# Effect of renal artery revascularization upon cardiac structure and function in atherosclerotic renal artery stenosis : Cardiac magnetic resonance sub-study of the ASTRAL trial

James Ritchie[1], Darren Green[1], Tina Chrysochou[1], Janet Hegarty[1], Kelly Handley[2], Natalie Ives[2], Keith Wheatley[2], Graeme Houston[3], Julian Wright[4], Ludwig Neyses[4], Nicholas Chalmers[4], Patrick Mark[5], Rajan Patel[5], Jon Moss[5], Giles Roditi[6], , David Eadington[7], Elena Lukaschuk[7], John Cleland[7] and Philip A Kalra[1]

[1]Salford Royal NHS Foundation Trust, UK, [2]University of Birmingham, UK, [3]Ninewells Hospital, Dundee, UK, [4]Central Manchester Foundation Trust, Manchester, UK, [5]Queen Elizabeth University Hospital, Govan, Glasgow, Scotland, [6]Glasgow Royal Infirmary and [7]Hull Royal Infirmary, Hull, UK

**Running header** – Cardiac structure and function following renal artery revascularization

**Corresponding author** – Prof Philip A Kalra

Dept of Renal Medicine

Salford Royal NHS Foundation Trust

Stott Lane

Salford

M6 8HD

Philip.kalra@srft.nhs.uk

**Word count** – 3216

**Abstract word count** – 287

## Abstract

### Background

Cardiac abnormalities are frequent in patients with atherosclerotic renovascular disease (ARVD). The ASTRAL trial studied the effect of percutaneous renal revascularization combined with medical therapy compared to medical therapy alone in 806 patients with ARVD.

### Methods

This was a pre-specified sub-study of ASTRAL, designed to consider the effect of percutaneous renal artery angioplasty and stenting on change in cardiac structure and function, measured using cardiac magnetic resonance (CMR) imaging.

Fifty-one patients were recruited from 6 selected ASTRAL centers. Fourty-four completed the study (medical therapy n=21; revascularization n=23). Full analysis of CMR was possible in 40 patients (18 medical therapy and 22 revascularization). CMR measurements of left and right ventricular end systolic (LV and RVESV) and diastolic volume (LV and RVEDV), ejection fraction (LVEF) and mass (LVM) were made shortly after recruitment, and before revascularization in the interventional group, and again after 12-months. Reporting was performed by CMR analysts blinded to randomization arm.

### Results

Groups were well matched for mean age (70 vs. 72 years), blood pressure (148/71 vs. 143/74 mmHg), degree of renal artery stenosis (75 vs. 75%) and co-morbid conditions.

In both randomized groups, improvements in cardiac structural parameters were seen at 12-months, but there were no significant differences between treatment groups. Median left ventricular changes between baseline and 12 months (medical vs.

revascularization) were LVEDV -1.9 vs. -5.8 ml, p=0.4; LVESV -2.1 vs. 0.3 ml, p=0.7; LVM -5.4 vs. -6.3 g, p=0.8 and LVEF -1.5 vs. -0.8%, p=0.7. Multivariate regression also found that randomized treatment assignment was not associated with degree of change in any of the CMR measurements.

**Conclusions**

In this sub-study of the ASTRAL trial, renal revascularization did not offer additional benefit to cardiac structure or function in unselected patients with ARVD.

**Clinical trials registration**

Current controlled trials number: ISRCTN59586944.

**Keywords** – Renal artery stenosis

Coronary artery disease

Revascularization

Cardiac MRI

Randomized controlled trial

## Introduction

Patients with atherosclerotic renovascular disease (ARVD) have a high prevalence of cardiac structural and functional abnormalities(1) and they are at high risk of cardiovascular mortality. A cross-sectional echocardiographic study of 79 ARVD patients showed that only 5% had structurally normal hearts, and that although left ventricular ejection fraction (LVEF) (mean 53%) was surprisingly well preserved, left ventricular hypertrophy (LVH) was present in 79% and evidence of diastolic dysfunction in 75%(2). This burden of structural abnormalities in patients with ARVD is higher than is seen in chronic kidney disease (CKD)(3,4) or hypertension(5).

There is evidence that increase in left ventricular mass (LVM) predisposes to development of chronic heart failure (CHF) in CKD of any cause(6). Heart failure, either flash pulmonary edema (FPE) or CHF, is a well-recognized clinical presentation for ARVD. Although the hearts of patients with FPE have not been subject to systematic study, Kane et al did examine the hearts of ARVD patients being referred for renal revascularization at the Mayo clinic(7), dividing patients into those with and without clinical heart failure; mean LVM was greater in those with CHF (LVM index 130±34 vs. 112±31 $g/m^2$). Randomized controlled trials comparing the addition of percutaneous renal artery revascularization to optimal medical therapy in ARVD have, at best, shown only minor and inconsistent benefits in blood pressure control(8-10). However, case-reports have described both reductions in circulating levels of angiotensin II following non-randomized intervention(11), and improvements in left ventricular structural and functional parameters(11,12).

The Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial commenced recruitment in 2002(9). The aim of this randomized controlled trial (RCT) in 806 patients with anatomically significant atherosclerotic RAS was to determine if renal revascularization provided additional clinical benefit to medical therapy. The primary outcome measure was renal functional improvement measured using serum creatinine, with secondary outcomes including blood pressure control, renal events, cardiovascular events and death. At the time of initiating recruitment into ASTRAL, there were no RCTs that had examined the effect of renal revascularization upon the hearts of patients with ARVD. This cardiac magnetic resonance (CMR) sub-study of ASTRAL was therefore developed, with the aim of examining the effects of revascularization upon cardiac structure and function within the setting of an RCT.

## Methods

### *Study design*

Full details of the design of ASTRAL have been published previously(9). In brief, this was a multicenter, non-blinded randomized clinical trial comparing rate of change in renal function between patients managed with percutaneous renal artery revascularization in addition to medical therapy against those managed with medical therapy alone. Support was received from the Medical Research Council UK, Kidney Research UK, and Medtronic. Ethical approval was granted by the West Midlands Multicentre Research Ethics Committee and the ethics committee relevant to each individual participating study center. All patients provided written consent. Ethical permission for the cardiac sub-studies was obtained after commencement of the main ASTRAL trial.

*Patient selection and randomization*

Patients were eligible for inclusion within the main ASTRAL study if they had at least one renal artery with an atherosclerotic stenosis suitable for percutaneous revascularization. Patients were not enrolled if the physician was certain that the patient definitely should or should not undergo renal revascularization. Patients with non-atheromatous disease, those who had undergone a previous revascularization procedure, required surgical revascularization or were considered to have a high probability of requiring revascularization within the next six-months on clinical grounds, were also excluded. Eligible patients were randomized in a 1:1 ratio to revascularization in addition to standard medical therapy versus medical therapy alone. Randomization was performed using a computerized minimized-randomization procedure with allocation determined following a telephone call to the central trial office.

For this study, all patients due to be randomized between January 2005 and October 2007 at the six United Kingdom recruiting centers with cardiac magnetic resonance imaging (CMR) capacity that were participating in the sub-study were approached for consent. No further inclusion criteria were applied. The only additional exclusion criterion was the presence of a contra-indication to magnetic resonance imaging (e.g. claustrophobia, implanted metal).

*Sample size*

At the time of design of this sub-study there were no published data that described change in CMR parameters following revascularization for RAS.. One published study of 20 patients with ischemic CHF suggested that 15 patients per arm would be

required to reliably detect a 3% change in left ventricular ejection fraction (LVEF); 12 patients to detect a 10 ml difference in left ventricular end-diastolic volume (LVEDV); and 9 patients to detect a 10 g/m change in left ventricular mass index (LVMI)(13). The sample size was therefore set at 25 patients in each treatment arm. Allowing for 15% dropout the total recruitment target was 58 patients.

*Treatment and follow-up*

Medical therapy and renal revascularization procedures were performed in accordance with local guidelines for each participating center as described previously. As in the main ASTRAL study protocol, patients in the CMR sub-study underwent a repeat assessment at 12-months which included repeat of baseline clinical measurements, creatinine, haemoglobin and review of prescribed medications. Estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft-Gault formula(14) as the study pre-dated widespread application of the MDRD formula. Blood pressure measurements were performed by trained staff using mercury sphygmomanometers after patients had been seated at rest for five minutes, with the elbow supported above the waist and the palm facing upwards. Three readings were taken, with the average of the second and third values recorded.

*Cardiac magnetic resonance imaging protocol and analysis*

A single unified CMR protocol was agreed between participating centers with imaging performed at baseline and 12-months following randomization. Imaging was performed with a 1.5-Tesla scanner using a phased array chest coil and gated with prospective or retrospective electrocardiographic triggering using fast imaging with steady-state precession. Transverse scout images were used to obtain left ventricular

vertical long-axis cine by aligning the LV apex with the center of the mitral valve at end expiration. From the ventricular long-axis image, a short axis view was obtained parallel to the mitral valve halfway between mitral annulus and LV apex at end expiration. From the short axis view the horizontal long-axis 4 chamber plane was aligned passing just above the inferior papillary muscle and through the lower anterior RV free wall where it meets the inferior wall. This was obtained as a cine image at end expiration. A diastolic image at end-expiration provided the reference image on which a stack of contiguous short-axis slices were positioned. Breath-hold short-axis cine sections were acquired from the atrio-ventricular ring to the apex, with 6.0-mm section thickness and a 4.0-mm gap and one or 2 sections per breath hold depending on patient abilities and scanner speed.

All scans were read by a single observer, who was an experienced CMR analyst, blinded to the date and order of the scan, as well as to all clinical information including randomization arm. End-systole was defined visually as the phase with the smallest LV volumes. In selection of the most basal slice for left ventricular analysis, slices were considered to be within the left ventricle if the blood volume was surrounded by 50% or more of ventricular myocardium. The apex was the most apical slice in which myocardium remains visible for analysis. On each end-diastolic frame, endocardial and epicardial borders were manually traced, and an endocardial border was traced on the end systolic frame. Papillary muscles and trabeculations were included with the LV mass while right ventricular trabeculations arising from the interventricular septum were excluded. Right ventricular volumes were obtained from true trans-axial cine sections. From these values end-diastolic and end-systolic

volumes were calculated as well as left ventricular myocardial mass determined by multiplying myocardial tissue volume by the specific gravity of 1.05.

*Outcome measures*

Cardiac structure and function was assessed using a variety of measures including left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), left ventricular ejection fraction (LVEF) and left ventricular mass (LVM) (and similarly for the right side).

*Statistical analysis*

Analyses were performed on an intention to treat basis with patients analysed in the treatment group to which they were randomized. For all CMR parameters both mean ± standard deviation and median [interquartile range] were calculated at baseline and 12-months. Mean differences between treatment groups were compared using Student's *t*-test with results presented as mean difference (95% confidence interval); median differences were compared using Wilcoxon 2-sample test. Multivariate regression models were constructed to consider the effects of clinically relevant baseline variables (treatment group, age, presence of diabetes, history of coronary heart disease, systolic blood pressure, diastolic blood pressure, degree of stenosis to most affected kidney, renal function, prescription of beta-blockers and renin angiotensin blockade, baseline ventricular measurement) on change in ventricular parameters at 12-months. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC, USA).

**Results**

*Patients and clinical characteristics*

A total of 806 patients were recruited to the main ASTRAL study. Between January 2005 and October 2007, 51 patients were enrolled into the CMR sub-study at the 6 participating sites. Seven patients dropped out due to death (n=1) or failure to complete 12-month CMR (n=6), giving a final study population of 44 (21 randomized to medical therapy, 23 to medical therapy plus revascularization. Three of the patients randomized to revascularization failed to undergo the stent insertion procedure; no patient in the medical therapy arm received revascularization. CMR quality was adequate for full analysis in 18 medical therapy and 22 revascularized patients.

Baseline patient characteristics and co-morbidities were well matched between treatment groups and were representative of the main study population (Table 1). All patients had a RAS of >50% on pre-randomization angiography (MR, CT or direct angiography) with mean RAS estimated at 75% in the most severely affected artery in each group. Mean serum creatinine in the medical group was 160 (range 74-242) μmol/L, compared with 146 (79-201) μmol/L in the revascularization group; no patients had a baseline creatinine in excess of 300 μmol/L. Height data were only available for a minority of patients, and consequently LVM data were considered without adjustment for patient height. In line with the findings of the main study, no significant difference in change in blood pressure or renal function existed between randomized treatment groups at 12-months.

*Cardiac MR imaging : left ventricular parameters*

At recruitment, all left ventricular structural parameters were similar between the medical and revascularization treatment groups with LVEDV median 130ml [IQR:

108 to 146] vs. 122ml [97 to 146]; LVESV 40ml [33 to 51] vs. 38 ml [29 to 60]; LVM 116g [98 to 134] vs. 110g [101 to 132] (Table 2). Non-significant improvements in these structural parameters were observed within both randomized arms between baseline and 12 months with median changes for medical and revascularization groups, respectively, being LVEDV -1.9ml [95% CI -21 to 4] and -5.8ml [95% CI -17 to 6]; LVESV -2.1ml [95% CI -5 to 4] and 0.3ml [95% CI -11 to 5]; LVM -5.4g [95% CI -12 to 6].and -6.3g [95% CI -15 to -0.2]. Comparisons between randomized groups were made for measured left ventricular values at 12-months and for the relative difference between the two arms for the change from baseline to 12-month values. In both analyses, no significant difference between randomized treatment groups was observed (Table 2).

At baseline, left ventricular ejection fraction was well preserved in both groups, medical therapy 69.5% [63 to 73], revascularization 69.2% [59 to 72] (Table 2). Within each treatment group, minimal differences in ejection fraction were observed at 12-months. There was no significant difference in the between group comparison of measured 12-month ejection fraction (Table 2) and relative change from baseline ejection fraction (Table 3).

*Cardiac MR imaging : differences in right ventricular parameters*

Although this sub-study was designed to assess differences in left sided parameters, right heart measurements were also obtained (Table 2). No difference in right ventricular EDV, ESV or ejection fraction was observed between groups either at baseline or at 12-months.

*Association between baseline variables and change in left ventricular parameters at 12-months*

Sufficiently complete data were available for 31 patients (15 medical therapy, 16 revascularized) to be included in multivariate regression models. Each model was constructed twice using either serum creatinine or eGFR as one of the co-variates in the model. No difference in results or overall model fit (defined using adjusted $R^2$) was observed so only results for models using eGFR are presented. Treatment allocation was not significantly associated with any left ventricular parameter (LVEDV, LVESV, LVM, or LVEF) at 12-months. However, a significant association between use of renin angiotensin blockade (RAB; angiotensin converting enzyme inhibitor or angiotensin receptor blocker) and certain ventricular measurements at 12-months was observed: LVEDV (parameter estimate 17.4 [standard error 7.4] p=0.03), LVESV (10.6 [4.1] p=0.02) and LVEF (-4.48 [2.1] p=0.04). LVEDV at 12 months was also associated with baseline diastolic blood pressure (0.90 [0.4] p=0.04).

*Complications of revascularization*

Procedural complications were not separately analyzed for this sub-study. In the main ASTRAL study, serious complications were observed in 23 of 403 patients randomized to revascularization. This included 2 deaths occurring within 30-days of intervention.

**Discussion**

This study has not identified any definitive evidence or even signals of additional benefit of renal artery revascularization on left or right ventricular structure or function in patients with atherosclerotic RAS and significant renal impairment.

This finding is in alignment with results of the Renal Artery Stenosis in Coronary Artery Disease (RASCAD) study(15), a randomized trial of 84 patients with atherosclerotic RAS identified on screening during non-emergency coronary angiography, and in which the effect of revascularization in addition to medical therapy was considered in relation to change in left ventricular mass index over a 12-month period. Although patient age was similar other demographics differed from those described in this ASTRAL sub-study, with patients recruited to RASCAD having a lesser degree of RAS (60%), lower systolic blood pressure (around 132 mmHg) and higher baseline eGFR (approximately 60 ml/min). Nevertheless, RASCAD also found that no additional reduction in LVMI was seen in revascularized patients in comparison with medically managed patients, and that LVMI did decrease in both randomised groups. As these two small randomized trials have not confirmed the findings of case series(12) that suggest a significant association between renal artery revascularization and improved left ventricular structure the potential of a false negative should be considered. In a 12-month echocardiographic series of 43 patients with varying degrees of RAS, LVM remained stable over the follow-up period(16). Only 8 of these patients underwent revascularization and there was a signal towards reduced LVMI and LVEDV index in this sub-group. However, these measurements were made using transthoracic echocardiography, which is much less accurate than CMR(17). As this study failed to recruit sufficient patients to satisfy the power calucation, it is possible that a genuine effect was missed. However, if this was the case, then the difference would be small and of limited clinical relevance.

The improvements in structural left ventricular measurements at 12-months seen in both of the randomized arms in this study may reflect appropriate use of pharmacotherapy. Since the first trials of percutaneous revascularization for RAS, the nature of what constitutes optimal medical therapy in renovascular disease has been better defined. Most notably there has been a better appreciation of the importance of use of RAB and statin therapy(18-20). RAB has a role in both preventing progression and inducing regression of left ventricular mass, independent of changes in blood pressure, in other populations(21,22). Although the effect of medication may have marginalized any potential benefits of revascularization in our study, it was surprising that we found use of RAB at baseline was associated with slight deterioration of LVEDV, LVESV and LVEF at 1 year.

A further question that merits discussion is whether more subtle measures of cardiac structural health should be considered. Contemporary CMR techniques permit assessment of myocardial edema and or fibrosis allowing in depth interrogation of myocardial pathology, potentially identifying patients at higher risk of cardiac events(23). Angiotensin II mediated hypertension has been shown to drive myocardial fibrosis(24,25); it may be that in our ARVD patients chronic overstimulation of the renin-aldosterone-angiotensin system had led to irreversible cardiac structural changes by the time of diagnosis. A developing body of literature suggests that a higher burden of myocardial edema (a precursor to development of fibrosis(26)) is associated with an increased likelihood of left ventricular remodeling(27,28), and so, theoretically, identification of patients with greater degrees of myocardial edema may select a group with greater likelihood of benefiting from revascularization. Given the systemic atheromatous burden associated with

ARVD, development of cardiac abnormalities will be a multifactorial process driven by pre-existing essential hypertension and/ or coronary artery disease as well as RAS. Some of these processes will be unaffected by revascularization. Hence, perhaps only those left ventricular abnormalities that are still progressing and are primarily related to RAS should be expected to improve after revascularization. Speckle track echocardiography can demonstrate more subtle abnormalities in myocardial function, manifest by changes in LV strain patterns, and this is being increasingly investigated in patients with CKD(29). Although CMR protocols with tagging can replicate this, we only evaluated conventional cardiac parameters in this study.

This study has limitations. Most importantly, the sample size was small and the sample size calculation may have been flawed because it was based on CMR data from a small number of patients with CHF, as little other data was available at the time of designing the study. However, given the similarity in outcome between randomized groups it seems unlikely that a larger sample size would have altered the overall findings in this patient group. It is noteworthy that this was a sub-study of a much larger ARVD population in which no overall benefit from renal artery revascularization was observed. As such it is perhaps unsurprising that no difference in change in cardiac structure of function was identified between groups. The issue of patient selection is also important to consider. The suggested bias towards recruitment of lower risk patients (less likely to benefit from revascularization) into ASTRAL has been widely discussed(30). In those case series that have described cardiac benefits from revascularization, patients have either had a greater burden of stenosis(12), or more severe symptoms of heart failure at baseline(11), than that seen in the ASTRAL population. It is plausible that a study targeting more specific cardiac

risk patient groups (e.g. ARVD patients with NYHA III-IV symptoms, or those with very severe hypertension) might demonstrate beneficial cardiac changes accompanying renovascular intervention.

In conclusion, in this study the addition of renal artery revascularization to standard medical therapy did not lead to any further changes in cardiac structure or function than management with medical therapy alone. This finding was in a patient cohort in whom no benefit from revascularization was observed in relation to rate of change in renal function, cardiovascular events, or death. Current guidelines recognize that some patients may be more likely to benefit from revascularization, for example patients with acute or chronic heart failure or with resistant hypertension(31) with supporting evident for this in large case series(32). These may be patient groups in whom improvements in cardiac structure are more likely to follow revascularization. This sub-study was inadequately powered to consider effects in specific sub-groups, and patients with acute heart failure were not included in ASTRAL. Future studies that investigate whether cardiac structural and functional changes might accompany renal artery revascularization should address carefully selected patient populations.

**Acknowledgement**

The ASTRAL Cardiac MR study was supported by a project grant from the British Heart Foundation.

## References

1. Chrysochou C, Kalra PA. Epidemiology and Natural History of Atherosclerotic Renovascular Disease. Progress in Cardiovascular Diseases 2009; 52: 184–195.

2. Wright JR, Shurrab AE, Cooper A, Kalra PR, Foley RN, Kalra PA. Left ventricular morphology and function in patients with atherosclerotic renovascular disease. Journal of the American Society of Nephrology 2005; 16: 2746–2753.

3. Middleton RJ, Parfrey PS, Foley RN. Left ventricular hypertrophy in the renal patient. Journal of the American Society of Nephrology 2001; 12: 1079–1084.

4. Bansal N, Keane M, Delafontaine P et al. A longitudinal study of left ventricular function and structure from CKD to ESRD: the CRIC study. Clinical Journal of the American Society of Nephrology 2013; 8: 355–362.

5. Mancia G, Carugo S, Grassi G et al. Prevalence of Left Ventricular Hypertrophy in Hypertensive Patients Without and With Blood Pressure Control: Data From the PAMELA Population. Hypertension 2002; 39: 744–749.

6. Foley RN, Parfrey PS, Kent GM, Harnett JD, Murray DC, Barre PE. Serial change in echocardiographic parameters and cardiac failure in end-stage renal disease. Journal of the American Society of Nephrology 2000; 11: 912–916.

7. Kane GC, Xu N, Mistrik E, Roubicek T, Stanson AW, Garovic VD. Renal artery revascularization improves heart failure control in patients with atherosclerotic renal artery stenosis. Nephrology Dialysis Transplantation 2010; 25: 813–820.

8. van Jaarsveld BC, Krijnen P, Pieterman H et al. The effect of balloon angioplasty on hypertension in atherosclerotic renal-artery stenosis. Dutch Renal Artery Stenosis Intervention Cooperative Study Group. The New England journal of medicine 2000; 342: 1007–1014.

9. ASTRAL Investigators, Wheatley K, Ives N et al. Revascularization versus medical therapy for renal-artery stenosis. The New England journal of medicine 2009; 361: 1953–1962.

10. Cooper CJ, Murphy TP, Cutlip DE et al. Stenting and medical therapy for atherosclerotic renal-artery stenosis. The New England journal of medicine 2014; 370: 13–22.

11. Chrysochou C, Sharma R, Kalra PA, Kalra PR. Improved left ventricular filling following bilateral renal artery stenting. International journal of cardiology 2011; 150: e40–e41.

12. Zeller T, Rastan A, Schwarzwälder U et al. Regression of left ventricular hypertrophy following stenting of renal artery stenosis. Journal of endovascular therapy : an official journal of the International Society of Endovascular Specialists 2007; 14: 189–197.

13. Bellenger NG, Davies LC, Francis JM, Coats AJ, Pennell DJ. Reduction in sample size for studies of remodeling in heart failure by the use of cardiovascular magnetic resonance. Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance 2000; 2: 271–278.

14. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31–41.

15. Marcantoni C, Zanoli L, Rastelli S et al. Effect of renal artery stenting on left ventricular mass: a randomized clinical trial. American journal of kidney diseases 2012; 60: 39–46.

16. Wright JR, Shurrab AE, Cooper A, Kalra PR, Foley RN, Kalra PA. Progression of cardiac dysfunction in patients with atherosclerotic renovascular disease. QJM 2009; 102: 695–704.

17. Gardner BI, Bingham SE, Allen MR. Cardiac magnetic resonance imaging for the assessment of cardiac volumes and regional function after myocardial infarction: an intrasubject comparison using simultaneous intrasubject recordings. Cardiovasc Ultrasound 2009; 18:7-38

18. Hackam DG, Duong-Hua ML, Mamdani M et al. Angiotensin inhibition in renovascular disease: a population-based cohort study. American Heart Journal 2008; 156: 549–555.

19. Chrysochou C, Foley RN, Young JF, Khavandi K, Cheung CM, Kalra PA. Dispelling the myth: the use of renin-angiotensin blockade in atheromatous renovascular disease. Nephrology Dialysis Transplantation 2012; 27: 1403–1409.

20. Hackam DG, Wu F, Li P et al. Statins and renovascular disease in the elderly: a population-based cohort study. European Heart Journal 2011; 32: 598–610.

21. Cowan BR, Young AA. Left ventricular hypertrophy and renin-angiotensin system blockade. Current hypertension reports 2009; 11: 167–172.

22. Tai DJ, Lim TW, James MT et al. Cardiovascular effects of angiotensin converting enzyme inhibition or angiotensin receptor blockade in hemodialysis: a meta-analysis. Clinical Journal of the American Society of Nephrology 2010; 5: 623–630.

23. Kuruvilla S, Janardhanan R, Antkowiak P et al. Increased extracellular volume and altered mechanics are associated with LVH in hypertensive

heart disease, not hypertension alone. JACC: Cardiovascular Imaging 2015; 8: 172–180.

24. Nicoletti A, Heudes D, Hinglais N et al. Left ventricular fibrosis in renovascular hypertensive rats. Effect of losartan and spironolactone. Hypertension 1995; 26: 101–111.

25. Ichihara S, Senbonmatsu T, Price E, Ichiki T, Gaffney FA, Inagami T. Angiotensin II type 2 receptor is essential for left ventricular hypertrophy and cardiac fibrosis in chronic angiotensin II-induced hypertension. Circulation 2001; 104: 346–351.

26. Davis KL, Laine GA, Geissler HJ, Mehlhorn U. Effects of myocardial edema on the development of myocardial interstitial fibrosis. Microcirculation 2000; 7(4):269-80

27. Ghugre NR, Pop M, Barry J. Quantitative magnetic resonance imaging can distinguish remodeling mechanisms after acute myocardial infarction based on the severity of ischemic insult. Magn Reson Med 2013; 70(4):1095-1105

28. Kubanek M, Sramko M, Maluskova J. Novel predictors of left ventricular reverse remodeling in Individuals with recent-onset dilated cardiomyopathy. J Am Coll Cardiol; 2013; 61(1):54-63

29. Wang H, Liu J, Yao X-D et al. Multidirectional myocardial systolic function in hemodialysis patients with preserved left ventricular ejection fraction and different left ventricular geometry. Nephrology Dialysis Transplantation 2012; 27: 4422–4429.

30. George JC, White CJ. Renal artery stenting: lessons from ASTRAL (Angioplasty and Stenting for Renal Artery Lesions). *JACC. Cardiovascular interventions*2010; 3: 786–787.

31. Hirsch AT, Haskal ZJ, Hertzer NR et al. ACC/AHA Guidelines for the Management of Patients with Peripheral Arterial Disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Associations for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (writing committee to develop guidelines for the management of patients with peripheral arterial disease)--summary of recommendations. *Journal of vascular and interventional radiology : JVIR*2006; 17: 1383–1397; quiz1398.

32. Ritchie J, Green D, Chrysochou C, Chalmers N, Foley RN, Kalra PA. High-risk clinical presentations in atherosclerotic renovascular disease: prognosis and response to renal artery revascularization. American journal of kidney diseases 2014; 63: 186–197.

**Table 1 – Baseline patient characteristics**

| | Medical Management (N = 21) | Revascularisation (N = 23) | P value |
|---|---|---|---|
| Demographic | | | |
| Mean age (range) – years | 70 (51 - 81) | 72 (53 - 85) | 0.47 |
| Male sex – % | 71% | 65% | 0.66 |
| | | | |
| Mean weight (range) – kg | 79 (60 – 105) | 75 (60 – 95) | 0.3 |
| Clinical | | | |
| Smoking status – % | | | |
| Current smoker | 26% | 28% | 0.92 |
| Former smoker | 58% | 56% | 0.89 |
| | | | |
| Coexisting conditions – % | | | |
| Diabetes | 40% | 32% | 0.58 |
| Coronary heart disease | 56% | 68% | 0.43 |
| Peripheral vascular disease | 47% | 28% | 0.25 |
| Stroke | 42% | 26% | 0.31 |
| Need for dialysis | 0 | 0 | - |
| Renal Function | | | |
| Serum Creatinine | | | |
| Mean (range) – µmol/litre | 160 (74 - 242) | 146 (79 - 201) | 0.24 |

| | | | |
|---|---|---|---|
| Level – % | | | |
| < 150 µmol/litre | 38% | 52% | 0.35 |
| 150-300 µmol/litre | 62% | 48% | |
| > 300 µmol/litre | 0 | 0 | |
| Rapid Increase in SCr * | 6% | 6% | 0.97 |
| | | | |
| Estimated glomerular filtration rate | | | |
| Mean (range) – ml/min | 42.4 (18.1 – 72.9) | 43.0 (17.0 – 89.8) | 0.89 |
| Level – % | | | |
| < 25 ml/min | 10% | 9% | 0.45 |
| 25-50 ml/min | 57% | 74% | |
| > 50 ml/min | 33% | 17% | |
| | | | |
| | | | |
| | | | |
| Related Laboratory Measures¶ | | | |
| Mean blood pressure (range) – mmHg | | | |
| Systolic | 148 (90 - 220) | 143 (113 - 186) | 0.58 |
| Diastolic | 71 (57 - 94) | 74 (52 - 102) | 0.53 |
| | | | |
| Mean total cholesterol (range) – mmol/litre | 4.5 (2.8 – 7.7) | 4.8 (3.2 – 14.8) | 0.75 |
| Renal anatomy | | | |
| Stenosis | | | |

| | | | |
|---|---|---|---|
| Mean (range) – % | 75.2 (50 - 90) | 75.4 (60 - 90) | 0.96 |
| Severity – % | | | |
| < 50% | 0 | 0 | 0.38 |
| 50-70% | 52% | 39% | |
| > 70% | 48% | 61% | |
| Mean length of kidney (range) – cm | 9.7 (7.5 – 11.5) | 9.5 (7.7 – 11.2) | 0.77 |
| Use of Concomitant medication | | | |
| Antihypertensive drug – % | | | |
| Any | 100% | 89% | 0.15 |
| Diuretic | 58% | 76% | 0.24 |
| Calcium-channel blocker | 79% | 41% | 0.02 |
| Beta-blocker | 47% | 53% | 0.74 |
| Angiotensin blockade | 53% | 65% | 0.46 |
| Alpha-blocker | 37% | 29% | 0.64 |
| Mean no. of antihypertensive drugs (range) | 2.8 (2 - 5) | 2.8 (1 – 5) | 0.92 |
| | | | |
| Antiplatelet drug – no./total no. (%) | | | |
| Any | 90% | 95% | 0.58 |
| Aspirin | 89% | 83% | 0.64 |
| | | | |
| Cholesterol lowering drug – no./total no. (%) | | | |
| Any | 94% | 95% | 0.97 |

| | | | |
|---|---|---|---|
| Statin | 100% | 94% | 0.32 |
| | | | |
| Warfarin – no./total no. (%) | 16% | 11% | 0.68 |
| | | | |

Angiotensin blockade defined as prescription of angiotensin converting enzyme inhibitor or angiotensin-receptor blocker

*Rapid increase in serum creatinine defined as an increase of greater than 100μmol/l or greater than 20% from baseline reading during the previous 1-year prior to randomisation

Table 2: Cardiac MRI data at baseline and 1 year

| | | Baseline | | 1 Year | | |
|---|---|---|---|---|---|---|
| | | **Medical Management (n=21)** | **Revasc (n=23)** | **Medical Management (n=18)** | **Revasc (n=22)** | **p between groups at 1 year** |
| **LVD volume (ml)** | Mean (SD) | 130.3 (26.0) | 133.2 (46.6) | 121.2 (35.2) | 132.9 (48.3) | 0.4 |
| | Median (IQR) | 129.7 (108.0, 145.9) | 122.4 (96.6, 145.5) | 124.7 (106.1, 146.1) | 118.5 (104.6, 114.5) | 1.0 |
| **LVS volume (ml)** | Mean (SD) | 44.6 (18.6) | 53.4 (46.6) | 44.0 (22.9) | 54.2 (45.8) | 0.4 |
| | Median (IQR) | 39.8 (32.6, 50.6) | 37.6 (28.7, 59.6) | 40.8 (26.2, 55.8) | 40.3 (26.9, 50.3) | 1.0 |
| **LV mass (g)** | Mean (SD) | 116.4 (28.6) | 111.4 (21.1) | 108.5 (30.6) | 104.3 (20.1) | 0.6 |
| | Median (IQR) | 116.1 (97.8, 134.4) | 110.1 (100.9, 132.3) | 106.8 (98.1, 128.1) | 103.8 (88.9, 111.9) | 0.5 |
| **Adjusted LV mass ($g/m^2$) *** | Mean (SD) | 62.2 (21.8) | 64.9 (14.2) | 57.9 (20.5) | 59.0 (13.4) | 0.9 |
| | Median (IQR) | 64.1 (41.9, 81.4) | 62.2 (55.2, 79.9) | 60.8 (40.4, 73.1) | 60.1 (54.5, 67.3) | 1.0 |
| **LV ejection fraction (%)** | Mean (SD) | 66.3 (10.3) | 63.8 (15.3) | 64.7 (13.1) | 63.3 (14.1) | 0.7 |
| | Median (IQR) | 69.5 (62.9, 72.6) | 69.2 (59.1, 72.3) | 65.0 (56.1, 74.2) | 66.0 (58.1, 72.1) | 0.8 |
| **RVD volume (ml)** | Mean (SD) | 122.7 (30.1) | 112.3 (22.7) | 118.3 (32.5) | 113.4 (21.9) | 0.6 |
| | Median (IQR) | 115.2 (100.4, 145.6) | 113.9 (93.4, 129.9) | 111.5 (89.8, 141.9) | 117.4 (98.4, 126.4) | 0.7 |
| **RVS volume (ml)** | Mean (SD) | 45.9 (16.6) | 39.3 (8.7) | 45.3 (16.7) | 40.8 (10.4) | 0.3 |
| | Median (IQR) | 42.4 (36.5, 54.8) | 39.0 (32.3, 44.3) | 43.9 (29.8, 62.6) | 39.1 (33.5, 49.6) | 0.5 |
| **RV mass (g)** | Mean (SD) | 34.4 (9.4) | 34.8 (7.0) | 34.3 (10.2) | 35.4 (10.5) | 0.7 |
| | Median (IQR) | 30.9 (27.1, 40.0) | 34.5 (29.3, 40.1) | 32.9 (29.8, 41.2) | 32.1 (28.5, 40.8) | 0.7 |
| **Adjusted RV mass ($g/m^2$) *** | Mean (SD) | 18.4 (3.8) | 19.4 (1.9) | 19.2 (6.1) | 21.7 (8.1) | 0.5 |
| | Median (IQR) | 19.0 (15.4, 22.5) | 19.5 (18.7, 20.8) | 21.4 (14.3, 23.6) | 20.0 (17.8, 24.6) | 0.9 |
| **RV ejection fraction (%)** | Mean (SD) | 62.8 (8.9) | 64.8 (5.3) | 61.8 (9.5) | 63.9 (6.8) | 0.4 |
| | Median (IQR) | 65.1 (56.8, 67.8) | 65.6 (61.8, 68.8) | 63.1 (54.3, 67.3) | 65.1 (57.4, 70.2) | 0.4 |

* For body surface area adjusted measurements, data available for 13 patients are baseline (7 medication, 6 PTRAS) and 17 patients at 12 months (8 medical, 9 PTRAS).

Table 3: Change in cardiac structural measurements between baseline and 1 year in medical management and PTRAS groups

| | | Medical Management | Revasc | p |
|---|---|---|---|---|
| **LVD volume (ml)** | Mean (SD) | -8.2 (18.7) | -0.8 (17.8) | 0.2 |
| | Median (IQR) | -1.9 (-21.5, 4.3) | -5.8 (-17.0, 5.9) | 0.4 |
| **LVS volume (ml)** | Mean (SD) | -1.4 (10.0) | -0.7 (11.5) | 0.8 |
| | Median (IQR) | -2.1 (-4.8, 3.8) | 0.3 (-11.3, 5.0) | 0.7 |
| **LV mass (g)** | Mean (SD) | -4.0 (14.0) | -6.9 (14.8) | 0.5 |
| | Median (IQR) | -5.4 (-11.9, 5.6) | -6.3 (-15.2, -0.2) | 0.8 |
| **Adjusted LV mass ($g/m^2$)** | Mean (SD) | -5.0 (7.2) | 0.9 (8.9) | 0.2 |
| | Median (IQR) | -7.7 (-9.4, 3.3) | 0.6 (-3.8, 7.6) | 0.3 |
| **LV ejection fraction (%)** | Mean (SD) | -0.9 (6.2) | 0.4 (5.0) | 0.5 |
| | Median (IQR) | -1.5 (-3.2, 3.8) | -0.8 (-3.0, 3.4) | 0.7 |
| **RVD volume (ml)** | Mean (SD) | -3.6 (20.7) | 1.9 (16.3) | 0.3 |
| | Median (IQR) | 0.2 (-10.2, 7.8) | 1.7 (-5.9, 6.1) | 0.7 |
| **RVS volume (ml)** | Mean (SD) | -0.3 (13.0) | 1.4 (9.1) | 0.6 |
| | Median (IQR) | 2.1 (-6.9, 10.0) | -0.9 (-3.6, 4.2) | 0.8 |
| **RV mass (g)** | Mean (SD) | -0.3 (7.8) | 0.8 (11.8) | 0.7 |
| | Median (IQR) | 0.2 (-3.1, 5.8) | -2.5 (-6.8, 2.4) | 0.6 |
| **Adjusted RV mass ($g/m^2$)** | Mean (SD) | 0.3 (5.0) | 1.1 (5.2) | 0.8 |
| | Median (IQR) | -1.1 (-2.1, 6.1) | 0.4 (-1.2, 6.0) | 0.8 |
| **RV ejection fraction (%)** | Mean (SD) | -0.9 (4.9) | -0.6 (5.8) | 0.9 |
| | Median (IQR) | -1.5 (-4.0, 0.8) | 1.2 (-4.2, 3.8) | 0.6 |