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Systematic Review and Meta analysis of Outcomes of Lower Extremity Peripheral Arterial Interventions in Patients with and without Chronic Kidney Disease or End Stage Renal Disease

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Short tweet: Clinical outcomes following lower extremity peripheral arterial disease interventions in patients with CKD/ESRD are unknown as these patients are typically excluded from RCTs. Read our meta-analysis on this at-risk group of patients.

Type of Research: Systematic review and meta-analysis

ABSTRACT

Objectives: Patients with chronic kidney disease (CKD) present with a higher risk of peripheral arterial disease (PAD). While individual studies have documented the association between CKD/ESRD and adverse outcomes in patients undergoing PAD interventions in an era of technological advances in peripheral revascularization, the magnitude of the effect size is unknown. Therefore, we aimed to perform a meta-analysis comparing outcomes of PAD interventions in patients with CKD/ESRD to patients with normal renal function, stratified by intervention type (endovascular vs. surgical), reflecting contemporary practices

Methods: Five databases were analyzed from January-2000 to June-2019 for studies comparing outcomes of lower extremity PAD interventions in patients with CKD/ESRD vs normal renal function. We included both endovascular and open interventions, with indication being either claudication or critical limb ischemia. We analyzed pooled odds ratio (OR) across studies with 95% CI using random effects model. Funnel plot and exclusion sensitivity analyses were used for bias assessment.

Results: Seventeen observational studies with 13,140 patients were included. All included studies except two accounted for unmeasured confounding either by a multivariable regression analysis or by case control matching. Maximum follow up was 114 months (range 0.5-114). Target lesion revascularization (TLR) was higher with CKD/ESRD compared to normal renal function (OR 1.68 (95% CI 1.25-2.27), P=.001). Major amputations (OR 1.97 (95% CI 1.37-2.83),P<.001) and long-term mortality (OR 2.28 (95% CI 1.45-3.58),P<.001) were higher with CKD/ESRD. Higher TLR rates with CKD/ESRD versus normal renal function were only seen with endovascular interventions but were not found to be different for surgical interventions.

Statistically significant higher rates of major amputations and long-term mortality were seen with CKD/ESRD compared with normal renal function, regardless of the intervention type.

Conclusions: Patients with CKD/ESRD undergoing lower extremity PAD interventions have worse outcomes when compared to patients with normal renal function. When stratifying our analyses by endovascular versus open surgical interventions, higher rates of TLR for CKD/ESRD were only seen with endovascular, and not in open surgical approaches. Major amputations and all-cause mortality were higher with CKD/ESRD, irrespective of the indication. Evidence-based strategies to manage this at risk population in PAD are essential.

KEY WORDS – CKD/ESRD, endovascular interventions, open surgical bypass, target lesion revascularization, mortality, major amputations, meta-analysis.

Abbreviations

ABI- ankle brachial pressure index

CI – confidence interval

CLI – chronic limb ischemia

CKD- chronic kidney disease

PAD – peripheral arterial disease

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analysis

TLR – target lesion revascularization

RCT- randomized controlled trials

OR – Odds ratio

INTRODUCTION

Peripheral arterial disease (PAD) is a major global health problem with a prevalence of ~237 million, predominantly in the lower and middle income countries [(1)]. Patients with chronic kidney disease (CKD) carry a relatively higher risk of developing atherosclerotic cardiovascular disease (CVD) than patients with normal renal function [(2, 3)]. This includes coronary artery disease (CAD), ischemic strokes and PAD. There is a two fold higher risk of having lower ankle brachial pressure indices (ABI) and PAD in patients with CKD [(4, 5)]. In the National Health and Nutrition Exam Survey (NHANES), almost 24% of the patients with CKD stage 3 or more had higher prevalence of PAD indicated by low ABI of <0.90 as compared with 4% in patients without CKD [(6)]. The presence of CKD in PAD patients is also associated with a 44% increased risk of perioperative as well a long-term mortality [(7, 8)].

Despite being a very high risk population with higher mortality, prior randomized controlled trials (RCTs) with PAD interventions have systematically excluded CKD patients [(9)]. The risk associated with CKD and PAD outcomes has not been formally quantified across studies, and it is also unknown whether the association between CKD and PAD outcomes is modified by the type of procedures patients undergo (endovascular versus open lower extremity interventions). While individual studies have documented the association between CKD/ESRD and adverse outcomes in patients undergoing PAD interventions (10), the magnitude of the overall effect size is unknown, especially in an era of technological advances in peripheral revascularization. To address these questions, we aimed (1) to compare procedural and prognostic outcomes, including target lesion revascularization (TLR), major amputations and long-term mortality, following lower extremity arterial interventions in patients with CKD/ESRD versus those with normal renal function and (2) to explore whether this association is modified by endovascular versus open interventions. We hypothesized that in patients undergoing lower extremity arterial interventions, CKD/ESRD is associated with worse outcomes as compared with normal renal function. We also hypothesized that the observed association between CKD/ESRD and outcomes following lower extremity interventions would not differ by procedure type.

MATERIALS AND METHODS

Data sources and search strategy

We searched 5 databases including PubMed, EMBASE, Scopus, Cochrane, and Web of Science for randomized and observational studies from inception to June 2019, using the following search terms: “chronic kidney disease”, “chronic renal failure”, “end stage renal disease”, “ESRD”, “peripheral arterial disease”, “peripheral artery disease” “peripheral vascular disease”, “hemodialysis”, “endovascular intervention”, “bypass surgery”, “bypass graft”, “bypass grafting” and their combinations. A secondary search of the references of the relevant articles was also performed. Only studies written in English language were included. his methodology has been validated and published in previous studies [11].

Study selection

Studies were required to meet the following inclusion criteria: (1) Randomized clinical trials, or observational studies of patients > 18 years of age with claudication or chronic limb ischemia (CLI) after the year 2000, (2) comparison of lower extremity arterial intervention (endovascular or surgical) outcomes in patients with and without CKD/ESRD, (3) report outcomes including target lesion revascularization, major amputation, or all-cause mortality, and (4) report event rates with sample sizes, odds ratio (OR) with a 95% confidence interval (CI), or similar comparative measure such as risk ratio (RR) or log OR.. Follow-up studies of the same cohort were included only once unless the follow-up study published data on different outcomes. Our search strategy was designed to be broad so as to include any observational study that compared CKD/ESRD to normal renal function in patients with PAD interventions so as to not miss any available study. The search strategy is shown in Supplementary Figure 1. With improvement in both surgical and endovascular revascularization techniques and equipment, we aimed to analyze outcomes of patients with renal dysfunction undergoing PAD interventions over the past two decades and thus we excluded studies prior to 2000.

Data extraction

Initial screening was performed using the titles of 8,014 studies obtained by our search criteria. This was performed by two investigators (M.A.N and B.A.S) to extract a list of eligible abstracts for full-text review. Full-text reviews were independently performed by M.A.N. and B.A.S. Results were compared and any discrepancy between the 2 reviewers was resolved by consulting the third reviewer (C.M.). The reviewers then extracted data from all available studies including patient baseline demographics and outcome variables. Baseline variables included age, sex, tobacco use, prior coronary artery disease or myocardial infarction, diabetes, hypertension, hyperlipidemia, prior lower extremity arterial interventions, lesion location, and lesion length showed in Supplementary Table I. When studies did not report the necessary raw data for effect size calculation, we calculated this from included figures and bar graphs using Engauge digitizer 4.1. Risk of bias assessment was performed using the New Castle Ottawa Scale (NOS) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) as shown in Supplementary Table II. The scale helps to analyze quality of non-randomized observational studies. It evaluates a study based on three domains– selection of study groups, comparability and ascertainment of outcome and exposure. The scale rates the quality of studies as good, fair and poor.

Patient selection

Supplementary table I shows the baseline characteristics of all studies that are included in this meta-analysis. The authors included observational studies comparing outcomes of lower extremity arterial interventions in patients with and without CKD/ESRD. Ultimately, the authors identified 18 observational studies with 21 comparison groups to be included in this analysis. These studies included patients with both critical limb ischemia (rest pain and/or tissues loss with/without gangrene) and claudication.

Definitions and Outcomes

CKD was defined as either kidney damage or a decreased glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 for at least 3 months. For patients with stage 1 and stage 2 CKD who tend to have GFR>90 mL/min/1.73 m^2, CKD was defined by the presence of 1) Albuminuria (albumin excretion > 30 mg/24 hr or albumin:creatinine ratio > 30 mg/g [> 3 mg/mmol]), 2) Urine sediment abnormalities, 3) Electrolyte and other abnormalities due to tubular disorders, 4) Histologic abnormalities, 5) Structural abnormalities detected by imaging, 6)History of kidney transplantation. ESRD was defined as stage 5 CKD with GFR of 10-15 mL/min/1.73 m^2 requiring dialysis.

Our primary outcome was target lesion revascularization (TLR), which was defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel for restenosis Secondary outcome measures included major amputations and long-term all-cause mortality.

Major amputation was defined as above-the-knee or below-the-knee amputations. All-cause mortality was defined as death from any cause follow-up. We stratified results based on endovascular or surgical intervention. Endovascular interventions included percutaneous balloon angioplasty with or without stenting. Open surgical repair refers to surgical bypass, patch repair or endarterectomy involving common femoral, superficial femoral, profunda femoris, or infra popliteal vessels.

Statistical analyses

The systematic review and meta-analysis was conducted in accordance with the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [(12)]. Effect sizes for the outcomes of interest across were pooled across the studies using a random effects model. We analyzed OR with 95% CI for all the outcomes from studies derived from event rates and their respective sample sizes.

Patients with CKD/ESRD were considered as the comparator group and patients with normal renal function as control. An OR > 1 denotes a higher risk for patients with CKD/ESRD in all analysis. Heterogeneity was determined by Cochrane's Q-statistics, and I^2 values of <25%, 25-50%, and 50-75% were considered to represent low, moderate, and high heterogeneity, respectively. Subgroup analysis was performed based on endovascular versus open surgical interventions. This was not a meta regression/test for interaction which was not possible in the absence of patient-level data. In order to look into the possibility of a differential effect size, we performed the subgroup analysis for hypothesis generating purposes only. Studies were mutually exclusive with respect to endovascular and open surgical interventions. Since ESRD patients are sicker compared with CKD patients, we also performed a sub group analysis of CKD versus normal renal function only studies and ESRD versus normal renal function only studies.

Funnel plot analyses were performed to explore publication bias and exclusion-sensitivity analyses were used for all outcomes, excluding the study with maximum weight, to examine the robustness of the findings. A meta-regression was conducted to study the effect of follow-up time on the individual outcomes of interest. A P-value of <0.05 was considered statistically significant. Analyses were performed by M.A.N. using Comprehensive Meta-analysis (version 3.3, Biostat, Englewood NJ) [(13)].

RESULTS

Study characteristics

The final analysis included 18 observational studies [(14-31)] with 21 comparison groups. Out of the 18 studies, one study [(27)] did not report our outcomes of interest and so our final analysis included 17 observational studies. All included studies except two (22, 26) accounted for unmeasured confounding either by a multivariable regression analyses or by case control matching. The study by Ogawa et al had predominantly

There were a total of 48,081 patients with a maximum follow-up of 114 months. The mean age of the entire cohort was 70.2 ± 2.1 years. A total of 72% of the patients were male and 40% had diabetes. An overview of patient and procedural characteristics is listed in Supplementary Table I. Risk of bias of the included studies is shown in Supplementary Table II. A summary of primary and secondary outcomes is shown in Figure 1.

Primary outcomes

Target lesion revascularization

Patients with CKD/ESRD had a 67% increased odds of TLR as compared with those with normal renal function (OR 1.68 (95% CI 1.25-2.27), P=.001) (Figure 2). Risk of bias was minimal, as assessed using a funnel plot (Supplementary Figure 2). Exclusion sensitivity analysis performed by exclusion of the study with maximum weight [24] did not alter the results of the analysis and overall heterogeneity became lower (I^2=27%). When stratifying by procedure type, higher rates of TLR in CKD/ESRD vs. non-CKD/ESRD were only seen in patients undergoing endovascular interventions (OR 1.84 (95% CI 1.32-2.56), P<.001) but not for this comparison in surgical revascularization (OR 1.09 (95% CI 0.53-2.24), P=.824). We then performed a sub analysis with ESRD only studies, excluding CKD studies to avoid dilution of results from lower stages of CKD. TLR was higher with ESRD patients compared with non ESRD patients (OR 1.89, 95% CI: 1.36-2.62, P<0.0001). When we analyzed CKD only studies, TLR was not different between CKD and non-CKD patients (OR 1.25, 95% CI: 0.71-2.20, P=0.443).

Secondary outcomes

Major amputations:

Overall, major amputation was was more common inpatients with CKD/ESRD (OR 1.97 (95% CI 1.37-2.83, P<.001) as compared with normal renal function (Figure 3). Risk of bias assessed using a funnel plot was minimal (Supplementary Figure 3) and heterogeneity was high with an I^2 of 74%. An exclusion sensitivity analysis performed using exclusion of the study with maximum weight [14] did not alter the results of the analysis but heterogeneity remained high (74%). Patients with CKD/ESRD had a higher rate of major amputation regardless of whether they underwent endovascular ((OR 1.85 (95% CI 1.26-2.72), P=.002) or surgical (OR 3.17 (95% CI 1.11-9.03), P=.031) revascularization, compared with their non-CKD/ESRD counterparts. We then performed a sub analysis with ESRD only and CKD only studies. Major amputations were higher in ESRD patients compared with non ESRD patients (OR: 2.11, 95% CI: 1.27-3.53, P=0.004) and in CKD patients compared with non-CKD patients (OR: 1.82, 95% CI: 1.04-3.18, P=0.036).

Long-term all-cause mortality

In the overall cohort, long-term mortality was significantly higher in patients with CKD/ESRD (OR 2.28 (95% CI 1.45-3.58) P<.001) (Figure 4). Risk of bias assessed using a funnel plot was high (Supplementary Figure 4) and heterogeneity was high with an I^2 of 89%. An exclusion sensitivity analysis performed using exclusion of the study with maximum weight [(24)] did not alter the results of the analysis and heterogeneity remained high (I^2=90%). Long-term mortality was higher in CKD/ESRD as compared with no CKD/ESRD, regardless of procedure type (for endovascular: OR 2.18 (95% CI 1.24-3.84), P=.007, for open surgical: OR 2.47 (95% CI 1.16-5.24), P=.019). We then performed a sub analysis with ESRD only studies. All-cause mortality was higher with ESRD patients compared with non ESRD patients (OR 1.96, 95% CI: 1.14-3.39, P=0.016). With CKD only studies, all-cause mortality was still higher with CKD compared with non-CKD patients (OR 2.89, 95% CI: 1.44-5.78, P=0.003).

DISCUSSION

In this meta analysis, lower extremity PAD intervention, patients with CKD/ESRD had 67% increased odds of needing a TLR as compared with patients with normal renal function. As for their long-term prognostic outcomes, patients with CKD/ESRD had around 2-fold increased odds of undergoing a major amputation or dying compared to patients with normal renal function. When stratifying our analyses by endovascular versus open surgical interventions, higher rates of TLR for CKD/ESRD were only seen in endovascular, and not in open surgical approaches. For major amputation and mortality outcomes, higher rates were seen with CKD/ESRD, regardless of procedure type.

There is limited data on TLR and primary patency rates following PAD interventions in patients with CKD. Studies have shown worse patency rates with PAD surgical interventions in CKD, reporting as high as 3.7-fold increased odds of clinical failure in dialysis-dependent patients compared with patients with normal renal function [(32)]. Similarly, in terms of patency for endovascular procedures, presence of CKD was found to be associated with worse long-term patency. In the STAR registry of endovascular interventions, there was a fourfold increased odds of having lower long-term patency in the presence of CKD (RR 4.0, P=.002) [(33)]. Our study found higher rates of TLR in the presence of CKD/ESRD with lower extremity PAD interventions.

Currently, there is no randomized data comparing endovascular and surgical interventions in patients with CKD/ESRD. Our study found that TLR after surgical revascularization in patients with CKD/ESRD was no different compared to patients with normal renal function, whereas for endovascular approaches, we did observe an increased risk of TLR Studies have shown that the presence of pre-dialysis CKD in PAD contributes to a pro-inflammatory and a pro-thrombotic milieu [(34)]. This, in addition to the traditional risk factors including advanced age, diabetes, hyperlipidemia, cigarette smoking, which are often seen in patients with CKD (4), may explain the higher TLR rates with endovascular intervention in patients with CKD/ESRD as seen in our study. Similarly, vascular calcification may occur much earlier in CKD/ESRD patients as compared with the general population. Clinically, this is manifested by diffuse calcified long segment lesions which are difficult to revascularize [35]. While this study did not directly compare outcomes of endovascular and surgical revascularization for PAD in patients with CKD/ESRD, our meta-analysis begs the question whether systematic efforts to study approaches for PAD interventions in high-risk populations such as patients with CKD are overdue. Testing the hypothesis in a randomized trial with selected patients who are good surgical candidates, whether performing open vs. endovascular revascularization leads to more favorable reintervention rates may be an important future question.

Long-term mortality was higher with CKD/ESRD when compared with normal renal function patients. Prior studies with PAD interventions in patients with CKD have shown higher mortality in CKD [36, 37], which is also seen in our analysis, but with this meta-analysis we were able to quantify the magnitude of the risk. Regardless odf the type of intervention patients underwent, mortality in CKD/ESRD patients was about 2-fold as high as compared with non CKD/ESRD patients. The 2016 ACC/AHA focused update [38] recommends considering both surgical revascularization (Class I, LOE C) and endovascular intervention (Class I, LOE B) for patients with CLI, as BASIL (Bypass versus Angioplasty in Severe Ischemic of the Leg) showed similar rates of survival [39]. This was not exclusive to patients with renal disease and so it is difficult to conclude what the best strategy is for patients with CKD/ESRD.

It is important to understand the surgical risks and perioperative morbidity and mortality associated with open surgical interventions while choosing a strategy. In a previously published meta analysis of surgical infra inguinal bypass outcomes, ESRD patients had higher major amputations at short term follow-up despite higher graft patency, along with higher perioperative mortality and morbidity including pneumonia, myocardial infarction and infections [40]. Endovascular intervention, on the other hand, is less invasive and expensive, lower complications rates with lower early mortality [41]. But even with improvement in endovascular techniques and with use of low profile devices, rates of major amputations at follow-up still remains high [42]. In our analysis, both endovascular and open interventions in patients with CKD/ESRD were associated with higher major amputations. The higher risk of amputation after EVT and bypass has been seen in other studies where advanced kidney disease (Stage 5/ESRD) was associated with higher risk of amputation, irrespective of revascularization strategy [36, 43]. In contrast, in patients without CKD/ESRD who undergo revascularization, there is evidence towards decreased risk of amputation with EVT and open surgery. In the BASIL trial [44], the only randomized trial of EVT vs surgical bypass, open surgery was associated with lower risk of amputation, two years after randomization. These results, in view of findings from our meta-analysis, may not be applicable to our patient population with CKD/ESRD and warrants further research on optimal treatment strategies for this group.

Future subgroup analysis work using the BEST-CLI trial data might be able to shed further light on outcomes for surgical or endovascular interventions for patients with CLI by comorbid CKD/ESRD status, as this trial did not exclude patients with this comorbidity (45). But until further randomized data become available, choice of procedure should be patient-centric based on individual patient risk factors, relative short and longterm risks, anticipated benefit, overall CKD/ESRD related prognosis and patient preference.

There are several limitations. A major limitation of this study is the observational nature of all included studies as CKD/ESRD patients have mostly been excluded from randomized controlled trials of PAD. Heterogeneity of some of our analyses were high. We used exclusion sensitivity analyses and funnel plots to reduce potential bias. Studies included both ESRD and CKD which could introduce bias considering differences between CKD and ESRD. Selection bias may have been introduced with higher-risk patients without adequate targets for bypass being referred for endovascular treatment as last resort to prevent amputation. This patient population with poor run-off characteristic of ESRD may explain the higher risk of TLR in CKD/ESRD patients treated with endovascular interventions. Finally, in studies with ESRD vs non ESRD groups, the ESRD patients were dialysis dependent regardless of their GFR. Non-ESRD group included patients who were not dialysis dependent and included a minority of patients (<20%) with Cr >1.2, but did not specify the GFR. The non CKD population included majority of patients with normal renal function and mild renal impairment (GFR >60). Finally, publication bias may always be an inherent limitation of any meta-analysis but the search criteria were designed to be comprehensive.

We conclude that patients with CKD/ESRD undergoing lower extremity PAD interventions have higher rates major amputations and long-term mortality as compared with patients without renal disease. Only patients with CKD on dialysis have higher rates of TLR as compared with patients with normal renal function. When stratifying by procedure type, TLR rates after surgical revascularization in patients with kidney disease were comparable to patients with normal kidney function. Our meta-analyis generated a hypothesis that warrants future randomized testing, i.e. that surgical revascularization may be associated with a more favorable risk-benefit ratio as compared with endovascular approaches in patients with CKD/ESRD undergoing PAD interventions. In the mean time, it is important to understand that comorbid

CKD confers a significantly higher risk of adverse treatment outcomes and prognosis, and that therapeutic advances to address PAD in this patient population are very much needed.

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Author Contribution:

All the authors participated in conception or design of the work, data collection, data analysis and interpretation, drafting the article, critical revision of the article and final approval of the version to be submitted. Statistical analysis was peformed by Dr Anantha-Narayanan and Dr Kim Smolderen.

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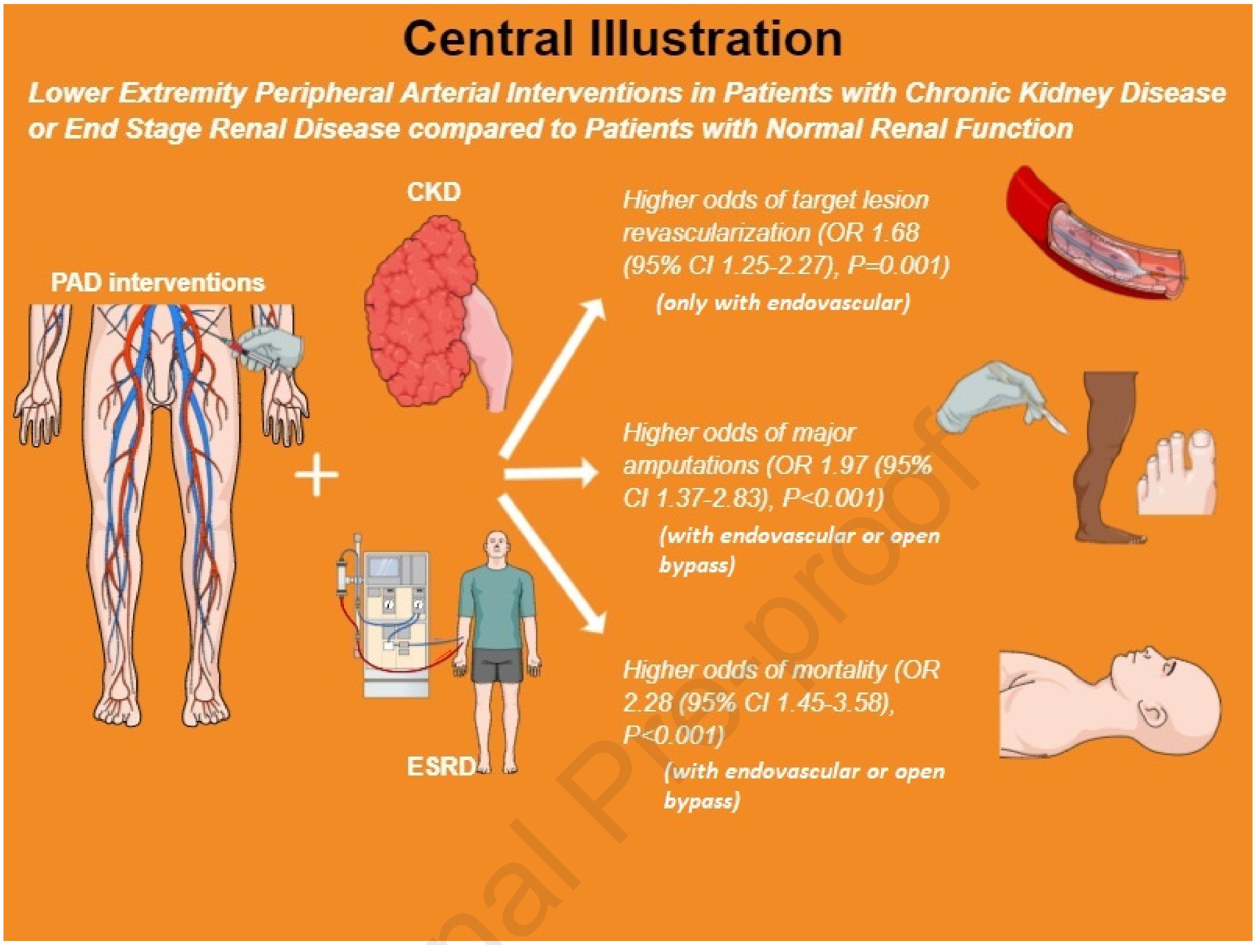
PUBMED search criteria:

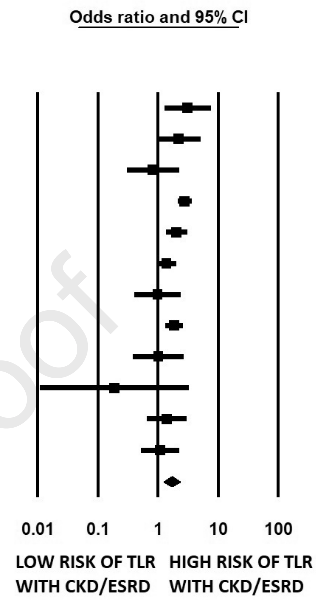
("renal insufficiency, chronic"[MeSH Terms] OR ("renal"[All Fields] AND "insufficiency"[All Fields] AND "chronic"[All Fields]) OR "chronic renal insufficiency"[All Fields] OR ("chronic"[All Fields] AND "kidney"[All Fields] AND "disease"[All Fields]) OR "chronic kidney disease"[All Fields]) OR ("kidney failure, chronic"[MeSH Terms] OR ("kidney"[All Fields] AND "failure"[All Fields] AND "chronic"[All Fields]) OR "chronic kidney failure"[All Fields] OR ("chronic"[All Fields] AND "renal"[All Fields] AND "failure"[All Fields]) OR "chronic renal failure"[All Fields]) OR ("kidney failure, chronic"[MeSH Terms] OR ("kidney"[All Fields] AND "failure"[All Fields] AND "chronic"[All Fields]) OR "chronic kidney failure"[All Fields] OR ("end"[All Fields] AND "stage"[All Fields] AND "renal"[All Fields] AND "disease"[All Fields]) OR "end stage renal disease"[All Fields]) OR ("kidney failure, chronic"[MeSH Terms] OR ("kidney"[All Fields] AND "failure"[All Fields] AND "chronic"[All Fields]) OR "chronic kidney failure"[All Fields] OR "esrd"[All Fields]) OR ("peripheral arterial disease"[MeSH Terms] OR ("peripheral"[All Fields] AND "arterial"[All Fields] AND "disease"[All Fields]) OR "peripheral arterial disease"[All Fields]) OR ("peripheral arterial disease"[MeSH Terms] OR ("peripheral"[All Fields] AND "arterial"[All Fields] AND "disease"[All Fields]) OR "peripheral arterial disease"[All Fields] OR ("peripheral"[All Fields] AND "artery"[All Fields] AND "disease"[All Fields]) OR "peripheral artery disease"[All Fields]) OR ("peripheral vascular diseases"[MeSH Terms] OR ("peripheral"[All Fields] AND "vascular"[All Fields] AND "diseases"[All Fields]) OR "peripheral vascular diseases"[All Fields] OR ("peripheral"[All Fields] AND "vascular"[All Fields] AND "disease"[All Fields]) OR "peripheral vascular disease"[All Fields]) OR ("haemodialysis"[All Fields] OR "renal dialysis"[MeSH Terms] OR ("renal"[All Fields] AND "dialysis"[All Fields]) OR "renal

dialysis"[All Fields] OR "hemodialysis"[All Fields]) OR (endovascular[All Fields] AND ("methods"[MeSH Terms] OR "methods"[All Fields] OR "intervention"[All Fields])) OR (bypass[All Fields] AND surgery,[All Fields]) OR (bypass[All Fields] AND ("transplants"[MeSH Terms] OR "transplants"[All Fields] OR "graft"[All Fields])) OR (bypass[All Fields] AND ("transplantation"[Subheading] OR "transplantation"[All Fields] OR "grafting"[All Fields] OR "transplantation"[MeSH Terms] OR "grafting"[All Fields])) AND (("2000/01/01"[PDAT] : "2019/06/31"[PDAT]) AND "humans"[MeSH Terms])


Central Illustration
Lower Extremity Peripheral Arterial Interventions in Patients with Chronic Kidney Disease or End Stage Renal Disease compared to Patients with Normal Renal Function
PAD interventions
CKD
+
ESRD
Higher odds of target lesion revascularization (OR 1.68 (95% CI 1.25-2.27), P=0.001)
(only with endovascular)
Higher odds of major amputations (OR 1.97 (95% CI 1.37-2.83), P<0.001)
(with endovascular or open bypass)
Higher odds of mortality (OR 2.28 (95% CI 1.45-3.58), P<0.001)
(with endovascular or open bypass)

Target lesion revascularization comparing CKD/ESRD to NR- stratified by endovascular versus open interventions

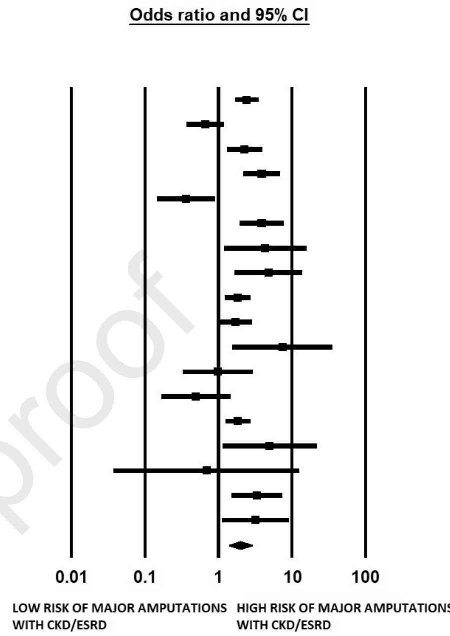
Group by Endo or open	Study name	Odds ratio	Lower limit	Upper limit	p-Value
ENDOVASCULAR	Katoaka et al	3.11	1.29	7.50	0.012
	Kawarada et al	2.22	0.96	5.11	0.062
	Meyer et al Endo	0.82	0.31	2.21	0.697
	Nakano et al	2.76	2.14	3.57	0.000
	Nakano et al 2013	2.04	1.39	3.00	0.000
	Ogawa et al	1.38	0.96	1.97	0.079
	Willenberg et al	0.98	0.40	2.38	0.967
		1.84	1.32	2.56	<0.001
OPEN SURGICAL	Kumada et al	1.02	0.39	2.67	0.972
	Meyer et al open	0.19	0.01	3.26	0.252
	Yamamoto et al	1.39	0.65	2.96	0.392
		1.09	0.53	2.24	0.824
OVERALL *(including endovascular and open surgical techniques)*		1.68	1.25	2.27	0.001



CKD - chronic kidney disease
ESRD - end stage renal disease
NR - normal renal function
TLR - target lesion revascularization

Major amputations comparing CKD/ESRD to NR - stratified by endovascular versus open interventions

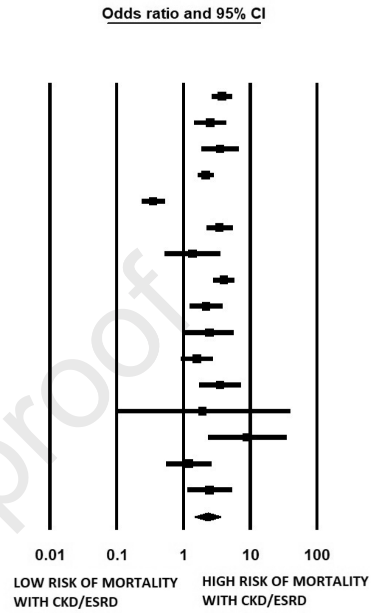
Group by Endovascular or open	Study name	Odds ratio	Lower limit	Upper limit	p-Value
ENDOVASCULAR	Baer Bositis et al	2.44	1.71	3.48	0.000
	Bakken et al claud	0.66	0.37	1.16	0.149
	Bakken et al CLI	2.26	1.31	3.91	0.003
	Davies et al	3.88	2.19	6.87	0.000
	Kawarada et al	0.37	0.15	0.90	0.029
	Kim HO et al	3.88	1.96	7.70	0.000
	Kumada et al 2008	4.33	1.20	15.65	0.025
	Meyer et al Endo	4.80	1.67	13.74	0.003
	Nakano et al	1.83	1.25	2.69	0.002
	Nakano et al 2013	1.71	1.04	2.80	0.033
	Ogawa et al	7.44	1.57	35.24	0.011
	Willenberg et al	0.97	0.33	2.89	0.960
	Xie JK et al	0.49	0.17	1.44	0.196
		1.85	1.26	2.72	0.002
OPEN SURGICAL	Kumada et al	4.99	1.15	21.64	0.032
	Meyer et al open	0.69	0.04	12.47	0.800
	Yamamoto et al	3.33	1.52	7.32	0.003
		3.17	1.11	9.03	0.031
OVERALL *(including endovascular and open surgical techniques)*		1.97	1.37	2.83	<0.001



CKD - chronic kidney disease
ESRD - end stage renal disease
NR - normal renal function
TLR - target lesion revascularization

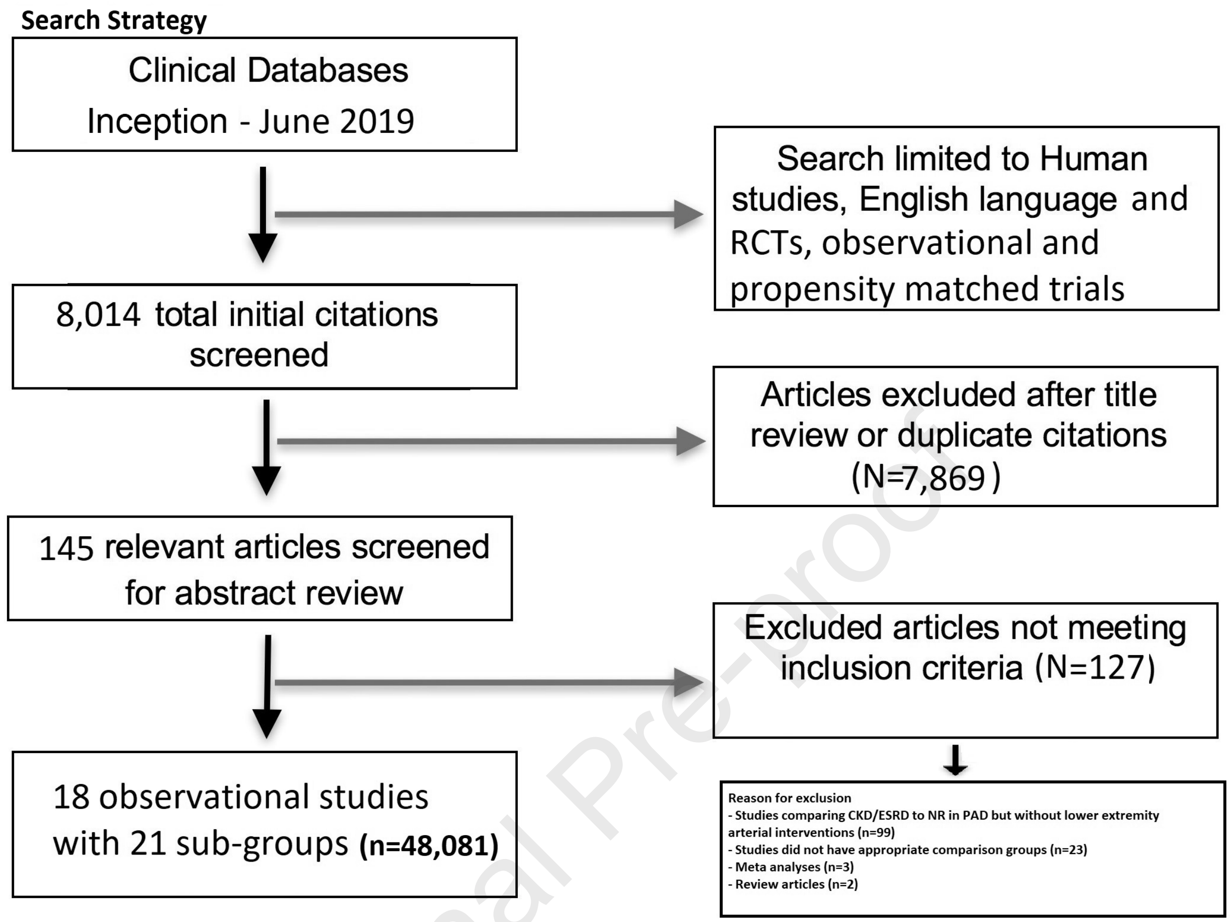
All cause mortality comparing CKD/ESRD to NR - stratified by endovascular versus open interventions

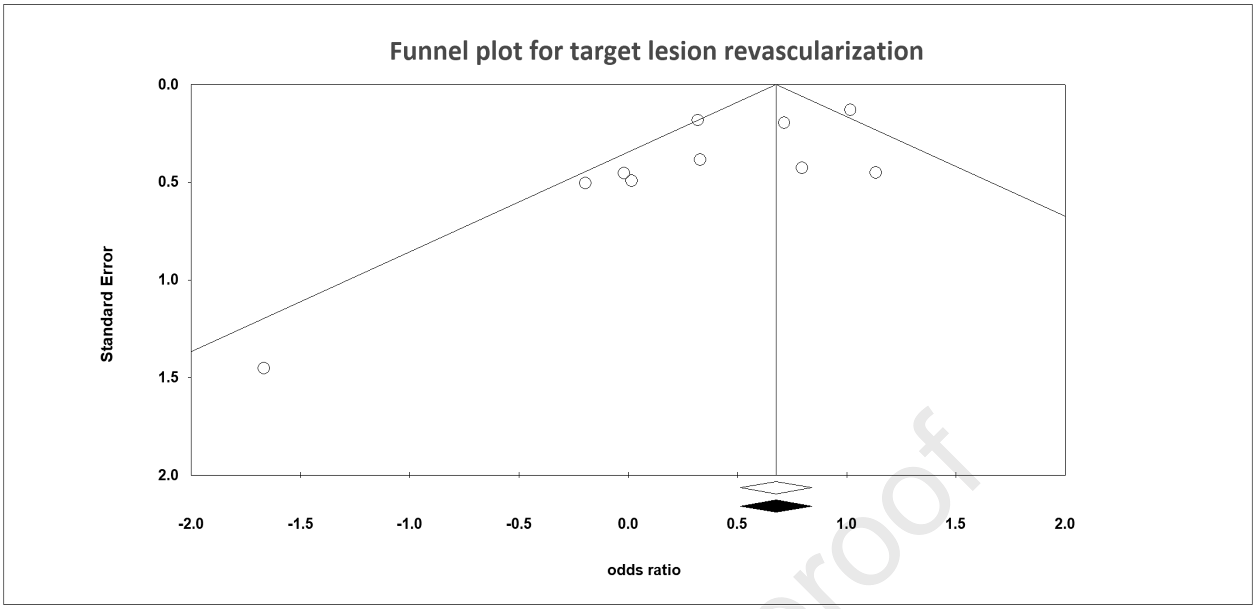
Group by Endovascular or open	Study name	Odds ratio	Lower limit	Upper limit	p-Value
ENDOVASCULAR	Baer Bositis et al	3.76	2.64	5.35	0.000
	Davies et al	2.50	1.44	4.35	0.001
	Kumada et al 2008	3.54	1.88	6.69	0.000
	Nakano et al	2.15	1.64	2.81	0.000
	Nakano et al 2013	0.35	0.24	0.52	0.000
	Ogawa et al	3.46	2.22	5.40	0.000
	Willenberg et al	1.36	0.53	3.52	0.524
	Xie JK et al	4.03	2.85	5.70	0.000
		2.18	1.24	3.84	0.007
OPEN SURGICAL	Kumada et al	2.43	1.07	5.53	0.034
	Lantis et al ESRD	1.59	0.93	2.73	0.091
	Lantis et al elevated cr	3.55	1.74	7.23	0.000
	Meyer et al open	1.93	0.09	39.35	0.669
	Redden et al	9.02	2.36	34.37	0.001
	Yamamota et al	1.20	0.55	2.59	0.649
		2.47	1.16	5.24	0.019
OVERALL *(including endovascular and open surgical techniques)*		2.28	1.45	3.58	<0.001

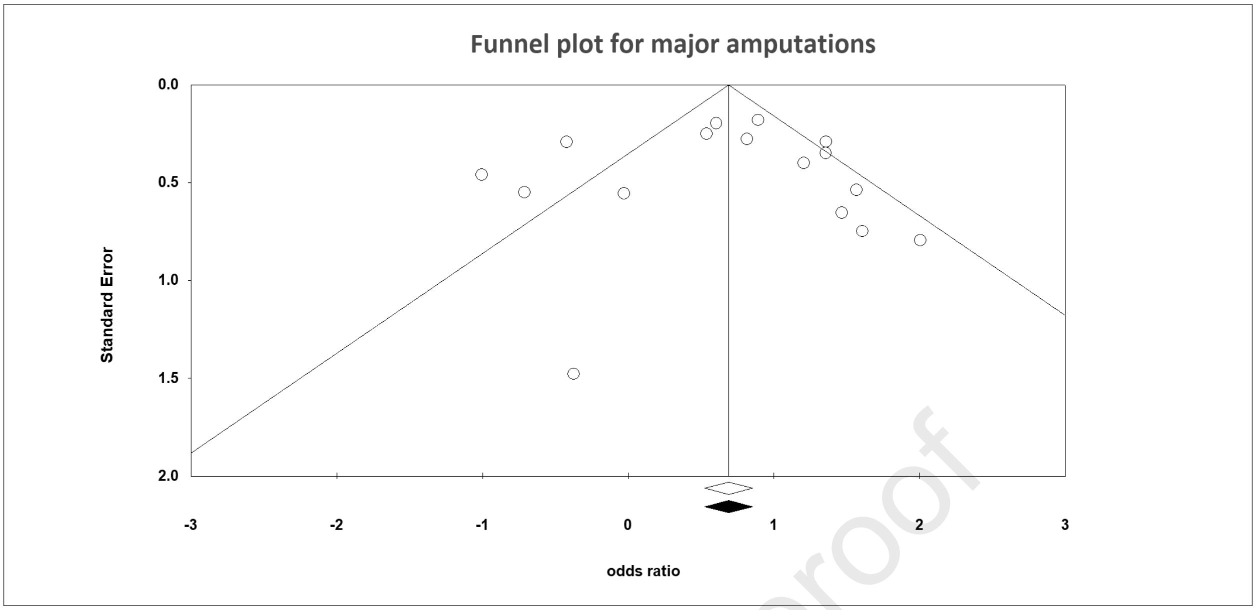


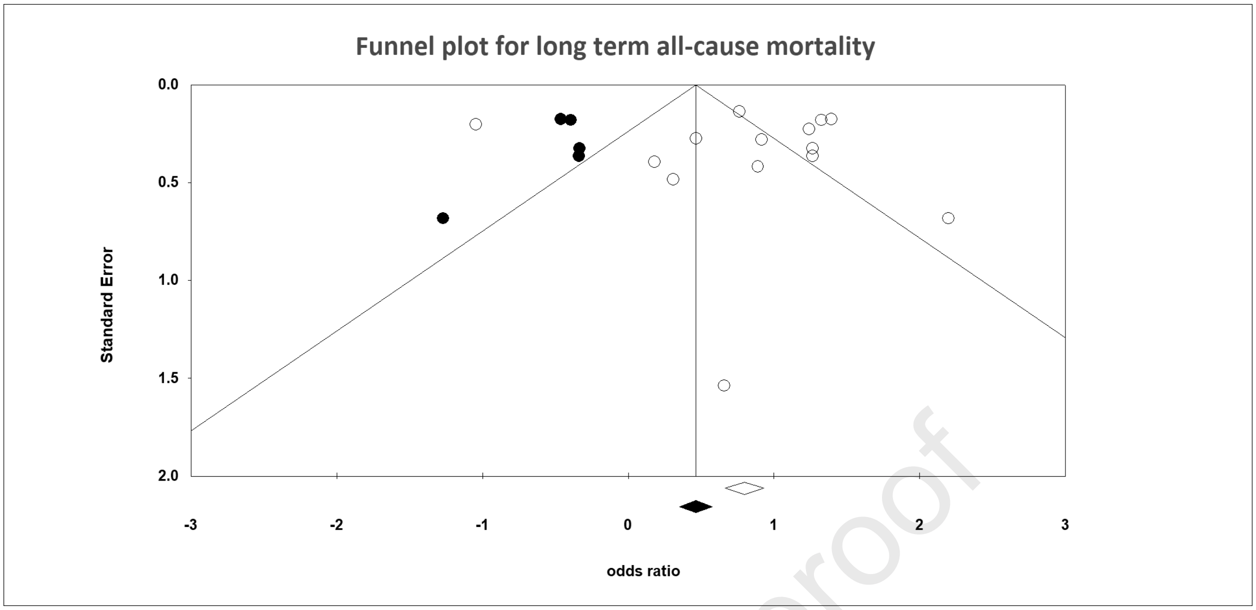
CKD - chronic kidney disease
ESRD - end stage renal disease
NR - normal renal function
TLR - target lesion revascularization

Journal Pre-proof


Search Strategy
Clinical Databases
Inception - June 2019
Search limited to Human studies, English language and RCTs, observational and propensity matched trials
8,014 total initial citations screened
Articles excluded after title review or duplicate citations (N=7,869)
145 relevant articles screened for abstract review
Excluded articles not meeting inclusion criteria (N=127)
18 observational studies with 21 sub-groups (n=48,081)
Reason for exclusion
- Studies comparing CKD/ESRD to NR in PAD but without lower extremity arterial interventions (n=99)
- Studies did not have appropriate comparison groups (n=23)
- Meta analyses (n=3)
- Review articles (n=2)


Funnel plot for target lesion revascularization
Standard Error
0.0
0.5
1.0
1.5
2.0
-2.0
-1.5
-1.0
-0.5
0.0
0.5
1.0
1.5
2.0
odds ratio


Funnel plot for major amputations
Standard Error
0.0
0.5
1.0
1.5
2.0
-3
-2
-1
0
1
2
3
odds ratio



Funnel plot for long term all-cause mortality
Standard Error
0.0
0.5
1.0
1.5
2.0
-3
-2
-1
0
1
2
3
odds ratio

Figure title and legends:

Figure 1- Central Illustration

CAPTION: Higher Odds of Target Lesion Revascularization, Major Amputations and Mortality with CKD/ESRD compared with normal renal function. CKD- Chronic kidney disease, ESRD- end stage renal disease

Figure 2. Target lesion revascularization comparing ESRD/CKD to normal renal function patients

CAPTION: CKD/ESRD patients had higher odds of target lesion revascularization compared with normal renal function in the overall cohort (P=.001). With endovascular interventions, CKD/ESRD patient had higher odds of target lesion revascularization with ESRD/CKD compared with normal renal function (P<.001). With open surgical bypass, TLR was similar between ESRD/CKD and normal renal function (P=.824)

Figure 3. Major amputations comparing CKD/ESRD to normal renal function patients

CAPTION: CKD/ESRD patients had higher odds of major amputations compared with normal renal function (P<.001). With Endovascular interventions, CKD/ESRD had higher odds of major amputations compared with normal renal function (P=.002). With open surgical bypass, CKD/ESRD had higher odds of major amputations compared with normal renal function (P=.031)

Figure 4. All-cause mortality comparing CKD/ESRD to normal renal function patients

CAPTION: CKD/ESRD patients was associated with higher odds of all-cause mortality compared with normal renal function (P<.001). With endovascular interventions, CKD/ESRD was associated with higher odds of all-cause mortality compared with normal renal function

(P=.007). With open surgical bypass, CKD/ESRD was associated with 147% increased odds of all-cause mortality compared with normal renal function (P=.019)

Online supplement

Supplementary Figure 1. PRISMA search strategy

CAPTION: Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow chart for study selection. CKD – chronic kidney disease, ESRD – end stage renal disease.

Supplementary Figure 2.- Funnel plot for bias assessment for target lesion revascularization

CAPTION: Funnel plot analyzing bias for target lesion revascularization showing minimal bias on visual assessment

*Each dot represents a study; y-axis represents the size of the study and the x-axis shows the study results

Supplementary Figure 3- Funnel plot for bias assessment for major amputations

CAPTION: Funnel plot analyzing bias major amputations showing minimal bias on visual assessment

*Each dot represents a study; y-axis represents the size of the study and the x-axis shows the study results

Supplementary Figure 4- Funnel plot for bias assessment for long-term all-cause mortality

CAPTION: Funnel plot analyzing bias for all-cause mortality showing minimal bias on visual assessment

*Each dot represents a study; y-axis represents the size of the study and the x-axis shows the study results

Tables

Supplementary table 1.

Baseline Demographics and Procedural Characteristics of Studies Comparing CKD/ESRD with normal renal function in PAD interventions

Supplementary table 2.

Risk of bias assessment using the modified New Castle Ottawa Scale