

Original Article

Do patients undergoing renal revascularization outside of the ASTRAL trial show any benefit? Results of a single centre observational study

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Abstract

Introduction/objectives. Though recent research has concluded that revascularization of atherosclerotic renal artery stenosis has no benefit for most patients, negative findings of the Angioplasty and STent for Renal Artery Lesions (ASTRAL) trial have been criticized in professional fora. Aim of the current study was to determine whether patients undergoing renal revascularization outside of ASTRAL showed any benefit. If so, could we determine a patient group that would benefit from intervention?

Methods. Patients undergoing renal revascularization outside of the ASTRAL trial between 2003 and 2007 at our institution were reviewed. The primary comparison was the rate of decline of renal function based on individual reciprocal creatinine plots for the periods leading up to and following revascularization. Those who showed any improvement in the mean slope were compared to those with a negative or neutral response.

Results. One hundred and twenty-seven patients underwent renal revascularization outside of ASTRAL. The majority [79 (62%)] showed some improvement in the rate of change in renal function, though overall this failed to reach statistical significance. Those who responded positively tended to be declining faster prior to intervention; they were less likely to require RRT (6 versus 29%), and if they did, it was significantly later (3.6 versus 0.7 years). Mortality was, however, similar in both groups. Subgroup analysis was undertaken of patients in whom kidney function was rapidly deteriorating prior to revascularization. The rate of change in this group showed a more sizeable improvement ($P = 0.05$). Nonetheless, a similar proportion of both groups required RRT and there was no evidence of improvement in overall mortality.

Conclusions. In keeping with ASTRAL's findings, our use of renal revascularization has produced no demonstrable benefit overall. There was a suggestion of benefit in patients with rapidly declining renal function in terms of delaying the need for renal replacement therapy, but improvements in cardiovascular outcomes have yet to be proven.

Introduction

Atherosclerotic renal artery stenosis (ARAS) is well established as a cause of secondary hypertension [1] and

chronic kidney disease, ultimately resulting in end-stage renal failure and early death [2, 3]. Estimates of prevalence in patients starting dialysis vary between 11.2 and 38.7% [4]. Patients with ARAS are also known to be at high risk of cardiovascular events (myocardial infarction, stroke, congestive cardiac failure and sudden cardiac death) [5] and may suffer early death for these reasons.

It was therefore proposed that revascularization of ARAS could improve blood pressure control and slow the progression of renal dysfunction [6, 7]. As techniques for endovascular therapy have improved [8], technical success has been achieved in 98% [9]. However, up to 2009 only three randomized clinical trials had been published comparing revascularization with medical therapy alone [10–12], and meta-analysis of the 210 patients demonstrated no clear benefit from revascularization at 6-month follow-up [13]. Nonetheless, general opinion persisted that intervention would be beneficial in patients with tight ARAS of a single functioning kidney or with bilateral ARAS, when kidney function is rapidly deteriorating, arterial hypertension is refractory to medication or with a history of flash pulmonary oedema not related to acute coronary syndrome.

The Angioplasty and STent for Renal Artery Lesions (ASTRAL) Investigators aimed to end this uncertainty by conducting the largest randomized controlled trial to date into treatment for ARAS [14]. In total, 806 patients, enrolled >5 years from 54 centres in the UK and 4 in Australia and New Zealand, were randomly allocated to either endovascular intervention plus medical therapy or medical therapy alone. The primary comparison was the rate of decline of renal function as measured by the mean slope of reciprocal serum creatinine (a measure that has a linear relationship with creatinine clearance) over time. Secondary end points were blood pressure control, time to first renal event [acute kidney injury (AKI), renal replacement therapy (RRT), nephrectomy or death from renal failure], time to first major cardiovascular event and mortality.

Though there was a tendency towards slower decline in renal function in the revascularization group (-0.07×10^{-3} L/ $\mu\text{mol}/\text{year}$ versus -0.13×10^{-3} L/ $\mu\text{mol}/\text{year}$, $P = 0.06$), the corresponding difference in serum creatinine at final follow-up was not significant ($P = 0.64$). Blood pressure

control improved similarly between the two groups (average systolic BP by 5 mmHg, average diastolic BP by 2 mmHg); there was no difference in the time to first renal or major cardiovascular event or in mortality (survival was 60% in the revascularization group versus 57%). However, a total of 31 serious complications occurred in 23 of 335 patients undergoing intervention (6.7%), including two deaths and three amputations of toes and limbs. The authors concluded no evidence of a worthwhile clinical benefit from revascularization in patients with atherosclerotic renovascular disease over medical therapy alone.

However, ethical conduct of any randomized controlled trial such as this requires clinical equipoise. Patients could be enrolled only if their own physician was uncertain as to whether revascularization would provide worthwhile clinical benefit. Thus, one might argue that the patients most likely to benefit were excluded and the trial only demonstrated no benefit in those for whom benefit was uncertain in the first place.

Our institution was one of the centres recruiting for ASTRAL; over the entire period, 14 of the 35 recruited patients were randomized to undergo revascularization as part of the trial's protocol. However, over the same period, there were substantially more patients undergoing renal revascularization outside of the trial. As patients were being enrolled into ASTRAL only if there was uncertainty as to the best course of action, presumably, for all the other patients intervention was deemed to be likely beneficial despite the lack of evidence.

The aims of the current investigation were to determine whether these patients were in any way different from those in the ASTRAL group, and whether it was possible to determine a patient group that would benefit from renal artery stenting.

Materials and methods

All patients referred for renal revascularization between 2003 and 2007 at Ninewells Hospital were reviewed. Laboratory database limitations meant that the period of study could not be extended back to 2000 as in the original ASTRAL study. A total of 137 of the 200 patients referred actually received an intervention due to the presence of angiographically significant stenosis (70–90%) with the kidney being >7–8 cm in length. Those undergoing revascularization as part of the ASTRAL protocol ($n = 10$) were excluded. The final cohort numbered 127. All patients had primary stent placement and the angiographic result deemed satisfactory. The primary comparison was the rate of decline of renal function: biochemical data were gathered from 2001 to 2009, reciprocal creatinine plots were constructed for each patient and the line of best fit calculated using an r^2 model of linear regression (using Microsoft Excel) for the periods leading up to and following revascularization. As the ASTRAL investigators had done, we must acknowledge the limitations of

using reciprocal creatinine slopes to describe renal functional outcome. The rate of change of estimated glomerular filtration rate may be more comprehensible to the reader, but the Modification of Diet in Renal Disease (MDRD) formula for estimating GFR relies on steady-state creatinine. Therefore, in patients with a rising creatinine (presumably, a significant number of our cohort), the MDRD formula will overestimate their GFR. Secondary end points were time to RRT and death. Assessment of blood pressure control was, unfortunately, beyond the scope of the present study.

Those who responded positively in any way to revascularization in terms of improvement in the mean slope ('responders') were then compared to those with a negative or neutral response ('non-responders') in terms of sex, age at time of revascularization, serum creatinine at time of revascularization, rate of decline of renal function leading up to revascularization, kidney size, degree of renal artery stenosis and whether revascularization was bi- or unilateral (using student's *t*-test and chi-square tests as appropriate). Limited access to patient data meant that further characterization in terms of body mass index, co-morbidities (e.g. diabetes, vascular disease), degree of hypertension and antihypertensive therapy was not possible. Subgroup analysis was undertaken of patients with tight ARAS of a single-functioning kidney or with bilateral ARAS, and in those for whom kidney function was rapidly deteriorating (defined as above the 80th centile in terms of rate of decline prior to intervention).

Results

Patients undergoing revascularization at Ninewells outside of the ASTRAL protocol were older and more likely to be female than those described in ASTRAL. Our patients also had a lower serum creatinine level at time of intervention (Table 1).

The median length of lead- (pre-intervention) and follow-up data was 3.2 and 2.9 years, respectively: similar to ASTRAL's mean follow-up of 34 months or 2.8 years. The median rate of change in renal function prior to revascularization was -0.5×10^{-3} L/ μ mol/year, and following revascularization, this was -0.02×10^{-3} L/ μ mol/year. The difference was not statistically significant ($P = 0.38$). Over the period of follow-up, 19 of the 127 patients (15%) required RRT after a median 1.3 years. Fifty-six (44%) had died after a median 2.2 years, 11 of whom (20%) had required RRT prior to death.

Some slowing of the rate of decline of renal function was observed in 79 patients (62%). There was, however, no significant difference in age or sex between responders and non-responders. Baseline creatinine was similar, but those who responded positively tended to have renal function declining faster prior to revascularization (median rate of progression -0.8×10^{-3} L/ μ mol/year versus -0.01×10^{-3} L/ μ mol/year in non-responders) (Table 2). There were no significant differences in terms of whether revascularization was bilateral or unilateral, or the degree of stenosis and kidney length on the side of revascularization.

Those who responded positively to revascularization were significantly less likely to require RRT (6 versus 29%), and if they did, it was significantly later (median 3.6 versus 0.7 years) (Figure 1). Mortality was, however, similar in both groups (Figure 2).

Subgroup analysis 1

Subgroup analysis was undertaken of patients with tight ARAS of a single functioning kidney or with bilateral ARAS. The median rate of change in renal function prior to revascularization was the same as the entire cohort (-0.5×10^{-3} L/ μ mol/year), and following revascularization this was not

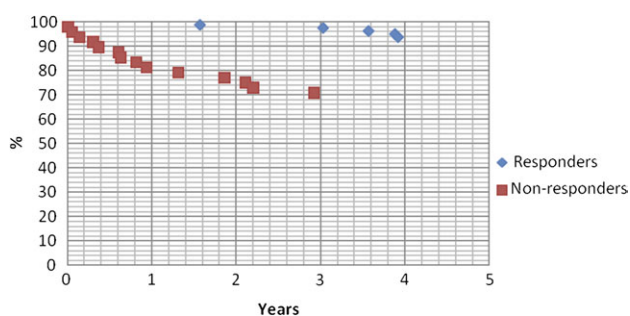
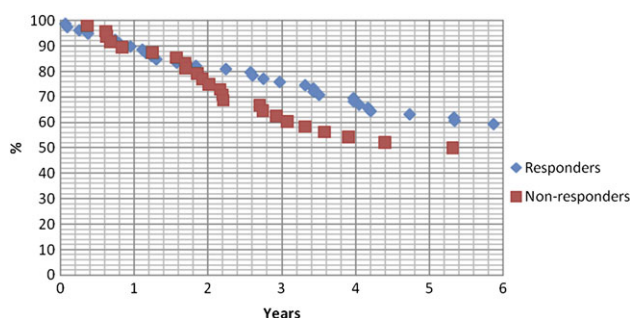
Table 1. Patient demographics: current study versus ASTRAL^a

	Current study ($n = 127$)	ASTRAL ($n = 806$)
Male sex (%)	87 (46%)	(63%)
Age at revascularization (years)	74.3 (median); 66.1–79.2 (IQ range)	70 (mean); 42–86 (range)
sCr prior to revascularization (μ mol/L)	163 (median); 129–210 (IQ range)	179 (mean); 66–331 (range)

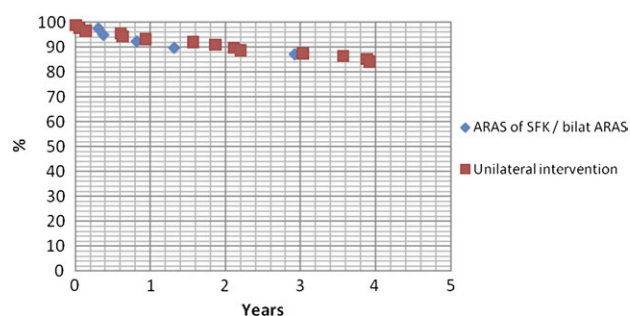
^aIQ, interquartile.

Table 2. ‘Responders’ versus ‘non-responders’

	Responders (n = 79)	Non-responders (n = 48)	P
Male sex (%)	35 (44%)	22 (46%)	0.86
Median age at revascularization (years)	73.8	75.7	0.82
IQ range (years)	65.8–79.2	65.8–78.0	
Median sCr prior to revascularization ($\mu\text{mol/L}$)	163	164	0.85
IQ range ($\mu\text{mol/L}$)	129–205	126–218	
Median rate of progression prior to revascularization ($\text{L}/(\mu\text{mol}/\text{year})$)	-0.8×10^{-3}	-0.01×10^{-3}	0.12
Bilateral revascularization (%)	23 (29%)	12 (25%)	0.61
Median degree of stenosis at site of revascularization (%)	75	80	0.12
IQ range (%)	60–80	70–90	
Median kidney length on side of revascularization (cm)	9.6	10	0.23
IQ range (cm)	8.7–10.4	9–10.8	
Need for RRT (%)	5 (6%)	14 (29%)	0.006
Median time to RRT following revascularization (years)	3.6	0.7	0.003
IQ range (years)	3.0–3.9	0.3–1.7	
All cause mortality (%)	32 (41%)	24 (49%)	0.37
Median time to death following revascularization (years)	2.6	2.1	0.47
IQ range (years)	1.1–4.0	1.5–3.0	
IQ range ($\text{L}/\mu\text{mol}/\text{year}$)	-1.3×10^{-3} to -0.5×10^{-3}	-0.4×10^{-3} to $+0.1 \times 10^{-3}$	

**Fig. 1.** RRT-free survival.**Fig. 2.** Overall survival.**Table 3.** Sub-group analysis 1

	Tight ARAS of SFK/bilateral ARAS (n = 39)	Unilateral intervention (n = 88)	P
Need for RRT (%)	5 (13%)	14 (16%)	0.65
Median time to RRT following revascularization (years)	0.8	1.7	0.35
IQ range (years)	0.4–1.3	0.6–2.8	
All cause mortality (%)	20 (51%)	36 (41%)	0.28
Median time to death following revascularization (years)	2.4	2.2	0.90
IQ range (years)	1.1–3.3	1.2–3.5	

**Fig. 3.** RRT-free survival.

significantly improved ($-0.2 \times 10^{-3} \text{ L}/\mu\text{mol}/\text{year}$, $P = 0.40$). Furthermore, there was no improvement in terms of RRT-free survival or overall mortality (Table 3, Figures 3 and 4).

Subgroup analysis 2

Subgroup analysis was also undertaken of those for whom kidney function was rapidly declining prior to intervention [defined as those above the 80th centile in terms of rate of decline ($n = 29$)]. Median rate of change in renal function

prior to revascularization was $-1.5 \times 10^{-3} \text{ L}/\mu\text{mol}/\text{year}$, and following revascularization, this was $+0.03 \times 10^{-3} \text{ L}/\mu\text{mol}/\text{year}$. In contrast, the median rate of change in those who were declining less rapidly prior to revascularization showed a less sizeable improvement ($-0.4 \times 10^{-3} \text{ L}/\mu\text{mol}/\text{year}$ pre-intervention and $-0.04 \times 10^{-3} \text{ L}/\mu\text{mol}/\text{year}$ post) ($P = 0.05$). Nonetheless, a similar proportion of both groups required RRT and there was no evidence of improvement in overall mortality (Table 4, Figures 5 and 6).

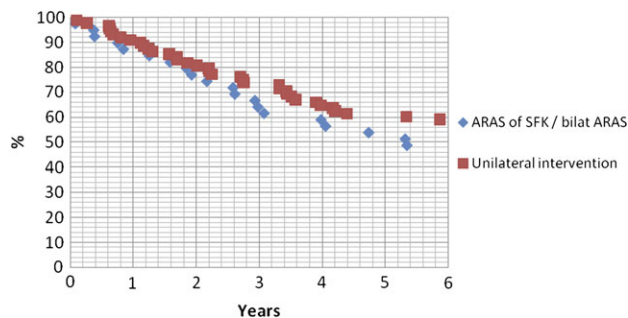


Fig. 4. Overall survival.

Table 4. Sub-group analysis 2

	More rapidly declining (n = 29)	More gradually declining (n = 98)	P
Need for RRT (%)	4 (14%)	15 (15%)	1
Median time to RRT following IQ range (year)	1.6 0.8–3.6	0.9 0.5–2.2	0.45
All cause mortality (%)	14 (48%)	42 (43%)	1
Median time to death following revascularization (years) IQ range (years)	3.5 1.3–4.3	2.1 1.0–3.0	0.06

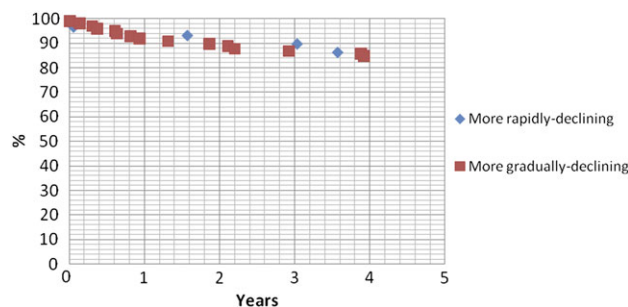


Fig. 5. RRT-free survival.

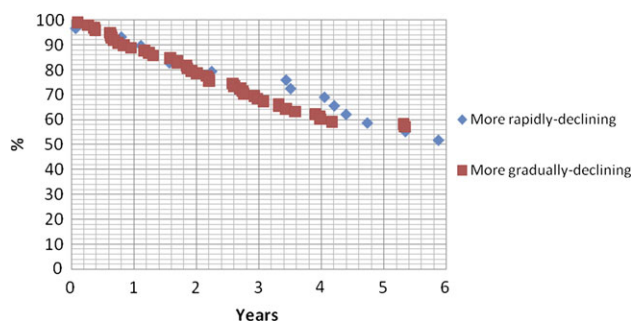


Fig. 6. Overall survival.

Complications

Documented peri-procedural complications included one haematoma at the puncture site (which subsequently became

infected and eventually required lower limb amputation), presumed contrast-induced nephropathy and cholesterol embolization. The incidence of peri-procedural AKI was 17 of 127 (13%), with four patients requiring long-term RRT after the procedure. Peri-procedural (30-day) mortality was 0.8%.

Discussion

Between 2000 and 2007, our institution recruited 35 patients into ASTRAL. However, even during the 5-year period of the present study (2003–2007), a further 127 patients underwent renal revascularization. Thus, the proportion of patients being considered for intervention outside of the trial was high (127/162, 78%). In the New England Journal of Medicine publication of ASTRAL, reference is made to the highest recruiting UK centre, Salford, in which only 24 of the 95 patients (25%) eligible for revascularization underwent the procedure outwith the trial. Our institution was the sixth highest of the 58 recruiting centres; the median number recruited by each centre was only 7 (ranging from 1 to 71). The marked variation in recruitment probably reflected the marked variation in opinion and practice due to the lack of evidence. Reliable data was, unfortunately, not available on the exact reason for revascularization, but limited information from radiology department request forms included patients with tight ARAS of a single functioning kidney or with bilateral ARAS, rapidly deteriorating renal function, refractory hypertension and recurrent flash pulmonary oedema. Given the majority of UK centres recruited very few patients into ASTRAL, the data from our institution is likely to closely reflect the practice in most UK centres at the time: intervention was undertaken in those thought likely to benefit from revascularization, who were effectively excluded from ASTRAL by the subjective principle of clinical equipoise.

The main limitation of any observational study is the lack of a control group. Analysis of individuals' reciprocal creatinine plots pre- and post-intervention did reveal a number of patients whose renal excretory function clearly improved following intervention. Indeed, the majority of patients [79 of 127 (62%)] showed some improvement. However, we do not know how many of these patients would have improved with medical therapy alone. Furthermore, renal function in itself is simply a surrogate marker. We were unable to demonstrate any survival advantage, but the study was underpowered to find any difference in mortality between responders and non-responders. Of note, mortality was high in both groups.

Caution must always be exercised in examining underpowered subgroups within trials as this is often misleading and can provide false-positive results. The use of multiple logistic regression analysis may have helped identify factors determining outcome (RRT-free survival, mortality), but given our sample size, it would be clearly inappropriate to make statements on any possible associations. Furthermore, only limited clinical data were available on the study population. Nonetheless, those whose renal function was declining most rapidly tended to show some improvement with intervention and these findings are supported by *post-hoc* analysis of the ASTRAL data [16]. Although the delayed need for RRT and

improved survival time were not statistically significant, one might expect ‘rapid decliners’ to require RRT sooner with an associated increase in early mortality. Statistical analysis of the data may therefore underrate the significance of the swing. The question remains, then, of whether revascularization is indicated in patients with rapidly deteriorating renal function, particularly with impending need for RRT. Future meta-analysis of data from ASTRAL, STAR [17] and (eventually) CORAL [18] may help answer this question.

Conclusion

These data have highlighted that our use of renal revascularization has produced no demonstrable benefit overall. We were not able to identify any subgroup of patients that had clearly benefited from the procedure, which has significant associated risk. Although the negative findings of ASTRAL have been criticized in professional fora [15], these data support its conclusion. Our practice is now limited essentially to patients with a history of recurrent flash pulmonary oedema not related to acute coronary syndrome.

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