancioglu R, Shaffer D, Helderman JH. Screening asymptomatic diabetic patients for coronary artery disease prior to renal transplantation. *Transplantation*. 2005;79:1453–1458. doi: 10.1097/01.TP.0000164147.60036.67
6. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151:264–269, w64. doi: 10.7326/0003-4819-151-4-200908180-00135
7. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;25:603–605. doi: 10.1007/s10654-010-9491-z
8. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JAC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928. doi: 10.1136/bmj.d5928
9. Viswanathan M, Patnode CD, Berkman ND, Bass EB, Chang S, Hartling L, Murad MH, Treadwell JR, Kane RL. Recommendations for assessing the risk of bias in systematic reviews of health-care interventions. *J Clin Epidemiol*. 2018;97:26–34. doi: 10.1016/j.jclinepi.2017.12.004
10. Murad MHMV, Ioannidis JPA, Prasad K, Cook DJ, Guyatt G. *Advanced Topics in Systematic Reviews: Fixed-Effects and Random-Effects Models*. The JAMA Network: McGraw Hill; 2014.
11. Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *Int J Epidemiol*. 2012;41:818–827. doi: 10.1093/ije/dys041
12. Murad MH, Mustafa RA, Schünemann HJ, Sultan S, Santesso N. Rating the certainty in evidence in the absence of a single estimate of effect. *Evid Based Med*. 2017;22:85–87. doi: 10.1136/ebmed-2017-110668
13. De Lima JJ, Gowdak LH, de Paula FJ, Muela HC, David-Neto E, Bortolotto LA. Coronary artery disease assessment and intervention in renal transplant patients: analysis from the KiHeart cohort. *Transplantation*. 2016;100:1580–1587. doi: 10.1097/TP.0000000000001157
14. Eschertzhuber S, Hohlrieder M, Boesmueller C, Pomaroli A, Steurer W, Junker T, Margreiter R, Hoerman C. Incidence of coronary heart disease and cardiac events in patients undergoing kidney and pancreatic transplantation. *Transplant Proc*. 2005;37:1297–1300. doi: 10.1016/j.transproceed.2004.12.022
15. Felix R, Saparia T, Hirose R, Almers L, Chau Q, Jonelis T, Zheng S, Zaroff J. Cardiac events after kidney transplantation according to pretransplantation coronary artery disease and coronary revascularization status. *Transplant Proc*. 2016;48:65–73. doi: 10.1016/j.transproceed.2015.12.028
16. Kahn MR, Fallahi A, Kim MC, Esquitin R, Robbins MJ. Coronary artery disease in a large renal transplant population: implications for management. *Am J Transplant*. 2011;11:2665–2674. doi: 10.1111/j.1600-6143.2011.03734.x
17. Lindley EM, Hall AK, Hess J, Abraham J, Smith B, Hopkins PN, Shihab F, Welt F, Owan T, Fang JC. Cardiovascular risk assessment and management in prerenal transplantation candidates. *Am J Cardiol*. 2016;117:146–150. doi: 10.1016/j.amjcard.2015.10.016
18. Singh N, Parikh S, Bhatt U, Vonvisger J, Nori U, Hasan A, Samavedi S, Andreoni K, Henry M, Pelletier R, et al. Cardiac stress test as a risk-stratification tool for posttransplant cardiac outcomes in diabetic kidney transplant recipients. *Transplantation*. 2012;94:1224–1229. doi: 10.1097/TP.0b013e31827147d8
19. Tita C, Karthikeyan V, Stroe A, Jacobsen G, Ananthasubramaniam K. Stress echocardiography for risk stratification in patients with end-stage renal disease undergoing renal transplantation. *J Am Soc Echocardiogr*. 2008;21:321–326. doi: 10.1016/j.echo.2007.06.004
20. Herzog CA, Simegn MA, Xu Y, Costa SP, Mathew RO, El-Hajjar MC, Gulati S, Maldonado RA, Daugas E, Madero M, et al. Kidney transplant list status and outcomes in the ISCHEMIA-CKD trial. *J Am Coll Cardiol*. 2021;78:348–361. doi: 10.1016/j.jacc.2021.05.001
21. Kamran H, Kupferstein E, Sharma N, Singh G, Sowers J, Whaley-Connell A, Yacoub M, Marmur J, Salifu M, McFarlane S. Revascularization versus medical management of coronary artery disease in prerenal transplant patients: a meta-analysis. *Cardiorenal Med*. 2018;8:192–198. doi: 10.1159/000487763
22. Farkouh ME, Sidhu MS, Brooks MM, Vlachos H, Boden WE, Frye RL, Hartigan P, Siami FS, Bittner VA, Chaitman BR, et al. Impact of chronic kidney disease on outcomes of myocardial revascularization in patients with diabetes. *J Am Coll Cardiol*. 2019;73:400–411.
23. Kumar N, Baker CSR, Chan K, Duncan N, Malik I, Frankel A, Ashby DR, McLean A, Palmer A, Cairns TD, et al. Cardiac survival after pre-emptive coronary angiography in transplant patients and those awaiting transplantation. *Clin J Am Soc Nephrol*. 2011;6:1912–1919. doi: 10.2215/CJN.08680910
24. Hemmelgarn BR, Southern D, Culleton BF, Mitchell LB, Knudtson ML, Ghali WA; APPROACH Investigators. Survival after coronary revascularization among patients with kidney disease. *Circulation*. 2004;110:1890–1895. doi: 10.1161/01.CIR.0000143629.55725.D9
25. Patel RK, Mark PB, Johnston N, McGeoch R, Lindsay M, Kingsmore DB, Dargie HJ, Jardine AG. Prognostic value of cardiovascular screening in potential renal transplant recipients: a single-center prospective observational study. *Am J Transplant*. 2008;8:1673–1683. doi: 10.1111/j.1600-6143.2008.02281.x
26. Manske CL, Wang Y, Rector T, Wilson RF, White CW. Coronary revascularisation in insulin-dependent diabetic patients with chronic renal failure. *Lancet*. 1992;340:998–1002. doi: 10.1016/0140-6736(92)93010-K
27. Rangaswami J, Bangalore S, Kaplan B, Birdwell KA, Wiseman AC, McCullough PA, Dadhania DM. Cardiovascular disease care fragmentation in kidney transplantation: a call for action. *Kidney Int*. 2019;96:568–571. doi: 10.1016/j.kint.2019.04.042
28. Lentine KL, Costa SP, Weir MR, Robb JF, Fleisher LA, Kasiske BL, Carithers RL, Ragosta M, Bolton K, Auerbach AD, et al. Cardiac disease evaluation and management among kidney and liver transplantation candidates: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *Circulation*. 2012;126:617–663. doi: 10.1161/CIR.0b013e31823eb07a
29. Chadban SJ, Ahn C, Axelrod DA, Foster BJ, Kasiske BL, Kher V, Kumar D, Oberbauer R, Pascual J, Pilmore HL, et al. KDIGO clinical practice guideline on the evaluation and management of candidates for kidney transplantation. *Transplantation*. 2020;104:S11–S103. doi: 10.1097/TP.0000000000003136
30. Nguyen M, Rumjaun S, Lowe-Jones R, Ster IC, Rosano G, Anderson L, Banerjee D. Management and outcomes of heart failure patients with CKD: experience from an inter-disciplinary clinic. *ESC Heart Fail*. 2020;7:3225–3230. doi: 10.1002/ehf2.12796