Outcomes of Percutaneous Renal Artery Revascularization versus Medical Therapy in Atherosclerotic Renal Artery Stenosis: A Meta-Analysis

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Abstract

**Background:** Atherosclerotic renovascular disease is an increasingly prevalent condition associated with other macrovascular diseases. To date, randomized controlled trials have demonstrated limited mortality benefit of revascularization with stenting when compared to medical therapy.

**Methods:** Trials were identified from the PubMed and Cochrane databases. Primary endpoints were overall mortality as well as mortality from cardiovascular and renal causes. Secondary endpoints included occurrence rates of major cardiovascular and renal events as well as change in systolic blood pressure over time. Intention to treat analysis was performed.

**Results:** Two large RCTs met inclusion criteria. The pooled data provided 1737 patients of which 862 were in the stented group and 875 received medical therapy alone. Overall mortality was slightly lower in the revascularized group, (RR= 0.93; 95% CI, 0.77-1.12, P= 0.67) however, the benefit was not statistically significant. The mortality benefit from cardiovascular and renal specific causes was not statistically significant. Additionally, the occurrence rate of major cardiovascular and renal events did not differ significantly between the revascularized and medical therapy groups. There was however, a modest decrease in systolic blood pressure over time in the revascularized patients compared to the patients receiving medical therapy alone (mean difference= -1.9mmHg; 95% CI, -3.80 to -0.06; P= 0.04).

**Conclusions:** In this meta-analysis of contemporary randomized controlled trials, successful renal artery angioplasty with stenting will provide a modest decrease in systolic blood pressure. However, this meta-analysis did not reach statistical significance to prove benefit of revascularization vs medical therapy alone with regards to mortality. We propose that effects of revascularization may not have equal effect on all patient subgroups. Perhaps if patients are restratified based on baseline chronic kidney disease staging, statistically significant mortality benefit will be elucidated.

INTRODUCTION

Atherosclerotic renal artery stenosis or atherosclerotic renovascular disease (ARVD) is a common condition with a mortality rate of approximately 16% annually. This is largely because of its associations with macrovascular diseases such as coronary artery disease (CAD) and peripheral arterial disease (PAD) [1]. The prevalence among persons older than 65 years of age may be as high as 7% [1-7]. Up to 30% of patients with CAD have evidence of ARVD and patients presenting with congestive heart failure (CHF) and flash pulmonary edema have an increased incidence and association with ARVD [8]. Over the last two decades there has been a rise in the use of percutaneous interventional renal artery revascularization for treatment of ARVD and surgical correction has fallen out of favor [3,9,10]. There have been multiple randomized controlled trials assessing the benefit of intervention versus medical therapy with regards to mortality, improved blood pressure control and change in renal function. To date, no single randomized trial or review series has demonstrated mortality benefit. Improvements in controlling blood pressure (BP) and in renal function recovery (defined as slowed progression or improvement in glomerular filtration rate (eGFR), have shown conflicting results [11,12]. Based on the absence of a preferred strategy for ARVD, we performed a meta-analysis using the current available studies to readdress potential benefits of percutaneous interventional approach vs medical therapy.

MATERIAL AND METHODS

**Study design**

Comparative trials of medical therapy versus revascularization have failed to confirm the benefits of intervention versus conservative management alone. Many of these studies were small and may have missed important treatment effects. We combined the results of two large randomized controlled trials,
CORAL and ASTRAL, that compared the effects of angioplasty with stenting to medical therapy alone in the treatment of ARVD.

Study selection

This review and meta-analysis was performed with standard protocols recommended by the preferred reporting items for systematic reviews and meta-analysis and the quality of reporting of meta-analysis groups for randomized trials [13]. The study search was performed in the PubMed database and Cochrane Library, using key words such as: “atherosclerotic renal artery stenosis”, “renal artery stenting”, “renal artery revascularization”, “renal artery angioplasty.” To be considered for inclusion, clinical studies had to be randomized trials comparing renal artery revascularization with medical therapy in hypertensive patients with atherosclerotic renal artery stenosis and a minimum follow up interval of 6 months. We included studies with only adult patients who had uncontrolled hypertension treated or untreated and moderate to severe (>50%) unilateral or bilateral atherosclerotic renal artery stenosis. Patients must be assigned randomly to either primary angioplasty with stenting or primary antihypertensive drug therapy as the principal intervention. Studies analyzing patients with fibromuscular dysplasia were excluded. Three evaluators (J.P., F.O.N., and E.E.) performed literature searches, and individually reviewed relevant articles and extracted data independently. Discrepancies between study design and obtained data were resolved by consensus if necessary.

Study endpoints

The primary outcome for this meta-analysis was a composite measure of overall mortality. We also analyzed individual components of the primary outcome including mortality secondary to cardiovascular and renal causes. Secondary outcomes included changes in blood pressure, renal function and the rate of occurrence of stroke, myocardial infarction, hospitalization for congestive heart failure (CHF), and progression of renal failure to dialysis dependent end-stage renal disease (ESRD).

Statistical analysis

Information on study design, sample size, demographic characteristics, outcome, and follow-up data were extracted and entered into a data sheet using a standardized protocol. The absolute numbers of events for each outcome of interest were extracted for the revascularized and medical therapy group. All absolute numbers of events for each outcome of interest were entered into a data sheet using a standardized protocol. The primary outcome for this meta-analysis was a composite measure of overall mortality. We also analyzed individual components of the primary outcome including mortality secondary to cardiovascular and renal causes. Secondary outcomes included changes in blood pressure, renal function and the rate of occurrence of stroke, myocardial infarction, hospitalization for congestive heart failure (CHF), and progression of renal failure to dialysis dependent end-stage renal disease (ESRD).

RESULTS

Trials and patient characteristics

Two RCTs meeting the pre-specified inclusion and exclusion criteria were identified. The ASTRAL trial [1] was an 806 patient multicenter randomized controlled trial conducted over the course of five years with the purpose of determining whether revascularization together with medical therapy improved renal function and other outcomes as compared with medical therapy alone in patients with atherosclerotic renal artery stenosis. Results did not demonstrate a mortality benefit with revascularization. The CORAL trial [5] was a 947 patient multicenter randomized controlled trial conducted over a median follow up period of 43 months (interquartile range 31-55 months) comparing revascularization with medical therapy alone. Results did not demonstrate a mortality benefit to revascularization technique. However, it did demonstrate a modest and statistically significant improvement in systolic blood pressure control.

The pooled data provided 1737 patients, of which 862 were in the stented group and 875 received medical therapy alone. The mean follow up period reported in these studies was 6 months. The mean baseline systolic blood pressure in both studies was greater than or equal to 149 mmHg. The change in diastolic blood pressure was not uniformly reported. The baseline patient characteristics can be found in Table (1). It was not possible to pool the results describing changes in renal function as the method of measurement was not uniform among the trials. The ASTRAL trial reported the change in serum creatinine level and the change in reciprocal serum creatinine. Baseline eGFR was reported, but the reciprocal serum creatinine was utilized throughout the rest of the study as a surrogate marker of the change in creatinine clearance over time. The CORAL trial elaborated on mortality from renal causes and progression of renovascular disease to permanent renal replacement but did not report changes in serum creatinine or eGFR.

Overall mortality

There was no significant between-group difference in overall mortality in either of the trials. When we compared all cause mortality between revascularized and nonrevascularized patients for composite results of both studies we found a small but statistically insignificant decrease in the risk ratio, 0.93 with 95% CI of 0.77 to 1.12 and P=0.67. Results for overall and cardiovascular and renal cause mortality are shown in Table (2) and Figure (1).

Cardiovascular Mortality

Overall there was no statistically significant difference in mortality from cardiovascular causes in revascularized versus nonrevascularized patients when the results are pooled, the risk ratio is 0.94 with a 95% CI of 0.7 to 1.24 and P = 0.96 (Table 2, Figure 2). Both trials individually did not demonstrate a significant difference in cardiovascular mortality either.

Mortality from Renal Causes

In both the ASTRAL and CORAL trials the mortality from renal causes constituted a relatively small proportion of deaths in both revascularized and nonrevascularized patients. There
Table 1: Baseline Patient Characteristics.

<table>
<thead>
<tr>
<th></th>
<th>ASTRAL</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>CORAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Mean Age</td>
<td>Male sex</td>
<td>History of Diabetes</td>
<td>History of Coronary Artery Disease</td>
<td>History of Smoking</td>
</tr>
<tr>
<td></td>
<td>of Patients</td>
<td>(range)-yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revascularized</td>
<td>403</td>
<td>70 (42-86)</td>
<td>254 (63%)</td>
<td>121 (30%)</td>
<td>192 (48%)</td>
<td>276 (68%)</td>
</tr>
<tr>
<td>Non-Revascularized</td>
<td>403</td>
<td>71 (43-88)</td>
<td>253 (63%)</td>
<td>115 (29%)</td>
<td>189 (49%)</td>
<td>301 (75%)</td>
</tr>
<tr>
<td>CORAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revascularized</td>
<td>459</td>
<td>69.3 (60-79)</td>
<td>234 (51%)</td>
<td>149 (32.4%)</td>
<td>122 (26.5%)</td>
<td>129 (28%)</td>
</tr>
<tr>
<td>Non-Revascularized</td>
<td>472</td>
<td>69 (60-78)</td>
<td>230 (48.9%)</td>
<td>162 (34.3%)</td>
<td>143 (30.2%)</td>
<td>152 (32.2%)</td>
</tr>
</tbody>
</table>

Table 2: Comparison of Mortality Outcomes in Revascularized vs Non-Revascularized Patients.

<table>
<thead>
<tr>
<th>End Point</th>
<th>Revascularized group (N=862)</th>
<th>Non-revascularized group(N=875)</th>
<th>Risk Ratio, M-H, Random(95%CI)</th>
<th>Absolute Risk Reduction(95%CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall mortality</td>
<td>166</td>
<td>182</td>
<td>0.93 (0.77-1.12)</td>
<td>-0.02(-0.05 to 0.02)</td>
<td>0.67</td>
</tr>
<tr>
<td>Death from Cardiovascular causes</td>
<td>83</td>
<td>90</td>
<td>0.94 (0.7-1.24)</td>
<td>0.01(-0.03 to 0.02)</td>
<td>0.96</td>
</tr>
<tr>
<td>Death from renal causes</td>
<td>12</td>
<td>18</td>
<td>0.68 (0.32-1.41)</td>
<td>0.00(-0.03 to 0.02)</td>
<td>0.03</td>
</tr>
<tr>
<td>Stroke</td>
<td>40</td>
<td>46</td>
<td>0.88 (0.58-1.34)</td>
<td>-0.01(-0.03 to 0.01)</td>
<td>0.43</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>66</td>
<td>64</td>
<td>1.04 (0.75-1.45)</td>
<td>0.00(-0.02 to 0.03)</td>
<td>0.67</td>
</tr>
<tr>
<td>Hospitalization for Congestive Heart Failure</td>
<td>86</td>
<td>99</td>
<td>0.88 (0.67-1.15)</td>
<td>-0.01(-0.05 to 0.02)</td>
<td>0.24</td>
</tr>
<tr>
<td>Permanent Renal Replacement Therapy</td>
<td>46</td>
<td>39</td>
<td>1.30 (0.62-2.68)</td>
<td>0.01(-0.01 to 0.03)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

was no statistically significant difference in mortality from renal causes in either the revascularized or nonrevascularized patient groups when the data from both the CORAL and ASTRAL trials are analyzed individually although there was a nonsignificant trend for benefit with revascularization when the composite of both trials is analyzed. The risk ratio of death from renal causes in revascularized versus nonrevascularized patients is 0.68 (95% CI 0.32 to 1.41 P=0.03).

**Incidence of major cardiovascular and renal events**

The incidence of stroke, myocardial infarction, hospitalization for CHF and permanent renal replacement therapy in the revascularized group compared to the nonrevascularized group was well described in both the ASTRAL and CORAL trials. Neither study individually demonstrated a statistically significant decrease in the incidence of these major cardiovascular or renal events. We found there was no statistically significant difference in the occurrence of these events. There was a small but statistically insignificant decrease in the risk ratio for stroke and hospitalization from CHF in the revascularized group compared to the nonrevascularized group. Conversely there was a small yet statistically insignificant increase in the risk ratio of the incidence of myocardial infarction and progression of renal failure to permanent renal replacement therapy. These results are illustrated in Table (2).

**Systolic blood pressure**

The composite effect of revascularization on systolic blood pressure (SBP) demonstrated a modest and statistically significant decrease in SBP compared to nonrevascularized patients. In the ASTRAL trial, during the five-year study period, systolic blood pressure decreased in both study groups, but there was no significant difference between the groups in this trial. In the CORAL trial systolic blood pressure declined in both the medical therapy only and stented group and was found to be modestly lower in the stented group than the medical therapy only group. When we combined the results of these studies we found a significant mean difference in systolic blood pressure.
to be 1.9 mmHg lower in the revascularized group versus the nonrevascularized group (95% CI -3.8 to -0.06; P=0.04). Results are shown in Table (3) and Figure (4).

DISCUSSION

A meta-analysis performed by Nordman et al published in 2003 suggested that balloon angioplasty conferred slightly better hypertension control than medical therapy alone as determined by a decrease in mean number of anti-hypertensive drugs that patients were on, but it was impossible to describe the changes in renal function as the method of measurement was not uniform among the trials [15,16]. Since then, two randomized controlled trials (STAR and ASTRAL) have been performed with the purpose of determining if revascularization together with medical therapy improved renal function compared with medical therapy alone. The results of these studies demonstrated that overall there was no significant benefit in revascularization over medical therapy alone with regards to the likelihood of recovery of renal function [1,4,17].

In 2009, Kalra et al. [7], performed a study to evaluate the efficacy of revascularization on renal artery stenosis, but classifying patients in different tiers, as per estimated glomerular filtration rate (eGFR). It was found that overall there was no statistical difference in change in eGFR from baseline to 1 year between the nonrevascularized and the revascularized group. However, when comparing the same outcome according to chronic kidney disease (CKD) tiers, significant improvement in renal function was found at 1 year in the revascularized cohorts compared to the non-revascularized patients with CKD stages 3, 4 and 5 at baseline (eGFR decreased by a mean of 22.6 mL/min/yr in the non-revascularized patients but only decreased by a mean of 11.2 mL/min/yr in the revascularized group (P<0.0001)) [18]. In addition, the magnitude of change in both systolic and diastolic BP was greater in the revascularized group when compared to non-revascularized group with baseline CKD stages 3-5. Such results were not found in patients with CKD stage 1 or 2 [19,20]. Although clinically very relevant, this conclusion came from substudy analysis.

The CORAL and ASTRAL trials did not find a statistically significant difference between revascularization versus medical therapy alone with regards to mortality nor major cardiovascular and renal end points. There is, however, a statistically significant decrease in systolic blood pressure in the intervention group compared to medical therapy alone. Additionally, with regard to the overall mortality as well as CV and renal mortality data, there is a trend to favor revascularization but it lacks statistical significance to truly demonstrate benefit, likely due to the sample size and statistical power of each trial. With regard to
mortality from renal causes, the trend did not achieve statistical significance likely because of the rarity of this particular event thus widening the confidence interval. For unclear reasons the decrease in systolic blood pressure in the intervention group did not translate to statistically significant improvements in mortality outcomes. It is possible this occurred because of relatively small patient size in each of the included studies; however, it is possible these discrepancies occurred because the benefits of renal artery stenting do not uniformly benefit all recipients equally [2]. As was demonstrated by Kalra et al., when patients were stratified based on baseline staging of chronic kidney disease it was found that the magnitude of benefit in terms of renal function and systolic blood pressure was far greater in patients with worse baseline CKD (stages 3-5) compared to those with CKD stages 1-2. It can be postulated that the patients included in our meta-analysis did not demonstrate larger benefit with revascularization in terms of blood pressure reduction, because they were not separated by baseline renal disease status. A revision with re-stratification of patients in the ASTRAL and CORAL trials based on their classes of baseline CKD would clarify this hypothesis. This may also elucidate whether or not revascularization confers benefit to patients with baseline worsened CKD regarding other clinical outcomes, including mortality.

**CONCLUSION**

Although with this meta-analysis there was no significant change in mortality, major cardiovascular and renal outcomes when we compared revascularization for ARVD to conservative medical therapy, there is improvement of blood pressure levels and baseline CKD stage 3-5, revascularization will lead to a greater magnitude of improvement in control of hypertension and decreased progression of renal failure and plausibly an improvement in mortality. While retrospective analysis of previous trials may or may not demonstrate this benefit [11,12,21,22], large scale randomized trials designed a priori are necessary to clarify if other outcome benefits can be achieved with revascularization.

**CONFLICTS OF INTEREST**

Drs. Powell, Ebin and Nascimento report no financial relationships or conflicts of interest regarding the content herein.

**REFERENCES**


