# Epidemiology of atherosclerotic renovascular disease: Clinical presentations, prognosis and treatment

A thesis submitted to the University of Manchester for the degree of Doctor of Philosophy (PhD) in the Faculty of Medical and Human Sciences

2013

Dr. James Ritchie

MB ChB

School of Medicine

Institute of Population Health

Center for Epidemiology

# LIST OF CONTENTS

**Word count: 57,536**

# LIST OF TABLES

# LIST OF FIGURES

**ABSTRACT**

The University of Manchester
Submitted by Dr. James Ritchie
For the degree of Doctor of Philosophy and entitled:
**Epidemiology of atherosclerotic renovascular disease: Clinical presentations, prognosis and treatment**
13/12/2013

Atherosclerotic renovascular disease (ARVD) is a significant cause of chronic kidney disease (CKD) and is associated with an increased risk for cardiovascular morbidity and mortality. Randomised controlled trials, representing over 2100 patients, have failed to demonstrate any prognostic benefit of percutaneous renal revascularisation when utilised in addition to standard medical therapy. This negative finding has been interpreted in three ways. Firstly, that ARVD may be an association of CKD and not a specific disease process. Secondly, that published studies have recruited low-risk patients who are least likely to benefit from revascularisation. Thirdly, that the focus of treatment for patients with ARVD should be optimal medical therapy, not renal revascularisation.

This research project had a series of linked aims. These were investigated in two large patient cohorts that had been accumulated at this centre over the last decade. These cohorts comprised > 900 patients with ARVD, the Salford Renovascular Database (SRVD), and > 2500 patients with all-cause CKD, the Chronic Renal Insufficiency Standards Implementation Study (CRISIS). The first aim was to consider whether ARVD should be considered as a specific cause of CKD. Here risks for death and progression to renal replacement therapy were compared between patients having ARVD as their primary cause of renal failure and patients with other coded causes of CKD. In this analysis, patients with ARVD had a greater risk for death and a lesser risk for RRT than patients with other forms of CKD.

The second aim of this thesis was to consider if specific patient sub-groups of ARVD could be identified. Patients in the SRVD with currently accepted high-risk clinical presentations were selected and outcomes compared to patients without a high-risk presentation. In this analysis, presentation with flash pulmonary oedema (but with not refractory hypertension or rapidly declining renal function) was associated with an increased risk for death and cardiovascular event. When the effects of revascularisation were considered in patients with high-risk presentations, a mortality benefit was observed in patients with flash pulmonary oedema and in patients presenting with rapidly declining renal function and refractory hypertension in combination. A separate analysis was performed in the SRVD to consider if a high-risk sub-group of ARVD patients could be identified using laboratory measurements. Here, a classification tree methodology was employed to identify ARVD patients with the greatest risk for progression to end stage kidney disease. The results of this analysis were converted into a practically applicable clinical scoring system incorporating renal function, proteinuria, medications, smoking history and renal artery occlusion.

The final aim of this thesis was to describe how the majority of ARVD patients should be treated. In this analysis of the SRVD effects of treatment with anti-platelet and beta-blocker therapy were considered, and shown to be associated with reduced risks for cardiovascular events and death.

# DECLARATION

No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

# COPYRIGHT STATEMENT

i. The author of this thesis (including any appendices and/or schedules to this thesis) owns certain copyright or related rights in it (the “Copyright”) and s/he has given The University of Manchester certain rights to use such Copyright, including for administrative purposes.

ii. Copies of this thesis, either in full or in extracts and whether in hard or electronic copy, may be made only in accordance with the Copyright, Designs and Patents Act 1988 (as amended) and regulations issued under it or, where appropriate, in accordance with licensing agreements which the University has from time to time. This page must form part of any such copies made.

iii. The ownership of certain Copyright, patents, designs, trade marks and other intellectual property (the “Intellectual Property”) and any reproductions of copyright works in the thesis, for example graphs and tables (“Reproductions”), which may be described in this thesis, may not be owned by the author and may be owned by third parties. Such Intellectual Property and Reproductions cannot and must not be made available for use without the prior written permission of the owner(s) of the relevant Intellectual Property and/or Reproductions.

iv. Further information on the conditions under which disclosure, publication and commercialisation of this thesis, the Copyright and any Intellectual Property and/or Reproductions described in it may take place is available in the University IP Policy (see http://documents.manchester.ac.uk/DocuInfo.aspx?DocID=487), in any relevant Thesis restriction declarations deposited in the University Library, The University Library’s regulations (see http://www.manchester.ac.uk/library/aboutus/regulations) and in The University’s policy on Presentation of Theses.

# ACKNOWLEDGEMENTS

I owe a significant debt of gratitude for the encouragement, advice and support that has been offered to me during this research experience. First and foremost I wish to thank my supervisor Professor Philip Kalra for managing to provide a clear direction of travel whilst simultaneously allowing me room to develop my own skills and interests. Phil's generosity in his time spent and contacts shared has offered me an incredible range of opportunity; I hope that in time I am able to repay this.

Secondly I wish to thank my co-supervisor Dr. Smeeta Sinha not only for encouraging my involvement with research from an early stage in my career, but also for her sound advice that your supervisor can be as important as the project. Whether she expected to supervise me when she offered this guidance remains unclear.... either way her feedback has been invaluable.

My advisor Professor Christi Deaton who early on encouraged me to try and think beyond individual research questions and to see the bigger picture.

In addition to my supervisory team I have been fortunate enough to receive support and guidance from a number of sources.

- Dr. Rob Foley who offered me a sabbatical period at the USRDS and provided me a priceless foundation in data handling and analysis.
- Dr. Darren Green for his company and for his brutally honest, insightful and entertaining reviews of my work.
- Dr. Constantina Chrysochou for having developed the renovascular database over previous years and for passing on some of her boundless enthusiasm.
- Dr. Helen Alderson and my other friends in the research group.
- Professor Peter Diggle for having generously supported my learning.
- The Salford Renal Research Fund and the Greater Manchester Comprehensive Local Research Network for their financial support.

Finally, I would like to thank all of the patients who have given their time and support to these studies. Without their contribution none of this work would have been possible.

# DEDICATION

Throughout my life, my parents have always encouraged me. Whilst I may not know all that they have done to support me, I hope that they know how much I appreciate them and everything they have done for me and my family.

The last three years would not have been possible without the love and support of my wife, Kate. She has shown incredible reserves of patience and understanding, and has been my motivation throughout. I cannot begin to describe how grateful I am for everything she has done. Without her and our wonderful daughter, Isla, I dread to think how I would have coped, nor when I would have completed this thesis! Credit for this work belongs equally to them, with any errors entirely my own.

I dedicate this thesis to my family.

# PREFACE

This thesis comprises of a series of observational studies that aim to improve our understanding of atherosclerotic renovascular disease and is presented in the alternative format.

The background section is comprised of work published as review articles or textbook chapters. The methods section provides a summary of the Salford Renovascular Database and the Chronic Renal Insufficiency Standards Implementation Study, the two epidemiological studies that formed the foundation of this work.

Each results chapter presents the results of an observational study and is given the title of the paper therein. All results chapters represent work that has either been published in a peer-reviewed medical journal or that is undergoing peer review at the time of submission. Details of journals and publishers are summarised in the section entitled “Published and Presented Work” and given again at the start of each chapter. Where appropriate, a link to the relevant IPR policy giving permission for reproduction in this thesis is provided. The content of the results chapters is presented exactly as has been submitted with modifications made only for consistency of style. For each chapter a section has been added before the abstract to describe the context of the study in relation to the other chapters in this thesis.

Due to the alternative format some inevitable overlap exists between the introductory sections and referencing. In line with University policy each published or submitted chapter is individually referenced. As this has resulted in a minimal number of sections that would be referenced in a standard thesis format, references are presented individually for each section to improve clarity.

# THE AUTHOR AND THE AUTHOR'S CONTRIBUTION

Prior to undertaking this research project I had received minimal exposure to either medical research or design of statistical analysis. These skills have been developed over the course of this project through a mixture of structured education at the University of Manchester, sabbatical periods at a range of institutions (most importantly the United States Renal Data System), and self directed learning from journals and electronic resources (notably the UCLA e-learning materials). I believe that these learning experiences, combined with the excellent supervision I have received have laid a solid foundation to use this experience as a platform to develop into an independent researcher.

All of the work presented here has been designed and led by myself. In all cases this includes study design, data collection and cleaning, statistical analysis and manuscript drafts. Due to the collaborative nature of medical research, contributions have been made by colleagues and these are acknowledged in the section entitled Published and Presented work. Again, I express my gratitude to all who have been involved.

Whilst I have been fortunate enough to be able to access data from two established observational studies, my experience of this research project has not been limited to secondary analysis. I have been actively involved in patient recruitment and follow-up, database maintenance and data cleaning. In addition I have undertaken extensive event verification work to ensure that all end-points are correctly coded. This is described in more detail in Chapter 3. This ground level involvement has provided a valuable insight into the challenges of working with larger scale data and has made a lasting impression on how I view data capture. I hope that the effort spent in maintaining the databases will benefit future research fellows and ultimately our patients.

# PUBLISHED AND PRESENTED WORK

The following published works are included as chapters in this alternative format thesis. Contributions of all co-authors are acknowledged here.

**Renovascular Hypertension**

Ritchie J, Green D, Chrysochou C, Kalra PA

*Oxford Textbook of Clinical Nephrology 4th Ed. Oxford University Press, in press*

Ritchie J - primary author

Green D, Chrysochou C - proof reading

Kalra PA - proof reading and main editor

**Atherosclerotic Renovascular Disease: Epidemiology and Clinical Manifestations**

Ritchie J, Kalra PA

*Renal Arterial Disease 1st Ed. Springer, in press.*

Ritchie J - primary author

Kalra PA - co-author and main editor

**ASTRAL and Beyond: Who is Appropriate to Consider for Renal Artery Revascularisation?**

Ritchie J, Kalra PA

*Vascular Disease Management. 2011(8):E12-20*

Ritchie J - primary author

Kalra PA - co-author and main editor

**High-Risk Clinical Presentations in Atherosclerotic Renovascular Disease: Prognosis and Response to Renal Artery Revascularisation**

Ritchie J, Green D, Chrysochou C, Chalmers N, Foley R, Kalra PA

American Journal of Kidney Disease. 2013. Epub ahead of print. DOI: 10.1053/j.ajkd.2013.07.020

Ritchie J - study design, data collection and analysis, primary author
Green D, Chrysochou C - proof reading and editorial advice
Chalmers N - reporting of interventional procedures
Foley R - review of statistical methodology
Kalra PA - study design, co-author, main editor

The following papers are included as thesis chapters and awaiting submission.

**Risk for Mortality and Renal Replacement Therapy in Atherosclerotic Renovascular Disease Compared to Other Causes of Chronic Kidney Disease**

Ritchie J, Green D, Alderson HV, Chiu D, Sinha S, Kalra PA

Ritchie J - study design, data collection and analysis, primary author
Green D, Alderson HV, Chiu D - proof reading
Sinha S - proof reading and editorial advice
Kalra PA - study design, main editor

**Predicting Progression to End Stage Kidney Disease in Atherosclerotic Renovascular Disease**

Ritchie J, Foley R, Green D, Chrysochou C, Kalra PA

Ritchie J - study design, data collection and analysis, primary author
Foley R - design of classification tree methodology
Green D, Chrysochou C - proof reading
Kalra PA - study design, main editor

**Comparing Doubly Robust Regression with Randomized Controlled Trials in Nephrology**

Ritchie J, Green D, Sinha S, Kalra PA

Ritchie J – study design, data collection and analysis, primary author
Green D, Sinha S – proof reading and editorial advice
Kalra PA – main editor

**Effects of Anti-Platelet Therapy and Beta-Blockade on Prognosis in Atherosclerotic Renovascular Disease**

Ritchie J, Green D, Alderson HV, Chiu D, Sinha S, Kalra PA

Ritchie J - study design, data collection and analysis, primary author
Green D, Alderson HV, Chiu D - proof reading
Sinha S - proof reading and editorial advice
Kalra PA - study design, main editor

The following presentations to learned societies have resulted from work related to this thesis.

**Benefits of Revascularisation for ARVD Patients with Flash Pulmonary Edema**

Poster presentation (TH-PO329) at the American Society of Nephrology annual meeting Philadelphia, USA, 2011

**Clinical Phenotypes Associate with Outcome in ARVD**

Poster presentation (FR-PO1406) at the American Society of Nephrology annual meeting Philadelphia, USA, 2011

**Predicting Progression to ESKD in Atherosclerotic Renovascular Disease: A Decision Tree Analysis**

Poster presentation (TH-PO355) at the American Society of Nephrology annual meeting San Diego, USA, 2012

**The Association Between Annual Change in Systolic Blood Pressure and Mortality in an All-Cause CKD Population**

Poster presentation (FR-PO420) at the American Society of Nephrology annual meeting San Diego, USA, 2012

**High-Risk Clinical Presentations in Atherosclerotic Renovascular Disease**

Poster presentation (SU341) at the World Congress of Nephrology Hong Kong, China, 2013.

**Comparing Double Robust Regression in Large Observational Studies with Randomized Controlled Trials in Nephrology**

Poster Presentation (PO-0501) at the UK Renal Association Annual Conference Bournemouth, UK, 2013.

# LIST OF ABBREVIATIONS

AAA - Abdominal aortic aneurysm

ACEi - Angiotensin converting enzyme inhibitors

AKI - Acute kidney injury

ARB - Angiotensin receptor blockers

ARVD - Atherosclerotic renovascular disease

ASTRAL - The Angioplasty and Stenting for Renal Artery Lesions Trial

AUC - Area under the curve

BNP - Brain natriuretic peptide

BOLD-MRI - Blood oxygen level dependent magnetic resonance imaging

CAD - Coronary artery disease

CCF - Chronic congestive cardiac failure

CIN - Contrast induced nephropathy

CKD - Chronic kidney disease

CKD-EPI - Chronic Kidney Disease Epidemiology Research Collaboration

CORAL - Cardiovascular Outcomes in Renal Artery Lesions Trial

CRISIS - Chronic Renal Insufficiency Standards Implementation Study

CTA - Computed tomography angiography

CVA - Cerebrovascular accident

CVD - Cerebrovascular disease

CVE - Cardiovascular event

DM - Diabetes mellitus

DNA - Deoxyribonucleic acid

DRASTIC - Dutch Renal Artery Stenosis Intervention Cooperative

DRE - Doubly robust estimator

DUS - Doppler ultrasound

eGFR - Estimated glomerular filtration rate

EMMA - Essai Multicentrique Medicaments vs. Angioplastie study

EPD - Embolic protection device

ESKD - End stage kidney disease

FPO - Flash pulmonary oedema

hs-CRP - Highly sensitive C-reactive protein

$H_0$ - Null hypothesis

IPTW - Inverse probability of treatment weighting

MACE - Major atherosclerotic cardiovascular event

MRA - Magnetic resonance angiography

MRI - Magnetic resonance imaging

NRI - Net reclassification index

NSF - Nephrogenic systemic fibrosis

NYHA - New York Heart Association

OMT - Optimal medical therapy

PTRAS - Percutaneous transluminal angioplasty and stenting

PV - Parenchymal volume

PV:SK-GFR - Parenchymal volume to single kidney glomerular filtration rate ratio

PVD - Peripheral vascular disease

RAAS - Renin angiotensin aldosterone system

RAO - Renal artery occlusion

RAS - Renal artery stenosis

RASCAD - Stenting of Renal Artery Stenosis in Coronary Artery Disease study

RAVE - Renal Atherosclerotic Revascularisation Evaluation study

RCT - randomised controlled trial

RDF - Rapidly declining renal function

RH - Refractory hypertension

ROC - Receiver operating curve

RR - Relative risk

RRT - Renal replacement therapy

SFK - Single functioning kidney

SHARP - Study of Heart and Renal Protection

SK-GFR - Single kidney glomerular filtration rate

SRVD - Salford Renovascular Database

STAR - STent placement in patients with Atherosclerotic Renal artery stenosis and impaired renal function trial

TIA - Transient ischaemic attack

USRDS - United States Renal data system

# CHAPTER 1 - BACKGROUND TO ATHEROSCLEROTIC RENOVASCULAR DISEASE

## 1.1 Epidemiology and clinical manifestations of atherosclerotic renovascular disease

Ritchie J, Kalra PA

*Published in Renal Arterial Disease (1st Edition), Springer - in press*

The term atherosclerotic renovascular disease (ARVD) describes both partial and total atheromatous occlusions of the renal arteries. These luminal narrowings often occur in conjunction with macrovascular disease in other organ systems, and have complex relationships with end-organ damage to the kidneys. In this chapter we explore the epidemiology of ARVD and describe the clinical consequences of this somewhat heterogeneous condition.

### 1.1.1 How is ARVD defined?

*Anatomical definition*

ARVD refers to a spectrum of changes ranging from any atherosclerotic narrowing of the arteries supplying the kidneys, through focal stenosis of one or more renal arteries, renal ischaemia and kidney atrophy, to the extreme of complete occlusion of the blood supply to one or both kidneys. Despite a wealth of published literature, consensus on what defines an anatomically 'significant' atherosclerotic renal artery stenosis (RAS) does not exist. Typically, research publications employ angiographic measurements, with a RAS in excess of either 50%, 60% or 75% deemed to be 'significant'. Whilst this is by no means unreasonable, the limitations of this approach should be considered. Firstly, data in which expanded balloons were used to generate an aorto-renal pressure gradient in humans with a unilateral RAS demonstrated that only when a stenosis reached 70-80% was there activation of the renin angiotensin aldosterone system (RAAS) [1]. Hence one could question the value of reports where RAS has been defined as <50% - although an easy counterpoint to this argument would be the increased mortality seen with even low degrees of RAS [2], presumably largely due to extra-renal vascular disease including organ injury related to the systemic inflammatory state of atherosclerosis. Secondly, such absolute definitions fail to consider possible compound effects of bilateral disease; for example, is a unilateral 50% stenosis of greater clinical significance than bilateral 40% stenoses?

*Syndromic definition*

Given that ARVD can be associated with perturbations in renal function, blood pressure, cardiac structure and function, and changes in mortality risk even where RAS is <50%, it is clear that a single biplane angiographic measurement is a blunt tool for determining overall 'significance' of disease. As such we would suggest that a stenosed renal artery, where there is associated evidence of either one or more of renal parenchymal damage, altered neuro-hormonal state or cardiac structural or functional change (with no alternative explanation), should be considered to be of clinical significance whatever the degree of RAS. We accept that this is somewhat esoteric, and much of the clinical data discussed in this chapter are based upon broader, structural definitions. Hence (unless otherwise specified), we have taken >50% focal RAS as being of clinically significance. The term 'Ischaemic Nephropathy' is now also widely utilised and refers to chronic kidney disease (CKD) that is caused by ARVD.

*Potential collateral circulation of the kidney*

In the majority of cases, development of atheroma in the renal artery is a chronic process. As such there is normally reciprocal development of collateral vessels supplying the diseased kidney to maintain parenchymal viability. Typically these collateral vessels form from lumbar arteries with inferior mesenteric, testicular / ovarian and suprarenal arteries also recognised as potential sources [3]. These vessels are able to contribute over 50% of basal renal blood flow. Animal models suggest that this collateral circulation begins to develop when main vessel stenosis exceeds 40-50% [4].

### 1.1.2 Prevalence of ARVD

*Unselected populations*

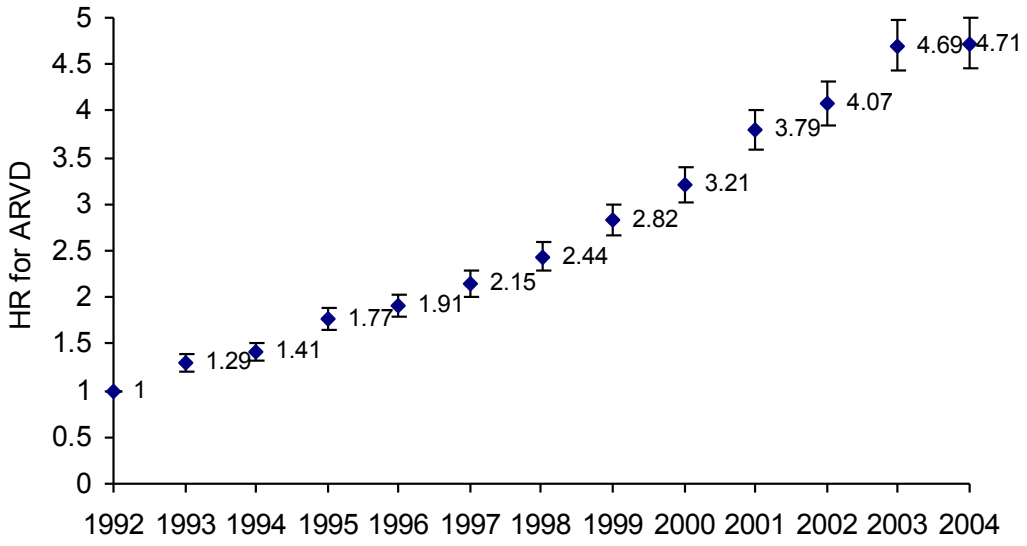
ARVD is often an asymptomatic disease, diagnosed during investigation for other vascular pathology or investigation of CKD. Despite the morbidity and mortality associated with the condition widespread screening is not justified for ARVD and as such limited data exist to describe the true population prevalence. Some of the best available information comes from a single study of "free-living" patients aged over 65 years living in the United States. Here, 834 patients underwent Doppler ultrasound (DUS) examination of their renal vessels, with an incidental RAS in excess of 60% identified in 6.8% of patients (with 12% of these being bilateral). Of note, patients with a positive investigation had significantly higher systolic blood pressures (142 vs. 134mmHg, p=0.007) [5]. This study is complimented by a review of over 1900 computed tomography angiograms performed in potential renal transplant donors, where evidence of atherosclerotic RAS (severity not specified) was found in 5% of patients; with a strong relationship to increasing age [6].

*Registry data*

Further information can be gleaned from analysis of claims data obtained from the Medicare random 5% denominator file and from coded diagnoses found in the reports of the US Renal Data System (USRDS). In an analysis of Medicare claims data from 1999-2001 (> 1.1 million patients aged over 67 years), the prevalence of ARVD diagnosed in this elderly population was 0.54% with the annual incidence for new diagnoses between 2000 and 2001 estimated at 3.7 cases per 1000 patient years [7]. A subsequent study examining Medicare claims data from more than 16 million patients between 1992 and 2004 described a similar incidence (3.09 cases per 1000 patient years) but noted a progressive increase in rates of diagnosis, with patients in the 2004 claims data 4.7 times more likely to receive a diagnosis of ARVD than those in the 1992 data [8], figure 1.1.1. Although these analyses have not been repeated in more recent years within Medicare, data from the USRDS suggests a reversal in this trend with reports between 2004 and 2009 describing falls in the overall prevalence (1.0% to 0.7%) and incidence (1.7% to 1.3%) of ARVD as a cause of end-stage kidney disease in the US dialysis population [9]. The most likely explanation for this biphasic pattern is increased enthusiasm for investigation during the 1990's

(with heightened physician awareness, improved access to diagnostic tools and ready availability of interventional treatment techniques), which has been tempered more recently in light of negative randomised controlled trials (RCT) into percutaneous intervention [10].

**Figure 1.1.1** - Relative annual prevalence of ARVD in Medicare population between 1992 and 2004, with 1992 as comparator group




*X-axis shows year; Y-axis shows hazard ratio for diagnosis of ARVD (adjusted for age, gender and co-morbidities). Point represent hazard ratio, bars represent 95% confidence intervals. Adapted from Kalra et al [8] with permission*

*Ethnic variation*

There is apparent substantial worldwide variability in the primary cause of RAS, which in itself may represent variations in chronic disease burdens in different parts of the world. Atheromatous causes represent over 90% of RAS cases in Western populations but sequelae from vasculitis are said to account for in excess of 60% of cases diagnosed in India and South Asia. Despite these geographic differences, however, there does not appear to be a racial bias for development of ARVD. In 324 patients evaluated for potential renovascular hypertension, Caucasian ethnicity was not an independent risk factor for positive investigation (OR 1.5, p=0.07) [11] and in the community based screening study by Hansen et al ethnic distribution was identical between groups with positive and negative DUS investigations (23% African-American, 77% Caucasian) [5]. When comparison has been made between non-Caucasian

populations investigated for ARVD, no significant difference in the proportion of positive investigations was noted between African-American and Hispanic patients [12]. No comparative studies have specifically addressed the Asian population; however a single centre study of 202 Japanese patients with risk factors for ARVD found evidence of RAS >50% in 20% of patients investigated using magnetic resonance angiography [13]. In a Japanese population of 729 patients with known cardiac or cerebrovascular disease ARVD was present in 5.2% of patients [14].

### 1.1.3 Prevalence of ARVD in selected populations

*Hypertensive populations*

Despite the frequent association of ARVD with hypertension, it is often questionable whether a given RAS lesion is causative; a rigorous definition of true 'renovascular hypertension' necessitates cure or substantial improvement in hypertension after dilatation of RAS [15]. Although there has not been a specific study addressing the prevalence of RAS in the general hypertensive population, a figure of 2% is widely quoted. Systematic review of angiographic studies of patients where renovascular hypertension was clinically suspected (e.g. elevated blood pressure at a young age; hypertension that was resistant to therapy) found a pooled prevalence of 14.1% [16]. In another study in which patients presenting to a German Emergency Room with uncontrolled hypertension (>180mmHg systolic and/or 100mmHg diastolic) were screened for causes of secondary hypertension, significant RAS was identified in 8.1% of patients [17]. The overall lack of data negatively affects the ability of physicians to predict the presence of ARVD in patients referred for investigation, with clinical suspicion for undiagnosed stenosis having a positive predictive value of only 40% [18].

*Chronic kidney disease and dialysis*

There are no data to inform us as to how rates of ARVD vary according to different stages of CKD. In the analyses of Medicare claims data, patients with CKD (estimated glomerular filtration rate [eGFR] <60ml/min/1.73m$^2$) were between 2.55 [8] and 4.6 [7] times more likely to have ARVD than those with higher eGFR, but these data do not provide insight into cause/effect relationships. In an analysis of claims data from 160,000 incipient United States dialysis patients

between 1996 and 2001, the overall prevalence of ARVD was 9.1%, but less than half of these cases had ARVD coded as their primary cause of renal failure [19]. Again, as this analysis was based on claims data rather than on the results of comprehensive screening the true prevalence is likely to have been under-reported. Indeed, rates of 22 to 41% have been reported in smaller studies that screened sequential patients at initiation of dialysis [20,21] (with bilateral disease present in 11-16% of patients).

*Prevalence in patients with other macrovascular disease*

ARVD is very commonly associated with atheromatous disease in other vascular beds and these associations are emphasised in Medicare data analyses, table 1.1.1 [7]. ARVD is frequently identified during investigation of patients with non-renal macrovascular diseases, although the clinical implications of this are not always certain. It is therefore of interest to specialists in many different disciplines including cardiology, vascular surgery, stroke medicine and hypertension. As a consequence there have been many studies undertaken in selected groups of patients with cardiovascular disease, and these populations are likely to be enriched with patients with ARVD.

*Coronary artery disease*

There are strong links between ARVD and coronary artery disease (CAD), with evidence of RAS (>50%) found in 15% of patients referred for diagnostic coronary angiography (with approximately one third of these patients having significant bilateral disease) [22,23]. These figures have remained constant over the last two decades despite increased awareness of modifiable vascular risk factors over this time. Table 1.1.2 shows the more recent larger studies that have examined the co-morbid presence of RAS in patients undergoing investigation for CAD [22,24-30]. That the relationship between CAD and ARVD is most probably a marker of overall atheromatous burden has been highlighted by there being a significant relationship between the number of diseased coronary vessels and probability of concurrent RAS (odds ratio of RAS in the presence of triple vessel disease / previous coronary bypass graft 1.74, compared to lesser burden of CAD) [22,25].

**Table 1.1.1** - Prevalence of ARVD in the US Medicare population showing macrovascular disease associations

| | Prevalence | | | |
|---|---|---|---|---|
| | **No ARVD (n=1,085,250)** | **ARVD (n=5875)** | **ARVD AHR* (95% CI)** | **p** |
| **Acute kidney injury** | 0.8 | 10.3 | 1.59 (1.43-1.77) | <0.001 |
| **Chronic kidney disease** | 2.3 | 24.6 | 4.61 (4.27-4.98) | <0.001 |
| **Hypertension** | 53.4 | 90.8 | 4.31 (3.93-4.73) | <0.001 |
| **Diabetes mellitus** | 17.9 | 32.5 | 0.89 (0.84-2.61) | 0.001 |
| **Coronary artery disease** | 24.9 | 66.8 | 2.45 (2.3-2.61) | <0.001 |
| **Congestive cardiac failure** | 13.6 | 37.6 | 1.01 (0.94-1.07) | 0.9 |
| **CVD/TIA** | 12 | 36.9 | 1.58 (1.49-1.67) | <0.001 |
| **Peripheral vascular disease** | 12.7 | 56 | 3.96 (3.74-4.2) | <0.001 |
| **Mesenteric ischemia** | 0.2 | 1.9 | 2.38 (1.93-2.93) | <0.001 |
| **AAA** | 0.5 | 6.4 | 3.38 (3.0-3.81 | <0.001 |

*Abbreviations: ARVD - atherosclerotic renovascular disease. AHR - adjusted hazard ration. CVD - cerebrovascular disease. TIA - transient ischaemic attack. AAA - abdominal aortic aneurysm.*
*Hazard ratios adjusted for age, gender and co-morbid diseases. Adapted from Kalra et al [7] with permission*

**Table 1.1.2** - Major studies examining the co-morbid presence of CAD and ARVD

| Author | Year of publication | Number of patients | Type of study | Prevalence of significant RAS | Factors associated with RAS |
|---|---|---|---|---|---|
| **Ollivier R et al** [24] | 2009 | 650 | Abdominal aortography following coronary angiography | 14.5% had RAS >50%, 3.1% bilateral disease | Male sex, multi-vessel CAD, hypertension, renal insufficiency |
| **Cohen M et al** [25] | 2005 | 843 | Abdominal aortography following coronary angiography | 11.7% had RAS ≥75% | Older age, higher creatinine levels, PVD, number of cardiovascular drugs hypertension, female sex, and 3-vessel coronary artery disease or previous coronary artery bypass graft |
| **Rigatelli G et al** [26] | 2005 | 205 | Abdominal aortography following coronary angiography | 19.5% had RAS ≥50%, 7.3% bilateral | ≥ 3-vessel CAD, age > 65 years, and ≥ 3 cardiac risk factors |
| **Wang Y et al** [27] | 2003 | 203 | Abdominal aortography following coronary angiography | 14.8% RAS ≥ 50%, 2.6% bilateral | Age, multivessel CAD |
| **Rihal CS et al** [28] | 2002 | 297 | Hypertensive patients, abdominal aortography following coronary angiography | 19.2% RAS >50%, 3.7% bilateral, 7% had RAS >70% | Systolic blood pressure, CVA/TIA, cancer |
| **Conlon P et al** [29] | 2001 | 3987 | Abdominal aortography following coronary angiography | 4.8% had unilateral RAS ≥75%, 0.8% bilateral ≥75% | Female sex, increasing age, hypertension, CCF, increased creatinine |
| **Uzu T et al** [30] | 1997 | 297 | Autopsy series identifying patients who had suffered a MI | 12% had , 28.6% of these had bilateral RAS | Hypertension, proteinuria and renal insufficiency |
| **Harding MB et al** [22] | 1992 | 1235 | Abdominal aortography following coronary angiography | >15% had RAS >50%, 11% unilateral, 4% bilateral disease | Age, severity of CAD, CCF, female sex, PVD |

*Qualifications - studies performed within the last two decades considering over 200 patients*

*Abbreviations: CAD - coronary artery disease. PVD - peripheral vascular disease. CCF - congestive cardiac failure. eGFR - estimated glomerular filtration rate. CVA - cerebrovascular accident. TIA - transient*

*Heart failure*

As would be anticipated, the frequent association of ARVD with CAD and hypertension can result in structural heart disease which can be detected in the majority of patients; consequent syndromes of cardiac dysfunction are also highly prevalent. In studies where renal vessels are imaged in patients with symptoms of chronic congestive cardiac failure (CHF), evidence of RAS >50% can be found in approximately 30-50 % of patients [31,32]. In a CHF population in Northern England, patients with significant RAS were more likely to have renal dysfunction, be taking higher doses of diuretics but lower doses of angiotensin blocking agents, to have prolonged hospital admissions and a negative outcome [32]. Clinical presentations with sudden onset or 'flash' heart failure can be life-threatening and may be the first indication of ARVD in about 10% of patients. The true incidence of this condition may be under-estimated due to the fact that renovascular investigation is undertaken only in a minority of patients with abrupt onset left ventricular failure. Patients with bilateral significant RAS or a solitary functioning kidney are those at greatest risk of this condition. Many of these patients with ARVD and heart failure have preserved left ventricular function, highlighting the relevance of diastolic parameters and measures of ventricular eccentricity.

*Cerebral vascular disease*

RAS can often be identified in patients who have suffered a stroke, with the highest rates observed in patients who also have significant carotid stenosis. In a post-mortem series of 346 patients with clinical evidence of stroke, RAS >75% could be identified in 10.4% of all patients (12.1% of patients with ischaemic stokes), with over 4 times as many patients with carotid stenosis (> 50%) having RAS than those without carotid stenosis [33]. When an earlier point of the natural history of vascular disease is considered, associations have been noted between the presence of ARVD and increased carotid-intimal thickness in patients with type II diabetes [34]. Although no data exist to describe progression to overt carotid vessel disease, carotid-intimal thickness is sometimes used as a surrogate marker for cardiovascular risk [35].

*Abdominal and peripheral vascular disease*

Due to the close anatomic proximity, coexistent disease of the abdominal aorta is commonly seen with ARVD. In a series of consecutive patients investigated with aortography for either abdominal aortic aneurysm (n=109) or aorto-occlusive disease (n=21), 38% and 33% of patients respectively had a RAS in excess of 50% [36]. Comparable figures can be found in other angiographic series which report RAS >50% in 24% of patients with an abdominal aortic aneurysm [37] and in 26% of patients investigated for aorto-iliac disease [38]. Many studies have sought to determine the co-existence of RAS with peripheral vascular disease (PVD), and RAS > 50% can be found in 30 - 40% of patients with symptomatic claudication; the larger studies are detailed in table 1.1.3 [36, 39-43]. As is the case with ARVD and CAD, the presence of significant RAS in patients with PVD is associated with an increased risk for major cardiovascular events and death during follow up. Hence in a study of 483 patients with symptomatic PVD, those with severe RAS (15.6% of all PVD patients had ≥ 60% RAS) had a 2.5-fold increased risk for occurrence of any of myocardial infarction, stroke, amputation and death and a 2.9-fold increased risk for death, compared to patients without RAS [39] over a median follow up time of 15 months.

**Table 1.1.3** - Major studies examining the co-morbid presence of aorto-iliac and PVD with ARVD

| Author | Year of publication | Number of patients | Type of study | Prevalence of significant RAS | Factors associated with RAS |
|---|---|---|---|---|---|
| **Amighi J et al** [39] | 2009 | 487 | Peripheral angiography followed by renal angiography | 15.6% had RAS ≥ 60% | |
| **Androes MP et al** [40] | 2007 | 200 | Peripheral angiography followed by renal angiography | 12% had RAS ≥50% | Hypertension, CAD, female, DM, aorto-iliac disease, age >60 years, multiple levels of PVD |
| **Leertouwer TC et al** [41] | 2001 | 386 | PVD suspected | 32.6 % had RAS ≥50%, 22.8% bilateral | Not analysed |
| **Iglesias JI et al** [38] | 2000 | 201 | Aorto-iliac | 26.4% had RAS >50% | Not analysed |
| **Swartbol P et al** [42] | 1992 | 405 | Peripheral angiography | 49.1%, 117 moderate, 14 severe RAS | Hypertension, age >70 yrs, smoking, pathological ECG |
| **Olin JW et al** [36] | 1990 | 395 | PVD/ AAA | 33-39% had RAS >50%, 13% bilateral | Hypertension, worse renal function |
| **Salmon P et al** [43] | 1990 | 374 | Peripheral angiography followed by renal angiography | 13.9% had RAS ≥ 50%, 5.9% bilateral | |

*Qualifications - studies performed within the last two decades considering over 200 patients*

*Abbreviations: CAD - coronary artery disease. PVD - peripheral vascular disease. AAA - abdominal aortic aneurysm. DM - diabetes mellitus*

### 1.1.4 Risk factors for development of ARVD

*Age*

Although it is clear that prevalence of ARVD increases with age, a finding that has not altered in over 50 years [44], conflicting data exist regarding the role of 'classical' vascular risk factors in the natural history of the condition. In our own local renovascular database, which comprises over 900 patients with ARVD referred from a 1.5 million population over 20 years, the median age of the population at ARVD diagnosis is 69.6 years and 8.6%, 29%, and 45.5% are made up of patients in their fifth, sixth and seventh decades, respectively; 87.1% of patients are aged > 60 years at study entry.

*Smoking*

Although high proportions of patients entered into interventional studies in ARVD have a smoking history. Within the Angioplasty and Stenting for Renal Artery Lesions trial (ASTRAL) 20% were current smokers and 50% ex-smokers [10]), there is no direct evidence that smoking *per se* increases risk for ARVD development. Data from our centre assessing 249 consecutive patients referred for diagnostic renal angiography did not show a significant difference in smoking history between patients with normal and abnormal renal vessels (55.4% vs. 68.7%) despite significantly higher levels of non-renal (and renal) atheromatous disease in the ARVD patients [45]. In contrast, a smaller study of 48 hypertensive patients investigated for RAS found significantly higher rates of smoking in patients with positive studies (19/21 vs. 16/27, p=0.04) [46]. It may have been important that the overwhelming majority of smokers with RAS in this study had a greater than 25 pack-year history. This finding has been replicated in a study of 45 incident dialysis patients investigated for possible ARVD. Here, 10 patients had a positive study, with a significantly greater pack year history than those patients with normal renal vessels (37 vs. 17 pack years, p=0.016) [20]. These data support a cumulative risk for development of ARVD. Equally, given the adverse effects of smoking on renal plasma flow, it is probable that (even in the absence of a direct effect on the physical stenosis), smoking could further complicate the already compromised intra-renal haemodynamics [47], predisposing to greater renal dysfunction.

*Diabetes mellitus*

Analysis of Medicare claims data suggests a link between diabetes and ARVD, with higher rates of diabetes seen in patients with ARVD (32.5% vs. 17.9% in patients without ARVD) and diabetic patients 1.3 time more likely to be diagnosed with ARVD [7,8]. These figures are comparable to the 30% diabetes prevalence in patients recruited into ASTRAL. In the Medicare data, it is possible that higher rates of CKD in the ARVD patients were a relevant confounding factor. However, a systematic review of risk factors has shown a pooled prevalence of ARVD of 20% in patients with diabetes and hypertension [16], making it likely that diabetes is a risk factor for development of ARVD.

*Hyperlipidaemia*

Little data exist to specifically link hyperlipidaemia with the development of ARVD, although as in the case with smoking, strong links with other atheromatous conditions make the relationship likely. Our own data showed a slightly higher prevalence of hyperlipidaemia (serum total cholesterol >5.2mmol/l) in patients found to have ARVD (61% vs. 48% in those without) [45]. Lipid profiles in ARVD patients follow the same pattern as in patients with coronary or carotid atheroma, with significantly reduced apolipoprotein A1 levels [48]. Other studies have shown increased levels of free-fatty acids (glycerol-glyceride) in patients with ARVD [49], though this may have more important implications for mortality than development of atheroma [50]. However, intervention with statins has been shown to prevent anatomical progression of RAS in a retrospective study, which provides some support to the pathogenic effect of hypercholesterolaemia in renal atherogenesis [51].

*Hypertension*

Of all the classical risk factors for the development of atherosclerosis, hypertension is the hardest to link to ARVD due to potential cause and effect relationships with both RAS and CKD. However, it is clear that elevated blood pressure is a major determinant of CKD in ARVD as it is associated with more severe histological intra-renal damage in ARVD [52], with greater rates of eGFR loss, and with the development of renal atrophy [53]. As such hypertension is an important risk factor for ischaemic nephropathy development despite the absence of direct causal evidence in RAS progression.

*Novel risk factors*

Several other circulating markers of cardiovascular risk have been evaluated regarding their relationship to ARVD e.g. Fibrinogen, highly sensitive C-reactive protein (hs-CRP), homocysteine, and lipoprotein(a) [54]. A positive relationship between both hs-CRP and homocysteine and ARVD have been shown in univariate analysis, but these associations have not been sustained in multivariate analysis, and so currently available data cannot inform us as to whether the elevated levels are a cause or result of ARVD [55].

### 1.1.5 Pathogenesis of Ischemic Nephropathy and development of renal parenchymal damage

Animal and human studies have shown that reduction in renal blood flow and activation of the RAAS typically occur only when RAS are high grade (>70-80%), and yet reductions in eGFR are observed with RAS of all degrees (i.e. minimal through to high-grade). It follows that the aetiology of renal impairment in ARVD is a multifactorial process, and not simply due to the 'ischaemic' effects of reduced blood flow within the kidney. Indirect confirmation of this hypothesis can be drawn from several studies which have failed to demonstrate an association between degree of RAS and level of renal function [56]. Importantly in ARVD, the amount of proteinuria (another marker of renal dysfunction and prognosis) does not relate to degree of RAS, although it is linked to level of renal function [57]. This suggests that damage to the 'substance' or parenchyma of the kidney is the main arbiter of renal dysfunction.

*Whole organ factors*

It is likely that a large proportion of the functional loss observed in ARVD relates to organ damage mediated by "whole organ factors" such as hypertensive damage and microembolisation. In samples taken from kidneys nephrectomised due to severe RAS mediated hypertension, evidence of atheroembolic damage was observed in 39% (though this may have in part been related to prior vascular instrumentation), with hypertensive damage seen in 52% [52]. In this series of 62 patients, severe tubulointerstitial atrophy was a near universal finding (94%), although advanced glomerulosclerosis was not a common finding.

*Animal models*

This histological pattern of disease can be readily induced in animal model of RAS suggesting that local factors may play an important role. Indeed, animal models have recently shown the fascinating natural history of how renal damage beyond a RAS unfolds, but it should be remembered that these represent relatively short-term changes in uncomplicated, 'pure' RAS – in humans, the pathogenesis is complicated by years of prior hypertension and atherosclerosis, and other contributing injurious factors including family history, smoking and medication.

*Local endothelial factors*

Hence in porcine models tubulointerstitial fibrosis develops rapidly following induction of RAS [58]. This occurs in conjunction with a marked thinning of the small blood vessels within the renal tissues - microvascular rarefaction [59] - a recognised factor in progression of kidney disease [60]. These changes are thought to relate to local down-regulation of vascular endothelial growth factor production and increased oxidative stress (shown by reduced levels of superoxide dismutase) in stenosed kidneys [61]. As these microvascular alterations occur within a short space of time after RAS formation, this may represent an early point in the natural history of the disease.

*Renin angiotensin aldosterone system*

Chronic stimulation of the RAAS is a well recognised feature of ARVD, with experimental data stretching back almost 80 years [62]. In addition to haemodynamic effects, angiotensin II contributes to the development of renal damage by enhancing expression of pro-fibrotic cytokines and growth factors, thus promoting tubulointerstitial fibrosis [63]. As such RAAS activation in ARVD likely has direct damaging effects as well as increasing vulnerability to acute changes in renal function precipitated by volume shifts. Increased levels of brain natriuretic peptide (released predominantly by cardiac myocytes, but also by glomerular epithelial and mesangial cells) may offer some protection from this by antagonising the RAAS [64].

*Effects of ARVD on the contralateral kidney*

As the majority of ARVD patients have a unilateral stenosis, the question of why so many patients have an overall reduction in renal function (defined by the crude measure of eGFR in clinical practice) is frequently raised. The most pertinent observation is that non-stenosed contralateral organs often do not have a preserved GFR, and can have the same degree of functional impairment (measured by isotope GFR) as the diseased organ [65]. In a series of 60 patients with unilateral stenosis (including cases of <50% stenosis and patients with fibromuscular disease), a significant difference in GFR between diseased and non-diseased sides was only observed where there was complete arterial occlusion on one side. When and how this reduction in function of the organ with the patent blood supply occurs is therefore a matter of clinical importance. Human histological studies have shown changes in non-stenotic organs which are very similar to those seen in RAS kidneys, and the effects of systemic hypertension on the contralateral organ function is thought to play a pre-eminent role [66]. Additionally, microvascular pressure mediated injury may be relevant in damage of the non-stenosed organ. This hypothesis is based on data from a series of 50 patients in whom magnetic resonance measurements of renal cortical volume were performed. Here there was a suggestion of compensatory hypertrophy in kidneys *contralateral* to a moderate / severe stenosis [67], which conceivably is a marker of glomerular hyperfiltration, and this is increasingly recognised as a long term risk factor for loss of renal function [68]. As with systemic hypertension, the pro-atherosclerotic milieu will also contribute to contralateral renal damage. In pig models, atheroma has been shown to exacerbate the effects of an induced physical stenosis and to associate with worse findings on histological examination [69,70]. With evidence of intra-renal atherosclerotic disease in the majority of ARVD patients it is likely that the reduction in renal function is also related to the atheromic environment.

*Identification of at-risk organs earlier in the natural history*

As described above, the parenchymal damage associated with ARVD is believed to be the main arbiter of renal dysfunction in ischaemic nephropathy. It has been understood for some time that as the burden of parenchymal damage increases, renal volume is lost [67]. Complimentary to this is the concept of "*hibernating parenchyma*" - renal tissue which has reduced function as a direct

result of the reduced blood flow associated with RAS, but which has not yet suffered irreversible histological damage [71]. Imaging studies suggest that it may be possible to identify kidneys with hibernating parenchyma before tissue is irretrievably damaged; one technique involves examining the ratio of parenchymal volume (measured by MRI) with isotope single kidney GFR values [72] (a high parenchymal volume:GFR signifying a kidney capable of improving its function with renal revascularisation). In the future such techniques may help identify patients in the early and potentially modifiable stages of the natural history of their disease.

### 1.1.6 Progression of disease in ARVD

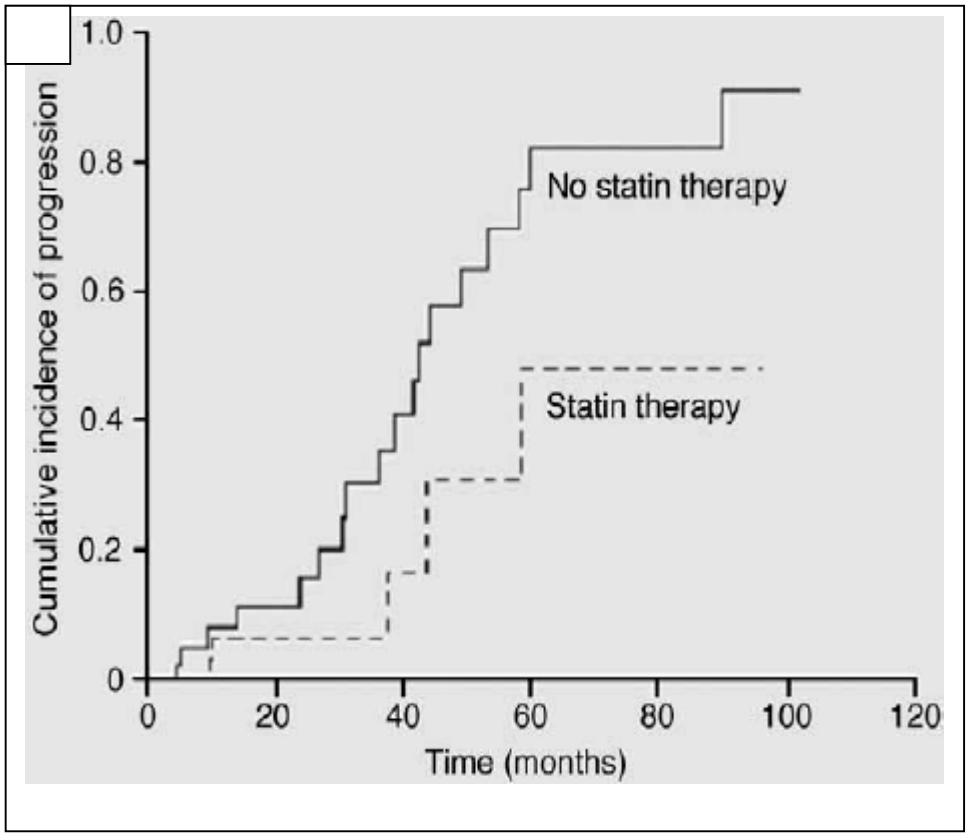
The epidemiology of ARVD has changed over the last few decades. Many early reports detailing the natural history of atherosclerotic RAS were limited by either small patient numbers, consideration of specific disease presentations, and, importantly, they were generated in an era when vasculoprotective pharmacotherapy (particularly statins) was unavailable.

*Progression of stenosis*

Historically the received wisdom was that ARVD was a progressive disease in terms of both degree of stenosis and loss of renal function. As discussed above, it is now evident that the absolute degree of RAS has limited value in determination of GFR; equally it is now clear that rates of RAS progression are much lower than previously thought – once the patient is under treatment. One of the earliest serial arteriographic studies was reported in 1984 and showed the progression of RAS (defined as > 75% stenosis) to be 44%, with progression to renal artery occlusion (RAO) seen in 16% of 85 patients over 52 months mean follow up up [73]. A study of 1189 patients a decade later showed significant RAS progression in 11.1% of patients during a mean interval of 2.6 years between angiographic studies [74]. Reports in the early 1990's observed significant progression of RAS in 35% of patients at 3 years and 51% of patients at 5 years [75]. This was associated with renal atrophy (>1cm shrinkage on ultrasound) in 21% of patients with significant RAS (>60%) compared to 5.5% in patients without RAS [53]. These figures are only of historical interest in the current era of statin therapy. Although available data are retrospective, in a study of 79 patients with ARVD, statin treated patients (n=40) were much less

likely to suffer progression of stenosis at 3-years (odds ratio 0.28, p=0.01) than non-statin treated patients [51], figure 1.1.2. Here evidence of RAS progression was observed in 6% of the statin group vs. 30% of the non-statin treated group. As such, and excluding acute luminal occlusions, rate of progression of RAS is now considered to be minimal if appropriately treated.

**Figure 1.1.2** - Cumulative incidence of renal artery disease progression stratified according to treatment with or without statin therapy




*Reproduced from Cheung et al [51] with permission*

*Progression of renal dysfunction*

Just as there have been changes in the rate of RAS progression as the medical management of ARVD has improved, several cohort and trial data sets suggest that modern therapeutic regimes may be having a positive influence on rate of loss of renal function over time. The key pharmacotherapies include statins and angiotensin blockade which are now readily utilised. Large scale RCT data have shown an average rate of eGFR loss in the region of 1-2ml/min/1.73m$^2$/year [10] - figures comparable to most other causes of CKD [76]. However, it is recognised that sub-groups of patients exist who lose function at a faster rate. Although it is not yet clear what patient phenotype are at highest risk from this, there is a view that this group may represent a distinct disease sub-type [77]. In parallel with a lower rate of loss of renal function has been a reduction in rates of progression to end stage kidney disease (ESKD). Between 1996 and 2000 in the United States the proportion of incident dialysis patients with a primary diagnosis of ARVD fell slightly from 5.5% to 4.7% - despite an increased rate of investigation for and diagnosis of ARVD [19]. Our own single centre data that includes 809 ARVD patients diagnosed between 1990 and 2009 has shown a stepwise reduction in the proportion of patients progressing to renal replacement therapy depending upon year of diagnosis. Between 1995 and 2000, 3.5% of patients diagnosed with ARVD progressed to ESKD, whilst comparable figures were 2.3% in patients diagnosed between 2000-2005 and only 0.8% of patients diagnosed after 2005 [44].

*Development of non-renal vascular disease*

There are extremely strong associations between ARVD and other macrovascular diseases. Importantly this is an on-going relationship, with higher rates of newly diagnosed vascular pathology seen in ARVD populations compared to their non-ARVD counterparts as evidenced by Medicare data from a decade ago - annual stroke rate 18 vs. 5%, congestive cardiac failure 20 vs. 6%, peripheral vascular disease 26 vs. 5% and ischaemic heart disease 30% vs. 7% [7]. The two most recently published RCT (both in the era of modern pharmacotherapy) have both observed an approximate 10% annual incidence of major cardiovascular events (ASTRAL data shown in Figure 3) [10,78]. Given the links between CAD and ARVD, a relationship with other cardiac structural / functional parameters is to be expected. In a cross-sectional echocardiographic

analysis, structural or functional abnormalities were observed in 95% of ARVD patients (n=79), with greater rates of left ventricular hypertrophy (78.5% vs. 46%), diastolic dysfunction (40.5% vs. 12%), and mass index (183 ±74 vs. 116 ±33g/m$^2$) present when compared to age and eGFR matched controls [79]. When echocardiography was repeated in 51 ARVD patients at 12-months, a significant increase in left ventricular dilatation was observed with a concurrent increase in the degree of eccentricity in left ventricular hypertrophy [80]; there were no patients at this time point described as having a normal heart by echocardiographic criteria.

### 1.1.7 Clinical presentations of ARVD

Many cases of ARVD are clinically silent, existing as part of a spectrum of diffuse vascular and / or chronic kidney disease. However, recognisable clinical presentations (or at least clinical scenarios in which ARVD should be considered) exist.

*Chronic congestive heart failure*

Chronic RAAS over activity (as found in ARVD) is a recognised factor in the development of abnormal left ventricular remodelling and dysfunction. With at least 30% of elderly CHF patients having demonstrable evidence of RAS [31,32], and over 13% of patients in ASTRAL requiring admission for fluid overload / heart failure over a median follow-up period of 33 months [10], it is important to determine if ARVD is merely associated with CHF (perhaps playing a role in an ischaemic aetiology of heart failure), or if a causal relationship exists. Although there are some non-systematic data to suggest that renal artery revascularisation can control symptoms of heart failure [81], the only published RCT that assessed the effects of intervention on cardiac structural parameters did not examine cardiac failure as an end-point [82]. Given the healthcare costs associated with CHF, this is an important field for further study.

*Acute cardiac failure*

Better defined is the syndrome of acute pulmonary oedema associated with ARVD - a presentation often termed “flash pulmonary oedema (FPO)”. This is classically defined to be symptoms of acute left ventricular failure in the presence of preserved ventricular function. Whilst high grade, bilateral RAS (or

high grade stenosis to a single functioning kidney) is recognised as a typical cause for this dramatic presentation (with 5-7% of ARVD patients presenting in this manner [83]), other potential causes include cardiac ischaemia or acute mitral valve dysfunction. In ARVD the postulated mechanism for development of FPE relates to excess aldosterone secretion. This leads both to volume expansion, but also to increased vascular permeability. Where this occurs in the presence of the increased vascular stiffness and left ventricular diastolic dysfunction associated with CKD and hypertension, abrupt physiological decompensation can result [84]. In the setting of a unilateral RAS the non-diseased kidney is able to suppress its own renin secretion so as to balance the aldosterone excess emanating from the stenosed side; however, this cannot occur as readily where disease is bilateral. Despite the frequency of cardiac abnormalities seen in ARVD, reductions in left ventricular systolic function are less frequent in comparison to the prevalence of diastolic abnormalities; hence is it likely our understanding of FPE will increase as more light is shed on the syndrome of 'Heart failure with preserved ejection fraction' [85].

*Renovascular hypertension*

ARVD is a recognised cause of secondary hypertension, accounting for 8% of patients with uncontrolled blood pressure (>180mmHg systolic and/or 100mmHg diastolic), which compares with 14% of such patients having primary or secondary hyperaldosteronism [17]. Although no specific data exist, it is likely that a higher prevalence of ARVD would be found if patients with treatment resistant (or refractory) hypertension were to be systematically screened for RAS. Given the extensive cardiovascular morbidity seen in ARVD, some patients actually have reduced blood pressure as a result of other health issues (e.g. CHF). This somewhat clouds the question of screening and suggests that alternative markers of vascular health (e.g. vascular stiffness or brain natriuretic peptide assay) are as important as blood pressure when considering the clinical impact of ARVD.

*Rapid loss of renal function*

As detailed previously, the overall rate of progressive eGFR loss in ARVD is slow when considering large cohorts or study populations as a whole. However, a proportion of patients present with more rapid loss of renal function - within

ASTRAL 97 patients (12%) had seen an increase in serum creatinine in excess of 1.13mg/dl (100µmol/L) or of 20% from baseline in the 12-months prior to randomisation [10]. Further analyses of the outcome and phenotypic characteristics of this sub-group are warranted as it is currently uncertain whether or not these patients had initially presented with acute kidney injury (AKI), or whether they continued to lose renal function at a faster rate than the remainder of the study population during extended follow-up. One hypothesis would be that these patients represent a sub-group in whom the 'hydraulic' effects of the RAS are more critical than parenchymal damage in determining renal dysfunction, and theoretically at least, a positive response to revascularisation might be anticipated.

*Acute kidney injury*

The incidence of AKI, either as a presenting feature or as a disease complication, is difficult to estimate in patients with ARVD. In our local data that involved 819 patients, we estimate that the rate of AKI as a presenting feature in ARVD is low - less than 2% of the overall population. In the context of chronic ARVD, modest AKI typically develops where an acute insult reduces perfusion pressure in the renal circulation to the point where parenchymal viability is compromised. Anuric presentations are limited to scenarios in which there is acute vascular occlusion preceding collateral development [86]. This is typically in the context of high-grade bilateral disease, or stenosis of a single functioning kidney, and such patients would be at increased risk of flash pulmonary oedema.

*Intolerance of renin-angiotensin blockade*

There is evidence that angiotensin blockade (with angiotensin converting enzyme inhibitors or angiotensin receptor blockers) confers prognostic benefit in patients with ARVD [87]. However, as much as this is accepted, there is no doubt that these agents are under prescribed in ARVD due to concerns regarding their potential to cause rapid decline in renal function. This is despite the accumulating evidence that patients are able to tolerate careful introduction of these agents even in the context of bilateral disease [88,89]. In a series of 621 patients with ARVD managed in this centre, a documented history of renal dysfunction related to angiotensin blockade was present in 71 (11%). Of these

patients, 40 were subsequently successfully re-challenged with angiotensin blockade (13 following revascularisation) without acute decline in renal function table 1.1.4 [88]. If patients who underwent a percutaneous interventional procedure are excluded, this still suggests that the true incidence of intolerance of ARVD patients to these agents is under 7%. The Cardiovascular Outcomes in Renal Artery Lesions (CORAL) trial [89] encouraged angiotensin II receptor blockade for first line anti-hypertensive therapy within the study and should offer further evidence regarding the tolerability of these agents in a high-risk population.

**Table 1.1.4** - Number of patients exposed to renin angiotensin blockade therapy, including tolerability on retrospective and prospective follow-up

| | **Total who were prospectively on RAB** | **Retrospective intolerance or side effect to RAB** | **Prospective intolerance or side effect to RAB** |
|---|---|---|---|
| | **n= 378** | **n= 74** | **n= 21** |
| **Age in years mean±SD [range]** | 71.4±9.3 [42-92] | 70.8±9.9 [46-87] | 72.9±8.7) [54-91] |
| **Unilateral RAS >60%, n (%)** | 148 (39.2%) | 25 (33.8%) | 9 (42.9%) |
| **Bilateral RAS >60%, n (%)** | 77 (20.4%) | 13 (17.6%) | 5 (23.8%) |

*Abbreviations: RAB renin angiotensin blockade. RAS - renal artery stenosis*
*Adapted from Chrysochou et al [90]*

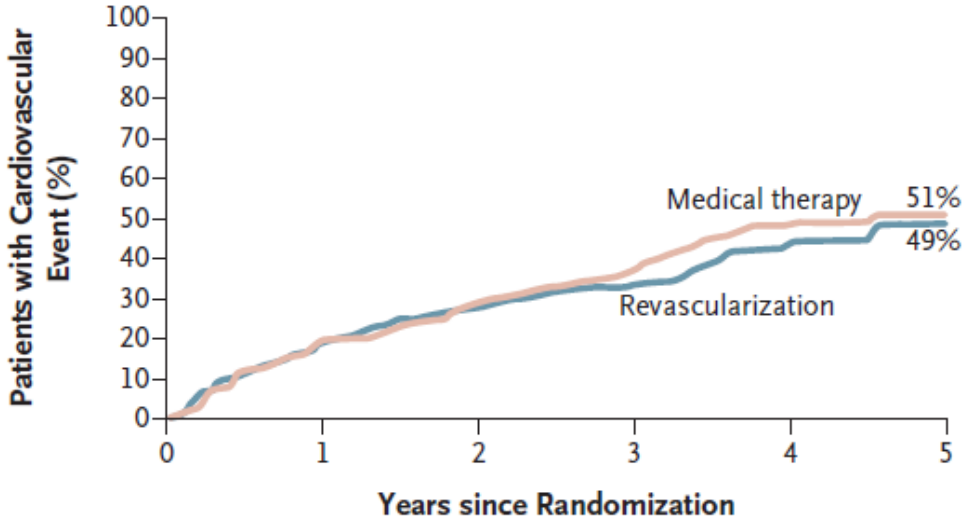
1.1.8 Prognosis in ARVD

The presence of ARVD has significant prognostic implications.

*Cardiovascular morbidity*

As we have described earlier, patients with ARVD suffer increased rates of macrovascular events and progressive disturbance in cardiac structure and function. Importantly, this increased risk exists even in patients with a <50% stenosis, reflecting the systemic nature of this condition. In prospective follow-up of 300 patients with varying degrees of ARVD (using essential hypertension as a control group), patients with >50% RAS had a hazard ratio for cardiovascular events of 2.8 and patients with a <50% RAS a hazard ratio of 2.3 (p for both <0.05) [90]. In ASTRAL, new macrovascular events occurred at a rate of 10% per year during 5 years of follow-up, figure 1.1.3 [10].

**Figure 1.1.3** - Time for first major cardiovascular event in ASTRAL




| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Revascularization | 403 | 278 | 200 | 133 | 77 | 33 |
| Medical therapy | 403 | 286 | 194 | 118 | 61 | 27 |

*Event defined as myocardial infarction, stroke, death from cardiovascular cause, hospitalization for angina, fluid overload or cardiac failure, coronary-artery revascularization or another peripheral arterial procedure. Hazard ratio for event in revascularization group 0.94 [95% CI 0.75-1.19], p=0.61. Reproduced from Wheatley et al [10] with permission.*

*Mortality*

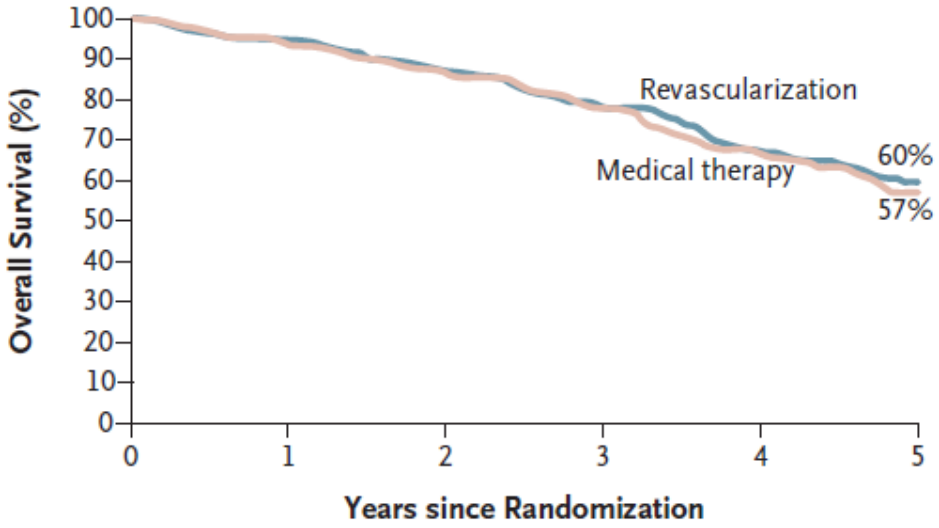
As expected, given the high rates of vascular disease at baseline and cardiovascular events that subsequently occur during follow-up, mortality is high in ARVD. Medicare data from 2001 showed that the chance of death was over 6 times that of progression to ESKD [7]. Whilst is it likely that in the current era risk for death is lower (e.g. annual mortality rate in this Medicare data 16% vs. 8% in ASTRAL (figure 1.1.4), data analysed in 2008), ARVD mortality is still considerably higher than in the general population (e.g. United Kingdom 2008 mortality rate for age group 65-69 years was approximately 2%) and was comparable with the 11% annual age-adjusted mortality in prevalent UK dialysis patients over the same time period. Limited historical data (again pre-statins) has suggested that the risk of death in ARVD is greater than in patients with most other causes of CKD, perhaps with the exception of diabetes. Also, there have not been any comparisons of outcome between different clinical presentations of ARVD. What is known is that adverse prognostic markers for mortality in ARVD include lower levels of baseline renal function (with marked increases in mortality where creatinine clearance, the forerunner of eGFR, at diagnosis is <25ml/min) [91], proteinuria in excess of 1g/24 hours [57], and extra-renal arterial disease (discussed below). Despite identification of these risk factors, the direct mechanism by which ARVD increases risk for death is not defined. The syndromes of diffuse vascular disease and disturbed cardiac structure are doubtless relevant, with the effects of chronic RAAS activation almost certainly playing a significant role, although separating out the contributions of these factors would be near impossible because of their inter-dependency.

*Mortality in association with other macrovascular disease*

An increased burden of extra-renal macrovascular disease is associated with increased risk for death in ARVD irrespective of how the relationship is examined. In a single centre study of patients under follow-up for ARVD, mortality was increased in those who also had CAD or PVD, and highest in patients who had both additional co-morbidities (percentage mortality over 50 months being 22% for ARVD alone, 37% for ARVD with PVD, 55% with CAD and 64% for ARVD with CAD and PVD) [92]. A reflection of this finding can be seen where patients with non-renal arterial disease are investigated for ARVD.

In this setting, patients found to have significant RAS have a significantly increased risk for death: 2.9x risk for death for PVD with ARVD vs. PVD alone [39]; CAD with ARVD vs. CAD alone 89% vs. 57% 4-year mortality [29].

**Figure 1.1.4** - Kaplan Meier curves for overall survival in ASTRAL




| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Revascularization | 403 | 337 | 257 | 178 | 109 | 46 |
| Medical therapy | 403 | 332 | 248 | 165 | 96 | 40 |

*Of 806 enrolled patients, 103 in the revascularization group and 106 in the medical therapy group died during the 5-year study period. Hazard ratio for death in the revascularization group 0.90 [95% CI 0.69-1.18], p=0.46. Reproduced from Wheatley et al [10] with permission.*

*Mortality of ARVD patients receiving dialysis*

Reverse epidemiology is frequently observed in dialysis patients, with ARVD providing another example of where findings in the pre-dialysis setting do not directly transfer to the renal replacement therapy population. In an analysis of over 146,000 incident dialysis patients registered in the US-RDS between 1996 and 2001, those with a diagnosis of ARVD (9% of all patients - though ARVD was only defined as the primary cause of ESKD in 5%) had a significantly lower risk for death (HR 0.94, p<0.0001) than patients without ARVD despite them having higher risks for developing CAD, CHF, PVD or cerebrovascular disease [19]. This finding is in contrast with an earlier single centre report of 683 dialysis patients in which ARVD was associated with a markedly reduced median survival time (27 vs. 51-months for non-ARVD patients) [93]. It is most likely that the difference between these studies is representative of either unmeasured confounding or potential survivor bias.

Conclusion

ARVD remains a common but still under-diagnosed condition with significant prognostic implications. Better recognition of the associated clinical syndromes may increase diagnostic sensitivity and allow targeted therapy.

## References


1. De Bruyne B, Manoharan G, Pijls NHJ, Verhamme K, Madaric J, Bartunek J, et al. Assessment of Renal Artery Stenosis Severity by Pressure Gradient Measurements. *J Am Coll Cardiol* 2006 Nov;48(9):1851–5.

2. Conlon PJ, Athirakul K, Kovalik E, Schwab SJ, Crowley J, Stack R, et al. Survival in renal vascular disease. *J Am Soc Nephrol*. 1998 Feb;9(2):252–6.

3. Hietala SO, Kunz R. Collateral circulation in stenosis or occlusion of the renal artery. *Cardiovasc Radiol*. 1979 Nov;2(4):249–55.

4. Eliska O. Blood flow through the collateral circulation of the kidney. *Angiologica*. 1966;3(6):333–42.

5. Hansen KJ, Edwards MS, Craven TE, Cherr GS, Jackson SA, Appel RG, et al. Prevalence of renovascular disease in the elderly: A population-based study. *J Vasc Surg*. 2002 Sep;36(3):443–51.

6. Lorenz EC, Vrtiska TJ, Lieske JC, Dillon JJ, Stegall MD, Li X, et al. Prevalence of renal artery and kidney abnormalities by computed tomography among healthy adults. *Clin J Am Soc Nephrol*. 2010 Mar;5(3):431–8.

7. Kalra PA, Guo H, Kausz AT, Gilbertson DT, Liu J, Chen S-C, et al. Atherosclerotic renovascular disease in United States patients aged 67 years or older: risk factors, revascularization, and prognosis. *Kidney Int*. 2005 Jul;68(1):293–301.

8. Kalra PA, Guo H, Gilbertson DT, Liu J, Chen S-C, Ishani A, et al. Atherosclerotic renovascular disease in the United States. *Kidney Int*. 2009 Oct 28;77(1):37–43.

9. Collins AJ, Foley RN, Herzog C, Chavers BM, Gilbertson D, Ishani A, et al. Excerpts From the US Renal Data System 2009 Annual Data Report. *Am J Kidney Dis*. 2010 Jan; 55(1):A6–A7.

10. ASTRAL Investigators, Wheatley K, Ives N, Gray R, Kalra PA, Moss JG, et al. Revascularization versus medical therapy for renal-artery stenosis. *N Engl J Med*. 2009 Nov 12;361(20):1953–62.

11. Jazrawi A, Darda S, Burke P, Daccarett M, Stehlik J, David S, et al. Is race a risk factor for the development of renal artery stenosis? *Cardiol Res Pract*. 2009;2009:817987.

12. Alhaddad IA, Blum S, Heller EN, Beato MA, Bhalodkar NC, Keriaky GE, et al. Renal artery stenosis in minority patients undergoing diagnostic cardiac catheterization: prevalence and risk factors. *J Cardiovasc Pharmacol Ther*. 2001 Apr;6(2):147–53.

13. Tanemoto M, Saitoh H, Satoh F, Satoh H, Abe T, Ito S. Predictors of undiagnosed renal artery stenosis among Japanese patients with risk factors of atherosclerosis. *Hypertens Res*. 2005 Mar;28(3):237–42.

14. Kawarada O, Yokoi Y, Morioka N, Takemoto K. Renal artery stenosis in cardio-and cerebrovascular disease: renal duplex ultrasonography as an initial screening examination. *Circulation.* 2007 Dec;71(12):1942–7.

15. Stimpel M, Groth H, Greminger P, Lüscher TF, Vetter H, Vetter W. The spectrum of renovascular hypertension. *Cardiology*. 1985;72 Suppl 1:1–9.

16. de Mast Q, Beutler JJ. The prevalence of atherosclerotic renal artery stenosis in risk groups: a systematic literature review. *J Hypertens.* 2009 Jul;27(7):1333–40.

17. Börgel J, Springer S, Ghafoor J, Arndt D, Duchna H-W, Barthel A, et al. Unrecognized

secondary causes of hypertension in patients with hypertensive urgency/emergency: prevalence and co-prevalence. *Clin Res Cardiol*. 2010 Aug;99(8):499–506.

18. Paven G, Waugh R, Nicholson J, Gillin A, Hennessy A. Screening tests for renal artery stenosis: a case-series from an Australian tertiary referral centre. *Nephrology*. 2006 Feb; 11(1):68–72.

19. Guo H, Kalra PA, Gilbertson DT, Liu J, Chen SC, Collins AJ, et al. Atherosclerotic Renovascular Disease in Older US Patients Starting Dialysis, 1996 to 2001. *Circulation*. 2006 Dec 18;115(1):50–8.

20. Appel RG, Bleyer AJ, Reavis S, Hansen KJ. Renovascular disease in older patients beginning renal replacement therapy. *Kidney Int.* 1995 Jul;48(1):171–6.

21. van Ampting JMA, Penne EL, Beek FJA, Koomans HA, Boer WH, Beutler JJ. Prevalence of atherosclerotic renal artery stenosis in patients starting dialysis. *Nephrol Dial Transplant*. 2003 May 31;18(6):1147–51.

22. Harding MB, Smith LR, Himmelstein SI, Harrison K, Phillips HR, Schwab SJ, et al. Renal artery stenosis: prevalence and associated risk factors in patients undergoing routine cardiac catheterization. *J Am Soc Nephrol*. 1992 May;2(11):1608–16.

23. Khosla S, Kunjummen B, Manda R, Khaleel R, Kular R, Gladson M, et al. Prevalence of renal artery stenosis requiring revascularization in patients initially referred for coronary angiography. *Cathet Cardiovasc Intervent*. 2003 Feb 19;58(3):400–3.

24. Ollivier R, Boulmier D, Veillard D, Leurent G, Mock S, Bedossa M, et al. Frequency and predictors of renal artery stenosis in patients with coronary artery disease. *Cardiovasc Revasc Med.* 2009 Jan;10(1):23–9.

25. Cohen MG, Pascua JA, Garcia-Ben M, Rojas-Matas CA, Gabay JM, Berrocal DH, et al. A simple prediction rule for significant renal artery stenosis in patients undergoing cardiac catheterization. *American Heart Association*. 2005 Dec;150(6):1204–11.

26. Rigatelli G, Roncon L, Rinuncini M, Giordan M, Bedendo E, Panin S, et al. Angiographic characteristics of renal arterial disease over the spectrum of coronary artery disease. *Am J Nephrol*. 2005 Mar;25(2):116–20.

27. Wang Y, Ho DSW, Chen WH, Wang YQ, Lam WF, Shen ZJ, et al. Prevalence and predictors of renal artery stenosis in Chinese patients with coronary artery disease. *Intern Med J*. 2003 Jul;33(7):280–5.

28. Rihal CS, Textor SC, Breen JF, McKusick MA, Grill DE, Hallett JW, et al. Incidental renal artery stenosis among a prospective cohort of hypertensive patients undergoing coronary angiography. *Mayo Clin. Proc*. 2002 Apr;77(4):309–16.

29. Conlon PJ, Little MA, Pieper K, Mark DB. Severity of renal vascular disease predicts mortality in patients undergoing coronary angiography. *Kidney Int*. 2001 Oct;60(4):1490–7.

30. Uzu T, Inoue T, Fujii T, Nakamura S, Inenaga T, Yutani C, et al. Prevalence and predictors of renal artery stenosis in patients with myocardial infarction. *Am J Kidney Dis*. 1997 May;29(5):733–8.

31. MacDowall P, Kalra PA, O'Donoghue DJ, Waldek S, Mamtora H, Brown K. Risk of morbidity from renovascular disease in elderly patients with congestive cardiac failure. *The Lancet*. 1998 Jul 4;352(9121):13–6.

32. de Silva R, Loh H, Rigby AS, Nikitin NP, Witte KKA, Goode K, et al. Epidemiology, associated factors, and prognostic outcomes of renal artery stenosis in chronic heart

failure assessed by magnetic resonance angiography. *Am J Cardiol*. 2007 Jul 15;100(2): 273–9.

33. Kuroda S, Nishida N, Uzu T, Takeji M, Nishimura M, Fujii T, et al. Prevalence of renal artery stenosis in autopsy patients with stroke. *Stroke*. 2000 Jan;31(1):61–5.

34. Horita Y, Tadokoro M, Taura K, Mishima Y, Miyazaki M, Kohno S, et al. Relationship between carotid artery intima-media thickness and atherosclerotic renal artery stenosis in type 2 diabetes with hypertension. *Kidney Blood Press. Res*. 2002;25(4):255–9.

35. Sibal L, Agarwal SC, Home PD. Carotid intima-media thickness as a surrogate marker of cardiovascular disease in diabetes. *Diabetes Metab Syndro Obes.* 2011;4:23-34

36. Olin JW, Melia M, Young JR, Graor RA, Risius B. Prevalence of atherosclerotic renal artery stenosis in patients with atherosclerosis elsewhere. *Am. J. Med*. 1990 Jan;88(1N): 46N–51N.

36. Olin JW, Melia M, Young JR, Graor RA, Risius B. Prevalence of atherosclerotic renal artery stenosis in patients with atherosclerosis elsewhere. *Am. J. Med*. 1990 Jan;88(1N): 46N–51N.

37. Valentine RJ, Myers SI, Miller GL, Lopez MA, Clagett GP. Detection of unsuspected renal artery stenoses in patients with abdominal aortic aneurysms: refined indications for preoperative aortography. *Ann Vasc Surg*. 1993 May;7(3):220–4.

38. Iglesias JI, Hamburger RJ, Feldman L, Kaufman JS. The natural history of incidental renal artery stenosis in patients with aortoiliac vascular disease. *Am. J. Med*. 2000 Dec 1;109(8):642–7.

39. Amighi J, Schlager O, Haumer M, Dick P, Mlekusch W, Loewe C, et al. Renal artery stenosis predicts adverse cardiovascular and renal outcome in patients with peripheral artery disease. *Eur. J. Clin. Invest.* 2009 Sep;39(9):784–92.

40. Androes MP, Langan EM, Kalbaugh CA, Blackhurst DW, Taylor SM, Youkey JR. Is incidental renal arteriography justified in a population of patients with symptomatic peripheral arterial disease? *Vasc Endovascular Surg*. 2007 Apr;41(2):106–10.

41. Leertouwer TC, Pattynama PM, van den Berg-Huysmans A. Incidental renal artery stenosis in peripheral vascular disease: a case for treatment? *Kidney Int*. 2001 Apr; 59(4):1480–3.

42. Swartbol P, Thorvinger BO, Pärsson H, Norgren L. Renal artery stenosis in patients with peripheral vascular disease and its correlation to hypertension. A retrospective study. *Int Angiol.* 1992 Jul;11(3):195–9.

43. Salmon P, Brown MA. Renal artery stenosis and peripheral vascular disease: implications for ACE inhibitor therapy. *Lancet*. 1990 Aug 4;336(8710):321.

44. Chrysochou C, Kalra PA. Epidemiology and Natural History of Atherosclerotic Renovascular Disease. *Progress in Cardiovascular Diseases*. 2009 Nov 12;52(3):184–95.

45. Shurrab AE, Mamtora H, O'Donoghue D, Waldek S, Kalra PA. Increasing the diagnostic yield of renal angiography for the diagnosis of atheromatous renovascular disease. *Br J Radiol*. 2001 Mar;74(879):213–8.

46. Black HR, Cooper KA. Cigarette smoking and atherosclerotic renal artery stenosis. *J Clin Hypertens*. 1986 Dec;2(4):322–30.

47. Gambaro G, Verlato F, Budakovic A, Casara D, Saladini G, Del Prete D, et al. Renal

impairment in chronic cigarette smokers. *J. Am. Soc. Nephrol.* 1998 Apr;9(4):562–7.

48. Scoble JE, de Takats D, Ostermann ME, Connolly JO, Scott NR, Beeso JA, et al. Lipid profiles in patients with atherosclerotic renal artery stenosis. *Nephron*. 1999;83(2):117–21.

49. Hood B, Brolin I, Kjellbo H, Angervall G. Serum lipids in renal artery stenosis and other hypertensive states. I. Abdominal aorta, renal arteries and fasting serum lipid levels. *Acta Med Scand*. 1966 May;179(5):575–82.

50. Pilz S, Scharnagl H, Tiran B, Seelhorst U, Wellnitz B, Boehm BO, et al. Free fatty acids are independently associated with all-cause and cardiovascular mortality in subjects with coronary artery disease. *J. Clin. Endocrinol. Metab*. 2006 Jul;91(7):2542–7.

51. Cheung CM, Patel A, Shaheen N, Cain S, Eddington H, Hegarty J, et al. The Effects of Statins on the Progression of Atherosclerotic Renovascular Disease. *Nephron Clin Pract*. 2007;107(2):c35–c42.

52. Keddis M, Garovic V, Bailey K. Ischaemic nephropathy secondary to atherosclerotic renal artery stenosis: clinical and histopathological correlates. *Nephrol Dial Transplant*. 2010 Nov;(25)11:3615-22

53. Caps MT, Zierler RE, Polissar NL, Bergelin RO, Beach KW, Cantwell-Gab K, et al. Risk of atrophy in kidneys with atherosclerotic renal artery stenosis. *Kidney Int.* 1998 Mar; 53(3):735–42.

54. Paraskevas KI, Hamilton G, Cross JM, Mikhailidis DP. Atherosclerotic renal artery stenosis: association with emerging vascular risk factors. *Nephron Clin Pract*. 2008;108(1):c56–66.

55. Dzielińska Z, Januszewicz A, Demkow M, Makowiecka-Cieśla M, Prejbisz A, Naruszewicz M, et al. Cardiovascular risk factors in hypertensive patients with coronary artery disease and coexisting renal artery stenosis. *J. Hypertens*. 2007 Mar;25(3):663–70.

56. Suresh M, Laboi P, Mamtora H, Kalra PA. Relationship of renal dysfunction to proximal arterial disease severity in atherosclerotic renovascular disease. *Nephrol Dial Transplant*. 2000 May;15(5):631–6.

57. Wright J, Shurrab A, Cheung C, Walkdek S, O'Donoghue D, Foley R, et al. A prospective study of the determinants of renal functional outcome and mortality in atherosclerotic renovascular disease. *Am J Kidney Dis*. 2002 Jun;39(6):1153–61.

58. Chade AR, Kelsen S. Renal microvascular disease determines the responses to revascularization in experimental renovascular disease. *Circ Cardiovasc Interv*. 2010 Aug;3(4):376–83.

59. Iliescu R, Fernandez SR, Kelsen S, Maric C, Chade AR. Role of renal microcirculation in experimental renovascular disease. *Nephrol Dial Transplant*. 2010 Apr;25(4):1079–87.

60. Kang D-H, Kanellis J, Hugo C, Truong L, Anderson S, Kerjaschki D, et al. Role of the microvascular endothelium in progressive renal disease. *J. Am. Soc. Nephrol.* 2002 Mar; 13(3):806–16.

61. Zhu X-Y, Chade AR, Rodriguez-Porcel M, Bentley MD, Ritman EL, Lerman A, et al. Cortical microvascular remodeling in the stenotic kidney: role of increased oxidative stress. *Arterioscler. Thromb. Vasc. Biol*. 2004 Oct;24(10):1854–9.

62. Goldblatt H, Lynch J, Hanzal RF, Summerville WW. Studies on experimental hypertension : i. The production of persistent elevation of systolic blood pressure by

means of renal ischemia. *J. Exp. Med*. 1934 Feb 28;59(3):347–79.

63. Wolf G. Angiotensin II as a mediator of tubulointerstitial injury. *Nephrol Dial Transplant*. 2000;15 Suppl 6:61–3.

64. Wolf K, Kurtz A, Pfeifer M, Höcherl K, Riegger GA, Krämer BK. Different regulation of left ventricular ANP, BNP and adrenomedullin mRNA in the two-kidney, one-clip model of renovascular hypertension. *Pflugers Arch.* 2001 May;442(2):212–7.

65. Farmer CK, Cook GJ, Blake GM, Reidy J, Scoble JE. Individual kidney function in atherosclerotic nephropathy is not related to the presence of renal artery stenosis. *Nephrol Dial Transplant.* 1999 Dec;14(12):2880–4.

66. Wright JR, Duggal A, Thomas R, Reeve R, Roberts IS, Kalra PA. Clinicopathological correlation in biopsy-proven atherosclerotic nephropathy: implications for renal functional outcome in atherosclerotic renovascular disease. *Nephrol Dial Transplant*. 2001 Apr; 16(4):765–70.

67. Gandy SJ, Armoogum K, Nicholas RS, McLeay TB, Houston JG. A clinical MRI investigation of the relationship between kidney volume measurements and renal function in patients with renovascular disease. *Br J Radiol.* 2007 Jan;80(949):12–20.

68. Ruggenenti P, Porrini EL, Gaspari F, Motterlini N, Cannata A, Carrara F, et al. Glomerular Hyperfiltration and Renal Disease Progression in Type 2 Diabetes. *Diabetes Care*. 2012 Oct;35(10):2061–8.

69. Urbieta-Caceres VH, Lavi R, Zhu X-Y, Crane JA, Textor SC, Lerman A, et al. Early atherosclerosis aggravates the effect of renal artery stenosis on the swine kidney. *Am. J. Physiol. Renal Physiol*. 2010 Jul;299(1):F135–40.

70. Chade AR, Rodriguez-Porcel M, Grande JP, Zhu X, Sica V, Napoli C, et al. Mechanisms of renal structural alterations in combined hypercholesterolemia and renal artery stenosis. *Arterioscler. Thromb. Vasc. Biol*. 2003 Jul 1;23(7):1295–301.

71. Tuttle KR. Renal parenchymal injury as a determinant of clinical consequences in atherosclerotic renal artery stenosis. *Am. J. Kidney Dis*. 2002 Jun;39(6):1321–2.

72. Cheung CM, Chrysochou C, Shurrab AE, Buckley DL, Cowie A, Kalra PA. Effects of renal volume and single-kidney glomerular filtration rate on renal functional outcome in atherosclerotic renal artery stenosis. *Nephrol Dial Transplant*. 2010 Apr;25(4):1133–40.

73. Schreiber MJ, Pohl MA, Novick AC. The natural history of atherosclerotic and fibrous renal artery disease. *Urol Clin North Am.* 1984 Aug;11(3):383-92

74. Crowley JJ, Santos RM, Peter RH, Puma JA, Schwab SJ, Phillips HR, et al. Progression of renal artery stenosis in patients undergoing cardiac catheterization. *Am J Cardiol*. 1998 Nov;136(5):913–8.

75. Caps M, Perissinotto C, Zierler R, Polissar N. Prospective study of atherosclerotic disease progression in the renal artery. *Circulation*. 1998 Dec;98(25):2866-72

76. Hoefield RA, Kalra PA, Baker P, Lane B, New JP, O'Donoghue DJ, et al. Factors associated with kidney disease progression and mortality in a referred CKD population. *Am. J. Kidney Dis*. 2010 Dec;56(6):1072–81.

77. Valluri A, Severn A, Chakraverty S. Do patients undergoing renal revascularization outside of the ASTRAL trial show any benefit? Results of a single centre observational study. *Nephrol Dial Transplant*. 2011 Sep 9.

78. Bax L, Woittiez A-JJ, Kouwenberg HJ, Mali WPTM, Buskens E, Beek FJA, et al. Stent

placement in patients with atherosclerotic renal artery stenosis and impaired renal function: a randomized trial. *Ann. Intern. Med*. 2009 Jun 16;150(12):840–8, W150–1.

79. Wright JR, Shurrab AE, Cooper A, Kalra PR, Foley RN, Kalra PA. Left ventricular morphology and function in patients with atherosclerotic renovascular disease. *J. Am. Soc. Nephrol*. 2005 Sep;16(9):2746–53.

80. Wright JR, Shurrab AE, Cooper A, Kalra PR, Foley RN, Kalra PA. Progression of cardiac dysfunction in patients with atherosclerotic renovascular disease. *QJM*. 2009 Sep 23;102(10):695–704.

81. 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. *Nephrol Dlal Transplant*. 2010 Mar;25(3):813–20.

82. Marcantoni C, Zanoli L, Rastelli S, Tripepi G, Matalone M, Mangiafico S, et al. Effect of Renal Artery Stenting on Left Ventricular Mass: A Randomized Clinical Trial. *Am J Kidney Dis*. 2012 Jul;60(1):39-46

83. Green D, Kalra PA. The heart in atherosclerotic renovascular disease. *Frontiers in Bioscience*. 4th ed. 2012 Jan 1;:856–64.

84. Rimoldi SF, Yuzefpolskaya M, Allemann Y, Messerli F. Flash pulmonary edema. *Progress in Cardiovascular Diseases*. 2009 Oct;52(3):249–59.

85. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. *European Heart Journal.* 2011 Mar;32(6):670–9.

86. Chrysochou C, Sinha S, Chalmers N, Kalra PR, Kalra PA. Anuric acute renal failure and pulmonary oedema: a case for urgent action. I*nt. J. Cardiol*. 2009 Feb 6;132(1):e31–3.

87. Hackam DG, Duong-Hua ML, Mamdani M, Li P, Tobe SW, Spence JD, et al. Angiotensin inhibition in renovascular disease: a population-based cohort study. *Am J Cardiol*. 2008 Sep;156(3):549–55.

88. 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. *Nephrol Dial Transplant*. 2011 Oct 12.

89. Cooper C, Murphy T, Matsumoto A, Steffes M, Cohen D, Jaff M, et al. Stent revascularization for the prevention of cardiovascular and renal events among patients with renal artery stenosis and systolic hypertension: Rationale and design of the CORAL trial. *Am J Cardiol*. 2006 Jul;152(1):59–66.

90. Dechering DG, Kruis H, Adiyaman A, Thien T, Postma CT. Clinical significance of low-grade renal artery stenosis. *Journal of Internal Medicine*. 2010 Jan 29;:1–11.

91. Cheung CM, Wright JR, Shurrab AE, Mamtora H, Foley RN, O'Donoghue DJ, et al. Epidemiology of renal dysfunction and patient outcome in atherosclerotic renal artery occlusion. *J. Am. Soc. Nephrol.* 2002 Jan;13(1):149–57.

92. Shurrab AE, MacDowall P, Wright J, Mamtora H, Kalra PA. The importance of associated extra-renal vascular disease on the outcome of patients with atherosclerotic renovascular disease. *Nephron Clin Pract*. 2003;93(2):C51–7.

93. Mailloux LU, Napolitano B, Bellucci AG, Vernace M, Wilkes BM, Mossey RT. Renal vascular disease causing end-stage renal disease, incidence, clinical correlates, and outcomes: a 20-year clinical experience. *Am. J. Kidney Dis*. 1994 Oct;24(4):622–9.

## 1.2 Diagnosis of ARVD

Ritchie J, Green D, Chrysochou C, Kalra PA
*Published in Renovascular Hypertension; Oxford Textbook of Clinical Nephrology (4th Edition), Oxford, Oxford University Press - in press.*
IPR policy: http://www.oxfordjournals.org/access_purchase/publication_rights.html

Preface

Methods for diagnosing ARVD have altered significantly over the past decade, with changes largely been driven by increased adoption of tools such as computed tomography and magnetic resonance imaging into clinical practice. Intra-arterial renal digital subtraction angiography remains the gold-standard investigation for ARVD, however this is rarely used in a diagnostic context due to the risk of procedural complications. Although a broad range of options for non-invasive diagnostic imaging exist, each method has limitations that should be considered. In this section the benefits and limitations of the most frequently used diagnostic approaches for ARVD are reviewed and future imaging techniques, currently under investigation, discussed.

### 1.2.1 Laboratory tests

The widespread availability of diagnostic imaging has largely rendered biochemical assessments of possible renovascular hypertension meaningless.

*Renin*

At population level elevated plasma renin levels are associated with increased risk for cardiovascular death [1]. Although it is intuitive and true that plasma renin activity may be particularly increased in patients with renal artery disease [2], this observation is of limited value as renin levels often decrease over time and elevated levels do not distinguish renal artery stenosis from other causes of hypertension [3]. Although renin measurements made in relation to administration of captopril are more sensitive for identification of renal artery stenosis, the specificity of this approach is low at 55% [4]. Directly measurement of renal vein renin levels by cannualtion of the inferior vena cava and comparison between left and right sides was investigated as an approach to select patients who would receive a blood pressure benefit from revascularisation. Even though 90% patients with a ratio of >1.5 between stenosed and non-stenosed organs saw a blood pressure benefit, over 60% of patients with a "negative" test also received benefit [3] limiting any clinical utility.

*Other markers of cardiovascular risk*

As the majority of cases of renovascular hypertension relate to ARVD, assessment of lipid profile is appropriate. Recent advances in the understanding of the pathogenesis of atherosclerosis have highlighted the role of inflammation, often measured by hs-CRP [5], with increased levels predictive of worse outcome [6]. Although increased levels of hs-CRP are observed in patients with ARVD compared to non-atherosclerotic controls [7], the presence of ARVD does not increase the value of hs-CRP in predicting major adverse cardiovascular events [8]. As such measurement of hs-CRP offers meaning in relation to overall prognosis, but not specifically in relation to ARVD.

1.2.2 Diagnostic imaging

*Digital subtraction angiography*

Intra-arterial renal digital subtraction angiography is considered the gold standard investigation to which other techniques for the assessment of renal artery stenosis are compared. This, however, is rarely a first line investigation due to reasons of cost [9] and risk of complications, including arterial dissection [10,11], AKI (though this risk may be mitigated by use of lower contrast volumes and iso-osmolar agents) [12] and death [10]. Furthermore, digital subtraction angiography provides only 2D images and inter-observer agreement for detection of significant stenosis is imperfect, ranging from 0.65 to 0.78 [13]. The calculation used for estimation of degree of stenosis following angiographic assessment is shown below.

$$\%\ stenosis = \left(\frac{Minimum\ lumen\ diameter}{Reference\ vessel\ diameter}\right) \times 100$$

A potential advantage of invasive angiography is the opportunity to measure the pressure gradient across the stenosis, with current suggesting that haemodynamic significance is associated with trans-lesional gradients in excess of 20mmHg [14]. A body of data suggest that use of pressure gradient measures performed at the time of interventional angiography may identify the patients in whom target blood pressures will be achieved following intervention [15,16]. A study of 53 consecutive patients undergoing renal artery revascularisation to treat hypertension found that a dopamine induced hyperaemic gradient in excess of 48mmHg may an important threshold value, with an area under the curve of 0.75 (95% confidence interval 0.61-0.88) for a >20mmHg reduction in systolic blood pressure following revascularisation [17]. It should be noted, however, that all of these data consider only patients with mild renal impairment with average baseline creatinine values of approximately 100µmol/L and no study has considered a medical control group.

A final consideration is regarding the opportunity to preform screening angiography for renal artery disease during other diagnostic or angiographic procedures, so called “drive by angiography”. Justification for this approach comes from the frequent co-existence of renal artery stenosis with peripheral

[18,19] and coronary arterial disease [20]. Although imaging of renal vessels following coronary angiography requires only a small extra volume of contrast and does not increase procedural morbidity or mortality [21] it is unlikely to significantly alter management [22]. As such, our position on opportunistic renal angiography stands in opposition to American guidelines that support this practice where there is a suspicion of concomitant renal artery disease [23].

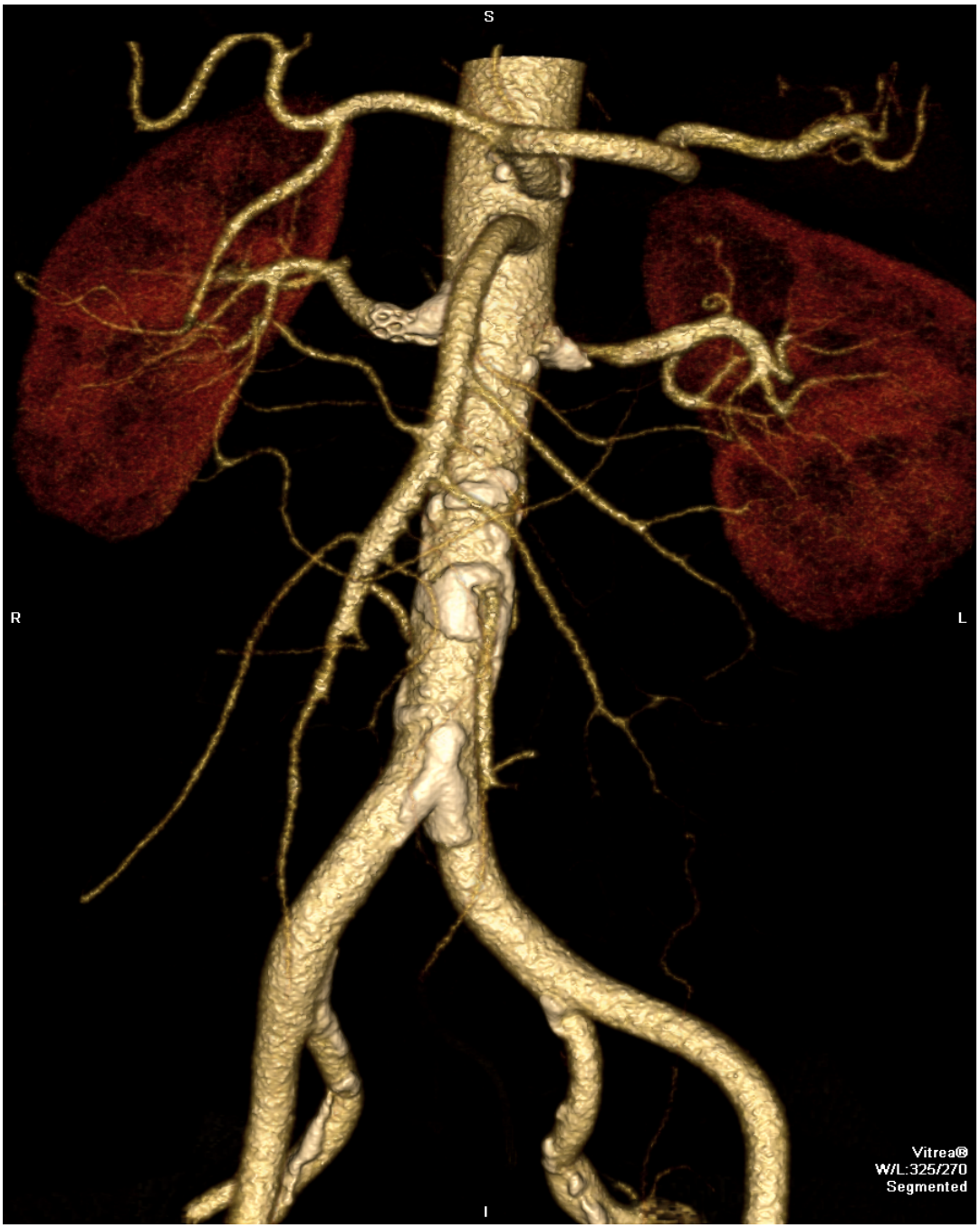
*Computed tomography angiography*

Computed tomography angiography (CTA) is a widely available tool in which overlapping transaxial images are obtained during delivery of a timed bolus of iodinated contrast [24], figure 1.2.1. Modern scanners permit identification of vessels as small as 0.5mm [25] and the speed of image capture allows all data to be obtained in single breath hold, eliminating artefact from respiratory movement [26]. Compared to intra-arterial digital subtraction angiography, CTA has an overall sensitivity and specificity of 94% and 93% respectively for the detection of renal artery stenosis [27] and when directly compared to magnetic resonance imaging in patients with renal impairment is a more accurate test [28]. Despite this the regional calcification commonly found in atherosclerotic renovascular disease [29] can make interpretation of CTA images challenging [30] and reduce inter-observer agreement [13]. Importantly CTA studies reporting the highest sensitivity and specificity values for diagnosis of renal artery stenosis have focused on patients with atheromatous disease. When significant numbers of patients with fibromuscular disease are included the reported sensitivity falls to 64% [13], reflecting the reduced accuracy of CTA in describing distal arterial segments [31].

The risk for developing contrast induced nephropathy (CIN) is considered a major limitation of CTA although the potential for anaphylactic reaction and increased malignancy risk due to radiation exposure (especially in young patients) should not be discounted [32]. There are no data to define the precise incidence of CIN following investigation for renal artery stenosis and overall incidence is falling due to better implemented risk prevention measures [33]. In the ASTRAL trial approximately 10% of patients suffered a potential CIN following interventional angiography [34]. As modern CTA protocols use a lesser

volume of contrast than interventional procedures, the incidence of CIN following CTA can be presumed to be lower.

**Figure 1.2.1** - Reconstructed computed tomography angiogram in treated atherosclerotic renovascular disease.




*The left renal artery is patent and the right renal artery is patent following percutaneous stenting. Image courtesy of Professor Jonathan Moss, Gartnavel Hospital, Glasgow.*

*Magnetic resonance angiography*

The high level of soft tissue contrast provided by magnetic resonance imaging (MRI) makes it an excellent tool for visualising the kidneys especially with the increased availability of high-field scanners and use of diffusion-weighted techniques [35]. Early methods to detect renal artery stenosis on MRI by flow visualisation, using time of flight or phase contrast sequences were susceptible to artefact due to the long acquisition times [36]. These methods have been superseded by magnetic resonance angiography (MRA) performed using gadolinium as a paramagnetic contrast agent [37], figure 1.2.2. This technique allows sequences to be performed in a single breath hold, allows visualisation of the renal arteries independent of flow effects [38], consequently increasing specificity and positive predictive value [36]. Compared to intra-arterial digital subtraction angiography, gadolinium enhanced MRA has a sensitivity of 96% and specificity of 93% for the diagnosis of renal artery stenosis [27]. However, in the setting of mild to moderate renal impairment MRA is less sensitive and specific than CTA [28] and, especially at lower levels of stenosis, can overestimate the degree of luminal loss [39].

Magnetic resonance angiography may also be less useful in diagnosis of non-atheromatous renal artery disease. Where comparison has been made between MRA and digital subtraction angiography images in patients with known fibromuscular disease, MRA had high sensitivity and specificity for identification of aneurysmal changes (sensitivity 100%, specificity 93%) and string of beads appearance (sensitivity 95%, specificity 93%), but appeared less suited to identifying stenoses (sensitivity 68%, specificity 94%) [40].

**Figure 1.2.2** - Magnetic resonance angiogram demonstrating left sided ostial renal artery stenosis

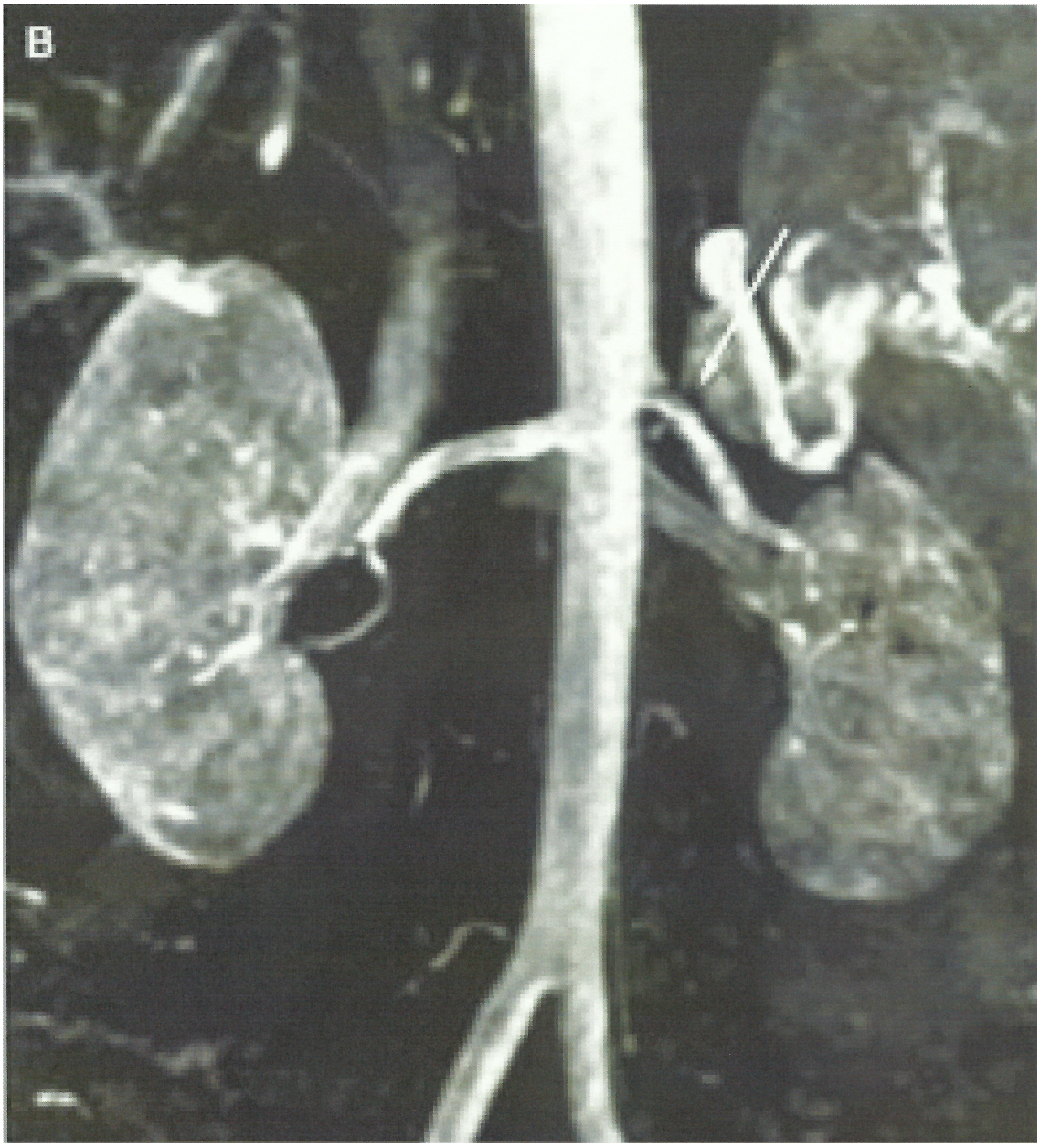
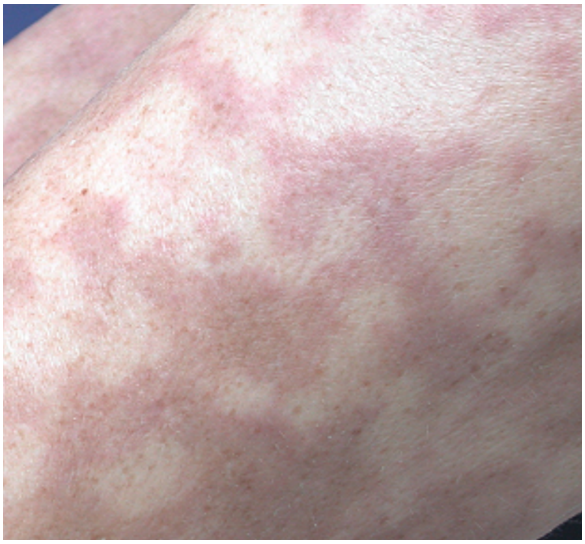



*Image supplied by Dr James Lay, Royal Bolton Hospital.*

*Nephrogenic systemic fibrosis*

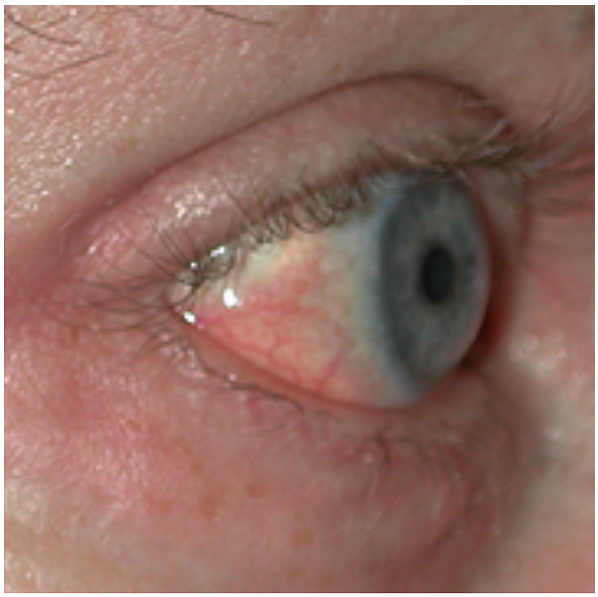
Although previously MRI and MRA have been considered safe tools due to the lack of exposure to ionising radiation and iodinated contrast media [41], a causal link has recently been identified between exposure to gadolinium based contrast agents and the development of nephrogenic systemic fibrosis (NSF) [42,43]. This is a condition of systemic fibrosis of the skin and internal organs (figures 1.2.3 and 1.2.4), typically presenting first in the legs, with a high associated mortality [44].

**Figure 1.2.3** - Patterned cutaneous plaques in nephrogenic systemic fibrosis



*Plaques can be seen to be red to purple coloured, thin and fixed. Reproduced from Girardi et al J Am Acad Dermatol (2011) 65;6:1095-1106 with permission.*

**Figure 1.2.4** - Scleral plaques in nephrogenic systemic fibrosis



*Yellow-white plaques and dilated capillary loops are visible. Reproduced from Girardi et al J Am Acad Dermatol (2011) 65;6:1095-1106 with permission.*

Nephrogenic systemic fibrosis appears to occur exclusively in patients with a liver transplant, acute kidney injury, chronic renal impairment with an eGFR <30ml/min/1.73m$^2$, or those on dialysis, with an estimated prevalence of 3% to 7% in patients with CKD 4 & 5 exposed to gadodiamide (Omniscan) one of the first contrast agents developed [45-47]. Inconsistent approaches to clinical and histological diagnosis when the condition was first reported, and deaths before

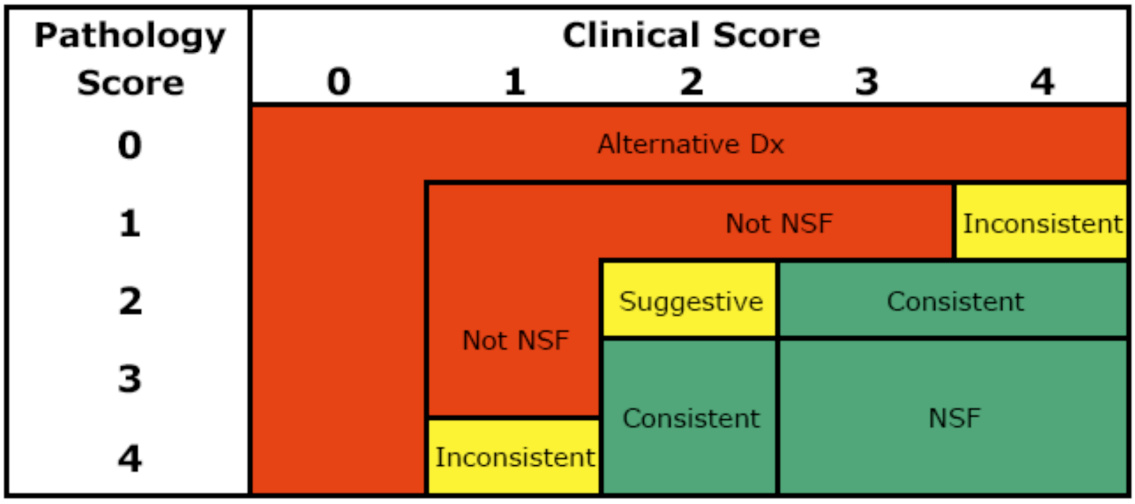
diagnosis may mean the true prevalence is higher than this. As a response to this concern, standardised clinical and pathological diagnostic criteria have been developed [48], table 1.2.1. Using this system, a score of three or greater on both the histological and clinical criteria is considered diagnostic, figure 1.2.5. Given the seriousness of development of nephrogenic systemic fibrosis, the uncertainty over the exact causal mechanism and the fact that signs of disease can develop over a period of days to years, there has been a great deal of caution in exposing patients with renal impairment to gadolinium containing agents. There is now a greater understanding that the level of risk for development of NSF varies both with the chemical structure of contrast agent used and the patient's level of renal function. The chance of developing NSF seems minimal in patients with stable stage 4 CKD, and appears to be exclusively related to the use of linear gadolinium agents [49], with no cases reported following the isolated use of the newer cyclical agents. Current recommendations contraindicate the use of linear agents in patient with an eGFR <30ml/min/1.73m$^2$ or on dialysis, and advise caution in the use of cyclical agents patients with CKD stage 4 or 5 [50].

In the absence of a defined cause for the development of NSF, optimal treatment strategies remain ill defined. Ultraviolet-A phototherapy appears to be of benefit for cutaneous lesions [51,52], with some data suggesting potential roles for rapamycin [53], sodium thiosulphate [54] and plasma exchange [55] to treat other complications.

**Table 1.2.1** - Diagnostic criteria for nephrogenic systemic fibrosis

| Major clinical criteria | Minor clinical criteria | Clinical score | | Histological criteria |
|---|---|---|---|---|
| Patterned plaques | Puckering / linear banding | 4 | >1 major criterion | Increased dermal cellularity (Score +1) |
| Joint contractures | Superficial plaque / patch | 3 | 1 Major criterion | CD34+ cells with tram tracking (Score +1) |
| “Cobblestoning” | Dermal papules | 2 | 1 Minor criterion | Thick and thin collagen bundles (Score +1) |
| Marked induration / Peau d’orange | Scleral plaques (age<45 years) | 1 | ≥1 or no minor criteria | Septal involvement (Score +1) |
| | | 0 | NSF excluded | Osseous metaplasia (Score +3) |
| | | | | Preserved elastic fibers (Score -1 *if absent*) |

**Figure 1.2.5** - Diagnosis and reporting grid for suspected nephrogenic systemic fibrosis




*Clinical and histological scores are defined in table 2.2.1. Reproduced from Girardi et al J Am Acad Dermatol (2011) 65;6:1095-1106 with permission.*

*Colour duplex ultrasonography*

Colour duplex ultrasonography permits two different approaches to the evaluation of renal vasculature, assessment of the main renal artery and assessment of the intra-renal arteries. Due to the non-invasive nature of the technique, the lack of ionising radiation or contrast, the wide availability of equipment, and (in the presence of a single renal artery) the high sensitivity and specificity offered [56], this is seen by many as the ideal tool with which to diagnose renal artery stenosis. However, full assessment is operator dependent and can be time consuming [57]. The quicker indirect method that assesses intra-renal arterial waveforms in the main renal artery searching for evidence of the "tardus-parvus" phenomenon is the least sensitive and specific method [58], likely due to variation in arterial compliance modulating this finding [59]. Use of direct Doppler parameters significantly increases sensitivity and specificity with measurement of the renal-aortic ratio [60] and renal-renal ratio [61] offering a greater degree of discrimination than the oft quoted parameter of a peak systolic velocity >200cm/s with associated post-stenotic turbulence [62]. These measures are best suited to the diagnosis of atherosclerotic renovascular disease, where the majority of stenoses are single and ostial [63,64]. Where the pattern of disease in the artery is irregular, such as in vasculitic or fibromuscular causes all of these measures have reduced utility [65]. Ultrasound studies can fail due to obese body habitus or distended bowel gas pattern, however it is likely that the widely quoted failure rates of 10-20% are over-estimates if appropriate bowel preparation is offered.

Assessment of the intra-renal intralobar arteries to calculate the renal resistive index has been suggested to improve the diagnostic accuracy of duplex ultrasound in the diagnosis of unilateral renal artery stenoses [66]. However, renal resistive index can be modulated by other factors, including age, presence of renal parenchymal disease [67] and heart rate [68]. Consequently current practice dues not advocate the use of threshold values of renal resistive index in the diagnosis of renal artery stenosis. Instead a comparative approach is used, with a side to side difference of >0.05 being the most commonly adopted parameter. This has a sensitivity and specificity of at least 77% and 94% for the diagnosis of >70% stenosis [66,69]. Initial enthusiasm for widespread adoption of measurement of resistive index to guide decisions regarding the need for

revascularisation followed publication of a retrospective study of 131 patients [70]. In these data a resistive index >0.8 appeared to identify patients who would not receive a benefit in renal function or blood pressure control following revascularisation. Subsequent studies failed to validate this finding [71-73] and it is uncertain as to whether the original data considered the stenotic or non-stenotic kidney [74].

*Novel ultrasound methodologies*

Limited hilar analysis measuring acceleration time has been proposed as a method by which ultrasonographic evaluation of renal artery stenosis may be simplified [75] however this technique lacks both sensitivity and specificity [76]. Intravascular ultrasound using blood flow velocity measurement to assess distal vascular disease has been assessed, but the invasive nature of this technique limits its use to research settings [77].

*Captopril renography*

Captopril renography only offers high levels of diagnostic sensitivity and specificity where there is preserved renal function and a unilateral stenosis. The overall results of this test are inferior to CTA and MRA and it is no longer used in routine clinical practice [78].

*Novel MRI techniques*

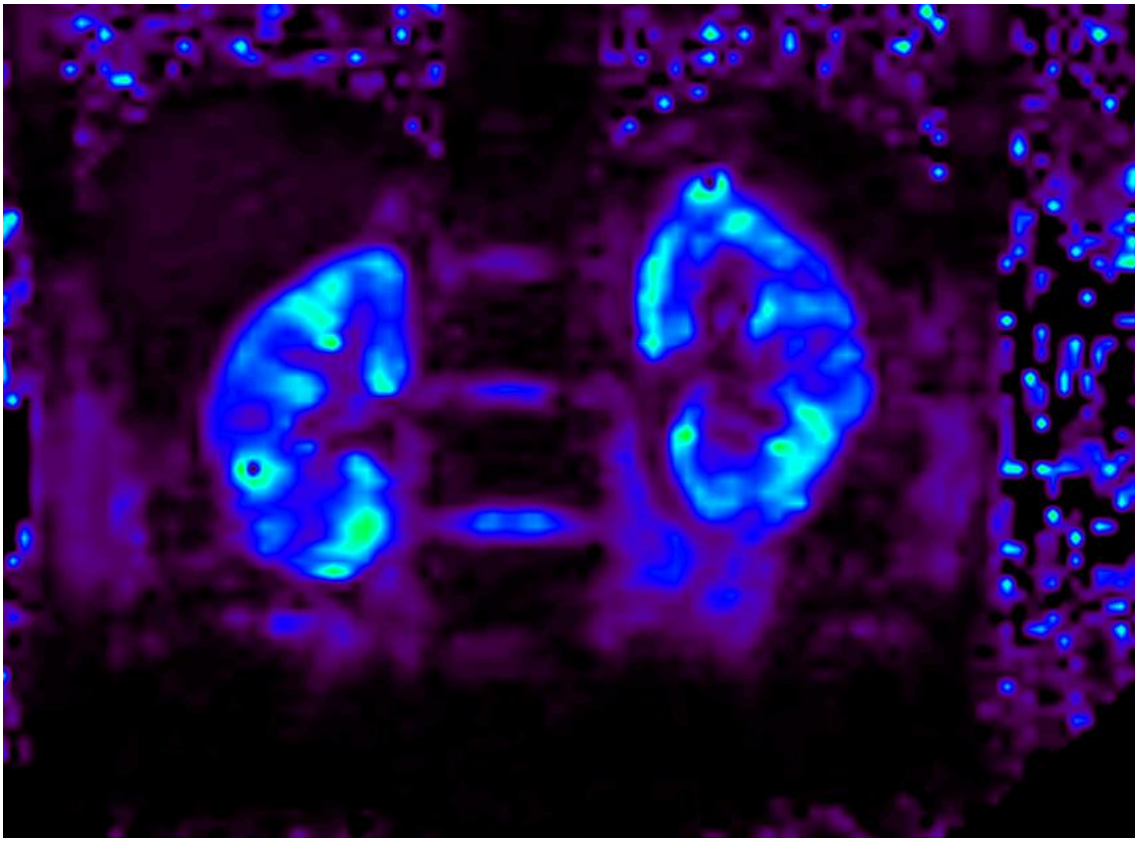
Following the controversy surrounding complications related to gadolinium exposure, MRI methods that do not require injection of these agents are under investigation. These typically require high field strength scanners (3-Tesla and above) and currently have limited availability.

*Blood oxygen level dependent magnetic resonance imaging*

Blood oxygen level dependent magnetic resonance imaging (BOLD-MRI), figure 1.2.6, exploits the fact that deoxyhemoglobin is paramagnetic and oxyhemoglobin diamagnetic [79]. Paramagnetic substances cause microscopic variations in the local magnetic field and consequently impact the MRI signal [80]. This signal loss can be measured and utilised to provide a measure of renal tissue deoxyhemoglobin, quantified by an R2* value [81]. Human data suggest that BOLD-MRI may be able to identify kidneys in which tissue oxygenation is

preserved despite significant stenosis [82] and that combining these data with isotopic GFR measurements may select patients in whom renal function may improve following revascularisation [83]. Although these data are promising further studies are required to better understand the effects of other disease states and medications on R2* measurements [84].

**Figure 1.2.6** - Blood oxygen level dependent magnetic resonance imaging in a patient with normal renal arteries



*Dark blue and purple areas represent regions of increasing hypoxaemia. Here the cortices of both kidneys are well oxygenated. Image supplied by Dr Constantina Chrysochou, Salford Royal Hospital.*

*Arterial spin labeling*

Arterial spin labeling uses magnetically labelled endogenous blood water as a tracer [85]. Currently most published data have utilised this technique to assess renal perfusion [86,87], however in a single small study arterial spin labelling has been shown to be able to reliably identify renal artery stenosis >70% [88]. With very recent data suggesting this method could be adapted to estimate single kidney GFR [89] there is potential for this approach to describe both structural and functional renal parameters in the future.

*Non-contrast magnetic resonance imaging*

Unlike BOLD-MRI and arterial spin labeling, non-contrast MRI can be performed using more widely available 1.5-Tesla scanners. Inversion pulses are applied during imaging to increase contrast between areas of static and non-static magnetisation thus enhancing the appearance of the blood signal [90]. Use of non-contrast MRI provides results generally comparable to computed tomography angiography [91] and contrast enhanced MRI [92] in identifying the existence of a stenosis but can provide false positive results and may overestimate degree of luminal loss [93].

## References


1. Alderman MH, Laragh JH, Sealey JE. More about plasma renin and cardiovascular mortality. *European Heart Journal*. 2011;32(21):2610–2612.

2. Pickering TGT. The role of laboratory testing in the diagnosis of renovascular hypertension. *Clin Chem*. 1991;37(10):1831–1837.

3. Rosner MHM. Renovascular hypertension: can we identify a population at high risk? *South Med J*. 2001;94(11):1058–1064.

4. Muller FBF, Sealey JEJ, Case DBD, et al. The captopril test for identifying renovascular disease in hypertensive patients. *Am J Med*. 1986;80(4):633–644.

5. Ross R. Atherosclerosis - An inflammatory Disease. *New England Journal of Medicine*. 1999;340(2):115–126.

6. Ridker PM, Paynter NP, Rifai N, Gaziano JM, Cook NR. C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds Risk Score for men. *Circulation*. 2008;118(22):2243–51.

7. Hommels MJ, van der Ven AJAM, Kroon AA, et al. C-reactive protein, atherosclerosis and kidney function in hypertensive patients. *J Hum Hypertens*. 2005;19(7):521–526.

8. Schlager O, Amighi J, Haumer M, et al. Inflammation and adverse cardiovascular outcome in patients with renal artery stenosis and peripheral artery disease. *Atherosclerosis*. 2009;205(1):314–318.

9. van Helvoort-Postulart D, Dirksen CD, Kroon AA, et al. Cost analysis of procedures related to the management of renal artery stenosis from various perspectives. *Eur Radiol*. 2006;16(1):154–160.

10. Waugh JR, Sacharias N. Arteriographic complications in the DSA era. *Radiology*. 1992;182(1):243–246.

11. Young N, Chi K-K, Ajaka J, McKay L, O'Neill D, Wong KP. Complications with outpatient angiography and interventional procedures. *Cardiovasc Intervent Radiol*. 2002;25(2): 123–126.

12. Karlsberg RP, Dohad SY, Sheng R, Panel IPCSI. Contrast-induced acute kidney injury (CI-AKI) following intra-arterial administration of iodinated contrast media. *J Nephrol*. 2010;23(6):658–666.

13. Vasbinder GBCG, Nelemans PJP, Kessels AGHA, et al. Accuracy of computed tomographic angiography and magnetic resonance angiography for diagnosing renal artery stenosis. *Ann Intern Med*. 2004;141(9):674–682.

14. 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. *J Vasc Interv Radiol*. 2006;17(9):1383–97.

15. Mitchell JAJ, Subramanian RR, White CJC, et al. Predicting blood pressure improvement in hypertensive patients after renal artery stent placement: renal fractional flow reserve. *Cathet Cardiovasc Intervent*. 2007;69(5):685–689.

16. Leesar MA, Varma J, Shapira A, et al. Prediction of hypertension improvement after stenting of renal artery stenosis: comparative accuracy of translesional pressure gradients, intravascular ultrasound, and angiography. *J Am Coll Cardiol*. 2009;53(25): 2363–2371.

17. Mangiacapra FF, Trana CC, Sarno GG, et al. Translesional pressure gradients to predict blood pressure response after renal artery stenting in patients with renovascular hypertension. *Circ Cardiovasc Interv*. 2010;3(6):537–542.

18. Olin JW, Melia M, Young JR, Graor RA, Risius B. Prevalence of atherosclerotic renal artery stenosis in patients with atherosclerosis elsewhere. *Am J Med*. 1990;88(1N):46N–51N.

19. Valentine RJ, Myers SI, Miller GL, Lopez MA, Clagett GP. Detection of unsuspected renal artery stenoses in patients with abdominal aortic aneurysms: refined indications for preoperative aortography. *Ann Vasc Surg*. 1993;7(3):220–224.

20. Harding MB, Smith LR, Himmelstein SI, et al. Renal artery stenosis: prevalence and associated risk factors in patients undergoing routine cardiac catheterization. *J Am Soc Nephrol*. 1992;2(11):1608–1616.

21. Rihal CS, Textor SC, Breen JF, et al. Incidental renal artery stenosis among a prospective cohort of hypertensive patients undergoing coronary angiography. *Mayo Clin Proc*. 2002;77(4):309–316.

22. Kumbhani DJ, Bavry AA, Harvey JE, et al. Clinical outcomes after percutaneous revascularization versus medical management in patients with significant renal artery stenosis: a meta-analysis of randomized controlled trials. *Am J Cardiol*. 2011;161(3): 622–630.

23. White CJ, Jaff MR, Haskal ZJ, et al. Indications for renal arteriography at the time of coronary arteriography: a science advisory from the American Heart Association Committee on Diagnostic and Interventional Cardiac Catheterization, Council on Clinical Cardiology, and the Councils on Cardiovascular Radiology and Intervention and on Kidney in Cardiovascular Disease. *Circulation*. 2006;114(17):1892–1895.

24. Krumme B, Blum U. Imaging of renal artery stenosis. *Curr Opin Urol*. 1998;8(2):77–82.

25. Luboldt W, Weber R, Seemann M, Desantis M, Reiser M. Influence of helical CT parameters on spatial resolution in CT angiography performed with a subsecond scanner. *Invest Radiol*. 1999;34(6):421–426.

26. Rubin GD, Dake MD, Napel S, et al. Spiral CT of renal artery stenosis: comparison of three-dimensional rendering techniques. *Radiology*. 1994;190(1):181–189.

27. Zhang HL, Sos TA, Winchester PA, Gao J, Prince MR. Renal artery stenosis: imaging options, pitfalls, and concerns. *Progress in Cardiovascular Diseases*. 2009;52(3):209–219.

28. Eriksson P, Mohammed AA, De Geer J, et al. Non-invasive investigations of potential renal artery stenosis in renal insufficiency. *Nephrol Dial Transplant*. 2010;25(11):3607–3614.

29. Tolkin L, Bursztyn M, Ben-Dov IZ, Simanovsky N, Hiller N. Incidental renal artery calcifications: a study of 350 consecutive abdominal computed tomography scans. *Nephrol Dial Transplant*. 2009;24(7):2170–2175.

30. van Straten M, Venema HW, Streekstra GJ, Reekers JA, Heeten den GJ, Grimbergen CA. Removal of arterial wall calcifications in CT angiography by local subtraction. *Med Phys*. 2003;30(5):761–770.

31. Galanski M, Prokop M, Chavan A, Schaefer C, Jandeleit K, Olbricht C. [Accuracy of CT angiography in the diagnosis of renal artery stenosis]. *Rofo*. 1994;161(6):519–525.

32. Lind Ramskov K, Thomsen HS. Nephrogenic systemic fibrosis and contrast medium-induced nephropathy: a choice between the devil and the deep blue sea for patients with reduced renal function? *Acta Radiol*. 2009;50(9):965–967.

33. McCullough PA. Contrast-Induced Acute Kidney Injury. *J Am Coll Cardiol*. 2008;51(15): 1419–28.

34. ASTRAL Investigators, Wheatley K, Ives N, et al. Revascularization versus medical therapy for renal-artery stenosis. *N Engl J Med*. 2009;361(20):1953–1962.

35. Artunc F, Rossi C, Boss A. MRI to assess renal structure and function. *Curr Opin Nephrol Hypertens*. 2011;20(6):669–675.

36. Tan, Brown, Tijssen, Ramsay. Magnetic Resonance Angiography for the Diagnosis of Renal Artery Stenosis: A Meta-analysis. *Clin Radiol*. 2002;57(7):8–8.

37. Prince MR, Yucel EK, Kaufman JA, Harrison DC, Geller SC. Dynamic gadolinium-enhanced three-dimensional abdominal MR arteriography. *J Magn Reson Imaging*. 1993;3(6):877–881.

38. Snidow JJ, Johnson MS, Harris VJ, et al. Three-dimensional gadolinium-enhanced MR angiography for aortoiliac inflow assessment plus renal artery screening in a single breath hold. *Radiology*. 1996;198(3):725–732.

39. Patel ST, Mills JL, Tynan-Cuisinier G, Goshima KR, Westerband A, Hughes JD. The limitations of magnetic resonance angiography in the diagnosis of renal artery stenosis: comparative analysis with conventional arteriography. *J Vasc Surg*. 2005;41(3):462–468.

40. Willoteaux SS, Faivre-Pierret MM, Moranne OO, et al. Fibromuscular dysplasia of the main renal arteries: comparison of contrast-enhanced MR angiography with digital subtraction angiography. *Radiology*. 2006;241(3):922–929.

41. Prince MRM, Arnoldus CC, Frisoli JKJ. Nephrotoxicity of high-dose gadolinium compared with iodinated contrast. *J Magn Reson Imaging*. 1996;6(1):162–166.

42. Marckmann PP, Skov LL, Rossen KK, et al. Nephrogenic systemic fibrosis: suspected causative role of gadodiamide used for contrast-enhanced magnetic resonance imaging. *J Am Soc Nephrol*. 2006;17(9):2359–2362.

43. Deo A, Fogel M, Cowper SE. Nephrogenic systemic fibrosis: a population study examining the relationship of disease development to gadolinium exposure. *Clin J Am Soc Nephrol*. 2007;2(2):264–267.

44. Swaminathan SS, High WAW, Ranville JJ, et al. Cardiac and vascular metal deposition with high mortality in nephrogenic systemic fibrosis. *Kidney Int*. 2008;73(12):1413–1418.

45. Marckmann P. An epidemic outbreak of nephrogenic systemic fibrosis in a Danish hospital. *Eur J Radiol*. 2008;66(2):187–190.

46. Shabana WM, Cohan RH, Ellis JH, et al. Nephrogenic systemic fibrosis: a report of 29 cases. *AJR Am J Roentgenol*. 2008;190(3):736–741.

47. Perez-Rodriguez J, Lai S, Ehst BD, Fine DM, Bluemke DA. Nephrogenic systemic fibrosis: incidence, associations, and effect of risk factor assessment--report of 33 cases. *Radiology*. 2009;250(2):371–377.

48. Girardi MM, Kay JJ, Elston DMD, Leboit PEP, Abu-Alfa AA, Cowper SES. Nephrogenic

systemic fibrosis: clinicopathological definition and workup recommendations. *J Am Acad Dermatol*. 2011;65(6):1095–10e7.

49. Martin DR, Krishnamoorthy SK, Kalb B, et al. Decreased incidence of NSF in patients on dialysis after changing gadolinium contrast-enhanced MRI protocols. *J Magn Reson Imaging*. 2010;31(2):440–446.

50. Thomsen HSH, Morcos SKS, Almén TT, et al. Nephrogenic systemic fibrosis and gadolinium-based contrast media: updated ESUR Contrast Medium Safety Committee guidelines. *Eur Radiol*. 2013;23(2):307–318..

51. Wahba IMI, White KK, Meyer MM, Simpson ELE. The case for ultraviolet light therapy in nephrogenic fibrosing dermopathy--report of two cases and review of the literature. *Nephrol Dial Transplant*. 2007;22(2):631–636.

52. Tran KT, Prather HB, Cockerell CJ, Jacobe H. UV-A1 therapy for nephrogenic systemic fibrosis. *Arch Dermatol*. 2009;145(10):1170–1174.

53. Swaminathan S, Arbiser JL, Hiatt KM, et al. Rapid improvement of nephrogenic systemic fibrosis with rapamycin therapy: possible role of phospho-70-ribosomal-S6 kinase. *J Am Acad Dermatol*. 2010;62(2):343–345.

54. Kadiyala D, Roer DA, Perazella MA. Nephrogenic Systemic Fibrosis Associated With Gadoversetamide Exposure: Treatment With Sodium Thiosulfate. *Am J Kidney Dis.* 2009;53(1):133–7.

55. Poisson JL, Low A, Park YA. The treatment of nephrogenic systemic fibrosis with therapeutic plasma exchange. *J Clin Apher*. 2013 28(4):317-20.

56. Hansen KJ, Tribble RW, Reavis SW, et al. Renal duplex sonography: evaluation of clinical utility. *J Vasc Surg*. 1990;12(3):227–236.

57. Spyridopoulos TNT, Kaziani KK, Balanika APA, et al. Ultrasound as a first line screening tool for the detection of renal artery stenosis: a comprehensive review. *Med Ultrason*. 2010;12(3):228–232.

58. de Oliveira IRIS, Widman AA, Molnar LJL, Fukushima JTJ, Praxedes JNJ, Cerri GGG. Colour Doppler ultrasound: a new index improves the diagnosis of renal artery stenosis. *Ultrasound Med Biol*. 2000;26(1):41–47.

59. Halpern EJ, Deane CR, Needleman L, Merton DA, East SA. Normal renal artery spectral Doppler waveform: a closer look. *Radiology*. 1995;196(3):667–673.

60. Drieghe B, Madaric J, Sarno G, et al. Assessment of renal artery stenosis: side-by-side comparison of angiography and duplex ultrasound with pressure gradient measurements. *European Heart Journal*. 2008;29(4):517–524.

61. Chain SS, Luciardi HH, Feldman GG, et al. Diagnostic role of new Doppler index in assessment of renal artery stenosis. *Cardiovasc Ultrasound*. 2006;4:4–4.

62. Baumgartner I, Lerman LO. Renovascular hypertension: screening and modern management. *European Heart Journal*. 2011;32(13):1590–1598.

63. Cicuto KP, McLean GK, Oleaga JA, Freiman DB, Grossman RA, Ring EJ. Renal artery stenosis: anatomic classification for percutaneous transluminal angioplasty. *AJR Am J Roentgenol*. 1981;137(3):599–601.

64. Kaatee R, Beek FJ, Verschuyl EJ, et al. Atherosclerotic renal artery stenosis: ostial or truncal? *Radiology*. 1996;199(3):637–640.

65. Li CJ, Wang L, Jiang XY, et al. Evaluation of renal artery stenosis with velocity parameters of Doppler sonography. *J Ultrasound Med*. 2006;25(6):735–734.

66. Zeller T, Frank U, Späth M, Roskamm H. Color duplex ultrasound imaging of renal arteries and detection of hemodynamically relevant renal artery stenoses. *Ultraschall Med*. 2001;22(3):116–12.

67. Zeller T, Bonvini RF, Sixt S. Color-coded duplex ultrasound for diagnosis of renal artery stenosis and as follow-up examination after revascularization. *Cathet Cardiovasc Intervent*. 2008;71(7):995–999.

68. Mostbeck GH, Gössinger HD, Mallek R, Siostrzonek P, Schneider B, Tscholakoff D. Effect of heart rate on Doppler measurements of resistive index in renal arteries. *Radiology*. 1990;175(2):511–513.

69. Schwerk WBW, Restrepo IKI, Stellwaag MM, Klose KJK, Schade-Brittinger CC. Renal artery stenosis: grading with image-directed Doppler US evaluation of renal resistive index. *Radiology*. 1994;190(3):785–790.

70. Radermacher J, Chavan A, Bleck J, et al. Use of Doppler ultrasonography to predict the outcome of therapy for renal-artery stenosis. *N Engl J Med*. 2001;344(6):410–417.

71. Zeller TT, Müller CC, Frank UU, et al. Stent angioplasty of severe atherosclerotic ostial renal artery stenosis in patients with diabetes mellitus and nephrosclerosis. *Cathet Cardiovasc Intervent*. 2003;58(4):510–515.

72. Krumme B, Hollenbeck M. Doppler sonography in renal artery stenosis--does the Resistive Index predict the success of intervention? *Nephrol Dial Transplant*. 2007;22(3): 692–696.

73. Rocha-Singh K, Jaff MR, Kelley EL. Renal artery stenting with noninvasive duplex ultrasound follow-up: 3-year results from the RENAISSANCE renal stent trial. *Cathet Cardiovasc Intervent*. 2008;72(6):853–862.

74. Krumme B. Renal Doppler sonography--update in clinical nephrology. *Nephron Clin Pract*. 2006;103(2):c24–8.

75. Nazzal M, Hoballah J, Miller EV, Sharp WJ, Kresowik TF, Corson J. Renal hilar Doppler analysis is of value in the management of patients with renovascular disease. *Am J Surg*. 1997;174(2):164–168.

76. Motew SJ, Cherr GS, Craven TE, et al. Renal duplex sonography: main renal artery versus hilar analysis. *J Vasc Surg*. 2000;32(3):462–9; 469–71.

77. Slovut DP, Lookstein R, Bacharach JM, Olin JW. Correlation between noninvasive and endovascular Doppler in patients with atherosclerotic renal artery stenosis: a pilot study. *Catheter Cardiovasc Interv*. 2006;67(3):426–433.

78. Vasbinder GB, Nelemans PJ, Kessels AG, Kroon AA, de Leeuw PW, van Engelshoven JM. Diagnostic tests for renal artery stenosis in patients suspected of having renovascular hypertension: a meta-analysis. *Ann Intern Med*. 2001;135(6):401–411.

79. Pauling L, Coryell CD. The Magnetic Properties and Structure of Hemoglobin, Oxyhemoglobin and Carbonmonoxyhemoglobin. *Proc Natl Acad Sci USA*. 1936;22(4): 210–216.

80. Ogawa S, Lee TM, Kay AR, Tank DW. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc Natl Acad Sci USA*. 1990;87(24):9868–9872.

81. Prasad PV, Edelman RR, Epstein FH. Noninvasive evaluation of intrarenal oxygenation

with BOLD MRI. *Circulation*. 1996;94(12):3271–3275.

82. Textor SC, Glockner JF, Lerman LO, et al. The Use of Magnetic Resonance to Evaluate Tissue Oxygenation in Renal Artery Stenosis. *J Am Soc Nephrol*. 2008;19(4):780–788.

83. Chrysochou C, Mendichovszky IA, Buckley DL, Cheung CM, Jackson A, Kalra PA. BOLD imaging: a potential predictive biomarker of renal functional outcome following revascularization in atheromatous renovascular disease. *Nephrol Dial Transplant* 2012;27(3):1013-9.

84. Warner L, Glockner JF, Woollard J, Textor SC, Romero JC, Lerman LO. Determinations of Renal Cortical and Medullary Oxygenation Using Blood Oxygen Level-Dependent Magnetic Resonance Imaging and Selective Diuretics. *Invest Radiol*. 2011;46(1):41–47.

85. Williams DS, Detre JA, Leigh JS, Koretsky AP. Magnetic resonance imaging of perfusion using spin inversion of arterial water. *Proc Natl Acad Sci USA*. 1992;89(1):212–216.

86. Kiefer C, Schroth G, Gralla J, Diehm N, Baumgartner I, Husmann M. A feasibility study on model-based evaluation of kidney perfusion measured by means of FAIR prepared true-FISP arterial spin labeling (ASL) on a 3-T MR scanner. *Acad Radiol*. 2009;16(1):79–87.

87. Artz NS, Sadowski EA, Wentland AL, et al. Reproducibility of renal perfusion MR imaging in native and transplanted kidneys using non-contrast arterial spin labeling. *J Magn Reson Imaging*. 2011;33(6):1414–1421.

88. Fenchel M, Martirosian P, Langanke J, et al. Perfusion MR imaging with FAIR true FISP spin labeling in patients with and without renal artery stenosis: initial experience. *Radiology*. 2006;238(3):1013–1021.

89. He X, Aghayev A, Gumus S, Ty Bae K. Estimation of single-kidney glomerular filtration rate without exogenous contrast agent. *Magn Reson Med*. 2013; Mar 6. Epub ahead of print. DOI 10.1002/mrm.24668.

90. Herborn CU, Watkins DM, Runge VM, Gendron JM, Montgomery ML, Naul LG. Renal arteries: comparison of steady-state free precession MR angiography and contrast-enhanced MR angiography. *Radiology*. 2006;239(1):263–268.

91. Pei Y, Shen H, Li J, et al. Evaluation of renal artery in hypertensive patients by unenhanced MR angiography using spatial labeling with multiple inversion pulses sequence and by CT angiography. *AJR Am J Roentgenol*. 2012;199(5):1142–1148.

92. Angeretti M, Lumia D, Canì A, et al. Non-enhanced MR angiography of renal arteries: comparison with contrast-enhanced MR angiography. *Acta Radiol*. 2013;54(7):749-56.

93. Braidy C, Daou I, Diop AD, et al. Unenhanced MR angiography of renal arteries: 51 patients. *AJR Am J Roentgenol*. 2012;199(5):W629–37.

## 1.3 Medical treatment of ARVD

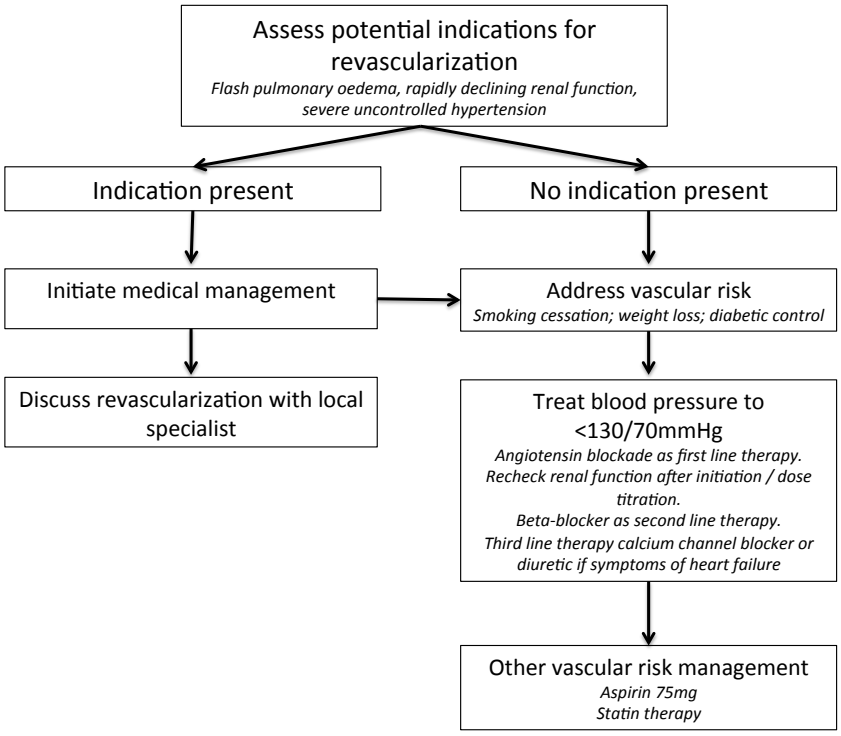
Ritchie J, Green D, Chrysochou C, Kalra PA

*Published in Renovascular Hypertension; Oxford Textbook of Clinical Nephrology (4th Edition), Oxford, Oxford University Press - in press.*

IPR policy: http://www.oxfordjournals.org/access_purchase/publication_rights.html

Despite numerous studies comparing medical therapy with revascularisation in ARVD, what constitutes optimal medical therapy is poorly defined. Treatment is prioritised at modifiable vascular risk factors. In addition to lifestyle interventions such as smoking cessation and rigorous control of glycaemia in diabetic patients, blood pressure control must be optimised and consideration given to the use of anti-platelet and lipid lowering medications. Figure 1.3.1 describes a pragmatic treatment algorithm.

**Figure 1.3.1** - Medical treatment of patients with atherosclerotic renovascular disease



### 1.3.1 Angiotensin blockade

Angiotensin blockade is considered first line therapy in CKD due to benefits on rate of loss of renal function exceeding what would be expected by the reduction in blood pressure alone [1]. Historically there has been underuse of these agents in patients with renal artery stenosis due to concerns regarding reduced glomerular filtration pressure [2]. Whilst a reduction in GFR can be precipitated by initiation of angiotensin blockade in ARVD, multiple other reasons exist for reductions in renal function following initiation of these agents (table 1.3.1) and any reductions in GFR can be reversed upon withdrawal of the agent [3]. Current data suggest that angiotensin blockade is better tolerated in ARVD then is generally believed. In a series of 36 patients with ARVD (26 revascularised, 10 medically managed), use of angiotensin blockade was not associated with a reduction in eGFR over a median follow up period of 88 months [4]. Another observational study has described 71 patients, previously angiotensin blockade naive, in whom renal artery stenosis had been diagnosed following an increase in serum creatinine following initiation of one of these agents [5]. Forty of these patients were subsequently recommenced on angiotensin blockade (thirteen following revascularisation), without detriment to renal function. Unfortunately data are not available to describe if the remaining 31 patients failed re-introduction of therapy or were not further exposed to angiotensin blockade. Despite this it is noteworthy that although angiotensin blockade is well tolerated in the chronic stable state, ARVD patients prescribed these agents have an increased risk for hospitalisation with acute kidney injury during intercurrent illnesses (hazard ratio 1.87 [95% CI 1.05-3.33], p=0.04), though this is lower than the risk associated with loop diuretics (hazard ratio 1.98 [95% CI 1.01-3.88], p=0.04) [6]. Despite this, angiotensin blockade can be considered first line therapy in ARVD due to significant reductions in risk for death and non-fatal cardiovascular events with two studies describing an almost 50% risk reduction for mortality associated with these agents [5,6]. The mechanism of this risk reduction is uncertain, but recent data from porcine models suggest angiotensin blockade my reduce renal fibrosis and aid preservation of the microvasculature [7]. There are no data to support the use of dual angiotensin blockade in ARVD.

**Table 1.3.1** - Causes of reduced renal function after initiation of angiotensin blockade

| **Causes of reduction in glomerular filtration rate associate with use of angiotensin blockade** | |
|---|---|
| Mean arterial pressure insufficient for adequate renal perfusion | |
| | Poor cardiac output |
| | Low systemic vascular resistance |
| Volume depletion | |
| Concurrent use of vasoconstrictor agents | |
| | Non steroidal anti-inflammatory drugs |
| | Cyclosporin |
| Renal vascular disease | |
| | Bilateral renal artery stenosis |
| | Stenosis to single functioning kidney |
| | Afferent arteriolar disease |
| | Diffuse small vessel atherosclerosis without focal ostial stenosis |

### 1.3.2 Beta blockade

In addition to excess renin angiotensin aldosterone activity, patients with renal artery stenosis have sympathetic over activity and elevated serum noradrenaline concentrations [8]. In conjunction, the arterial baroreflex response to elevated sympathetic activity is reset upwards and becomes less sensitive [9]. Survival benefits associated with beta-blockade are well described in essential hypertension, congestive heart failure and following myocardial infarction [10,11], phenotypes all commonly observed in the context of renal artery disease. There are no data to suggest that beta-blockade results in better blood pressure control in the setting of renovascular hypertension. Indeed the American Society of Hypertension define pairing of a beta-blocker with angiotensin blockade as a relatively ineffective combination to treat hypertension [12]. However in a series of 40 patients undergoing medical treatment for atherosclerotic renal artery stenosis use of beta blockers as second line therapy was associated with a greater proportion of patients exhibiting stabilisation in degree of stenosis compared to those using calcium channel blockers or dual angiotensin blockade (75% vs. 54% vs. 50%) [13]. Other data suggest a potential benefit in renal function in revascularised patients treated with nebivolol in addition to angiotensin blockade post procedure [14]. Given the relationship between renal

function and blood pressure and degree of renal artery stenosis and blood pressure, these data would argue for a second line role for beta-blockade.

### 1.3.3 Other anti-hypertensive medications

Due to the salt and water retention caused by excess activity of the renin angiotensin aldosterone system, a mechanistic argument for the use of diuretic therapy can be made for patients with ARVD. Use of these agents is considered key in the management of resistant hypertension [15]. Although diuretics are one of the least well tolerated classes of anti-hypertensive, tolerability is improved when used in combination with other agents [12]. In addition, diuretics result in a fully additive blood pressure reduction when used as part of a combined management strategy [16]. Specific data regarding the use of diuretics in ARVD is anticipated from CORAL, where diuretics are specified as second line therapy [17]. Calcium channel blockers result in an additive blood pressure reduction when combined with all classes of anti-hypertensive medications other than alpha blockers [12]. Few specific data exist regarding their use in ARVD.

### 1.3.4 Anti-platelet medications

Anti-platelet therapy is accepted as a standard treatment in ARVD due to the significant extra-renal burden of atheroma [18]. In chronic stable disease there are no data to compare outcome between different classes of anti-platelet agents. In CKD aspirin therapy is generally considered efficacious and safe [19], though debate is on going [20]. Despite this uncertainty, aspirin is seen as a first line treatment due to the reduced activity and increased bleeding risk observed in CKD patients prescribed clopidogrel [21]. Current research into anti-platelet therapy in ARVD is focused on optimal treatment [22,23] around time of percutaneous revascularisation.

### 1.3.5 Statin therapy

Statin therapy is a rational choice in ARVD given the burden of systemic vascular disease and the associations between these agents and reduced rates of loss of renal function [24,25] and cardiovascular events in CKD patients [26]. In addition to this, statins retard progressive loss of renal luminal diameter [27] and

are associated with reduced renal fibrosis in pig models of RAS [28]. Risk for death and ESKD associated with statin therapy was analysed in a cohort of 104 ARVD patients in which hyperlipidaemia patients (n=68, mean cholesterol 5.2mmol/L) were treated with a statin and patients without hyperlipidaemia (n=36, mean cholesterol 4.7mmol/L) were not. In this study, statin treated patients had a reduced risk for ESKD (hazard ratio 0.2 [95% CI 0.1-0.6], p=0.006) and death (hazard ratio 0.13 [95% CI 0.04-0.4], p=0.001) [29]. A similar reduction in risk for death has been described in revascularised patients (hazard ratio 0.71 [95% CI 0.53-0.95], p=0.02) [30]. In a series of 91 patients who underwent percutaneous renal artery angioplasty and stenting, statin use was significantly associated with a reduced risk for re-stenosis (HR 0.35 [95% CI 0.16-0.74], p=0.006) [31].

## References


1. Jafar TH, Schmid CH, Landa M, et al. Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. *Ann Intern Med*. 2001;135(2):73–87.

2. Bart BA, Gattis WA, Diem SJ, O'Connor CM. Reasons for underuse of angiotensin-converting enzyme inhibitors in patients with heart failure and left ventricular dysfunction. *Am J Cardiol*. 1997;79(8):1118–1120.

3. van de Ven PJ, Beutler JJ, Kaatee R, Beek FJ, Mali WP, Koomans HA. Angiotensin converting enzyme inhibitor-induced renal dysfunction in atherosclerotic renovascular disease. *Kidney Int*. 1998;53(4):986–993.

4. Sofroniadou S, Kassimatis T, Srirajaskanthan R, Reidy J, Goldsmith D. Long-term safety and efficacy of renin-angiotensin blockade in atherosclerotic renal artery stenosis. *Int Urol Nephrol*. 2012;44(5):1451–1459.

5. 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. *Nephrol Dial Transplant*. 2012;27(4):1403-9.

6. Hackam DG, Duong-Hua ML, Mamdani M, et al. Angiotensin inhibition in renovascular disease: a population-based cohort study. *American Heart Journal*. 2008;156(3):549–555.

7. Zhang X, Eirin A, Li Z-L, et al. Angiotensin receptor blockade has protective effects on the poststenotic porcine kidney. *Kidney Int*. 2013:84(4):767-75.

8. Johansson M, Elam M, Rundqvist B, et al. Differentiated response of the sympathetic nervous system to angiotensin-converting enzyme inhibition in hypertension. *Hypertension*. 2000;36(4):543–548.

9. Grassi GG, Cattaneo BMB, Seravalle GG, Lanfranchi AA, Mancia GG. Baroreflex control of sympathetic nerve activity in essential and secondary hypertension. *Hypertension*. 1998;31(1):68–72.

10. Chobanian AVA, Bakris GLG, Black HRH, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289(19):2560–2572.

11. Antman EM, Hand M, Armstrong PW, et al. 2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: developed in collaboration With the Canadian Cardiovascular Society endorsed by the American Academy of Family Physicians: 2007 Writing Group to Review New Evidence and Update the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction, Writing on Behalf of the 2004 Writing Committee. *Circulation*. 2008;117(2):296–329.

12. Gradman AHA, Basile JNJ, Carter BLB, et al. Combination therapy in hypertension. *Journal of the American Society of Hypertension*. 2010;4(2):90–98.

13. Cianci R, Martina P, Borghesi F, et al. Revascularization versus medical therapy for renal artery stenosis: antihypertensive drugs and renal outcome. *Angiology*. 2011;62(1):92–99.

14. Duranay M, Kanbay M, Akay H, et al. Nebivolol improves renal function in patients who underwent angioplasty due to renal artery stenosis: a pilot study. *Nephron Clin Pract*. 2010;114(3):c213–7.

15. Myat A, Redwood SR, Qureshi AC, Spertus JA, Williams B. Resistant hypertension. *BMJ*. 2012;345:e7473–e7473.

16. Chrysant SGS. Antihypertensive effectiveness of low-dose lisinopril-hydrochlorothiazide combination. A large multicenter study. Lisinopril-Hydrochlorothiazide Group. *Arch Intern Med*. 1994;154(7):737–743.

17. Cooper C, Murphy T, Matsumoto A, et al. Stent revascularization for the prevention of cardiovascular and renal events among patients with renal artery stenosis and systolic hypertension: Rationale and design of the CORAL trial. *American Heart Journal*. 2006;152(1):59–66.

18. Colyer WR, Cooper CJ. Management of renal artery stenosis: 2010. *Curr Treat Options Cardiovasc Med*. 2011;13(2):103–113.

19. Jardine MJ, Ninomiya T, Perkovic V, et al. Aspirin Is Beneficial in Hypertensive Patients With Chronic Kidney Disease. *J Am Coll Cardiol*. 2010;56(12):956–965.

20. Palmer SC, Di Micco L, Razavian M, et al. Effects of antiplatelet therapy on mortality and cardiovascular and bleeding outcomes in persons with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med*. 2012;156(6):445–459.

21. Best PJ, Steinhubl SR, Berger PB, et al. The efficacy and safety of short- and long-term dual antiplatelet therapy in patients with mild or moderate chronic kidney disease: Results from the Clopidogrel for the Reduction of Events During Observation (CREDO) Trial. *American Heart Journal*. 2008;155(4):7–7.

22. Kanjwal K, Cooper CJ, Virmani R, et al. Predictors of embolization during protected renal artery angioplasty and stenting: Role of antiplatelet therapy. *Cathet Cardiovasc Intervent*. 2010;76(1):16–23.

23. Cooper CJ, Haller ST, Colyer W, et al. Embolic protection and platelet inhibition during renal artery stenting. *Circulation*. 2008;117(21):2752–2760.

24. Shah S, Paparello J, Danesh FR. Effects of statin therapy on the progression of chronic kidney disease. *Advances in Chronic Kidney Disease*. 2005;12(2):187–195.

25. Huskey J, Lindenfeld J, Cook T, et al. Effect of simvastatin on kidney function loss in patients with coronary heart disease: findings from the Scandinavian Simvastatin Survival Study (4S). *Atherosclerosis*. 2009;205(1):202–206.

26. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *The Lancet*. 2011;377(9784): 2181–2192..

27. Cheung CM, Patel A, Shaheen N, et al. The Effects of Statins on the Progression of Atherosclerotic Renovascular Disease. *Nephron Clin Pract*. 2007;107(2):c35–c42.

28. Chade AR, Zhu X-Y, Grande JP, Krier JD, Lerman A, Lerman LO. Simvastatin abates development of renal fibrosis in experimental renovascular disease. *J Hypertens*. 2008;26(8):1651–1660.

29. Silva VS, Martin LC, Franco RJS, et al. Pleiotropic Effects of Statins May Improve Outcomes in Atherosclerotic Renovascular Disease. *Am J Hypertens*. 2008;21(10): 1163–1168.

30. Bates MC, Campbell JE, Stone PA, Jaff MR, Broce M, Lavigne PS. Factors affecting long-term survival following renal artery stenting. *Cathet Cardiovasc Intervent*. 2007;69(7):1037–1043

31. Corriere MA, Edwards MS, Pearce JD, Andrews JS, Geary RL, Hansen KJ. Restenosis after renal artery angioplasty and stenting: incidence and risk factors. *J Vasc Surg*. 2009;50(4):813–819.

## 1.4 ASTRAL and beyond: Who is appropriate to consider for renal artery revascularization?

Ritchie J, Kalra PA

*Vascular Disease Management. 2011(8):E12-20*

Abstract

ASTRAL and the four randomized control trials that preceded it have shown that unselected revascularization in atherosclerotic renovascular disease is not an appropriate intervention. Despite this, there are clinical situations where renal artery revascularization is of great patient benefit. In this review we discuss the different presentations of ARVD and the effects of revascularization for each.

## Introduction

ARVD is an endemic condition that presents the clinician with challenging treatment decisions. ASTRAL [1] was a landmark prospective trial comparing standard medical therapy to standard medical therapy and renal revascularization in 806 patients with ARVD. Its main findings were that there was no difference between the two arms in terms of renal functional, blood pressure, cardiovascular event or mortality outcomes. Given that over 6% of patients suffered a significant complication during revascularisation, the trial results have been important in minimising patient exposures to potentially harmful procedures. However, they have increased uncertainty amongst clinicians as to when revascularization is appropriate. In this article we set out to highlight the different ways in which ARVD can present and discuss the arguments for revascularization in each clinical situation.

## Clinical presentations and arguments to revascularize

The often silent nature of ARVD makes exact comment on its incidence hard to pass. A large study of Medicare patients aged over 65 years found an incidence of 0.5% or 3.7 per 1000 patient years [2]; this is likely to be an underestimate because disease screening would only have been undertaken in symptomatic or other selected patients, and community Doppler ultrasound screening has shown a 7% prevalence in the elderly US population [3] whereas United Kingdom Registry data defines ARVD as the primary disease in over 10% of incident dialysis patients [4].

Given the heterogeneous renal artery anatomy, renal parenchymal damage and extra-renal vascular associations of ARVD a variety of clinical syndromes are observed, each of which carries its own arguments for and against revascularization. These are:

- Hypertension
    - Refractory hypertension
- Facilitation of RAAS blockade
- Chronic kidney disease
    - Rapidly declining renal function
- Acute kidney injury
    - Dialysis dependent ARVD
- Flash pulmonary edema
- Congestive cardiac failure
- Severe anatomical ARVD
- Incidental ARVD

### 1.4.1 Hypertension

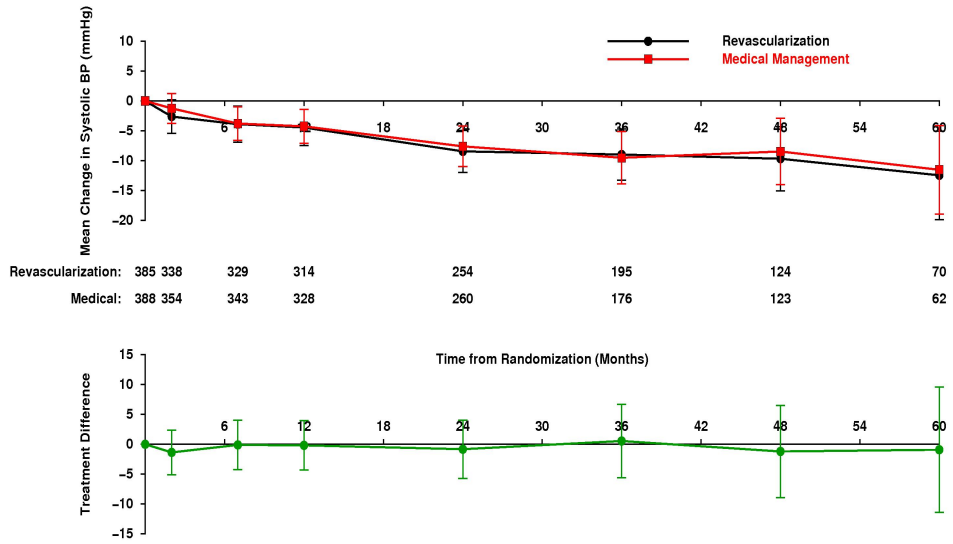
Over 95% of patients with ARVD will have hypertension and up to 2% of all hypertensives will have RAS, but a causal association is unlikely in the majority [5]. Indeed, the role of revascularization for hypertension is a contentious area. RAS reduces perfusion to the kidney, triggering activation of the RAAS and resulting in marked vasoconstriction with salt and water retention and other detrimental effects. As well as increasing blood pressure this contributes to ongoing renal functional deterioration and other target organ damage.

Prior to commencement of ASTRAL there had been three small RCT which compared revascularization to medical therapy and assessed blood pressure outcomes in ARVD [6-8]. The Dutch Renal Artery Stenosis Intervention Cooperative (DRASTIC) study demonstrated a reduction in systolic blood pressure at twelve months in the angioplasty group, though this was only seen when blood pressure was checked with an automated machine, not replicated when a sphygmomanometer was used [7]. DRASTIC also reported improved blood pressures in the patient population who crossed over from the medical arm to revascularization because of refractory hypertension at three months.

These benefits were not seen in the other RCTs, though the Essai Multicentrique Medicaments vs. Angioplastie (EMMA) trial [6] and DRASTIC both suggested a minor reduction in the need for oral anti-hypertensive medications following revascularization. Meta-analysis of these trials was limited due to their heterogeneity and did not support renal revascularization to treat hypertension [9]. The Dutch led Stent Placement in Patients With Atherosclerotic Renal Artery Stenosis and Impaired Renal Function (STAR) study recruited 140 patients and was published just prior to ASTRAL. Patients were randomized between percutaneous revascularization and medical therapy and no differences were observed in terms of blood pressure control [10]. Over a median follow up period of 34 months in ASTRAL, the homogeneity of blood pressure in each arm was confirmed with no difference in the systolic or diastolic blood pressures in either limb of the trial, figure 1.4.1. Patients enrolled into ASTRAL did have lower baseline systolic blood pressures (150/76mmHg compared to 162/68mmHg in STAR) than those in the other trials but were on comparable numbers of anti-hypertensive agents.

In light of the available data, it would seem that the idea of undertaking renal revascularization for most cases of hypertension has been rebuffed. However, two areas remain for discussion – refractory hypertension and revascularization to facilitate renin angiotensin blockade.

**Figure 1.4.1** - Mean change in systolic blood pressure over time in ASTRAL




*Reproduced from Wheatley et al [1] with permission.*

*Refractory hypertension*

Refractory hypertension is defined as uncontrolled blood pressure (greater than 160/90mmHg) despite the use of three or more different anti-hypertensive medications. Treatment can present serious challenges to the clinician with past decisions escalating as far as nephrectomy to control blood pressure. Thankfully this approach is now rarely considered, but use of renal revascularization for resistant hypertension is a poorly understood area with no specific trial data. When the patient groups in STAR [10] and ASTRAL are taken as a whole, neither fits the above definition making it difficult to draw conclusions. However, some patients did fit the criteria and post-hoc analysis of these trials in collaboration with results from CORAL may further enlighten us in the future. Until then, the best information can be drawn form the DRASTIC [7] data in which the baseline demographics meet the definition for resistant hypertension. As mentioned above, revascularization did not improve blood pressure control, but did reduce the number of anti-hypertensive medications required in this study. Until there is more data, many clinicians will feel obliged to attempt revascularization when RAS exists in association with multi drug resistant hypertension, or when drug-related renal dysfunction limits therapeutic options as discussed below.

One final point of interest on this topic is the potential role of biomarkers. Brain natriuretic peptide (BNP) is one biomarker with promising data. A small single centre prospective study in patients with ARVD and resistant hypertension found that patients with serum BNP levels of >80pg/ml prior to intervention were much more likely to benefit from revascularization [11]. In animal models, BNP synthesis and release is stimulated by release of angiotensin II [12]. BNP antogonises the RAAS and promotes natriuresis. Therefore, it may be that the elevated BNP levels are a marker of an overactive RAAS, a marker of cardiac strain secondary to chronic atrial overstretch, or a combination of these and other factors. This pilot data is interesting but more investigations are needed to validate its significance.

1.4.2 Renin angiotensin aldosterone blockade

Effective blockade of the RAAS is one of the most significant advances of recent years with effective blood pressure control, anti-proteinuric effects and benefits to cardiac function all available as results of treatment. Angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) are excellent treatments for renovascular driven hypertension, but there are widely held reservations about their use in the setting of ARVD, especially in patients with bilateral significant disease. It cannot be disputed that ACEi or ARB use can precipitate a fall in GFR; however in the setting of unilateral RAS with a normally functioning contralateral kidney most patients avoid this fate. However, experience of use of RAAS blockade in the setting of significant bilateral ARVD, without detriment to renal function, is now growing [13].

Despite this general tolerance to therapy there are some patients who cannot tolerate RAAS blockade without significant reduction in renal function. In view of the high prevalence of CKD and proteinuria in ARVD, these patients will be missing out on the specific renoprotective effects of these medications, as well as potential benefits of reduced cardiovascular events and mortality, and reduced chronic dialysis initiation [14]. Hence, the indication of renal revascularization to permit ACEi or ARB use is an attractive one. The Renal Atherosclerotic Revascularization Evaluation (RAVE) study [15] is a single centre randomized prospective pilot study comparing revascularization over standard medical therapy. One of three specified secondary objectives is a comparison of blood pressures and type of anti-hypertensive agents used between each arm of the trial. Though only a pilot study with a target of 20 patients enrolled, this may provide prospective data regarding anti-hypertensive tolerance after revascularization. Until the results are available we are reliant on retrospective data, which shows that revascularization can safely permit RAAS blockade in significant bilateral ARVD in those patients who were intolerant prior to the procedure [13,16].

We would, therefore, advocate consideration of revascularization when patients with RAS have a strong clinical need for and yet biochemical proof of intolerance to RAAS blockade.

1.4.3 Chronic kidney disease

Before ASTRAL was published over 15% of patients with a new diagnosis of ARVD in the US were undergoing revascularization procedures [2]. Prior to ASTRAL, previous RCTs had significant shortcomings which limited the quality of evidence provided - small patient groups, short follow up periods, and high cross-over rates from the conservative therapy arm. In the STAR study only 60% of patients in the interventional arm truly underwent revascularization [10]. ASTRAL enrolled 806 patients with an average age of 70 years and eGFR of 40ml/min at baseline. The primary end point of progressive loss of renal function was common to all of these studies. Neither ASTRAL nor any of the other RCTs has demonstrated a significant difference in renal function between arms of optimal medical therapy (OMT) or OMT and revascularization. CORAL [17] is ongoing and it will be some time before results are available, so present advice is built upon the available information. Hence, there is no evidence that renal revascularization is indicated in ARVD with otherwise asymptomatic stable CKD.

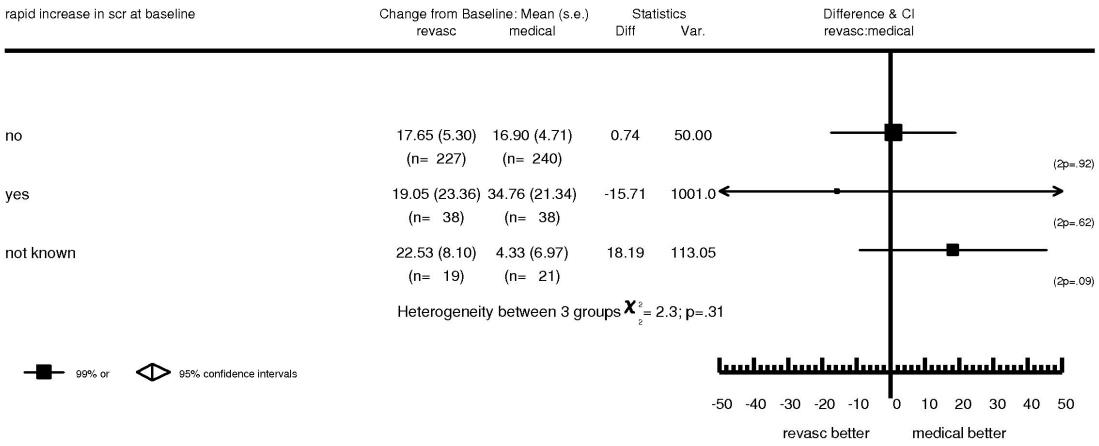
Again, however, there are subtleties which merit discussion. For example, increased levels of proteinuria are predictive of poor outcomes in ARVD-related CKD [18], and this is likely to be a major marker of parenchymal injury. A one size fits all approach to intervention is rarely if ever appropriate and patient selection must be considered. If intervening in stable CKD is not beneficial overall then the question of intervening in the sub-group of patients with more rapid loss of function must be considered as a separate issue.

1.4.4 Rapidly declining function

ASTRAL pre-specified a secondary analysis of a sub-group of patients with rapidly declining renal function (defined as a 20% or 100 umol/l increase in creatinine within the previous year), and there were 96 patients who eventually fulfilled these criteria. At one year patients in the revascularization arm had a reduction in their serum creatinine, but confidence intervals were wide and the result not statistically significant, figure 1.4.2. There will be CORAL patients who fit this clinical category but it may take a meta-analysis drawn from CORAL, ASTRAL and STAR to provide a reliable answer regarding benefit of revascularization in this clinical setting. Until then, the decision will remain

discretionary, but given the prognostic, financial and emotional costs of dialysis, revascularization may seem appropriate for this patient group.

**Figure 1.4.2** - Mean change in serum creatine at twelve months in ASTRAL, stratified by rapid increase in serum creatinine




*Reproduced from Wheatley et al [1] with permission*

## 1.4.5 Acute Kidney Injury

Despite a lack of firm evidence and the impossibility of undertaking a meaningful trial, there is a consensus view that the occurrence of oligo-anuric AKI in patients with significant ARVD is a strong indication for renal revascularization and this is supported by case reports of patient rescue from dialysis [19]. Most case reports and series describe patients with bilateral ARVD or with a chronic unilateral occlusion and a high grade contralateral lesion [20]. In a chronic setting, as renal blood flow drops below that of the kidney's ability to regulate glomerular flow, function is reduced but viability of renal parenchyma preserved by development of collateral circulation (e.g. from the lumbar and capsular vessels). Should another insult subsequently compromise perfusion further the system decompensates and AKI follows. This is a different physiological process to acute renal artery occlusion, where acute renal parenchymal ischemia is the predominant process.

The key questions in the setting of AKI are patient selection and investigation. The rate of decline in kidney function has been shown to be a predictor of success following revascularization, whilst there is conflicting data over the

usefulness of renal size and baseline creatinine [21]. This may be a reflection of the different pathophysiological processes involved (i.e. severity of ischemia vs. chronic parenchymal damage) and its applicability to clinical practice is uncertain.

Options for investigation for underlying severe RAS in the patient with AKI appear very limited as MRA is not a safe tool because of risk of nephrogenic systemic fibrosis and there are justifiable concerns regarding the repeated use of iodinated contrast in acute renal impairment. In skilled hands, Doppler ultrasound is the best option, providing reliable information about both kidney size and blood flow non-invasively. MAG3 nuclear scans have also been used to detect potentially viable tissue.

Timing of revascularization is the final issue, and naturally the earliest possible intervention seems most logical. The differentiation between acute vascular occlusion (which would require immediate intervention) and an acute insult developing on the background of chronic ischaemia and a collateral supply (there are reports of recovery from dialysis up to 42 days after loss of renal perfusion) [22], can sometimes be made in light of clinical history (e.g. acute loin pain, prior angiography) but this will not always be the case.

Consensus advocates consideration of renal artery revascularization in the setting of AKI in the presence of known or new bilateral ARVD.

### 1.4.6 Revascularization to escape dialysis

There are also reports in the literature of chronic haemodialysis patients becoming independent of dialysis following renal revascularization. Although anecdotal, these cases have occurred when intervention was undertaken primarily to try to assist with uncontrolled hypertension, or when preserved renal volume (see below) was an important factor in predicting dialysis discontinuation [23]. These reports are interesting but they almost certainly describe a minority of patients who commence chronic dialysis without prior investigation for RAS.

### 1.4.7 Flash pulmonary oedema

The complex interplay between the heart and the kidneys is well recognized and ARVD provides a clear clinical environment for this interconnection to occur, as it is commonly associated with increased ventricular stiffness and left ventricular hypertrophy, with 95% of patients with ARVD having abnormalities of cardiac structure or function [24] and little physiological reserve to adjust to changes in the circulating volume.

AVRD drives hypertension primarily through RAAS activation. In addition to pertubations in salt and water homeostasis, with reduced natruresis, excess RAAS stimulation increases pulmonary capillary permeability and mediates endothelial dysfunction, with potential consequences of salt and water retention and cardiac dysfunction. In some cases of unilateral RAS, a normally functioning contralateral kidney can suppress its own renin secretion so acting as a homeostatic safety valve. When disease is bilateral, or if there is only a single functioning kidney, this escape route is lost and acute pulmonary edema can occur. Almost 95% of patients with ARVD who present with FPO have bilateral disease [25].

There are no prospective randomized data to inform our treatment of FPO in the setting of ARVD. Several case reports or series describing successful treatment have been published [5] and these are summarized in table 1.4.1. In one retrospective series of 207 patients who underwent renal revascularization, 39 patients with recurrent episodes of heart failure requiring hospital admission were identified. All of these latter patients had bilateral disease and, if both kidneys were considered viable, underwent bilateral revascularization. Admissions to hospital for symptomatic pulmonary edema reduced from 2.4 to 0.3 admissions per year over a 21 month average follow up [26].

There is clear current consensus to advocate renal revascularization for recurrent pulmonary edema in the setting of significant bilateral ARVD, as the procedure can be life-saving for some [27].

**Table 1.4.1** - Reports of revascularization for acute and chronic heart failure

| Authors and publication year | Acute or chronic | Number of cases | CAD | Left ventricular systolic dysfunction | RAS degree | CCF end point |
|---|---|---|---|---|---|---|
| Weatherford et al 1997 [47] | Acute | 5 | 2/5 cases | No | 1 severe bilateral, 4 severe unilateral to SFK | No FPO during a mean 57 month follow up |
| Messina et al 1992 [48] | Acute | 17 | 11/17 cases | 6/17 cases | Severe bilateral | No FPO during mean follow up of 2.4 years |
| Pickering et al 1998 [49] | Acute | 11 | 5/11 cases | No | 7 bilateral, 2 unilateral to SFK, 2 unilateral | 10/11 no further FPO |
| Bloch et al 1999 [50] | Both | 19 acute, 6 chronic | 15/25 cases | 4/25 cases | 22 bilateral, 3 unilateral | 18/25 no recurrence, 3 FPO and 4 CCF at 1 year |
| Gray et al 2002 [26] | Both | 39 | Unknown | Unknown | 18/39 severe bilateral, 21/39 severe unilateral to SFK | Reduction in hospitalization for heart failure |
| Kane et al 2009 [51] | Chronic | 163 | 65%-74% of subjects | LV ejection fraction 47%-49% | >70% stenosis | Reduction in hospitalization and NYHA class in those who were revascularized |
| Missouris et al 2000 [52] | Chronic | 9 | Unknown | Unknown | 4 severe bilateral, 5 severe unilateral | Echo normalized in one, free from heart failure in another |
| Khosla et al 1997 [53] | Chronic | 28 | 24/28 patients | 22/28 patients | >70% stenosis, 8 unilateral, 20 bilateral | 16/28 improvement in NYHA class |
| Meissner et al 1988 [54] | Chronic | 6 | Yes | Yes | Severe bilateral or unilateral to SFK | Undefined clinical improvement |

*Adapted from Chrysochou et al [5] with permission.*
*Abbreviations: SFK - single functioning kidney. FPO - Flash pulmonary oedema. CCF - Chronic congestive cardiac failure. NYHA - New York Heart Association. RAS - Renal artery stenosis. CAD - Coronary artery disease.*

1.4.8 Chronic congestive cardiac failure

Chronic RAS activation and the neurohormonal repercussions have been shown to contribute to left ventricular remodeling and dilatation leading to symptoms of CCF. As up to 30% of patients with CCF have been shown to have some degree of ARVD [28], a mechanistically attractive proposition is to reduce RAAS stimulation and activity by revascularising this patient population.

Published trials do not provide any evidence to support renal revascularization in patients with more chronic heart failure, although case reports and retrospective series (table 1.4.1) again highlight potential benefit, but these risk positive reporting bias. Two sub-studies of ASTRAL using cardiac MRI and echocardiography (still due to report) have been designed to assess the impact of revascularization on cardiac structure and function, as has an Italian echocardiographic study, RASCAD (Stenting of Renal artery Stenosis in Coronary Artery Disease) [29]. These will provide the first firm data, which may be supplemented by CORAL, which has specified hospitalization for CCF as a primary end point.

Until then the most robust RCT data is available from ASTRAL's secondary end point of major cardiac events. One of these was hospitalization for fluid overload and or heart failure, and this occurred in 12% of the revascularized patients and 15% of those medically treated (p=0.22) [1].

We feel that the issue of renal artery revascularization for patients with chronic heart failure is worthy of RCT investigation in the future, but at the current time there is little evidence to support intervention except in potentially life-threatening situations (e.g. acute decompensation).

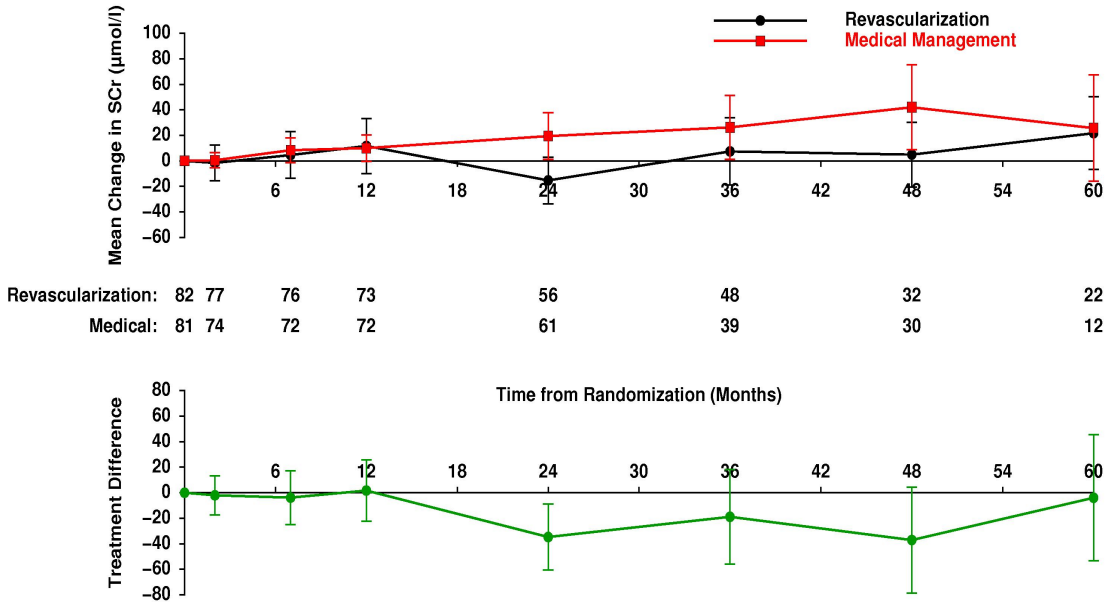
1.4.9 Severe anatomical ARVD

Severe stenosis is a difficult term to define, as outside of animal models the relationship between degree of RAS and alteration of flow or perfusion to the kidney has been poorly characterised. Lesions which could be considered mild or moderate at <50-60% may have an impact on mortality [30], giving them clinical significance. However, in patients with co-existent CAD mortality does

relate to the grade of RAS, with patients having RAS lesions > 75% having a significantly higher mortality than lesions under 75%.

So is renal revascularization indicated simply because a patient has a high degree of RAS, irrespective of clinical presentation? The DRASTIC study did not find a difference in the blood pressure outcomes for the revascularization arm when stenosis of >70% was compared to that of 50%-70% [7]. This finding was further studied in a post hoc analysis of ASTRAL. Here cases of bilateral stenosis >70%, or stenosis >70% in a single functioning kidney, were assessed and no difference in renal function or mortality was seen between the two randomized arms in a total of 163 patients with this anatomy, figure 1.4.3.

**Figure 1.4.3** - Mean change in serum creatinine in sub-set of ASTRAL patients with severe anatomical disease




*Severe anatomical disease defined as bilateral >70% stenosis or stenosis >70% to a single functioning kidney. Criteria for inclusion in this analysis satisfied by 163 patients. Reproduced from Wheatley et al [1] with permission.*

Accepting the limitations highlighted in critiques of these studies, which correctly suggest that there may have been over estimation of RAS severity in some cases, it is still difficult to recommend revascularization based on an angiographic finding alone. The increased mortality with increasing grade of

stenosis is interesting but does not prove a causal relationship, as, for example, more severe RAS is known to occur in patients with greater CAD burden [31]. Hence, ARVD forms part of a systemic process and this diffuse disease process is more likely to be the cause of increased mortality than the grade of stenosis alone.

In the absence of specific clinical complications we do not recommend revascularization based on the grade of stenosis alone. The possible caveat to this is preservation of functional renal mass in patients who can be shown to have a 'functionally significant' RAS, as discussed below.

1.4.10 Preservation of renal mass

Historically, many renal revascularization procedures were undertaken with the aim of preserving functioning renal mass.The term 'hibernating parenchyma' has been applied to describe kidneys that show functional improvement after revascularization, supposedly indicative of renal tissue that has not yet undergone permanent damage [32]. In these situations the hypothesis is that the haemodynamic consequence of a given RAS is the cause of renal dysfunction and that irreversible parenchymal injury has yet to occur. As such, the term 'functionally significant stenosis' may be a suitable alternative term.

Renal bipolar length, though a widely used measurement, has been shown to be poor at predicting remaining parenchymal volume (PV), but MRI studies have shown that the latter is the best predictor of single kidney glomerular filtration rate (SK-GFR) [33]. Recently the assessment of the ratio of kidney volume to function (PV:SK-GFR) by MRI scanning has demonstrated that patients with a high ratio and significant ARVD are significantly more likely to have renal functional benefit from revascularization compared to those with low PV:SK-GFR [34].

We hypothesise that the above findings are explained by a disproportionately low GFR for a given PV being reflective of a reduced plasma flow caused by a functionally significant stenosis. Further insights are gleaned from the finding that chronically ischaemic kidneys have higher renal vein oxygen saturations when compared to non stenosed contralateral kidneys. This could suggest that

oxygen uptake is more reduced than renal blood flow in these situations, but whether this is a cause or effect of renal injury is unknown [35]. BOLD provides measurements that correlate with tissue deoxyhaemoglobin levels. Although this is not a specific marker for renal ischaemia in AVRD, it provides reproducible data in both native kidneys and allografts and provides both structural and functional information. Studies have demonstrated BOLD imaging can distinguish between potentially viable kidneys with ARVD (>70% stenosis) and non-viable kidneys [36], and there is hope that BOLD imaging may help in selecting patients most likely to benefit from revascularization. Until then, assessments of parenchymal or cortical volume in relation to individual kidney function in kidneys with RAS may help clinicians in the decision making process, especially when the clinical presentation is not compelling in favour of intervention.

### 1.4.11 Incidental ARVD

Vascular disease is a systemic process and significant ARVD is highly prevalent in those patients undergoing investigations for disparate disease (e.g. for CAD and PVD). Between 15% and 29% of patients being investigated by coronary angiography have ARVD discovered, with 5% of the total number having bilateral disease [37]. The incidence is even higher in patients being investigated for lower limb arterial disease or aortic disease, with around 40% of patients being found to have significant ARVD [38]. Retrospective data has shown incidental ARVD in the setting of PVD to be a significant, independent, predictor for mortality, though this does not inform us as to whether it is a cause or marker of poor outcomes [39].

The justification for further assessment and treatment of incidentally discovered RAS has little evidence-based support. In one retrospective case review in which 124 patients noted to have ARVD during an alternative angiographic procedure underwent formal imaging of the renal vessels this demonstrated a >70% stenosis in 78 patients. Of these, 58 underwent percutaneous revascularization (38 followed up for 12 months). Renal function did not significantly alter between the groups, and the suggestion that revascularization may have improved blood pressures was only noted in the group who underwent increases in pharmacotherapy [40].

The strongest evidence again derives from ASTRAL. Many of the 806 patients within the study were asymptomatic, and it is likely that a high proportion of cases were incidentally diagnosed. The results clearly showed that unselected revascularization for patients with RAS in whom there were no compelling clinical reasons for intervention provided no overall health benefit. Therefore, in the absence of other indications, we would view incidental ARVD as an indication for standard medical therapy, not revascularization.

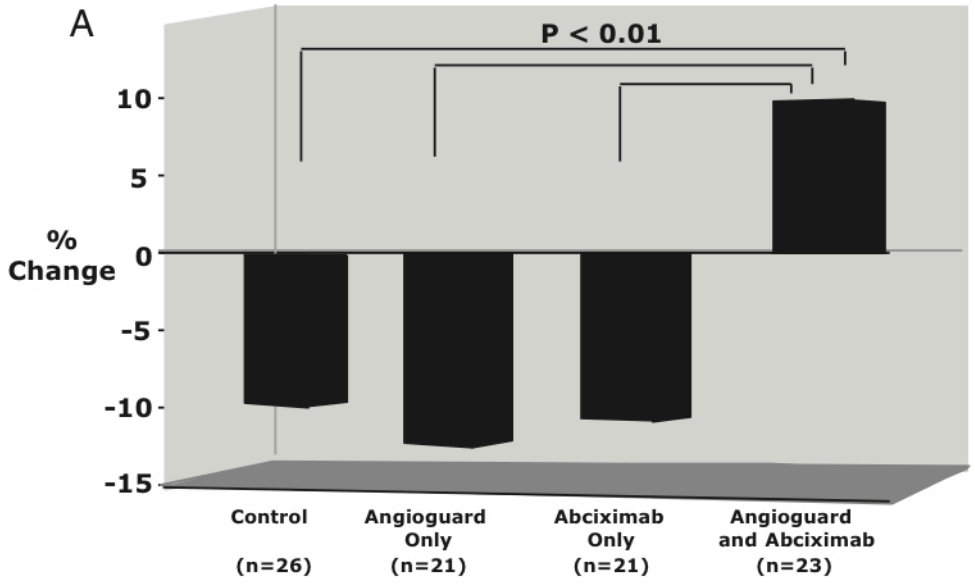
### 1.4.12 Complications of renal artery revascularization

When recommending any interventional procedure, one must balance the risks and benefits for the individual patient. The technical success of renal revascularization by percutaneous angioplasty and stenting is high with initial angiographic success of 94 -100% [41]. This applies irrespective of whether the definition for success is a post-revascularization residual stenosis of <10% or <50%. However, renal artery revascularization is not without complications. Even in the experienced hands of the skilled operator, almost 3% of patients have a major vascular complication and meta-analysis suggests an overall mortality of 1% [41]. In ASTRAL there was a 6.8% risk of serious adverse events in patients receiving intervention [1]. Lesser complications such as groin haematoma, puncture site trauma or minor renal dysfunction associated with contrast agents are much more common at up to 10% [41].

An additional issue that must be considered is the long term procedural success. In one study of follow up with duplex ultrasound following renal intervention, restenosis free survival was 50% at twelve months and 40% at eighteen months [42]. Further, use of drug eluting stents may improve long term patency but they have not been validated to the extent that has occurred with their use in treatment of CAD [43]. Another measure which must be considered is how best to utilize anti-platelet agents. Aspirin has a historical perspective in treatment of ARVD, and most RCTs allow anti-platelet use in line with local policy. This lack of standardization may confound some of the published data and warrants further consideration when future trials are designed.

There is also developing interest in the use of embolic protection devices (EPDs) to accompany stenting, aiming to capture the atheromatous fragments which may be dislodged during the procedure and cause subsequent downstream occlusions and parenchymal damage. Complete EPDs capture more of this debris, but have not demonstrated superior results to partial devices [44]. Some prospective trials have suggested that EPD use is more likely to lead to improved renal function post-procedure [45], however this is not a consistent finding and some results suggest EPD in conjunction with glycoproteinIIb/IIIa inhibition may be a superior approach [46]. Theoretically here, the EPD collects large particles, whilst the glycoprotein inhibitor attenuates the effects of the particles too fine to be trapped figure 1.4.4. A proportion of patients in CORAL have used EPDs and this may add further information.

**Figure 1.4.4** - Percentage change in eGFR following percutaneous renal artery revascularization between controls, EPD alone, abciximab alone and EPD with abciximab




*Reproduced from Cooper et al [46] with permission*

Conclusions

In conclusion, despite a landmark randomized control trial, decisions to undertake revascularization in certain clinical presentations of ARVD remain contentious. Definitive advice to revascularize patients is still largely based upon consensus opinion. ASTRAL has helped steer clinicians away from undertaking carte blanche intervention in those patients with RAS and stable CKD, moderate hypertension and especially in largely asymptomatic patients or those with incidentally discovered disease. This is highly important given the significant risks that can accompany revascularization. However, some patients undoubtedly benefit from revascularization and more investigation is merited to help identify the patient sub-sets who will potentially benefit.

Currently, compelling support for renal revascularization is apparent when high-grade RAS co-exists with:

- Severe or dialysis dependent AKI
- acute pulmonary edema
- patients with very resistant hypertension
- facilitation of RAAS blockade in patients who need therapy but in whom renal functional intolerance is present

Other potential areas merit further study. Most clinicians would feel uncomfortable not intervening in a patient with RAS and rapidly declining renal function, and until a possible meta-analysis of STAR, ASTRAL and CORAL is available, this remains a reasonable rationale for revascularization. Further information from ASTRAL and RASCAD on the effects of revascularization on cardiac structure and function will be available in the near future, but until then, and until a randomized trial on the clinical effects of intervention on RAS in CCF is undertaken, revascularization for chronic heart failure has little evidence base.

Most new data over the next few years will likely address the role of biomarkers in patient selection, or the issue of determining which kidneys have hibernating parenchyma associated with functionally significant stenoses. Available evidence does not support revascularization based on stenosis severity, but in the future we will learn more about the importance of renal volumes and how to

select patients who have not yet developed downstream irreversible renal parenchymal damage.

The final message is that screening for ARVD in asymptomatic CKD patients or in those with treatable hypertension will add little to their care and only increase therapeutic uncertainty.

## References


1. ASTRAL Investigators, Wheatley K, Ives N, et al. Revascularization versus medical therapy for renal-artery stenosis. *N Engl J Med*. 2009;361(20):1953–1962.

2. Kalra PA, Guo H, Gilbertson DT, et al. Atherosclerotic renovascular disease in the United States. *Kidney International*. 2009;77(1):37–43.

3. Hansen KJ, Edwards MS, Craven TE, et al. Prevalence of renovascular disease in the elderly: A population-based study. *Journal of Vascular Surgery*. 2002;36(3):443–451.

4. Farrington K, Udayaraj U, Gilg J, Feehally J. UK Renal Registry 11th Annual Report (December 2008): Chapter 3 ESRD incident rates in 2007 in the UK: national and centre-specific analyses. *Nephron Clin Pract*. 2009;111 Suppl 1:c13–41.

5. Chrysochou C, Kalra PA. Epidemiology and Natural History of Atherosclerotic Renovascular Disease. *Progress in Cardiovascular Diseases*. 2009;52(3):184–195.

6. Plouin PF, Chatellier G, Darné B, Raynaud A. Blood pressure outcome of angioplasty in atherosclerotic renal artery stenosis: a randomized trial. Essai Multicentrique Medicaments vs Angioplastie (EMMA) Study Group. *Hypertension*. 1998;31(3):823–829.

7. 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. *N Engl J Med*. 2000;342(14):1007–1014.

8. Webster J, Marshall F, Abdalla M, et al. Randomised comparison of percutaneous angioplasty vs continued medical therapy for hypertensive patients with atheromatous renal artery stenosis. Scottish and Newcastle Renal Artery Stenosis Collaborative Group. *J Hum Hypertens*. 1998;12(5):329–335.

9. Ives NJ, Wheatley K, Stowe RL, et al. Continuing uncertainty about the value of percutaneous revascularization in atherosclerotic renovascular disease: a meta-analysis of randomized trials. *Nephrol Dial Transplant*. 2003;18(2):298–304.

10. Bax L, Woittiez A-JJ, Kouwenberg HJ, et al. Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function: a randomized trial. *Ann Intern Med*. 2009;150(12):840–8.

11. Silva JA, Chan AW, White CJ, et al. Elevated brain natriuretic peptide predicts blood pressure response after stent revascularization in patients with renal artery stenosis. *Circulation*. 2005;111(3):328–333.

12. Wiese S, Breyer T, Dragu A, et al. Gene expression of brain natriuretic peptide in isolated atrial and ventricular human myocardium: influence of angiotensin II and diastolic fiber length. *Circulation*. 2000;102(25):3074–3079.

13. 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. *Nephrol Dial Transplant*. 2012;27(4):1403-9

14. Hackam DG, Duong-Hua ML, Mamdani M, et al. Angiotensin inhibition in renovascular disease: a population-based cohort study. *American Heart Association*. 2008;156(3): 549–555.

15. Tobe SW, Atri M, Perkins N, Pugash R, Bell CM. Renal athersosclerotic revascularization evaluation (RAVE study): study protocol of a randomized trial [NCT00127738]. *BMC Nephrol*. 2007;8:4.

16. Khosla S, Ahmed A, Siddiqui M, et al. Safety of angiotensin-converting enzyme inhibitors

in patients with bilateral renal artery stenosis following successful renal artery stent revascularization. *Am J Ther*. 2006;13(4):306–308.

17. Cooper C, Murphy T, Matusumoto A, et al. Stent revascularization for the prevention of cardiovascular and renal events among patients with renal artery stenosis and systolic hypertension: Rationale and design of the CORAL trial. *American Heart Association*. 2006;152(1):59–66.

18. Suresh M, Laboi P, Mamtora H, Kalra PA. Relationship of renal dysfunction to proximal arterial disease severity in atherosclerotic renovascular disease. *Nephrol Dial Transplant*. 2000;15(5):631–636.

19. Chrysochou C, Sinha S, Chalmers N, Kalra PR, Kalra PA. Anuric acute renal failure and pulmonary oedema: a case for urgent action. *Int J Cardiol*. 2009;132(1):e31–3.

20. Dwyer KM, Vrazas JI, Lodge RS, et al. Treatment of acute renal failure caused by renal artery occlusion with renal artery angioplasty. *Am J Kidney Dis*. 2002;40(1):189–194.

21. Muray S, Martín M, Amoedo ML, et al. Rapid decline in renal function reflects reversibility and predicts the outcome after angioplasty in renal artery stenosis. *Am J Kidney Dis*. 2002;39(1):60–66.

22. Pontremoli R, Rampoldi V, Morbidelli A, Fiorini F, Ranise A, Garibotto G. Acute renal failure due to acute bilateral renal artery thrombosis: successful surgical revascularization after prolonged anuria. *Nephron*. 1990;56(3):322–324.

23. Thatipelli M, Misra S, Johnson CM, et al. Renal artery stent placement for restoration of renal function in hemodialysis recipients with renal artery stenosis. *J Vasc Interv Radiol*. 2008;19(11):1563–1568.

24. Wright JR, Shurrab AE, Cooper A, Kalra PR, Foley RN, Kalra PA. Left ventricular morphology and function in patients with atherosclerotic renovascular disease. *J Am Soc Nephrol*. 2005;16(9):2746–2753.

25. McMahon CJ, Hennessy M, Boyle G, Feely J, Meaney JFM. Prevalence of renal artery stenosis in flash pulmonary oedema: determination using gadolinium-enhanced MRA. *Eur J Intern Med*. 2010;21(5):424–428. doi:10.1016/j.ejim.2010.04.003.

26. Gray BH, Olin JW, Childs MB, Sullivan TM, Bacharach JM. Clinical benefit of renal artery angioplasty with stenting for the control of recurrent and refractory congestive heart failure. *Vasc Med*. 2002;7(4):275–279.

27. 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. *J Vasc Interv Radiol*. 2006;17(9):1383–97.

28. MacDowall P, Kalra PA, O'Donoghue DJ, Waldek S, Mamtora H, Brown K. Risk of morbidity from renovascular disease in elderly patients with congestive cardiac failure. *The Lancet*. 1998;352(9121):13–16.

29. Marcantoni C, Zanoli L, Rastelli S, et al. Stenting of renal artery stenosis in coronary artery disease (RAS-CAD) study: a prospective, randomized trial. *J Nephrol*. 2009;22(1): 13–16.

30. Conlon PJ, Little MA, Pieper K, Mark DB. Severity of renal vascular disease predicts

mortality in patients undergoing coronary angiography. *Kidney International*. 2001;60(4): 1490–1497.

31. Conlon PJ, Crowley J, Stack R, et al. Renal artery stenosis is not associated with the development of acute renal failure following coronary artery bypass grafting. *Ren Fail*. 2005;27(1):81–86.

32. Tuttle KR. Renal parenchymal injury as a determinant of clinical consequences in atherosclerotic renal artery stenosis. *Am J Kidney Dis*. 2002;39(6):1321–1322.

33. Cheung CM, Shurrab AE, Buckley DL, et al. MR-derived renal morphology and renal function in patients with atherosclerotic renovascular disease. *Kidney International*. 2006;69(4):715–722.

34. Cheung CM, Chrysochou C, Shurrab AE, Buckley DL, Cowie A, Kalra PA. Effects of renal volume and single-kidney glomerular filtration rate on renal functional outcome in atherosclerotic renal artery stenosis. *Nephrology Dialysis Transplantation*. 2010;25(4): 1133–1140.

35. Nielsen K, Rehling M, Henriksen JH. Renal vein oxygen saturation in renal artery stenosis. *Clin Physiol*. 1992;12(2):179–184.

36. Textor SC, Glockner JF, Lerman LO, et al. The Use of Magnetic Resonance to Evaluate Tissue Oxygenation in Renal Artery Stenosis. *Journal of the American Society of Nephrology*. 2008;19(4):780–788.

37. Khosla S, Kunjummen B, Manda R, et al. Prevalence of renal artery stenosis requiring revascularization in patients initially referred for coronary angiography. *Cathet Cardiovasc Intervent*. 2003;58(3):400–403.

38. Olin JW, Melia M, Young JR, Graor RA, Risius B. Prevalence of atherosclerotic renal artery stenosis in patients with atherosclerosis elsewhere. *Am J Med*. 1990;88(1N):46N–51N.

39. Mui K-WK, Sleeswijk MM, van den Hout HH, van Baal JJ, Navis GG, Woittiez A-JA. Incidental renal artery stenosis is an independent predictor of mortality in patients with peripheral vascular disease. *J Am Soc Nephrol*. 2006;17(7):2069–2074.

40. Suliman A, Imhoff L, Greenberg JI, Angle N. Renal stenting for incidentally discovered renal artery stenosis: is there any outcome benefit? *Ann Vasc Surg*. 2008;22(4):525–533.

41. Leertouwer TC, Gussenhoven EJ, Bosch JL, et al. Stent placement for renal arterial stenosis: where do we stand? A meta-analysis. *Radiology*. 2000;216(1):78–85.

42. Corriere MA, Edwards MS, Pearce JD, Andrews JS, Geary RL, Hansen KJ. Restenosis after renal artery angioplasty and stenting: incidence and risk factors. *J Vasc Surg*. 2009;50(4):813–819.

43. Zähringer M, Sapoval M, Pattynama PMT, et al. Sirolimus-eluting versus bare-metal low-profile stent for renal artery treatment (GREAT Trial): angiographic follow-up after 6 months and clinical outcome up to 2 years. *J Endovasc Ther*. 2007;14(4):460–468.

44. Kanjwal K, Haller S, Steffes M, et al. Complete versus partial distal embolic protection during renal artery stenting. *Cathet Cardiovasc Intervent*. 2009;73(6):725–730.

45. Holden A, Hill A, Jaff MR, Pilmore H. Renal artery stent revascularization with embolic protection in patients with ischemic nephropathy. *Kidney International*. 2006;70(5):948–955.

46. Cooper CJ, Haller ST, Colyer W, et al. Embolic protection and platelet inhibition during renal artery stenting. *Circulation*. 2008;117(21):2752–2760.

47. Weatherford DA, Freeman MB, Regester RF, Serrell PF, Stevens SL, Goldman MH. Surgical management of flash pulmonary edema secondary to renovascular hypertension. *Am J Surg*. 1997;174(2):160–163.

48. Messina LM, Zelenock GB, Yao KA, Stanley JC. Renal revascularization for recurrent pulmonary edema in patients with poorly controlled hypertension and renal insufficiency: a distinct subgroup of patients with arteriosclerotic renal artery occlusive disease. *J Vasc Surg*. 1992;15(1):73–80.

49. Pickering TGT, Herman LL, Devereux RBR, et al. Recurrent pulmonary oedema in hypertension due to bilateral renal artery stenosis: treatment by angioplasty or surgical revascularisation. *Lancet*. 1988;2(8610):551–552.

50. Bloch MJ, Trost DW, Pickering TG, Sos TA, August P. Prevention of recurrent pulmonary edema in patients with bilateral renovascular disease through renal artery stent placement. *Am J Hypertens*. 1999;12(1 Pt 1):1–7.

51. 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(3):813–820..

52. Missouris CG. “Apparent” heart failure: a syndrome caused by renal artery stenoses. *Heart*. 2000;83(2):152–155.

53. Khosla S, White CJ, Collins TJ, Jenkins JS, Shaw D, Ramee SR. Effects of renal artery stent implantation in patients with renovascular hypertension presenting with unstable angina or congestive heart failure. *Am J Cardiol*. 1997;80(3):363–366.

54. Meissner M. Renal artery stenosis in heart failure. *Am J Cardiol*. 1988;62(17):1307–1308.

# CHAPTER 2 - AIMS AND OBJECTIVES OF THIS RESEARCH PROJECT

Important knowledge gaps exist in the ARVD literature. As this research project is based on analysis of established cohort data (described in detail in Chapter 3), research questions that would maximise the value of these resources were identified.

The first questions relate to patient outcomes in ARVD. Previous studies that have considered prognosis in patients with ARVD have used the general population as a referent group and only adjusted crudely for the presence of CKD. Given the increased risks for death and dialysis seen in patients with renal impairment of any cause, it cannot be assumed that ARVD has the same prognostic relevance in the context of CKD. This issue is relevant as many of the studies that describe patient benefit from PTRAS have been performed in populations with relatively preserved renal function, and the 'negative' RCT performed in patients with more advanced CKD.

The second aspect of the question of prognosis in ARVD relates to clinical presentation. International guidelines support PTRAS for selected phenotypes (often designed '*high-risk*' presentations) of ARVD. However the evidence base for doing so is weak and there is a lack of evidence that these presentations are actually associated with a worse clinical outcome. Hence the first two objectives of this project are to:

1 To define the prognostic significance of ARVD in comparison with other causes of CKD.
*Null hypothesis ($H_0$) - The presence of ARVD does not confer a worse prognosis than other causes of CKD.*

2 To consider if clinical phenotype has a relationship with prognosis or response to percutaneous revascularization in ARVD.
*$H_0$ - Clinical presentation of ARVD is not associated with a difference in outcome or treatment response.*

A further knowledge gap relates to identification of ARVD patients with the greatest risk for progression to ESKD. In ASTRAL the observed annual rate of loss of renal function was approximately 10 times slower than had been expected based on previous data. As the primary study end-point related to loss of renal function, this may have masked any benefit from revascularisation. The importance of this is dependent on whether all ARVD patients have a similar risk for progression to ESKD or if certain patients have an increased risk. Hence the third objective of this project is to describe the characteristics of ARVD patients who progress to ESKD and:

| | |
|---|---|
| 3 | To develop a risk stratification system to allow early identification of ARVD patients with the greatest risk for progression to end stage kidney disease.<br>*$H_0$ - Risk for progression to ESKD in ARVD cannot be predicted.* |

The final identified research question relates to medical therapy in ARVD. Beyond angiotensin blockade and statin use, data regarding other drug therapies is limited, with substantial variation existing in medications usage between RCT. As rates of PTRAS for ARVD have fallen since ASTRAL it is imperative optimal medical therapy is accurately defined to standardise and improve patient care. The fourth aim of this project is therefore:

| | |
|---|---|
| 4 | To improve the evidence as to what constitutes optimal medical therapy in ARVD.<br>*$H_0$ - Prognosis in ARVD is not affected by pharmacotherapy.* |

A final theme of this project, found in each results chapter, is to explore alternative statistical methodologies beyond the standard regression models commonly applied to cohort studies. The aim of this is to limit confounding, and provide results that are both statistically accurate and clinically meaningful.

As this thesis is presented in the alternative format, the aim of each results chapter, and it's position in relation to these aims and objectives, is restated at the start of each chapter.

# CHAPTER 3 - METHODOLOGY

Preface

This chapter describes the cohort studies analysed in each results chapter. As this thesis is presented in the alternative format, sections of this chapter will overlap with the methods text in the results chapters. This chapter, however, provides a greater level of detail regarding study design and conduct, ethical approval, data capture and event verification.

As a range of analytical approaches have been used throughout this thesis, this chapter provides a summary of the most commonly used statistical methodologies. Descriptions of analyses specific to each chapter are presented in the methods section of that chapter.

## 3.1 Ethical Approval and Funding

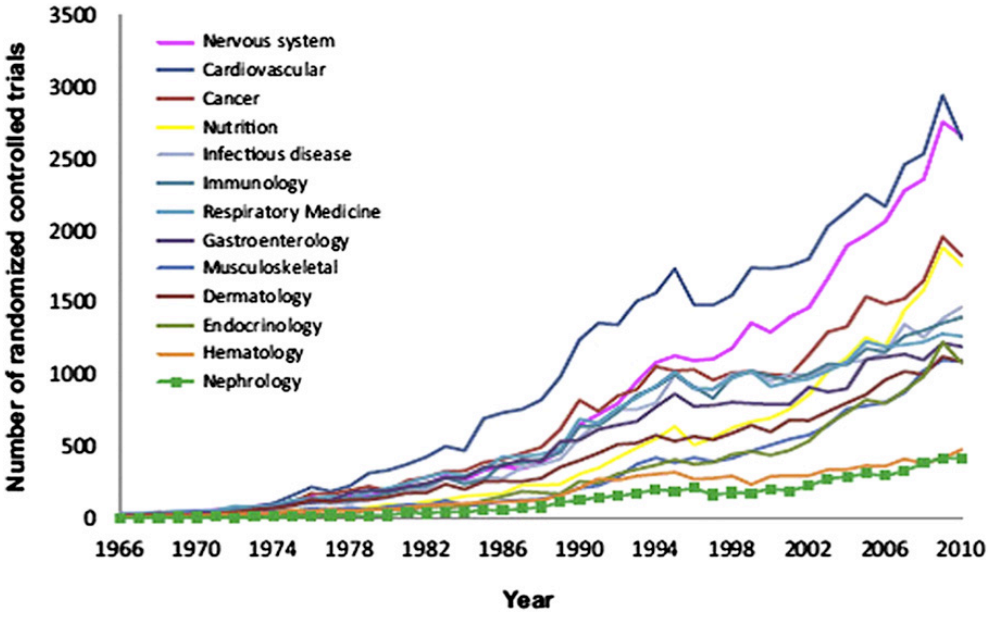
Data for this thesis have been obtained from two studies both of which have received approval from the Wrightington Wigan and Leigh Research Ethics Committee. These studies are the Salford Renovascular Databases (SRVD), REC 07/Q1410/33, and the Chronic Renal Insufficiency Standards Implementation Study (CRISIS), REC 05/Q1404/187.

Funding support for this work has been received from the Renal Research Fund (Salford Royal NHS Foundation Trust).

## 3.2 Rationale for the SRVD and CRISIS

RCT can provide the highest quality of evidence but have historically been under-represented in nephrology compared to other medical specialties, figure 3.1 [1]. As a consequence, practice has often been dictated by trials performed in the general population or by robust observational studies. The SRVD and CRISIS were established to provide a board range of longitudinal patient level phenotypic data that could be interrogated to accurately describe the natural history of patients with ARVD and CKD. These studies have led to publications relating to the use of statin therapy and angiotensin blockade in ARVD [2,3] and factors affecting progression of CKD [4,5].

**Figure 3.1** - Number of randomized controlled trials performed in nephrology and 12 other specialities of internal medicine




*Reproduced from Samuels et al [1]*

## 3.3 Study design, inclusion and exclusion criteria

### *3.3.1 Salford Renovascular Database*

The Salford Renovascular Database is an open-ended prospective observational study of outcomes in ARVD. The study was established in 1995 with recruitment ongoing since this point (969 patients recruited as of December 2013). Screening is performed by electronically identifying all patients referred for MRA, CTA or renal digital subtraction angiography. Patients are recruited from Salford Royal NHS Foundation Trust although diagnostic imaging may have occurred at a different site. All patients with a new diagnosis of ARVD are considered for enrollment into the SRVD. Patients are approached by their normal health-care provider and provided with an approved patient information sheet. After a minimum period of 24 hours (usually 1 to 3 months) informed consent is taken from those prepared to participate by an appropriately trained research doctor. Due to the observational nature of the SRVD, participation is not affected by enrollment to other clinical trials.

*Inclusion criteria*

- Atherosclerotic renal artery stenosis of any degree unilaterally or bilaterally
- Age over 18-years
- Able to provide informed consent

*Exclusion criteria*

- Non-atheromatous RAS (fibromuscular disease, vasculitic or other)

### *3.3.2 Chronic Renal Insufficiency Standards Implementation Study*

The Chronic Renal Insufficiency Standards Implementation Study is an open-ended prospective observational study of outcome in a referred non-dialysis CKD population (2728 patients recruited as of December 2013). The study was established in 2002 with recruitment ongoing since this point. Screening for recruitment is performed on patients attending nephrology clinics at Salford Royal NHS Foundation Trust. The approach to recruitment is as for the SRVD with the addition of specifically trained research nurses aiding in obtaining information consent.

*Inclusion criteria*

- Referred for or under follow up for management of CKD
- Non-dialysis CKD
- Age over 18 years
- Able to provide informed consent

*Exclusion criteria*

- Expectation of death or progression to dialysis within six-months of recruitment
- Treatment with maintenance hemodialysis or CKD due to failing kidney transplant

## 3.4 Recorded information

### *3.4.1 Salford Renovascular Database*

Information are collected at enrollment and then annually as follows:

- Demographic information (age, gender, ethnicity).
- Clinical presentation and recruitment to any RCT of ARVD.
- Angiographic information (type and date of study, degree of renal artery stenosis, revascularization procedures and clinical indication).
- Co-morbid data (macrovascular history, diabetic status, smoking history).
- Medication data (number and type of anti-hypertensive medications, use of anti-platelet and statin therapy).
- Blood pressure (mean value of two readings taken seated after 5 minutes of rest).
- Laboratory data (creatinine, proteinuria, total cholesterol).

### *3.4.2 Chronic Renal Insufficiency Standards Implementation Study*

Information are collected at enrollment and then annually as follows:

- Demographic information (age, gender, ethnicity, height, weight, employment status, marital status, functional status)
- Coded primary cause of CKD
- Co-morbid data (macrovascular disease history, history of heart failure, diabetic status, smoking status, alcohol consumption)
- Medication data (number and type of anti-hypertensive medications, use of anti-platelet and statin therapy are all coded for. All other prescribed medications are recorded in free text form).

- Blood pressure (mean value of two readings taken seated after 5 minutes of rest).
- Laboratory data (full renal profile, cholesterol profile, inflammatory markers, haemoglobin and haematinics, proteinuria, stored samples for future DNA and biomarker analyses).

### *3.4.3 Sources of information*

All records are updated annually by trained clinicians or research nurses. Information are obtained using a structured data collection pro-forma with reference to clinical records where appropriate.

## 3.5 Patient management

Patient management is not altered by recruitment to either the SRVD or to CRISIS. All patients are treated in line with contemporaneous national and international guidelines [6-8]. Revascularisation procedures in the SRVD have been performed for indications defined by published guidelines [8] or due to recruitment to a randomised trial [9,10]. In all cases percutaneous angioplasty with bare metal stenting has been performed. No cases of surgical revascularisation are included. Revascularisation procedures have not been documented on an intention to treat basis. Technical success of revascularisation is defined in line with international standards for practice as a residual stenosis of <30% or a trans-lesional pressure gradient of less than 10mmHg [11].

### *3.5.1 Impact on patient care*

Although direct management is not affected by recruitment to either study annual visits are longer to allow complete data collection and any supplementary investigations specified below. All additional laboratory tests are performed synchronously with routine clinic bloods to mitigate the need for additional venesection. Both studies have been regularly discussed with the Hope Kidney Patient Association and their views addressed. Alternations to the study protocols are again discussed with patient representatives and recruited patients are informed of any changes both in writing and verbally at their next study visit.

### *3.5.2 Data protection*

All researchers are trained in Good Clinical Practice and renew this training on at least a three yearly basis. Patient data are handled in accordance with the Data Protection Act of 1998 and the University of Manchester Data Protection Policy as required by the Code of Research Conduct (http://documents.manchester.ac.uk/display.aspx?DocID=2804). Patients are assigned a study identifier that is only linked to their NHS number. Any laboratory samples processed at a site other than Salford Royal NHS Foundation Trust are only labeled with their study identifier.

## 3.6 Event definition and verification

### *3.6.1 Death*

Cause and date of death were obtained from electronic patient records or contact with primary care providers. Verification of these data was made using data obtained from the Office for National Statistics.

### *3.6.2 Renal Replacement Therapy and End Stage Kidney Disease*

In the SRVD and in CRISIS the date of initiation of chronic renal replacement (RRT) therapy, defined as start of haemodialysis, peritoneal dialysis or transplantation is recorded. All case records were reviewed to ensure all chronic RRT events were and to verify that no episodes of acute dialysis were coded as chronic RRT (eight cases identified in the SRVD, six cases identified in CRISIS).

There are no published UK data to describe the proportion of patients who opt for supportive care in preference to RRT. In Australia a ratio of approximately 1:1 exists [12]. As this would represent a patient group in whom kidney disease had progressed to the same point as those who opted to commence e.g. dialysis, a composite end-point of ESKD was defined. This included patients commencing RRT and patients with an eGFR <10ml/min/1.73m$^2$ who did not commence RRT. An eGFR of <10ml/min/1.7m$^2$ was selected as being representative of the median eGFR beneath which dialysis is commenced in the United Kingdom [13] and consistent with European consensus opinion on when dialysis treatment should be initiated [14]. To identify the date of first eGFR <10ml/min/1.73m$^2$, all available laboratory data were reviewed to identify the first recorded date of eGFR <10 ml/min/1.73m$^2$. To ensure that AKI were not included in this definition, a second out-

patient eGFR value <10 ml/min/1.73m$^2$ or an eGFR trajectory consistent with progressive loss of renal function was required to assign a label of ESKD.

### *3.6.3 Cardiovascular Events*

In the SRVD the date and type of the first recorded cardiovascular event after diagnosis is recorded as a pre-specified end-point. In CRISIS cardiovascular event data are updated on an annual basis however date values are not recorded. As such cardiovascular event data within the SRVD were considered in Cox regressions, and in CRISIS were considered in logistic regressions. Cardiovascular events were defined as:

- Myocardial infarction or acute coronary syndrome
- New onset angina pectoris
- Coronary revascularisation procedure for known angina pectoris
- Hospitalisation for pulmonary oedema or arrhythmia
- Stoke (ischaemic or haemorrhagic)
- Transient ischaemic attack

For all patients, case records were reviewed to verify documented events and to identify any further events. Where possible events were verified by clinical records – cardiac enzyme rise, electrocardiogram or chest X-ray changes for coronary events, neurological imaging for stroke and procedural records for revascularisation procedures. When these data were not available due to events being treated at a different hospital, coded diagnoses on clinical letters were utilised. These were verified by reference to primary care records.

## 3.7 Laboratory Analyses

Standard biochemical and haematological parameters are recorded from samples processed at clinic visits. All blood samples are collected by trained phlebotomy, nursing or medical staff.

### *3.7.1 Renal function*

Since 12th June 2007 all measurements of serum creatinine have been performed in a standardized manner on a Roche Modular P analyzer using a blank rated and compensated Jaffe reaction. Results are aligned to the Isotope Dilution Mass Spectrometry (IDMS) method. These measurements are subject to internal quality control and participation in the National External Quality Assessment Scheme. Prior to this measurements were made using using an uncompensated kinetic Jaffe method on Roche Integra and Modular P analyzers. An offset of -18µmol/L was applied to these measurements to account for reaction due to non-creatinine chromogens and standardize creatinine values between time periods [15]. Based on the standardized serum creatinine values, the CKD Epidemiology Collaboration (CKD-EPI) equation [16] was used to generate validated estimates of GFR values using the formula:

$$
\begin{aligned}
eGFR = \quad & 141 \times \min\left(\frac{sCr}{\kappa}, 1\right)^{\propto} \\
& \times \max\left(\frac{sCr}{\kappa}, 1\right)^{-1.209} \\
& \times 0993^{Age} \\
& \times 1.018\ [if\ female] \\
& \times 1.159\ [if\ black]
\end{aligned}
$$

Where sCr = serum creatinine in mg/dL (calculated as µmol/L/88.4), α = -0.329 if female and -0.411 if male, κ = 0.7 if female and 0.9 if male; min = the minimum of sCr/ κ or 1 and max = the maximum of sCr/ κ or 1.

The CKD-EPI formula was chosen in preference to the 4-variable MDRD equation as the majority of patients in the SRVD and CRISIS had an eGFR in excess of 30ml/min/1.73m$^2$ at baseline and the CKD-EPI formula has been shown less likely to misclassify patients with higher measured GFR values as having low eGFR values [17].

### *3.7.2 Proteinuria*

Measurement of proteinuria has changed over the lifetime of the SRVD and CRISIS. Prior to October 2006 measurement of 24-hour urinary protein was routine local practice with spot urine protein creatinine ratios adopted from this point. To standardize values, spot measurements were converted into 24-hour values by dividing the concentration of protein by the concentration of creatinine. This approach has been shown to provide well correlated results where eGFR is in excess of 15ml/min/1.73m$^2$ [18]. Where urine creatinine concentrations were not reported, age and gender appropriate population average values were substituted [19].

### *3.7.3 Additional samples*

In addition to routinely measured parameters patients in each study provide a single sample of deoxyribonucleic acid (DNA) and baseline and annual plasma and serum samples (maximum 15ml). DNA samples are taken to the Clinical Sciences Building at Salford Royal NHS Foundation Trust on the day of collection for storage. Samples are labeled by study identifier and transferred in batches to the Centre for Integrated Genomics Medical Research at the University of Manchester for DNA extraction. Serum and plasma samples are transferred to the Clinical Sciences Building at Salford Royal NHS Foundation Trust within four hours of being taken and frozen at -80$^{O}$C in the Salford Biological Repository. Responsibility for the care of these samples lies with the renal department at Salford Royal NHS Foundation Trust.

### *3.7.4 Investigations specific to CRISIS*

In addition to the above samples, patients recruited to CRISIS are invited to participate in evaluation of arterial stiffness. This is assessed using a Syphgmocor or Vicorder device by measurement of pulse wave velocity and augmentation index.

## 3.8 Summary of Statistical Methodology

All statistical analyses have been performed in SAS version 9.2 (SAS Institute, Cary, NC) under license to the University of Manchester or in R version 3.0.1 (http://www.R-project.org). As this thesis is presented in the alternative format detailed information of the methodology used for each analysis is presented within the relevant results chapter. A summary of the most commonly used techniques is given below.

Continuous data were visualized using scatterplots, histograms and quantile-quantile plots to identify outlying data points and to assess the distribution of the data. Where a non-parametric distribution existed either a non-parametric methodology was used in analysis or a transformation applied to approximate normality (natural log transformation for positively skewed data, square-root or natural log transformation for negatively skewed data). Parametric continuous data are presented as mean±standard deviation, non-transformed non-parametric data are presented as median [interquartile range] and categorical data as number [percentage]. Continuous data were compared between groups using either ANOVA or t-test and categorical data compared using Chi-squared test.

Survival analyses were performed using Cox proportional hazards regression with results presented as hazard ratio (HR) with 95% confidence interval (CI) in brackets. In all cases proportionality of hazard was initially assessed visually using Kaplan-Meier curves. For the final model a test of proportionality was applied to the log-time interaction variables to assess $H_0$, proportional risk, versus $H_1$, non-proportional risk. Here a non-significant alpha value was taken as evidence that the null hypothesis was not rejected and proportionality accepted. In addition, for the SRVD, the effect of year of diagnosis of ARVD (grouped into 1995-2000; 2000-2005 and 2005 onwards) was also considered as an interaction term with the independent variables in exploratory Cox regressions. In all cases the alpha value was non-significant. This was taken as evidence that year of angiography did not influence the effect of the independent variable on outcome. Results of Cox regressions are presented as hazard ratio [95% confidence interval]. Where appropriate, these analyses are complimented by presentation of absolute event rates and relative risk for event. Event rates were manually

calculated and presented as number of events per 100 patient-years follow-up. Relative risk for events was calculated in a Poisson regression.

Details of any other novel statistical methodologies are provided in the relevant results chapters. Unless otherwise specified statistical significance was defined as an alpha value of <0.05.

**Table 3.1** - Interaction of time with event free survival in relation to renal artery revascularisation

| | Parameter estimate | Standard error | p |
|---|---|---|---|
| | | **Death** | |
| **1995 - 2000** | | *Referent* | |
| **2000 - 2005** | 0.56 | 0.32 | 0.18 |
| **2005 - 2010** | -0.07 | 0.44 | 0.87 |
| | | **End stage kidney disease** | |
| **1995 - 2000** | | *Referent* | |
| **2000 - 2005** | 0.26 | 0.60 | 0.66 |
| **2005 - 2010** | 1.02 | 0.58 | 0.08 |
| | | **Cardiovascular event** | |
| **1995 - 2000** | | *Referent* | |
| **2000 - 2005** | 1.68 | 1.13 | 0.14 |
| **2005 - 2010** | 1.80 | 1.12 | 0.10 |

*Table shows parameter estimates (adjusted for patient age, estimated glomerular filtration rate, blood pressure and degree of proteinuria) for the effect on year of diagnosis of ARVD on risk for outcome in relation to percutaneous renal artery revascularisation. Where results do not reach statistical significance this is taken as evidence that risk for outcome is not related to year of diagnosis.*
*Cardiovascular event defined as myocardial infarction / acute coronary syndrome; hospitalisation for pulmonary edema or dysrhythmia; stroke or transient ischaemic attack; new onset of symptomatic angina or deterioration of existing angina requiring interventional procedure.*
*End stage kidney disease defined as initiation of chronic renal replacement therapy, transplantation or estimated glomerular filtration rate <10ml/min/1.73m$^2$*

## Chapter 3


1. Samuels JA, Molony DA. Randomized controlled trials in nephrology: state of the evidence and critiquing the evidence. *Advances in Chronic Kidney Disease*. 2012;19(1): 40–46.

2. Cheung CM, Patel A, Shaheen N, et al. The Effects of Statins on the Progression of Atherosclerotic Renovascular Disease. *Nephron Clin Pract*. 2007;107(2):c35–c42.

3. 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. *Nephrol Dial Transplant*. 2012;27(4):1403-9

4. Eddington H, Hoefield R, Sinha S, et al. Serum phosphate and mortality in patients with chronic kidney disease. *Clin J Am Soc Nephrol*. 2010;5(12):2251–2257.

5. Hoefield RA, Kalra PA, Baker PG, et al. The use of eGFR and ACR to predict decline in renal function in people with diabetes. *Nephrology Dialysis Transplantation*. 2011;26(3): 887–892..

6. Goddard J, Harris K, Turner N. *UK Renal Association eCKD guide*. Available at: http://www.renal.org. Accessed December 12, 2011.

7. British Cardiac Society, British Hypertension Society, Diabetes UK, HEART UK, Primary Care Cardiovascular Society, Stroke Association. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart*. 2005;91 Suppl 5:v1–52.

8. 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. *J Vasc Interv Radiol*. 2006;17(9):1383–97; quiz 1398.

9. ASTRAL Investigators, Wheatley K, Ives N, et al. Revascularization versus medical therapy for renal-artery stenosis. *N Engl J Med*. 2009;361(20):1953–1962.

10. Cooper C, Murphy T, Matsumoto A, et al. Stent revascularization for the prevention of cardiovascular and renal events among patients with renal artery stenosis and systolic hypertension: Rationale and design of the CORAL trial. *American Heart Association*. 2006;152(1):59–66.

11. Martin LG, Rundback JH, Wallace MJ, et al. Quality improvement guidelines for angiography, angioplasty, and stent placement for the diagnosis and treatment of renal artery stenosis in adults. *J Vasc Interv Radiol*. 2010;21(4):421–30– quiz 230.

12. Australian Institute of Health and Welfare. End-stage kidney disease in Australia. 2011:1–60.

13. Brand S, Hall M, Bieber B, et al. International Differences in eGFR at Dialysis Start: Results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *American Society of Nephrology Renal Week- 2012*.

14. Tattersall J, Dekker F, Heimbürger O, et al. When to start dialysis: updated guidance following publication of the Initiating Dialysis Early and Late (IDEAL) study. *Nephrology Dialysis Transplantation*. 2011;26(7):2082–2086.

15. Peake M, Whiting M. Measurement of serum creatinine-current status and future goals. *Clin Biochem Rev*. 2006;27(4):173–184.

16. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604–612.

17. Murata K, Baumann NA, Saenger AK, Larson TS, Rule AD, Lieske JC. Relative performance of the MDRD and CKD-EPI equations for estimating glomerular filtration rate among patients with varied clinical presentations. *Clinical Journal of the American Society of Nephrology*. 2011;6(8):1963–1972.

18. Ali A, Asif NN, Yaqub S, Kashif W, Merchant D, Yazdant I. Spot urine protein: creatinine ratio versus 24 hour urine protein at various levels of GFR patients referred to a tertiary care hospital of Pakistan. *J Pak Med Assoc*. 2008;58(9):476–479.

19. Barr DB, Wilder LC, Caudill SP, Gonzalez AJ, Needham LL, Pirkle JL. Urinary Creatinine Concentrations in the U.S. Population: Implications for Urinary Biologic Monitoring Measurements. *Environ Helath Perspect*. 2005;113(2):192-200

# CHAPTER 4 - RESULTS

# CHAPTER 4.1

## Risks for Mortality and Renal Replacement Therapy in Atherosclerotic Renovascular Disease Compared to Other Causes of Chronic Kidney Disease

Ritchie J, Green D, Alderson HV, Chiu D, Sinha S, Kalra PA

Preface

Given the negative results from trials of percutaneous revascularisation current treatment for ARVD does not meaningfully differ from general care of the patient with CKD. Given the commonality in treatment, it has been suggested that there may be limited value in defining ARVD as a specific disease entity.

In this analysis we consider if clinically significant differences in patient outcome exist between ARVD and other forms of chronic kidney disease to support ARVD being defined as a disease process in its own right.

> *$H_0$ - The presence of ARVD does not confer a worse prognosis than other causes of CKD.*
> *$H_1$ - The presence of ARVD does confer a worse prognosis than other causes of CKD, supporting its position as a specific disease entity.*

Abstract

*Background*

Patients with ARVD have an increased risk for death and RRT compared to the general population. No data exist to describe prognosis in ARVD compared to other causes of CKD.

*Methods*

Patients were selected from two prospective observational studies of outcome in ARVD and CKD. Multivariate Cox regression was used to compare risk for RRT and death (both prior to and following initiation of RRT) between patients with ARVD and other causes of CKD.

*Results*

Of 1472 patients (563 [38%] ARVD, 909 [62%] non-ARVD), 242 [16%] progressed to RRT and 640 [44%] died over a median follow-up period of 4.1 [IQR 2.4-5.6] years. Patients with ARVD had an increased risk for death (HR 1.5 [95% CI 1.2-1.8], p<0.001) but not for RRT (HR 1.0 [95% CI 0.7-1.4], p=0.9). The largest increase in risk for death was observed relative to renal limited diseases e.g. pyelonephritis (HR 2.4 [95% CI 1.3-4.5], p=0.004) and interstitial/infiltrative disease (HR 2.2 [95% CI 1.3-4.5], p=0.02). No difference in risk for death existed between ARVD and diabetic nephropathy (HR 1.0 [95% CI 0.8-1.3], p=0.8). Following initiation of RRT, patients with ARVD had a significantly increased risk for death compared to patients without ARVD (HR 3.3 [95% CI 2.2-5.0], p<0.001).

*Conclusions*

Patients with ARVD as a cause of CKD have an increased risk for death both prior to and following initiation of RRT. Further work should seek to identify modifiable risk factors relevant to prognosis.

Introduction

Prospective studies have demonstrated that ARVD is associated with increased risk for vascular morbidity and mortality [1], with strong supporting data found in retrospective analyses of the Medicare 5% denominator files. Here a 1.5x to 2.3x increased risk for death was found in prevalent ARVD patients [2] with a similar level of risk described in incident ARVD patients [3]. Studies describing risk for progression to RRT in ARVD are more scarce. In another analysis of Medicare data, incident ARVD patients were found to have significantly increased risk for initiation of RRT [3]. However, interpretation of this finding is confounded by several factors. Firstly the coded data do not define whether ARVD was the primary cause of CKD in these patients. Although renal artery disease has been found in over a quarter of elderly patients with end stage kidney disease [4], the proportion of incident dialysis patients where ARVD is defined as the primary renal disease varies from 2% to 27% [5,6]. A further confounding issue in the Medicare analyses for both mortality and RRT is that, although adjusted for the effect of coded for CKD on outcome, the referent group was formed by the general population. As such these studies cannot inform us as to how risk differs between patients with CKD secondary to ARVD and CKD due to other specific causes. Finally, despite the increased mortality risk associated with ARVD in the pre-dialysis population, studies considering survival in ARVD patients following initiation of RRT are few and conflicting. A single center analysis of 683 haemodialysis patients described a significantly increased risk for death in patients with ARVD compared to patients with other causes of end stage kidney disease [7]. In contrast, registry analysis of over 146,000 incident US dialysis patients found a reduced risk for death in patients in whom ARVD was their primary cause of renal failure, when compared against other cause of ESKD [8].

This study aims to:

1 – compare risk for death and progression to RRT between patients with ARVD as their primary cause of renal failure and patients with other defined causes of CKD.

2 – compare prognosis following initiation of RRT between patients with ARVD and patients with other causes of ESKD.

Subjects and methods

*Patient population and management*

Patients were selected from two well-established observational studies, the Salford Renovascular Database [9] and the Chronic Renal Insufficiency Standards Implementation Study [10]. The SRVD and CRISIS are both prospective observational studies of outcome in CKD and have received approval from the regional ethics committee. The SRVD was established in 1995 to prospectively include all patients diagnosed with ARVD referred for management at our nephrology center (catchment population 1.5 million). CRISIS was established in 2002, with the majority of referred patients aged over 18 years and an eGFR under 60ml/min/1.73m$^2$ (not requiring immediate referral for dialysis) approached for consent in an unselected fashion. Both studies record baseline demographic (age, gender, ethnicity), co-morbid (smoking status, previous and incident macrovascular events, medications) and clinical data (blood pressure, serum urea, creatinine, proteinuria). Nephrology residents and trained research nurses update patient records on an annual basis. Pre-defined end-points for both studies are all-cause mortality and progression to chronic RRT, defined as initiation of chronic haemodialysis, peritoneal dialysis or transplantation. Where possible, information is obtained from local electronic health records, with patient-reported data used when this is not available.

All patients are treated independently of recruitment to the SRVD or CRISIS. Management is in accordance with national guidelines [11-13], with a number of ARVD patients treated with percutaneous renal artery angioplasty and stenting in line with prevailing clinical consensus [14], and a proportion revascularised following recruitment to randomised trials [1,15].

*Inclusion criteria and assignment of primary cause of CKD*

Patients were considered suitable for inclusion in this analysis where there were complete baseline co-morbid, blood pressure and renal biochemical data, and a defined primary cause of CKD. Imaging records for patients recruited to CRISIS were reviewed to identify any cases of ARVD not captured in the SRVD. Patients were defined as having ARVD as their primary renal disease where there was a minimum 50% unilateral stenosis and no other primary cause of CKD documented by a consultant nephrologist. Patients with ARVD and <50% stenosis, or ARVD and an alternative documented primary cause of CKD were excluded from analysis. In patients without evidence of ARVD, primary renal disease was assigned following a review of the clinical notes made by the patient's consultant nephrologist. Where more than one possible diagnosis existed the case was discussed by three nephrologists and the most probable dominant cause assigned (e.g. based upon the presence or absence of retinopathy or neuropathy when diabetes co-existed with hypertension). Where a quorum could not be reached, or no clearly documented cause of CKD existed, the patient was excluded from analysis. Causes of CKD within CRISIS were grouped into 8 categories:

*Diabetic nephropathy* – including type I and type II diabetes mellitus.
*Pyelonephritis* – including reflux nephropathy.
*Interstitial and infiltrative renal disease* – interstitial nephritis, myelomatous disease, amyloid and sarcoid.
*Structural disease* – congenital urinary tract abnormalities, obstructive uropathy, renal stone disease and traumatic or surgical loss of kidney.
*Cystic renal disease* – polycystic kidney and medullary cystic disease
*Vasculitic glomerulonephritis* – ANCA related conditions, Goodpasture's disease, IgA nephropathy, membranoproliferative and lupus nephritis (acute presentations excluded).
*Other glomerulonephritis* – membranous nephropathy and focal segmental glomerulosclerosis.
*Hypertensive renal disease* – including cases of malignant hypertension (with ARVD excluded).

*Statistical methodology*

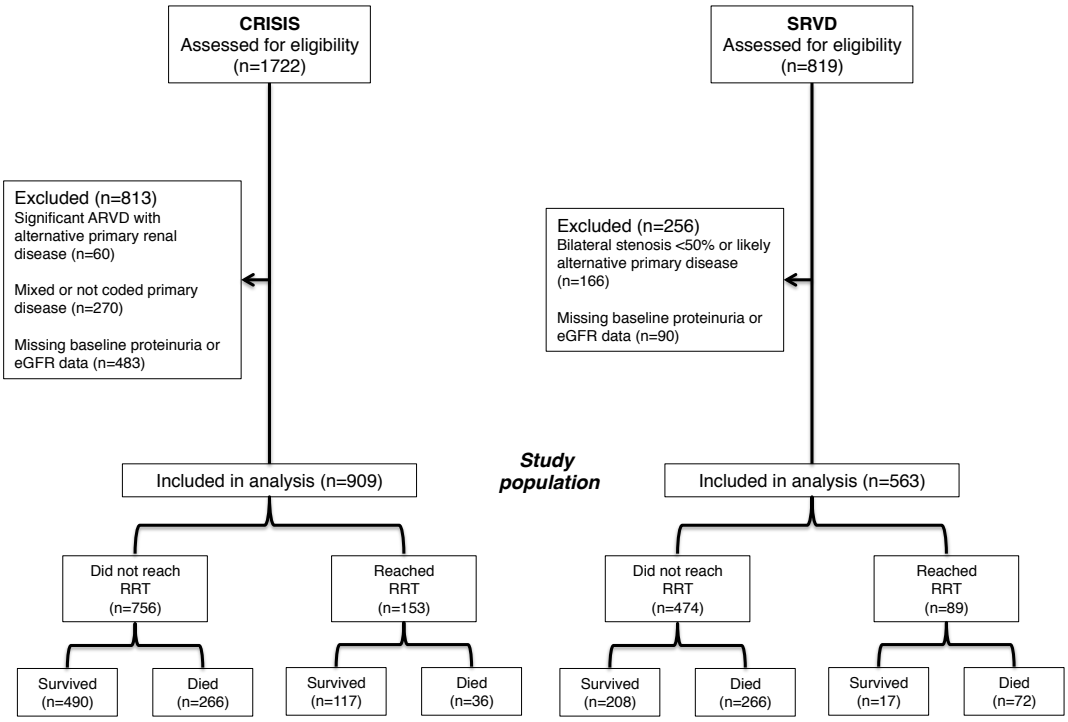
Normally distributed continuous data are presented as mean±standard deviation and non-parametric data as median [interquartile range]. Categorical data are presented as number [percentage]. Comparisons between continuous variables were made using ANOVA methodology appropriate to the distribution of the data; comparisons between categorical baseline variables were made using Chi-squared test and factorial logistic regression. Survival analyses were performed using Cox proportional hazards regression with multivariate models constructed using co-variates with a clinically plausible relationship to outcome. For end-points of death and RRT time zero was defined as date of recruitment with censoring occurring at date of end-point or most recent clinical follow-up. For the end-point of death following initiation of RRT, time zero was defined as date of first chronic RRT with censoring occurring at death or most recent clinical follow-up. Results are presented as hazard ratio [95% confidence interval] with statistical significance defined as an alpha value of $<0.05$ unless otherwise stated. Time averaged rates of change in blood pressure and renal function were calculated using unconditional growth models with an unstructured covariance matrix. Risk for end-points associated with these values were compared non-parametrically using restricted cubic splines (adjusted for clinically relevant covariates) between ARVD and non-ARVD groups [16]. All analyses were performed in SAS version 9.2 (SAS Institute, Cary, NC, USA) under license to the University of Manchester.

Results

*Study population*

A total of 2541 patient records (SRVD = 819; CRISIS = 1722) were considered. From CRISIS, 60 patients were excluded due to ARVD co-existing with another documented primary cause of CKD, with a further 753 excluded due to incomplete baseline data, or no documented cause of CKD, giving a CRISIS population of 909 patients. From the SRVD, 166 patients were excluded due to <50% stenosis, with 90 further patients excluded due to incomplete baseline data, giving a SRVD population of 563 patients. The total population for analysis therefore comprised of 1472 patients with a median follow-up time of 4.1 [IQR 2.4-5.6] years, figure 4.1.1. Average follow-up times were comparable for each disease group table 4.1.1.

**Figure 4.1.1** - Patient selection and summary outcomes.




*Abbreviations: CRISIS – Chronic Renal Insufficiency Standards Implementation Study. SRVD – Salford Renovascular Database. RRT – renal replacement therapy*

**Table 4.1.1** - Median follow up time divided by primary disease group

| Group | Median follow-up time in years [interquartile range] |
|---|---|
| Diabetic nephropathy | 4.0 [2.6-5.5] |
| Pyelonephritis | 4.7[3.2-7.2] |
| Interstitial / infiltrative | 4.4 [3.2-6.2] |
| Structural renal disease | 4.7 [3.2-7.1] |
| Cystic renal diseases | 4.7 [3.5-6.1] |
| Vasculitic glomerulonephritis | 4.5 [3.3-7.1] |
| Other glomerulonephritis | 4.4 [3.1-7.3] |
| Hypertensive renal disease | 4.0 [2.7-5.2] |
| Atherosclerotic renovascular disease | 4.0 [1.7-5.8] |
| All non-ARVD patients combined | 4.2 [3.0-5.6] |

*Abbreviations – ARVD: atherosclerotic renovascular disease*

Primary renal disease was defined as diabetic nephropathy in 210 [14.3%] patients, pyelonephritis in 67 [4.5%], interstitial disease in 44 [3.0%], structural renal disease in 41 [2.8%], cystic disease in 58 [3.9%], vascuitic glomerulonephritis in 109 [7.4%], other glomerulonephritis in 61 [4.1%], hypertensive disease in 319 [21.7%] and ARVD in 563 [38.3%], figure 4.1.2.

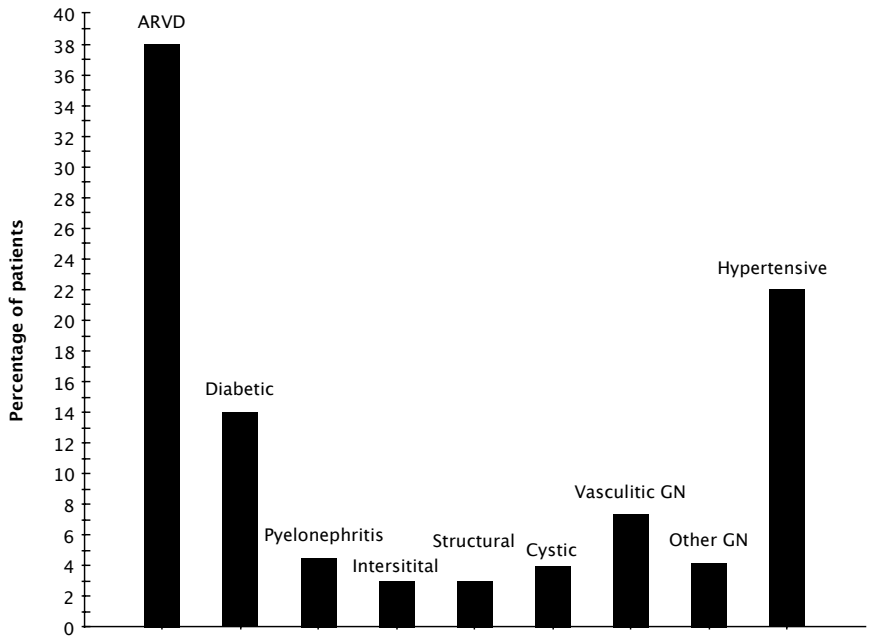



**Figure 4.1.2** Distribution of primary diseases within study population.

*Abbreviations:*
*ARVD Atherosclerotic renovascular disease*
*GN glomerulonephritis*

*Baseline demographics*

When non-ARVD causes of CKD were considered together (n=909 [61.8%]), patients with ARVD were older (70.0±9 vs. 64.6±14 years, p<0.001), more proteinuric (0.64 [IQR 0.2-1.2] vs. 0.2 [IQR 0.1-0.6] g/24 hours, p<0.001), and with a greater burden of macrovascular co-morbidity (myocardial infarction 30% vs. 17%; cerebrovascular disease 37% vs. 17%, peripheral vascular disease 39% vs. 17%, p<0.001 for all). Mean baseline eGFR was 33ml/min/1.73m$^2$ in both groups, table 4.1.2.

Similar demographic differences were observed when comparison was made between patients with ARVD as their primary cause of CKD and other individual causes of CKD. Patients in the pyelonephritis and cystic disease groups were youngest (54.8±18 and 56.2±14 years respectively); patients with diabetic nephropathy had the lowest baseline eGFR (30.7±15ml/min/1.73m2). Patients with ARVD as their primary cause of CKD had the highest baseline blood pressure of any group, even when compared to those coded as having hypertensive renal disease (157±30/81±16mmHg vs. 139±21/71±12mmHg, p<0.05), table 4.1.3.

**Table 4.1.2** - Baseline demographics of ARVD and non-ARVD populations.

| | ARVD n=563 | Non-ARVD CKD n=909 | p |
|---|---|---|---|
| **Age** | 70+/-9.2 | 64.6+/-14.2 | <0.001 |
| **Male** | 319 (56.7%) | 579 (63.7%) | 0.007 |
| **eGFR** | 33+/-17.9 | 33.5+/-15.2 | 0.5 |
| **24 hour proteinuria** | 0.64 (0.2-1.2) | 0.2 (0.1-0.62) | <0.001 |
| **Systolic blood pressure** | 157.5+/-29.7 | 135.9+/-21.5 | <0.001 |
| **Diastolic blood pressure** | 80.9+/-16.3 | 72.9+/-11.6 | <0.001 |
| **Maximum unilateral stenosis** | 77.3+/-19.3 | na | - |
| **Patency score** | 92.3+/-40.7 | na | - |
| **Diabetes mellitus** | 165 (29.3%) | 335 (36.9%) | 0.003 |
| **Myocardial infarction** | 169 (30%) | 157 (17.3%) | <0.001 |
| **Stroke/TIA** | 207 (36.8%) | 150 (16.5%) | <0.001 |
| **Peripheral vascular disease** | 218 (38.8%) | 156 (17.2%) | <0.001 |
| **Statin** | 287 (51.5%) | 577 (63.5%) | <0.001 |
| **Angiotensin blockade** | 267 (47.4%) | 584 (64.2%) | <0.001 |
| **Revascularisation** | 129 (23%) | na | - |
| **Current smoker §** | 93 (31.8%) | 123 (13.5%) | <0.001 |
| **Ex-smoker** | 131 (44.9%) | 496 (54.6%) | 0.004 |
| **Never smoked** | 68 (23.3%) | 290 (31.9%) | 0.005 |

*Abbreviations; eGFR - estimated glomerular filtration rate (CKD-EPI); TIA – transient ischaemic attack. Patency score defined as combined left and right renal artery patency, where a score of 200 represents bilateral 0% stenosis and a score of 0 represents bilateral 100% stenosis. Angiotensin blockade defined as use of either / or angiotensin converting enzyme inhibitor or angiotensin receptor blocker. § smoking data in the SRVD available for 52% of patients. Current smoking defined as smoking at time of recruitment or cessation of smoking within 1-year of recruitment. Ex-smoker defined as having stopped smoking for >1-year prior to recruitment.*

**Table 4.1.3** - Baseline demographics of ARVD and specific non-ARVD groups.

| | ARVD n=563 | Diabetes ^ n=210 | PN n=67 | Interstitial n=44 | Structural n=41 | Cystic n=58 | Vasculitic GN n=109 | Other GN n=61 | Hypertensive n=319 | p |
|---|---|---|---|---|---|---|---|---|---|---|
| **Age** | 70+/-9.2 | 64.7+/-12.2** | 54.8+/-18.3** | 62.6+/-13** | 62.5+/-14.5** | 56.2+/-14.4** | 58.2+/-14.8** | 59.2+/-14.2** | 71.9+/-9.9* | <0.001 |
| **Male** | 319 (56.7%) | 144 (68.6%)* | 30 (44.8%)* | 23 (52.3%) | 26 (63.4%) | 24 (41.4%)* | 77 (70.6%)* | 37 (60.7%) | 218 (68.3%)* | <0.001 |
| **eGFR** | 33+/-17.9 | 30.7+/-15 | 35.3+/-17.7 | 34.1+/-14.9 | 32.5+/-14.6 | 35.9+/-17.1 | 36.1+/-16.8 | 37.4+/-17.3* | 33+/-13.1 | 0.05 |
| **Proteinuria** | 0.9+/-1.2 | 0.9+/-1.4 | 0.5+/-0.7* | 0.5+/-0.8* | 0.7+/-0.9 | 0.2+/-0.4** | 1.1+/-1.5 | 1.6+/-2** | 0.3+/-0.6** | <0.001 |
| **SBP** | 157.5+/-29.7 | 136.7+/-22.6** | 129.2+/-16.9** | 130.6+/-20.3** | 135.8+/-21.3** | 131.7+/-20.6** | 135.8+/-21.4** | 134.6+/-22.9** | 138.7+/-21.3** | <0.001 |
| **DBP** | 80.9+/-16.3 | 70.4+/-11** | 75.1+/-9.8* | 74.6+/-10.6* | 77.3+/-10.7 | 77+/-12* | 76.3+/-11.8* | 75.2+/-11.4* | 71+/-11.8** | <0.001 |
| **Unilateral stenosis** | 77.3+/-19.3 | . | . | . | . | . | . | . | . | . |
| **Patency score** | 92.3+/-40.7 | . | . | . | . | . | . | . | . | . |
| **Diabetes** | 165 (29.3%) | 210 (100%)** | 7 (10.4%)* | 7 (15.9%) | 9 (22%) | 4 (6.9%)* | 11 (10.1%)** | 10 (16.4%) | 80 (25.1%) | <0.001 |
| **MI** | 169 (30%) | 44 (21%)* | 4 (6%) | 5 (11.4%) | 4 (9.8%) | 5 (8.6%) | 6 (5.5%)* | 4 (6.6%) | 85 (26.6%)** | <0.001 |
| **Stroke/TIA** | 207 (36.8%) | 37 (17.6%) | 7 (10.4%) | 6 (13.6%) | 4 (9.8%) | 10 (17.2%) | 6 (5.5%)* | 7 (11.5%) | 73 (22.9%)* | <0.001 |
| **PVD** | 218 (38.8%) | 45 (21.4%)* | 8 (11.9%) | 6 (13.6%) | 5 (12.2%) | 3 (5.2%) | 7 (6.4%)* | 5 (8.2%) | 77 (24.1%)** | <0.001 |
| **Statin** | 287 (51.5%) | 155 (73.8%)** | 25 (37.3%)* | 19 (43.2%) | 17 (41.5%) | 27 (46.6%) | 59 (54.1%) | 43 (70.5%)* | 232 (72.7%)** | <0.001 |
| **A2B** | 267 (47.4%) | 159 (75.7%)** | 39 (58.2%) | 19 (43.2%)* | 13 (31.7%)** | 43 (74.1%)* | 79 (72.5%)* | 48 (78.7%)* | 184 (57.7%) | <0.001 |
| **Revascularisation** | 129 (23%) | | | | | | | | | |
| **Current smoker** § | 93 (31.8%) | 26 (12.4%)** | 13 (19.4%) | 8 (18.2%) | 4 (9.8%)** | 5 (8.6%)** | 14 (12.8%)** | 11 (18%)* | 42 (13.2%)** | <0.001 |
| **Ex-smoker** | 131 (44.9%) | 117 (55.7%)* | 25 (37.3%) | 21 (47.7%) | 21 (51.2%) | 28 (48.3%) | 59 (54.1%) | 28 (45.9%) | 197 (61.8%)** | 0.001 |
| **Never smoked** | 68 (23.3%) | 67 (31.9%)* | 29 (43.3%)** | 15 (34.1%) | 16 (39%)* | 25 (43.1%)** | 36 (33%) | 22 (36.1%)* | 80 (25.1%) | 0.003 |

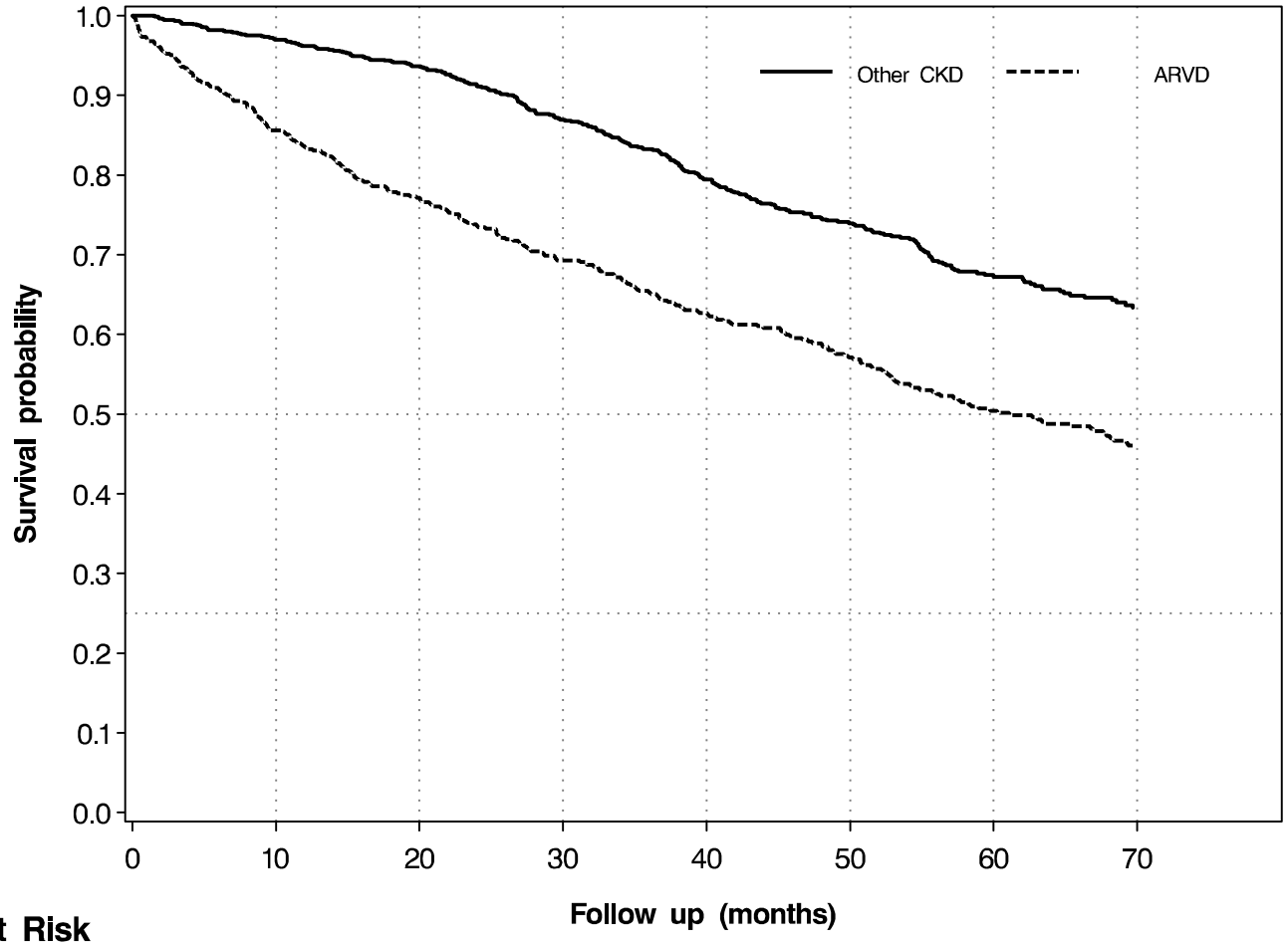
Quoted p-value is for overall between group comparison. Statistically significant differences between ARVD and individual groups are shown for each variable (*p<0.05; **p<0.001).
^ in the diabetic nephropathy group, 177 [84%] have type II and 33 [16%] have type I diabetes mellitus. § smoking data in the SRVD available for 52% of patients.
*Abbreviations; PN – pyelonephritis; GN – glomerulonephritis; eGFR - estimated glomerular filtration rate (CKD-EPI equation); SBP – systolic blood pressure; DBP – diastolic blood pressure; MI – myocardial infarction; TIA – transient ischaemic attack; PVD – peripheral vascular disease; A2B - angiotensin blockade defined as use of either / or angiotensin converting enzyme inhibitor or angiotensin receptor blocker. Patency score defined as combined left and right renal artery patency, where a score of 200 represents bilateral 0% stenosis and a score of 0 represents bilateral 100% stenosis. Current smoking defined as smoking at time of recruitment or cessation of smoking within 1-year of recruitment. Ex-smoker defined as having stopped smoking for >1-year prior to recruitment.*

*Risk for death*

Over the observed period, 640 [43.5%] patients died. The greatest proportion of patient deaths occurred in the ARVD group [60.0%]. Diabetic and hypertensive renal disease had the next highest proportions (42.9% and 40.4% respectively), with the lowest proportion of deaths in the pyelonephritis group [16.4%]. In other disease groups, between 20 and 30% of patients died (structural 29.3%, other glomerulonephritis 24.6%, vasculitic glomerulonephritis 22.0%, cystic 20.7%, interstitial 20.5%). In univariate analysis, ARVD patients had a significantly increased risk for death compared to all non-ARVD causes of CKD combined (HR 1.80 [95% CI 1.5-2.1], p<0.001; figure 4.1.3). This association persisted in multivariate analysis (HR 1.47 [95% CI 1.2-1.8], p<0.001), adjusted for age, gender, eGFR, proteinuria, systolic blood pressure, diabetes and macrovascular history (composite of previous myocardial infarction, stroke, transient ischaemic attack or peripheral vascular disease), with the greatest risk for death observed in patients with ARVD and stage 5 CKD at baseline (HR 2.01 [95% CI 1.3-3.0], p=0.001). When ARVD was compared to other individual causes of CKD, a statistically significant increased risk for death was observed in univariate and multivariate analysis compared to patients with pyelonephritis (HR 2.44 [95% CI 1.3-4.5], p=0.004), interstitial renal disease (HR 2.22 [95% CI 1.2-4.4], p=0.02), vasculitic glomerulonephritis (HR 1.96 [95% CI 1.3-3.0], p=0.003), other vasculitis (HR 1.72 [95% CI 1.0-3.3], p=0.05) and hypertensive renal disease (HR 1.43 [95% CI 1.2-1.8], p=0.001). For cystic and structural disease, a statistically significant increase in risk was observed in univariate analysis but not in multivariate analysis (HR 1.73 [95% CI 1.0-3.3], p=0.07 and HR 1.61 [95% CI 0.9-3.2], p=0.1 respectively). When patients with ARVD were compared to patients with diabetic nephropathy no alteration in risk for death was observed (HR 1.03 [95% CI 0.8-1.2], p=0.8), table 4.1.4.

As no significant difference in risk for mortality existed between patients with ARVD and diabetic nephropathy, risk for death associated with the presence of diabetes was considered. In non-ARVD patients the presence of diabetes was associated with a significantly increased risk for death (HR 1.63 [95% CI 1.3-2.1], p<0.001), however this finding was not observed in ARVD patients (HR 1.01 [95% CI 0.8-1.3], p=0.9).

**Figure 4.1.3** - Kaplan Meier survival curves for ARVD and non-ARVD causes of CKD




| Number at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Other CKD | 906 | 843 | 782 | 682 | 504 | 321 |
| ARVD | 562 | 469 | 394 | 335 | 265 | 187 |

*Solid line represents non-ARVD patients; dashed line represents ARVD patients.*

*X-axis shows time in months from recruitment.*
*Y-axis shows survival probability.*

*Abbreviations: ARVD – atherosclerotic renovascular disease; CKD – chronic kidney disease.*

**Table 4.1.4 -** Risk for death in atherosclerotic renovascular disease compared to other causes of chronic kidney disease.

| | Univariate HR (95% CI) | p | Multivariate HR (95% CI) | p |
|---|---|---|---|---|
| | | *All non-ARVD CKD* | | |
| **ARVD vs. CKD** | 1.8 (1.54-2.11) | <0.001 | 1.47 (1.23-1.76) | <0.001 |
| **Stage 3** | 1.79 (1.39-2.29) | <0.001 | 1.31 (1-1.73) | 0.05 |
| **Stage 4** | 1.51 (1.16-1.95) | 0.002 | 1.26 (0.96-1.64) | 0.1 |
| **Stage 5** | 2.42 (1.65-3.56) | <0.001 | 2.01 (1.34-3.03) | 0.001 |
| | | *Specific causes* | | |
| **Diabetes** | 1.28 (1.02-1.60) | 0.035 | 1.03 (0.76-1.25) | 0.8 |
| **Pyelonephritis** | 4.17 (2.27-7.69) | <0.001 | 2.44 (1.33-4.54) | 0.004 |
| **Interstitial** | 3.13 (1.59-5.88) | 0.001 | 2.22 (1.15-4.35) | 0.02 |
| **Structural** | 2.33 (1.30-4.17) | 0.004 | 1.61 (0.90-3.21) | 0.1 |
| **Cystic** | 3.23 (1.82-5.88) | <0.001 | 1.73 (1.01-3.33) | 0.07 |
| **Vasculitic glomerulonephritis** | 3.03 (2.01-4.54) | <0.001 | 1.96 (1.25-3.01) | 0.003 |
| **Other glomerulonephritis** | 2.70 (1.61-4.54) | <0.001 | 1.72 (1.01-3.33) | 0.05 |
| **Hypertensive** | 1.33 (1.09-1.64) | 0.006 | 1.43 (1.15-1.79) | 0.001 |

*Multivariate analysis adjusted for age, gender, eGFR, proteinuria, systolic blood pressure, diabetes and macrovascular history (composite of myocardial infarction, cerebrovascular event or peripheral vascular disease).*
*All hazard ratios represent risk for death in patients with ARVD.*
*Abbreviations: ARVD – atherosclerotic renovascular disease; CKD – chronic kidney disease*

*Risk for renal replacement therapy*

Overall 242 (16.4%) patients progressed to RRT. The greatest proportion was seen in patients with cystic disease (39.7%). This was followed by structural disease (24.4%), other glomerulonephritis (21.3%), diabetic nephropathy (20.0%), and then vasculitic glomerulonephritis (19.3%). The sixth greatest proportion of patients progressing to RRT was seen in patients with ARVD (15.8%), followed by pyelonephritis (14.9%), interstitial disease (11.4%) and finally hypertensive renal disease (9.1%). No significant difference in risk for RRT was observed between ARVD and non-ARVD CKD. When compared with individual causes of CKD, the only group in which a significant difference in risk for RRT was observed compared to ARVD was cystic kidney disease (HR 3.93 [95% CI 2.3-6.7], p<0.001), table 4.1.5.

**Table 4.1.5 -** Risk for renal replacement therapy.

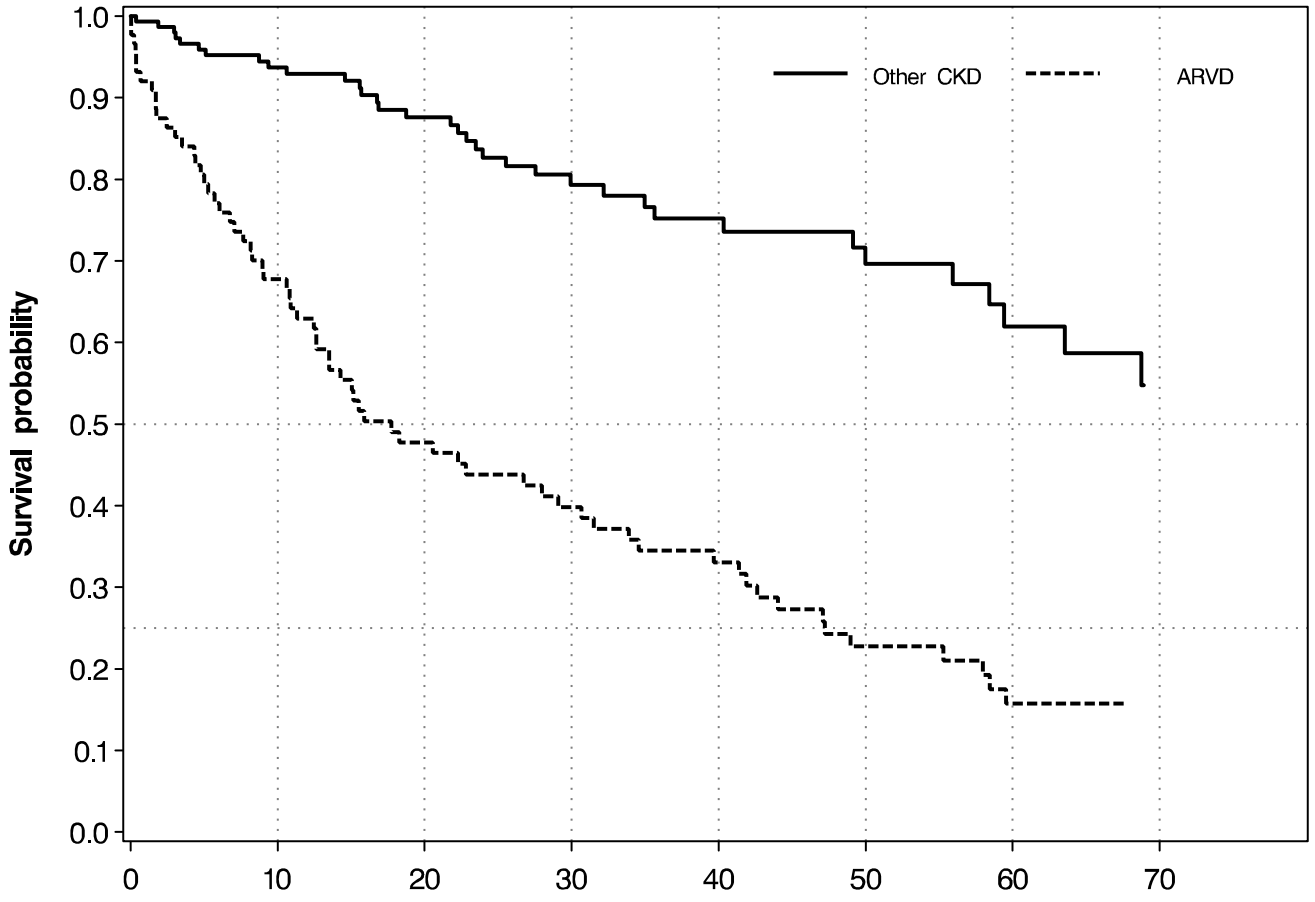
| | Univariate HR (95% CI) | p | Multivariate HR (95% CI) | p |
|---|---|---|---|---|
| | | *All non-ARVD CKD* | | |
| **ARVD vs. CKD** | 0.93 (0.71-1.22) | 0.601 | 1.01 (0.73-1.39) | 0.9 |
| **Stage 3** | 1.05 (0.57-1.95) | 0.872 | 1.63 (0.77-3.44) | 0.2 |
| **Stage 4** | 0.64 (0.4-1.02) | 0.063 | 0.8 (0.48-1.34) | 0.4 |
| **Stage 5** | 0.79 (0.51-1.21) | 0.272 | 0.97 (0.6-1.56) | 0.9 |
| | | *Specific causes* | | |
| **Diabetes** | 1.36 (0.93-1.99) | 0.114 | 1.05 (0.7-1.59) | 0.8 |
| **Pyelonephritis** | 0.91 (0.47-1.75) | 0.77 | 0.73 (0.35-1.52) | 0.4 |
| **Interstitial** | 0.69 (0.28-1.69) | 0.412 | 0.65 (0.26-1.65) | 0.4 |
| **Structural** | 1.49 (0.77-2.87) | 0.239 | 0.73 (0.35-1.54) | 0.4 |
| **Cystic** | 2.66 (1.67-4.24) | <0.001 | 3.93 (2.32-6.68) | <0.001 |
| **Vasculitic glomerulonephritis** | 1.18 (0.73-1.9) | 0.51 | 0.84 (0.49-1.43) | 0.5 |
| **Other glomerulonephritis** | 1.29 (0.72-2.32) | 0.394 | 0.93 (0.5-1.73) | 0.8 |
| **Hypertensive** | 0.57 (0.37-0.88) | 0.011 | 0.79 (0.5-1.26) | 0.3 |

*Multivariate analysis adjusted for age, gender, eGFR, proteinuria, diabetes, systolic blood pressure, macrovascular history.*
*Upper rows describe risk for renal replacement therapy in patients with ARVD compared to all other causes of CKD.*
*Lower rows (specific causes) describe risk for RRT in specific groups of CKD causes compared to patients with ARVD. Abbreviations: ARVD – atherosclerotic renovascular disease; CKD – chronic kidney disease*

*Risk for death following initiation of renal replacement therapy*

In multivariate analysis (adjusted for age, gender and presence of diabetes at start of RRT), patients with ARVD had a significantly increased risk for death following initiation of RRT (HR 3.31 [95% CI 2.2-5.0], p<0.001) compared to non-ARVD CKD, with a 50% survival probability at 16 months (figure 4.1.4). When considered against individual causes of CKD patient numbers were small, but signals to increased risk were seen relative to each other disease category, reaching statistical significance when ARVD patients were compared to those with diabetic nephropathy (HR 2.22 [95% CI 1.2-4.2], p=0.01), cystic disease (HR 2.56 [95% CI 1.0-6.7], p=0.05), and vasculitic glomerulonephritis (HR 7.69 [95% CI 1.8-32.2], p=0.004), table 4.1.6. As the SRVD only records the *first* macrovascular event occurring after diagnosis and not subsequent events it was not possible to adjust this analysis for co-morbid burden at the time of initiating RRT. This may have introduced unmeasured confounding into this analysis.

**Figure 4.1.4** - Kaplan Meier survival curves for ARVD and non-ARVD causes of ESKD after initiation of renal replacement therapy




| Number at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Other CKD | 151 | 113 | 81 | 52 | 38 | 22 |
| ARVD | 88 | 50 | 33 | 25 | 16 | 9 |

*Solid line represents non-ARVD patients; dashed line represents ARVD patients.*

*X-axis shows time in months following initiation of renal replacement therapy.*
*Y-axis shows survival probability.*

*Abbreviations: ARVD – atherosclerotic renovascular disease; CKD – chronic kidney disease.*

**Table 4.1.6 -** Risk for death in atherosclerotic renovascular disease patients following initiation of renal replacement therapy compared to other causes of chronic kidney disease.

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | **HR (95% CI)** | **p** | **HR (95% CI)** | **p** |
| **Non-ARVD CKD (n=153)** | 4.03 (2.69-6.04) | <0.001 | 3.31 (2.19-5.01) | <0.001 |
| **Diabetes (n=42)** | 3.00 (1.64-5.56) | <0.001 | 2.22 (1.18-4.17) | 0.01 |
| **Pyelonephritis (n=10)** | 7.69 (1.89-33.3) | 0.005 | 4.00 (0.97-16.7) | 0.06 |
| **Interstitial (n=5)** | 2.86 (0.69-11.1) | 0.147 | 4.17 (0.98-16.6) | 0.05 |
| **Structural (n=10)** | 3.22 (1.0-10.0) | 0.05 | 2.56 (0.81-8.33) | 0.1 |
| **Cystic (n=23)** | 4.35 (1.79-10.5) | 0.001 | 2.56 (1.0-6.67) | 0.05 |
| **Vasculitic GN (n=21)** | 12.5 (3.13-49.9) | <0.001 | 7.69 (1.88-32.2) | 0.004 |
| **Other GN (n=13)** | 5.56 (1.39-24.8) | 0.017 | 3.57 (0.86-14.2) | 0.08 |
| **Hypertensive (n=29)** | 2.38 (1.15-5.0) | 0.02 | 1.85 (0.87-3.85) | 0.1 |

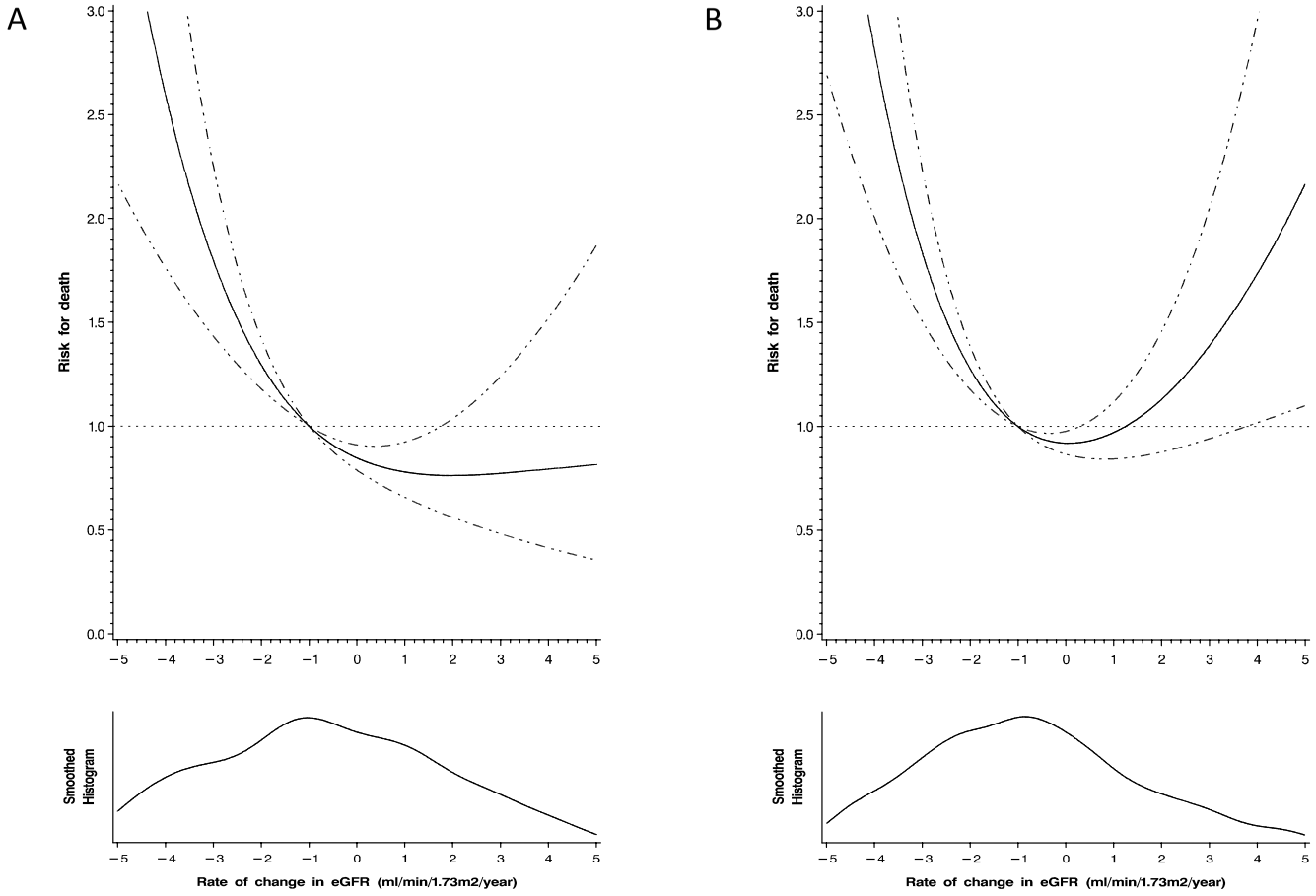
*Multivariate analysis adjusted for age, gender and diabetic status. GN - glomerulonephritis*

*Rate of change in blood pressure and renal function*

The median rate of change in eGFR within the study population was -1.0 [IQR -3 to 1] ml/min/1.73m$^2$/year. In both ARVD and non-ARVD causes of CKD higher rates of annual eGFR loss associated with significantly increased risk for death. A U-shaped risk for death was observed in non-ARVD causes of CKD with significantly increased risk for death seen in patients with an annual rate of eGFR increase in excess of 4ml/min/1.73m$^2$/year compared to the median rate of loss of approximately 1.5ml/min/1.73m$^2$/year. This finding was not observed in ARVD patients, figure 4.1.5.

When risk for death in relation to rate of change in systolic blood pressure was considered, a U-shaped mortality curve was observed for ARVD but not in non-ARVD causes of CKD. In both groups a significantly increased risk for death was associated with high annual reductions in systolic blood pressure (ARVD >9mmHg/year reduction; non-ARVD >6mmHg/year reduction). An increased risk for death was also associated with annual increases in blood pressure in excess of 5mmHg/year in ARVD patients, figure 4.1.6.

**Figure 4.1.5 -** Adjusted hazard ratio for death in relation to annual rate of eGFR change



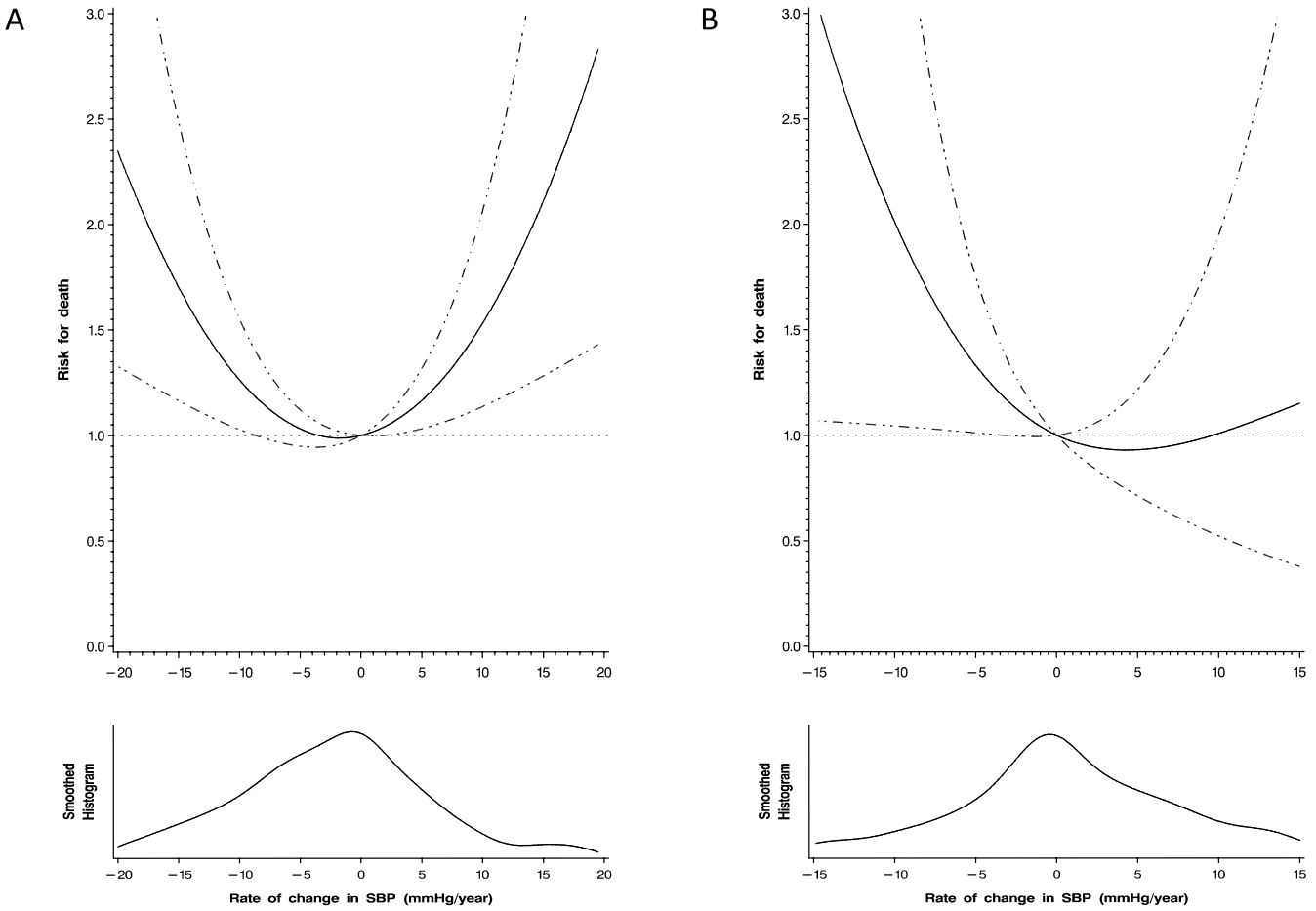

*Panel A represents patients with ARVD; panel B patients with non-ARVD CKD.*

*Upper sections:*
*X-axis shows annual rate of change in estimated glomerular filtration rate (ml/min/1.73m2/year).*
*Y-axis shows hazard ratio for death adjusted for age, gender, proteinuria and baseline estimated glomerular filtration rate).*
*Solid line represents hazard ratio; dashed lines represent 95% confidence intervals.*

*Lower sections:*
*smoothed histogram showing distribution of patients between values of rate of change.*

*Abbreviations: ARVD – atherosclerotic renovascular disease; CKD – chronic kidney disease.*

**Figure 4.1.6 -** Adjusted hazard ratio for death in relation to annual rate of systolic blood pressure change




*Panel A represents patients with ARVD; panel B patients with non-ARVD CKD.*

*Upper sections:*
*X-axis shows annual rate of change in systolic blood pressure (mmHg/year).*
*Y-axis shows hazard ratio for death adjusted for age, gender, eGFR, proteinuria and baseline systolic blood pressure).*
*Solid line represents hazard ratio; dashed lines represent 95% confidence intervals.*

*Lower sections:*
*smoothed histogram showing distribution of patients between values of rate of change.*

*Abbreviations: ARVD – atherosclerotic renovascular disease; CKD – chronic kidney disease.*

Discussion

Previous analysis of claims data from the United States general population has demonstrated an increased risk for death in patients coded as having ARVD compared to the general population [3]. Our data add to this; firstly by demonstrating that this elevated risk exists in a population with moderate to advanced CKD, where the uremic milieu may have been expected to be a competing and potentially dominant prognostic factor compared to the presence/absence of ARVD [17]. Secondly we have shown that the increased mortality risk associated with ARVD spans stages of CKD, and exists relative to most other groups of primary renal disease. As cause of death data were not universally available, cause-specific mortality was not considered in this analysis. However, where this information was documented, cardiovascular causes accounted for the greatest proportion of deaths, consistent with other reports of ARVD and CKD [1,17]. Whilst the presence of ARVD is considered as a relevant prognostic factor in some cardiovascular assessment guidelines [18], many commonly utilised risk stratification tools such as the Framingham score perform poorly in CKD [19]. We therefore interpret our findings as suggestive of a pathophysiological divergence in the development of vascular risk between causes of CKD. Given the frequent coexistence of non-renal atheroma in ARVD [20,21], it is credible that these patients are exposed to a compounded vascular risk; initially a classical atherosclerotic insult, with nephrological factors such as uremia, anemia and increased vascular stiffness accumulating latterly [22,23]. This hypothesis would be consistent with our observation that the greatest difference in mortality risk was found between ARVD and renal-limited diseases such as pyelonephritis and glomerulonephritis, and that no significant difference existed in comparison with either diabetic or hypertensive nephropathy. As both diabetes and hypertension have causal and prevalent relationships with systemic atheroma [24], their vascular risk profile is more likely to mirror ARVD then glomerulonephritis. However, we note that the relative risk between ARVD and diabetic / hypertensive patients may also have been affected both by undiagnosed cases of ARVD and the fact that diabetes and hypertension have been linked to the development of ARVD [25,26]. Studies in the general population aged over 65 years have shown a 6.8% prevalence of ARVD [27]. As the mean baseline age in CRISIS patients was 64 years, a lower population prevalence may be anticipated in our cohort. However, as we were

only able to identify ARVD in 3.5% of recruited patients it is possible that a number of patients in the comparator groups had undiagnosed disease. Alternatively the lower than expected number of cases may represent our local interest in ARVD, with the majority of identified patients managed in a specialist clinic from which they are targeted for recruitment to the SRVD. We also accept that hypertensive renal disease may be both a cause and effect of ARVD, with over 50% of ARVD patients having renal histological changes consistent with hypertensive renal disease [26].

Another possible explanation for the difference in risk for death between ARVD and non-ARVD patients is suggested by the analysis of blood pressure data. In both groups, large annual reductions in systolic blood pressure associated with increased risk for death. Although interpretation of these results is limited by a lack of information regarding cardiac function (as neither study protocoled echocardiographic investigation), this may represent a surrogate marker of accumulating cardiovascular structural and functional abnormalities [28,29]. However, in ARVD a statistically significant increased risk for death was also associated with rises in systolic blood pressure of >5mmHg/year. This may represent cases in which stenosis has progressed, with greater burdens of luminal loss previously associated with increased risk for death.

When ARVD patients with/without diabetes mellitus were considered we did not identify an increased risk for death in diabetic patients. To our knowledge this is a novel finding, and in contrast to the increased mortality risk associated with diabetes in the general and CKD populations [30,31]. In a previous study from our center, mortality risk was considered in 98 ARVD patients, of whom 14 had diabetic nephropathy (defined as proteinuria >1g/24 hours or 0.3g/24hours with evidence of non-renal microvascular disease). Here, no increased risk for death was seen in patients with ARVD and diabetic nephropathy (relative risk 1.04, p=0.9) [32]. Our finding is novel in that we have considered diabetes as a co-morbid disease, not an alternative cause of CKD. Whilst we are unable to comment on clinically relevant confounding factors such as glycemic control and duration of diabetes, we interpret this finding as suggesting that the presence of ARVD is such a dominant risk factor for death that other clinical influences become relatively less important.

Our finding of reduced survival in ARVD following initiation of RRT is consistent with an early report of outcomes in 683 dialysis patients [7], but contrasts with results from a registry analysis of 146,973 incident dialysis patients where a reduced risk for death was noted in the 5.2% of patients with ARVD as their primary cause of ESKD [8]. The authors of this study highlighted the unexpected nature of their finding and noted several possible confounding issues including disparities between claims and coding data. We also suggest that our criteria for defining ARVD as a primary cause of CKD are potentially more stringent, with no minimum percentage stenosis required by the Medicare coding system. Consequently our study population could be seen to have had more 'severe' disease. This suggestion is supported by the greater co-morbid burden seen in our ARVD study population compared to registry data with cerebrovascular disease in 46% vs. 15%, and peripheral vascular disease in 38% vs. 30%. As the burden of co-morbidities described in our population is more consistent with that seen in RCT [1] we believe that this may have been an important confounding issue in the Medicare data.

In our cohort the average annual proportion of ARVD patients progressing to RRT was 3.95%, close to the figure of 4.4% seen in ASTRAL [1]. Though it may have been anticipated that the excess risk for death in ARVD would result in a reduced risk for RRT compared to other causes of CKD, this was not the overall case. In our data, dependent on level of proteinuria, the mean rate of eGFR loss in ARVD patients was between 1 and 2ml/min/1.73m$^2$/year. Almost identical figures were observed in the non-ARVD study population, consistent with eGFR trajectories seen in other studies of CKD [33]. As the mean baseline eGFR in our study cohort was 35ml/min/1.73m$^2$ a greater duration of follow-up would be required to demonstrate any separation between groups. This is supported by the increased risk for progression to RRT seen in patients with cystic renal disease, a population in which more rapid progression of CKD has previously been described [34].

In all causes of CKD an increased risk for death was associated with more rapid rates of loss of renal function, consistent with previous reports [35] . However, in non-ARVD patients, a statistically significantly increased risk was also

associated with increases in eGFR in excess of 4ml/min/1.73m$^2$/year/. Potentially this finding may relate to a number of patients who were inappropriately referred for management of CKD when they in fact had severe AKI, a presentation associated with increased long-term mortality risk [36]. An alternative explanation is that this represents patients in whom GFR was not rising, but eGFR values increased due to weight loss and reduced muscle mass, markers of protein-energy malnutrition and poor prognosis [37]. Potentially this pattern was not observed in ARVD due the increased risk associated with artifactual increases in eGFR being balanced by genuine cases of improved renal function related to revascularisation or optimised angiotensin blockade [9].

Finally, we must consider the limitations of this study beyond the previously discussed possibility that undiagnosed cases of ARVD may have been included within comparator groups, as only a minority of the latter patients underwent renal angiography. We acknowledge the limitations of using eGFR values and of using clinic rather than ambulatory measurements of blood pressure. Further to this, our diagnostic groups were arbitrarily assigned, and based on a clinical rather than histological assessment. At our center it is not routine practice to undertake renal biopsy for cases of suspected diabetic or hypertensive nephrosclerosis. Consequently, although our findings are an accurate representation of local practice, an element of uncertainty exists in our assignment of CKD causes. Finally, we have only been able to describe prognosis from date of diagnosis or recruitment. This fails to account for a run-in period of risk in which e.g. ARVD, hypertension, diabetes or indeed CKD may have been present but undiagnosed, introducing the possibility of lead-time bias.

In conclusion, this work has confirmed the widely held believe that, relative to other causes of CKD, ARVD is associated with increased risk for death both prior to and following initiation of renal replacement therapy.

## References


1. ASTRAL Investigators, Wheatley K, Ives N, et al. Revascularisation versus medical therapy for renal-artery stenosis. *N Engl J Med*. 2009;361(20):1953–1962.

2. Kalra PA, Guo H, Gilbertson DT, et al. Atherosclerotic renovascular disease in the United States. *Kidney Int*. 2009;77(1):37–43.

3. Kalra PA, Guo H, Kausz AT, et al. Atherosclerotic renovascular disease in United States patients aged 67 years or older: risk factors, revascularisation, and prognosis. *Kidney Int*. 2005;68(1):293–301.

4. Herrera AH, Davidson RA. Renovascular disease in older adults. *Clin Geriatr Med*. 1998;14(2):237–254.

5. Fatica RA, Port FK, Young EW. Incidence trends and mortality in end-stage renal disease attributed to renovascular disease in the United States. *Am J Kid Dis*. 2001;37(6):1184–1190.

6. van Ampting JMA, Penne EL, Beek FJA, Koomans HA, Boer WH, Beutler JJ. Prevalence of atherosclerotic renal artery stenosis in patients starting dialysis. *Nephrol Dial Transplant*. 2003;18(6):1147–1151.

7. Mailloux LU, Napolitano B, Bellucci AG, Vernace M, Wilkes BM, Mossey RT. Renal vascular disease causing end-stage renal disease, incidence, clinical correlates, and outcomes: a 20-year clinical experience. *Am J Kidney Dis*. 1994;24(4):622–629.

8. Guo H, Kalra PA, Gilbertson DT, et al. Atherosclerotic Renovascular Disease in Older US Patients Starting Dialysis, 1996 to 2001. *Circulation*. 2006;115(1):50–58.

9. 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. *Nephrol Dial Transplant*. 2012;27(4):1403-1409.

10. Hoefield RA, Kalra PA, Baker PG, et al. The use of eGFR and ACR to predict decline in renal function in people with diabetes. *Nephrol Dial Transplant*. 2011;26(3):887–892.

11. Goddard J, Harris K, Turner N. The UK Renal Association eCKD guide. Available at: http://www.renal.org. Accessed December 12, 2011.

12. National Institute for Health and Clinical Excellence 2008. Chronic Kidney Disease NICE Guideline CG73. *London: National Institute for Health and Care Excellence*. 2008:1–36.

13. British Cardiac Society, British Hypertension Society, Diabetes UK, HEART UK, Primary Care Cardiovascular Society, Stroke Association. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart*. 2005;91 Suppl 5:v1–52.

14. 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. *J Vasc Interv Radiol*. 2006;17(9):1383–97.

15. Cooper C, Murphy T, Matsumoto A, et al. Stent revascularisation for the prevention of cardiovascular and renal events among patients with renal artery stenosis and systolic hypertension: Rationale and design of the CORAL trial. *American Heart Association*.

2006;152(1):59–66.

16. Durrleman S, Simon R. Flexible regression models with cubic splines. *Statist Med*. 1989;8(5):551-61.

17. Tonelli M. Chronic Kidney Disease and Mortality Risk: A Systematic Review. *Journal of the American Society of Nephrology*. 2006;17(7):2034–2047.

18. Guidelines for the Assessment of Absolute Cardiovascular Disease Risk. *National Vascular Disease Prevention Alliance - Heart Foundation of Australia*. 2009.

19. Weiner DE, Tighiouart H, Elsayed EF, et al. The Framingham Predictive Instrument in Chronic Kidney Disease. *J Am Coll Cardiol*. 2007;50(3):8–8.

20. Khosla S, Kunjummen B, Manda R, et al. Prevalence of renal artery stenosis requiring revascularisation in patients initially referred for coronary angiography. *Cathet Cardiovasc Intervent*. 2003;58(3):400–403.

21. Kuroda S, Nishida N, Uzu T, et al. Prevalence of renal artery stenosis in autopsy patients with stroke. *Stroke*. 2000;31(1):61–65.

22. Locatelli F, Pietro Pozzoni, Tentori F, del Vecchio L. Epidemiology of cardiovascular risk in patients with chronic kidney disease. *Nephrol Dial Transplant*. 2003;18 Suppl 7:vii2–vii9.

23. Moe SM, Chen NX. Pathophysiology of vascular calcification in chronic kidney disease. *Circ Res*. 2004;95(6):560–567.

24. Pasterkamp G. Methods of accelerated atherosclerosis in diabetic patients. *Heart*. 2013;99(10):743–749.

25. de Mast Q, Beutler JJ. The prevalence of atherosclerotic renal artery stenosis in risk groups: a systematic literature review. *J Hypertens*. 2009;27(7):1333–1340.

26. Keddis M, Garovic V, Bailey K. Ischaemic nephropathy secondary to atherosclerotic renal artery stenosis: clinical and histopathological correlates. *Nephrol Dial Transplant 2010;25(11):3615-22*.

27. Hansen KJ, Edwards MS, Craven TE, et al. Prevalence of renovascular disease in the elderly: A population-based study. *Journal of Vascular Surgery*. 2002;36(3):443–451.

28. 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(10): 695–704.

29. Whitman IR, Feldman HI, Deo R. CKD and sudden cardiac death: epidemiology, mechanisms, and therapeutic approaches. *J Am Soc Nephrol*. 2012;23(12):1929–1939.

30. Emerging Risk Factors Collaboration, Seshasai SRK, Kaptoge S, et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med*. 2011;364(9): 829–841.

31. Quiroga B, Verdalles U, Reque J, García de Vinuesa S, Goicoechea M, Luño J. Cardiovascular events and mortality in chronic kidney disease (stages I-IV). *Nefrologia*. 2013;33(4):539–545.

32. Wright J, Shurrab A, Cheung C, et al. A prospective study of the determinants of renal functional outcome and mortality in atherosclerotic renovascular disease. *Am J Kidnet Dis*. 2002;39(6):1153–1161.

33. Turin TC, James M, Ravani P, et al. Proteinuria and Rate of Change in Kidney Function in a Community-Based Population. *J Am Soc Nephrol*. 2013.

34. Hoefield RA, Kalra PA, Lane B, O'Donoghue DJ, Foley RN, Middleton RJ. Associations of baseline characteristics with evolution of eGFR in a referred chronic kidney disease cohort. *QJM*. 2013;106(10):915-24.

35. Al-Aly Z, Zeringue A, Fu J, et al. Rate of kidney function decline associates with mortality. *J Am Soc Nephrol*. 2010;21(11):1961–1969.

36. Lafrance J-P, Miller DR. Acute kidney injury associates with increased long-term mortality. *J Am Soc Nephrol*. 2010;21(2):345–352.

37. Cano NJ, Miolane-Debouit M, Léger J, Heng A-E. Assessment of Body Protein: Energy Status in Chronic Kidney Disease. *Semin Nephrol*. 2009;29(1):8–8.

# CHAPTER 4.2

## High-risk Clinical Presentations in Atherosclerotic Renovascular Disease: Prognosis and Response to Renal Artery Revascularisation

Ritchie J, Green D, Chrysochou C, Chalmers N, Foley R, Kalra PA
American Journal of Kidney Disease. 2013. Epub ahead of print. DOI: 10.1053/j.ajkd.2013.07.020


Preface

Current international guidelines support the use of percutaneous transluminal angioplasty and stenting (PTRAS) in ARVD for specific clinical presentations, often referred to as 'high-risk presentations' *(level of evidence: B)*. These guidelines are based on uncontrolled case series and important questions remain. Firstly, does prognosis vary with presentation of ARVD? Secondly, given the negative findings of randomised studies of PTRAS in stable patients with ARVD, are there any specific presentations of ARVD in which PTRAS may improve prognosis.

This analysis builds on the previous chapter, where evidence was presented to support ARVD being classified as a specific disease, by questioning whether ARVD is a homogeneous or heterogeneous disease. We consider if 'high-risk' presentations are associated with a worse prognosis and if these presentations may exhibit a more favorable response to PTRAS.

> *$H_0$ - Clinical presentation in ARVD is not associated with a difference in patient outcome or response to revascularisation.*
> *$H_1$ - Specific clinical presentations of ARVD are associated with worse prognosis or different response to PTRAS. As such, ARVD should not be considered as a single homogeneous disease state.*

Abstract

*Background*

Current trial data may not be directly applicable to patients with the highest risk presentations of ARVD, including flash pulmonary oedema (FPO), rapidly declining renal function (RDF) and refractory hypertension (RH). We consider the prognostic implications of these presentations and response to percutaneous revascularisation.

*Study design*

Single-center prospective cohort study; retrospectively analysed

*Setting and participants*

467 patients with ARVD >50%, managed according to clinical presentation and physician/patient preference.

*Predictors*

Presentation with FPO (n=37, 7.8%), RH (n=116, 24.3%), or RDF (n=46. 9.7%) compared to low-risk presentation with none of these phenotypes (n=230, 49%). Percutaneous revascularisation.

*Outcomes*

Death, cardiovascular event (CVE), ESKD.

*Results*

During a median follow-up of 3.8 (IQR 1.8-5.8) years, 55% died, 33% suffered a CVE and 18% reached ESKD. Revascularisation was performed in 32% of FPO, 28% of RDF, and 28% of RH patients. In medically managed patients, FPO associated with increased risk for death (HR 2.2 [95% CI 1.4-3.5], p<0.001) and CVE (HR 3.1 [95% CI 1.7-5.5], p<0.001) but not ESKD when compared to the low-risk phenotype. No increased risk for any end-point was observed in patients presenting with RDF or RH. Compared to medical management, revascularisation associated with reduced risk for death (HR 0.4 [95% CI 0.2-0.9], p=0.01) but not CVE or ESKD in patients presenting with FPO. Revascularisation was not significantly associated with reduced risk for any end-point in RDF or RH. When these presentations were present in

combination (n=31), revascularisation associated with reduced risk for death (HR 0.15 [95% CI 0.02-0.9], p=0.04) and CVE (HR 0.23 [0.1-0.6], p=0.02).

*Limitations*

Observational study; retrospective analysis; potential treatment bias.

*Conclusions*

This analysis supports guidelines citing FPO as an indication for renal artery revascularisation in ARVD. Presentation with a combination of RDF and RH may also benefit from revascularisation. This may represent a sub-group worthy of further investigation in more robust trials.

Introduction

Atherosclerotic renovascular disease affects significant patient numbers, and associates with increased morbidity and mortality [1]. Until publication of ASTRAL in 2009 [2], 16% of incident ARVD patients in the US underwent renal artery revascularisation [3], despite a lack of clear evidence for benefit, and with some risk of complications [4]. ASTRAL demonstrated that for patients with ARVD and largely stable chronic kidney disease, revascularisation did not offer any overall benefits versus medical therapy, a finding mirrored in clinical practice [5]. There has been a subsequent fall in the number of renal revascularisation procedures, with United Kingdom hospital episode statistics showing a 70% reduction between 2006 and 2010 [6].

A limitation which reduced the generalisability of ASTRAL's findings is that it included a higher proportion of stable and lower-risk patients than might be typical of those referred for revascularisation in clinical practice. Despite limited evidence supporting the practice, patients have historically been revascularised to treat FPO, refractory hypertension and rapidly declining renal function, with published guidelines endorsing this approach [7]. Clinical consensus and physician preference resulted in many of these patients being revascularised outside of ASTRAL and thus excluded from analysis. For example, at the highest recruiting center for ASTRAL there were 283 patients eligible for randomisation during the period of the trial, and of these 71 (25%) underwent randomisation, with 24 (8.5%) revascularised outside of the study. It is likely that these were patients considered to have a 'definite' clinical indication for intervention. As ASTRAL and other smaller randomised controlled trials have effectively ended the practice of revascularisation for RAS in clinically stable patients, it can be reasonably assumed that most revascularisation procedures performed outside of a trial setting are now for one of the above indications. However, although for each presentation there are case reports describing improved clinical status following revascularisation [8-11], none of these clinical sub-groups have been robustly studied in a controlled trial, and no study has included a medical control group or assessed major clinical end-points such as death. Until such data are available, interrogation of high-quality non-randomised cohort data can provide important guidance.

This study aims to consider:

1 – if presentation with FPO, refractory hypertension or rapidly declining renal function is associated with an increased risk for death, cardiovascular event or progression to ESKD compared to presentation without any of these phenotypes.

2 – the effect of revascularisation compared to medical management for each high-risk presentation.

3 – if the effect of revascularisation compared to medical management differs in patients with two or more high-risk presentations.

## Methods

*Description of the cohort and inclusion criteria*

Since 1995, all patients referred to our tertiary renal center (catchment population 1.55 million) diagnosed with ARVD (either by intra-arterial digital subtraction angiography or computed tomography / magnetic resonance angiography) have been entered into a prospectively populated database. Each patient record is updated annually by nephrology residents and contains details of imaging results, clinical presentation, co-morbidities, cardiovascular events, prescribed medications, blood pressure and laboratory measurements (eGFR calculated using CKD-EPI [12]). Baseline details are defined at the time of diagnostic imaging.

Inclusion criteria for this analysis were complete baseline data and a minimum 50% unilateral RAS on biplane measurement. Patients with a unilateral occlusion and insignificant contralateral stenosis were excluded, as this pattern of disease was felt unlikely to benefit from percutaneous revascularisation. Approval was granted by the regional ethics committee.

*Management*

All patients have been managed in accordance with published guidelines for vascular protective therapies and UK Renal Association blood pressure targets [13]. Patients have undergone revascularisation either due to prevailing beliefs of managing clinicians or after entry into a randomised trial (ASTRAL n=35, CORAL n=2) rather than because of a definitive departmental protocol. All renal revascularisation procedures were performed in accordance with standard protocols for angioplasty coupled with bare metal stenting and standard anti-platelet therapy. Embolic protection devices have not been deployed; no surgical bypass procedures were performed.

*Definition of exposures*

High-risk presentations were identified by retrospective review of the database and medical notes by two independent observers. Where disparity of opinion existed, cases were discussed to reach consensus.

**Flash pulmonary oedema** was defined clinically. All patients with at least one episode of rapid onset acute decompensated heart failure [14] were considered and medical records and echocardiographic data reviewed. Where there was evidence of an alternative etiology (e.g. acute myocardial infarction or arrhythmia) or documented chronic congestive cardiac failure / left ventricular ejection fraction <40%, patients were not defined as having FPO.

**Refractory hypertension** was defined in accordance with European Society for Hypertension/European Society of Cardiology guidelines as blood pressure above target (>140mmHg systolic and/or >90mmHg diastolic) despite use of three or more different classes of anti-hypertensive agents (including a diuretic) [15].

**Rapidly declining renal function** was defined as in ASTRAL as serum creatinine at angiography >1.2x or 100µmol/L (1.14 mg/dl) higher than a baseline reading within the previous six-months.

Patients with none of the above presentations were classified as **low-risk**.

*Follow-up, definition and ascertainment of outcomes*

Time zero was defined as date of diagnostic angiography. Censoring occurred at the earliest of 31st July 2011, death, or last patient encounter. Pre-defined study end-points were:

**Death** - date and, where available, cause of death.

**First documented cardiovascular event** - defined as myocardial infarction / acute coronary syndrome; hospitalisation for pulmonary edema or dysrhythmia; stroke or transient ischaemic attack; new onset of symptomatic angina or deterioration of existing angina requiring interventional procedure. Date of index event or diagnostic procedure is recorded.

**End-stage kidney disease** - defined as the earliest documented occurrence of chronic dialysis, transplantation, or eGFR<10ml/min/1.73m$^2$ (the level beneath which dialysis is typically initiated in the UK).

*Statistics*

Normally distributed values are presented as mean ± standard deviation, with non-normal data presented as median (interquartile range). Baseline continuous variables were compared using analysis of variance methods appropriate to distribution of data, with categorical variables compared using Chi-squared test.

Survival analysis was performed using Cox proportional hazards weighted by inverse probability of treatment assignment [16]. Probability of treatment was calculated by logistic regression using clinically relevant variables with an alpha value of <0.1 in univariate analysis. Age, eGFR, proteinuria, blood pressure and burden of stenosis were entered into the model, table 4.2.1. As the majority of patients had a degree of bilateral disease, a patency score was calculated, with a score of 200 representing 0% stenosis bilaterally, and a score of 0 representing bilateral 100% stenosis [17]. Cox models were adjusted for presence of diabetes mellitus, and baseline use of angiotensin blockade where appropriate. Individual models were constructed for each disease presentation.

Unadjusted event rates were manually calculated, with relative rates calculated using Poisson regression adjusted for the above co-variates. Predicted time to death for different values of continuous baseline variables were assessed graphically by negative binomial regression.

Time averaged rate of change in renal function was calculated using an unconditional linear growth model (unstructured covariance matrix) to allow for variation in eGFR within subjects. Differences in annual blood pressure records were compared between groups using repeated measures analysis of variance. Statistical significance was defined as an alpha value of $<0.05$.

Analyses were performed to compare the effect of putative high-risk presentations on outcome (using low-risk patients as referent group), and the effect of revascularisation vs. medical therapy within each high-risk group. Hence the first comparisons were between patients with an individual high-risk presentation and low risk patients (e.g. patients with refractory hypertension as an isolated presentation vs. patients with no high-risk presentation). The second comparison was between treatments within each presentation (e.g. revascularised patients with refractory hypertension vs. medically managed patients with refractory hypertension). Refractory hypertension and rapid loss of function were considered in isolation. Due to limited patient numbers, all patients with FPO were considered (i.e. including those with FPO and another high-risk presentation).

All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA) licensed to the University of Manchester.

**Table 4.2.1 -** Results of logistic regression for probability of revascularisation

| | Parameter estimate (standard error) | p |
|---|---|---|
| **Age (years)** | -0.39 (0.01) | 0.001 |
| **Estimated glomerular filtration rate (ml/min/1.73m$^2$)** | 0.002 (0.006) | 0.3 |
| **Systolic blood pressure (mmHg)** | 0.007 (0.004) | 0.04 |
| **Proteinuria (g/24 hours)** | -0.08 (0.1) | 0.4 |
| **Patency score** | -0.01 (0.002) | <0.001 |
| **c-statistic** | 0.67 | |

*Patency score describes an overall assessment of patency of dominant renal artery, where a maximum score of 200 represents bilateral 0% stenosis and a minimum score of 0 represents bilateral 100% stenosis. c-statistic describes overall model fit.*

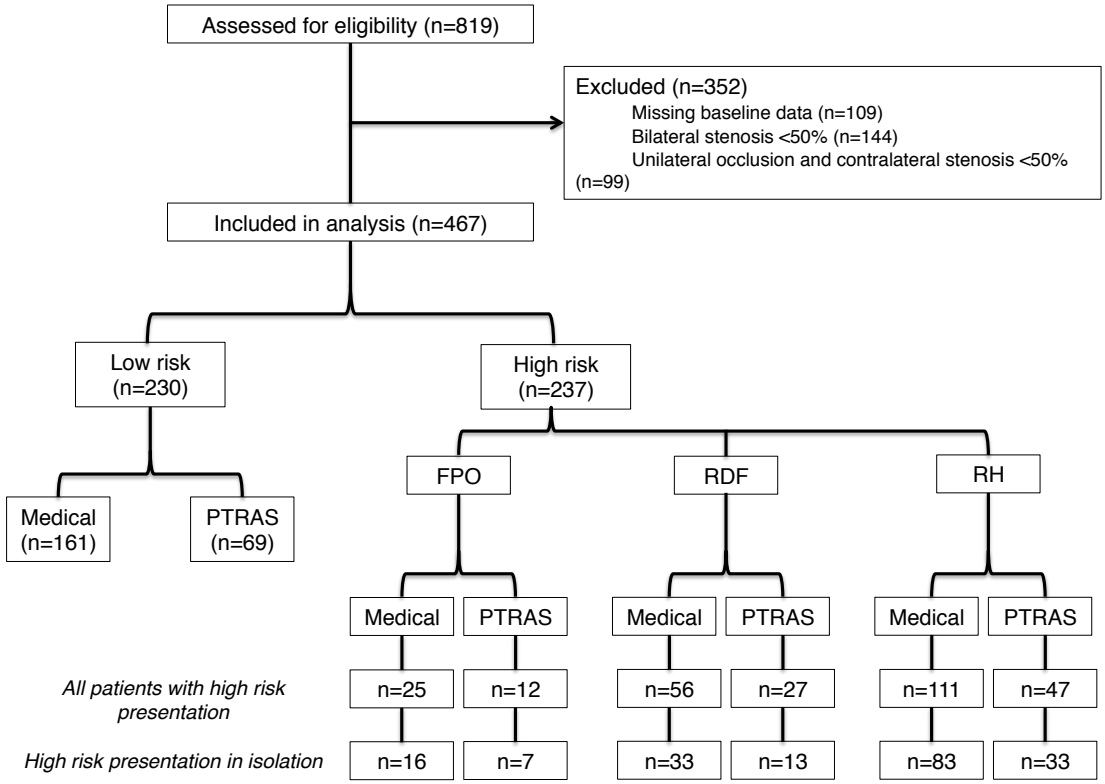
Results

A total of 819 patient records were reviewed, with 109 excluded due to incomplete baseline data, 144 excluded due to RAS <50%, and 99 excluded due to unilateral occlusion with stenosis <50% on the contralateral side. Data from 467 patients were analysed with a median follow-up of 3.8 (IQR 1.8-5.8) years.

One or more high-risk presentation was exhibited by 237 (51%) patients, 58 (24%) of which received revascularisation; 230 (49%) of patients were classified as low-risk, with 69 (30%) of these receiving revascularisation. Overall, 37 patients had FPO (12 [32%] revascularised), 83 had rapidly declining renal function (27 [33%] revascularised) and 158 refractory hypertension (47 [30%] revascularised). The patients presenting in only one high-risk group were FPO 23 (7 [30%] revascularised); rapidly declining function 46 (13 [28%] revascularised) and refractory hypertension 116 (33 [28%] revascularised). Multiple high-risk presentations were identified in 45 patients (42 having 2 presentations, 3 having all 3). Of these patients, 16 (36%) were revascularised. Patient selection and distribution is described in figure 4.2.1.

Across the entire cohort revascularised patients were significantly younger than medically managed patients (68 vs. 71 years), with lower patency scores (79 vs. 96) and higher blood pressures (163/83mmHg vs. 155/79mmHg). Co-morbidities were evenly matched, with the exception of a higher rate of previous myocardial infarction in the revascularisation group (39 vs. 30%). For each individual high-risk presentation, patient characteristics were evenly matched, although revascularised patients were younger in the FPO group and had a lower patency score in the refractory hypertension group. Complete baseline data are presented in table 4.2.2 and 4.2.3 with summary outcome data presented in tables 4.2.4 and 4.2.5. Baseline demographics of excluded patients are presented in table 4.2.6.

**Figure 4.2.1** - Patient selection and distribution between clinical presentations.




*PTRAS – percutaneous renal artery angioplasty and bare metal stenting. FPO – flash pulmonary oedema. RDF – rapidly declining renal function. RH – refractory hypertension*

**Table 4.2.2 -** Baseline demographics for all patients, and low-risk and flash pulmonary edema subgroups

| | All patients n=467 | | | Low risk patients n=237 | | | FPO n=37 | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Medical n=340** | **PTRAS n=127** | **p** | **Medical n=179** | **PTRAS n=58** | **p** | **Medical n=25** | **PTRAS n=12** | **p** |
| **Age** | 71±9 | 68±9 | <0.001 | 71±9 | 68±9 | <0.001 | 71±9 | 68±9 | <0.001 |
| **eGFR** | 35±20 | 37±21 | 0.5 | 35±20 | 37±21 | 0.5 | 35±20 | 37±21 | 0.5 |
| **24 hour urinary protein** | 0.8±1.1 | 0.8±0.8 | 0.8 | 0.8±1.1 | 0.8±0.8 | 0.8 | 0.8±1.1 | 0.8±0.8 | 0.8 |
| **Systolic blood pressure** | 155±30 | 163±30 | 0.01 | 155±30 | 163±30 | 0.01 | 155±30 | 163±30 | 0.01 |
| **Diastolic blood pressure** | 79±17 | 83±16 | 0.03 | 79±17 | 83±16 | 0.03 | 79±17 | 83±16 | 0.03 |
| **Number of blood pressure medications** | 2.5±1.3 | 2.8±1.4 | 0.1 | 2.5±1.3 | 2.8±1.4 | 0.1 | 2.5±1.3 | 2.8±1.4 | 0.1 |
| **Total cholesterol** | 174±46 | 182±46 | 0.2 | 174±46 | 182±46 | 0.2 | 174±46 | 182±46 | 0.2 |
| **Left stenosis (%)** | 53±32 | 62±31 | 0.01 | 53±32 | 62±31 | 0.01 | 53±32 | 62±31 | 0.01 |
| **Right stenosis (%)** | 51±32 | 60±34 | 0.01 | 51±32 | 60±34 | 0.01 | 51±32 | 60±34 | 0.01 |
| **Patency score** | 96±44 | 79±45 | <0.001 | 96±44 | 79±45 | <0.001 | 96±44 | 79±45 | <0.001 |
| **Angina** | 114 (34%) | 50 (39%) | 0.3 | 114 (34%) | 50 (39%) | 0.3 | 114 (34%) | 50 (39%) | 0.3 |
| **Myocardial infarction** | 101 (30%) | 49 (39%) | 0.07 | 101 (30%) | 49 (39%) | 0.07 | 101 (30%) | 49 (39%) | 0.07 |
| **Stoke / TIA** | 128 (38%) | 54 (43%) | 0.3 | 128 (38%) | 54 (43%) | 0.3 | 128 (38%) | 54 (43%) | 0.3 |
| **Peripheral vascular disease** | 129 (38%) | 55 (43%) | 0.3 | 129 (38%) | 55 (43%) | 0.3 | 129 (38%) | 55 (43%) | 0.3 |
| **Diabetes** | 112 (33%) | 39 (31%) | 0.7 | 112 (33%) | 39 (31%) | 0.7 | 112 (33%) | 39 (31%) | 0.7 |
| **Smoking history** | 60 (18%) | 23 (18%) | 0.9 | 60 (18%) | 23 (18%) | 0.9 | 60 (18%) | 23 (18%) | 0.9 |
| **Angiotensin blockade** | 162 (48%) | 66 (52%) | 0.4 | 162 (48%) | 66 (52%) | 0.4 | 162 (48%) | 66 (52%) | 0.4 |
| **Aspirin** | 178 (53%) | 77 (61%) | 0.1 | 178 (53%) | 77 (61%) | 0.1 | 178 (53%) | 77 (61%) | 0.1 |
| **Statin** | 189 (56%) | 69 (55%) | 0.8 | 189 (56%) | 69 (55%) | 0.8 | 189 (56%) | 69 (55%) | 0.8 |

*Abbreviations: PTRAS - percutaneous renal artery angioplasty and bare metal stenting. eGFR - estimated glomerular filtration rate (CKD-EPI). TIA - transient ischaemic attack.*
*Units: eGFR - ml/min/1.73m$^2$; proteinuria - grams per 24 hours; blood pressure mmHg; cholesterol mg/dL.*
*Patient groups for individual presentations are mutually exclusive. Patients with rapid loss of renal function and refractory hypertension have a single disease presentation and do not feature in any other group. The flash pulmonary edema group contains patients with flash pulmonary edema as a lone presentation and patients with flash pulmonary edema in combination with either refractory hypertension or rapid loss of renal function; none of these patients are represented in other groups. Patients in the low risk group are those without flash pulmonary edema, refractory hypertension or rapid loss of renal function and represent a single category of patients.*

**Table 4.2.3 -** Baseline demographics for subgroups of patients with rapidly declining renal function, refractory hypertension or these presentations in combination

| | Rapidly declining renal function n=46 | | | Refractory hypertension n=116 | | | Rapidly declining renal function and refractory hypertension n=31 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Medical n=33 | PTRAS n=13 | p | Medical n=83 | PTRAS n=33 | p | Medical n=20 | PTRAS n=11 | p |
| **Age** | 74±6 | 72±4 | 0.3 | 71±10 | 68±11 | 0.2 | 72±8 | 71±7 | 0.7 |
| **eGFR** | 29±13 | 29±15 | 0.9 | 38±20 | 35±20 | 0.4 | 31±12 | 35±22 | 0.5 |
| **24 hour urinary protein** | 0.7±0.6 | 0.5±0.5 | 0.4 | 0.8±0.9 | 0.7±0.6 | 0.8 | 0.8±0.8 | 0.7±0.5 | 0.7 |
| **Systolic blood pressure** | 147±27 | 141±24 | 0.5 | 165±24 | 175±25 | 0.06 | 161±17 | 177±21 | 0.03 |
| **Diastolic blood pressure** | 77±16 | 75±9 | 0.7 | 79±14 | 87±18 | 0.01 | 83±16 | 86±14 | 0.6 |
| **Number of blood pressure medications** | 2.2±1.4 | 2.4±0.7 | 0.7 | 3.6±1.1 | 3.5±1.5 | 0.9 | 3.6±1 | 4.2±1.1 | 0.1 |
| **Total cholesterol** | 170±42 | 159±35 | 0.3 | 174±46 | 201±43 | 0.01 | 174±46 | 166±50 | 0.7 |
| **Left stenosis (%)** | 49±32 | 60±32 | 0.3 | 53±33 | 65±32 | 0.08 | 53±36 | 62±33 | 0.5 |
| **Right stenosis (%)** | 48±29 | 52±23 | 0.6 | 44±34 | 65±33 | <0.001 | 62±21 | 70±28 | 0.4 |
| **Patency score** | 103±37 | 88±32 | 0.2 | 103±42 | 70±41 | <0.001 | 85±43 | 68±47 | 0.3 |
| **Angina** | 14 (42%) | 8 (62%) | 0.2 | 24 (29%) | 13 (39%) | 0.3 | 6 (30%) | 4 (36%) | 0.7 |
| **Myocardial infarction** | 12 (36%) | 7 (54%) | 0.3 | 20 (24%) | 11 (33%) | 0.3 | 4 (20%) | 3 (27%) | 0.6 |
| **Stoke / TIA** | 12 (36%) | 5 (39%) | 0.9 | 29 (35%) | 18 (55%) | 0.05 | 14 (70%) | 3 (27%) | 0.02 |
| **Peripheral vascular disease** | 8 (24%) | 6 (46%) | 0.2 | 36 (43%) | 13 (39%) | 0.7 | 5(25%) | 3 (27%) | 0.9 |
| **Diabetes** | 14 (42%) | 6 (46%) | 0.8 | 28 (34%) | 8 (24%) | 0.3 | 6(30%) | 7 (64%) | 0.07 |
| **Smoking history** | 5 (15%) | 2 (15%) | 0.9 | 17 (20%) | 6 (18%) | 0.8 | 2 (10%) | 2 (18%) | 0.5 |
| **Angiotensin blockade** | 17 (52%) | 6 (46%) | 0.7 | 51 (61%) | 19 (58%) | 0.7 | 13 (65%) | 9 (82%) | 0.3 |
| **Aspirin** | 9 (27%) | 11 (85%) | <0.001 | 54 (65%) | 21 (64%) | 0.9 | 10 (50%) | 7 (64%) | 0.5 |
| **Statin** | 22 (67%) | 11 (85%) | 0.2 | 58 (70%) | 14 (42%) | 0.01 | 16 (80%) | 11 (100%) | 0.1 |

*Abbreviations: PTRAS - percutaneous renal artery angioplasty and bare metal stenting. eGFR - estimated glomerular filtration rate (CKD-EPI). TIA - transient ischaemic attack.*
*Units: eGFR - ml/min/1.73m$^2$; proteinuria - grams per 24 hours; blood pressure mmHg; cholesterol mg/dL.*
*Patient groups for individual presentations are mutually exclusive. Patients with rapid loss of renal function and refractory hypertension have a single disease presentation and do not feature in any other group. The flash pulmonary edema group contains patients with flash pulmonary edema as a lone presentation and patients with flash pulmonary edema in combination with either refractory hypertension or rapid loss of renal function; none of these patients are represented in other groups. Patients in the low risk group are those without flash pulmonary edema, refractory hypertension or rapid loss of renal function and represent a single category of patients.*

**Table 4.2.4 -** Summary event data for overall study population and low risk and flash pulmonary oedema subgroups

| | **All patients** | | | **Low risk patients** | | | **Flash pulmonary oedema** | | |
|---|---|---|---|---|---|---|---|---|---|
| | All n=467 | Medical n=340 | PTRAS n=127 | All n=237 | Medical n=179 | PTRAS n=58 | All n=37 | Medical n=25 | PTRAS n=12 |
| **Death** | 255 (55%) | 189 (56%) | 66 (52%) | 135 (57%) | 104 (58%) | 31 (53%) | 26 (50%) | 19 (76%) | 7 (58%) |
| **Cardiovascular event** | 155 (33%) | 110 (32%) | 45 (35%) | 71 (30%) | 54 (30%) | 17 (29%) | 17 (46%) | 12 (48%) | 5 (41%) |
| **End stage kidney disease** | 83 (18%) | 60 (18%) | 23 (18%) | 43 (18%) | 32 (18%) | 11 (19%) | 9 (24%) | 6 (24%) | 3 (25%) |

**Table 4.2.5 -** Summary event data for subgroups of patients with rapidly declining renal function, refractory hypertension or these presentations in combination

| | **Rapidly declining renal function** | | | **Refractory hypertension** | | | **Rapidly declining renal function and refractory hypertension** | | |
|---|---|---|---|---|---|---|---|---|---|
| | All n=46 | Medical n=33 | PTRAS n=13 | All n=46 | Medical n=33 | PTRAS n=13 | All n=46 | Medical n=33 | PTRAS n=13 |
| **Death** | 21 (46%) | 15 (45%) | 6 (46%) | 21 (46%) | 15 (45%) | 6 (46%) | 21 (46%) | 15 (45%) | 6 (46%) |
| **Cardiovascular event** | 14 (30%) | 9 (28%) | 5 (38%) | 14 (30%) | 9 (28%) | 5 (38%) | 14 (30%) | 9 (28%) | 5 (38%) |
| **End stage kidney disease** | 7 (15%) | 5 (15%) | 2 (15%) | 7 (15%) | 5 (15%) | 2 (15%) | 7 (15%) | 5 (15%) | 2 (15%) |

*Abbreviations: PTRAS – percutaneous renal artery angioplasty and bare metal stenting.*
*Cardiovascular event defined as myocardial infarction / acute coronary syndrome; hospitalisation for pulmonary edema or dysrhythmia; stroke or transient ischaemic attack; new onset of symptomatic angina or deterioration of existing angina requiring interventional procedure.*
*End stage kidney disease defined as initiation of chronic renal replacement therapy, transplantation or estimated glomerular filtration rate <10ml/min/1.73m$^2$*

**Table 4.2.6 -** Comparison of baseline demographics of included and excluded patients

| | Included in analysis n=467 | Excluded from analysis n=343 | p |
|---|---|---|---|
| **Age (years)** | 70.2±9.1 | 69.3±10.4 | 0.2 |
| **eGFR (ml/min/1.73m²)** | 35.4±20.1 | 40±24.7 | <0.001 |
| **24 hour urinary protein (g/24 hours)** | 0.8±1.1 | 0.7±1.3 | 0.3 |
| **Systolic blood pressure (mmHg)** | 156.7±29.9 | 153.7±28.1 | 0.2 |
| **Diastolic blood pressure (mmHg)** | 80.3±16.6 | 80.3±14.9 | 0.9 |
| **Number of antihypertensive agents** | 2.6±1.3 | 2.3±1.3 | <0.001 |
| **Total cholesterol (mg/dL)** | 174±46 | 178±54 | 0.6 |
| **Patency score** | 92.4±44.3 | 125.6±41.3 | <0.001 |
| **Angina** | 164(35.2%) | 121(34.5%) | 0.8 |
| **Myocardial infarction** | 150(32.1%) | 89(25.4%) | 0.04 |
| **Stoke / transient ischaemic attack** | 182(39%) | 113(32.1%) | 0.04 |
| **Peripheral vascular disease** | 184(39.4%) | 115(32.8%) | 0.05 |
| **Diabetes** | 151(32.3%) | 102(29%) | 0.3 |
| **Smoking history** | 83(17.8%) | 44(12.5%) | 0.04 |
| **Angiotensin blockade** | 228(48.8%) | 158(44.9%) | 0.3 |
| **Aspirin** | 255(55.3%) | 184(52.9%) | 0.5 |
| **Statin** | 258(56%) | 170(48.9%) | 0.04 |

*Abbreviations: eGFR – estimated glomerular filtration rate (CKD-EPI)*
*Patency score describes an overall assessment of patency of dominant renal artery, where a maximum score of 200 represents bilateral 0% stenosis and a minimum score of 0 represents bilateral 100% stenosis.*
*Normally distributed continuous variables expressed as mean ± standard deviation. Non-parametric continuous variables expressed as median (interquartile range). Categorical variables expressed as number (percentage).*
*Patients excluded from analysis due to missing baseline data or bilateral stenosis <50% on biplane measurement.*

Medically managed patients with FPO had an increased hazard ratio for death and cardiovascular event compared to low-risk medically managed patients - death HR 2.2 [95% CI 1.4-3.5]; cardiovascular event HR 3.1 [95% CI 1.7-5.5], p<0.001 for both; but not for ESKD HR 1.9 [95% CI 0.8-4.4], p=0.1. No significantly increased risk for any end-point was observed in patients with rapidly declining renal function or refractory hypertension, table 4.2.7.

**Table 4.2.7** - Associations between high-risk presentations and risk for end-point in medically managed patients

| | **FLASH PULMONARY OEDEMA** | | **RAPIDLY DECLINING RENAL FUNCTION** | | **REFRACTORY HYPERTENSION** | |
|---|---|---|---|---|---|---|
| | **Hazard ratio (95% confidence interval)** | **p** | **Hazard ratio (95% confidence interval)** | **p** | **Hazard ratio (95% confidence interval)** | **p** |
| **Death** | 2.19 (1.39-3.47) | <0.001 | 0.69 (0.42-1.12) | 0.1 | 0.82 (0.59-1.14) | 0.2 |
| **Cardiovascular event** | 3.07 (1.71-5.51) | <0.001 | 0.77 (0.41-1.48) | 0.4 | 1.1 (0.67-1.62) | 0.9 |
| **End stage kidney disease** | 1.89 (0.81-4.43) | 0.1 | 0.72 (0.381-1.69) | 0.5 | 0.82 (0.45-1.51) | 0.5 |

*Cardiovascular event defined as myocardial infarction / acute coronary syndrome; hospitalisation for pulmonary edema or dysrhythmia; stroke or transient ischaemic attack; new onset of symptomatic angina or deterioration of existing angina requiring interventional procedure.*
*End stage kidney disease defined as initiation of chronic renal replacement therapy, transplantation or estimated glomerular filtration rate <10ml/min/1.73m$^2$*

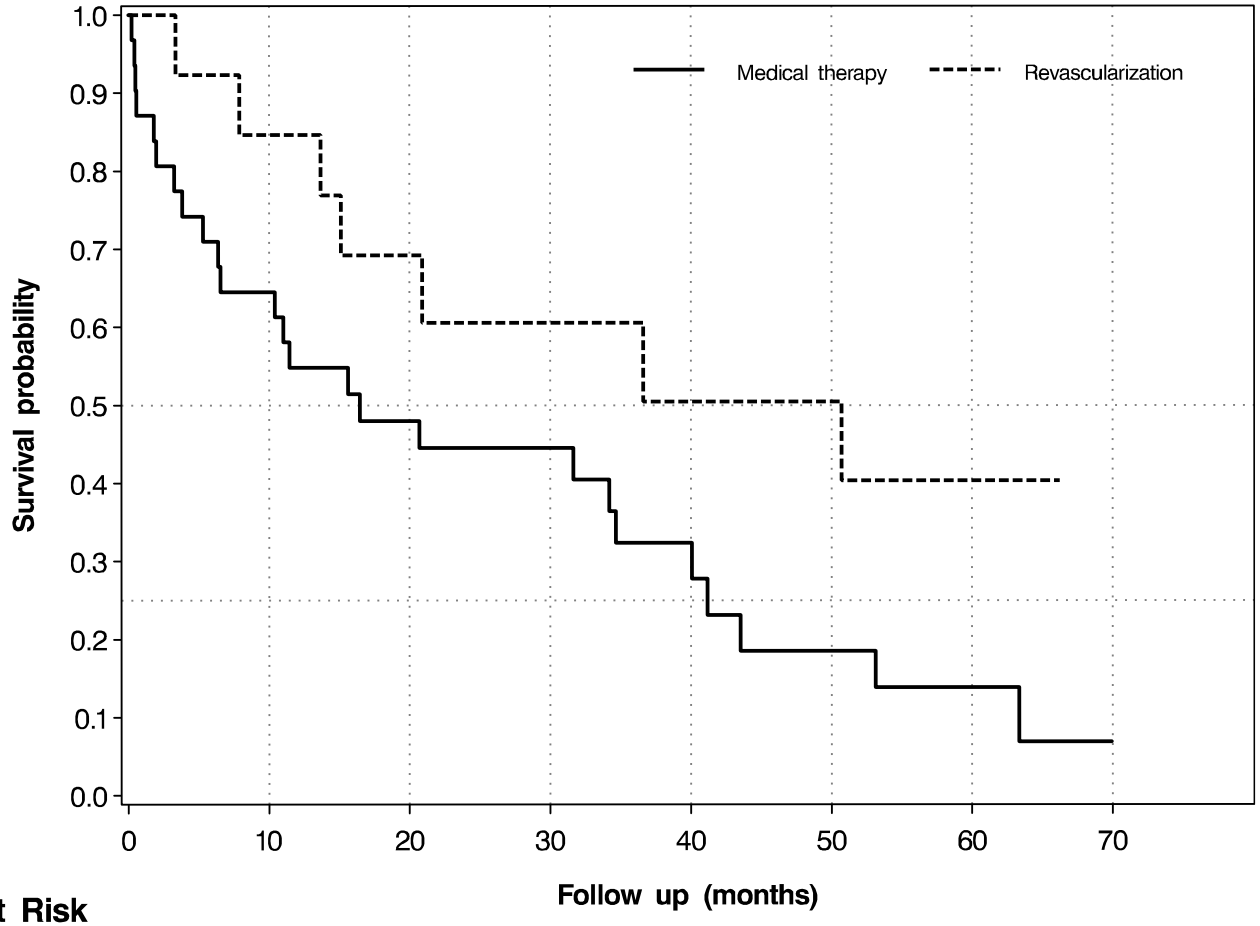
In the whole cohort, 127 (27%) patients were revascularised with a 93% documented technical success rate and 4.8% major complication rate. Median time from diagnosis to revascularisation was 5.1 (IQR 2.7-10.4) months. The effects of revascularisation were analysed on an intention to treat basis. When low-risk patients were considered alone, revascularisation was not associated with any significant change in hazard ratio for any major end-point (HR death 0.8 [95% CI 0.7-1.2]; cardiovascular event 1.0 [95% CI 0.8-1.2]; ESKD 1.0 [95% CI 0.7-1.4]).

In patients with FPO, revascularisation was associated with a significant reduction in risk for death (HR 0.43 [95% CI 0.2-0.9], p=0.01, figure 4.5.2) with a corresponding reduction in event rate (deaths/100 patient years: revascularisation 14, medical 37, p=0.02). This survival benefit was observed across all levels of baseline eGFR, figure 4.2.3. Although no reduction in hazard ratio for cardiovascular event or ESKD was observed in revascularised FPO patients (HR 1.1 [95% CI 0.4-3.0] and 1.4 [95% CI 0.4-5.2] respectively, p for both >0.7), a non-significant trend towards lower cardiovascular event rates was seen in revascularised patients, revascularisation 14, medical 32/100 patient years, p=0.2.

No difference in risk for death or ESKD was observed in revascularised patients who presented with rapidly declining renal function or refractory hypertension. However, non-significant increases in risk for cardiovascular events were seen in revascularised patients in both of these groups; rapidly declining renal function HR 1.76 [95% CI 0.8-3.8], p=0.2, refractory hypertension HR 1.3 [95% CI 0.8-1.9], p=0.3. The same trend was observed when event rates were considered for these presentations (medical vs. revascularisation); rapidly declining renal function 9 vs. 12/100 patient years, p=0.4, refractory hypertension 9 vs. 12/100 patient years, p=0.3. Complete data are presented in table 4.2.8.

Limited patient numbers precluded meaningful assessment of combined FPO and rapidly declining renal function (8 patients, 3 revascularised), or FPO and refractory hypertension (8 patients, 2 revascularised). However, sufficient patients presented with refractory hypertension and rapid loss of renal function (31 patients, 11 revascularised) for analysis. In this patient group, medical treatment was associated with an increased risk for cardiovascular events and ESKD (HR 2.1 [95% CI 1.2-3.8] and 2.4 [95% CI 1.3-3.9] respectively, p for both <0.02), but not death (HR 1.2 [95% CI 0.8-2.0], p=0.4). Revascularisation was associated with significant reductions both in risk for death (HR 0.12 [95% CI 0.02-0.77], p=0.03, figure 4.2.4) and cardiovascular event (HR 0.28 [95% CI 0.1-0.6], p<0.001). Insufficient end-points existed (8 in medical group, 1 in revascularisation group) to meaningfully comment on risk for progression to ESKD, table 4.2.8.

**Figure 4.2.2 -** Kaplan Meier survival plot for patients presenting with flash pulmonary oedema




| Number at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Medical therapy | 31 | 17 | 13 | 8 | 4 | 2 |
| Revascularization | 13 | 11 | 6 | 6 | 5 | 4 |

*Solid line represents patients managed with medical therapy; dashed line represents patients treated with percutaneous renal artery angioplasty and bare metal stenting.*

*X-axis shows time in months from diagnostic angiography. Y-axis shows event free survival.*

**Figure 4.2.3** - Predicted time to death by eGFR and treatment type in patients presenting with flash pulmonary oedema

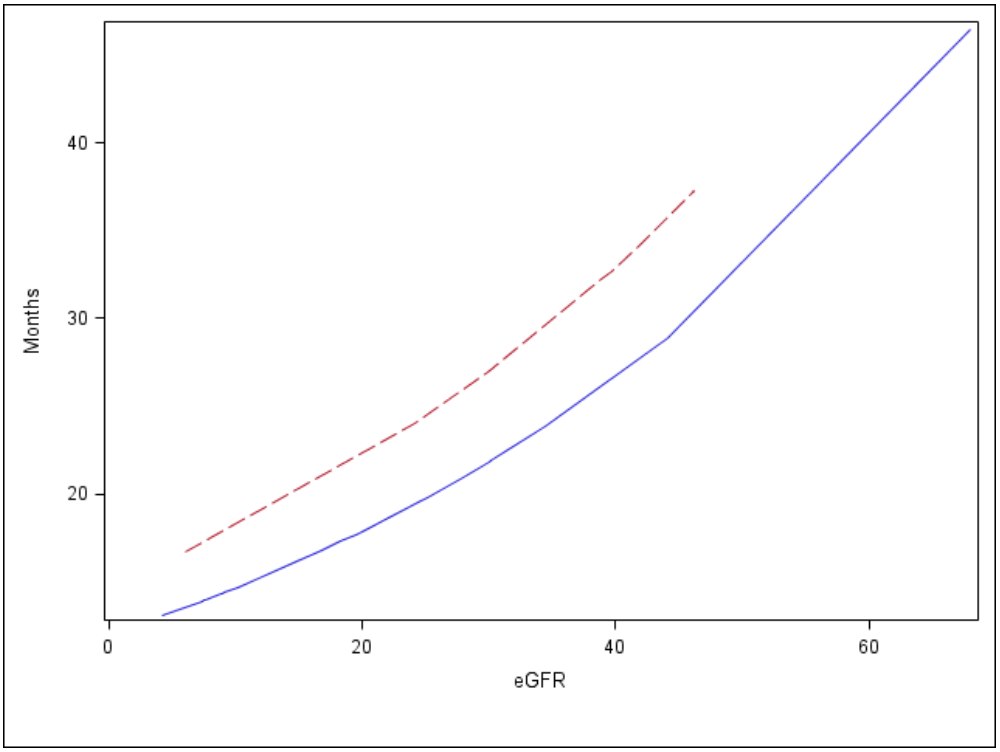



*Figure shows survival time for patients presenting with flash pulmonary oedema who died during follow-up period divided by treatment type.*
*X-axis – estimated glomerular filtration rate at time of diagnostic angiography (ml/min/1.73m$^2$)*
*Y-axis – time to death from diagnostic angiography (months)*
*Solid line – medically treated patients*
*Dashed line – patients treated with percutaneous renal angioplasty and bare metal stenting*

**Table 4.2.8** - Effect of revascularisation on risk for and rate of end-points divided by clinical presentation for patients presenting with flash pulmonary oedema or rapidly declining renal function

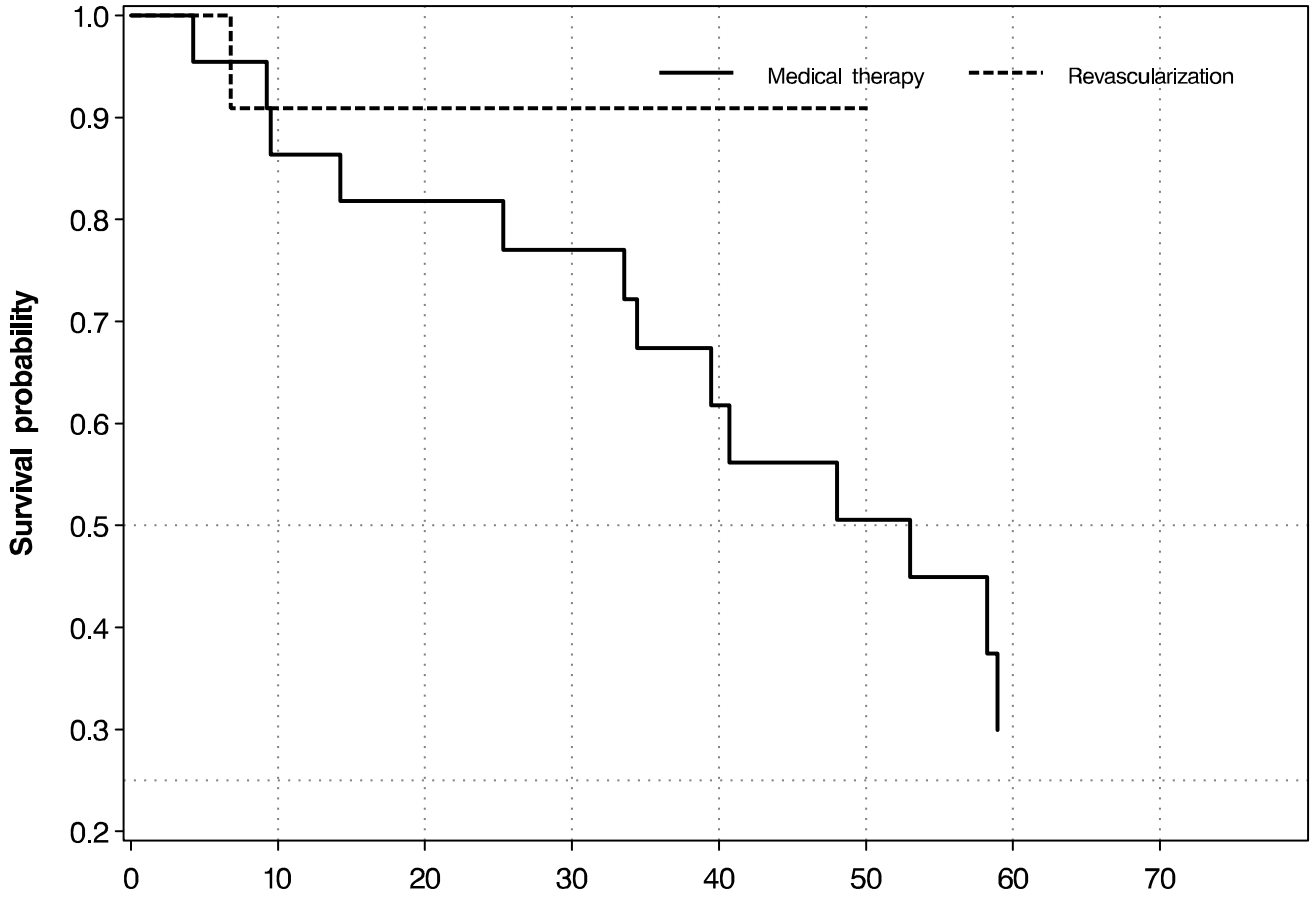
| | FLASH PULMONARY OEDEMA | | | | | RAPIDLY DECLINING RENAL FUNCTION | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **HR (95% CI)** | **p** | **ER (95% CI)** | **RR (95%CI)** | **p** | **HR (95% CI)** | **p** | **ER (95% CI)** | **RR (95%CI)** | **p** |
| **Death** | 0.43 (0.20-0.91) | 0.01 | 37 (23-57) vs. 14 (7-29) | 0.36 (0.16-0.8) | 0.02 | 0.8 (0.43-1.43) | 0.5 | 11 (7-18) vs. 10 (4-20) | 0.91 (0.37-2.3) | 0.9 |
| **CVE** | 1.13 (0.41-3.01) | 0.8 | 31 (18-52) vs. 14 (6-32) | 0.44 (0.16-1.26) | 0.2 | 1.76 (0.84-3.81) | 0.2 | 9 (5-15) vs. 12 (5-28) | 1.54 (0.52-4.3) | 0.4 |
| **ESKD** | 1.36 (0.35-5.2) | 0.7 | 12 (5-27) vs. 7 (2-22) | 0.60 (0.15-2.41) | 0.5 | 0.76 (0.36-2.17) | 0.6 | 4 (2-10) vs. 3 (1-14) | 0.84 (0.18-4.1) | 0.8 |

**Table 4.2.9** - Effect of revascularisation on risk for and rate of end-points divided by clinical presentation for patients presenting with refractory hypertension in isolation or in combination with rapidly declining renal function

| | REFRACTORY HYPERTENSION | | | | | RAPIDLY DECLINING RENAL FUNCTION AND REFRACTORY HYPERTENSION | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **HR (95% CI)** | **p** | **ER (95% CI)** | **RR (95%CI)** | **p** | **HR (95% CI)** | **p** | **ER (95% CI)** | **RR (95%CI)** | **p** |
| **Death** | 1.09 (0.77-1.55) | 0.6 | 12 (8-19) vs. 12 (8-16) | 1.05 (0.62-1.80) | 0.8 | 0.15 (0.02-0.94) | 0.04 | 18 (11-30) vs. 2 (0.3-16) | 0.14 (0.01-0.99) | 0.01 |
| **CVE** | 1.30 (0.79-1.9) | 0.3 | 9 (6-13) vs. 12 (8-21) | 1.43 (0.75-2.8) | 0.3 | 0.28 (0.1-0.79) | 0.02 | 19 (10-32) vs. 8 (2-24) | 0.4 (0.11-1.4) | 0.1 |
| **ESKD** | 1.25 (0.71-2.26) | 0.3 | 4 (3-7) vs. 4 (2-9) | 1.10 (0.41-2.97) | 0.8 | *Insufficient end-points* | | | | |

*Abbreviations: PTRAS - percutaneous renal artery angioplasty and bare metal stenting. CI - confidence interval. CVE - cardiovascular event. ESKD - end stage kidney disease.*
*Results are expressed as hazard ratio, event rate per 100 patient years or relative rate with 95% confidence interval in parenthesis.*
*Poisson model adjusted for age, renal function, proteinuria, blood pressure, overall renal artery patency, gender, presence of diabetes and use of angiotensin blockade.*
*Cox model adjusted for presence of diabetes and use of angiotensin blockade where appropriate with weighting for inverse probability of treatment calculated from age, renal function, blood pressure, proteinuria and overall real artery patency score.*

**Figure 4.2.4 -** Kaplan Meier survival plot for patients presenting with rapidly declining renal function and refractory hypertension




| Number at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Medical therapy | 22 | 19 | 17 | 13 | 10 | 4 |
| Revascularization | 11 | 10 | 9 | 6 | 5 | 3 |

*Solid line represents patients managed with medical therapy; dashed line represents patients treated with percutaneous renal artery angioplasty and bare metal stenting.*

*X-axis shows time in months from diagnostic angiography. Y-axis shows event free survival.*

Within the entire cohort, the median rate of loss of renal function was 2ml/min/1.73m$^2$/year with no significant difference between medically managed and revascularised patients. No difference in rate of eGFR loss was observed between medically treated and revascularised patients in any high-risk sub-group. Systolic and diastolic blood pressures fell in both medically treated and revascularised patients within each group. No significant differences in blood pressure reductions between medical and revascularisation groups was observed for any high-risk presentation, with the exception of a greater reduction in diastolic blood pressure in revascularised patients with refractory hypertension at baseline, table 4.2.10.

**Table 4.2.10** - Annual differences in blood pressure and renal function between treatment groups

| | | Year 0 | Year 1 | Year 2 | Year 3 | p within group | p between groups |
|---|---|---|---|---|---|---|---|
| **Flash pulmonary oedema** | | | | | | | |
| **Number of patients with available data** | *Medical* | 25 | 16 | 12 | 9 | - | - |
| | *PTRAS* | 12 | 10 | 6 | 3 | - | - |
| **Systolic blood pressure (mmHg)** | *Medical* | 152±31 | 137±28 | 138±34 | 132±19 | 0.2 | 0.1 |
| | *PTRAS* | 171±21 | 155±17 | 142±25 | 144±21 | 0.05 | |
| **Diastolic blood pressure (mmHg)** | *Medical* | 78±17 | 73±13 | 73±17 | 71±8 | 0.4 | 0.2 |
| | *PTRAS* | 83±12 | 81±11 | 75±8 | 86±8 | 0.5 | |
| **Median annual eGFR change (ml/min/1.73m²)** | *Medical* | 0.0 (-3.9 to +0.01) | | | | | 0.3 |
| | *PTRAS* | 0.1 (-4.8 to +0.7) | | | | | |
| **Rapidly declining renal function** | | | | | | | |
| **Number of patients with available data** | *Medical* | 33 | 29 | 25 | 18 | - | - |
| | *PTRAS* | 13 | 13 | 12 | 9 | - | - |
| **Systolic blood pressure (mmHg)** | *Medical* | 151±28 | 144±24 | 142±25 | 147±34 | 0.3 | 0.1 |
| | *PTRAS* | 139±22 | 141±33 | 131±16 | 139±23 | 0.8 | |
| **Diastolic blood pressure (mmHg)** | *Medical* | 79±16 | 76±15 | 75±14 | 75±15 | 0.4 | 0.02 |
| | *PTRAS* | 74±9 | 69±14 | 66±11 | 63±13 | 0.07 | |
| **Median annual eGFR change (ml/min/1.73m²)** | *Medical* | -0.38 (-3.1 to 0.0) | | | | | 0.3 |
| | *PTRAS* | -2.2 (-3.7 to 0.0) | | | | | |
| **Refractory hypertension** | | | | | | | |
| **Number of patients with available data** | *Medical* | 83 | 72 | 53 | 43 | - | - |
| | *PTRAS* | 33 | 29 | 24 | 20 | - | - |
| **Systolic blood pressure (mmHg)** | *Medical* | 166±23 | 158±25 | 152±23 | 147±24 | <0.001 | 0.5 |
| | *PTRAS* | 175±24 | 156±29 | 148±27 | 155±21 | <0.001 | |
| **Diastolic blood pressure (mmHg)** | *Medical* | 80±14 | 78±13 | 77±13 | 73±14 | <0.001 | 0.3 |
| | *PTRAS* | 87±17 | 80±13 | 76±12 | 79±14 | 0.001 | |
| **Median annual eGFR change (ml/min/1.73m²)** | *Medical* | -2.6 (-5.8 to 0.1) | | | | | 0.5 |
| | *PTRAS* | -1.2 (-4.9 to 0.0) | | | | | |
| **Rapidly declining renal function and refractory hypertension** | | | | | | | |
| **Number of patients with available data** | *Medical* | 20 | 18 | 16 | 13 | - | - |
| | *PTRAS* | 11 | 10 | 9 | 6 | - | - |
| **Systolic blood pressure (mmHg)** | *Medical* | 157±19 | 157±27 | 147±24 | 157±29 | 0.3 | 0.6 |
| | *PTRAS* | 177±21 | 150±17 | 146±17 | 132±27 | 0.001 | |
| **Diastolic blood pressure (mmHg)** | *Medical* | 81±16 | 74±12 | 73±11 | 76±9 | 0.03 | 0.8 |
| | *PTRAS* | 86±13 | 70±14 | 74±13 | 70±19 | 0.03 | |
| **Median annual eGFR change (ml/min/1.73m²)** | *Medical* | -3.2 (-11 to 0.5) | | | | | 0.3 |
| | *PTRAS* | -2.2 (-6.7 to 1.0) | | | | | |

Discussion

This cohort of 467 patients, with an overall 27% revascularisation rate – comparable to that seen in Medicare claims data [3], includes the largest series of patients with FPO, and the only series of FPO patients to include a medical comparator group. These data, representing over 15 years of clinical practice, reflect the findings of ASTRAL and other randomised trials in a "*real-life"* setting - that for an unselected population of ARVD patients, revascularisation does not alter any hard clinical outcome. This top-line finding is because low-risk patients do not benefit. With the most recent trials describing the potential for serious complications of revascularisation [2,18], acceptance of this is vital to prevent exposure of patients to unnecessary risks. However, this study emphasises that a significant proportion of patients with ARVD (51% in this cohort) present in a manner that could be considered higher-risk based upon current guidance.

We have demonstrated that of these three putative high-risk presentations, only FPO can be considered to be an adverse prognostic marker, with significantly increased risks for death and cardiovascular events associated with this presentation in medically managed patients. As importantly, we have shown an association between revascularisation and a reduced risk for death for this presentation. While Cox analysis did not demonstrate a reduction in risk for cardiovascular events in revascularised FPO patients, a result in contrast with existing data[8], there was a trend towards reduced event rates. We would, therefore, suggest the apparent lack of benefit from revascularisation in terms of cardiovascular events could be a function of improved survival in a high-risk patient group. Our findings provide support for current guidelines [7] citing FPO as an indication for revascularisation. This is important as the guidelines are largely based upon consensus opinion as underpinning data has predominantly derived from case-series [8,19,20]. Previous reports have demonstrated revascularisation for FPO can significantly reduce the rate of hospitalisation with decompensated heart failure [8]. Potentially, revascularisation may also improve the structural cardiac changes seen in ARVD as described in case reports [21,22]. It remains to be seen whether cardiac imaging sub-studies of ASTRAL provide further pathophysiological insights [23].

No association with increased risk for any end-point, nor any reduction in risk associated with revascularisation, was observed in patients presenting with rapidly declining function or refractory hypertension. However, there was a suggestion that these phenotypes may be important when presenting in combination. Although patient numbers were small, significant reductions in risk for death and cardiovascular event were associated with revascularisation in patients with both of these phenotypes at baseline. This combination could conceivably be a clinical manifestation of a specific anatomical pattern amenable to revascularisation e.g. high-grade anatomical stenosis with preserved renal parenchymal volume [24]. However, due to the range of diagnostic imaging methods and timeframe over which data were acquired, estimation of renal volume could not be performed. Further study is required, but our findings would suggest that when the clinician is faced with an ARVD patient with this combination, revascularisation could be considered.

An important question raised by these results is whether either rapid loss of renal function or refractory hypertension truly represents a high-risk clinical presentation of ARVD. We would suggest that refractory hypertension *by the definition employed here* does not. This may partly relate to the blunt nature of clinic blood pressure as a marker of cardiovascular health with e.g. left ventricular dysfunction confounding by “masking” hypertension. Alternatively this may reflect the fact that significantly elevated blood pressure is found even in ‘low-risk’ ARVD patients, or that successful treatment of hypertension can be achieved by pharmacological methods in this patient group. Given the established effects of uncontrolled blood pressure in CKD [25] it would be patently false to claim that no risk is associated with extreme values of blood pressure in ARVD. However, our analysis suggests that there may be value in reconsidering where the threshold for increased risk lies in this patient group. The assessment of rapid loss of renal function is again uncertain. Our data conflict with the sub-group analysis of patients with rapidly declining renal function within ASTRAL where revascularised patients showed a trend to reduced loss of renal function at 12-months. In another study that compared medically managed patients from the United Kingdom, with revascularised patients managed at a German center, a benefit in renal function at one year was seen in revascularised patients with CKD stage 4/5 [26]. The disparity in

outcomes may be explained by the longer follow up period in our study (i.e. a non-sustained improvement in eGFR), or a difference in practice between countries in the twin center study [26], with approximately 50% of revascularised patients with rapidly declining renal function in our cohort classified as CKD stage 3 at baseline. Patient-level analysis of existing randomised trials, examining different definitions of rapidly declining function and refractory hypertension may be of value.

Although the findings were non-significant, the trends towards increased cardiovascular risk in revascularised patients with rapid loss of renal function and (to a lesser extent) refractory hypertension, merit consideration. This may reflect unmeasured differences between treatment groups, which although well matched for overall cardiovascular history at baseline may have had important differences in e.g. burden of coronary atheroma.

In this study, the average rate of loss of renal function across all groups was 2ml/min/1.73m$^2$/year, only double that which might be accepted with aging [27], a fact of importance for the design of future trials. This suggests limited utility in future studies considering progression to ESKD as an end-point. With an overall baseline eGFR of 33ml/min/1.73m$^2$ in this study (and similar values in published trials), a prolonged follow-up period would be required to observe any difference in renal functional outcomes.

These analyses have been performed in a patient cohort where detailed clinical and laboratory data have been prospectively and studiously collected over 15 years. Whilst the single center patient management, rigor of data collection, and real-life setting are strengths of the work, there are still important limitations of what is a retrospective analysis – primarily a lack of randomisation of patients and the likelihood of selection bias. Although analyses were weighted for probability of receiving treatment, statistical techniques cannot account for unmeasured or intangible clinical factors, and uncontrolled confounding must be considered a possibility. Patient and event numbers limiting our ability to adjust within Cox models may have compounded this. Furthermore it is inappropriate to claim that weighting by a selection of clinical measurements can completely reflect the complexity of making a treatment decision. That only 25% of

potentially high-risk patients were revascularised may imply an unspecified selection bias (e.g. with only the most unwell patients undergoing intervention), but this may also reflect the difficulty of the decision making process based upon currently available data and known risks of intervention. Although intervention at time of diagnostic angiography is performed by many centers, this has not been a standard practice at our center. As our dataset records only those interventions that were actually undertaken as opposed to planned, it is possible that a small number of patients referred for revascularisation may have died prior to receiving treatment. As patients were analysed by treatment received this should be considered as a possible confounding issue. However, review of the notes of medically managed FPO patients identified only one such patient who died waiting for revascularisation. Interventional procedures for FPO also occurred over a shorter time frame with median time to revascularisation 1.6 [IQR 0.3-5.9] months. Other relevant limitations of our study should also be highlighted. Stenosis grade was assessed in biplane measurement only (without measurement of renal resistive index or pressure gradient), and no information regarding rationale for investigation of ARVD was available (with variation in approach to diagnostic testing potentially influencing results). In addition, 32% of cases were diagnosed using magnetic resonance angiography, which may overestimate degree of stenosis [28]. Medication type, but not dosage is not recorded, and the models used do not account for longitudinal changes in therapy or blood pressure. In addition clinical presentation was defined at the time of diagnostic angiography. Although local practice is to review the indication for intervention immediately prior to revascularisation, we cannot account for any change in status between diagnosis and intervention. Finally, although our revascularisation rate is comparable to Medicare data, the rate of intervention for FPO is lower than might be anticipated, suggesting either a treatment bias or a limitation of our definition. With 40% of FPO patients in this series having bilateral stenosis >50%, we believe we successfully identified patients with a significant burden of renal arterial disease. As such, the lower than anticipated intervention rates may reflect the time period over which these data have been recorded and the variation in access to revascularisation services.

In summary, although this study has limitations we believe that it provides strong data confirming FPO as a risk factor for adverse outcomes in ARVD and supporting revascularisation for this presentation. The data regarding management of refractory hypertension and rapidly declining function are less clear - in part due to imprecision of definition of the conditions, and in part due to other confounders (e.g. changes in medications), which were not available for analysis. Although medically managed patients with sole rapidly declining function or refractory hypertension did not have increased risk for end-points, the observed benefits from revascularisation in the sub-group where refractory hypertension and rapidly declining function co-existed warrant further study to confirm the results and elucidate potential mechanisms.

## References


1. Kalra PA, Guo H, Gilbertson DT, et al. Atherosclerotic renovascular disease in the United States. Kidney International. 2009;77(1):37–43.

2. ASTRAL Investigators, Wheatley K, Ives N, et al. Revascularisation versus medical therapy for renal-artery stenosis. N. Engl. J. Med. 2009;361(20):1953–1962.

3. Kalra PA, Guo H, Kausz AT, et al. Atherosclerotic renovascular disease in United States patients aged 67 years or older: risk factors, revascularisation, and prognosis. Kidney International. 2005;68(1):293–301.

4. Leertouwer TC, Gussenhoven EJ, Bosch JL, et al. Stent placement for renal arterial stenosis: where do we stand? A meta-analysis. Radiology. 2000;216(1):78–85.

5. Valluri A, Severn A, Chakraverty S. Do patients undergoing renal revascularisation outside of the ASTRAL trial show any benefit? Results of a single centre observational study. Nephrol Dial Transplant. 2012;27(2):734-738.

6. United Kingdom Hospital Episode Statistics. Available at: http://www.hesonline.co.uk. Accessed December 12, 2011.

7. 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. J Vasc Interv Radiol. 2006;17(9):1383–1397.

8. Kane GC, Xu N, Mistrik E, Roubicek T, Stanson AW, Garovic VD. Renal artery revascularisation improves heart failure control in patients with atherosclerotic renal artery stenosis. Nephrology Dialysis Transplantation. 2010;25(3):813–820.

9. Kanamori H, Toma M, Fukatsu A. Improvement of renal function after opening occluded atherosclerotic renal arteries. J Invasive Cardiol. 2009;21(9):E171–174.

10. Chrysochou C, Sinha S, Chalmers N, Kalra PR, Kalra PA. Anuric acute renal failure and pulmonary oedema: a case for urgent action. Int. J. Cardiol. 2009;132(1):e31–33.

11. Kuznetsov E, Schifferdecker B, Jaber BL, Soukas P, Liangos O. Recovery of acute renal failure following bilateral renal artery angioplasty and stenting. Clin. Nephrol. 2007;68(1): 32–37.

12. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann. Intern. Med. 2009;150(9):604–612.

13. UK Renal Association eCKD guide. Available at: http://www.renal.org. Accessed December 12, 2011.

14. Rimoldi SF, Yuzefpolskaya M, Allemann Y, Messerli F. Flash pulmonary edema. Progress in Cardiovascular Diseases. 2009;52(3):249–259.

15. Mancia G, De Backer G, Dominiczak A, et al. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). European Heart Journal. 2006;28(12):1462–1536.

16. Lunceford JKJ, Davidian MM. Stratification and weighting via the propensity score in estimation of causal treatment effects: a comparative study. Statist. Med. 2004;23(19): 2937–2960.

17. Suresh M, Laboi P, Mamtora H, Kalra PA. Relationship of renal dysfunction to proximal arterial disease severity in atherosclerotic renovascular disease. Nephrol Dial Transplant. 2000;15(5):631–636.

18. Bax L, Woittiez A-JJ, Kouwenberg HJ, et al. Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function: a randomised trial. Ann. Intern. Med. 2009;150(12):840–848.

19. Bloch MJ, Trost DW, Pickering TG, Sos TA, August P. Prevention of recurrent pulmonary edema in patients with bilateral renovascular disease through renal artery stent placement. Am J Hypertens. 1999;12(Pt 1):1–7.

20. Gray BH, Olin JW, Childs MB, Sullivan TM, Bacharach JM. Clinical benefit of renal artery angioplasty with stenting for the control of recurrent and refractory congestive heart failure. Vasc Med. 2002;7(4):275–279.

21. Wright JR, Shurrab AE, Cooper A, Kalra PR, Foley RN, Kalra PA. Left ventricular morphology and function in patients with atherosclerotic renovascular disease. J. Am. Soc. Nephrol. 2005;16(9):2746–2753.

22. Chrysochou C, Sharma R, Kalra PA, Kalra PR. Improved left ventricular filling following bilateral renal artery stenting. Int. J. Cardiol. 2011;150(1):e40–41.

23. Hegarty J, Wright JR, Kalra PR, Kalra PA. The heart in renovascular disease--an association demanding further investigation. Int. J. Cardiol. 2006;111(3):339–342.

24. Cheung CM, Chrysochou C, Shurrab AE, Buckley DL, Cowie A, Kalra PA. Effects of renal volume and single-kidney glomerular filtration rate on renal functional outcome in atherosclerotic renal artery stenosis. Nephrology Dialysis Transplantation. 2010;25(4): 1133–1140.

25. Klahr S, Levey AS, Beck GJ, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. N. Engl. J. Med. 1994;330(13):877–884.

26. Kalra PA, Chrysochou C, Green D, et al. The benefit of renal artery stenting in patients with atheromatous renovascular disease and advanced chronic kidney disease. Cathet. Cardiovasc. Intervent. 2010;75(1):1–10.

27. Hemmelgarn BR, Zhang J, Manns BJ, et al. Progression of kidney dysfunction in the community-dwelling elderly. Kidney International. 2006;69(12):2155–2161.

28. Patel ST, Mills JL, Tynan-Cuisinier G, Goshima KR, Westerband A, Hughes JD. The limitations of magnetic resonance angiography in the diagnosis of renal artery stenosis: comparative analysis with conventional arteriography. J. Vasc. Surg. 2005;41(3):462–468.

# CHAPTER 4.3

**Predicting Progression to End Stage Kidney Disease in Atherosclerotic Renovascular Disease**

Ritchie J, Foley R, Green D, Chrysochou C, Kalra PA

Preface

It is recognized that in ARVD the risk for death exceeds that for progression to ESKD. However, each year in ASTRAL approximately 4% of patients reached a renal end-point. Although case reports of improvement in renal function following PTRAS are widely available, randomised studies have not demonstrated an overall benefit in terms of reduced progression to ESKD following revascularisation. It is appropriate to question if these negative findings have been biased by patients at low risk for ESKD being randomised.

The previous results chapters have demonstrated that ARVD should be considered as a specific cause of CKD, and that there is prognostic value in further classifying ARVD by clinical phenotype. This analysis complements these findings by attempting to identify what, if any, are the common characteristics between ARVD patients progressing to ESKD, and thus define a further high-risk sub-type.

> *$H_0$ - Risk for progression to ESKD in ARVD cannot be reliably predicted.*
> *$H_1$ - Patients with ARVD and the greatest risk for progression to ESKD can be identified at an early stage of disease.*

Abstract

Currently there are limited data to describe which patients with ARVD have the greatest risk for progression to ESKD. In this study we consider 565 patients with ARVD ≥50% of whom 113 (20%) progressed to ESKD over a median follow-up time of 14.8 [IQR 5.4-34.5] months. Cox regression and classification tree methodologies were used to identify threshold values of standard clinical measurements with the greatest sensitivity and specificity for predicting progression to ESKD. Results of these analyses were used to generate an ordinal scoring system, grouping patients into low, intermediate and high risk for progression to ESKD. Compared to the low risk group, patients of intermediate risk had a hazard ratio for ESKD of 2.7 (95% CI 1.0-7.5), p=0.06 and patients in the high risk group a HR of 20.4 (95% CI 7.4-56.2), p<0.001. This increased risk persisted when death was considered as a competing end-point; HR 1.5 (95% CI 1.1-2.2), p=0.02 and HR 2.1 (95% CI 1.3-3.2), p=0.002 respectively. When compared to previously described markers of risk for ESKD in ARVD (eGFR <25ml/min/1.73m$^2$ and proteinuria >1g/24 hours), our proposed scoring system increased area under the curve from 0.66 to 0.76 with a net reclassification index of 0.66, p=0.02. Although our proposed model requires external validation, this appears to be a promising method to identify ARVD patients with the greatest risk for progression to ESKD.

Introduction

Atherosclerotic renovascular disease can be identified in 6% of asymptomatic adults aged over 65 [1] and in over 20% of patients with other vascular diseases [2,3]. Although risk for death in ARVD outweighs that for progression to end stage kidney disease, 4% of patients progress to requiring renal replacement therapy each year [4]. This figure may underestimate the true burden of ESKD associated with ARVD, as it does not consider patients who opt for conservative care. Despite randomised trials now having considered in excess of 1200 ARVD patients [5], no analysis has considered if there are common or defining characteristics in the patients who progressed to ESKD. Although degree of renal artery stenosis does not correlate with renal function [6], level of proteinuria does [7], with more rapid loss of eGFR described in patients with a greater degree of proteinuria, a marker of renal parenchymal injury [8]. In addition an increased risk for progression to RRT has been associated with an eGFR of between 10 and 25 ml/min at time of diagnosis [7]. As such, current opinion holds that markers of renal parenchymal health or damage are the most important arbiters of renal prognosis [9].

This study aims to

1 – describe the prognostic value of a range of routinely measured clinical parameters in predicting progression to ESKD in ARVD and their relative importance.

2 – use this information to develop a risk stratification system for predicting progression to ESKD in ARVD.

3 – compare the predictive value of this system between patients with and without ARVD as their primary cause of their renal failure.

Methods

*Study populations and clinical data*

Patients were selected from two prospective observational studies based at our center, the SRVD and CRISIS [10,11]. The SRVD is a prospectively populated database containing details of all patients referred to our renal center since 1995 diagnosed with ARVD by digital subtraction angiography, non-invasive angiography (computed tomography and magnetic resonance angiography), or duplex ultrasound. CRISIS is a prospective observational study of outcome in an all-cause referred CKD population established in 2002. In both studies baseline demographic information (age, ethnicity, gender, height, weight), details of co-morbid conditions (diabetes, previous macrovascular events), blood pressure, medication and laboratory data (creatinine, eGFR, proteinuria, cholesterol) are recorded and annually updated by nephrology residents and trained research nurses. In addition the SRVD records details of clinical presentation and revascularisation procedures, and CRISIS records details of primary renal diagnosis defined by ICD-10 criteria. Degree of renal artery stenosis is recorded as percentage stenosis to the dominant artery of the most affected kidney and also as a combined renal artery patency score [6], where a maximum score of 200 represents bilateral 0% stenosis and a minimum score of 0 bilateral renal artery occlusion. Specific presentations defined in the SRVD include refractory hypertension (defined as blood pressure >140mmHg systolic and/or 90mmHg diastolic despite use of three or more different classes of antihypertensive agents of which one was a diuretic [12]), and rapidly declining renal function (defined as serum creatinine at time of diagnosis of ARVD >1.2x or 100mol/L higher than a baseline value obtained in the previous six-months [4]). The regional ethics committee granted approval for both studies, with written consent obtained for all patients recruited to CRISIS.

Patients in both studies are managed in accordance with published guidelines [13,14]. A proportion of patients in the SRVD have undergone percutaneous angioplasty and bare metal stenting due to enrollment in randomised trials [4,15] or due to physician / patient preference in line with prevailing clinical consensus and with reference to international guidelines [16].

*Time zero and study end points*

Time zero for patients recruited to the SRVD is defined as date of diagnostic angiography. Time zero for patients recruited to CRISIS is defined as date of consent. Progression to ESKD was the primary study end-point. This was defined as the earliest documented occurrence of initiation of chronic dialysis or transplantation or of an eGFR <10ml/min/1.73m$^2$. This value was selected as it is the level beneath which dialysis is typically initiated in the United Kingdom.

*Study and analysis inclusion criteria*

Patients are eligible for inclusion in the SRVD if is evidence of any degree of renal artery stenosis. All patients aged over 18 years, able to provide informed consent and with evidence of CKD are approached for recruitment to CRISIS. Exclusion criteria for recruitment include previous renal transplantation and predicted patient or renal survival of less than six months.

Patients from the SRVD were included in this analysis if they had complete baseline data and ARVD defined as their primary cause of CKD (minimum 50% unilateral stenosis with no other documented primary cause of renal failure). For comparative analyses, patients from CRISIS with complete baseline data were included.

*Statistical analysis*

For baseline variables parametric continuous data are presented as mean ± standard deviation, non-parametric continuous data as median [interquartile range] and categorical data as number [percentage]. Comparisons between baseline variables were made using ANVOA and Chi-squared tests. Univariate survival analyses were performed on the SRVD using Cox proportional hazards regression. Multivariate analysis was performed using stepwise selection of variables with a clinically plausible relationship to progression to ESKD.

To identify key threshold values of variables associated with progression to ESKD, a classification tree analysis was performed using the methodology described by Foley et al [17]. Here, all continuous variables were divided into whole number categorical variables (e.g. age greater than or less than 60 years). For all values of all variables, sensitivity (exposure in those progressing to ESKD) and specificity (non-exposure in those not progressing to ESKD) were calculated and combined into a single vector of $Max_{Sn+Sp}$. This combined value was chosen to value both positive and negative predictive accuracy. For each threshold value, logistic regression was performed to assess the significance of that value in relation to risk for progression to ESKD. Any threshold value with an alpha value in excess of 0.05 was deemed to not be statistically significant, and discounted. The same process was performed for baseline categorical variables. All statistically significant results were aggregated and ranked by $Max_{Sn+Sp}$. The threshold value of the variable with the highest $Max_{Sn+Sp}$ formed the first node of a classification tree, and was used to dichotomise the study population into two groups. The above process was repeated within both groups to identify further nodes. Division of each group continued until statistical significance was exhausted. Two classification trees were generated; one in which dichotomising variables were retained in subsequent analyses (i.e. eGFR could feature as both the first and third node), and one in which they were excluded from subsequent analysis.

Cox regression was used to assess the relative risk for ESKD between each terminal node of the classification tree. Subsequently threshold values from the classification tree were assigned to an ordinal scoring system, which was again

assessed using a Cox model. The fit of this scoring system was assessed using receiver operating curve (ROC) analysis with results presented as area under the curve (AUC) values. To consider the benefits of using the ordinal scoring system instead of established measures of risk, two assessments were made: change in AUC (ΔAUC) and net reclassification index (NRI [standard error]), Pencina equation 8 [18].

Results

*Demographics*

A total of 819 patients with ARVD were represented in the SRVD; 110 were excluded due to incomplete baseline biochemical data and a further 144 excluded due to <50% renal artery stenosis, giving a population of 565 patients for analysis. At the time of diagnostic angiography, mean patient age was 70±9 years, eGFR 35±20ml/min/1.73m$^2$ and proteinuria 0.6 [IQR 0.2-1.2] g/24hours. Mean stenosis to the dominant artery of the most affected kidney was 78±19%, with 182 [32%] of patients having a unilateral occlusion and 224 [40%] of patients having bilateral >50% stenosis. Over a median follow period of 39.6 [IQR 15.6-69.6] months, 113 patients progressed to ESKD. Median time to ESKD in these patients was 14.8 [IQR 5.4-34.5] months. Compared to patients who did not reach ESKD (due either to death or non-progression), patients who reached ESKD were significantly younger (68.0±9.4 vs. 70.6±8.8 years, p=0.006), with a lower eGFR (20.0±13.4 vs. 39.2±19.8ml/min/1.73m$^2$, p<0.001), greater level of proteinuria (0.96 [IQR 0.6-1.8] vs. 0.55 [IQR 0.2-1.1] g/24hours) and with fewer patients prescribed angiotensin blockade or statin therapy (32.7 vs. 51.1% and 38.4 vs. 54.9% respectively). Although mean renal artery stenosis did not statistically significantly differ between patients who progressed or did not progress to ESKD (81% vs. 77%, p=0.1), a greater proportion of patients who progressed to ESKD had a unilateral renal artery occlusion (44% vs. 29%, p=0.002). Overall, 131 [23%] of patients underwent percutaneous renal artery revascularisation, with no significant difference in rate of intervention between patients who progressed and did not progress to ESKD (21% vs. 24%, p=0.6). Complete demographic data are presented in table 4.3.1.

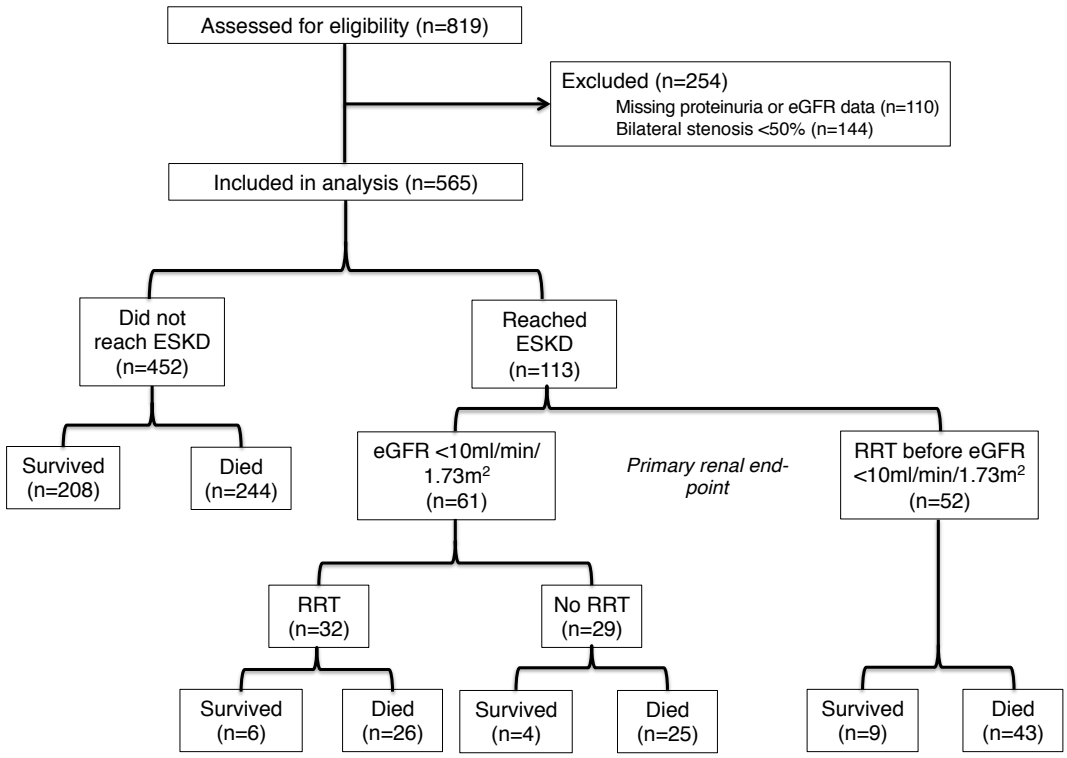
Of the patients who progressed to ESKD, 52 [46%] commenced RRT before having a recorded eGFR <10ml/min/1.73m$^2$ within the database. Of the 61 patients defined as reaching ESKD due to an eGFR <10ml/min/1.73m$^2$, 32 [52%] subsequently commenced RRT and 29 [48%] did not, figure 4.3.1.

**Table 4.3.1** - Baseline demographics of the Salford Renovascular Database

| | All patients N=565 | Did not progress to ESKD N=452 | Progressed to ESKD N=113 | p |
|---|---|---|---|---|
| **Age (years)** | 70.1±9 | 70.6±8.8 | 68±9.4 | 0.006 |
| **Male** | 242 (42.9%) | 197 (43.7%) | 45 (39.8%) | 0.5 |
| **eGFR (ml/min/1.73m$^2$)** | 35.4±20.2 | 39.2±19.8 | 20±13.4 | <0.001 |
| **Proteinuria (g/24 hours)** | 0.63 (0.2-1.2) | 0.55 (0.2-1.1) | 0.96 (0.6-1.8) | <0.001 |
| **Systolic blood pressure (mmHg)** | 157.2±29.7 | 157.8±30 | 154.8±28.5 | 0.3 |
| **Diastolic blood pressure (mmHg)** | 80.8±16.4 | 81.2±16.8 | 80±14 | 0.6 |
| **Total cholesterol (mmol/L)** | 4.6±1.2 | 4.6±1.2 | 4.6±1.3 | 0.8 |
| | *Co-morbidities* | | | |
| **Diagnosed hypertension** | 490 (86.7%) | 391 (86.5%) | 99 (87.6%) | 0.8 |
| **Angina** | 195 (34.6%) | 155 (34.4%) | 40 (35.4%) | 0.8 |
| **Myocardial infarction** | 171 (30.3%) | 137 (30.4%) | 34 (30.1%) | 0.9 |
| **Stroke or transient ischaemic attack** | 208 (36.8%) | 156 (34.5%) | 52 (46%) | 0.02 |
| **Peripheral vascular disease** | 219 (38.8%) | 176 (39%) | 43 (38.1%) | 0.8 |
| **Diabetes mellitus (type II)** | 167 (29.6%) | 127 (28.1%) | 40 (35.4%) | 0.1 |
| **Smoking history** | 225 (39.8%) | 194 (42.9%) | 31 (27.4%) | 0.004 |
| **Intolerance of angiotensin blockade** | 61 (10.8%) | 52 (11.6%) | 9 (8%) | 0.3 |
| | *Medications* | | | |
| **Angiotensin blockade** | 268 (47.4%) | 231 (51.1%) | 37 (32.7%) | <0.001 |
| **Aspirin** | 304 (54.5%) | 248 (55.6%) | 56 (50%) | 0.3 |
| **Statin** | 288 (51.6%) | 245 (54.9%) | 43 (38.4%) | 0.002 |
| **Number of antihypertensive medications** | 2.5±1.5 | 2.5±1.5 | 2.5±1.5 | 0.6 |
| | *Renal artery parameters and clinical presentation* | | | |
| **Maximum unilateral stenosis** | 78.3±18.9 | 77.4±18.9 | 81±20.7 | 0.1 |
| **Patency score** | 91.2±41.6 | 91.2±40.8 | 91.2±43.2 | 0.9 |
| **Unilateral >70% stenosis** | 360 (63.7%) | 286 (63.3%) | 74 (65.5%) | 0.7 |
| **Unilateral renal artery occlusion** | 182 (32.2%) | 132 (29.2%) | 50 (44.2%) | 0.002 |
| **Bilateral >50% stenosis** | 224 (39.6%) | 185 (40.9%) | 39 (34.5%) | 0.2 |
| **Bilateral >70% stenosis** | 73 (12.9%) | 56 (12.4%) | 17 (15%) | 0.4 |
| **Renal artery revascularisation** | 131 (23.2%) | 107 (23.7%) | 24 (21.2%) | 0.6 |
| **Rapid loss of renal function** | 93 (16.5%) | 75 (16.6%) | 18 (15.9%) | 0.9 |
| **Refractory hypertension** | 187 (33.1%) | 151 (33.4%) | 36 (31.9%) | 0.7 |

*Abbreviations: ESKD - end stage kidney disease (defined as chronic renal replacement therapy or eGFR <10ml/min/1.3m$^2$). eGFR - estimated glomerular filtration rate (CKD-EPI equation). Definitions: Angiotensin blockade - prescription of angiotensin converting enzyme inhibitor or angiotensin receptor blocker. Rapid loss of renal function - serum creatinine at the time of diagnostic angiography greater than 1.2x or 100µmol/L higher than a baseline reading from the previous six-months. Refractory hypertension - blood pressure >140mmHg systolic and/or >90mmHg diastolic despite use of three or more different classes of anti-hypertensive medications, one of which was a diuretic. Patency score - combined left and right renal artery patency, where a score of 200 represents bilateral 0% stenosis and a score of 0 represents bilateral 100% stenosis. Smoking history - current or previous smoking.*

**Figure 4.3.1** - Patient selection and outcomes from the Salford Renovascular Database




*Abbreviations: eGFR - estimated glomerular filtration rate (ml/min/1.73m2). ESKD - end stage kidney disease (defined as initiation of chronic renal replacement therapy or eGFR <10ml/min/ 1.73m$^2$).*

*Variables associated with progression to ESKD*

In univariate analysis, an association with altered risk for progression to ESKD was observed for nine baseline variables. Increased risk was associated with proteinuria, diabetes mellitus, and unilateral renal artery occlusion. Reduced risk for ESKD was associated with increasing age and eGFR, smoking history, angiotensin blockade and statin therapy. When adjusted for baseline age, eGFR and proteinuria, reduced risk for ESKD was also associated with higher diastolic blood pressures, and aspirin use, table 4.3.2).

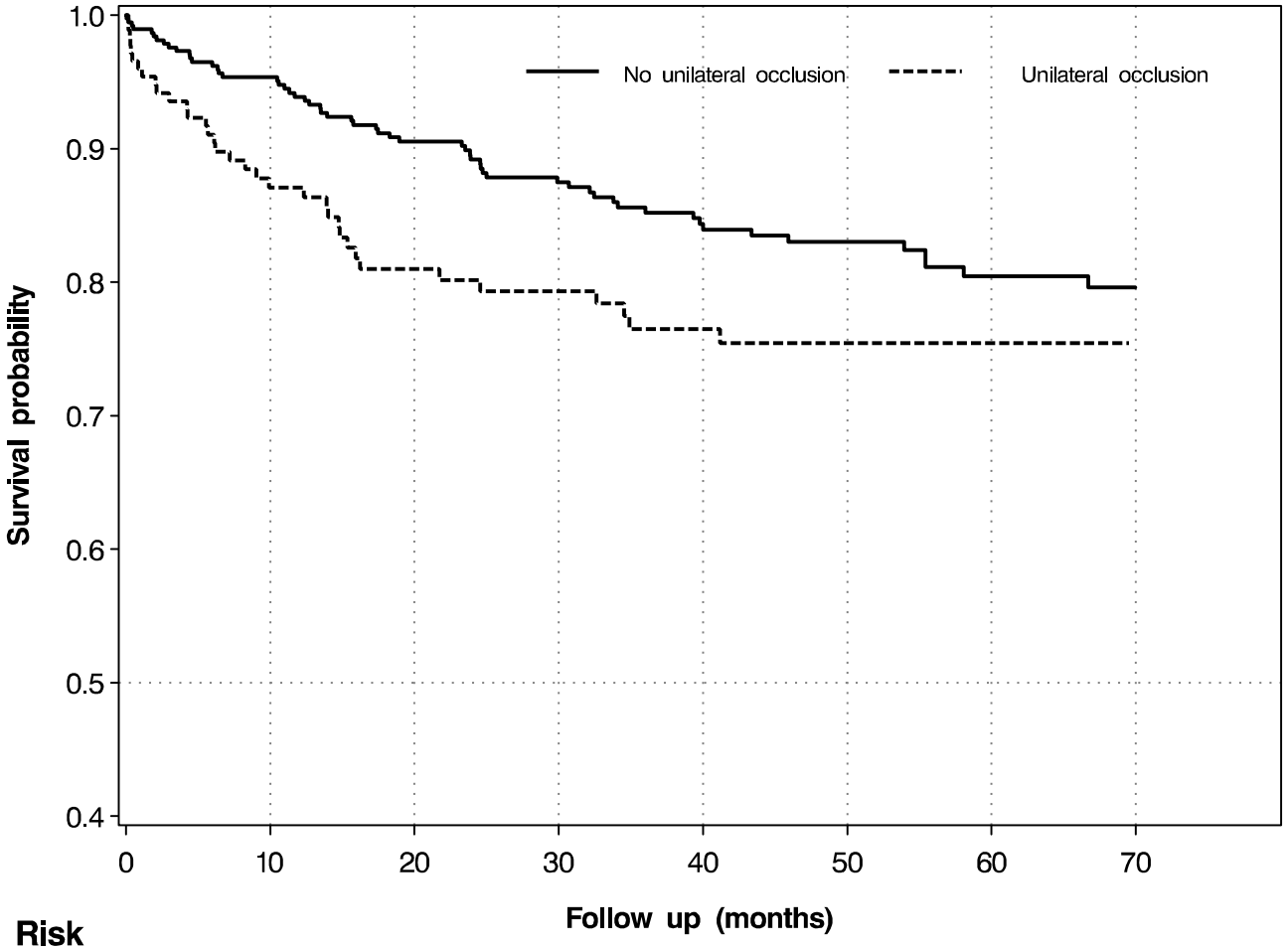
In stepwise multivariate analysis, the greatest risk for progression to ESKD was associated with unilateral renal artery occlusion (HR 1.6 [95% CI 1.1-2.4], p=0.02 figure 4.3.2) and increasing proteinuria (HR 1.2 [95% CI 1.1-1.3], p<0.001 for every 1g/24hour increase). Significant reductions in risk were associated with angiotensin blockade (HR 0.6 [95% CI 0.4-0.9], p=0.04) and positive smoking history (HR 0.55 [95% CI 0.3-0.9], p=0.03). Other variables retained in the model were age (HR 0.96 [95% CI 0.94-0.99], p=0.001 for every 1-year increase), eGFR (HR 0.92 [95% CI 0.90-0.94], p<0.001 for every 1ml/min/1.73m$^2$ increase) and diastolic blood pressure (HR 0.99 [95% CI 0.97-1.0], p=0.04). Renal artery revascularisation was not associated with any significant change in risk in any analysis.

**Table 4.3.2** - Associations of baseline variables with progression to end stage kidney disease

| | Univariate analysis | | Multivariate analysis (age, eGFR, proteinuria adjusted) | |
|---|---|---|---|---|
| | **Hazard ratio (95% confidence interval)** | **p** | **Hazard ratio (95% confidence interval)** | **p** |
| **Age (years)** | 0.98 (0.96-1) | 0.09 | 0.97 (0.95-0.99) | 0.01 |
| **Male** | 0.90 (0.61-1.32) | 0.6 | 1.00 (0.68-1.48) | 0.9 |
| **eGFR (ml/min/1.73m$^2$)** | 0.92 (0.9-0.94) | <0.001 | 0.92 (0.9-0.94) | <0.001 |
| **Proteinuria (g/24 hours)*** | 1.02 (1.01-1.03) | <0.001 | 1.02 (1.01-1.03) | <0.001 |
| **Systolic blood pressure (mmHg)** | 1 (0.99-1) | 0.2 | 1 (0.99-1) | 0.1 |
| **Diastolic blood pressure (mmHg)** | 0.99 (0.98-1) | 0.1 | 0.99 (0.98-1) | 0.03 |
| **Total cholesterol (mmol/L)*** | 0.99 (0.97-1.01) | 0.5 | 1 (0.97-1.02) | 0.7 |
| *Co-morbidities* | | | | |
| **Diagnosed hypertension** | 0.77 (0.44-1.36) | 0.4 | 0.97 (0.55-1.72) | 0.9 |
| **Angina** | 1.04 (0.7-1.54) | 0.8 | 0.88 (0.59-1.32) | 0.5 |
| **Myocardial infarction** | 0.99 (0.66-1.49) | 0.9 | 1.11 (0.74-1.68) | 0.6 |
| **Intolerance of angiotensin blockade** | 0.76 (0.37-1.56) | 0.4 | 0.95 (0.46-1.96) | 0.9 |
| **Stroke or transient ischaemic attack** | 1.25 (0.85-1.82) | 0.3 | 1.19 (0.81-1.75) | 0.38 |
| **Peripheral vascular disease** | 0.99 (0.67-1.46) | 0.9 | 1 (0.67-1.5) | 0.9 |
| **Diabetes mellitus (type II)** | 1.41 (0.95-2.1) | 0.09 | 1.01 (0.67-1.52) | 0.9 |
| **Smoking history** | 0.49 (0.32-0.75) | 0.001 | 0.47 (0.28-0.66) | <0.001 |
| *Medications* | | | | |
| **Angiotensin blockade** | 0.57 (0.39-0.86) | 0.007 | 0.62 (0.41-0.93) | 0.02 |
| **Aspirin** | 0.78 (0.54-1.14) | 0.2 | 0.72 (0.49-1.06) | 0.1 |
| **Statin** | 0.55 (0.37-0.81) | 0.002 | 0.53 (0.36-0.79) | 0.002 |
| **Number of antihypertensive medications** | 0.99 (0.85-1.16) | 0.9 | 0.98 (0.84-1.14) | 0.8 |
| *Renal artery parameters and clinical presentation* | | | | |
| **Maximum unilateral stenosis** | 1.01 (1-1.02) | 0.1 | 1.01 (1-1.02) | 0.1 |
| **Patency score** | 1 (0.99-1) | 0.7 | 1 (1-1) | 0.9 |
| **Unilateral >70% stenosis** | 1.1 (0.74-1.64) | 0.6 | 1.21 (0.8-1.83) | 0.4 |
| **Unilateral occlusion** | 1.78 (1.22-2.62) | 0.003 | 1.74 (1.18-2.57) | 0.005 |
| **Bilateral >50% stenosis** | 0.83 (0.56-1.24) | 0.4 | 0.78 (0.52-1.17) | 0.2 |
| **Bilateral >70% stenosis** | 1.37 (0.8-2.33) | 0.2 | 1.25 (0.73-2.15) | 0.4 |
| **Renal artery revascularisation** | 0.75 (0.47-1.20) | 0.2 | 0.71 (0.44-1.22) | 0.2 |
| **Rapid loss of renal function** | 1.02 (0.62-1.7) | 0.9 | 1.13 (0.68-1.89) | 0.6 |
| **Refractory hypertension** | 1.03 (0.69-1.54) | 0.9 | 0.97 (0.64-1.45) | 0.9 |

*Abbreviations: eGFR – estimated glomerular filtration rate (CKD-EPI equation).*
*Definitions: patency score – combined renal artery patency where a maximum score of 200 represents bilateral 0% stenosis and a minimum score of 0 represents bilateral 100% stenosis. Angiotensin blockade – prescription of angiotensin converting enzyme inhibitor or angiotensin receptor blocker. Rapid loss of renal function – serum creatinine at the time of diagnostic angiography greater than 1.2x or 100µmol/L higher than a baseline reading from the previous six-months. Refractory hypertension – blood pressure >140mmHg systolic and/or >90mmHg diastolic despite use of three or more different classes of anti-hypertensive medications, one of which was a diuretic. Patency score – combined left and right renal artery patency, where a score of 200 represents bilateral 0% stenosis and a score of 0 represents bilateral 100% stenosis. Smoking history – current or previous smoking.*
*Quoted hazard ratios are for the presence of a binary variable and for single unit increases in continuous variables unless marked by a * where hazard ratios are for a 0.1 unit increase in continuous variables.*

**Figure 4.3.2** - Kaplan Meier survival plots for patients with and without renal artery occlusion




| Number at Risk | | | | | | |
|---|---|---|---|---|---|---|
| No unilateral occlusion | 379 | 317 | 265 | 219 | 170 | 111 |
| Unilateral occlusion | 177 | 121 | 95 | 77 | 67 | 60 |

*Solid line represents patients with bilaterally non-occluded renal arteries. Dashed line represents patients with unilateral renal artery occlusion or stenosis to a single functioning kidney.*

*y-axis shows probability of dialysis free survival; x-axis shows time in months from date of diagnostic angiography.*

*Threshold value analysis*

When variables were ranked by $Max_{Sn+Sp}$, an eGFR ≤26ml/min/1.73m$^2$ was the most discriminatory measure for identifying patients at greatest risk for progression to ESKD (sensitivity 0.75, specificity 0.73, odds ratio 8.3 [95% CI 5.2-13.3], p<0.001). This was followed in descending order by proteinuria ≥0.3g/24 hours (sensitivity 0.93, specificity 0.39), age <51 years (sensitivity 0.92, specificity 0.04), systolic blood pressure ≥112mmHg, statin use, angiotensin blockade, previous cerebrovascular event and unilateral renal artery occlusion. In this threshold value analysis, the high odds ratios for e.g. eGFR ≤26ml/min/1.73m$^2$ compared to the hazard ratio for eGFR in the multivariate Cox model are representative of this variable being considered in a categorical rather than a continuous form.

As an eGFR ≤26ml/min/1.73m$^2$ had the greatest $Max_{Sn+Sp}$ for predicting progression to ESKD this formed the first classification tree node and dichotomised the study population into those with an eGFR >26ml/min/1.73m$^2$ (n=358) and those with an eGFR ≤26ml/min/1.73m$^2$ (n=207). In the second round of analysis for patients with an eGFR ≤26ml/min/1.73m$^2$ an eGFR of ≤14ml/min/1.73m$^2$ had the greatest $Max_{Sn+Sp}$ (sensitivity 0.60, specificity 0.73). In the second round of analysis for patients with an eGFR >26ml/min/1.73m$^2$ the variable with the greatest $Max_{Sn+Sp}$ was proteinuria ≥0.3g/24 hours (sensitivity 0.89, specificity 0.40). Complete data are presented in table 4.3.3 with the final classification tree shown in figure 4.3.3.

When variables already used in the classification tree were not retained in subsequent rounds of analysis, proteinuria ≥0.3g/24 hours had the greatest $Max_{Sn+Sp}$ both for patients with an eGFR >26ml/min/1.73m$^2$ (sensitivity 0.89, specificity 0.40) and for patients with an eGFR ≤26ml/min/1.73m$^2$ (sensitivity 0.94, specificity 0.34). Complete data are presented in table 4.3.4 and figure 4.3.4.

**Table 4.3.3** - Threshold values for discriminating between progression and non-progression to end stage kidney disease ranked by combined sensitivity plus specificity (previously identified variables retained in subsequent analyses)

| | | | | | Unadjusted analysis | | Age adjusted analysis | |
|---|---|---|---|---|---|---|---|---|
| Variable | Threshold value | Sens | Spec | Sens + spec | Odds ratio ESKD (95% CI) | p | Odds ratio ESKD (95% CI) | p |
| *Overall population* | | | | | | | | |
| eGFR | 26ml/min/ 1.73m$^2$ | 75.2 | 73.2 | 148.4 | 8.28 (5.15-13.32) | <0.001 | 9.15 (5.61-14.95) | <0.001 |
| Proteinuria | 0.3g/24 hours | 92.9 | 38.7 | 131.6 | 8.29 (3.94-17.44) | <0.001 | 7.94 (3.77-16.72) | <0.001 |
| Age | 51 years | 92 | 3.5 | 95.6 | 0.43 (0.18-0.99) | 0.047 | - | - |
| Systolic blood pressure | 112 | 90.2 | 4.8 | 95 | 0.47 (0.22-1) | 0.05 | 0.45 (0.21-0.96) | 0.04 |
| Statin use | Yes | 38.4 | 54.9 | 93.3 | 0.51 (0.33-0.78) | 0.002 | 0.52 (0.34-0.8) | 0.003 |
| Angiotensin blockade | Yes | 32.7 | 51.1 | 83.8 | 0.47 (0.3-0.72) | 0.001 | 0.44 (0.28-0.69) | <0.001 |
| Stoke or TIA | Yes | 46 | 34.5 | 80.5 | 1.62 (1.07-2.46) | 0.024 | 1.62 (1.06-2.47) | 0.025 |
| Unilateral renal artery occlusion | Yes | 44.2 | 29.2 | 73.5 | 1.92 (1.26-2.94) | 0.002 | 1.89 (1.23-2.89) | 0.003 |
| *eGFR ≤26ml/min/1.73m$^2$* | | | | | | | | |
| eGFR | 14ml/min/ 1.73m$^2$ | 60 | 72.7 | 132.7 | 4 (2.22-7.22) | <0.001 | 4.32 (2.35-7.95) | <0.001 |
| Proteinuria | 0.3g/24 hours | 94.1 | 34.4 | 128.5 | 8.4 (3.16-22.33) | <0.001 | 7.78 (2.91-20.79) | <0.001 |
| Cholesterol | 3.8mmol/L | 81 | 41 | 121.9 | 2.95 (1.22-7.15) | 0.017 | 2.97 (1.20-7.18) | 0.018 |
| Age | 54 | 90.6 | 0.8 | 91.4 | 0.08 (0.01-0.65) | 0.018 | - | - |
| Statin | Yes | 35.3 | 52.9 | 88.2 | 0.49 (0.27-0.86) | 0.013 | 0.47 (0.26-0.85) | 0.012 |
| Angiotensin blockade | Yes | 28.2 | 52.5 | 80.7 | 0.36 (0.2-0.64) | 0.001 | 0.31 (0.16-0.57) | <0.001 |
| Stroke / TIA | Yes | 43.5 | 29.5 | 73 | 1.84 (1.03-3.29) | 0.039 | 1.84 (1.02-3.32) | 0.042 |
| *eGFR >26ml/min/1.73m$^2$* | | | | | | | | |
| Proteinuria | 0.3g/24 hours | 89.3 | 40.3 | 129.6 | 5.63 (1.66-19.01) | 0.005 | 5.19 (1.53-17.63) | 0.008 |
| eGFR | 36ml/min/ 1.73m$^2$ | 57.1 | 68.5 | 125.6 | 2.9 (1.32-6.34) | 0.008 | 4.01 (1.74-9.27) | 0.001 |
| Age | 44 years | 92.9 | 0.9 | 93.8 | 0.12 (0.02-0.75) | 0.023 | - | - |
| Systolic blood pressure | 116mmHg | 85.7 | 4.7 | 90.4 | 0.3 (0.09-0.97) | 0.044 | 0.24 (0.07-0.8) | 0.02 |
| Cholesterol | 2.5mmol/L | 88.2 | 1.2 | 89.4 | 0.09 (0.01-0.59) | 0.012 | 0.06 (0.01-0.56) | 0.005 |
| *eGFR ≤26ml/min/1.73m$^2$ and eGFR ≤14ml/min/1.73m$^2$* | | | | | | | | |
| Proteinuria | 0.8g/24 hours | 74.5 | 47.1 | 121.6 | 2.6 (1.03-6.53) | 0.042 | 2.39 (0.94-6.08) | 0.068 |
| Angiotensin blockade | Yes | 17.6 | 44.1 | 61.8 | 0.27 (0.1-0.73) | 0.01 | 0.26 (0.09-0.74) | 0.011 |
| *eGFR ≤26ml/min/1.73m$^2$ and eGFR >14ml/min/1.73m$^2$* | | | | | | | | |
| Proteinuria | 0.3g/24hours | 94.1 | 39.8 | 133.9 | 10.56 (2.38-46.92) | 0.002 | 9.75 (2.18-43.63) | 0.003 |
| Cholesterol | 3.9mmol/L | 76.2 | 53.1 | 129.3 | 3.63 (1.19-11.09) | 0.024 | 3.75 (1.21-11.15) | 0.023 |
| Age | 61 years | 73.5 | 11.4 | 84.9 | 0.36 (0.13-0.97) | 0.044 | - | - |
| Stroke / TIA | Yes | 52.9 | 31.8 | 84.8 | 2.41 (1.07-5.41) | 0.033 | 2.44 (1.07-5.6) | 0.034 |

*continued over*

*eGFR ≤26ml/min/1.73m² and proteinuria ≥0.3g/24 hours*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| eGFR | 43ml/min/ 1.73m² | 84 | 49.8 | 133.8 | 5.2 (1.73-15.67) | 0.003 | 7.4 (2.31-23.75) | 0.001 |
| Proteinuria | 0.27g/24hours | 16 | 98.1 | 114.1 | 9.86 (2.3-42.33) | 0.002 | 9.04 (2.09-39.14) | 0.003 |
| Systolic blood pressure | 110mmHg | 88 | 3 | 91 | 0.22 (0.05-0.96) | 0.044 | 0.14 (0.03-0.65) | 0.012 |
| Cholesterol | 2.5mmol/L | 86.7 | 2 | 88.7 | 0.13 (0.02-0.87) | 0.035 | 0.08 (0.02-0.76) | 0.014 |
| Age | 64 years | 60 | 21.3 | 81.3 | 0.41 (0.17-0.97) | 0.042 | - | - |

*eGFR >26ml/min/1.73m² and proteinuria <0.3g/24 hours*

Limit of statistical significance

*eGFR ≤26ml/min/1.73m² and eGFR ≤14ml/min/1.73m² and proteinuria ≥0.8g/24 hours*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Cholesterol | 3.7mmol/L | 93.3 | 50 | 143.3 | 14 (1.06-185.46) | 0.045 | 19.24 (1.35-195.50) | 0.052 |
| Bilateral >50% stenosis | Yes | 39.5 | 72.2 | 111.7 | 0.25 (0.07-0.85) | 0.026 | 0.26 (0.08-0.93) | 0.038 |
| Patency score | 20 | 10.5 | 66.7 | 77.2 | 0.24 (0.06-0.98) | 0.047 | 0.2 (0.04-0.95) | 0.037 |
| Bilateral >70% stenosis | Yes | 15.8 | 44.4 | 60.2 | 0.23 (0.07-0.84) | 0.026 | 0.23 (0.06-0.91) | 0.037 |
| Peripheral vascular disease | Yes | 42.1 | 11.1 | 53.2 | 5.82 (1.17-28.96) | 0.032 | 4.95 (0.97-25.18) | 0.054 |
| Angiotensin blockade | Yes | 13.2 | 38.9 | 52 | 0.24 (0.06-0.9) | 0.035 | 0.2 (0.05-0.91) | 0.037 |

*eGFR ≤26ml/min/1.73m² and eGFR ≤14ml/min/1.73m² and proteinuria <0.8g/24 hours*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Patency | 120 | 46.2 | 12.5 | 58.7 | 0.12 (0.02-0.77) | 0.025 | 0.12 (0.02-0.76) | 0.026 |

*eGFR ≤26ml/min/1.73m² and eGFR >14ml/min/1.73m² and proteinuria ≥0.3g/24 hours*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Cholesterol | 3.9mmol/L | 75 | 56.3 | 131.3 | 3.86 (1.13-13.19) | 0.031 | 3.84 (1.12-13.14) | 0.035 |
| Age | 60 years | 75 | 7.1 | 82.1 | 0.23 (0.06-0.84) | 0.026 | - | - |

*eGFR ≤26ml/min/1.73m² and eGFR >14ml/min/1.73m² and proteinuria <0.3g/24 hours*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Number of antihypertensive medications | 5 | 50 | 96.9 | 146.9 | 31 (1.02-940.92) | 0.049 | 23.05 (0.63-847.93) | 0.088 |
| Age | 57 years | 50 | 3.1 | 53.1 | 0.03 (0-0.98) | 0.049 | - | - |

*eGFR >26ml/min/1.73m² and proteinuria ≥0.3g/24 hours and eGFR ≤43ml/min/1.73m²*

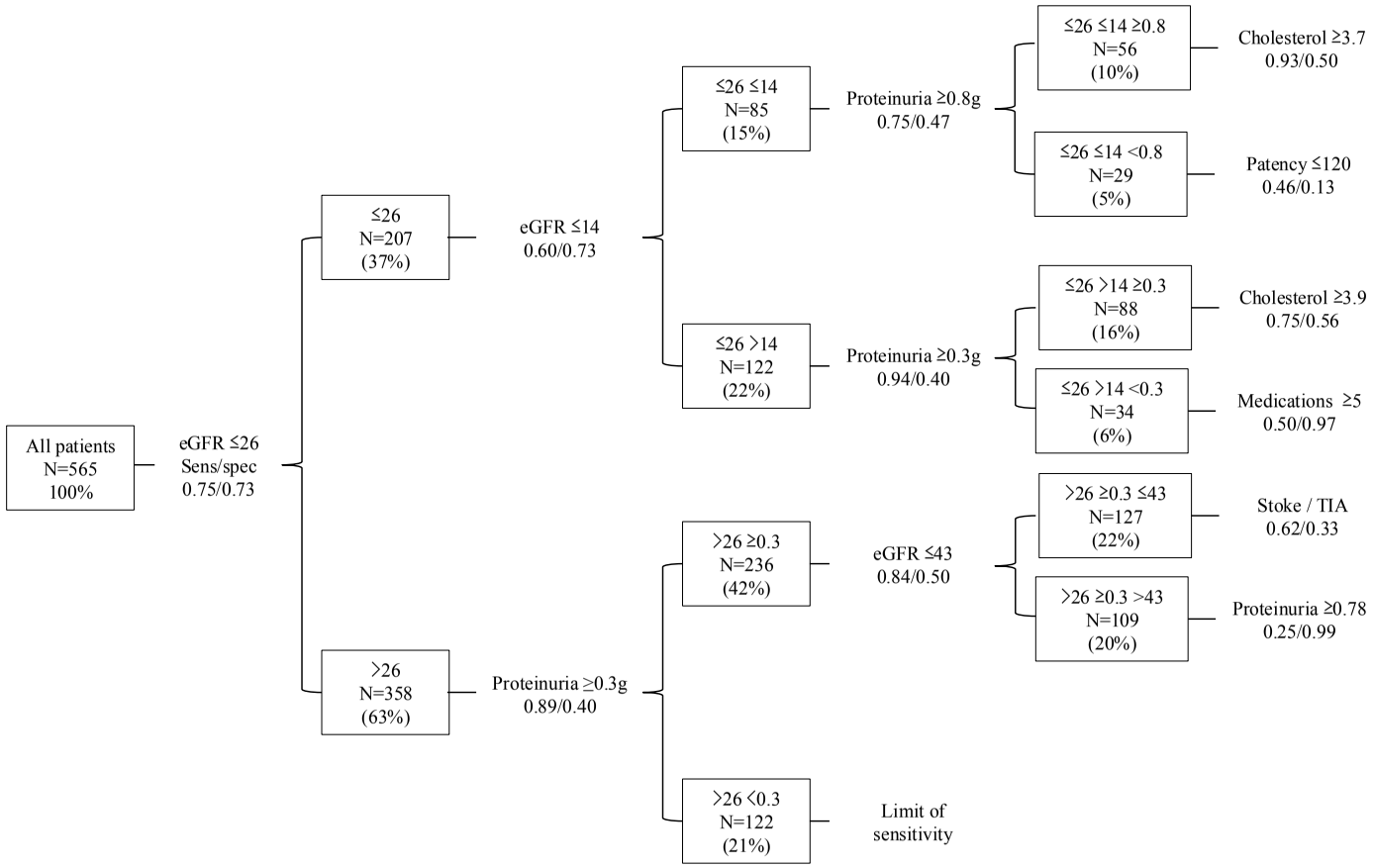
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Stoke / TIA | Yes | 61.9 | 32.5 | 94.4 | 3.38 (1.29-8.84) | 0.013 | 3.45 (1.25-9.53) | 0.017 |
| Age | 44 years | 90.5 | 0.9 | 91.3 | 0.08 (0.01-0.95) | 0.045 | - | - |
| Systolic blood pressure | 119mmHg | 81 | 4.5 | 85.5 | 0.2 (0.05-0.83) | 0.026 | 0.14 (0.03-0.63) | 0.01 |

*eGFR >26ml/min/1.73m² and proteinuria ≥0.3g/24 hours and eGFR >43ml/min/1.73m²*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Proteinuria | 0.78g/24hours | 25 | 98.9 | 123.9 | 31 (1.54-623.14) | 0.025 | 28.86 (1.41-591.17) | 0.029 |
| Cholesterol | 2.5mmol/L | 75 | 1.5 | 76.5 | 0.05 (0-0.92) | 0.044 | 0.03 (0-0.89) | 0.036 |
| Rapidly declining renal function | Yes | 50 | 8.5 | 58.5 | 10.75 (1.33-86.88) | 0.026 | 10.86 (1.33-88.59) | 0.026 |

*Abbreviations: Sens - sensitivity. Spec - specificity. ESKD - end stage kidney disease (defined as initiation of chronic renal replacement therapy or eGFR <10ml/min/1.73m²). eGFR - estimated glomerular filtration rate. TIA - transient ischemic attack. Patency score defined as the total percentage bilateral reduction in diameter of renal arteries, where a maximum score of 200 represents bilateral 0% stenosis and a minimum score of 0 represents bilateral 100% stenosis. Angiotensin blockade defined as prescription of angiotensin converting enzyme inhibitor and / or angiotensin II receptor blocker at time of diagnostic angiography. Rapidly declining renal function defined as a serum creatinine level greater than 1.2x or 100µmol/L increased compared to a baseline reading taken in the six months prior to diagnostic angiography. Value for sensitivity is the percentage of patients with the risk factor who progressed to ESKD. Value for specificity is the percentage of patients without the risk factor who did not progress to ESKD. Threshold values for age, eGFR, and blood pressure were considered in 1-unit intervals. Threshold values for proteinuria and cholesterol were considered in 0.1-unit intervals.*

**Figure 4.3.3** - Classification tree with variables retained




*Abbreviations and units: eGFR - estimated glomerular filtration rate (ml/min/1.73m²). Proteinuria - 24 hour urinary protein excretion (g/24hours). Cholesterol - total serum cholesterol (mmol/L). Patency - combined renal artery patency score (where a score of 200 represents bilateral 0% occlusion and a score of 0 represents bilateral 100% occlusion). Medications - number of different classes of antihypertensive medications. Stroke/TIA - history of stroke or transient ischaemic attack. Sens - sensitivity. Spec - specificity.*

*Each node represents the value of the variable with the greatest combined sensitivity and specificity for predicting progression to end stage kidney disease. At each division subgroups are defined by dividing the study population in relation to the defined variable. In this analysis variables used at a parent node are considered in subsequent analyses. Complete data for each node are presented in supplementary table 4.3.3.*

**Table 4.3.4** - Threshold values for discriminating between progression and non-progression to end stage kidney disease ranked by combined sensitivity plus specificity (previously identified variables not retained in subsequent analyses)

| | | | | | Unadjusted analysis | | Age adjusted analysis | |
|---|---|---|---|---|---|---|---|---|
| Variable | Threshold value | Sens | Spec | Sens + spec | Odds ratio ESKD (95% CI) | p | Odds ratio ESKD (95% CI) | p |
| *Overall population* | | | | | | | | |
| eGFR | 26ml/min/ 1.73m$^2$ | 75.2 | 73.2 | 148.4 | 8.28 (5.15-13.32) | <0.001 | 9.15 (5.61-14.95) | <0.001 |
| Proteinuria | 0.3g/24 hours | 92.9 | 38.7 | 131.6 | 8.29 (3.94-17.44) | <0.001 | 7.94 (3.77-16.72) | <0.001 |
| Age | 51 years | 92 | 3.5 | 95.6 | 0.43 (0.18-0.99) | 0.047 | - | - |
| Systolic blood pressure | 112 | 90.2 | 4.8 | 95 | 0.47 (0.22-1) | 0.05 | 0.45 (0.21-0.96) | 0.04 |
| Statin use | Yes | 38.4 | 54.9 | 93.3 | 0.51 (0.33-0.78) | 0.002 | 0.52 (0.34-0.8) | 0.003 |
| Angiotensin blockade | Yes | 32.7 | 51.1 | 83.8 | 0.47 (0.3-0.72) | 0.001 | 0.44 (0.28-0.69) | <0.001 |
| Stoke or TIA | Yes | 46 | 34.5 | 80.5 | 1.62 (1.07-2.46) | 0.024 | 1.62 (1.06-2.47) | 0.025 |
| Unilateral occlusion | Yes | 44.2 | 29.2 | 73.5 | 1.92 (1.26-2.94) | 0.002 | 1.89 (1.23-2.89) | 0.003 |
| *eGFR ≤26ml/min/1.73m$^2$* | | | | | | | | |
| Proteinuria | 0.3g/24 hours | 94.1 | 34.4 | 128.5 | 8.4 (3.16-22.33) | <0.001 | 7.78 (2.91-20.79) | <0.001 |
| Cholesterol | 3.8mmol/L | 81 | 41 | 121.9 | 2.95 (1.22-7.15) | 0.017 | 2.97 1.23-7.17) | 0.018 |
| Age | 54 | 90.6 | 0.8 | 91.4 | 0.08 (0.01-0.65) | 0.018 | - | - |
| Statin | Yes | 35.3 | 52.9 | 88.2 | 0.49 (0.27-0.86) | 0.013 | 0.47 (0.26-0.85) | 0.012 |
| Angiotensin blockade | Yes | 28.2 | 52.5 | 80.7 | 0.36 (0.2-0.64) | 0.001 | 0.31 (0.16-0.57) | <0.001 |
| Stroke / TIA | Yes | 43.5 | 29.5 | 73 | 1.84 (1.03-3.29) | 0.039 | 1.84 (1.02-3.32) | 0.042 |
| *eGFR >26ml/min/1.73m$^2$* | | | | | | | | |
| Proteinuria | 0.3g/24 hours | 89.3 | 40.3 | 129.6 | 5.63 (1.66-19.01) | 0.005 | 5.19 (1.53-17.63) | 0.008 |
| Age | 44 years | 92.9 | 0.9 | 93.8 | 0.12 (0.02-0.75) | 0.023 | - | - |
| Systolic blood pressure | 116mmHg | 85.7 | 4.7 | 90.4 | 0.3 (0.09-0.97) | 0.044 | 0.24 (0.07-0.8) | 0.02 |
| Cholesterol | 2.5mmol/L | 88.2 | 1.2 | 89.4 | 0.09 (0.01-0.59) | 0.012 | 0.06 (0.01-0.51) | 0.005 |
| *eGFR ≤26ml/min/1.73m$^2$ and proteinuria ≥0.3g/24 hours* | | | | | | | | |
| Cholesterol | 3.8mmol/L | 82.1 | 40.4 | 122.5 | 3.1 (1.14-8.47) | 0.027 | 3.16 (1.18-8.52) | 0.028 |
| Age | 54 years | 90.1 | 1.2 | 91.3 | 0.11 (0.01-0.89) | 0.039 | - | - |
| Patency score | 115 | 67.9 | 18.6 | 86.5 | 0.48 (0.24-0.99) | 0.047 | 0.5 (0.29-1.0) | 0.057 |
| Angiotensin blockade | Yes | 27.2 | 48.8 | 76 | 0.39 (0.2-0.75) | 0.004 | 0.33 (0.17-0.66) | 0.002 |

*continued over*

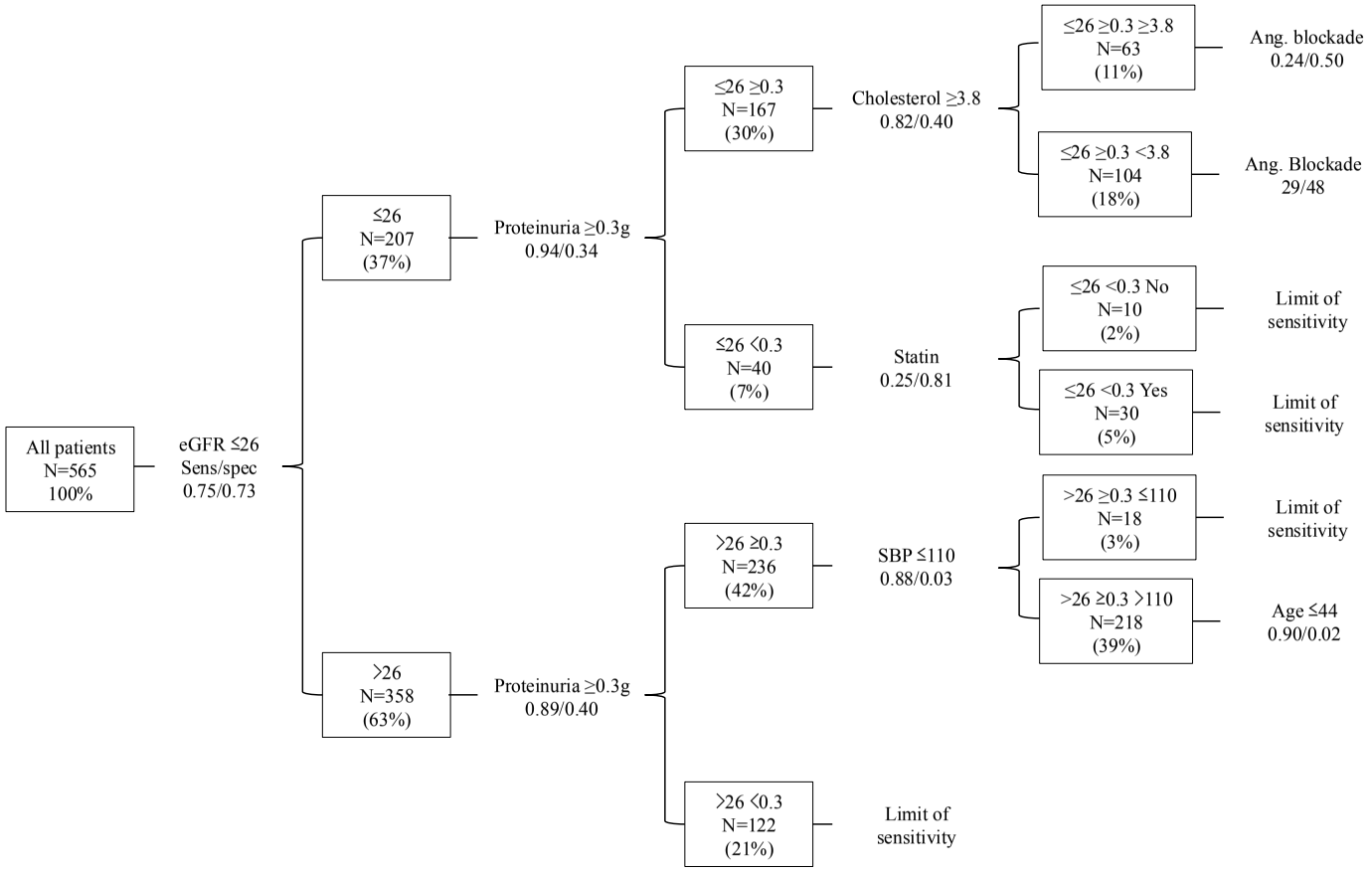
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| *eGFR ≤26ml/min/1.73m² and proteinuria <0.3g/24 hours* | | | | | | | | |
| Statin | Yes | 25 | 80.6 | 105.6 | 0.08 (0.01-0.89) | 0.04 | 0.07 (0.01-0.85) | 0.037 |
| *eGFR >26ml/min/1.73m² and proteinuria ≥0.3g/24 hours* | | | | | | | | |
| Systolic blood pressure | 110mmHg | 88 | 3 | 91 | 0.22 (0.05-0.96) | 0.044 | 0.14 (0.03-0.65) | 0.012 |
| Cholesterol | 2.5mmol/L | 86.7 | 2 | 88.7 | 0.13 (0.02-0.87) | 0.035 | 0.08 (0.01-0.81) | 0.014 |
| Age | 64 years | 60 | 21.3 | 81.3 | 0.41 (0.17-0.97) | 0.042 | - | - |
| *eGFR >26ml/min/1.73m² and proteinuria <0.3g/24 hours* | | | | | | | | |
| Limit of statistical significance | | | | | | | | |
| *eGFR ≤26ml/min/1.73m² and proteinuria ≥0.3g/24 hours and serum cholesterol ≥3.8mmol/L* | | | | | | | | |
| Angiotensin blockade | Yes | 24.2 | 50 | 74.2 | 0.32 (0.11-0.93) | 0.037 | 0.23 (0.07-0.74) | 0.014 |
| *eGFR ≤26ml/min/1.73m² and proteinuria ≥0.3g/24 hours and serum cholesterol <3.8mmol/L* | | | | | | | | |
| Angiotensin blockade | Yes | 29.2 | 48.2 | 77.4 | 0.44 (0.2-1) | 0.049 | 0.41 (0.17-0.95) | 0.037 |
| Stoke/ TIA | Yes | 47.9 | 28.6 | 76.5 | 2.3 (1.02-5.17) | 0.044 | 2.14 (0.94-4.86) | 0.069 |
| Smoking history | Yes | 2.1 | 17.9 | 19.9 | 0.1 (0.01-0.8) | 0.03 | 0.09 (0.01-0.76) | 0.027 |
| *eGFR >26ml/min/1.73m² and proteinuria ≥0.3g/24 hours and systolic blood pressure ≥110mmHg* | | | | | | | | |
| Age | 44 years | 90.9 | 1.5 | 92.4 | 0.16 (0.02-0.99) | 0.048 | - | - |
| Cholesterol | 2.5mmol/L | 86.7 | 2.1 | 88.8 | 0.14 (0.02-0.92) | 0.04 | 0.09 (0.01-0.89) | 0.017 |

*Abbreviations: Sens - sensitivity. Spec - specificity. ESKD - end stage kidney disease (defined as initiation of chronic renal replacement therapy or eGFR <10ml/min/1.73m²). eGFR - estimated glomerular filtration rate. TIA - transient ischemic attack.*

*Patency score defined as the total percentage bilateral reduction in diameter of renal arteries, where a maximum score of 200 represents bilateral 0% stenosis and a minimum score of 0 represents bilateral 100% stenosis. Angiotensin blockade defined as prescription of angiotensin converting enzyme inhibitor and / or angiotensin II receptor blocker at time of diagnostic angiography. Smoking history defined as current or previous cigarette smoking at time of diagnostic angiography.*

*Value for sensitivity is the percentage of patients with the risk factor who progressed to ESKD. Value for specificity is the percentage of patients without the risk factor who did not progress to ESKD. Threshold values for age, eGFR, and blood pressure were considered in 1-unit intervals. Threshold values for proteinuria and cholesterol were considered in 0.1-unit intervals.*

**Figure 4.3.4** - Classification tree with variables not retained




*Abbreviations and units: eGFR - estimated glomerular filtration rate (ml/min/1.73m²). Proteinuria - 24 hour urinary protein excretion (g/24hours). Cholesterol - total serum cholesterol (mmol/L). Statin - prescription of statin therapy at time of diagnostic angiography. SBP - systolic blood pressure (mmHg). Ang. Blockade - prescription of angiotensin blockade at time of diagnostic angiography (angiotensin converting enzyme inhibitor and / or angiotensin receptor blocker). Age - calendar age in years. Sens - sensitivity. Spec - specificity.*

*Each node represents the value of the variable with the greatest combined sensitivity and specificity for predicting progression to end stage kidney disease. At each division subgroups are defined by dividing the study population in relation to the defined variable. In this analysis variables used at a parent node are excluded from subsequent analyses. Complete data for each node are presented in supplementary table 4.3.4.*

*Relative hazard for progression to ESKD*

When the terminal branch of each classification tree was considered in a Cox model (using the lowest risk branch as the referent group), a progressive increase in risk for ESKD was noted with the greatest increase in risk associated with the highest branch of the classification tree (HR 102 [95% CI 31-338], p<0.001), table 4.3.5.

**Table 4.3.5** - Risk for end stage kidney disease by terminal nodes of classification trees

| | Variables retained | | | | Variables not retained | | | |
|---|---|---|---|---|---|---|---|---|
| | Description | n | HR (95% CI) | p | Description | n | HR (95% CI) | p |
| **Node 1** | eGFR >26, proteinuria <0.3 | 122 | Referent | | eGFR >26, proteinuria <0.3 | 122 | Referent | |
| **Node 2** | eGFR >43, proteinuria ≥0.3 | 109 | 1.45 (0.3-6.5) | 0.629 | eGFR >26, proteinuria ≥0.3, SBP >110 | 218 | 4.79 (1.4-16) | 0.011 |
| **Node 3** | eGFR 26-43, proteinuria ≥ 0.3 | 127 | 9.6 (2.9-32.2) | <0.001 | eGFR >26, proteinuria ≥0.3, SBP ≤110 | 18 | 8.16 (1.6-40.5) | 0.01 |
| **Node 4** | eGFR ≤26, eGFR >14, proteinuria <0.3 | 34 | 3.26 (0.5-19.5) | 0.196 | eGFR ≤26, proteinuria <0.3, statin prescribed | 30 | 1.87 (0.2-18) | 0.589 |
| **Node 5** | eGFR ≤26, eGFR >14, proteinuria ≥0.3 | 88 | 24.7 (7.5-80.9) | <0.001 | eGFR ≤26, proteinuria <0.3, statin not prescribed | 10 | 15.16 (3.1-75.2) | 0.001 |
| **Node 6** | eGFR ≤14, proteinuria <0.8 | 29 | 32.28 (9.1-115) | <0.001 | eGFR ≤26, proteinuria ≥0.3, cholesterol <3.8 | 104 | 38.34 (11.9-123.8) | <0.001 |
| **Node 7** | eGFR ≤14, proteinuria ≥0.8 | 56 | 102.48 (31.1-338.2) | <0.001 | eGFR ≤26, proteinuria ≥0.3, cholesterol ≥3.8 | 63 | 35.94 (11-117.9) | <0.001 |

*Abbreviations and units: HR – hazard ratio. 95% CI – 95% confidence interval. eGFR – estimated glomerular filtration rate, (ml/min/1.73m$^2$). Proteinuria – 24 hour urinary protein excretion (g/24 hours). SBP – systolic blood pressure (mmHg). Referent node (node 1) is the lowest branch of the classification tree.*

To increase clinical utility and account for factors identified as important in the Cox models, threshold values from the classification tree and variables from the multivariate Cox analysis were used to develop an ordinal scoring system with a range of possible scores from 0 (lowest risk) to 8 (greatest risk). As the aim of this was aid clinicians in making predictions of risk for individual patients, threshold eGFR values were rounded to more easy to remember numbers. Details of the scoring system are presented in table 4.3.6.

**Table 4.3.6** - Proposed ordinal scoring system

| | **Score 0** | **Score 1** | **Score 2** |
|---|---|---|---|
| **eGFR (ml/min/1.73m²)** | >45 | 25-45 | <25 |
| **Proteinuria (g/24 hours)** | <0.3 | 0.3-0.8 | >0.8 |
| **Angiotensin blockade** | Yes | No | - |
| **Statin** | Yes | No | - |
| **Unilateral renal artery occlusion** | No | Yes | - |
| **Smoking history** | Yes | No | - |

*Abbreviations and definitions: eGFR – estimated glomerular filtration rate (CKD-EPI equation). Unilateral renal artery occlusion – 100% unilateral stenosis or single functioning kidney. Angiotensin blockade – prescription of angiotensin converting enzyme inhibitor or angiotensin receptor blocker. Smoking history – current or previous smoking.*

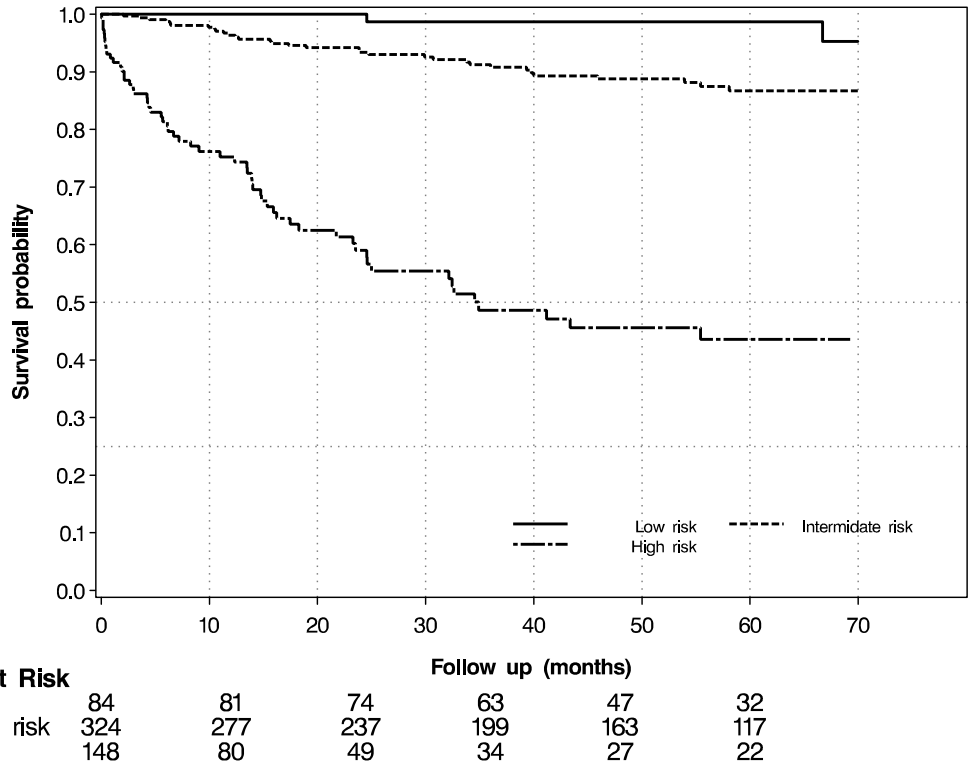
The scoring system was applied to the study population and patients then aggregated into three categories where hazard ratios were comparable within each group: low-risk (score 0,1,2 n=85, 15.1%); intermediate-risk (score 3,4,5 n=325, 57.5%) and high-risk (score 6,7,8 n=155, 27.4%). Using the low-risk group as the referent category, unadjusted and age adjusted hazard ratios for progression to ESKD were calculated. Adjusted for age, patients in the intermediate-risk group did not have a statistically significantly increased risk for ESKD (HR 2.7 [95% CI 1.0-7.5], p=0.06), but patients in the high-risk group did (HR 20.4 [95% CI 7.4-56.2], p<0.001). Complete data are presented in table 4.3.7 with ESKD free survival curves presented in figure 4.3.5. As many of the identified variables are associated with risk for death as well as ESKD, these end-points were considered as competing risks in a cause specific Cox model. Here an increased risk for ESKD was associated with both the medium risk group (HR 1.5 [95% CI 1.1-2.2], p=0.02) and the high-risk group (HR 2.1 [95% CI 1.3-3.2], p=0.002).

**Table 4.3.7** - Risk for end stage kidney disease associated with groups of ordinal risk score

| | Frequency | Number reaching ESKD | Events per 100 patient years | Unadjusted model | | Age adjusted model | |
|---|---|---|---|---|---|---|---|
| | | | | Hazard ratio (95% CI) | p | Hazard ratio (95% CI) | p |
| **Low risk (score 0,1,2)** | 85 | 4 (5%) | 1.0 (0.3-2.6) | Referent | | Referent | |
| **Intermediate risk (score 3,4,5)** | 325 | 37 (11%) | 2.4 (1.7-3.3) | 2.59 (0.9-7.3) | 0.071 | 2.67 (1-7.5) | 0.062 |
| **High risk (score 6,7,8)** | 155 | 73 (47%) | 23 (18-29) | 19.23 (7-52.9) | <0.001 | 20.4 (7.4-56.2) | <0.001 |

*Abbreviations: ESKD - end stage kidney disease (chronic renal replacement therapy or eGFR <10ml/min/1.73m$^2$). 95% CI - 95% confidence interval.*
*Frequency describes number of patients in each risk group. Results of two Cox models are presented, the first containing risk group as a sole exploratory variable, and the second adjusted for patient age.*

**Figure 4.3.5** - Kaplan Meier ESKD free survival plots divided by groups of ordinal risk score




| Number at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Low risk | 84 | 81 | 74 | 63 | 47 | 32 |
| Intermidate risk | 324 | 277 | 237 | 199 | 163 | 117 |
| High risk | 148 | 80 | 49 | 34 | 27 | 22 |

*Risk groups defined using the ordinal scoring system described in table 4.3.6 and divided by groups described in table 4.3.7. Solid line represents patients low risk group; dashed line represents intermediate risk group; interrupted solid line represents high-risk group.*
*y-axis shows probability of ESKD free survival; x-axis shows time in months from date of diagnostic angiography.*

To consider if results of the proposed risk scoring system were specific to patients with ARVD, the ordinal scoring system was applied to 1198 patients all-cause CKD patients from the Chronic Renal Insufficiency Standards Implementation Study (CRISIS). Here the majority of patients were classified as low-risk (n=576, 48%) or intermediate-risk (n=586, 49%), with very few patients classified as high-risk (n=36, 3%). This was despite 4% of CRISIS patients having a diagnosis of ARVD (of whom 15% had a renal artery occlusion) and there being limited differences in baseline characteristics from the SRVD, table 4.3.8. Overall 104 [8.7%] patients in CRISIS progressed to ESKD, of whom 81 [78%] were in the intermediate risk group. In CRISIS being in the intermediate risk group associated with an increased risk for ESKD (HR 5.7 [95% CI 3.2-10.1], $p<0.001$) with too few events in the high-risk group (n=9) to meaningfully comment on risk in these patients.

**Table 4.3.8** - Comparison of baseline characteristics between Salford Renovascular Database and Chronic Renal Insufficiency Standards Implementation Study

| | SRVD N=565 | CRISIS N=1198 | p |
|---|---|---|---|
| **Age (years)** | 70.1+/-9 | 65+/-14 | <0.001 |
| **Male** | | | |
| **eGFR (ml/min/1.73m$^2$)** | 35.4+/-20.2 | 34+/-15.4 | 0.1 |
| **Proteinuria (g/24 hours)** | 0.63 (0.2-1.2) | 0.20 (0.1-0.6) | <0.001 |
| **Systolic blood pressure (mmHg)** | 157.2+/-29.7 | 135.9+/-21.6 | <0.001 |
| **Diastolic blood pressure (mmHg)** | 80.8+/-16.4 | 72.8+/-11.6 | <0.001 |
| **Total cholesterol (mmol/L)** | 4.6+/-1.2 | 4.6±1.3 | 0.8 |
| | *Co-morbidities* | | |
| **Angina** | 195 (34.6%) | 100 (8.6%) | 0.8 |
| **Myocardial infarction** | 171 (30.3%) | 208 (18%) | 0.9 |
| **Stroke or transient ischaemic attack** | 208 (36.8%) | 185 (16%) | 0.02 |
| **Peripheral vascular disease** | 219 (38.8%) | 206 (17.8%) | 0.9 |
| **Diabetes mellitus (type II)** | 167 (29.6%) | 396 (34.2%) | 0.2 |
| **Smoking history** | 225 (39.8%) | 792 (68.4%) | 0.4 |
| | *Medications* | | |
| **Angiotensin blockade** | 268 (47.4%) | 742 (64.1%) | <0.001 |
| **Aspirin** | 304 (54.5%) | 493 (42.6%) | 0.3 |
| **Statin** | 288 (51.6%) | 725 (62.6%) | 0.002 |
| **Number of antihypertensive medications** | 2.5+/-1.5 | 2.5+/-1.5 | 0.2 |
| | *Renal artery parameters** | | |
| **ARVD diagnosed** | 565 (100%) | 46 (4.0%) | |
| **Maximum unilateral stenosis** | 78.3+/-18.9 | 68.4+/-22.5 | 0.002 |
| **Patency score** | 91.2+/-41.6 | 105.6+/-41.6 | 0.02 |
| **Unilateral >70% stenosis** | 360 (63.7%) | 25 (54.3%) | 0.7 |
| **Unilateral renal artery occlusion** | 182 (32.2%) | 7 (15.2%) | 0.002 |
| **Bilateral >50% stenosis** | 224 (39.6%) | 16 (34.8%) | 0.2 |
| **Bilateral >70% stenosis** | 73 (12.9%) | 4 (8.7%) | 0.5 |

*Abbreviations: SRVD - Salford Renovascular Database. CRISIS - Chronic Renal Insufficiency Standards Implementation Study. eGFR - estimated glomerular filtration rate.*
*Definitions: Angiotensin blockade - prescription of angiotensin converting enzyme inhibitor or angiotensin receptor blocker. Patency score - combined left and right renal artery patency, where a score of 200 represents bilateral 0% stenosis and a score of 0 represents bilateral 100% stenosis. Smoking history - current or previous smoking.*
** values for renal artery parameters are presented only for patients with an angiographic diagnosis of atherosclerotic renovascular disease*

*Sensitivity / specificity analysis*

The utility of the ordinal scoring model was assessed against previously described prognostic cut off values for eGFR (above and below 25ml/min/1.73m$^2$ 7) and proteinuria (above and below 1g/24 hours 8, reduced to 0.8g/24 hours to allow more direct comparison), table 4.3.9. Compared to a baseline eGFR of <25ml/min/1.73m2 as the predictor variable (AUC 0.62), addition of remainder of the scoring system increased AUC to 0.77 (ΔAUC 0.15), with a net reclassification index of 0.58 [0.09], p<0.0001. Compared to a high baseline level of proteinuria (>0.8g/24 hours, AUC 0.62), addition of the remainder of the scoring system increased AUC to 0.79 (ΔAUC 0.16) with a NRI of 0.75 [0.09], p<0.0001. When baseline risk was defined by eGFR <25ml/min/1.73m2 and proteinuria >0.8g/24 hours, addition of the remainder of the scoring system gave a ΔAUC of 0.17 with a NRI of 0.51 [0.08], p<0.0001. When the scoring system was applied to the CRISIS population, AUC was 0.70.

**Table 4.3.9** - Sensitivity and specificity analyses for the proposed ordinal scoring system

| | | Following addition of other components of ordinal scoring system | | | |
|---|---|---|---|---|---|
| **Established risk factor** | **Area under curve for the established risk factor alone** | **Area under curve** | **Change in area under curve** | **Net reclassification index (standard error)** | **p** |
| **eGFR <25ml/min/1.73m$^2$** | 0.62 | 0.77 | 0.15 | 0.58 (0.09) | <0.0001 |
| **Proteinuria >0.8g/24 hours** | 0.62 | 0.79 | 0.16 | 0.75 (0.09) | <0.0001 |
| **eGFR <25 and proteinuria >0.8** | 0.59 | 0.75 | 0.17 | 0.51 (0.08) | <0.0001 |
| **eGFR <25 or proteinuria >0.8** | 0.66 | 0.76 | 0.10 | 0.66 (0.06) | 0.02 |

*Abbreviations: eGFR – estimated glomerular filtration rate (CKD-EPI equation).*
*Markers of risk described in previous studies are presented in the left hand column with associated area under the curve from ROC analysis. The following columns describe results of ROC analysis following addition of other components of the proposed ordinal scoring system.*

*Outcome in patients not progressing to ESKD*

Of the 452 patients who did not progress to ESKD, 208 [46%] were alive at time of censoring and 244 [54%] dead. Survivors were younger (69.3±9.5 vs. 71.7±8.1 years, p=0.004), with a lower burden of stenosis (74±18 vs. 80±20%, p<0.001) and had a markedly higher baseline eGFR (44±21 vs. 35±17ml/min/ 1.73m$^2$, p<0.001). Median rate of loss of eGFR did not significantly differ between survivors and non-survivors (1.87ml/min/1.73m$^2$/year vs. 1.24ml/min/ 1.73m$^2$/year reduction, p=0.7), table 4.3.10.

**Table 4.3.10** - Baseline characteristics in patients not progressing to end stage kidney disease divided by mortality status at censoring

| | **Alive N=208** | **Dead N=244** | **p** |
|---|---|---|---|
| **Age (years)** | 69.3+/-9.5 | 71.7+/-8.1 | 0.004 |
| **Male** | 86 (41.5%) | 111 (45.5%) | 0.4 |
| **eGFR (ml/min/1.73m$^2$)** | 44.4+/-21.2 | 34.8+/-17.4 | <0.001 |
| **eGFR slope (ml/min/1.73m$^2$/year)** | -1.87 (-3.9-0.4) | -1.24 (-5.5-0.1) | 0.7 |
| **Proteinuria (g/24 hours)** | 0.42 (0.1-1.0) | 0.61 (0.2-1.2) | 0.2 |
| **Systolic blood pressure (mmHg)** | 157.2+/-27.9 | 158.7+/-32.1 | 0.6 |
| **Diastolic blood pressure (mmHg)** | 80.4+/-14.8 | 81.6+/-18.4 | 0.4 |
| **Total cholesterol (mmol/L)** | 4.6+/-1.1 | 4.6+/-1.3 | 0.9 |
| | *Co-morbidities* | | |
| **Diagnosed hypertension** | 192 (92.3%) | 199 (81.6%) | 0.001 |
| **Angina** | 63 (30.4%) | 92 (37.9%) | 0.1 |
| **Myocardial infarction** | 58 (27.9%) | 79 (32.5%) | 0.3 |
| **Stroke or transient ischaemic attack** | 70 (33.7%) | 86 (35.2%) | 0.7 |
| **Peripheral vascular disease** | 75 (36.1%) | 101 (41.6%) | 0.2 |
| **Diabetes mellitus (type II)** | 59 (28.4%) | 68 (27.9%) | 0.9 |
| **Smoking history** | 119 (57.2%) | 75 (30.7%) | <0.001 |
| **Intolerance of angiotensin blockade** | 15 (7.2%) | 37 (15.2%) | 0.008 |
| | *Medications* | | |
| **Angiotensin blockade** | 124 (59.6%) | 107 (43.9%) | 0.001 |
| **Aspirin** | 122 (59.2%) | 126 (52.5%) | 0.2 |
| **Statin** | 142 (68.9%) | 103 (42.9%) | <0.001 |
| **Number of antihypertensive medications** | 2.5+/-1.5 | 2.5+/-1 | 0.01 |
| | *Renal artery parameters and clinical presentation* | | |
| **Maximum unilateral stenosis** | 73.8+/-18 | 80.1+/-19.8 | <0.001 |
| **Patency score** | 96.8+/-40 | 86.4+/-40.8 | 0.005 |
| **Unilateral >70% stenosis** | 117 (56.3%) | 169 (69.3%) | 0.004 |
| **Unilateral renal artery occlusion** | 37 (17.8%) | 95 (38.9%) | <0.001 |
| **Bilateral >50% stenosis** | 82 (39.4%) | 103 (42.2%) | 0.5 |
| **Bilateral >70% stenosis** | 20 (9.6%) | 36 (14.8%) | 0.1 |
| **Renal artery revascularisation** | 54 (26%) | 53 (21.7%) | 0.3 |
| **Rapid loss of renal function** | 41 (19.7%) | 34 (13.9%) | 0.1 |
| **Refractory hypertension** | 75 (36.1%) | 76 (31.1%) | 0.3 |

*Abbreviations: eGFR - estimated glomerular filtration rate.*
*Definitions: Angiotensin blockade - prescription of angiotensin converting enzyme inhibitor or angiotensin receptor blocker. Patency score - combined left and right renal artery patency, where a score of 200 represents bilateral 0% stenosis and a score of 0 represents bilateral 100% stenosis. Smoking history - current or previous smoking. Rapid loss of renal function - serum creatinine at the time of diagnostic angiography greater than 1.2x or 100µmol/L higher than a baseline reading from the previous six-months. Refractory hypertension - blood pressure >140mmHg systolic and/or >90mmHg diastolic despite use of three or more different classes of anti-hypertensive medications, one of which was a diuretic.*

Discussion

The primary goal of this analysis was to identify the baseline characteristics most strongly associated with risk for progression to ESKD in surviving ARVD patients. As with previous studies, we have demonstrated that eGFR and proteinuria are the key influences on prognosis, a finding consistent with other studies of loss of renal function in CKD [19] and aligned with the concept that in ARVD measures of parenchymal health are more important than anatomical parameters. By utilising a classification tree methodology we have added to the understanding of the hierarchical importance of these markers and shown that eGFR is the feature most dominantly associated with increased risk. Importantly we have also found that the eGFR threshold for this increased risk may be set at a lower level of renal function than in other causes of CKD. In our cohort the greatest risk for ESKD was found in well established CKD stage 4 (eGFR ≤26ml/min/1.73m$^2$) compared to other studies of all-cause CKD populations which have described significantly increased risk from CKD stage 3a and below [20]. In a recent meta-analysis of data from the Chronic Kidney Disease Prognosis Consortium a non-linear relationship between mortality risk and eGFR was described, with the hazard ratio for death only exceeding 1.5 as patients approached stage 4 CKD [21]. By comparison, risk for death in ARVD increases at higher eGFR values with a 40% mortality rate seen at 3-years in patients with ARVD and an eGFR >50ml/min/1.73m$^2$ [7]. As in a previous analysis of the SRVD we have demonstrated an average annual rate of loss of renal function of 2ml/min/1.73m$^2$ we hypothesize that the lesser risk for progression to ESKD in ARVD patients with more preserved renal function at time of diagnosis is representative of the excess mortality associated with this condition, with this effect demonstrated by the reduced (though still significant) risk for ESKD seen in the competing risks analysis. Importantly, our proposed model does not distinguish between reasons for patients not reaching ESKD. This may explain the counter-intuitive finding of reduced risk for ESKD associated with smoking, a factor more strongly associated with increased risk for death [22] rather than progression of CKD [23].

The pattern of risk for ESKD associated with increasing levels of proteinuria is consistent with other studies in the general CKD population. In our multivariate model, a 1g/24hour increase in urinary protein excretion was associated with a

22% increase in risk for progression to ESKD. This is comparable to other studies of CKD that have described 8-50% increases in risk for comparable elevations in urinary protein excretion [11,24]. As with other studies, our data also show that whilst large increases in proteinuria associate with increased risk for progression to ESKD, smaller elevations also have prognostic significance with the classification tree highlighting increased risk where proteinuria exceeds 0.3g/24hours. Although our data do not inform us as to whether this is a modifiable risk as is the case in other causes of CKD [25] the reduced risk for RRT seen when ARVD patients are treated with angiotensin blockade suggests that it may be [10]. The modifiable nature of proteinuria as a risk factor, and the greater quantity of urinary protein excretion required to increase risk at lower eGFR values may explain the dominance of baseline eGFR in determining prognosis. In predictive models generated in other CKD cohorts, proteinuria is not a significant prognostic factor in multivariate analysis [26].

To be adopted into clinical practice, a risk stratification system must be both clinically useful and economically viable. In sensitivity / specificity analysis, the AUC of our proposed scoring system exceeded 0.75, a value that compares favorably to the median AUC of 0.74 (range 0.50-0.83) reported for the widely utilised Framingham Cardiovascular Risk score [27]. Furthermore when the scoring system was compared to threshold eGFR and proteinuria values previously associated with increased risk for ESKD in ARVD [7,8] AUC was notably increased, with NRI values that would be considered strong evidence for improved classification [28]. As such we believe the proposed system passes the test of clinical utility. Although we acknowledge that there is potential for the addition of further parameters to increase the AUC and/or further improve discrimination, we feel that this study demonstrates the prognostic value of routinely performed clinical measurements, something that must be optimised before the usefulness of novel markers (currently under investigation [29]) can be fully assessed. Given that our system mandates no investigations beyond those performed in a standard nephrology clinic we also believe our proposed system passes the test of cost effectiveness.

The comparable AUC value of 0.70 found when the scoring system was applied to the CRISIS CKD population highlights the commonality of eGFR and

proteinuria as risk factors for ESKD across the spectrum of renal disease. However, in ARVD patients, risk for ESKD was focused in the highest risk category, whereas in CRISIS risk clustered in the intermediate risk category. Again we suggest that increased mortality in ARVD patients compared to other forms of CKD [30] is the most likely explanation for this difference and believe that this information may have value in relation to service delivery. With only one observed ESKD event per 100 patient years in ARVD patients in the low risk category, and 2.4 events in the intermediate risk category, the low probability of requiring RRT may allow management of these patients to be safely returned to primary care. Conversely, newly diagnosed ARVD patients classified as high-risk could be prioritized for closer monitoring, and dialysis planning as required.

Based on published trial data [4,5], it is unsurprising that renal artery revascularisation did not feature in either the Cox model or the classification tree as a prognostically relevant variable. Whilst reports do exist of improvements in renal function following revascularisation, this benefit is most likely to be observed in highly selected patient populations [31] that systematically differ from patients represented in the SRVD. As a previous cross-sectional analysis had not described a difference in creatinine clearance between patients with unilateral stenosis, bilateral stenosis or unilateral renal artery occlusion [6] it was also anticipated that degree of stenosis would not be of prognostic importance. Although this was the case when luminal loss was considered as a continuous variable (both as percentage stenosis to the most affected kidney and as a combined patency score [6]), we report the novel finding of unilateral renal artery occlusion being independently associated with increased risk for progression to ESKD. In a 2002 series of 25 patients with renal artery occlusion (n=14) or >50% unilateral stenosis (n=11) more rapid annual loss of eGFR was observed in patients with occlusive disease (-8.2 vs. -4.9ml/min/1.73m$^2$/year) [7]. In patients with unilateral non-occlusive renal artery stenosis compensatory hypertrophy of the non-stenosed organ can occur to balance reductions in the function of the diseased kidney [32,33]. The worse prognosis observed in our study in patients with occlusive disease may represent the end-point of this adaptive response and a rapid functional loss similar to that seen following the compensatory hyperfiltration phase of incipient diabetic nephropathy [34].

This study has several limitations. Firstly we have defined a precise level of renal function where risk is greatest, this is based on eGFR measurements, the limitations of which have been broadly discussed and we fully acknowledge [35]. We would, however, stress that the aim of this study was to produce a risk stratification system based upon readily available clinical data and that direct measurements of GFR are rarely available in real-life practice. Secondly, our definition of ARVD as a primary cause of CKD is somewhat arbitrary. In many studies 'significant' renal artery stenosis is defined as 70% or greater loss of luminal diameter. As the authors consider ARVD to be part of a systemic condition we do not feel that our acceptance of a lesser degree of stenosis is incorrect, but we do accept that some of the biplane diagnostic methods utilised (most notably magnetic resonance angiography) may have over estimated the burden of stenosis [36]. We also accept that hypertension can be both a cause and effect of renal artery stenosis and as such overlap exists between hypertensive nephrosclerosis and ischaemic nephropathy [37]. Equally without biopsy data it is possible that other glomerular diseases may also be present in patients with an otherwise incidental renal artery stenosis. As such we cannot be certain that there are no cases where we have defined CKD as being due to ARVD as opposed to an alternative undiagnosed pathology. Finally we must address the question of practical application. As a number of studies have demonstrated that revascularisation does not reduce risk for RRT or slow rate of loss of renal function in ARVD [4] it is appropriate to ask what practical benefit our proposed system could offer to clinicians and patients. A major criticism of recent trial design has been that the unselected nature of patients recruited into the RCT may have reduced the probability of observing a treatment benefit. We would suggest that one possible use of our proposed system is to aid future study design by identifying the patients at greatest risk for ESKD – especially when renal function is to be considered a key end-point. Although it may be counterintuitive to consider revascularisation in patients with very advanced CKD, a dual center study has previously suggested that the greatest probability of renal functional improvement following revascularisation is seen in patients with more advanced CKD [38].

In conclusion this study has shown that through use of readily available clinical data it is possible to select ARVD patients with low and high probabilities of progressing to ESKD. Although external validation is required, our proposed system aid future study design and allow more efficient service delivery.

## References


1. Hansen KJ, Edwards MS, Craven TE, et al. Prevalence of renovascular disease in the elderly: A population-based study. *J Vasc Surg*. 2002;36(3):443–451.

2. Harding MB, Smith LR, Himmelstein SI, et al. Renal artery stenosis: prevalence and associated risk factors in patients undergoing routine cardiac catheterization. *J Am Soc Nephrol*. 1992;2(11):1608–1616.

3. Kuroda S, Nishida N, Uzu T, et al. Prevalence of renal artery stenosis in autopsy patients with stroke. *Stroke*. 2000;31(1):61–65.

4. ASTRAL Investigators, Wheatley K, Ives N, et al. Revascularisation versus medical therapy for renal-artery stenosis. *N Engl J Med*. 2009;361(20):1953–1962..

5. Kumbhani DJ, Bavry AA, Harvey JE, et al. Clinical outcomes after percutaneous revascularisation versus medical management in patients with significant renal artery stenosis: a meta-analysis of randomised controlled trials. *Am Heart J*. 2011;161(3):622–630.

6. Suresh M, Laboi P, Mamtora H, Kalra PA. Relationship of renal dysfunction to proximal arterial disease severity in atherosclerotic renovascular disease. *Nephrol Dial Transplant*. 2000;15(5):631–636.

7. Cheung CM, Wright JR, Shurrab AE, et al. Epidemiology of renal dysfunction and patient outcome in atherosclerotic renal artery occlusion. *J Am Soc Nephrol*. 2002;13(1):149–157.

8. Wright J, Shurrab A, Cheung C, et al. A prospective study of the determinants of renal functional outcome and mortality in atherosclerotic renovascular disease. *Am Journal Kidney Dis*. 2002;39(6):1153–1161.

9. Ritchie J, Green D, Kalra PA. Current views on the management of atherosclerotic renovascular disease. *Ann Med*. 2012;44 Suppl 1:S98–S110.

10. 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. *Nephrol Dial Transplant*. 2012;27(4):1403-09.

11. Hoefield RA, Kalra PA, Baker P, et al. Factors associated with kidney disease progression and mortality in a referred CKD population. *Am J Kidney Dis*. 2010;56(6): 1072–1081.

12. Mancia G, De Backer G, Dominiczak A, et al. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2006;28(12):1462–1536.

13. UK Renal Association eCKD guide [Internet]. [cited 2011 Dec 12]. Available from: http://www.renal.org.

14. British Cardiac Society, British Hypertension Society, Diabetes UK, HEART UK, Primary Care Cardiovascular Society, Stroke Association. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart*. 2005;91 Suppl 5:v1–52.

15. Cooper C, Murphy T, Matsumoto A, et al. Stent revascularisation for the prevention of cardiovascular and renal events among patients with renal artery stenosis and systolic hypertension: Rationale and design of the CORAL trial. *Am Heart J*. 2006;152(1):59–66.

16. 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. *J Vasc Interv Radiol*. 2006;17(9):1383–97.

17. Foley RN, Wang C, Snyder JJ, Rule AD, Collins AJ. Kidney function and risk triage in adults: threshold values and hierarchical importance. *Kidney Int*. 2011;79(1):99–111.

18. Pencina MJ, D'Agostino RB, D'Agostino RB, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Statist Med*. 2008;27(2):157–72.

19. Levey ASA, de Jong PEP, Coresh JJ, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int*. 2011;80(1):17–28.

20. Johnson ES, Thorp ML, Yang X, Charansonney OL, Smith DH. Predicting Renal Replacement Therapy and Mortality in CKD. *Am Journal Kidney Dis*. 2007;50(4):7–7.

21. Nitsch DD, Grams MM, Sang YY, et al. Associations of estimated glomerular filtration rate and albuminuria with mortality and renal failure by sex: a meta-analysis. *BMJ*. 2013;346:f324–f324.

22. Shlipak MG, Fried LF, Cushman M, et al. Cardiovascular mortality risk in chronic kidney disease: comparison of traditional and novel risk factors. *JAMA*. 2005;293(14):1737–1745.

23. Orth SR, Hallan SI. Smoking: a risk factor for progression of chronic kidney disease and for cardiovascular morbidity and mortality in renal patients--absence of evidence or evidence of absence? *Clin J Am Soc Nephrol*. 2008;3(1):226–236.

24. Landray MJ, Emberson JR, Blackwell L, et al. Prediction of ESRD and death among people with CKD: the Chronic Renal Impairment in Birmingham (CRIB) prospective cohort study. *Am J Kidney Dis*. 2010;56(6):1082–1094.

25. Jafar TH, Stark PC, Schmid CH, et al. Proteinuria as a modifiable risk factor for the progression of non-diabetic renal disease. *Kidney Int*. 2001;60(3):1131–1140.

26. Drawz PE, Goswami P, Azem R, Babineau DC, Rahman M. A Simple Tool to Predict End-Stage Renal Disease within 1 Year in Elderly Adults with Advanced Chronic Kidney Disease. *J Am Geriatr Soc*. 2013;61(5):762-8.

27. Tzoulaki I, Liberopoulos G, Ioannidis JPA. Assessment of Claims of Improved Prediction Beyond the Framingham Risk Score. *JAMA*. 2009;302(21):2345–2352.

28. Pencina MJM, D'Agostino RBR, Pencina KMK, Janssens ACJWA, Greenland PP. Interpreting incremental value of markers added to risk prediction models. *Am J Epidemiol*. 2012;176(6):473–481.

29. Haller ST, Kalra PA, Ritchie JP, et al. Effect of CD40 and sCD40L on Renal Function and Survival in Patients With Renal Artery Stenosis. *Hypertension* 2013;61(4):894–900..

30. Kalra PA, Guo H, Kausz AT, et al. Atherosclerotic renovascular disease in United States patients aged 67 years or older: risk factors, revascularisation, and prognosis. *Kidney International*. 2005;68(1):293–301.

31. Chrysochou C, Mendichovszky IA, Buckley DL, Cheung CM, Jackson A, Kalra PA. BOLD imaging: a potential predictive biomarker of renal functional outcome following revascularisation in atheromatous renovascular disease. *Nephrol Dial Transplant*. 2012 Mar;27(3):1013-9.

32. Miyamori I, Yasuhara S, Takeda Y, et al. Effects of converting enzyme inhibition on split renal function in renovascular hypertension. *Hypertension*. 1986;8(5):415–421.

33. Rossignol PP, Chatellier GG, Azizi MM, Plouin P-FP. Proteinuria in renal artery occlusion is related to active renin concentration and contralateral kidney size. *J Hypertens*. 2002;20(1):139–144.

34. Zerbini G, Bonfanti R, Meschi F, et al. Persistent renal hypertrophy and faster decline of glomerular filtration rate precede the development of microalbuminuria in type 1 diabetes. *Diabetes*. 2006;55(9):2620–2625.

35. Murata K, Baumann NA, Saenger AK, Larson TS, Rule AD, Lieske JC. Relative performance of the MDRD and CKD-EPI equations for estimating glomerular filtration rate among patients with varied clinical presentations. *Clin J Am Soc Nephrol*. 2011;6(8): 1963–1972.

36. Patel ST, Mills JL, Tynan-Cuisinier G, Goshima KR, Westerband A, Hughes JD. The limitations of magnetic resonance angiography in the diagnosis of renal artery stenosis: comparative analysis with conventional arteriography. *J Vasc Surg*. 2005;41(3):462–468.

37. Keddis M, Garovic V, Bailey K. Ischaemic nephropathy secondary to atherosclerotic renal artery stenosis: clinical and histopathological correlates. *Nephrol Dial Transplant.* 2010 Nov;25(11):3615-22.

38. Kalra PA, Chrysochou C, Green D, et al. The benefit of renal artery stenting in patients with atheromatous renovascular disease and advanced chronic kidney disease. *Cathet Cardiovasc Intervent*. 2010;75(1):1–10.

# CHAPTER 4.4

## Comparing Doubly Robust Regression with Randomised Controlled Trials in Nephrology

Ritchie J, Green D, Sinha S, Kalra PA

*Under review by BMC Medical Research Methodology*



Preface

Randomised controlled trials provide the gold standard of evidence. However the cost of performing such studies, especially in topics that have previously been the subject of randomised study, limits the number performed. In addition, randomised trials are poor tools for the study of rare diseases or distant end-points. Observational study can overcome some of these limitations. However, to produce valid results, care must be taken to ensure that confounding effects are minimised.

This chapter aims to introduce, demonstrate and validate a novel statistical methodology, doubly robust regression. This methodology benefits the analysis of observational data as it allows simultaneous, independent, consideration of the effect of co-variates on exposure and outcome.

As this methodology is not in routine use and is applied in chapter 4.5, this analysis is included to provide evidence that application of this technique to the SRVD and CRISIS databases produces accurate results.

Abstract

Background

Randomised controlled trials are the gold standard test of interventions. Due to limitations including cost, delay and generalizability, observational study is a popular alternative. The doubly robust estimator (DRE) is an analytical methodology combining outcome and probability of treatment regressions. This theoretically protects against model misspecification. We consider its utility in real-life studies.

Methods

Inclusion and exclusion criteria from two RCT (ASTRAL and SHARP) were applied to two observational studies of kidney disease, the Salford Renovascular Database and the Chronic Renal Insufficiency Standards Implementation Study. Cox regressions adjusted for outcome and inverse probability of treatment weighting (IPTW) were made and compared to DRE results. End-points were as for the original RCT. Analyses were repeated with intentional model misspecifications.

Results

Baseline characteristics in the SRVD (n=508) and CRISIS (n=406) were similar to published RCT. Revascularisation occurred in 14% of patients (SRVD); 55% were statin treated (CRISIS). Correctly specified regression models estimated treatment effects comparable to RCT results although with a lower level of statistical significance. Where models were incorrectly specified, treatment effect estimates from the DRE remained stable, those from Cox models varied – e.g. risk for death associated with renal artery revascularisation vs. medical therapy: fully specified DRE relative risk (RR) 0.99 [95%CI 0.8-1.3], p=0.9, fully specified Cox IPTW regression hazard ratio (HR) 0.89 [95%CI 0.9-1.2], p=0.9. Misspecified model; DRE RR 0.95 [95%CI 0.7-1.2], p=0.7, Cox IPTW model HR 0.86 [95%CI 0.7-1.0], p=0.05.

Conclusions

In real-world studies the DRE provides stable estimates of treatment effect even when one regression model is incorrectly specified.

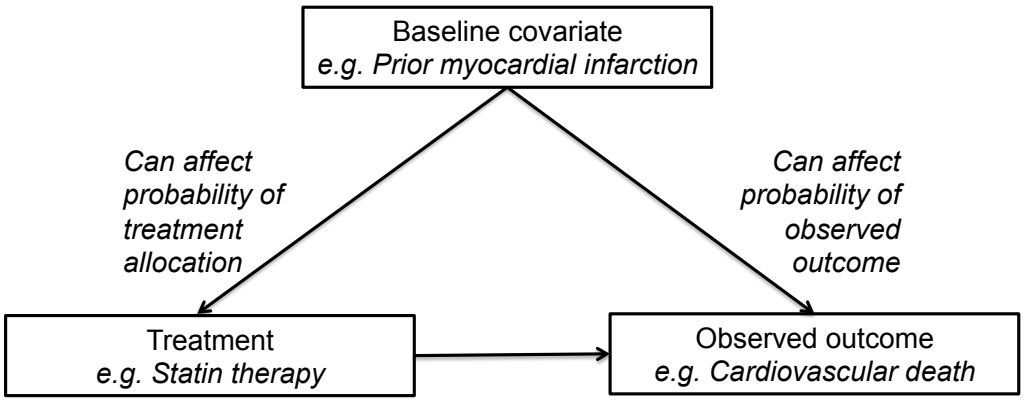
Introduction

When considering the role of a therapeutic intervention on patient outcome, RCT are the gold standard. However, large disparities exist in the number of RCT performed by different medical specialties, and substantial variability exists in the quality of studies performed [1]. Historically, nephrology compares poorly to other fields with only 1.15% of citations prior to 2004 being RCT [2]. There is a resultant tendency for nephrologists to extrapolate results from trials performed in the general population, or to rely on non-randomised studies. Consequently many guidelines for the management of patients with chronic kidney disease are based, at least in part, on the results of observational studies [3], with recent years seeing a rapid expansion in such research [4-7]. Although the results of observational studies can align with RCT data [8], the tendency for non-randomised data to overstate treatment effects, often due to selection bias or confounding is well described [9]. Selection bias arises as individual subjects cannot be compared against themselves (a counterfactual outcome) and must therefore be compared to a similar but non-identical patient. If exacting thought is not given to study design and selection of patient groups for analysis, systemic differences can occur and reduce the validity of results. Confounding occurs when variables affecting probability of treatment or risk for outcome are not equally distributed between groups (figure 4.4.1). Confounding can be controlled for by use of propensity scores [10-12] and outcome regression analysis [13]. However, these approaches are typically performed independently of each other and require that all relevant variables are included in the model and in the correct format. Where a regression model is not correctly specified, results may lack validity.

The doubly robust estimator (DRE) is a novel methodology that simultaneously combines outcome regression with propensity score weighting so the effect of baseline covariates on treatment assignment and patient outcome are simultaneously considered. In this methodology, models for both probability of treatment and observed outcome are specified separately, allowing the effects of a measured covariate to be considered in *one or both* models with variable specification and form able to vary between models [14,15]. Initially, two distinct models are generated - one modeling the effects of covariates on outcome for each treatment assignment (a classical multivariate regression), and one

modeling treatment assignment as a function of covariates (a propensity score). Combining these models generates an output that is a function of both observed outcome and predicted outcome (weighted by propensity score). Assessment of the bias term in each of these models allows one correct model to take precedence over, or zero out the other [15]. The standard error of the final model can then be calculated based on the sandwich estimator (equation 21 Lunceford and Davidian) [16]. The DRE therefore provides a valid estimate of treatment effect when one or both models are correctly specified, providing protection against misspecification in one of the models [15].

**Figure 4.4.1** - Confounding in observational data




*Prior myocardial infarction affects the chance of both a patient receiving statin therapy and reaching the end-point of cardiovascular death. These effects cannot be assumed to be equal.*

This paper aims to demonstrate how use of the DRE may contribute to reporting of observational data by comparing results from the DRE to more commonly utilised regression techniques. Analyses are initially performed with fully specified models and then repeated with deliberately introduced errors in model specification to consider how results of each methodology can vary under these conditions. To aid interpretation by the reader these comparisons are made in relation to the findings of published RCT.

Subjects and methods

*Patient population*

The population for analysis was drawn from two previously described observational studies, CRISIS [17,18] and the SRVD [19,20]. Respectively, these are prospective observational studies of outcome and progression of renal failure in an all-cause CKD and ARVD population. Both studies have approval from the regional ethics committee with written consent obtained from participants. Clinical and demographic information, including details of co-morbidities, are recorded at time of recruitment and annually thereafter. Pre-specified end-points for both studies are death (data obtained from electronic patient records or the United Kingdom Office of National Statistics via the National Health Service Medical Research Information Service) and initiation of chronic RRT, defined as haemodialysis, peritoneal dialysis or transplantation.

*Selection of randomised controlled trials for comparison*

Studies for comparison were selected from major nephrology RCT where a parallel interest existed in our research databases. Any study whose findings had become an accepted standard of care by the time of initiating recruitment for our observational studies was not considered (e.g. RCT showing the benefit of renin angiotensin blockade in diabetic nephropathy) [21,22], nor was any trial based in the pediatric or transplantation population, nor any trial considering a novel interventional device or investigational medical product.

*Analytical technique*

Populations for analysis were identified from the SRVD and CRISIS by applying inclusion and exclusion criteria for enrollment into the original RCT. Average baseline demographics are described in the same format as the original RCT. For each study, regression models for probability of treatment and probability of outcome were separately defined using any recorded baseline variable where a documented relationship or clinically plausible link existed. For continuous variables linearity was assessed using restricted cubic splines. Where a non-linear relationship existed an appropriate transformation was made. Using fully specified models, three regression analyses were performed. Firstly a Cox model adjusted for effects of baseline variables on outcome, secondly a Cox model weighted by inverse probability of treatment (IPTW), and thirdly the DRE

was applied using the methodology described by Funk et al [15]. To demonstrate the effects of misspecification within each regression model the above analyses were repeated with the outcome model and subsequently the IPTW model incorrectly designated. Results from Cox models are presented as hazard ratio with 95% confidence intervals in brackets. Results from the DRE are presented as both predicted percentage of events in each group (control vs. intervention) and as relative risk RR with 95% confidence interval in brackets. For all analyses time zero was defined as date of recruitment with censoring occurring at the maximum follow-up time reported in the original RCT. Analyses were performed in SAS version 9.2 (SAS institute, Cary, NC, USA) licensed to the University of Manchester.

Results

*Study and patient selection*

The two RCT identified for comparison were ASTRAL [23] and the Study of Heart and Renal Protection (SHARP) [24]. An overview of these studies is presented in table 4.4.1. Comparison with ASTRAL was made from patients in the SRVD, where data were available on 819 patients. In total 253 subjects were excluded from the SRVD based on RCT inclusion / exclusion criteria, table 4.4.2; 89 due to incomplete baseline data, and 164 due to <50% stenosis or presentation with a high-risk clinical phenotype. A further 58 patients were excluded due to revascularisation occurring >1year after diagnostic angiography giving a population for analysis of 508. Comparison with SHARP was made using patient data from CRISIS. Of 2252 enrolled patients, 634 were excluded due to incomplete baseline data or failure to satisfy inclusion criteria, with a further 1212 removed due to satisfying one or more exclusion criteria (almost universally a history of myocardial infarction or coronary revascularisation procedure), giving a population for analysis of 406.

**Table 4.4.1** - Randomised trials selected for comparison

| Study and year | Description | Primary end-points suitable for comparison | Secondary end-points suitable for comparison |
|---|---|---|---|
| ASTRAL (2009) | Revascularisation vs. optimal medical therapy for atheromatous renovascular disease | Rate of change in renal function (reciprocal of serum creatinine) | All-cause mortality<br>Progression to end-stage kidney disease |
| SHARP (2011) | Assessment of combination therapy with simvastatin and ezetimibe in a chronic kidney disease (and dialysis) population | Major atherosclerotic events (composite of non-fatal myocardial infarction or stroke, arterial revascularisation or cardiac death) | All-cause mortality<br>Non-fatal myocardial infarction |

*Abbreviations: ASTRAL - Angioplasty and stenting for renal artery lesions trial. SHARP - Study of heart and renal protection*

**Table 4.4.2** - Details of application of randomised trial inclusion / exclusion criteria to observational data

| | RandomisED TRIAL INCLUSION CRITERIA | |
|---|---|---|
| | ***STUDY CRITERIA*** | ***METHOD OF MATCHING FROM SRVD / CRISIS*** |
| **ASTRAL** | Substantial anatomical renal artery stenosis potentially suitable for endovascular revascularisation | Only patients with focal stenosis of >50% (by direct angiography/CTA/MRA) included |
| | Uncertainty if there is a worthwhile clinical benefit from revascularisation | Patients with flash pulmonary edema, or rapidly declining renal function in combination with refractory hypertension excluded. |
| | *Nb – intervention in ASTRAL was angioplasty and stenting. This practice was fully adopted locally after 1999 therefore patients revascularised before this date were excluded from analysis.* | |
| **SHARP** | Age over 40 years with a serum creatinine of at least 150 µmol/L in men and 130 mol/L in women | Matched directly for these criteria |
| | *Nb – in SHARP treatment arm was simvastatin 20mg plus ezetimibe 10mg. Here groups were defined by statin treated / not statin treated.* | |

| | RandomisED TRIAL EXCLUSION CRITERIA | |
|---|---|---|
| | ***STUDY CRITERIA*** | ***METHOD OF MATCHING FROM SRVD / CRISIS*** |
| **ASTRAL** | Nonatheromatous cardiovascular disease | Data not available |
| | Previous revascularisation for renal artery stenosis | Patients previously revascularised excluded |
| **SHARP** | Definite history of myocardial infarction or coronary revascularisation | All patients with previous myocardial infarction and / or coronary revascularisation (percutaneous or surgical) excluded |
| | Functioning renal transplant | Matched for directly |
| | History of chronic liver disease | Data not available |
| | Alanine aminotransferase or aspartate aminotransferase greater than 1.5x upper limit of normal | Only data for alanine aminotransferase available – matched for directly by this |
| | Active inflammatory muscle disease or creatine kinase greater than 3x upper limit of normal | Data not available |
| | Definite contraindication to statin therapy | Data not available |
| | Pre-menopausal women not using reliable method of contraception | Not matched for as all appropriate counseling prior to initiation of treatment is a local standard of care |
| | Uremic emergency within 2 months | Not matched for |

*Abbreviations: ASTRAL - Angioplasty and stenting for renal artery lesions trial. SHARP - Study of heart and renal protection. CRISIS - Chronic renal insufficiency standards implementation study. eGFR - estimated glomerular filtration rate. CTA - computed tomography angiography. MRA - magnetic resonance angiography*

*Baseline patient characteristics*

Of the 508 patients selected from the SVRD, 14% (n=73) underwent percutaneous renal artery angioplasty and bare metal stenting (PTRAS), with the remaining patients 86% of patients (n=435) forming the medical control group. Patient characteristics in both treatment groups were similar to those in ASTRAL for age, gender, presence of diabetes and degree of stenosis. However, patients in ASTRAL had a higher baseline eGFR (SRVD vs. RCT – 33.8 vs. 40.3ml/min/1.73m$^2$ in PTRAS group; 34.3 vs. 39.8ml/min/1.73m$^2$ in medical group), and lower blood pressures (159/80 vs. 149/76mmHg in PTRAS group; 155/80 vs. 152/76mmHg in medical group).

Of the 406 patients selected from CRISIS, 55% (n=224) were statin treated from recruitment to censoring and 45% (n=182) statin naive from recruitment to censoring. Baseline characteristics were similar between patients in CRISIS and those in SHARP the only notable disparity being in the proportion of patients with diabetes. In SHARP 23% of patients in each arm were diabetic whereas in CRISIS 33% of statin treated patients were diabetic compared to 11% in the non-statin group. Complete baseline data are presented in table 4.4.3. Median follow-up for patients in the SRVD was 44 months [IQR 20-59] compared to 24 months in ASTRAL, and 4.7 years [IQR 2.7-5.0] for patients in CRISIS compared to 4.9 years in SHARP.

**Table 4.4.3** - Comparison of baseline characteristics between randomised trials and observational data

| | ASTRAL* | | | | SHARP ** | | | |
|---|---|---|---|---|---|---|---|---|
| | Revascularisation | | Medical therapy | | Lipid lowering | | Control | |
| | RCT (n=403) | SRVD (n=73) | RCT (n=403) | SRVD (n=435) | RCT (n=4560) | CRISIS (n=224) | RCT (n=4620) | CRISIS (n=182) |
| **Age** | 70 [42-86] | 69 [42-83] | 71 [43-88] | 70 [40-92] | 62 (12) | 67 (11) | 62 (12) | 66 (12) |
| **Male (%)** | 63 | 60 | 63 | 60 | 63 | 61 | 62 | 59 |
| **eGFR (ml/min/1.73m$^2$)** | 40.3 [5-124] | 33.8 [6-90] | 39.8 [7-122] | 34.3 [4-95] | 26.6 (13) | 30.6 (13) | 26.6 (13) | 32.0 (15) |
| **Systolic blood pressure (mmHg)** | 149 [87-270] | 159 [95-230] | 152 [90-241] | 155 [90-240] | 139 (22) | 138 (22) | 139 (22) | 140 (22) |
| **Diastolic blood pressure (mmHg)** | 76 [45-120] | 80 [56-130] | 76 [46-130] | 80 [40-140] | 79 (13) | 74 (12) | 79 (13) | 77 (12) |
| **Diabetes (%)** | 31 | 32 | 29 | 27 | 23 | 33 | 23 | 12 |
| **Degree of renal artery stenosis** | 76 [40-100] | 78 [50-100] | 75 [20-99] | 77 [50-100] | - | | - | |

*Abbreviations: ASTRAL - Angioplasty and stenting for renal artery lesions trial. SHARP - Study of heart and renal protection. RCT -Randomised controlled trial. SRVD - Salford renovascular database. CRISIS - Chronic renal insufficiency standards implementation study. eGFR - estimated glomerular filtration rate*

** continuous variables presented as mean value [range].*
*** continuous variables presented as mean (standard deviation).*

*Identification of covariates for inclusion in regression models*

From the SRVD patient age, systolic blood pressure, eGFR, proteinuria and degree of renal artery stenosis were selected for estimation of likelihood of revascularisation. Both age and proteinuria had non-linear relationships and were therefore converted into categorical format (age ≥ or < 75 years and proteinuria ≥ or <1g/24 hours). Within CRISIS, age, urinary protein to creatinine ratio, diabetes mellitus, history of macrovascular disease (prior myocardial infarction, stroke or transient ischaemic attack and peripheral vascular disease) and cholesterol to high-density lipoprotein ratio were selected for estimation of likelihood of receiving statin therapy. Again age had a non-linear relationship and was converted into a categorical variable (≥ or < 62 years).

Co-variates identified for inclusion in the outcome models were generally common between study end-points although optimal form (i.e. continuous or categorical) varied. In the analyses considering the effects of revascularisation, age was considered as a continuous variable in relation to death and cardiovascular events, but as a categorical variable (≥ or <75 years) in relation to initiation of renal replacement therapy. Complete details of each model are presented in table 4.4.4.

**Table 4.4.4** - Details of regression model specifications

| ASTRAL | | | | | |
|---|---|---|---|---|---|
| **Probability of treatment** | | | **Outcome** | | |
| ***Variable*** | ***Parameter estimate (SE)*** | ***p*** | ***Death*** | ***Cardiovascular event*** | ***Renal replacement therapy*** |
| Age <75 years | 0.33 (0.3) | 0.2 | Age (years) | Age (years) | Age <75 years |
| Systolic blood pressure (mmHg) | 0.03 (0.004) | 0.4 | Systolic blood pressure (mmHg) | Estimated glomerular filtration rate (ml/min/ 1.73m$^2$) | Estimated glomerular filtration rate <25ml/ min/1.73m$^2$ |
| Estimate glomerular filtration rate (ml/min/ 1.73m$^2$) | 0.001 (0.007) | 0.3 | Cerebrovascular event, myocardial infarction, peripheral vascular disease | Cerebrovascular event, myocardial infarction, peripheral vascular disease | Proteinuria (g/24 hours) |
| Renal artery stenosis >80% | 0.61 (0.3) | <0.001 | Angiotensin blockade | Proteinuria >1g/24 hours | Diabetes mellitus |
| Proteinuria >1g/24 hours | -0.27 (0.2) | 0.3 | Estimated glomerular filtration rate (ml/min/ 1.73m$^2$) | Diabetes mellitus | Angiotensin blockade |
| C-statistic for probability of treatment model | 0.62 | | Proteinuria (g/24 hours) | | |
| | | | Diabetes mellitus | | |
| | | | Degree of stenosis (%) | | |
| **SHARP** | | | | | |
| **Probability of treatment** | | | **Outcome** | | |
| ***Variable*** | ***Parameter estimate (SE)*** | ***p*** | ***Death*** | ***Major atherosclerotic cardiovascular event*** | ***Non-fatal myocardial infarction*** |
| Age >62 years | -0.37 (0.2) | 0.08 | Age >62 years | Age (years) | Age (years) |
| Proteinuria (g/24 hours) | 0.01 (0.001) | 0.03 | Haemoglobin (g/dL) | Systolic blood pressure (mmHg) | Systolic blood pressure (mmHg) |
| Diabetes mellitus | 1.37 (0.3) | <0.001 | Estimated glomerular filtration rate (ml/min/ 1.73m$^2$) | Aspirin | Aspirin |
| Cholesterol to high density lipoprotein ratio (mmol/L) | 0.42 (0.1) | <0.001 | Smoking history | Estimated glomerular filtration rate (ml/min/ 1.73m$^2$) | Estimated glomerular filtration rate (ml/min/ 1.73m$^2$) |
| Cerebrovascular event, myocardial infarction, peripheral vascular disease | 0.37 (0.3) | 0.2 | Diabetes mellitus | Diabetes mellitus | Diabetes mellitus |
| C-statistic for probability of treatment model | 0.73 | | Myocardial infarction | Cerebrovascular event, myocardial infarction, peripheral vascular disease | Cerebrovascular event, myocardial infarction, peripheral vascular disease |
| | | | Cerebrovascular event | Smoking history | Smoking history |

*Variables listed are those identified for inclusion in regression models. Where continuous variables are presented without a threshold value e.g. age (years), risk is linear and variable was best modeled in a continuous form. Where continuous variables are presented with a threshold value e.g. age >62 years, risk was non-linear and categorical transformation made. Definitions: Angiotensin blockade defined as prescription of angiotensin converting enzyme inhibitor and/or angiotensin II receptor blocker. Cerebrovascular event defined as stoke or transient ischaemic attack. Smoking history defined as current or previous tobacco smoking.*

*Results from the SRVD*

Summary event data from the SRVD are presented in table 4.4.5. Where regression models were fully specified the DRE and both Cox models described treatment effects consistent with published RCT data. In ASTRAL mortality was 40% in the revascularisation arm and 43% in the medical therapy arm, HR 0.9 [95% CI 0.7-1.2]. Analysis of the SRVD using the DRE predicted 46% mortality in both treatment groups (RR 0.99 [95% CI 0.8-1.3], p=0.9), with non-significant reductions in risk described in the Cox outcome regression HR 0.77 [95% CI 0.5-1.2], p=0.2 and the Cox IPTW regression HR 0.89 [0.9-1.2], p=0.9. For cardiovascular events (ASTRAL: 51% vs. 49%, HR 1.05 [95%CI 0.9-1.2]), fewer events occurred in the SRVD but with a comparable difference in risk between treatment groups. The DRE predicted events in 35% of medically treated patients and in 36% of revascularised patients (RR 1.03 [95% CI 0.9-1.1], p=0.9). Cox regression adjusted for outcome described a HR 1.01 [95% CI 0.7-1.6], p=0.9, and Cox IPTW regression a HR of 1.11 [95% CI 0.9-1.3], p=0.2. For progression to end stage kidney disease (ASTRAL 8% vs. 8%, HR 0.97 [95% CI 0.7-1.4]) the DRE predicted events in 20% of medically treated patients and in 23% of revascularised patients (RR 1.18 [95% CI 0.8-1.8], p=0.4), with Cox outcome regression describing a HR of 0.91 [95% CI 0.8-1.8], p=0.7 and Cox IPTW regression a HR of 1.11 [95% CI 0.5-1.6], p=0.3.

When regression models were deliberately misspecified (with only patient age retained as a co-variate), results of the DRE did not meaningfully alter – e.g. death (medical vs. revascularisation): correctly specified models 46 vs. 46%; outcome regression misspecified 45 vs. 43%; IPTW regression misspecified 46 vs. 43%. The Cox outcome regression remained stable for all end-points when incorrectly specified. However when the IPTW model was incorrectly specified, the Cox model became unstable and generated results inconsistent with RCT findings – death HR 0.86 [0.7-1.0], p=0.05; cardiovascular event HR 1.13 [95% CI 0.9-1.3], p=0.1. Complete results are presented in table 4.4.6.

**Table 4.4.5** - Absolute event numbers in the Salford Renovascular Database

| | Death | Cardiovascular event | Renal replacement therapy |
|---|---|---|---|
| Medical Therapy n=435 | 183 [42%] | 132 [30%] | 76 [17%] |
| PTRAS n=73 | 29 [40%] | 29 [40%] | 17 [23%] |

*Results are presented as number of events [percentage].*

**Table 4.4.6** - Results of regression analyses in the Salford Renovascular Database

| | Results from ASTRAL | Doubly robust estimator | | Cox regressions Hazard ratio (95% CI) | |
|---|---|---|---|---|---|
| | *Event rate (medical vs. PTRAS)* | *Event rates (medical vs. PTRAS)* | *RR (95% CI)* | *Outcome regression* | *IPTW* |
| | | **Death** | | | |
| **Fully specified model** | 43 vs. 40% HR 0.90 (95%CI 0.69-1.18) | 46 vs. 46% | 0.99 (0.8-1.3) p=0.9 | 0.77 (0.5-1.2) p=0.2 | 0.89 (0.9-1.2) p=0.9 |
| **Intentional misspecification (outcome)** | - | 45 vs. 43% | 0.95 (0.7-1.3) p=0.7 | 0.88 (0.6-1.3) p=0.5 | - |
| **Intentional misspecification (IPTW)** | - | 46 vs. 43% | 0.95 (0.7-1.2) p=0.7 | - | 0.86 (0.7-1.0) p=0.05 |
| | | **Cardiovascular event** | | | |
| **Fully specified model** | 49 vs. 51% HR 0.94 (95%CI 0.75-1.19) | 35 vs. 36% | 1.03 (0.9-1.1) p=0.9 | 1.01 (0.7-1.6) p=0.9 | 1.11 (0.9-1.3) p=0.2 |
| **Intentional misspecification (outcome)** | - | 35 vs. 37% | 1.08 (0.8-1.5) p=0.7 | 1.13 (0.8-1.7) p=0.6 | - |
| **Intentional misspecification (IPTW)** | - | 34 vs. 35% | 1.03 (0.9-1.1) p=0.9 | - | 1.13 (0.9-1.3) p=0.1 |
| | | **End stage kidney disease** | | | |
| **Fully specified model** | 22 vs. 22% HR 0.97 (95%CI 0.67-1.40) | 20 vs. 23% | 1.18 (0.8-1.8) p=0.4 | 0.91 (0.5-1.6) p=0.7 | 1.11 (0.9-1.4) p=0.3 |
| **Intentional misspecification (outcome)** | - | 19 vs. 23% | 1.17 (0.7-1.9) p=0.5 | 1.06 (0.6-1.8) p=0.8 | - |
| **Intentional misspecification (IPTW)** | - | 19 vs. 21% | 1.08 (0.7-1.7) p=0.7 | - | 1.15 (0.9-1.4) p=0.2 |

*Results for analyses with fully specified models are adjusted for variables presented in table 4.4.4. For intentionally misspecified models only patient age is retained in the model listed in the left hand column. As the doubly robust estimator specifies a regression model for both probability of treatment and for outcome, in misspecified models one regression is appropriately specified and one misspecified.*
*Results of the doubly robust estimator are presented as percentage of patients predicted to each the end-point (control vs. interventional group) and as a relative risk. Results of Cox regressions are presented as hazard ratios with 95% confidence intervals in parentheses.*

*Results from CRISIS*

Summary event data from CRISIS are presented in table 4.4.7. Where both regression models were fully specified, application of the DRE to CRISIS predicted treatment effects consistent with RCT findings although with greater numbers of patients suffering an event. In SHARP 13.4% of control patients and 11.3% of treated patients suffered a major atherosclerotic cardiovascular event (MACE) (RR 0.83 [95% CI 0.7-0.9], p=0.002), with 24% of patients in each treatment group dying (RR 1.02 [95% CI 0.9-1.1], p=0.63). For MACE in CRISIS the DRE predicted events in 23% vs. 18% of patients (RR 0.79 [95% CI 0.4-1.5], p=0.5), and death in 33% of control vs. 30% of statin treated patients (RR 0.88 [95% CI 0.6-1.3], p=0.9). Occurrences of non-fatal myocardial infarction were very similar in SHARP (3.4% vs. 2.9%, p=0.12) and in the DRE results from CRISIS (3.4% vs. 2.3%, p=0.7). None of the results from the DRE meaningfully altered in response to misspecification in either the outcome or IPTW regression model.

The fully specified Cox outcome regressions for non-fatal myocardial infarction and all-cause mortality estimated similar effect sizes as seen in the RCT (HR 0.85 [95% CI 0.2-3.8], p=0.8 and HR 0.86 [95% CI 0.6-1.2], p=0.4 respectively), with little difference in results noted with misspecification of the regression model. For MACE, the fully specified Cox outcome regression did not describe a significant reduction in risk (HR 0.86 [95% CI 0.5-1.5], p=0.6). However, when the regression model was misspecified the alpha value moved towards statistical significance (HR 0.7 [95% CI 0.4-1.1], p=0.1). For all-cause mortality, Cox IPTW regression produced results consistent with the original RCT. However, for MACE and, to a lesser extent non-fatal myocardial infarction, the IPTW model produced more extreme results with large differences generated by model misspecification (MACE – fully specified IPTW model HR 0.30 [95% CI 0.2-0.7], p=0.004; misspecified model HR 0.68 [95% CI 0.3-1.4], p=0.3). Complete data are presented in table 4.4.8.

**Table 4.4.7** - Absolute event numbers in the CRISIS database

| | MACE | Non-fatal myocardial infarction | Death (all-cause) |
|---|---|---|---|
| No statin group n=182 | 30 [16%] | 3 [1.6%] | 61 [33%] |
| Statin group n=224 | 38 [17%] | 4 [1.8%] | 65 [29%] |

*Results are presented as number of events [percentage].*

**Table 4.4.8** - Results of regression analyses in the CRISIS Database

| | Results from SHARP | Doubly robust estimator | | Cox regressions Hazard ratio (95% CI) | |
|---|---|---|---|---|---|
| | *Event rate (control vs. lipid lowering)* | *Event rates (control vs. statin)* | *RR (95% CI)* | *Outcome regression* | *IPTW* |
| **Major atherosclerotic cardiovascular events** | | | | | |
| **Fully specified model** | 13.4 vs. 11.3% RR 0.83 (95%CI 0.74-0.94) | 23 vs. 18% | 0.79 (0.4-1.5) p=0.5 | 0.86 (0.5-1.5) p=0.6 | 0.30 (0.2-0.7) p=0.004 |
| **Intentional misspecification (outcome)** | - | 22 vs. 18% | 0.83 (0.4-1.6) p=0.6 | 0.7 (0.4-1.1) p=0.1 | - |
| **Intentional misspecification (IPTW)** | - | 18 vs. 18% | 0.98 (0.6-1.5) p=0.9 | - | 0.68 (0.3-1.4) p=0.3 |
| **Non fatal myocardial infarction** | | | | | |
| **Fully specified model** | 3.4 vs. 2.9% RR 0.92 (95%CI 0.76-1.11) | 3.4 vs. 2.3% | 0.68 (0.1-3.5) p=0.7 | 0.85 (0.2-3.8) p=0.8 | 0.10 (0.01-2.6) p=0.2 |
| **Intentional misspecification (outcome)** | - | 3.0 vs. 2.0% | 0.60 (0.1=4.3) p=0.6 | 0.58 (0.1-2.3) p=0.4 | - |
| **Intentional misspecification (IPTW)** | - | 2.3 vs. 2.2% | 0.94 (0.3-4.0) p=0.9 | - | 0.60 (0.1-4.2) p=0.6 |
| **All cause mortality** | | | | | |
| **Fully specified model** | 24.1 vs 24.6% RR 1.02 (95%CI 0.94-1.11) | 33 vs. 30% | 0.88 (0.6-1.3) p=0.6 | 0.86 (0.6-1.2) p=0.4 | 0.86 (0.6-1.2) p=0.4 |
| **Intentional misspecification (outcome)** | - | 32 vs. 28% | 0.83 (0.5-1.3) p=0.4 | 0.91 (0.6-1.3) p=0.6 | - |
| **Intentional misspecification (IPTW)** | - | 34 vs. 31% | 0.90 (0.7-1.2) p=0.5 | - | 0.91 (0.7-1.2) p=0.5 |

*Results for analyses with fully specified models are adjusted for variables presented in table 4.4.4. For intentionally misspecified models only patient age is retained in the model listed in the left hand column. As the doubly robust estimator specifies a regression model for both probability of treatment and for outcome, in misspecified models one regression is appropriately specified and one misspecified.*
*Results of the doubly robust estimator are presented as percentage of patients predicted to each the end-point (control vs. interventional group) and as a relative risk. Results of Cox regressions are presented as hazard ratios with 95% confidence intervals in parentheses.*

Discussion

These analyses present several findings relevant to those involved in the analysis, reporting and interpretation of observational data. Firstly we have demonstrated that, provided that the observational dataset is sufficiently large, application of RCT inclusion and exclusion criteria can generate patient groups with measured characteristics closely resembling published studies. Given that the broad range of patients entered into observational studies will often limit the validity of unselected comparison with RCT findings, this is a timely reminder for researchers to design focused analyses when working with large registries. Secondly, we have shown that although the DRE does not exactly duplicate RCT findings, most likely due to unmeasured heterogeneity between RCT and observational study populations, the estimates of average treatment effect consistently align with published results. Whilst the fully specified outcome and IPTW regression models also generated findings common with RCT the fact that the DRE provides percentage values for events in addition to a measure of relative risk means the results can be more easily interpreted by clinicians and patients with a narrower grounding in the nuance of statistical analysis. Although we acknowledge that we are introducing our own bias, the authors believe that the reporting of such percentage values would be helpful in aiding readers to consider both clinical effect size and level of statistical significance (accepting of course many other ways of doing so already exist). Thirdly, we have demonstrated that the resilience of the DRE to model misspecification previously shown in simulated datasets [25] extends, as expected, to real-life data. Whilst in essence a "proof of concept" finding, we feel that such a demonstration may offer clinicians a degree of conviction in the methodology that no amount of algebraic proof can provide.

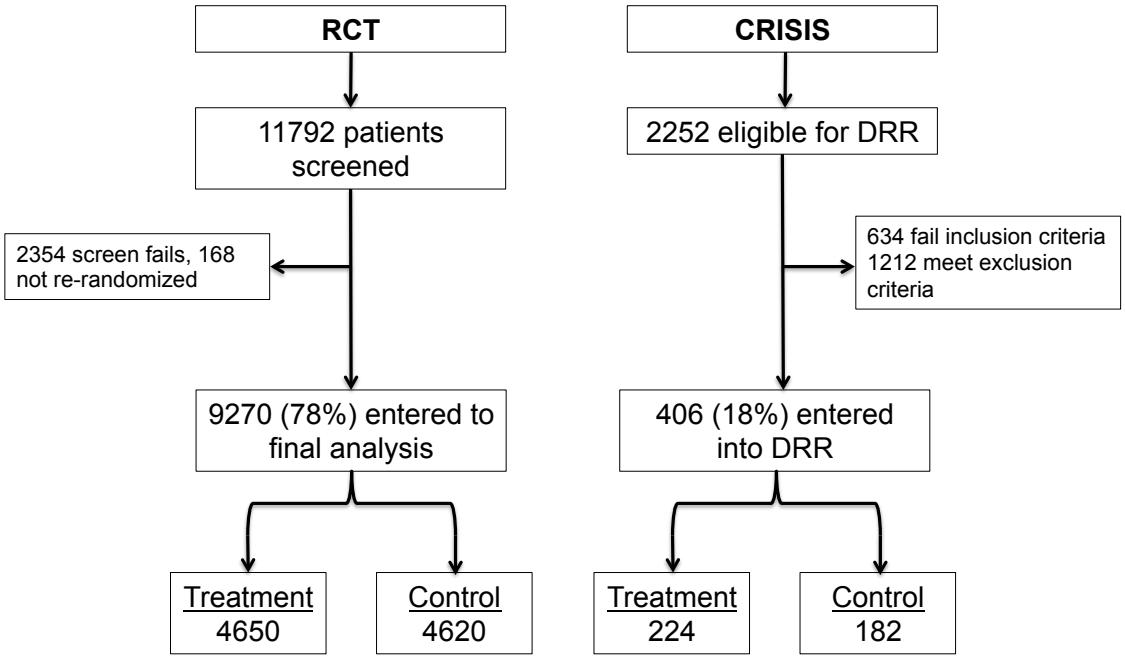
The accuracy and stability of the DRE confer it broad suitability for analysis of observational data. As analysis of any observational data is dependent upon the fields recorded, we postulate that the DRE may offer a degree of protection from imperfect study design. Given the time lag between inception and maturity of observational studies, clinical knowledge may often evolve to the point where, at time of analysis, documentation of an additional covariate may be seen to be desirable. If this covariate is thought (but not confirmed) to have relevance only to treatment assignment *or* outcome then DRE may limit

concerns about inadequate specification of the regression model. The authors, however, emphasize that no statistical methodology can salvage a poorly designed study and note that where both regression models in the DRE are incorrect the level of error is magnified [15] . A further consideration is that even in a carefully considered analysis the decision between modeling for outcome or probability of treatment can be difficult. Whilst both regressions can be performed and model fit statistics considered to select the “optimum” analysis, it is uncommon for such detailed information on model building to be presented in the medical literature [26]. If uncertainty exists regarding the suitability of either model specification, it is conceivable that reporting of the DRE in addition to the regression models could function as a ‘deciding vote’. For the example of MACE in CRISIS, the Cox outcome regression did not describe any significant difference in risk associated with use of statins, whereas the IPTW model described a significantly reduced risk. Given that the DRE is stable in the setting of one model being incorrectly specified and its results are comparable to the Cox outcome regression it becomes clear that in this setting the IPTW model is the less valid analysis. Presentation of DRE findings in addition to outcome and IPTW regressions may help distinguish the best fitting model from merely the “most statistically significant” which may be more likely to be considered for publication [27,28]. Finally there is no reason to limit use of the DRE to observational studies. Differences between patient groups can occur in smaller RCT [29] and the DRE could be applied where an imbalance exists in clinically relevant variables. Alternatively, the DRE could be used to help define the external validity of published RCT, or aid design of randomised study.

The goal of this paper has been to introduce the DRE and its utility to a general audience, not to claim that well considered regression models are in any way inadequate. As with other methodologies, the DRE functions best when the regression equations are carefully considered. The DRE is not a technique that replaces careful study and analysis design, but it can function as a safety net where unintentional errors occur. As such, limitations of this methodology are common with any approach to analyzing observational data. The most important of these is that results of the DRE are only as valid as the population and dataset from which they are drawn. Without the benefit of randomisation, unmeasured covariates may play an important confounding role. A further

limitation is the size and maturity required of observational studies to apply the techniques described. In SHARP, 78% of screened patients were recruited (though this does not account for pre-screen exclusions), a figure that compares very favorably to the 18% of patients in CRISIS suitable for analysis, figure 4.4.2.

**Figure 4.4.2** - Flow diagram describing patient selection into SHARP from trial and observational data.




*Abbreviations: SHARP - Study of Heart and Renal Protection, RCT – randomised controlled trial, CRISIS – Chronic Renal Insufficiency Standards Implementation Study*

This low "recruitment rate" resulted in a study population from the observational data approximately 1/15$^{th}$ that of SHARP's and may explain why the 5% reduction in MACE in the statin group in CRISIS did not attain the level of statistical significance associated with the 2.1% reduction seen in SHARP. With a final number needed to treat in excess of 40 to prevent a MACE in SHARP, large-scale collaboration would have been needed to provide more data – an approach we hope will develop as other studies such as the Chronic Renal Insufficiency Cohort mature [5]. Joint efforts such as this could also facilitate the study of more rare conditions (e.g. calciphylaxsis) or treatments where ethical consensus precludes randomised study (e.g. renal artery revascularisation for acute decompensated heart failure [30]). This type of coordinated approach may

partially mitigate the financial burden of maintaining high-quality observational studies, which although cheaper than RCT, can still carry a significant cost. A final limitation worthy of emphasis is that observational study will never be placed to describe effects of novel treatments, nor able to provide the same quality of safety data as randomised study. Due to the design of our SRD database, we can report a 4% serious complication rate following renal artery revascularisation (comparable to other series [31]), but are unable to offer information regarding e.g. myopathy or hepatic derangement secondary to statin therapy.

In conclusion we believe that use of the DRE may aid reporting and interpretation of observational studies. Reporting of this methodology in parallel with more established regression techniques may encourage more critical discussion of the statistical models used to report observational data.

## References


1. Samuels JA, Molony DA. Randomised controlled trials in nephrology: state of the evidence and critiquing the evidence. *Adv Chronic Kidney Dis*. 2012;19(1):40–46.

2. Strippoli GFM, Craig JC, Schena FP. The number, quality, and coverage of randomised controlled trials in nephrology. *J Am Soc Nephrol*. 2004;15(2):411–419.

3. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl*. 2009;(113):S1–130.

4. Hoefield RA, Kalra PA, Baker PG, et al. The use of eGFR and ACR to predict decline in renal function in people with diabetes. *Nephrol Dial Transplant*. 2011;26(3):887–892.

5. Lash JP, Go AS, Appel LJ, et al. Chronic Renal Insufficiency Cohort (CRIC) Study: baseline characteristics and associations with kidney function. *Clin J Am Soc Nephrol*. 2009;4(8):1302–1311.

6. Landray MJ, Emberson JR, Blackwell L, et al. Prediction of ESRD and death among people with CKD: the Chronic Renal Impairment in Birmingham (CRIB) prospective cohort study. *Am J Kidney Dis*. 2010;56(6):1082–1094.

7. Fliser D, Kronenberg F, Kielstein JT, et al. Asymmetric dimethylarginine and progression of chronic kidney disease: the mild to moderate kidney disease study. *J Am Soc Nephrol*. 2005;16(8):2456–2461. doi:10.1681/ASN.2005020179.

8. Benson K, Hartz AJ. A comparison of observational studies and randomised, controlled trials. *N Engl J Med*. 2000;342(25):1878–1886.

9. Odgaard-Jensen J, Vist GE, Timmer A, et al. Randomisation to protect against selection bias in healthcare trials. *Cochrane Database Syst Rev*. 2011;13(4). doi: 10.1002/14651858.MR000012.pub3.

10. Rosenbaum P, Rubin D. The Central Role of the Propensity Score in Observational Studies for Causal Effects. *Biometrika*. 1983;70(1):41–55.

11. Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology*. 2000;11(5):550–560.

12. Hernán MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. *Epidemiology*. 2000;11(5):561–570.

13. Barker L, Brown C. Logistic regression when binary predictor variables are highly correlated. *Statist Med*. 2001;20:1431–1442.

14. Robins JM, Rotnitzky A, Zhao LP. Estimation of Regression Coefficients When Some Regressors Are Not Always Observed. *J Am Stat Assoc*. 1994;89(427):846–866.

15. Funk MJ, Westreich D, Wiesen C, Sturmer T, Brookhart MA, Davidian M. Doubly Robust Estimation of Causal Effects. *Am J Epidemiol*. 2011;173(7):761–767.

16. Lunceford JKJ, Davidian MM. Stratification and weighting via the propensity score in estimation of causal treatment effects: a comparative study. *Statist Med*. 2004;23(19): 2937–2960.

17. Hoefield RA, Kalra PA, Lane B, O'Donoghue DJ, Foley RN, Middleton RJ. Associations of baseline characteristics with evolution of eGFR in a referred chronic kidney disease

cohort. *QJM*. 2013.

18. Ritchie J, Rainone F, Green D, et al. Extreme Elevations in Blood Pressure and All-Cause Mortality in a Referred CKD Population: Results from the CRISIS Study. *Int J Hypertens*. 2013; doi: 10.1155/2013/597906. [Epub ahead of print].

19. 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(10): 695–704.

20. 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. *Nephrol Dial Transplant*. 2012;27(4):1403-1409.

21. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345(12):861–869.

22. Berl T, Hunsicker LG, Lewis JB, et al. Impact of achieved blood pressure on cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial. *J Am Soc Nephrol*. 2005;16(7):2170–2179.

23. ASTRAL Investigators, Wheatley K, Ives N, et al. Revascularisation versus medical therapy for renal-artery stenosis. *N Engl J Med*. 2009;361(20):1953–1962.

24. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *The Lancet*. 2011;377(9784): 2181–2192.

25. Emsley R, Lunt M, Pickles A, Dunn G. Implementing double-robust estimators of causal effects. *Stata Journal*. 2008;8(3):334-353.

26. Bagley SC, White H, Golomb BA. Logistic regression in the medical literature:. *J Clin Epidemiol*. 2001;54(10):979–985.

27. Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. *The Lancet*. 1991;337(8746):867–872.

28. Hopewell S, Loudon K, Clarke MJ. Publication bias in clinical trials due to statistical significance or direction of trial results. *Cochrane Database Syst Rev*. 2009;21(1): doi: 10.1002/14651858.MR000006.pub3.

29. Schulz KF, Grimes DA. Generation of allocation sequences in randomised trials: chance, not choice. *The Lancet*. 2005;359:515–519.

30. 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 revascularisation. *Am J Kidney Dis*. 2013; doi: 10.1053/j.ajkd.2013.07.020. [Epub ahead of print].

31. Leertouwer TC, Gussenhoven EJ, Bosch JL, et al. Stent placement for renal arterial stenosis: where do we stand? A meta-analysis. *Radiology*. 2000;216(1):78–85.

# CHAPTER 4.5

## Effects of Anti-Platelet Therapy and Beta-Blockade on Prognosis in Atherosclerotic Renovascular Disease

Ritchie J, Green D, Alderson HV, Chiu D, Sinha S, Kalra PA

Preface

Randomised trials of PTRAS in ARVD have considered the effects of this treatment in comparison to optimal medical therapy (OMT). However, data to define OMT in ARVD are limited, with many treatments offered due to their historical perspective. Given the potential for adverse events with even well established pharmacotherapies this represents an important gap in our knowledge.

Results chapters 4.1-4.3 have aimed to better define ARVD as a disease and provide information regarding specific scenarios where PTRAS may be of clinical benefit. This has reinforced that for the vast majority of ARVD patients, revascularisation is not an appropriate intervention. This final chapter acknowledges that for most patients with ARVD, OMT should be considered as the treatment of choice and therefore attempts to improve our understanding of what this is. As the definition of OMT has varied over time, confounding effects on treatment assignment and patient outcome are important. We therefore use the technique of doubly robust regression introduced in chapter 4.4 to consider two commonly prescribed medications.

> *$H_0$ - Treatment with anti-platelet and / or beta-blocker therapies does not improve prognosis in ARVD.*
> *$H_1$ - Treatment with anti-platelet and / or beta-blocker therapies is associated with improved prognosis in ARVD. This information can be used to better define OMT.*

Abstract

Background

Angiotensin blockade and statin therapy are established as first line treatments in ARVD. However, the effects of other therapies are less well defined. We consider the prognostic effects of anti-platelet therapy and beta-blockade in relation to death, non-fatal cardiovascular events and dialysis.

Design

Retrospective analysis of 529 patients with ≥50% renal artery stenosis. Separate analyses were performed on patients not prescribed either anti-platelet therapy or beta-blockade at time of diagnosis.

Results

There were 226 patients [42%] not prescribed anti-platelet therapy at time of diagnosis (62 started on treatment within 1-year of diagnosis) and 318 patients [60%] not prescribed a beta-blocker at time of diagnosis (29 started on treatment within 1-year). In multivariate Cox regression, both treatments were associated with a reduced risk for death before initiation of dialysis although this only achieved statistical significance in anti-platelet treated patients (HR death 0.53 [95% CI 0.32-0.86], p=0.01; in beta-blocker treated patients HR 0.52 [95% CI 0.25-1.09], p=0.09). No alteration in risk for non-fatal cardiovascular events was observed in Cox regression, but an increased risk for dialysis was associated with both therapies (anti-platelet HR 2.67 [95% CI 1.12-6.33], p=0.03; beta-blocker HR 4.18 [95% CI 1.48-11.79], p=0.01) despite no difference in rate of eGFR loss.

Conclusions

In ARVD treatment with anti-platelet therapy and beta-blockade may reduce risk for death. This survivor effect may increase risk for progression to dialysis.

Introduction

A series of randomised controlled trials have compared the effects of optimal medical therapy and percutaneous renal artery angioplasty and stenting on patient outcomes in ARVD [1-5]. These trials, which considered unselected patients, failed to demonstrate a clear treatment benefit from PTRAS, with this finding borne out in meta-analysis [6]. An important confounding issue when comparing these trials and applying their findings to clinical practice is the lack of a consensus definition of optimal medical therapy in ARVD. Whilst there is now convincing (though non-randomised) evidence to support the use of angiotensin blockade [7,8] and statin therapy [9] as first line medical therapies, substantial variability exists in how these and other medications were used in published RCT, table 4.51.

The inequality in anti-platelet use between studies may relate to a lack of clear evidence of benefit associated with these drugs in patients with CKD [10] and concerns regarding bleeding risk [11]. However, given the significant burden of vascular co-morbidity associated with ARVD [12-14], it is plausible that these drugs may have beneficial effects were defined as a first line therapy in the recently published CORAL trial [15]. Despite this, research has focused on their effects around the time of PTRAS [16,17], the rate of which is declining [18].

Beyond angiotensin blockade, optimal anti-hypertensive therapy in ARVD is ill-defined. In an all-cause CKD population with heart failure, beta-adrenergic blockade has been shown to reduce mortality [19]. Sympathetic overactivity is recognised in ARVD [20], as is the near universal presence of cardiac structural or functional abnormality [21,22]. As such, it is credible to consider if this class of medication may be associated with improved prognosis in ARVD.

In this study we perform an analysis of outcomes in relation to anti-platelet and beta-blocker use in a referred ARVD cohort.

**Table 4.5.1** - Medication usage in published randomised controlled trials

| | EMMA | SNRASCG | DRASTIC | STAR | ASTRAL |
|---|---|---|---|---|---|
| **Anti-platelet agent** | Aspirin 100mg daily specified in study protocol. | Numbers and dose not specified but aspirin recommended for all patients able to tolerate the drug. | Aspirin 300mg daily in angioplasty group. Not specified in treatment group. | Aspirin 75-100mg daily specified in protocol for all patients. | 72% prescribed antiplatelet at baseline (67% prescribed aspirin) |
| **Angiotensin blockade** | Data not specified. | 0% | Data not specified. | 56% | 35% |
| **Beta blocker** | | Data not specified but 2 of atenolol, bendrofluazide calcium channel blocker recommended as first line therapy. | 15% of patients prescribed a combination of atenolol and amlodipine; 21% of patients prescribed a combination of enalapril and hydrochlorthiazide. | Data not specified. | 46% |
| **Diuretic** | | | | | 64% |

Aims and objectives

This study aims to

1 – describe the associations between treatment with anti-platelet agents and beta-blockers and risk for the end-points of death, dialysis and cardiovascular events in an ARVD population complicated by CKD

2 – describe the tolerability of these agents

3 – consider if these agents may have prognostic benefit in addition to angiotensin blockade and statin therapy, medications previously shown to improve outcomes in ARVD.

Methods and materials

*Study population and selection criteria*

Patients were identified from the SRVD. This study has received approval from the regional ethics committee and has been described previously [23]. In brief the SRVD is a prospective observational study of all patients referred for management of ARVD at our secondary care nephrology unit. Baseline demographic, clinical, co-morbid and renal laboratory data are captured and annually updated by nephrology residents. Data are obtained from patient interviews and local electronic health records.

Inclusion criteria for analysis were ≥50% stenosis to either kidney, complete baseline data, and no documented prescription of the medication under consideration at time of diagnosis of ARVD. This design was adopted to limit analyses to patients where therapies were potentially initiated in response to the diagnosis of ARVD. Patients were excluded from analysis if they had a documented intolerance or allergy to the medication in question or a definite indication for renal artery revascularisation, e.g. flash pulmonary edema [23,24]. The latter exclusion was adopted to remove patients in whom medical therapy could be considered inappropriate.

*Treatment*

Patient care is not affected by recruitment to the SRVD. All patients are treated in line with national guidelines [25,26]. A proportion of patients have undergone PTRAS according to the view of their treating clinician and with reference to

contemporaneous international guidelines [24], or as part of a randomised study [5,15].

*Definition of exposures*

Two separate analyses were performed to consider medication effects. The first was for anti-platelet medications (a composite of aspirin, dipyridamole and clopidogrel) and the second for beta-blockers (bisoprolol, atenolol, carvidolol, nebivolol, propanolol). No distinction was made between single and dual anti-platelet therapy or class of beta-blocker (i.e. β 1, β2, or non-selective). For each analysis, patients prescribed the class of drug in question at time of diagnostic angiography were excluded. Two study groups were identified from the remaining patients, those commenced on the drug within 12-months of diagnosis (and maintained on the drug) and those not commenced on the drug.

*End-points*

End-points identified from the SRVD for this study were death, initiation of renal replacement therapy (defined as chronic dialysis or transplantation) and first non-fatal cardiovascular event (defined as myocardial infarction or acute coronary syndrome, cerebrovascular event or transient ischaemic attack, new onset angina pectoris or coronary revascularisation procedure).

*Statistical analysis*

The distribution of all continuous variables was visually assessed using probability-probability plots. Normally distributed continuous variables are presented as mean±standard deviation and were compared between treatment groups using Student's t-test. Non-parametric continuous variables were compared using the Kruskal-Wallis test and are presented as median [interquartile range].

For survival analyses, time zero was defined as the date of diagnostic angiography with censoring occurring at most recent clinical follow-up. Exploratory univariate survival analysis was performed using Cox proportional hazards regression with results presented as hazard ratio [95% confidence interval]. Multivariate survival analysis was performed using the doubly robust estimator described by Funk et al [27]. The DRE simultaneously considers the

effect of co-variates on probability of receiving treatment and on outcome with the estimate of treatment effect remaining unbiased even if one of these models is specified incorrectly. As the DRE is based on a logistic model, events within 5-years of diagnosis were considered for these analyses with results presented as percentage of patients predicted to reach the end point in question [95% confidence interval]. Rate of change in renal function was estimated using a fixed and random effects model with results presented as parameter estimate [standard error].

Finally, based on the results of these analyses and previous data, an *optimal* combination of baseline treatments was defined and patient outcomes assessed in relation to this in a series of Cox regressions. For these analyses time zero was defined as date of diagnostic angiography. In addition for *optimal* therapy, changes in risk over time were assessed graphically by plotting the log-time interaction between prescribed baseline therapy and days from diagnostic angiography (adjusted for patient age, renal function and proteinuria) [28]. Analyses were performed in SAS version 9.2 (SAS Institute, Cary, NC, USA) under license to the University of Manchester and R version 3.0.1 using the simPH package [29].

Results

At the time of analysis 819 patients were represented in the SRVD. One hundred and sixty five were excluded due to <50% renal artery stenosis, 88 excluded due to incomplete baseline data, and 37 due to presentation with flash pulmonary edema giving a possible study population of 529 patients. Of these 226 (43%) were not prescribed an anti-platelet agent and 318 (60%) were not prescribed a beta-blocker at time of angiography, figure 4.5.1. Median follow-up time for the 226 patients not prescribed an anti-platelet at baseline was 3.8 years [IQR 1.5-5.8], with 62 patients (27%) commenced on one of these agents within 12-months of diagnosis and 164 (73%) not. Median follow-up time for the 318 patients not prescribed a beta-blocker at baseline was 3.6 years [IQR 1.5-6.0], with 29 patient (9%) commenced on beta-blockade within 12-months of diagnosis and 289 (91%) not. Beyond 12-months use of beta-blockade remained largely consistent between groups, however 18% of patients prescribed an anti-platelet agent had discontinued treatment, a figure similar to previous studies of anti-platelet therapy in CKD [30] - table 4.5.2.

**Figure 4.5.1** - Patient selection and distribution

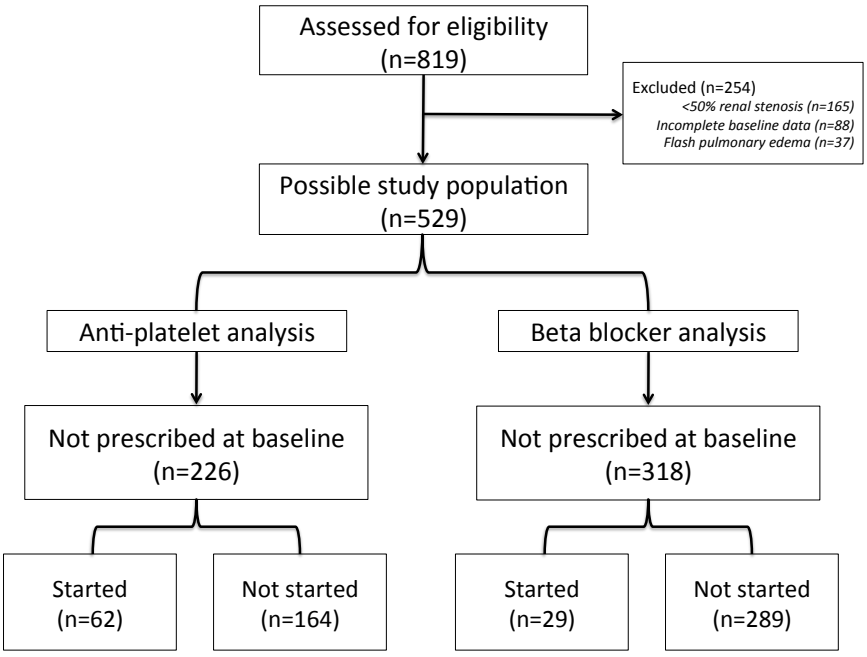


**Table 4.5.2** - Changes in medication usage over time

| | Angiography | | 1-year | | 2-years | | 3-years | | 4-years | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** |
| **Beta-blocker** | 29 | 0% | 29 | 100% | 26 | 100% | 23 | 96% | 19 | 90% |
| **No beta-blocker** | 289 | 0% | 234 | 0% | 191 | 5.2% | 160 | 5.6% | 121 | 5.0% |
| **Anti-platelet** | 62 | 0% | 60 | 82% | 49 | 76% | 45 | 68% | 37 | 73% |
| **No anti-platelet** | 164 | 0% | 124 | 9% | 103 | 13% | 86 | 20% | 67 | 20% |

*Abbreviations: n - number of patients still alive at this point. % - percentage of surviving patients prescribed either beta-blocker of anti-platelet therapy.*

*Baseline demographics*

Patients commenced on an anti-platelet agent after diagnosis were younger than those not started on this therapy (67±11 vs. 70±10 years, p=0.04), with a higher mean eGFR at diagnosis (38±19 vs. 31±19ml/min/1.73m$^2$, p=0.01), lower level of proteinuria (0.7±0.6 vs. 0.9±0.8 g/24 hours, p=0.04), and a greater proportion of patients prescribed a beta-blocker (47% vs. 26%, p<0.001). Patients started on a beta-blocker after diagnosis had a higher baseline systolic blood pressure (174±27 vs. 155±28mmHg, p<0.001) and a higher eGFR (43±16 vs. 33±19ml/min/1.73m$^2$, p<0.001) than patients not started on a beta-blocker. Detailed baseline patient characteristics are presented in table 4.5.3.

**Table 4.5.3** - Baseline patient demographics

| | Anti-platelet therapy | | | Beta-blocker therapy | | |
|---|---|---|---|---|---|---|
| | **Started after diagnosis n=62** | **Not started n=164** | **p** | **Started after diagnosis n=29** | **Not started n=289** | **p** |
| | | | ***Demographics and renal function*** | | | |
| **Age (years)** | 67.3+/-10.5 | 70.4+/-9.9 | 0.04 | 71+/-6.3 | 71.2+/-8.9 | 0.89 |
| **Male** | 33(53.2%) | 86(52.4%) | 0.92 | 15(51.7%) | 172(59.5%) | 0.42 |
| **eGFR (ml/min/1.73m$^2$)** | 37.7+/-18.7 | 30.8+/-19 | 0.01 | 43.4+/-15.7 | 33+/-18.9 | <0.001 |
| **Proteinuria (g/24 hours)** | 0.7+/-0.6 | 0.9+/-0.8 | 0.04 | 0.9+/-0.8 | 0.9+/-1.4 | 0.92 |
| | | | ***Renal artery disease and clinical presentation*** | | | |
| **Percentage stenosis** | 80 [70-100] | 82.5 [60-100] | 0.6 | 70 [65-90] | 80 [60-100] | 0.01 |
| **Patency score** | 90.9+/-36.5 | 91.7+/-44.8 | 0.9 | 87.9+/-44 | 95+/-39.5 | 0.37 |
| **PTRAS** | 17(27.4%) | 28(17.1%) | 0.08 | 7(24.1%) | 58(20.1%) | 0.6 |
| **Rapidly declining renal function** | 9(14.5%) | 26(15.9%) | 0.8 | 7(24.1%) | 50(17.3%) | 0.36 |
| **Refractory hypertension** | 25(40.3%) | 37(22.6%) | 0.01 | 11(37.9%) | 75(26%) | 0.17 |
| | | | ***Blood pressure and medications*** | | | |
| **Systolic blood pressure (mmHg)** | 163.1+/-26.8 | 161.3+/-31.9 | 0.7 | 174+/-26.6 | 154.8+/-28.2 | <0.001 |
| **Diastolic blood pressure (mmHg)** | 83.7+/-12 | 83.8+/-17.9 | 0.95 | 86.6+/-16.5 | 80.7+/-15.8 | 0.06 |
| **Number of blood pressure medications** | 3 [2-4] | 2 [1-3] | <0.001 | 2 [1-3] | 2 [1-3] | 0.9 |
| **Angiotensin blockade** | 32(51.6%) | 67(40.9%) | 0.15 | 15(51.7%) | 140(48.4%) | 0.74 |
| **Beta-blocker / anti-platelet** | 28(46.7%) | 41(25.8%) | <0.001 | 21(72.4%) | 162(56.1%) | 0.09 |
| **Statin** | 25(41.7%) | 51(31.9%) | 0.17 | 18(64.3%) | 142(49.8%) | 0.14 |
| | | | ***Co-morbidities*** | | | |
| **Myocardial infarction** | 9(14.5%) | 29(17.8%) | 0.56 | 8(27.6%) | 80(27.8%) | 0.98 |
| **Cerebrovascular event** | 20(32.3%) | 49(29.9%) | 0.73 | 13(44.8%) | 97(33.6%) | 0.22 |
| **Peripheral vascular disease** | 26(41.9%) | 47(28.8%) | 0.06 | 15(51.7%) | 114(39.6%) | 0.2 |
| **Diabetes mellitus** | 15(24.2%) | 42(25.6%) | 0.83 | 11(37.9%) | 86(29.8%) | 0.36 |

*Abbreviations and definitions – Percentage stenosis is percentage loss of lumen to the most affected kidney. Patency score defined as (200-left side stenosis-right side stenosis), where a score of 200 therefore represents bilateral 0% stenosis and a score of 0 represents bilateral 100% stenosis. PTRAS – percutaneous renal artery angioplasty and stenting. Cerebrovascular event defined as previous stroke or transient ischaemic attack. Angiotensin blockade defined as prescription of angiotensin converting enzyme inhibitor and / or angiotensin II receptor blocker. Rapidly declining renal function defined as serum creatinine at time of angiography greater than 1.2x or µ100 mol/L (1.14mg/dL) greater than a baseline reading taken within the previous six-months. Refractory hypertension defined as blood pressure above 140mmHg and / or 90mmHg despite use of three or greater different classes of antihypertensive medications, one of which is a diuretic.*

*Event free survival*

In the anti-platelet analysis 145 (64%) of patients died, 34 (15%) progressed to RRT and 67 (30%) suffered a non-fatal cardiovascular event. In the beta-blocker analysis 200 (63%) of patients died, 43 (14%) progressed to RRT, and 107 (34%) suffered a non-fatal cardiovascular event. In univariate analysis both anti-platelet and beta-blocker therapy were associated with a reduced risk for all-cause mortality (HR 0.60 [95% CI 0.4-0.9] and HR 0.47 [95% CI 0.3-0.8] respectively, p for both =0.01), figures 4.5.2 and 4.5.3. No statistically significant difference in risk for renal replacement therapy or cardiovascular event was associated with either treatment, table 4.5.4. In multivariate analysis adjusted for the effect of baseline co-variates on probability of treatment and on outcome using the DRE, a lower proportion of deaths before dialysis were predicted for anti-platelet and beta-blocker treated patients. In addition, a reduction in overall mortality was also predicted for both treatments (proportion of deaths treated vs. not treated: anti-platelet 33% [95% CI 20-46%] vs. 51% [95% CI 43-59%], p=0.02; beta-blocker 21% [95% CI 5-38%] vs. 46% [95% CI 40-53%], p=0.005).

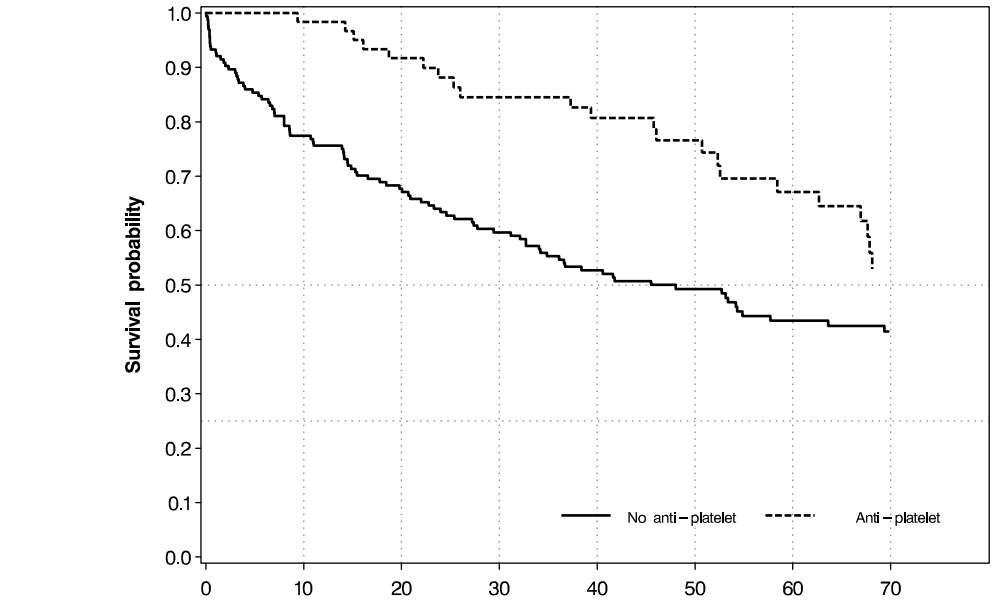
**Table 4.5.4** - Univariate survival analyses

| | Anti-platelet | | Beta-blocker | |
|---|---|---|---|---|
| | **HR (95% CI)** | **p** | **HR (95% CI)** | **p** |
| **Death** | 0.6 (0.4-0.9) | 0.01 | 0.47 (0.26-0.85) | 0.01 |
| **Renal replacement therapy** | 1.28 (0.62-2.65) | 0.5 | 1.11 (0.44-2.84) | 0.82 |
| **Cardiovascular event** | 0.88 (0.52-1.51) | 0.65 | 1.01 (0.57-1.81) | 0.97 |

*Hazard ratios are for patients prescribed anti-platelet therapy / beta-blocker. Referent group is patient not prescribed these agents. Renal replacement therapy defined as initiation of chronic haemodialysis, peritoneal dialysis or transplantation. Cardiovascular event defined as myocardial infarction, acute coronary syndrome, stroke, transient ischaemic attack, new onset angina or coronary revascularisation.*

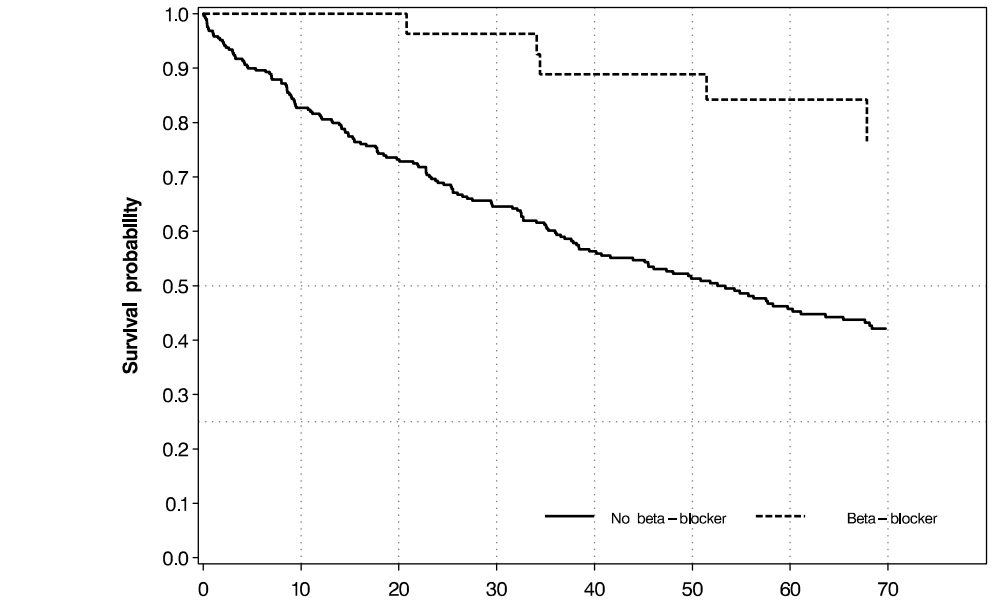
Results of the DRE for progression to renal replacement therapy described an increased risk in anti-platelet and in beta-blocker treated patients (anti-platelet 23% [95% CI 13-33%] vs. 12 [95%CI 7-17%], p=0.05; beta-blocker 38% [95% CI 29-47%] vs. 9% [5-13%], p<0.001). No statistically significant alteration in risk for cardiovascular event was associated with anti-platelet therapy, however a reduction in risk was associated with beta-blocker (21% [95% CI 16-25%] vs. 9% [95% CI 5-13%], p=0.02). Complete results of the multivariate regressions are shown in table 4.5.5.

**Figure 4.5.2** - Kaplan Meier survival curve for all-cause mortality in anti-platelet treated and not treated patients




| Number at Risk | | | | | | |
|---|---|---|---|---|---|---|
| No anti-platelet | 164 | 124 | 103 | 86 | 67 | 50 |
| Anti-platelet | 61 | 60 | 49 | 45 | 37 | 27 |

**Figure 4.5.3** - Kaplan Meier survival curve for all-cause mortality in beta-blocker treated and not treated patients




| Number at Risk | | | | | | |
|---|---|---|---|---|---|---|
| No beta-blocker | 289 | 234 | 191 | 160 | 121 | 94 |
| Beta-blocker | 29 | 29 | 26 | 23 | 19 | 12 |

*Dashed line represents treated patients, solid line represents non-treated patients. X-axis, survival time in months. Y-axis, survival probability.*

**Table 4.5.5** - Results of doubly robust regressions

| | Antiplatelet group events (95% confidence interval) | No antiplatelet group events (95% confidence interval) | p | Relative risk (95% confidence interval) | p |
|---|---|---|---|---|---|
| **Death** | 33.4% (20-46%) | 50.9% (43-59%) | 0.02 | 0.66 (0.43-0.99) | 0.05 |
| **Renal replacement therapy** | 22.8% (13-33%) | 11.8% (7-17%) | 0.05 | 1.91 (1.08-3.40) | 0.03 |
| **Non-fatal cardiovascular event** | 26.1% (11-37%) | 23.7% (17-31%) | 0.7 | 1.11 (0.65-1.86) | 0.71 |
| **Death before dialysis** | 22.5 (11-34%) | 42.9% (35-51%) | 0.003 | 0.52 (0.31-0.89) | 0.02 |

| | Beta-blocker group events (95% confidence interval) | No beta-blocker group events (95% confidence interval) | p | Relative risk (95% confidence interval) | p |
|---|---|---|---|---|---|
| **Death** | 21.3% (5.1-37.5%) | 46.2% (39.9-52.5%) | 0.005 | 0.46 (0.21-0.99) | 0.04 |
| **Renal replacement therapy** | 38.1% (28.8-47.4%) | 8.9% (5.4-12.5%) | <0.001 | 4.27 (2.75-6.62) | <0.001 |
| **Non-fatal cardiovascular event** | 20.5% (15.7-25.4%) | 27.8% (22.4-33.5%) | 0.02 | 0.74 (0.60-0.90) | 0.003 |
| **Death before dialysis** | 17.6% (4.5-30.8%) | 39.0% (32.8-45.2%) | 0.004 | 0.45 (0.21-0.97) | 0.04 |

*Results from the doubly robust estimator are presented as percentage of patients predicted to reach end-point in a five-year period with bootstrapped 95% confidence interval in parenthesis. Renal replacement therapy defined as initiation of chronic haemodialysis, peritoneal dialysis or transplantation. Cardiovascular event defined as myocardial infarction, acute coronary syndrome, stroke, transient ischaemic attack, new onset angina or coronary revascularisation. Probability of treatment model in all cases calculated for age, eGFR, patency score, systolic blood pressure, myocardial infarction, and history of cerebrovascular disease.*
*Mortality outcome analysis adjusted for age, eGFR, proteinuria, statin therapy, anti-platelet therapy*
*RRT outcome analysis adjusted for age, eGFR, blood pressure and proteinuria*
*CVE outcome analysis adjusted for age, eGFR, proteinuria, statin therapy, anti-platelet therapy, and macrovascular history*

*Rate of change in renal function*

In a mixed and random effects model for rate of change in eGFR the parameter estimate for annual rate of change in log eGFR was -0.06 [SE 0.02], equivalent to a 6% annual reduction in eGFR (or approximately 2ml/min/1.73m$^2$/year from a baseline eGFR of 35ml/min/1.73m$^2$). No significant alteration in rate of loss of eGFR was associated with anti-platelet use (parameter estimate 0.01 [SE 0.03], p=0.8) or with beta-blocker use (parameter estimate -0.01 [SE 0.03], p=0.8). Full results of the mixed effects model are presented in table 4.5.6.

**Table 4.5.6** - Results of fixed and random effects model for rate of change in estimated glomerular filtration rate

| | **Anti-platelet therapy** | | | **Beta-blocker therapy** | | |
|---|---|---|---|---|---|---|
| | **Parameter estimate** | **Standard error** | **p** | **Parameter estimate** | **Standard error** | **p** |
| | | | ***Fixed effects*** | | | |
| **Intercept** | 0.42 | 0.07 | <0.001 | 0.48 | 0.06 | <0.001 |
| **Treatment group** | 0.04 | 0.03 | 0.161 | 0.02 | 0.04 | 0.622 |
| **Baseline log eGFR** | 0.89 | 0.02 | <0.001 | 0.87 | 0.02 | <0.001 |
| **Proteinuria** | -0.04 | 0.02 | 0.017 | -0.02 | 0.01 | 0.041 |
| | | | ***Random effects*** | | | |
| **Annual change in log eGFR** | -0.06 | 0.02 | <0.001 | -0.07 | 0.01 | <0.001 |
| **Interaction of annual rate of change in eGFR with treatment group** | 0.01 | 0.03 | 0.821 | -0.01 | 0.03 | 0.791 |

*Abbreviations: eGFR – estimated glomerular filtration rate.*
*As natural log transformation applied to eGFR values the parameter effects for annual change in eGFR can be considered in terms of percentage annual change. A parameter estimate of -0.06 is therefore equivalent to a 6% annual reduction in eGFR.*

*Complications*

As the recruitment period for the SRVD preceded local adoption of electronic health records, detailed bleeding event data could only be obtained from a retrospective notes review for 165 (73%) of patients. Of these 49 were anti-platelet treated and 116 were not antiplatelet treated (71% and 70% of each group respectively). No significant difference in overall bleeding events was observed between groups (29% in anti-platelet group vs. 28% in non anti-platelet group, p=0.9). When subdivided by major bleeding episodes, occurrences of haemoglobin <10g/dL and occurrences of haemoglobin <8g/dL the same pattern was observed, table 4.5.7.

**Table 4.5.7** - Bleeding complications

| | Anti-platelet treated | Not anti-platelet treated | p |
|---|---|---|---|
| **Major bleeding event** | 5.4% | 9.6% | 0.40 |
| **Haemoglobin <10g/dl** | 19.6% | 17.3% | 0.75 |
| **Haemoglobin <8g/dl** | 9% | 15% | 0.30 |
| **Composite of any event** | 29% | 28% | 0.96 |

*Major bleeding event defined as hospitalisation for blood loss resulting in a reduction in haemoglobin or hospital stay where length of admission was extended by bleeding complications.*

*Optimal medical therapy*

Based on the above findings and previously published data, optimal medical therapy was defined as angiotensin blockade, statin therapy, anti-platelet therapy and beta-blockade. At baseline 44 (9%) patients were prescribed all four of these agents, 136 (26%) were prescribed 3, 162 (31%) were prescribed two, 118 (23%) were prescribed one and 55 (10%) were prescribed zero. Patients prescribed all four medications were younger, with lower blood pressures, and higher eGFRs but a greater burden of cardiovascular co-morbidities, table 4.5.8.

**Table 4.5.8** - Baseline patient demographics divided by number of optimal medications prescribed

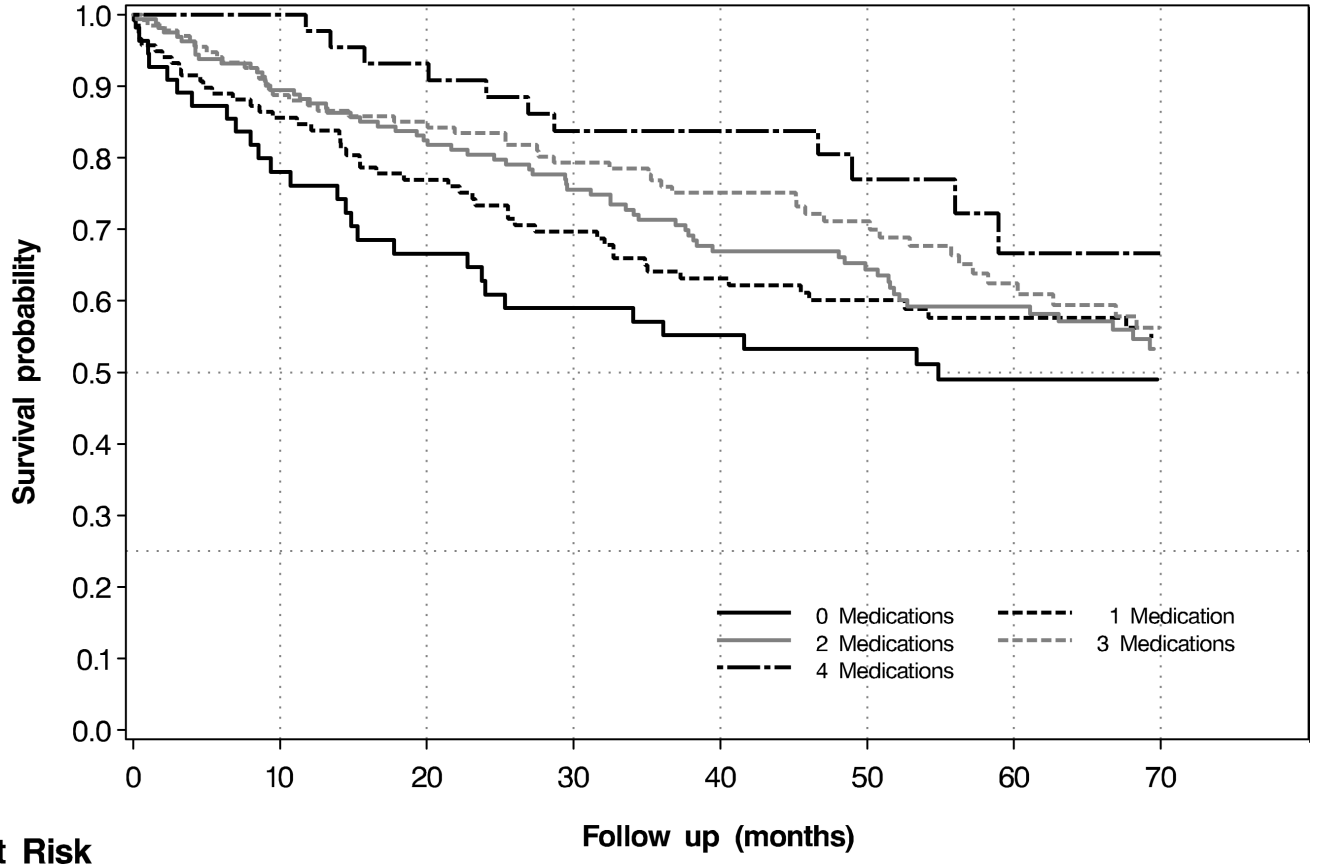
| | Total number of prescribed "optimal" baseline medications | | | | | |
|---|---|---|---|---|---|---|
| | **0 n=55** | **1 n=118** | **2 n=162** | **3 n=136** | **4 n=44** | **p** |
| | | | ***Demographics and renal function*** | | | |
| **Age (years)** | 73.3+/-8.6* | 69+/-10.3 | 69.7+/-8.9 | 70.7+/-8.8 | 68.3+/-9.9 | 0.028 |
| **Male** | 31 (56.4%) | 65 (55.1%) | 88 (54.3%) | 87 (64%) | 25 (56.8%) | 0.509 |
| **eGFR (ml/min/1.73m²)** | 31+/-21 | 33.1+/-20.4 | 33.4+/-16.9 | 35.6+/-16.9 | 32.2+/-12.8 | 0.527 |
| **Proteinuria (g/24 hours)** | 1+/-0.8 | 0.9+/-0.9 | 1+/-1.4 | 0.8+/-1.4 | 0.7+/-1 | 0.455 |
| | | | ***Renal artery disease and clinical presentation*** | | | |
| **Percentage stenosis** | 95 [60-100] | 90 [60-100] | 75 [60-99] | 70 [60-90] | 75 [60-95] | 0.013 |
| **Patency score** | 86.7+/-45.9 | 93+/-41 | 93.8+/-40.1 | 96.3+/-36.8 | 89.2+/-45.4 | 0.614 |
| **PTRAS** | 7 (12.7%) | 20 (16.9%) | 44 (27.2%) | 31 (22.8%) | 14 (31.8%) | 0.06 |
| **Rapidly declining renal function** | 8 (14.5%) | 10 (8.5%)* | 28 (17.3%) | 31 (22.8%)* | 10 (22.7%) | 0.04 |
| **Refractory hypertension** | 7 (12.7%)* | 25 (21.2%)* | 56 (34.6%) | 68 (50%)** | 20 (45.5%) | <0.001 |
| | | | ***Blood pressure and medications*** | | | |
| **Systolic blood pressure (mmHg)** | 165.9+/-29.9* | 159.8+/-28.7 | 158.8+/-30 | 152.3+/-28.9 | 151.6+/-30.8 | 0.025 |
| **Diastolic blood pressure (mmHg)** | 88.9+/-18.1** | 83.5+/-14.7** | 82+/-15.9* | 77.3+/-15.6 | 73.5+/-16.3 | <0.001 |
| **Number of blood pressure medications** | 1 [1-2] ** | 1 [1-3] ** | 1 [1-3] ** | 3 [2-4]* | 4 [3-4] | <0.001 |
| **Angiotensin blockade** | 0 (0%) | 35 (29.7%)** | 71 (43.8%)** | 103 (75.7%)** | 44 (100%) | <0.001 |
| **Anti-platelet** | 0 (0%)** | 39 (33.1%)** | 110 (67.9%)** | 119 (87.5%)* | 44 (100%) | <0.001 |
| **Statin** | 0 (0%)** | 18 (15.3%)** | 87 (53.7%)** | 122 (89.7%)* | 44 (100%) | <0.001 |
| **Beta-blocker** | 0 (0%)** | 26 (22%)** | 56 (34.6%)** | 64 (47.1%)** | 44 (100%) | <0.001 |
| | | | ***Co-morbidities*** | | | |
| **Myocardial infarction** | 12 (21.8%)* | 26 (22%)* | 43 (26.5%) | 51 (37.5%) | 23 (52.3%) | 0.001 |
| **Cerebrovascular event** | 13 (23.6%)* | 43 (36.4%) | 61 (37.7%) | 47 (34.6%) | 22 (50%) | 0.112 |
| **Peripheral vascular disease** | 17 (30.9%) | 43 (36.4%) | 59 (36.4%) | 63 (46.3%) | 19 (43.2%) | 0.228 |
| **Diabetes mellitus** | 11 (20%) | 29 (24.6%) | 43 (26.5%) | 54 (39.7%)* | 15 (34.1%) | 0.022 |

*Abbreviations and definitions – Patency score defined as (200-left side stenosis-right side stenosis), where a score of 200 therefore represents bilateral 0% stenosis and a score of 0 represents bilateral 100% stenosis. PTRAS – percutaneous renal artery angioplasty and stenting. Cerebrovascular event defined as previous stroke or transient ischaemic attack. Angiotensin blockade defined as prescription of angiotensin converting enzyme inhibitor and / or angiotensin II receptor blocker. Rapidly declining renal function defined as serum creatinine at time of angiography greater than 1.2x or µ100 mol/L (1.14mg/dL) greater than a baseline reading taken within the previous six-months. Refractory hypertension defined as blood pressure above 140mmHg and / or 90mmHg despite use of three or greater different classes of antihypertensive medications, one of which is a diuretic.*

*P value presented in the table is for overall trend between groups. Direct comparisons are also made between patients prescribed all four medications and smaller numbers. Here results are presented in the table, with * representing p<0.05 and ** representing p<0.001 compared to patients prescribed all four agents. For continuous variables, overall comparison and between group comparisons made using ANOVA. For categorical variables comparisons made using factorial logistic regression.*

In multivariate Cox regression (adjusted for age, proteinuria and eGFR), no statistically significant increase in risk for RRT was associated with being prescribed less than all four medications. However, compared to patients prescribed all four of these medications, a trend towards increasing risk for overall mortality was observed as the number of prescribed medications fell (three medications, HR death 1.4 [95% CI 0.8-2.5], p=0.3; two medications HR 1.7 [95% CI 0.9-2.9], p=0.08, one medication HR 2.0 [95% CI 1.1-3.6], p=0.02, zero medications HR 1.8 [95% CI 0.97-3.3], p=0.06), figure 4.5.4. For death before dialysis, a statistically significant increase in risk was associated with being prescribed fewer than all four medications (3 medications HR 1.6 [95% CI 0.8-3.1], p=0.1, 2 medications HR 1.9 [95% CI 1.01-3.6], p=0.05, 1 medication HR 2.4 [95% CI 1.3-4.6], p=0.01, 0 medications HR 2.2 [95% CI 1.1-4.4], p=0.03). In contrast a trend towards reduced risk for cardiovascular events was observed in patients prescribed fewer medications although this reached statistical significance in patients prescribed none of the four optimal medications (HR 0.4 [95% CI 0.2-0.7], p<0.001). Complete results are presented in table 4.5.9.

**Figure 4.5.4** - Kaplan Meier survival curve for all-cause mortality divided by number of 'optimal' baseline medications




*Based on prescribed medications at time of diagnostic angiography. Optimal medications defined as angiotensin blockade, beta-blockade, statin, and anti-platelet therapy.*

*X-axis, survival time in months. Y-axis, survival probability.*

**Number at Risk**

| | | | | | | |
|---|---|---|---|---|---|---|
| 0 Medications | 55 | 40 | 32 | 30 | 26 | 22 |
| 1 Medication | 118 | 98 | 81 | 69 | 56 | 46 |
| 2 Medications | 162 | 141 | 118 | 98 | 82 | 58 |
| 3 Medications | 135 | 116 | 103 | 89 | 66 | 42 |
| 4 Medications | 44 | 43 | 39 | 33 | 25 | 12 |

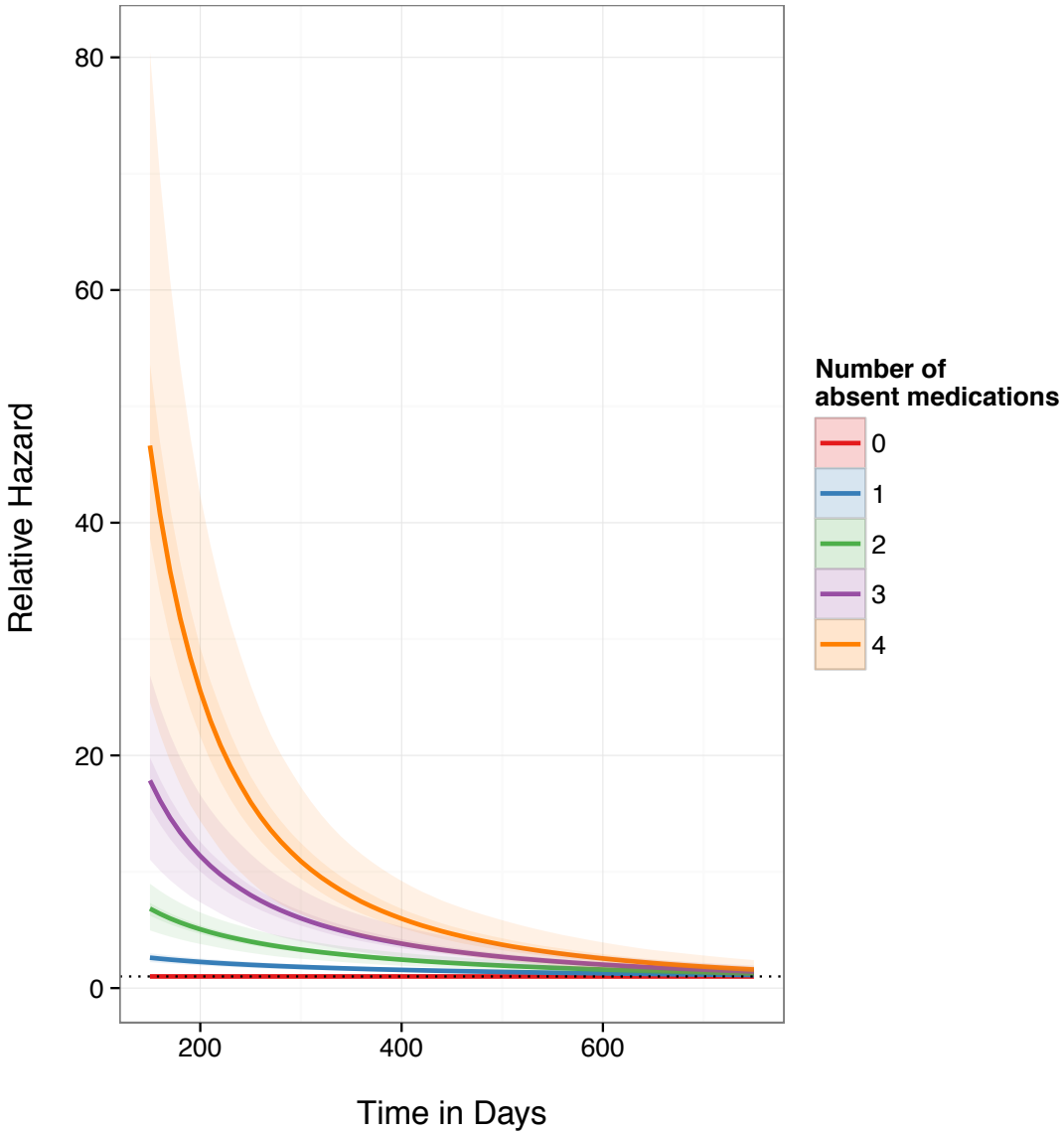
**Table 4.5.9** - Cox survival analysis for optimal baseline medications

| | Death | | Renal replacement therapy | | Cardiovascular event | | Death before dialysis | |
|---|---|---|---|---|---|---|---|---|
| | **HR (95% CI)** | **p** | **HR (95% CI)** | **p** | **HR (95% CI)** | **p** | **HR (95% CI)** | **p** |
| **4 Meds n=44** | *Referent* | | *Referent* | | *Referent* | | *Referent* | |
| **3 Meds n=136** | 1.41 (0.79-2.53) | 0.25 | 0.76 (0.27-2.16) | 0.61 | 0.64 (0.38-1.09) | 0.1 | 1.62 (0.84-3.1) | 0.15 |
| **2 Meds n=162** | 1.67 (0.95-2.93) | 0.08 | 1.09 (0.43-2.78) | 0.85 | 0.72 (0.44-1.19) | 0.2 | 1.90 (1.01-3.58) | 0.05 |
| **1 Med n=118** | 2.02 (1.14-3.57) | 0.02 | 1.68 (0.67-4.25) | 0.27 | 0.58 (0.34-0.99) | 0.05 | 2.40 (1.26-4.57) | 0.01 |
| **0 Meds n=55** | 1.80 (0.97-3.33) | 0.06 | 1.13 (0.34-3.69) | 0.84 | 0.35 (0.17-0.71) | <0.001 | 2.19 (1.1-4.35) | 0.03 |
| **Age** | 1.03 (1.02-1.04) | <0.001 | 0.96 (0.94-0.98) | <0.001 | 1.02 (1-1.04) | 0.04 | 1.03 (1.02-1.05) | <0.001 |
| **eGFR** | 0.98 (0.97-0.98) | <0.001 | 0.93 (0.91-0.95) | <0.001 | 0.99 (0.99-1) | 0.21 | 0.98 (0.97-0.98) | <0.001 |
| **Proteinuria** | 1.11 (1.02-1.21) | 0.01 | 1.25 (1.13-1.38) | <0.001 | 1.06 (0.95-1.19) | 0.3 | 1.04 (0.92-1.18) | 0.51 |

*Optimal medications defined as angiotensin blockade (angiotensin converting enzyme inhibitor and / or angiotensin II receptor blocker), statin, beta-blockade and anti-platelet therapy (aspirin, clopidogrel or dipyridamole). Referent group for comparison is patients prescribed all four of these medications at time of diagnostic angiography. Hazard ratios for continuous variables are for one unit increases.*
*Renal replacement therapy defined as initiation of chronic haemodialysis, peritoneal dialysis or transplantation. Cardiovascular event defined as myocardial infarction, acute coronary syndrome, stroke, transient ischaemic attack, new onset angina or coronary revascularisation.*

When the effect of time on risk for death before dialysis was considered, a reduction in the degree of risk associated with being prescribed fewer medications was observed as time from diagnostic angiography increased, figure 4.5.5. By 400 days from date of diagnosis of ARVD, the risk associated with being on zero or one medications compared to all four remained statistically significantly increased relative to patents prescribed all four medications at time of diagnosis, but had reduced by a factor of approximately 20. By 500 days all confidence intervals overlapped suggesting there was no significant difference in risk related to baseline medications in patients who had survived to this point.

**Figure 4.5.5** - Effect of time on risk for death divided by number of optimal baseline medications




*X-axis shows time in days from diagnostic angiography. Y-axis shows risk for death. Solid lines represents estimated hazard ratios, shaded areas represent 95% confidence intervals. Red line represents patients prescribed all four optimal medications at time of angiography and forms the referent group.*

Discussion

The primary finding of these analyses is a reduced risk for death before dialysis in ARVD patients who are commenced on anti-platelet therapy. This risk is independent of other factors known to associate with risk for mortality in CKD such as age, eGFR and proteinuria [31,32]. This finding is consistent with the results of studies of patients with atherosclerotic disease in the general population [33,34]. However, it contrasts with results of a sub-group meta-analysis of 31 studies including 11701 patients with CKD, where no clear mortality benefit was observed [10]. This disparity may relate to differences in the study populations, with the meta-analysis having considered patients with stable or no cardiovascular disease – a stark contrast to the multi-morbid patients in the SRVD. As the presence of CKD due to ARVD could be considered evidence of end organ damage, our study has addressed secondary rather than primary prevention. Other hypotheses for a mechanism of benefit from anti-platelets therapy in ARVD can also be postulated. Potentially patients with ARVD have a vascular risk profile determined more by atheroma than by medial vascular calcification [35] and therefore more amenable to modification via anti-platelet mechanisms. Measurement of surrogate markers of vascular stiffness by pulse wave velocity or augmentation index is not routinely performed at our center leaving us unable to address this question directly. Alternatively the interaction between inflammation and development of atheroma may be relevant [36]. In ARVD high degrees of inflammation and oxidative stress exist, and are linked to risk for cardiovascular mortality [37] and in the general population the benefits of aspirin therapy have been shown to be greatest in patients with the most elevated CRP levels [38]. These data were not available for analysis in the SRVD to further consider this hypothesis. That the association between anti-platelet therapy and reduced risk for death only reached statistical significance in the pre-dialysis time frame is an interesting observation. Whilst this may be a consequence of competing risk factors in the complex metabolic environment of dialysis [39], efficacy of anti-platelet agents in this context can also be considered. Greater degrees of aspirin resistance are reported as eGFR falls [40] as is an increased risk for death in haemodialysis patients treated with aspirin and/or clopidogrel [41]. As such we believe these results suggest a possible role for anti-platelet therapy in the pre-dialysis phase but advocate caution in their use beyond this point.

We interpret the increased risk for progression to RRT in anti-platelet treated patients as a survivor effect. This is supported by the fact that rate of loss of eGFR was not modulated by treatment with these agents, consistent with other reports of aspirin use in advanced CKD [42]. Hence, whilst the increased risk for RRT does not represent a safety issue, there may be implications for service planning and delivery. In relation to other side-effects of treatment, we did not identify an increased risk for major bleeding episodes in anti-platelet treated patients. However due to the retrospective nature of this analysis and the available data in electronic health records, we are unable to directly comment on minor bleeding episodes. Given that almost one in five patients initiated on anti-platelet therapy had discontinued treatment twelve-months later, this may be an important issue. In a post-hoc analysis of 18,597 CKD patients from the Hypertension Optimal Treatment (HOT) trial an overall increased risk for any bleeding event in aspirin treated patients (HR 1.52 [95% CI 1.1-2.08]), although this only reached statistical significance in patients with an eGFR <60ml/min/ 1.73m$^2$ [11]. A meta-analysis of anti-platelet treated CKD patients with stable cardiovascular disease did not replicate this overall finding but did identify an increased risk for minor bleeding (HR 1.70 [95%CI 1.44-2.02) [10]. Although direct comparison between studies is limited by the range of definitions applied to minor and major bleeding events this appears to be a relevant issue.

We acknowledge the potential confounding issue of considering anti-platelets as a single class of medication given their different modes of actions and efficacy in clinical practice [43,44]. However we do not believe this will have had a meaningful impact on our results as 92% of patients in the anti-platelet group were prescribed aspirin mono-therapy. We accept that use of dual therapy (predominantly aspirin and clopidogrel) may be a further confounder, with different outcomes associated with this strategy in primary prevention [45] and specific secondary prevention settings [46,47]. A final limitation is a lack of data regarding concomitant medications other than anti-hypertensive agents. Although debate still continues regarding the interaction between clopidogrel and proton pump inhibitors this was an effect we could not consider in our models [48].

A secondary finding of this work is the reduction in risk for death in beta-blocker treated patients. There are few published data to place this result in context. In a three way study comparing ramipril, metoprolol and amlodipine as first line anti-hypertensive agents in a CKD population there was no difference in eGFR slope or a composite end-point of ESRD/death between ramipril and metoprolol treated patients [49]. However, this was a trial of first-line anti-hypertensive therapy and over 75% of patients in our beta-blocker analysis were prescribed at least one additional anti-hypertensive medication (with the majority of these prescribed angiotensin blockade). The strongest data to support beta blockade in CKD are derived from a meta-analysis of eight randomised controlled trials. Here a statistically significant reduction in risk for death was identified in patients with CKD and left ventricular systolic failure, but insufficient evidence was identified to comment on their role in patients without heart failure [19]. In ARVD cardiac structural and functional abnormalities are almost universal [21]. It is plausible that beta-blockade may improve mortality by improving these changes e.g. by reducing left ventricular mass index [51]. Further study incorporating echocardiographic measurements may be of use. An alternative hypothesis for a mechanism of benefit is that beta-blockade may reduce proteinuria, a key arbiter of prognosis in ARVD and CKD [51]. In rat models treatment with nebivolol has been shown to reduce proteinuria and confer structural benefits to podocytes [52]. This effect has also been demonstrated in small scale human studies [53]. Due to variations in local practice over time, proteinuria data were not available to analyse in a longitudinal manner; however where data existed, a signal to reduced proteinuria after 12-months of beta-blocker therapy was noted (baseline vs. 12-months, beta-blocker treated 0.59 vs. 0.48g/24 hours; non beta-blocker treated 0.58 vs. 0.57g/24 hours).

As with anti-platelet therapy, we interpret the increased risk for RRT associated with beta-blocker therapy as a survivor effect. However, unlike for anti-platelet therapy, a reduction in risk for non-fatal cardiovascular events was associated with beta-blocker therapy. Studies in the general population have demonstrated an overall reduction in risk for cardiovascular events in beta-blocker treated patients, but this overall reduction in risk has been driven by a lower stroke rate rather than a reduction in coronary artery disease [54]. Due to limited patient and event numbers we cannot meaningfully comment on whether this pattern was

replicated within our cohort and larger scale analysis would be required. Given the small number of patients and events we are cautious in interpreting these finding with any certainty.

An attempt was made to review available electrocardiograms performed on patients included in this analysis to identify conduction abnormalities that may have arisen as a consequence of beta-blocker therapy. However, due to the time period over which data were collected few traces were available for review on our electronic records. This compounded by the fact that contemporaneous baseline readings were even less readily available, means that we are unable to comment on beta-blocker side effects beyond noting that only a minority of patients discontinued these agents. A more important limitation in regards our analysis of beta-blockade is a lack of pulse rate data. This information may have provided a valuable insight into distinguishing between a renal or a cardiac mechanism for improved survival given the expanding body of literature defining heart rate as a treatment target in patients with heart failure [55].

Although our attempt to define and assess optimal therapy in ARVD is simplistic, this was the only approach that could yield appropriately sized comparator groups. In addition, we accept that more thoughtful consideration of other agents is required before optimal medical therapy can be accurately defined. However we note that agents such as calcium channel blockers may be considered a less viable therapy due to issues of tolerance [56] progression of stenosis [57], and limited utility in the setting of heart failure. Despite these important limitations, we believe that this analysis offers some of the clearest guidance currently available.

Although we were not able to assess the relative impact of specific combinations of groupings of drugs, the increased risk for death when patients were prescribed only zero to two of these four agents seems clear and credible. Whilst the reduced risk for cardiovascular events in patients prescribed fewer medications at first seems counter-intuitive, we believe this is representative of the increased mortality observed in patients prescribed fewer of these drugs, and we stress that this analysis considered non-fatal cardiovascular events (as cause of death data were not universally available). As such the increased risk

for cardiovascular events in patients prescribed fewer medications is interpreted as a survivor effect. Future analyses should consider cause specific mortality. Finally we must consider the alteration in risk pattern over time in relation to the number of *optimal* prescribed baseline. We believe this is a plausible finding as it is not credible to suggest that a (modifiable) baseline risk factor will have the same influence after two or more years follow-up. This changing risk will relate to survivor effect, alterations in prescribed medications and accrual of other risk factors.

Whilst limitations specific to each analysis have been considered above, the more general limitations of this retrospective study must also be addressed. Whilst our electronic health records are comprehensive for events occurring at our hospital we cannot be certain that adverse events occurring at other sites have been fully documented. Whilst it is standard practice to update clinic letters with a summary of major inter-current illnesses, the level of detail cannot be expected to match that of a complete admission record. In addition due to the study design neither the indication for, nor the dose of the medication was available. Indication for treatment is likely to have the greatest importance in relation to beta-blocker therapy and will have a confounding role in the analysis of medication efficacy over time. Whilst maintenance doing for anti-platelet therapies is consistent across the United Kingdom, this is not the case for beta-blockers and equivalence in dosing regimes for different agents cannot be presumed [58]. Here we have assumed that treatments were commenced in response to the diagnosis of ARVD. Whilst we suggest that this is likely for the majority of cases, we cannot be certain that treatments were not introduced in response to a vascular event near to the time of diagnostic angiography. Given the variable risk associated with time from e.g. myocardial infarction this may have again introduced unmeasured confounding [59]. Finally, although a notes review was performed to identify patients with a documented allergy or previous intolerance the possibility of selection bias persists.

In conclusion, this analysis has demonstrated that treatment with anti-platelet therapy and beta-blockade can, reduce risk for mortality in ARVD. Further work is required to consider effects on cause-specific mortality and drug side effects,

but these agents could now be considered appropriate treatment following initiation of angiotensin blockade and statin therapy.

## References


1. Webster J, Marshall F, Abdalla M, et al. Randomised comparison of percutaneous angioplasty vs continued medical therapy for hypertensive patients with atheromatous renal artery stenosis. Scottish and Newcastle Renal Artery Stenosis Collaborative Group. J Hum Hypertens 1998;12(5):329–35.

2. Plouin PF, Chatellier G, Darné B, Raynaud A. Blood pressure outcome of angioplasty in atherosclerotic renal artery stenosis: a randomised trial. Essai Multicentrique Medicaments vs Angioplastie (EMMA) Study Group. Hypertension 1998;31(3):823–9.

3. 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. N Engl J Med 2000;342(14):1007–14.

4. Bax L, Woittiez A-JJ, Kouwenberg HJ, et al. Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function: a randomised trial. Ann Intern Med 2009;150(12):840–8, W150–1.

5. ASTRAL Investigators, Wheatley K, Ives N, et al. Revascularisation versus medical therapy for renal-artery stenosis. N Engl J Med 2009;361(20):1953–62.

6. Kumbhani DJ, Bavry AA, Harvey JE, et al. Clinical outcomes after percutaneous revascularisation versus medical management in patients with significant renal artery stenosis: a meta-analysis of randomised controlled trials. American Heart Association 2011;161(3):622–630.e1.

7. Hackam DG, Duong-Hua ML, Mamdani M, et al. Angiotensin inhibition in renovascular disease: a population-based cohort study. American Heart Association 2008;156(3):549–55.

8. 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. Nephrol Dial Transplant 2011;

9. Cheung CM, Patel A, Shaheen N, et al. The Effects of Statins on the Progression of Atherosclerotic Renovascular Disease. Nephron Clin Pract 2007;107(2):c35–c42.

10. Palmer SC, Di Micco L, Razavian M, et al. Effects of antiplatelet therapy on mortality and cardiovascular and bleeding outcomes in persons with chronic kidney disease: a systematic review and meta-analysis. Ann Intern Med 2012;156(6):445–59.

11. Jardine MJ, Ninomiya T, Perkovic V, et al. Aspirin Is Beneficial in Hypertensive Patients With Chronic Kidney Disease. J Am Coll Cardiol 2010;56(12):956–65.

12. Khosla S, Kunjummen B, Manda R, et al. Prevalence of renal artery stenosis requiring revascularisation in patients initially referred for coronary angiography. Cathet Cardiovasc Intervent 2003;58(3):400–3.

13. Kuroda S, Nishida N, Uzu T, et al. Prevalence of renal artery stenosis in autopsy patients with stroke. Stroke 2000;31(1):61–5.

14. Shurrab AE, Mamtora H, O'Donoghue D, Waldek S, Kalra PA. Increasing the diagnostic yield of renal angiography for the diagnosis of atheromatous renovascular disease. Br J Radiol 2001;74(879):213–8.

15. Cooper C, Murphy T, Cutlip DE, et al. Stenting and medical therapy for atherosclerotic renal artery stenosis. NEJM Nov 2013; ePub ahead of print. DOI 10.1056/NEJMoa1310753.

16. Cooper CJ, Haller ST, Colyer W, et al. Embolic protection and platelet inhibition during renal artery stenting. Circulation 2008;117(21):2752–60.

17. Mousa AY, Broce M, Campbell J, et al. Clopidogrel use before renal artery angioplasty with/without stent placement resulted in tertiary procedure risk reduction. Journal of Vascular Surgery 2012;56(2):416–23.

18. United Kingdom Hospital Episode Statistics [Internet]. www.hesonline.co.uk. [cited 2011 Dec 12]

19. Badve SV, Roberts MA, Hawley CM, et al. Effects of beta-adrenergic antagonists in patients with chronic kidney disease: a systematic review and meta-analysis. J Am Coll Cardiol 2011;58(11):1152–61.

20. Johansson M, Herlitz H, Jensen G, Rundqvist B, Friberg P. Increased cardiovascular mortality in hypertensive patients with renal artery stenosis. Relation to sympathetic activation, renal function and treatment regimens. J Hypertens 1999;17(12 Pt 1):1743–50.

21. Wright JR, Shurrab AE, Cooper A, Kalra PR, Foley RN, Kalra PA. Left ventricular morphology and function in patients with atherosclerotic renovascular disease. J Am Soc Nephrol 2005;16(9):2746–53.

22. 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(10): 695–704.

23. 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 Revascularisation. Am J Kidney Dis 2013;

24. 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. J Vasc Interv Radiol. 2006;17(9):1383–97; quiz1398.

25. British Cardiac Society, British Hypertension Society, Diabetes UK, HEART UK, Primary Care Cardiovascular Society, Stroke Association. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. Heart. 2005;91 Suppl 5:v1–52.

26. UK Renal Association eCKD guide. [cited 2011 Dec 12]. Available from: http://www.renal.org

27. Funk MJ, Westreich D, Wiesen C, Sturmer T, Brookhart MA, Davidian M. Doubly Robust Estimation of Causal Effects. American Journal of Epidemiology 2011;173(7):761–7.

28. Keele, Luke. Proportionally Difficult: Testing for Nonproportional Hazards in Cox Models. Polit Anal 2010;:mpp044v1–mpp044v1.

29. Gandrud C. simPH: An R package for showing estimates for interactive and nonlinear effects from Cox proportional hazard models. 2013;:1–18. Available from: http://christophergandrud.github.io/simPH/

30. Yusuf S, Zhao F, Mehta SR, Chrolavicus S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment

elevation. NEJM 2001;345(7):494-502.

31. Tonelli M. Chronic Kidney Disease and Mortality Risk: A Systematic Review. Journal of the American Society of Nephrology 2006;17(7):2034–47.

32. Hemmelgarn BR, Manns BJ, Lloyd A, et al. Relation between kidney function, proteinuria, and adverse outcomes. JAMA 2010;303(5):423–9.

33. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324(7329):71–86.

34. Wong PF, Chong L-Y, Stansby G. Antiplatelet therapy to prevent cardiovascular events and mortality in patients with intermittent claudication. JAMA 2013;309(9):926–7.

35. Moe SM, Chen NX. Pathophysiology of vascular calcification in chronic kidney disease. Circ Res 2004;95(6):560–7.

36. Rattazzi M, Puato M, Faggin E, Bertipaglia B, Grego F, Pauletto P. New markers of accelerated atherosclerosis in end-stage renal disease. J Nephrol 2003;16(1):11–20.

37. Lerman LO, Textor SC, Grande JP. Mechanisms of tissue injury in renal artery stenosis: ischaemia and beyond. Progress in Cardiovascular Diseases 2009;52(3):196–203.

38. Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomised controlled trials. JAMA 2006;295(3):306–13.

39. Tentori FF, Blayney MJM, Albert JMJ, et al. Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: the Dialysis Outcomes and Practice Patterns Study (DOPPS). American Journal of Kidney Diseases 2008;52(3): 519–30.

40. Tanrikulu AM, Ozben B, Koc M, Papila-Topal N, Ozben T, Caymaz O. Aspirin resistance in patients with chronic renal failure. J Nephrol 2011;24(5):636–46.

41. Chan KE, Lazarus JM, Thadhani R, Hakim RM. Anticoagulant and Antiplatelet Usage Associates with Mortality among Haemodialysis Patients. J Am Soc Nephrol 2009;20(4): 872–81.

42. Evans M, Fored CM, Bellocco R, et al. Acetaminophen, aspirin and progression of advanced chronic kidney disease. Nephrology Dialysis Transplantation 2009;24(6): 1908–18.

43. Bhatt DL, Fox KAA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med 2006;354(16):1706–17.

44. Squizzato A, Keller T, Romualdi E, Middeldorp S. Clopidogrel plus aspirin versus aspirin alone for preventing cardiovascular disease. Cochrane Database Syst Rev 2011; (1):CD005158.

45. Wang TH, Bhatt DL, Fox KAA, et al. An analysis of mortality rates with dual-antiplatelet therapy in the primary prevention population of the CHARISMA trial. European Heart Journal 2007;28(18):2200–7.

46. Deo SV, Dunlay SM, Shah IK, et al. Dual anti-platelet therapy after coronary artery bypass grafting: is there any benefit? A systematic review and meta-analysis. J Card Surg 2013;28(2):109–16.

47. Mulukutla SR, Marroquin OC, Vlachos HA, et al. Benefit of long-term dual anti-platelet

therapy in patients treated with drug-eluting stents: from the NHLBI dynamic registry. Am J Cardiol 2013;111(4):486–92.

48. Kwok CS, Loke YK. Inconsistencies surrounding the risk of adverse outcomes with concomitant use of clopidogrel and proton pump inhibitors. Expert Opin Drug Saf 2012;11(2):275–84.

49. Wright JT, Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. JAMA 2002;288(19):2421–31.

50. Zoccali C, Benedetto FA, Mallamaci F, et al. Left ventricular mass monitoring in the follow-up of dialysis patients: prognostic value of left ventricular hypertrophy progression. Kidney International 2004;65(4):1492–8.

51. Chrysochou C, Cheung CM, Durow M, et al. Proteinuria as a predictor of renal functional outcome after revascularisation in atherosclerotic renovascular disease (ARVD). QJM 2009;102(4):283–8.

52. Toblli JE, Cao G, Giani JF, Muñoz MC, Angerosa M, Dominici FP. Long-term treatment with nebivolol attenuates renal damage in Zucker diabetic fatty rats. J Hypertens 2011;29(8):1613–23.

53. Erley CM, Harrer U, Kramer BK, Risler T. Renal hemodynamics and reduction of proteinuria by a vasodilating beta blocker versus and ACE inhibitor. Kidney Int 1992;41:1297-1303.

54. Wiysonge CS, Bradley HA, Volmink J. Beta-blockers for hypertension. Cochrane Database Syst Rev Aug 2012.

55. Hori M, Okamoto H. Heart rate as a target of treatment of chronic heart failure. J Cardiol 2012;60(2):86–90.

56. Burke TA, Sturkenboom MC, Lu S-E, Wentworth CE, Lin Y, Rhoads GG. Discontinuation of antihypertensive drugs among newly diagnosed hypertensive patients in UK general practice. J Hypertens 2006;24(6):1193–200.

57. Cianci R, Martina P, Borghesi F, et al. Revascularisation versus medical therapy for renal artery stenosis: antihypertensive drugs and renal outcome. Angiology 2011;62(1):92–9.

58. McGill JB. Optimal use of beta-blockers in high-risk hypertension: a guide to dosing equivalence. Vasc Health Risk Manag 2010;6:363–72.

59. Nauta ST, Deckers JW, Akkerhuis KM, van Domburg RT. Short- and long-term mortality after myocardial infarction in patients with and without diabetes: changes from 1985 to 2008. Diabetes Care 2012;35(10):2043–7.

# CHAPTER 5 - DISCUSSION

This series of observational studies of ARVD presents a series of clinically relevant findings.

The first theme of this thesis has been to better define ARVD as a specific disease. The first two results chapters demonstrated that it is correct to consider ARVD as a disease process that differs from other causes of CKD in terms of major outcomes, and also that ARVD is not a homogeneous condition. This theme of disease sub-classification was expanded in the third chapter where, using standard clinical measurements, a patient phenotype with the greatest risk for ESKD was identified. By considering the difference in ESKD outcomes associated with this phenotype in ARVD and CKD populations, the value of defining ARVD as a unique cause of CKD was reinforced. Thus, ARVD has been defined as a disease in terms of its clinical and biochemical characteristics.

The second theme of this thesis has been the treatment of ARVD. Here, two clinical scenarios (FPO and rapid loss of renal function in combination with refractory hypertension), where PTRAS is associated with clinical benefit have been identified. This finding is complemented by novel information regarding how the remaining majority of ARVD patients should be medically treated. The finding that both anti-platelet medications and beta-blockers are associated with clinical benefit has the potential to improve outcomes for large numbers of ARVD patients.

A final, non-clinical, theme woven through this thesis has been that of robust statistical analyses. Established methodologies such as Cox regression are superb tools. However, with the exponential growth in available data from observational studies and other sources, there is a need to consider novel methodologies that will allow maximal benefit to be obtained from these resources. Throughout these analyses every attempt has been taken to present data in such a way that statistical and clinical significance are linked, with novel analytical approaches undertaken for this purpose rather than for their own sake. The focus on the need for both positive and negative predictive value to be considered is also drawn from this view.

5.1 Key results

**Risks for mortality and renal replacement therapy in atherosclerotic renovascular disease compared to other causes of chronic kidney disease**

This research project began one year after the publication of ASTRAL [1]. Although at the time this RCT represented the largest study of treatment in ARVD, publication had generated more debate than consensus. One important question raised was whether the patients recruited to ASTRAL (and previous RCT) could be considered sufficiently unwell to have warranted consideration for PTRAS. Many editorials and review articles suggested ASTRAL had been biased against PTRAS by recruiting patients who were too 'well' [2,3] and that many of these patients could instead have been viewed as part of a generic CKD continuum. As previous comparative studies of outcome in ARVD had focused on the general non-CKD population, this study was designed to consider what prognostic differences exist between patients with ARVD and other causes of renal disease across the spectrum of CKD.

This analysis demonstrated an increased risk for death, but not RRT in patients with ARVD and similar baseline characteristics to those seen in ASTRAL. This finding supports the suggestion that ARVD can be considered as a distinct condition from CKD based on its prognosis, even where patients and disease are clinically stable. Importantly, however, this analysis also demonstrated a low annual rate of eGFR loss of approximately 1.5ml/min/1.73m$^2$/year in patients with ARVD. This rate of change, also seen in ASTRAL, was markedly lower than previous reports describing an annual 4-5ml/min/1.73m$^2$ fall in eGFR [4]. Hence whilst our results support defining ARVD as a specific disease even at levels of stenosis where renal haemodynamics may not be affected, they also question the utility of considering progression to ESKD as a clinical end-point in RCT of ARVD. Importantly in relation to this point, the follow-up period for ASTRAL has now been extended to 10-years. This will allow accurate assessment of long term renal outcomes, a relevant question given data demonstrating variability in patient trajectories to ESKD in the general CKD population [5].

**High-risk Clinical Presentations in Atherosclerotic Renovascular Disease: Prognosis and Response to Renal Artery Revascularisation**

This is the first study to consider in detail the clinical presentations of ARVD that are accepted as indications for PTRAS in published guidelines [6]. Previous reports of revascularisation for FPO, refractory hypertension and rapidly declining renal function exist, however none of these has accurately defined prognosis in relation to other presentations of ARVD, nor included a medical comparator group when considering the effects of PTRAS.

This analysis has validated FPO being considered as a high-risk presentation, with significantly increased risks for death and cardiovascular event associated with this phenotype of ARVD. The validity of treating rapidly declining renal function and refractory hypertension with PTRAS has, however, been called into question. Whilst the findings in this study may be explained by how these latter two presentations have been defined, this highlights the danger of transposing arbitrary definitions into clinical practice without strong evidence for doing so.

Based on the available data it has been impossible to suggest a mechanistic cause for the improved survival seen in patients with FPO treated with PTRAS. Our data show that, consistent with RCT of PTRAS in ARVD [7], the benefit is not a function of improved blood pressure control or a reduced rate of eGFR loss. It is tempting, therefore, to speculate that the improved survival relates to improvement in cardiac structural and functional parameters. Whilst this is credible [8], the hypothesis is inconsistent with RCT data from clinically stable ARVD patients [9]. In addition, the aetiology of FPO is multifactorial, involving some or all of increased capillary permeability [10], excess RAAS activation [11], impaired sodium handling [12], and sympathetic over activation [13].

The finding of improved survival in patients who presented with the combination of rapid loss of renal function and refractory hypertension was unexpected. Although the limited patient and event numbers for this clinical category mean that this result should be interpreted with caution it may still represent an important finding. In the discussion of chapter 4.2, it was hypothesised that presentation with rapid loss of renal function and refractory hypertension in combination may represent the clinical phenotype of patients with renal

impairment in the setting of preserved renal volume [14]. Subsequently a preliminary analysis of previous work from this center has been performed. In this study radioisotopic assessments of GFR (iGFR) were made in 16 patients using measurement of $^{51}$Cr-Ethylenediaminetetraacetic acid clearance, and $^{99m}$Tc-dimercaptosuccinic acid scintigraphy both prior to, and four months after PTRAS. These measurements were related to MRI measurements of renal parenchymal volume. In a post-hoc evaluation of this work, the combination of RDF and RH was identified in 31% of patients, with significantly higher baseline PV:skGFR values in this group (55.6±107 vs. 9.4±5.6, p=0.02) and significantly greater percentage increases in iGFR following PTRAS (363±483 vs. 50.7±39%, p=0.02).

**Predicting Progression to End Stage Kidney Disease in Atherosclerotic Renovascular Disease**

Accurate prognostication presents a challenge even to experienced clinicians. The existing literature describing which factors have the greatest prognostic impact on risk for ESKD in ARVD is limited, with little consideration given to the interaction of GFR and proteinuria. In addition much of these data are drawn from small patient populations and pre-date widespread adoption of angiotensin blockade in ARVD [15,16]. The study reported is unique in that by using a classification tree, it provides information regarding the hierarchical importance of routinely measured vascular risk factors and places them in context with medical and interventional therapies.

We believe that the improved positive and negative classification provided by this model (evidenced by the NRI of between 0.6 and 0.75) provides clear evidence of its clinical utility in accurately ascribing low and high-risk groupings. As the suggested model had an area under the curve of approximately 0.8 there is potential for improvement, perhaps by the addition of biomarkers such as CD40 and soluble CD40 ligand, markers of platelet activation that have been shown to associate with loss of renal function in ARVD [17]. However, the fact that the current model uses standard clinical measurements means that this system the potential to rapidly translate into clinical practice. Additionally, given the existing level of sensitivity and specificity, any new marker would need a

remarkably strong association with ESKD in ARVD to meaningfully increase the c-statistic of this model [18].

**Comparing Doubly Robust Regression with Randomized Controlled Trials in Nephrology**

Confounding remains an ever present bias in observational research, and debate regarding optimal analytical approaches persist in the statistical literature [19,20]. A key attraction of the doubly robust estimator lies in its ability to simultaneously model for probability of treatment and outcome. This can be achieved by means that any researcher familiar with developing regression models would be able to apply. When this research project began, the DRE had been demonstrated only in theoretical data sets. Subsequently it has appeared in a small number of medical publications [21,22]. The aim of this analysis was to explore the methodology and introduce it in real-world studies to support its use in chapter 4.5.

**Effects of Anti-Platelet Therapy and Beta-Blockade on Prognosis in Atherosclerotic Renovascular Disease**

Despite the fact that RCT have unequivocally demonstrated parity between optimal medical therapy and PTRAS in unselected patients with ARVD there has been minimal research interest in defining what constitutes optimal medical therapy. This hypothesis generating study aimed to identify any associations between anti-platelet treatment and beta-blocker therapy and clinical outcomes in patients with ARVD. These drugs were selected due to their common usage and biologically plausible mechanisms of benefit in this patient group. The significant mortality benefits and, in the case of beta-blockers, reduction in cardiovascular events suggests that there is indeed an optimal medical treatment strategy in ARVD. This has bearing not only for patient care, but also for RCT design and analysis. In a further, limited assessment of the SRVD patients who had been prescribed ≤2 of the 4 optimal medications at angiography (statin, anti-platelet, beta-blockade, angiotensin blockade) had a signal towards reduced mortality associated with PTRAS (HR 0.7 [95% CI 0.5-1.0], p=0.06) whilst patients prescribed ≥3 optimal medications did not (HR 0.7 [95% CI 0.4-1.3], p=0.2). This demonstrates the potential for bias within and between RCT due to variation in medication usage.

The consideration of the interaction between time from angiography and effect of medical therapy is an important facet to this analysis. Where this is not considered the effect of baseline therapy on prognosis can be overstated and patients / clinicians unintentionally misled [23].

By beginning to define an optimal treatment strategy for hypertension in ARVD, this chapter makes a contribution that may be of use to nephrology community. Current guidelines place a focus on blood pressure goals [24] with little information on the optimal approach for achieving this. In the general hypertension literature, significant effort has been directed towards comparative analyses of antihypertensive agents to define optimal treatment strategies. [25,26]. This chapter suggests a need for this approach to be translated into the renal community.

## 5.2 Limitations

Although each separate study has considered limitations specific to the analysis therein, it is appropriate to acknowledge other general limitations of these works.

All data were collected in a prospective, protocoled manner; however, these analyses were retrospectively designed. As a consequence potentially desirable data such as echocardiographic parameters are not available. This has at times restricted our ability to provide a mechanistic insight to complement the clinical findings.

Although patients were recruited to both the SRVD and CRISIS from Salford Royal NHS Foundation Trust and affiliated satellite units, these projects are to all intents and purposes single center studies. As such, the fallacy of constant risk (the assumption that relevance of a disease or intervention does not change between populations of time periods) [27] is an important consideration if the findings of this work are to be applied at other centers. This is particularly relevant in relation to PTRAS, where clinical practice and accepted indications may vary between regions. A pooled analysis including data from other centers to consider any effect of geographic location in relation to outcomes following

PTRAS would be desirable to substantiate the findings presented within this thesis.

The SRVD was reviewed prior to analysis to identify and remove any patients in whom ARVD was not coded as their primary cause of renal disease. Although absolute numbers of patients with a more likely cause of CKD were small, a range of other pathologies including diabetic renal disease (n=14) and IgA nephropathy (n=2) were identified. Potentially other undiagnosed cases of these and other primary renal diseases may have co-existed with ARVD in the SRVD.

The time period over which data have been collected (especially for the SRVD, established 14 years before the start of this project) is a strength and a limitation of the data. Although the long follow-up period is beneficial in relation to end-point analyses, standards of care are constantly evolving. No significant interactions with time were observed in exploratory analyses of key independent variables (revascularisation, clinical phenotype), however this issue may have greater relevance in relation to intercurrent events such as myocardial infarction with a reduction in absolute events numbers and improved survival observed nationally over the study period [28].

### 5.3 Strengths of this research project

Despite the above limitations, these studies are derived from one of the largest non-registry, non-RCT ARVD populations to be reported in the literature. The single center basis permitted meticulous verification of events, providing a robust data set.

Synchronous recruitment to ARVD and CRISIS provided a unique resource to compare disease types within the same patient population, managed by the same clinicians. As such, a minimum of bias will exist in the comparative analyses between these study populations.

Statistical analyses have been designed with care to consider confounding effects on both treatment assignment and on patient outcome, either by probability of treatment weighting or use of the doubly robust estimator. In

addition efforts have been made to present results in a clinically meaningful manner, with event rates or proportions of patients affected presented alongside hazard ratios.

For the risk stratification score positive and negative predictive value have been valued throughout, both in identifying threshold values using sensitivity and specificity, and in assessing the use of the score by using a net reclassification index rather than area under the curve in isolation.

5.4 Response to CORAL

In the weeks directly preceding the submission of this thesis, the results of the CORAL trial were published. CORAL was a randomised controlled trial of medical therapy compared to medical therapy with PTRAS in ARVD with several key differences compared to ASTRAL.

- The primary study end-point in CORAL was the occurrence of a major cardiovascular or renal event (defined as "*a composite of death from cardiovascular or renal causes, stroke, myocardial infarction, hospitalization for congestive heart failure, progressive renal insufficiency, or the need for permanent renal replacement therapy*"). In ASTRAL the primary study end-point was rate of change in renal function, with cardiovascular and renal events considered as secondary end-points.

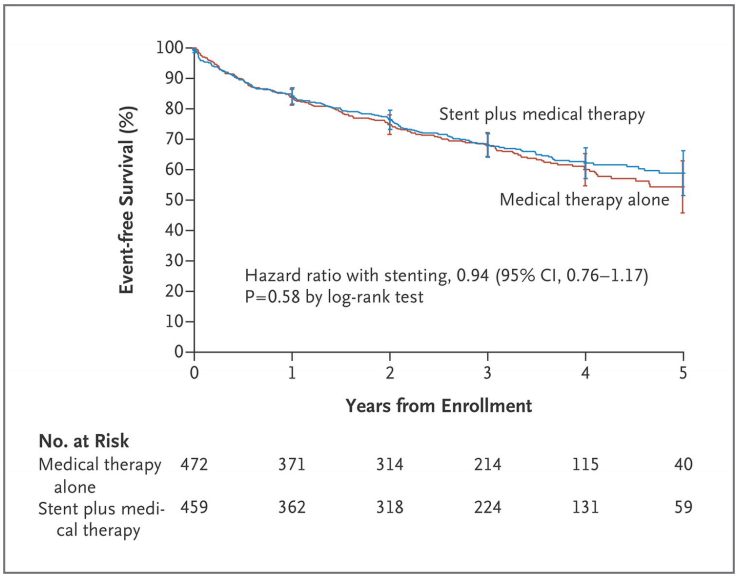
- In CORAL, diagnostic angiograms of patients considered suitable for recruitment were reviewed at a core laboratory using a standardised analysis program. This feature was designed to specifically address criticism of ASTRAL that patients with "insignificant" stenoses may have been recruited.

- In ASTRAL, medical therapy was defined by local protocols, whereas in CORAL treatment was in line with a study protocol (candesartan ± hydrochlorthiazide with amlodipine and atorvastatin).

At baseline, mean age and systolic blood pressures were similar in both ASTRAL and CORAL (age 70 years, systolic blood pressure 150mmHg), with similar proportions of patients having diabetes mellitus (33% vs. 30%). Investigator reported degrees of RAS were similar between studies (ASTRAL 75%, CORAL 73%), though the mean stenosis as measured by the reference laboratory for CORAL was 67%. A more even gender balance was seen in CORAL (51% male vs. 63% male in ASTRAL), and patients in CORAL had more preserved renal function at recruitment (eGFR 58ml/min/1.73m$^2$ vs. 40ml/min/1.73m$^2$ in ASTRAL)

Over a 5-year period, 5322 patients were screened and 947 randomised to CORAL (480 medical therapy, 476 medical therapy plus PTRAS). Sixteen patients were withdrawn from the study due to issues of scientific integrity at one site, giving a final study population of 931 patients (472 medical therapy, 459 medical therapy plus PTRAS). Over a median follow-up period of 43 months [IQR 31-55], 35% of patients in each treatment group reached the primary composite end-point, figure 5.1. No significant difference in outcome between treatment groups was observed when components of the primary end-point were analysed individually. In analyses of secondary end-points (including death and progression to RRT), there was no significant difference in outcome between groups. The authors ultimately concluded that "*…renal-artery stenting did not confer a significant benefit with respect to the prevention of clinical events when added to comprehensive, multifactorial medical therapy in people with atherosclerotic renal-artery stenosis and hypertension or chronic kidney disease.*"

**Figure 5.1** – Kaplan Meier survival curves for the composite primary outcome of major cardiovascular or renal event in CORAL




*Reproduced with permission from NEJM Cooper et al, 2013. Copyright Massachusetts Medical Society*

The results of CORAL do not alter the conclusions of this work. A key conclusion in this thesis is that it is important to consider the clinical presentation of a patient with ARVD rather than making an assessment based on the degree of RAS seen on imaging. As with ASTRAL and the four preceding RCT, recruitment to CORAL was unselected. Hence in the light of the results presented in this thesis the overall probability of a treatment benefit being observed in CORAL was low. Importantly, however, of the patients who were screened but not recruited to CORAL, only 210 patients [5%] were excluded due to physician preference. As such there may be a number of patients in CORAL with a high-risk clinical presentation suitable for a future analysis. This is discussed further in chapter 6.

In CORAL only 24 patients [2.5%] progressed to requiring chronic RRT and 166 patients [17.8%] had a 30% or greater reduction in their eGFR. Although no data are presented on the average rate of loss in renal function, this is consistent with our finding that loss of eGFR in ARVD is slow at <2ml/min/1.73m$^2$/year. Additionally this supports the finding from the classification tree analysis that a low eGFR (<26ml/min/1.73m$^2$) at time of diagnosis is the factor most strongly associated with risk for progression to ESKD.

## Chapter 5


1. ASTRAL Investigators, Wheatley K, Ives N, et al. Revascularisation versus medical therapy for renal-artery stenosis. *N Engl J Med*. 2009;361(20):1953–1962.

2. White CJ. Kiss my astral: one seriously flawed study of renal stenting after another. *Cathet Cardiovasc Intervent*. 2010;75(2):305–307.

3. Weinberg MD, Olin JW. Stenting for atherosclerotic renal artery stenosis: one poorly designed trial after another. *Cleve Clin J Med*. 2010;77(3):164–171.

4. Harden PN, MacLeod MJ, Rodger RS, et al. Effect of renal-artery stenting on progression of renovascular renal failure. *The Lancet*. 1997;349(9059):1133–1136.

5. O'Hare AM, Batten A, Burrows NR, et al. Trajectories of kidney function decline in the 2 years before initiation of long-term dialysis. *Am J Kidney Dis*. 2012;59(4):513–522.

6. 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. *J Vasc Interv Radiol*. 2006;17(9):1383–97.

7. Kumbhani DJ, Bavry AA, Harvey JE, et al. Clinical outcomes after percutaneous revascularisation versus medical management in patients with significant renal artery stenosis: a meta-analysis of randomized controlled trials. *American Heart Association*. 2011;161(3):622–630.

8. Chrysochou C, Schmitt M, Siddals K, Hudson J, Fitchet A, Kalra PA. Reverse cardiac remodelling and renal functional improvement following bilateral renal artery stenting for flash pulmonary oedema. *Nephrology Dialysis Transplantation*. 2013;28(2):479–483.

9. Marcantoni C, Zanoli L, Rastelli S, et al. Effect of Renal Artery Stenting on Left Ventricular Mass: A Randomized Clinical Trial. *Am J Kidney Dis*. 2012;60(1):39-46

10. West JBJ, Mathieu-Costello OO. Stress failure of pulmonary capillaries in the intensive care setting. *Schweiz Med Wochenschr*. 1992;122(20):751–757.

11. Lohmeier TET, Mizelle HLH, Reinhart GAG, Montani JPJ. Influence of angiotensin on the early progression of heart failure. *Am J Physiol Regul Integr Comp Physiol*. 2000;278(1):R74–R86.

12. Garovic VD, Textor SC. Renovascular hypertension and ischemic nephropathy. *Circulation*. 2005;112(9):1362-74

13. Lenders JWM, Eisenhofer G, Mannelli M, Pacak K. Phaeochromocytoma. *The Lancet*. 2005;366(9486):665–675.

14. Cheung CM, Chrysochou C, Shurrab AE, Buckley DL, Cowie A, Kalra PA. Effects of renal volume and single-kidney glomerular filtration rate on renal functional outcome in atherosclerotic renal artery stenosis. *Nephrology Dialysis Transplantation*. 2010;25(4): 1133–1140.

15. Cheung CM, Wright JR, Shurrab AE, et al. Epidemiology of renal dysfunction and patient outcome in atherosclerotic renal artery occlusion. *J Am Soc Nephrol*. 2002;13(1):149–157.

16. Wright JT, Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA*. 2002;288(19):2421–2431.

17. Haller ST, Kalra PA, Ritchie JP, et al. Effect of CD40 and sCD40L on Renal Function and Survival in Patients With Renal Artery Stenosis. *Hypertension.* 2013;61(4):894–900.

18. Cook NR. Statistical evaluation of prognostic versus diagnostic models: beyond the ROC curve. *Clin Chem*. 2008;54(1):17-23

19. Smith HL. Matching with multiple controls to estimate treatment effects in observational studies. *Sociological methodology*. 1997.

20. Vittinghoff EE, McCulloch CEC. Relaxing the rule of ten events per variable in logistic and Cox regression. *American Journal of Epidemiology*. 2007;165(6):710–718.

21. Finkle WDW, Der JSJ, Greenland SS, et al. Risk of fractures requiring hospitalization after an initial prescription for zolpidem, alprazolam, lorazepam, or diazepam in older adults. *J Am Geriatr Soc*. 2011;59(10):1883–1890.

22. Sudan M, Kheifets L, Arah OA, Olsen J. Cell phone exposures and hearing loss in children in the Danish National Birth Cohort. *Paediatr Perinat Epidemiol*. 2013;27(3): 247–257.

23. Boutitie F, Gueyffier F, Pocock SJ, Boissel JP. Assessing treatment-time interaction in clinical trials with time to event data: a meta-analysis of hypertension trials. *Statist Med*. 1998;17(24):2883–2903.

24. National Institute for Health and Clinical Excellence. CG73 Chronic Kidney Disease NICE Guideline. 2008:1–36.

25. Davis BR, Cutler JA, Gordon DJ. Major outcomes in high risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. *JAMA*. 2002;288(23):2981-97

26. Wright JT, Dunn JK, Cutler JA, et al. Outcomes in hypertensive black and nonblack patients treated with chlorthalidone, amlodipine, and lisinopril. *JAMA*. 2005;293(13): 1595–1608.

27. Nicholl J. Case-mix adjustment in non-randomised observational evaluations: the constant risk fallacy. *J Epidemiol Community Health*. 2007;61(11):1010–1013.

28. Smolina K, Wright FL, Rayner M, Goldacre MJ. Determinants of the decline in mortality from acute myocardial infarction in England between 2002 and 2010: linked national database study. *BMJ*. 2012;344:d8059.

29. Cooper CJ, Murphy TP, Cutlip DE, et al. Stenting and Medical Therapy for Atherosclerotic Renal-Artery Stenosis. *N Engl J Med*. 2013. ePub ahead of print. doi10.1056/NEJMoa1310753.

# CHAPTER 6 - SUGGESTIONS FOR FUTURE WORK

Many of the findings in this thesis have the potential for rapid translation into clinical practice, however clear opportunities for further study exist.

*Flash pulmonary edema*

Although the presented data have provided evidence of benefit from PTRAS in patients with ARVD and FPO, we have been unable to offer a mechanistic insight. Although neither the cardiac MRI sub-study of ASTRAL [1], nor the RASCAD trial [2] have demonstrated any cardiac structural changes associated with PTRAS, both of these studies have been performed in low-risk populations. In contrast, reports detailing dramatic changes cardiac structure following PTRAS in patient with ARVD and FPO exist [3]. Given the relative scarcity of acute presentations of ARVD with FPO, a protocol driven study to define a mechanism of benefit is unlikely to be able to recruit significant patient numbers over a realistic timeframe. As such, we suggest that a clinical registry would be the best way to advance knowledge in this setting.

*Rapid loss of renal function and refractory hypertension in combination*

Given the limited patient and event numbers with this clinical presentation in the SRVD there is a need to validate these findings. Collaborative work with other centers [4] and post-hoc analysis of patient level RCT data from ASTRAL and CORAL [5,6] are the two most promising avenues.

As noted in chapter 5, preliminary analysis of a separate study of ARVD from our center appears supportive of the suggestion that this presentation may be a clinical phenotype of patients with a preserved PV:skGFR ratio and a more detailed analysis of these data is planned. However, given the limited patient numbers contained in this MRI / isotope GFR study, further work will be needed. This clinical phenotype could also be assessed against other potential markers of success following PTRAS. These include preserved renal parenchymal oxygenation, assessed by BOLD-MRI [7], and elevated serum BNP levels [8].

*Sub-group analyses of RCT data*

As suggested above, there is the potential to attempt to use patient level RCT data to validate the findings from this thesis regarding patients with high-risk clinical presentations of ARVD. In addition to this, a pooled analysis of RCT and SRVD data could be undertaken to consider if common characteristics exist between patients who die or reach ESKD. This approach could be extended to describe any common characteristics of patients in whom there was clinical improvement following revascularisation and would add to our understanding of patient phenotypes in ARVD.

*External validation of the ordinal risk scoring system derived from the classification tree analysis*

External validation is required for the risk stratification system presented in chapter 4.3. There are a number of possible resources in which this could occur, and discussions have been opened with the Birmingham Trials Clinical Unit to undertake this in the ASTRAL dataset. In a preliminary analysis of the 155 SRVD patients categorised into the high-risk group, a signal towards reduced risk for ESKD associated with revascularisation has been noted (HR 0.54 [95% CI 0.24-1.19], p=0.12). A post-hoc analysis of data from ASTRAL and/or CORAL to consider the effect of revascularisation in the high-risk patients represented in these RCT could be of value.

*Expansion of the classification tree / risk assessment methodology*

In chapter 4.3, the potential value of identifying patients with the greatest risk for progression to ESKD was framed in terms of service planning and predicting future RRT requirements. Clearly the potential exists for this approach to be applied to other specific causes of CKD. These results could then be extrapolated to local CKD populations to aid planning of dialysis services.

A second extension of this approach could be to better consider the competing risks of death and ESKD. Although the assessment of the scoring system considered death as an overall competing risk, it would be desirable to extend the classification tree methodology to handle this issue at each node. By defining the relative risk for death and ESKD at each point, a greater quantity of information regarding the interactions between clinical risk factors would be

made available and a more accurate picture of the natural history of ARVD would begin to emerge. Further extending this to consider changes in risk over time, e.g. incorporating newly started medical therapies, would add to our knowledge of where and how risk can be modified.

*Optimal medical therapy*

The attempt to standardise medical treatment in CORAL will, if successfully undertaken, provide further valuable information regarding the role of angiotensin blockade, anti-platelet therapy, and statin use in ARVD. However the question as to what represents optimal second line anti-hypertensive therapy will remain unanswered. Whilst post-hoc analyses may again provide useful information, this is a question that goes beyond ARVD as a specific disease. The use of angiotensin blockade in CKD has become an oft-repeated manta, transcending its evidence base of diabetic and proteinuric disease [9]. We are currently designing an analysis of CRISIS to generate further preliminary data regarding different classes of anti-hypertensive drugs in CKD but believe that this will prove to be a question worthy of specific prospective study.

## Chapter 6


1. Kalra PA, Ives N, Handly K, et al. Effect of Renal Revascularization on Cardiac Structure and Function in Atherosclerotic Renovascular Disease: LB-PO3162. American Society of Nephrology Annual Meeting, Philadelphia, 2011.

2. 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(1): 39-46

3. Chrysochou C, Schmitt M, Siddals K, Hudson J, Fitchet A, Kalra PA. Reverse cardiac remodelling and renal functional improvement following bilateral renal artery stenting for flash pulmonary oedema. *Nephrology Dialysis Transplantation*. 2013;28(2):479–483.

4. Schwarzwälder U, Hauk M, Zeller T. RADAR - A randomised, multi-centre, prospective study comparing best medical treatment versus best medical treatment plus renal artery stenting in patients with haemodynamically relevant atherosclerotic renal artery stenosis. *Trials*. 2009;10:60.

5. ASTRAL Investigators, Wheatley K, Ives N, et al. Revascularization versus medical therapy for renal-artery stenosis. *N Engl J Med*. 2009;361(20):1953–1962.

6. Cooper CJ, Murphy TP, Cutlip DE, et al. Stenting and Medical Therapy for Atherosclerotic Renal-Artery Stenosis. *N Engl J Med*. 2013. ePub ahead of print. doi:10.1056/NEJMoa1310753.

7. Chrysochou C, Mendichovszky IA, Buckley DL, Cheung CM, Jackson A, Kalra PA. BOLD imaging: a potential predictive biomarker of renal functional outcome following revascularization in atheromatous renovascular disease. *Nephrology Dialysis Transplantation*. 2012;27(3):1013-19.

8. Silva JA, Chan AW, White CJ, et al. Elevated brain natriuretic peptide predicts blood pressure response after stent revascularization in patients with renal artery stenosis. *Circulation*. 2005;111(3):328–333.

9. Sarafidis PA, Ruilope LM. Aggressive blood pressure reduction and renin-angiotensin system blockade in chronic kidney disease: time for re-evaluation? *Kidney International*. 2013. Epub ahead of print. doi:10.1038/ki.2013.355.

# CHAPTER 7 - ADDITIONAL REFERENCES

## Chapter 3


1. Samuels JA, Molony DA. Randomized controlled trials in nephrology: state of the evidence and critiquing the evidence. *Advances in Chronic Kidney Disease*. 2012;19(1): 40–46.

2. Cheung CM, Patel A, Shaheen N, et al. The Effects of Statins on the Progression of Atherosclerotic Renovascular Disease. *Nephron Clin Pract*. 2007;107(2):c35–c42.

3. 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. *Nephrol Dial Transplant*. 2012;27(4):1403-9

4. Eddington H, Hoefield R, Sinha S, et al. Serum phosphate and mortality in patients with chronic kidney disease. *Clin J Am Soc Nephrol*. 2010;5(12):2251–2257.

5. Hoefield RA, Kalra PA, Baker PG, et al. The use of eGFR and ACR to predict decline in renal function in people with diabetes. *Nephrology Dialysis Transplantation*. 2011;26(3): 887–892..

6. Goddard J, Harris K, Turner N. *UK Renal Association eCKD guide*. Available at: http://www.renal.org. Accessed December 12, 2011.

7. British Cardiac Society, British Hypertension Society, Diabetes UK, HEART UK, Primary Care Cardiovascular Society, Stroke Association. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart*. 2005;91 Suppl 5:v1–52.

8. 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. *J Vasc Interv Radiol*. 2006;17(9):1383–97; quiz 1398.

9. ASTRAL Investigators, Wheatley K, Ives N, et al. Revascularization versus medical therapy for renal-artery stenosis. *N Engl J Med*. 2009;361(20):1953–1962.

10. Cooper C, Murphy T, Matsumoto A, et al. Stent revascularization for the prevention of cardiovascular and renal events among patients with renal artery stenosis and systolic hypertension: Rationale and design of the CORAL trial. *American Heart Association*. 2006;152(1):59–66.

11. Martin LG, Rundback JH, Wallace MJ, et al. Quality improvement guidelines for angiography, angioplasty, and stent placement for the diagnosis and treatment of renal artery stenosis in adults. *J Vasc Interv Radiol*. 2010;21(4):421–30– quiz 230.

12. Australian Institute of Health and Welfare. End-stage kidney disease in Australia. 2011:1–60.

13. Brand S, Hall M, Bieber B, et al. International Differences in eGFR at Dialysis Start: Results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *American Society of Nephrology Renal Week- 2012*.

14. Tattersall J, Dekker F, Heimbürger O, et al. When to start dialysis: updated guidance following publication of the Initiating Dialysis Early and Late (IDEAL) study. *Nephrology Dialysis Transplantation*. 2011;26(7):2082–2086.

15. Peake M, Whiting M. Measurement of serum creatinine-current status and future goals. *Clin Biochem Rev*. 2006;27(4):173–184.

16. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604–612.

17. Murata K, Baumann NA, Saenger AK, Larson TS, Rule AD, Lieske JC. Relative performance of the MDRD and CKD-EPI equations for estimating glomerular filtration rate among patients with varied clinical presentations. *Clinical Journal of the American Society of Nephrology*. 2011;6(8):1963–1972.

18. Ali A, Asif NN, Yaqub S, Kashif W, Merchant D, Yazdant I. Spot urine protein: creatinine ratio versus 24 hour urine protein at various levels of GFR patients referred to a tertiary care hospital of Pakistan. *J Pak Med Assoc*. 2008;58(9):476–479.

19. Barr DB, Wilder LC, Caudill SP, Gonzalez AJ, Needham LL, Pirkle JL. Urinary Creatinine Concentrations in the U.S. Population: Implications for Urinary Biologic Monitoring Measurements. *Environ Helath Perspect*. 2005;113(2):192-200

## Chapter 5


1. ASTRAL Investigators, Wheatley K, Ives N, et al. Revascularization versus medical therapy for renal-artery stenosis. *N Engl J Med*. 2009;361(20):1953–1962.

2. White CJ. Kiss my astral: one seriously flawed study of renal stenting after another. *Cathet Cardiovasc Intervent*. 2010;75(2):305–307.

3. Weinberg MD, Olin JW. Stenting for atherosclerotic renal artery stenosis: one poorly designed trial after another. *Cleve Clin J Med*. 2010;77(3):164–171.

4. Harden PN, MacLeod MJ, Rodger RS, et al. Effect of renal-artery stenting on progression of renovascular renal failure. *The Lancet*. 1997;349(9059):1133–1136.

5. O'Hare AM, Batten A, Burrows NR, et al. Trajectories of kidney function decline in the 2 years before initiation of long-term dialysis. *Am J Kidney Dis*. 2012;59(4):513–522.

6. 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. *J Vasc Interv Radiol*. 2006;17(9):1383–97.

7. Kumbhani DJ, Bavry AA, Harvey JE, et al. Clinical outcomes after percutaneous revascularization versus medical management in patients with significant renal artery stenosis: a meta-analysis of randomized controlled trials. *American Heart Association*. 2011;161(3):622–630.

8. Chrysochou C, Schmitt M, Siddals K, Hudson J, Fitchet A, Kalra PA. Reverse cardiac remodelling and renal functional improvement following bilateral renal artery stenting for flash pulmonary oedema. *Nephrology Dialysis Transplantation*. 2013;28(2):479–483.

9. Marcantoni C, Zanoli L, Rastelli S, et al. Effect of Renal Artery Stenting on Left Ventricular Mass: A Randomized Clinical Trial. *Am J Kidney Dis*. 2012;60(1):39-46

10. West JBJ, Mathieu-Costello OO. Stress failure of pulmonary capillaries in the intensive care setting. *Schweiz Med Wochenschr*. 1992;122(20):751–757.

11. Lohmeier TET, Mizelle HLH, Reinhart GAG, Montani JPJ. Influence of angiotensin on the early progression of heart failure. *Am J Physiol Regul Integr Comp Physiol*. 2000;278(1):R74–R86.

12. Garovic VD, Textor SC. Renovascular hypertension and ischemic nephropathy. *Circulation*. 2005;112(9):1362-74

13. Lenders JWM, Eisenhofer G, Mannelli M, Pacak K. Phaeochromocytoma. *The Lancet*. 2005;366(9486):665–675.

14. Cheung CM, Chrysochou C, Shurrab AE, Buckley DL, Cowie A, Kalra PA. Effects of renal volume and single-kidney glomerular filtration rate on renal functional outcome in atherosclerotic renal artery stenosis. *Nephrology Dialysis Transplantation*. 2010;25(4): 1133–1140.

15. Cheung CM, Wright JR, Shurrab AE, et al. Epidemiology of renal dysfunction and patient outcome in atherosclerotic renal artery occlusion. *J Am Soc Nephrol*. 2002;13(1):149–157.

16. Wright JT, Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA*. 2002;288(19):2421–2431.

17. Haller ST, Kalra PA, Ritchie JP, et al. Effect of CD40 and sCD40L on Renal Function and Survival in Patients With Renal Artery Stenosis. *Hypertension.* 2013;61(4):894–900.

18. Cook NR. Statistical evaluation of prognostic versus diagnostic models: beyond the ROC curve. *Clin Chem*. 2008;54(1):17-23

19. Smith HL. Matching with multiple controls to estimate treatment effects in observational studies. *Sociological methodology*. 1997.

20. Vittinghoff EE, McCulloch CEC. Relaxing the rule of ten events per variable in logistic and Cox regression. *American Journal of Epidemiology*. 2007;165(6):710–718.

21. Finkle WDW, Der JSJ, Greenland SS, et al. Risk of fractures requiring hospitalization after an initial prescription for zolpidem, alprazolam, lorazepam, or diazepam in older adults. *J Am Geriatr Soc*. 2011;59(10):1883–1890.

22. Sudan M, Kheifets L, Arah OA, Olsen J. Cell phone exposures and hearing loss in children in the Danish National Birth Cohort. *Paediatr Perinat Epidemiol*. 2013;27(3): 247–257.

23. Boutitie F, Gueyffier F, Pocock SJ, Boissel JP. Assessing treatment-time interaction in clinical trials with time to event data: a meta-analysis of hypertension trials. *Statist Med*. 1998;17(24):2883–2903.

24. National Institute for Health and Clinical Excellence. CG73 Chronic Kidney Disease NICE Guideline. 2008:1–36.

25. Davis BR, Cutler JA, Gordon DJ. Major outcomes in high risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. *JAMA*. 2002;288(23):2981-97

26. Wright JT, Dunn JK, Cutler JA, et al. Outcomes in hypertensive black and nonblack patients treated with chlorthalidone, amlodipine, and lisinopril. *JAMA*. 2005;293(13): 1595–1608.

27. Nicholl J. Case-mix adjustment in non-randomised observational evaluations: the constant risk fallacy. *J Epidemiol Community Health*. 2007;61(11):1010–1013.

28. Smolina K, Wright FL, Rayner M, Goldacre MJ. Determinants of the decline in mortality from acute myocardial infarction in England between 2002 and 2010: linked national database study. *BMJ*. 2012;344:d8059.

29. Cooper CJ, Murphy TP, Cutlip DE, et al. Stenting and Medical Therapy for Atherosclerotic Renal-Artery Stenosis. *N Engl J Med*. 2013. ePub ahead of print. doi: 10.1056/NEJMoa1310753.

## Chapter 6


1. Kalra PA, Ives N, Handly K, et al. Effect of Renal Revascularization on Cardiac Structure and Function in Atherosclerotic Renovascular Disease: LB-PO3162. American Society of Nephrology Annual Meeting, Philadelphia, 2011.

2. 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(1): 39-46

3. Chrysochou C, Schmitt M, Siddals K, Hudson J, Fitchet A, Kalra PA. Reverse cardiac remodelling and renal functional improvement following bilateral renal artery stenting for flash pulmonary oedema. *Nephrology Dialysis Transplantation*. 2013;28(2):479–483.

4. Schwarzwälder U, Hauk M, Zeller T. RADAR - A randomised, multi-centre, prospective study comparing best medical treatment versus best medical treatment plus renal artery stenting in patients with haemodynamically relevant atherosclerotic renal artery stenosis. *Trials*. 2009;10:60.

5. ASTRAL Investigators, Wheatley K, Ives N, et al. Revascularization versus medical therapy for renal-artery stenosis. *N Engl J Med*. 2009;361(20):1953–1962.

6. Cooper CJ, Murphy TP, Cutlip DE, et al. Stenting and Medical Therapy for Atherosclerotic Renal-Artery Stenosis. *N Engl J Med*. 2013. ePub ahead of print. doi:10.1056/NEJMoa1310753.

7. Chrysochou C, Mendichovszky IA, Buckley DL, Cheung CM, Jackson A, Kalra PA. BOLD imaging: a potential predictive biomarker of renal functional outcome following revascularization in atheromatous renovascular disease. *Nephrology Dialysis Transplantation*. 2012;27(3):1013-19.

8. Silva JA, Chan AW, White CJ, et al. Elevated brain natriuretic peptide predicts blood pressure response after stent revascularization in patients with renal artery stenosis. *Circulation*. 2005;111(3):328–333.

9. Sarafidis PA, Ruilope LM. Aggressive blood pressure reduction and renin-angiotensin system blockade in chronic kidney disease: time for re-evaluation? *Kidney International*. 2013. Epub ahead of print. doi:10.1038/ki.2013.355.