Original Paper

Revascularization versus Medical Management of Coronary Artery Disease in Prerenal Transplant Patients: A Meta-Analysis

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Keywords

Revascularization · Coronary artery disease · Renal transplant · Medical management

Abstract

Introduction: End-stage renal disease requiring renal transplantation comprises a growing patient population at risk for cardiovascular disease (CVD) morbidity and mortality in large part due to accelerated atherosclerosis. Consequently, these patients are at even higher risk of major surgical CVD mortality. A paucity of research has addressed the posttransplantation CVD outcomes related to different treatment strategies in this patient population and therefore, there are no specific preoperative guidelines regarding management of coronary artery disease in this high-risk population undergoing renal transplantation. **Objective:** Through meta-analysis we compare coronary revascularization to medical management prior to renal transplantation in patients who are found to have significant obstructive coronary artery disease. **Results:** A total of 6 studies were deemed suitable out of 777 articles reviewed. This included 260 patients who received medical management and 338 who received coronary revascularization. There were 36 events in the revascularization and 57 events in the medical management group. One study only reported hazard ratios but no CVD outcomes. Comprehensive Meta-Analysis software was used to calculate pooled odds ratio with 95% confidence intervals (CI) for the fixed effects. The data is presented as forest plots. The pooled odds ratio

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with 95% CI for the fixed effects was 1.415 (95% CI 0.885–2.263), $p = 0.147$, indicating that there is no difference in CVD outcomes between pretransplant treatment strategy. This observation suggests that the CVD outcomes posttransplantation are not affected when optimal medical therapy is used instead of coronary revascularization.

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Introduction

Chronic kidney disease (CKD) is known to be a strong risk factor for cardiovascular disease and although patients with end-stage renal disease (ESRD) often benefit from renal transplantation (RT), the number one cause of mortality in this population is cardiovascular disease [1, 2]. As such, many patients referred for RT require cardiovascular optimization and undergo an extensive cardiac workup ranging from simply an EKG to coronary angiography. The nature of this workup has been the point of much research over the past few years. The following question arises when a patient with an abnormal stress test undergoes coronary angiography and is found to have significant obstruction of the coronaries. Would revascularization (with either percutaneous coronary intervention or coronary artery bypass surgery) improve outcomes posttransplantation in comparison to medical management? This exact question has been addressed in regards to vascular surgeries, most notably in the DECREASE V study [3], concluding that patients with pre-op revascularization did not improve outcomes. But little is known among patients with significant coronary artery disease (CAD) going for RT. Consequently, this meta-analysis sets out to review the literature of post-op outcomes of patients with significant coronary obstruction prior to RT who underwent either coronary revascularization versus medical management.

Methods

A PubMed search was performed using combinations of the keywords kidney transplant or renal transplant with either coronary revascularization, cardiovascular screening, major adverse cardiovascular events, percutaneous coronary intervention, or CAD management. Exclusion criteria included (1) studies prior to 1997, (2) studies that only looked at one arm of the research (i.e., only a revascularization group), (3) studies that only recorded pre-transplantation results, (4) studies that compared percutaneous coronary intervention to coronary artery bypass surgery but not to a medical management group, (5) studies that only looked at screening but not treatment of the CAD, and (6) studies that did not report the crude data but only hazard ratios or odds ratios. All other studies were included. This is summarized as a flow diagram in Figure 1. It should be noted that only 1 randomized control study was found to address this question but was excluded as the study was performed in 1992 when the medical management included calcium channel blockers and aspirin [4]. All other studies included were aimed to address other questions but also collected data on patients with obstructive CAD who underwent either revascularization or medical management. The data was analyzed using CMA package V3 (Biostat, USA). Mantel-Haenszel method (Mantel and Haenszel, 1959) was used for calculating the weighted pooled odds ratio under the fixed effects model. Heterogeneity statistic was incorporated to calculate the summary odds ratio under the random effects model (DerSimonian and Laird, 1986). The data is reported as odds ratios with 95% confidence intervals (CI).

Results

There are a total of 6 studies included in the meta-analysis. This resulted in a total of 598 subjects. Of these, 260 were in the medical management group and 338 were in the revascularization group. Five studies reported the primary cardiovascular outcomes. One study [27]

Fig. 1. Flow diagram showing the article selection process for final meta-analysis.

Fig. 2. Forrest plot showing odds of having cardiovascular mortality among patients with coronary artery disease receiving standard medical therapy (MM) versus revascularization (REV), post renal transplantation.

only reported the hazard ratio and thus, total number of cardiovascular outcomes was not available for this study. Of the 5 studies, there were 36 events in the revascularization and 57 events in the medical management group. Figure 2 depicts the forest plots of studies included along with the odds ratio and 95% CI. The pooled odds ratio with 95% CI for the fixed effects was 1.415 (95% CI 0.885–2.263), $p = 0.147$. These results indicate that compared to pretransplant revascularization, medical management is no different in terms of posttransplant cardiovascular outcomes. The heterogeneity observed for the studies included was $Q = 19.587$, $I^2 = 74.47$, $p < 0.01$.

Discussion

The results of our meta-analysis show that preoperative cardiac revascularization does not affect posttransplantation mortality compared to medical management for individuals undergoing renal transplant. One of the major challenges in understanding therapeutic strat-

egies for individuals with CAD and impaired renal function stems from the fact that renal impairment usually leads to exclusion from clinical trials [5]. To our knowledge, this is the first meta-analysis evaluating the preoperative cardiac management of patients undergoing RT. Our meta-analysis incorporated all the recent data within the past decade. Study designs for diagnosis of CAD varied between trials and all trials incorporated retrospective data from single transplant centers. There were different populations represented with varying incidences of CAD in this study.

According to the organ procurement and transplant registry 2012 annual survey, there were 88,874 people on the waiting list and 16,487 candidates successfully receiving transplants [6]. The median waiting time for renal transplant in 11- to 17-year-old recipients between 2011 and 2014 was 680 days. The number of people waiting for transplant has steadily risen and currently there are 106,207 people waiting for RT [7]. Individuals with CKD and ESRD requiring hemodialysis and have CAD or acute coronary syndromes have poorer outcomes [8, 9]. Therefore, it is imperative to balance the risk of preoperative coronary angiography accelerating the need for dialysis, potential bleeding risk with dual antiplatelet therapy, and potential delay in delivery of procured kidneys versus postprocedural atherosclerotic complications.

CKD and ESRD lead to activation of renin-angiotensin-aldosterone system, oxidative stress, and inflammation, with increased cytokines and dyslipidemia leading to acceleration of atherosclerosis [10–12]. Additionally, myocardial structural changes, endothelial dysfunction, and vascular calcification, combined with dialytic and electrolyte changes, result in a 14-fold increase in sudden cardiac death [11, 13, 14]. On the other hand, platelet dysfunction combined with excess dosing of antiplatelet and antithrombotic medication in patients with renal insufficiency results in increased morbidity and mortality [15]. Most importantly, there is emerging data highlighting the limited utilization of evidence-based pharmacologic therapies in patients with CKD or ESRD compared to those with normal renal function [16, 17]. This could partly be explained by the fact that nearly 80% of ESRD subjects and 75% of CKD subjects are excluded from trials and thus, evidence-based pharmacologic interventions cannot be readily applied to the renally impaired population [5].

The only randomized trial exploring management of CAD in renal transplant candidates is by Manske et al. from 1992 [4]. In this study, they performed coronary angiography in 151 individuals with insulin-dependent diabetes and found obstructive CAD in 31 subjects. Twenty-six of the subjects agreed to randomization. At the end of 8.4 months, 10 of 13 individuals in the medical arm and 2 of 13 individuals in the revascularization arm had cardiovascular events. There were also 4 deaths in the medical arm. It is important to note that the medical arm in this study consisted of aspirin and calcium channel blockers. Since the study by Manske et al. [4], advances in preoperative medical management have led to improvement in postoperative cardiovascular outcomes, which is comparable to preoperative invasive management of CAD. The POISE study has shown that preoperative use of metoprolol succinate prior to intermediate or high-risk noncardiac surgery leads to reduced postoperative myocardial infarction. It is important to note that renal impairment was part of the inclusion criteria in the POISE study [18]. Similarly, the CARP trial showed that revascularization of preoperative stable CAD did not reduce mortality, myocardial infarction, stroke, or death 30 days postoperatively [19]. It must be noted that the CARP trial excluded patients with CKD and ESRD, and subsequent follow-up of subjects with creatinine ≥ 3.5 mg/dL revealed that they had a 4-fold increase in mortality, though it is unclear what pharmacologic therapy these subjects received [20]. Additionally, the BARI 2D trial has shown that diabetic patients are more likely to have diffuse CAD and have improved outcomes when treated with coronary artery bypass graft and optimal medical therapy. Therefore, it is necessary to recognize that the findings of Manske et al. [4] are limited due to a small sample size with

suboptimal medical therapy and optimal surgical treatment of diabetics leading to a positive finding. More recently, Kumar et al. [21] have noted that preemptive revascularization prior to transplantation leads to increased survival at 1 and 3 years posttransplant. The conclusions of this study are limited as it was nonrandomized and participants were asked if they wanted revascularization or not. Refusing revascularization may be an indicator of poor underlying medical condition and inability to adhere to medical therapy.

Although cardiac catheterization to define coronary anatomy is the gold standard, it is not without risks. Noninvasive stress testing is thus preferred to evaluate for CAD prior to transplantation. Prior studies have reported variable sensitivity and specificity of noninvasive stress testing for detection of CAD [22, 23]. In this meta-analysis, Singh et al. [24] and Tita et al. [25] used preoperative stress echocardiography to risk-stratify patients. Though these studies were not powered to assess the benefit of preoperative revascularization versus medical management, appropriate preoperative noninvasive stress imaging seems to be associated with better medical management. Singh et al. [24] found that if the pretransplant stress test result was negative, transplantation could proceed with a low risk of posttransplant adverse cardiac events. This supports the use of noninvasive stress testing to risk-stratify pretransplant candidates. In addition, Singh et al. [24] found no significant difference between the patients with no significant CAD and those with significant lesions who underwent revascularization. Interestingly, both of these studies, compared to Lindley et al. [26] and Kahn et al. [27], had better preoperative noninvasive echocardiography sensitivity and negative predictive values [24–27]. Therefore, modest differences in noninvasive stress imaging can help identify individuals that will benefit from medical management and reduce the need for invasive diagnosis.

The study by Eschertzhuber et al. [28] in our meta-analysis favors revascularization. Eschertzhuber et al. [28] found that patients awaiting transplant with proven high-risk profile for posttransplant cardiac events can undergo transplantation safely if they are revascularized. In addition, they concluded that candidates for kidney transplant who had a history of CAD but no workup or treatment were at tremendous risk for posttransplant cardiac events. This supports the data suggesting pretransplant screening for CAD in candidates for renal transplant should include noninvasive testing and if needed, coronary angiography.

In addition to preoperative medical therapy, Felix et al. [29] present a unique perspective on anatomic data of posttransplant CAD. Of the 33 subjects in this analysis who experienced posttransplant primary outcome requiring coronary angiography, 74% were observed to have CAD progression in a new anatomic location. This posttransplant cardiovascular outcome would not have been prevented simply with pretransplant revascularization. This suggests that plaque stability and progression are commonly vulnerable in this population despite transplant [29]. Complicating the postoperative management further is the fact that reported compliance to optimal medical therapy is in the range of 10–60%. This range is widely affected by timing of transplant, comorbid conditions such as diabetes or peripheral vascular disease, lack of data on medication efficacy in this population, known drug interactions between calcineurin inhibitors with statins and angiotensin receptor blockers, and risk of bleeding [30, 31].

In conclusion, our meta-analysis suggests that preoperative medical management versus revascularization does not lead to significant difference in posttransplant cardiac outcomes. Theoretically, careful risk stratification using noninvasive testing, meticulous perioperative hemodynamic monitoring, and closer postoperative follow-up to monitor for medication adherence can possibly lead to better outcomes in this particular patient population. Further prospective randomized trials are needed to define which subsets of patients might benefit from pretransplant intensified medical management or from revascularization.

Statement of Ethics

This meta-analysis uses published data from published studies, no ethics committee approval is necessary.

Disclosure Statement

Authors have nothing to disclose.

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