Atherosclerotic renovascular disease: risk prediction and selection for revascularization

A thesis submitted to the University of Manchester for the Degree of Doctor of Philosophy (PhD) in the Faculty of Biology, Medicine and Health

Dr Diana Vassallo
MD, MRCP

2017

School of Medical Sciences
Division of Cardiovascular Sciences
# Table of Contents

- List of figures .................................................................................................................. 4
- List of tables ..................................................................................................................... 5
- List of textboxes ............................................................................................................... 7
- Abstract ............................................................................................................................. 8
- Declaration ......................................................................................................................... 9
- Copyright statement ......................................................................................................... 10
- Acknowledgements .......................................................................................................... 11
- Dedication ......................................................................................................................... 12
- Preface ............................................................................................................................... 13
- The author and the author’s contribution ........................................................................ 14
- Published and presented work ......................................................................................... 15
- List of abbreviations ......................................................................................................... 18

## Chapter 1 - Introduction ......................................................................................... 23
  1.1 Atherosclerotic renovascular disease – epidemiology, pathophysiology and current challenges .................................................................................................................. 24
  1.2 Progress in the treatment of atherosclerotic renovascular disease – the conceptual journey and the unanswered questions ........................................................................................................ 52
  1.3 From Anatomy to function – diagnosis of atherosclerotic renal artery stenosis ........ 76

## Chapter 2 - Aims and Objectives ............................................................................ 111

## Chapter 3 - Methodology ....................................................................................... 115
  3.1 Ethical Approval ............................................................................................................ 117
  3.2 Study Design .............................................................................................................. 118
  3.3 Data collection ............................................................................................................ 119
  3.4 Biomarker Analysis .................................................................................................... 122
  3.5 Key-end-points and verification ................................................................................ 126
  3.6 Patient management ................................................................................................... 128
  3.7 Statistical Analysis - overview .................................................................................. 129

## Chapter 4 - Results ................................................................................................. 134
  4.1 Three decades of atherosclerotic renovascular disease management – changing outcomes in an observational study .......................................................................................... 135
  4.2 The importance of proteinuria and prior cardiovascular disease in all major clinical outcomes of atherosclerotic renovascular disease – a single-centre observational study ... 150
  4.3 The effect of revascularization in patients with anatomically-significant atherosclerotic renovascular disease presenting with high-risk clinical features ................................................. 167
  4.4 Association of novel biomarkers with major clinical outcomes in atherosclerotic renovascular disease ........................................................................................................................ 191
4.5 Design of a clinical risk calculator for major clinical outcomes in patients with atherosclerotic renovascular disease. ..................................................................................................................216

Chapter 5 - Conclusion ..............................................................................................................................231
  5.1 Key results ........................................................................................................................................232
  5.2 Limitations ........................................................................................................................................236
  5.3 Strengths .........................................................................................................................................238

Chapter 6 - Suggestions for future work ..................................................................................................241
Appendix 1 ...............................................................................................................................................247
Appendix 2 ...............................................................................................................................................251

Word count – 54,398
List of Figures

Figure 1.3.1 Example of angiography, ultrasound measurements and translesional pressure gradient in a right-sided ARAS..........................................................83

Figure 1.3.2 CT angiography with a 3D reconstruction. The arrow denotes a right-sided renal artery stenosis.................................................................91

Figure 1.3.3 Swine model of ARAS with unenhanced 4D flow MRI............................................92

Figure 1.3.4 Arterial –spin labeling magnetic resonance showing mild (30%) left RAS and severe (90%) right RAS in a 70-year-old man..............................................95

Figure 4.1.1 Proportion of patients in each group receiving specific vascular protective agents (renin angiotensin blockade, beta-blockers, statins or aspirin) at time of diagnosis. ...........141

Figure 4.1.2(a-d) Kaplan-Meier curves for time to (a) Death, (b) ESKD, (c) CVE and (d) any event for each group).................................................................142

Figure 4.1.3 Number of patients diagnosed with ARVD and number of revascularization procedures performed each year in relation to important events and turning points in the history of management of ARVD. ..................................................143

Figure 4.3.1 Flowchart illustrating selection of study population.............................................172

Figure 4.3.2 (a – h) Kaplan-Meier curves showing time to death for revascularized and non-revascularized combined high-risk (patients with at least one of flash pulmonary edema, deteriorating renal function or severe hypertension) and control patients.........................181

Figure 4.4.1 Flowchart describing selection of study population ..............................................197

Figures 4.4.2 (a – d) Effect of individual biomarkers upon hazard ratio for death, progression to end-stage kidney disease (ESKD), cardiovascular events (CVE) and any event when added to baseline model........................................................................204

Figure 4.4.3 Kaplan-Meier curves showing the effect of revascularization on death, progression to end-stage kidney disease (ESKD), cardiovascular events (CVE) and any event in patients with serum N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels and below standard cut-off of 300pg/ml.................................207

Figure 4.5.1 Atherosclerotic renovascular disease risk calculator ...........................................223
List of Tables

Table 1.1.1 Major studies published since 2000 investigating the prevalence of ARVD in different patient groups .................................................................27
Table 1.2.1 Milestones in the history of management of ARVD .................................................................53
Table 1.2.2 Uncontrolled studies of surgery, renal revascularization or medical therapy for ARVD over the past decades .............................................................................56
Table 1.2.3 Controlled studies of renal revascularization or medical therapy for ARVD over the past few decades ...........................................................................................................61
Table 1.2.4 Indications for revascularization in ARVD ..................................................................................71
Table 1.3.1 Studies reporting blood pressure or renal functional response to revascularization by baseline translesional pressure gradient. .................................................................80
Table 1.3.2 Selected studies comparing Duplex ultrasound criteria against catheter angiography .................................................................................................................................85
Table 1.3.3 Studies reporting blood pressure or renal functional response to revascularization by baseline Duplex-ultrasound parameters ...........................................................................88
Table 1.3.4 Sensitivity and specificity of putative diagnostic risk prediction scores for significant unilateral ARAS .................................................................................................................98
Table 1.3.5 Reasonable Indications for Percutaneous revascularization of ARAS from ACCF/AHA Guidelines. Reproduced with permission from 83 .........................................................100
Table 1.3.6 Prospective studies comparing different imaging modalities performed over the past 10 years. ..........................................................................................................................101
Table 4.1.1 Baseline characteristics for whole cohort and for the four groups .........................................................139
Table 4.1.2 Percentage of ARVD patients with and without documented macrovascular disease (MVD) on vascular protective therapy .................................................................................141
Table 4.1.3 Rate of eGFR decline calculated from slope of linear regression for the whole cohort and the individual groups ...........................................................................................................141
Table 4.1.4 Median time to end-points for each group and for cohort as a whole (in months) obtained from non-adjusted Kaplan-Meier curves ........................................................................142
Table 4.1.5 Hazard ratio for endpoints in each time period compared to 1986-2000 (reference group), adjusted for age, gender, blood pressure, comorbidities (Macrovascular disease, diabetes, congestive heart failure and flash pulmonary oedema) eGFR and degree of proteinuria at baseline ............................................................................................................143
Table 4.2.1 Baseline characteristics for entire cohort and for patients who reached and did not reach end-points. ..........................................................................................................................156
Table 4.2.2 Rate of eGFR decline per year for patients who reached clinical end-points and those who remained event-free ........................................................................................................157
Table 4.2.3 Comparison of baseline characteristics between revascularized (R) and non-revascularized (NR) patients ......................................................................................................................158
Table 4.2.4 Univariable and multivariable association between baseline variable and clinical end-points. ........................................................................................................................................159
Table 4.3.1 Comparison of baseline characteristics and estimated glomerular filtration rate (eGFR) slope between control and high-risk patients and between high-risk revascularized and high-risk non-revascularized patients. .................................................................173

Table 4.3.2 Comparison of baseline characteristics and estimated glomerular filtration rate (eGFR) slope between revascularized and non-revascularized high-risk patients, patients with bilateral $\geq 70\%$ renal artery stenosis (RAS) and patients with $<1g$/day baseline proteinuria. .................................................................175

Table 4.3.3 Incidence rate per 100 patient years of clinical end-points in study population ....178

Table 4.3.4 Summary of clinical end-points in study population. ................................180

Table 4.3.5 Effect of high-risk features, bilateral renal artery disease and proteinuria on clinical end-points in study population .........................................................180

Table 4.3.6 Effect of revascularization on median time to clinical outcomes (in months) in patients with bilateral $\geq 70\%$ RAS and in those with $<1g$/day baseline proteinuria. ..............182

Table 4.3.7 Effect of revascularization on clinical end-points in control, overall high-risk and in specific high-risk clinical presentation groups .................................................................183

Table 4.3.8 Effect of revascularization on clinical end-points in patients with bilateral renal artery disease and patients with proteinuria $<1g$/day .........................................................184

Table 4.3.9 Effect of revascularization on clinical end-points in patients with $\geq 1g$/day proteinuria at baseline. ........................................................................................................185

Table 4.4.1 Comparison between study population and patients recruited into the Salford Renovascular Study who had no biomarker data available ........................................198

Table 4.4.2 Baseline characteristics, serum biomarkers and clinical outcomes subdivided by chronic kidney disease (CKD) Stage and renal artery stenosis (RAS) severity. Bold data indicates a statistically significant difference with a p value less than 0.05. ..199

Table 4.4.3 Multivariable model based on base model (shaded area) and combination of those biomarkers that are individually statistically significant when adjusted for base model...202

Table 4.4.4 Model fit and overall net reclassification index for base model, the base model in combination with all biomarkers, and base model with N-terminal prohormone of brain natriuretic peptide (NT-proBNP) only, for each clinical end-point. ......................205

Table 4.4.5 Reclassification table showing event and non-event NRI for prediction of all end-points..................................................................................................................206

Table 4.4.6 Comparison of baseline characteristics and serum biomarkers for revascularized and non-revascularized patients. .................................................................208

Table 4.4.7 Median time to end-points in months for revascularized and non-revascularized patients with high-sensitivity cardiac Troponin T (hs-cTNT) and Cystatin C levels below and above median. ......................................................................................208

Table 4.5.1 Baseline characteristics of study population........................................220

Table 4.5.2 Risk factors for long-term clinical end-points ....................................220

Table 4.5.3 Predicted survival probabilities for revascularized and non-revascularized patients with different clinical phenotypes obtained using risk calculator. ........................................223
List of Textboxes

Textbox 1.1.1 Complications post-endovascular renal revascularization .......................................................... 39

Textbox 1.3.1 Tresholds of translesional gradients for haemodynamically significant ARAS by intra-arterial pressure wire. ......................................................................................................................... 83

Textbox 1.3.2 Advantages and disadvantages of duplex ultrasound for diagnosis of renal artery stenosis ............................................................................................................................................. 84

Textbox 1.3.3 Diagnostic algorithm for using duplex ultrasound to determine haemodynamically significant ARAS proposed by Zeller and colleagues .......................................................... 87

Textbox 1.3.4 Developmental framework of incremental steps required for comprehensive validation of diagnostic methods of ARAS ............................................................................................. 102
Abstract
The University of Manchester
Dr Diana Vassallo
For the degree of Doctor of Philosophy
Atherosclerotic renovascular disease: risk prediction and selection for revascularization
01/08/2017

Recent large randomized controlled trials (RCTs) have shown that renal revascularization does not confer added benefit to unselected patients with atherosclerotic renovascular disease (ARVD) treated with multi-targeted medical therapy. Results suggest that contemporary medical vascular protection therapy has contributed to improved clinical outcomes in ARVD. However, patients with ‘high-risk’ clinical features have largely been excluded from RCTs and there is consistent observational evidence that this specific patient subgroup may gain benefit from revascularization. Timely identification of these patients through risk stratification and prediction of outcomes post-revascularization remain important challenges.

The main aims of this epidemiological research project were to explore how treatment and clinical end-points in ARVD have evolved over the past three decades, to identify the determinants of long-term end-points in ARVD, to investigate the effect of revascularization in a selected ‘high-risk’ subgroup, to investigate novel biomarker association of key end-points and finally to develop a clinical risk prediction model that can aid risk stratification and patient selection for revascularization. These individual studies were all based on a local database that includes details of demographic and clinical data for patients with ARVD referred to our tertiary renal centre between 1986 and 2014. Primary end-point measures included death, progression to end-stage kidney disease, cardiovascular events and a composite end-point composed of the first of any of the above events.

Management of ARVD has been influenced by RCT results, leading to a decline in the number of revascularization procedures performed. Traditional cardiovascular risk factors together with baseline renal function and proteinuria are the most important determinants of adverse events in ARVD thus advocating the use of multi-targeted medical therapy and aggressive risk factor control in all patients with ARVD. Nonetheless ARVD is a heterogenous condition and results of this research project show that revascularization can be of benefit in patients with rapidly deteriorating renal function, bilateral severe ARVD and/or <1g/day baseline proteinuria. A panel of novel biomarkers may have incremental risk predictive value when used in conjunction with more traditional risk factors, and NT-proBNP levels may aid patient selection for revascularization. A simple clinical risk-prediction score based on easily obtainable variables may be used as a bedside tool to help risk stratification and facilitate patient selection for revascularization, thus encouraging a more patient-specific therapeutic approach.
Declaration

No portion of the work referred to in the 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 she 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 commercialization of this thesis, the Copyright and any Intellectual Property University IP Policy (see http://documents.manchester.ac.uk/display.aspx?DocID=24420), in any relevant Thesis restriction declarations deposited in the University Library, The University Library’s regulations (see http://www.library.manchester.ac.uk/about/regulations/) and in The University’s policy on Presentation of Theses.
Acknowledgements

I am forever indebted to my supervisor Professor Kalra without whom none of this research would have been possible. His boundless enthusiasm, guidance and unrelenting support have encouraged me to develop new skills and interests, and helped instill confidence in both my work and myself. He also facilitated collaboration with other research groups that served to enhance this research project further. I will always feel extremely privileged to have been given this opportunity to work with such an inspirational and exceptional supervisor.

Secondly I would like to thank my co-supervisor Dr Constantina Chrysochou for her constant encouragement, reassurance and insight. I would also like to thank Dr Rachel Middleton, my research advisor for her sensible advice and for providing a friendly ear when required.

In addition to my supervisory team, I would also like to express my sincere gratitude to the following individuals:
- Dr Jim Ritchie, whom I consider the fount of all statistical knowledge and who despite a busy schedule, always found the time to share some of his pearls of wisdom with me.
- Dr Darren Green for his honest criticism and insightful review of my work
- Dr Helen Alderson for patiently teaching me the ropes with regards to statistical analyses, particularly in relation to R, and for all the survival tips she provided along the way.
- Dr Ags Odudu for his passion for the written word and for helping me discover the beauty of a concise, well-written paper.
- Professor Nicolas Vuilleumier and his team for kindly agreeing to share biomarker data for the purposes of my project and for the valuable review of my statistical analyses.
- Professor Rob Foley for his remarkable expertise in data analyses.
- All my predecessors for the countless hours spent on meticulous data collection for the Salford Renovascular database – Dr Jim Ritchie, Dr Constantina Chrysochou, Dr Aladdin Shurrab, Dr Ching Cheung and Dr Julian Wright.
- The Salford Royal Renal Research Fund for financial support.

Finally, I would like to thank all the patients on the Salford Renovascular database. Without their contribution none of this work would have been possible.
Dedication

Despite the distance, my family has been a constant source of support throughout my whole research journey. I would have never been able to finish this research without their encouragement, laughter and love.

I would like to dedicate this thesis to my parents and my sister Daphne.
Preface

This thesis comprises a series of observational studies that have been carried out to enhance our understanding of atherosclerotic renovascular disease. The individual chapters of this thesis are presented in a format suitable for publication in a peer-reviewed journal hence this thesis is styled in the ‘Literature Report and Journal Paper Format’. Papers that have already been published or are in press are listed in the section ‘Published and Presented Work’ and publication details are again summarized at the beginning of each published chapter. Where appropriate, permission for reproduction of published articles in this thesis has been sought from each publisher. Each chapter is a true reflection of the manuscript that has been submitted to the journal, however some editing was necessary to ensure consistency of style. Data that was published as supplementary data due article length restrictions has been incorporated into the respective chapters in thesis to facilitate readability. A short preface at the start of each chapter serves to link the chapters together and to the main theme of the thesis.

The introductory section consists of a general overview that highlights current knowledge about the epidemiology of ARVD, and the challenges and unanswered questions that characterize management of this condition, followed by two published review articles. This is followed by a summary of the aims and objectives for each individual study in this research project. The methodology section provides details about the Salford Renovascular Database, a long-running epidemiological project that forms the basis of this research. This section provides an overview of data collection, statistical analyses and the techniques used to analyze the laboratory data presented in this thesis. The results section is subdivided into individual observational studies that have been written in journal paper format and have either been published or are still under peer review at time of thesis submission. Final conclusions and suggestions for future work are presented after the results section.

In line with University policy, each published or submitted chapter is referenced individually, and all other sections are also individually referenced to maintain a consistent format throughout the whole thesis.
The author and the author’s contribution

Prior to embarking on this research project my experience of research was limited to data collection mostly for clinical audit purposes. This audit experience however served me well as the first 6 months of my research were purely dedicated to updating the Salford Renovascular Database. Data collection for this research project was obviously on a much larger scale compared to my previous experiences, hence this introduced me to the challenges, and the rewards, of accurate data capture. The methods used for data collection are described in more detail in Chapter 3.

I developed my data analysis skills mainly through self-directed learning from textbooks and dedicated websites, and also by attending educational seminars at the University of Manchester. Regular discussion with my research mentors also proved invaluable to enhance my understanding of the more challenging statistical concepts and equipped me with the necessary skills required to design the observational studies included in this thesis. My writing style has also evolved steadily throughout this research project, in parallel with the development of a deeper critique of my own work and increased receptiveness to external criticism. I have drafted all manuscripts presented in this thesis.

While I was responsible for data collection, study design and statistical analysis for all studies, each chapter is the result of collaboration with various co-authors, whose individual contribution is greatly appreciated and is detailed in the section ‘Published and Presented Work’. The laboratory biomarker analyses described in Chapter 3 and Chapter 4.4 have been performed in an external laboratory and I was only responsible for the statistical analyses of the results. The risk calculator designed in Chapter 4.5 was developed with the help and guidance of an experienced epidemiologist.

I believe the numerous intellectual challenges I have experienced over the past three years, punctuated with some very rewarding ‘eureka’ moments, and the constant encouragement I have received throughout this whole adventure, have laid the groundwork for my eventual development into an independent researcher.
Published and Presented Work

The following papers are included as chapters in this thesis and have been published in peer-reviewed journals. I wish to acknowledge the contribution of my co-authors.

1. **Progress in the treatment of atherosclerotic renovascular disease: the conceptual journey and the unanswered questions.**
   Vassallo D, Kalra PA
   Vassallo D – Main author
   Kalra PA – Co-author, main editor

2. **From anatomy to function: diagnosis of atherosclerotic renal artery stenosis**
   Odudu A, Vassallo D, Kalra PA
   Odudu A – Co-author
   Vassallo D – Co-author (equal division of work with first co-author)
   Kalra PA – Main editor

   I have written the following sections of this co-authored paper:
   - Ultrasound
   - Novel Ultrasound techniques
   - Radionuclide scans
   - Computed Tomograph (CT) angiography
   - Dynamic Contrast-Enhanced CT
   - Serum and Urine Biomarkers
   - Clinical Risk scores and phenotypes
   - High-risk phenotypes
   - Expert Commentary
   - Advantages and Disadvantages of Duplex US for diagnosis of renal artery stenosis
   - Tables 6 – 10

3. **Three decades of atherosclerotic renovascular disease management – changing outcomes in an observational study.**
4. The importance of proteinuria and prior cardiovascular disease in all major clinical outcomes of atherosclerotic renovascular disease – a single-centre observational study
Vassallo D, Ritchie J, Green D, Chrysochou C, Kalra PA
BMC Nephrol. 2016 Dec 7;17(1):198

Vassallo D – Study design, data collection, data analysis, primary author
Ritchie J, Green D, Chrysochou C – data analysis, co-authors
Kalra PA – study design, main editor

5. The effect of revascularization in patients with anatomically significant atherosclerotic renovascular disease presenting with high-risk clinical features.
Vassallo D, Ritchie J, Green D, Chrysochou C, Kalra PA

Vassallo D – Study design, data collection, data analysis, primary author
Ritchie J, Green D, Chrysochou C – data analysis, co-authors
Kalra PA – study design, main editor

The following papers have been included as chapters and are under peer review or awaiting submission:

1. Association of novel biomarkers with major clinical outcomes in atherosclerotic renovascular disease

Vassallo D – Study design, data collection, data analysis, primary author
Alderson H – data analysis
Vuilleumier – co-author, data analysis
Pagano S, Virzi J – laboratory analysis
Ritchie J, Green D, Chrysochou C – co-authors
Kalra PA – study design, main editor
2. **Design of a clinical risk calculator for major clinical outcomes in patients with atherosclerotic renovascular disease**
   Vassallo D, Foley R, Ritchie J, Green D, Chrysochou C, Kalra PA

Vassallo D – Study design, data collection, data analysis, primary author
Foley R – data analysis, co-author
Ritchie J, Green D, Chrysochou C – data analysis, co-authors
Kalra PA – study design, main editor

The following poster presentations at learned societies have resulted from work related to this research project.

1. **Three decades of atherosclerotic renovascular disease management - changing outcomes in an observational study**
   Vassallo D, Green D, Ritchie J, Chrysochou C, Kalra PA
   Poster presentation at ERA-EDTA 53rd Congress, Vienna, Austria, 2016 (MP314) and UK Kidney Week, Birmingham, UK, 2016 (P089).

2. **Longterm outcomes in atherosclerotic renovascular disease - a single-centre observational study.**
   Vassallo D, Ritchie J, Green D, Chrysochou C, Kalra PA
   Poster presentation at the ERA-EDTA 53rd Congress, Vienna, Austria, 2016 (SP300) and UK Kidney Week, Birmingham, UK, 2016 (P090).

3. **The effect of revascularization in patients with atherosclerotic renovascular disease (ARVD) and high-risk clinical features – a single-centre observational study.**
   Vassallo D, Green D, Ritchie J, Chrysochou C, Kalra PA
   Poster presentation at the American Society of Nephrology annual meeting, Chicago, USA 2016 (SA-PO806) and UK Kidney Week, Liverpool, UK, 2017 (PO-125).

4. **Determinants of long-term outcomes in ‘high-risk’ and ‘low-risk’ patients with atherosclerotic renovascular disease.**
   Vassallo D, Green D, Ritchie J, Chrysochou C, Kalra PA
   Poster presentation at the American Society of Nephrology annual meeting, Chicago, USA 2016 (SA-PO805) and UK Kidney Week, Liverpool, UK, 2017 (PO-126).

5. **Association of novel Biomarkers with long-term outcomes in atherosclerotic renovascular disease.**
   Vassallo D, Alderson H, Ritchie J, Green D, Chrysochou C, Kalra PA
Poster presentation at the ERA-EDTA 54th Congress, Madrid, Spain, 2017 (MP378) and UK Kidney Week, Liverpool, UK, 2017 (PO-057).

6. Design of a clinical risk calculator for major clinical outcomes in patients with atherosclerotic renovascular disease
   Vassallo D, Alderson H, Ritchie J, Green D, Chrysochou C, Kaira PA
   Poster presentation at the American Society of Nephrology annual meeting, New Orleans, USA 2017 (TH-PO470).
List of Abbreviations

3D – three-dimensional
4D – four-dimensional
$^{51}$Cr-EDTA – 51Chromium-labelled ethylenediaminetetraacetic acid
AAA – abdominal aortic aneurysm
ABPM – ambulatory blood pressure monitoring
ACCF – American College of Cardiology Foundation
ACEI – angiotensin converting enzyme inhibitor
AHA – American Heart Association
AIC – Akaike Information Criterion
AKI – acute kidney injury
ANOVA – Analysis of Variance
Anti- apoA-1 IgG – anti-apolipoprotein A-1 immunoglobulin G
ARAS – atherosclerotic renal artery stenosis
ARB – angiotensin receptor blocker
ARVD – atherosclerotic renovascular disease
ASL – arterial spin labelling
ASTRAL trial – angioplasty and stenting of renal artery lesions trial
AUC – area under the curve
BNP – brain natriuretic peptide
BOLD – blood oxygen level dependent
BSA – Bovina serum albumin
CA – catheter angiography
CCF – congestive cardiac failure
CEUS – contrast-enhanced ultrasound
CHF – congestive heart failure
CI – confidence interval
CIN – contrast-induced nephropathy
CKD – chronic kidney disease
CKD-EPI – chronic kidney disease epidemiology collaboration equation
CORAL – cardiovascular outcomes in renal atherosclerotic lesions
CR – captopril renography
CRISIS – chronic renal insufficiency standards implementation study
CTA – computed tomograph angiography
CT – computed tomography
CVD – cerebrovascular disease
CVE – cardiovascular event
DBP – diastolic blood pressure
DCE-MRI – dynamic contrast enhanced magnetic resonance angiography
DM – diabetes mellitus
DRASTIC study – Dutch renal artery stenosis intervention cooperative study
dRI – side-to-side difference in resistance index
DUS – duplex ultrasound
EDV – end-diastolic volume
eGFR – estimated glomerular filtration rate
EH – essential hypertension
ELICA – electrochemiluminescence immunoassay
ELISA – enzyme-linked immunoassay
EMMA study – Essai multicentrique medicaments versus angioplastie
ESKD – end-stage kidney disease
FFR – fractional flow reserve
FGF-23 – fibroblast growth factor-23
FMD – fibromuscular dysplasia
FPE – flash pulmonary oedema
Gd - gadolinium
GFR – glomerular filtration rate
HbA1c – Glycated haemoglobin
HDL – high-density lipoproteins
HMG – hyperaemic mean gradient
HSG – hyperaemic systolic gradient
HR – hazard ratio
hs-cTNT – high-sensitivity cardiac troponin T
HTML – hypertext markup language
IADSA – intra-arterial digital subtraction angiography
IDI – integrated discrimination improvement
IDMS – Isotope Dilution Mass Spectrometry
IHD – ischaemic heart disease
IQR – interquartile range
isoSK-GFR – isotopic single kidney glomerular filtration rate
IVDSA – intra-venous digital subtraction angiography
KIM-1 – kidney injury molecule-1
KW – Kruskal-Wallis
LC-MS – liquid chromatography-mass spectrometry
LRAS – Left renal artery stenosis
LVH – left ventricular hypertrophy
LVMI – left ventricular mass index
MAG3 - mercaptoacetyltriglycine
MDRD – modified diet in renal disease
MeSH – medical subjects headings
MI – myocardial infarction
MPO – myeloperoxidase
MR – magnetic resonance
MRA – magnetic resonance angiography
MVD – macrovascular disease
MWU – Mann-Whitney U
NGAL – neutrophil gelatinase-associated lipocalin
NHS – National Health Service
NR – not reported
NSF – nephrogenic systemic fibrosis
NRI – net reclassification index
NT-proBNP – N-terminal prohormone of brain natriuretic peptide
OD – optical density
OPG – osteoprotegerin
P_a – aortic pressure
PCR – protein creatinine ratio
P_d – distal pressure
Pd – pressure distal to stenosis
PSV – peak systolic velocity
PTH – parathyroid hormone
PTRA – percutaneous transluminal renal angioplasty
PTRAS – percutaneous transluminal renal angioplasty and stenting
PV – parenchymal volume
PVD – peripheral vascular disease
Q – maximal blood flow
Q_m – normal maximal blood flow
R – renal microvascular resistance
RAAS – renin angiotensin aldosterone system
RAO – renal artery occlusion
RAB – renin angiotensin blockade
RAR – renal aortic ratio
RAS – renal artery stenosis
RAS-CAD – stenting of renal artery stenosis in coronary artery disease study
RCT – randomized controlled trial
RF – renal failure
RI – resistance index
RMG – resting mean gradient
ROC – receiver operating characteristic
RR – relative risk
RRAS – Right renal artery stenosis
RRT – renal replacement therapy
RVH – renovascular hypertension
SBP – systolic blood pressure
sCR – serum creatinine
SK-GFR – single kidney glomerular filtration rate
SPSS – statistical package for the social sciences
STAR study – stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function study
VC – variation coefficients
$X^2$ - Chi square test
Chapter 1 - Introduction
1.1 Atherosclerotic renovascular disease – epidemiology, pathophysiology and current challenges

Preface:
This introductory chapter defines atherosclerotic renovascular disease (ARVD) and illustrates the epidemiology, pathophysiology and the different clinical presentations of this condition. Treatment recommendations for this condition are discussed in light of the results of recent large randomized controlled trials (RCTs). Important clinical unmet needs and challenges faced by clinicians managing this condition are also highlighted.

Introduction:
Atherosclerotic renovascular disease (ARVD) refers to atheromatous stenoses of one or both renal arteries and as expected, occurs more frequently with increasing age and in the presence of cardiovascular risk factors such as diabetes, smoking and hypertension. Although ARVD is very often asymptomatic and usually discovered incidentally during investigation for extrarenal atherosclerotic disease, in some patients it can present with florid symptoms of cardiovascular instability or rapidly deteriorating renal function, and is a frequent cause of significant morbidity and mortality\(^1\).

The heterogenous nature of this condition poses a significant diagnostic and management dilemma to the physician. Despite significant progress in imaging techniques, accurate determination of the functional significance of a stenosis remains difficult. In addition, percutaneous revascularization carries a risk of complications and does not guarantee improved outcomes. Recent large prospective trials in ARVD have shown that revascularization does not confer any added benefit to optimal medical therapy in unselected populations and this has led to an overall decline in the number of revascularization procedures performed\(^2,3\). However, there is observational evidence that subgroups of patients with a ‘high-risk’ phenotype such as those patients presenting with recurrent flash pulmonary oedema, refractory hypertension or rapidly declining renal function, do benefit from revascularization\(^4\). Identifying these patients in a timely manner remains a considerable challenge.

Pathogenesis:
Atherosclerotic renovascular disease typically occurs in the context of systemic atherosclerosis and the inflammatory milieu that accompanies this condition. As expected, risk factors for this condition include smoking, diabetes, hypertension and a genetic predisposition to atheromatous disease\(^5\).

The exact degree of stenosis that defines significant renal artery stenosis (RAS) is still a matter of debate amongst clinicians. Historically, cross-sectional or two-dimensional RAS of more than 50% on invasive angiography was sufficient to establish a diagnosis of ARVD. Studies using
latex casts and haemodynamic measurements however suggested that detectable hypoxia only occurs at a stenosis of 70-80% on two-dimensional invasive angiographic imaging. This is in keeping with improved understanding of renal physiology; renal blood flow is in excess of the metabolic needs of the kidney and complex autoregulation mechanisms can support renal metabolism over a wide range of renal blood flow and perfusion pressures. Both animal and human studies have in fact shown that a reduction in renal blood flow sufficient to cause activation of the renin-angiotensin system is still associated with well-preserved tissue oxygenation and stable cortico-medullary oxygen gradients. However, it is thought that more severe or prolonged vascular occlusion can overwhelm these adaptive mechanisms and activate an inflammatory cascade, which culminates in microvascular rarefaction and irreversible renal fibrosis.

Analysis of venous blood draining from stenosed kidneys reveals significantly higher levels of pro-inflammatory mediators such as monocyte chemoattractant protein-1 (MCP-1), interleukin-6 (IL-6), interferon-gamma (IFN-γ), and tumour necrosis factor-alpha (TNF-α) compared to kidneys from patients with essential hypertension, despite similar blood pressure control and renin-angiotensin system blockade. These cytokines mediate ‘homing’ of inflammatory cells such as macrophages, B- and T-lymphocytes within the renal parenchyma, leading to matrix accumulation, collagen deposition, microvascular rarefaction and irreversible renal fibrosis. Blood from non-stenosed contralateral kidneys also demonstrates elevated cytokine levels although to a lesser extent than the stenosed side, suggesting that even in unilateral RAS, both kidneys are at risk of parenchymal inflammation and remodelling.

Irreversible renal parenchymal remodeling, in conjunction with target organ injury from systemic insults typically associated with ARVD, such as chronic hypertension, diabetes and increasing age, are thought to underpin the neutral results of RCTs. Indeed, restoration of arterial patency was not associated with improved clinical outcomes in the majority of patients recruited into these studies. In contrast, revascularization leads to ‘cured’ hypertension or improved blood pressure control in up to 86% of patients with fibromuscular dysplasia. These patients are characteristically younger, with few, if any, systemic co-morbidities hence the post-stenotic renal parenchyma is usually relatively intact.

As described in more detail below, another potential reason for the lack of positive response to revascularization reported in RCTs is that a large proportion of recruited patients did not have haemodynamically-significant stenoses. The actual haemodynamic and functional significance of a stenosis is difficult to determine from two-dimensional visual estimation, as this does not take into account three-dimensional flow patterns, plaque geometry or collateral circulation. Invasive renal angiography is nowadays rarely used to diagnose or risk stratify ARVD and patients almost invariably undergo non-invasive renal artery imaging, namely computed tomographic imaging (CTA) or magnetic resonance imaging (MRA). Although as described in Chapter 1.3 these imaging techniques are highly sensitive and specific, studies have shown...
that non-invasive two-dimensional imaging can overestimate the degree of stenosis\textsuperscript{15,18,19}. Novel imaging techniques such as multi-parametric magnetic resonance imaging may potentially have a role in establishing functional significance in the future\textsuperscript{19}.

For the purpose of this thesis, we have considered the combination of the two-dimensional cut-off of >70% RAS on CTA or MRA and clinical presentation with at least one ‘high-risk’ feature (uncontrolled hypertension, rapidly deteriorating renal function or flash pulmonary oedema) as diagnostic of haemodynamically-significant ARVD. Expert consensus statements in fact recognize that revascularization may be ‘appropriate’ in these individuals, although stenosis severity was sometimes determined invasively in the studies underpinning these recommendations\textsuperscript{17,20}. None of the patients recruited into our observational studies underwent invasive physiological tests to determine haemodynamic significance of RAS, in keeping with routine clinical practice. Moreover, we believe that the definition of ‘clinically significant’ RAS cannot be limited to the degree of anatomical RAS. Atherosclerotic renovascular disease is a very complex condition that does not exist in isolation, and even RAS of 50% can be associated with a three-fold increased risk of death\textsuperscript{21} and a four-fold-increased risk of cardiovascular events\textsuperscript{22}, hence, as discussed below, there is a need for more accurate risk stratification for patients with this condition.

**Epidemiology**

The true incidence and prevalence of ARVD are unknown, due to variable definitions, use of different imaging modalities and fluctuating enthusiasm in investigation for this condition. Estimates of the prevalence of ARVD also vary depending on the type of population studied (Table 1.1.1). A sub-study from the Cardiovascular Health Study from the US, showed that up to 6.8% of healthy people aged over 65 years were found to have clinically silent ARVD\textsuperscript{23}. However, the majority of epidemiological studies in ARVD have been carried out in populations enriched with documented systemic atherosclerosis or cardiovascular risk factors; prevalence rates in these patients are much higher, although the presence of ARVD does not imply functional significance and commonly represents an incidental finding in patients with widespread atherosclerosis. Indeed, incidental ARVD has been reported in up to a quarter of patients with peripheral vascular disease and in a third of patients with abdominal aortic aneurysms\textsuperscript{24}. As expected, patients with ARVD usually have evidence of other macrovascular disease such as coronary (67%), peripheral arterial (56%) and cerebrovascular atherosclerotic disease (37%)\textsuperscript{5}.

Although there is a paucity of modern epidemiological studies in ARVD, there is a strong suggestion that the incidence and prevalence of this condition have evolved significantly over the past few years. Administrative insurance claims data report a three-fold increase in diagnosis between 1992 and 2004; this may reflect both an increasingly ageing population with a greater atherosclerotic burden and increased accessibility to non-invasive imaging in
Table 1.1.1 Major studies published since 2000 investigating the prevalence of ARVD in different patient groups (adapted from 24,25)

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Author, year</th>
<th>Study population</th>
<th>Mean Age in years +/- SD</th>
<th>Diagnostic method</th>
<th>RAS definition</th>
<th>Prevalence RAS, N/Sample size (%)</th>
<th>Factors associated with presence of ARVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Population</td>
<td>Lorenz, 201026</td>
<td>Potential living kidney donors</td>
<td>43.0 +/- 12.0</td>
<td>CTA</td>
<td>-</td>
<td>103/1957 (5.3%)</td>
<td>-</td>
</tr>
<tr>
<td>Tolkin, 200927</td>
<td>Consecutive patients undergoing abdominal CT for investigation of non-renal abdominal pathology</td>
<td>61.0 +/- 13.0</td>
<td>CTA</td>
<td>&gt;50% stenosis</td>
<td>10/350 (2.9%)</td>
<td>Increasing age, male gender, hypertension and hypercholesterolaemia were strongly associated with renal artery calcification (RAC). The severity of RAC correlated significantly with the degree of RAS (r=0.7).</td>
<td></td>
</tr>
<tr>
<td>Hansen, 200223</td>
<td>Healthy elderly volunteers</td>
<td>77.0 +/- 5.0</td>
<td>Doppler ultrasound</td>
<td>Renal peak systolic velocity &gt;1.8m/s</td>
<td>57/834 (6.8%)</td>
<td>Increasing age, increasing systolic blood pressure, decreased HDL-C</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>Postma, 201228</td>
<td>Diabetes mellitus and hypertension</td>
<td>59.0 +/- 8.5</td>
<td>MRA</td>
<td>&gt;50% stenosis</td>
<td>18/54 (33%)</td>
<td>Dyslipidaemia, baseline diastolic blood pressure, lower renal function at baseline</td>
</tr>
<tr>
<td>Vasbinder, 200429</td>
<td>Diastolic blood pressure &gt;95mmHg and suspected RAS</td>
<td>52.0 +/- 12.0</td>
<td>DSA as gold standard</td>
<td>&gt;50% stenosis</td>
<td>45/356 (12.6%)</td>
<td>12/356 (3.4%) - bilateral &gt;50%</td>
<td>-</td>
</tr>
<tr>
<td>Reference</td>
<td>Condition</td>
<td>SBP/DBP or Antihypertensive Drugs</td>
<td>Study Method</td>
<td>Stenosis</td>
<td>Findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>-----------</td>
<td>----------------------------------</td>
<td>--------------</td>
<td>----------</td>
<td>----------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Jaarsveld, 2001&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Therapy-resistant hypertension</td>
<td>51.2 +/- 12.4</td>
<td>DSA</td>
<td>&gt;50% stenosis</td>
<td>89/439 (20.3%) 20/439 (4.6%) - bilateral &gt;50% stenosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valabhji, 2000&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Diabetes mellitus and hypertension (SBP &gt;160mmHg or DBP &gt;90mmHg or use of antihypertensive drugs)</td>
<td>61 (56-65)</td>
<td>MRA</td>
<td>&gt;50% stenosis</td>
<td>20/117 (17.1%) 1/117 (0.9%) - bilateral &gt;50% stenosis Clinical features of atherosclerotic disease were not statistically associated with presence of RAS. Femoral bruit was predictive of RAS.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Courreges, 2000&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Diabetes mellitus and severe hypertension (treatment with &gt; 3 antihypertensive drugs)</td>
<td>N/a</td>
<td>Arteriography or MRA</td>
<td>&gt;70% stenosis</td>
<td>34/208 (16.3%) Male gender, smoking, insulin requirement, decreased reanal function, severe hypertension, extrarenal macrovascular disease.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Disease Ollivier, 2009&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Consecutive patients undergoing CAG and renal angiography</td>
<td>67.0 +/- 10.0</td>
<td>Angiography</td>
<td>&gt;50% stenosis</td>
<td>94/650 (14.5%) 20/650 (3.1%) - &gt;50% bilateral Male sex, multi-vessel coronary artery disease, hypertension, renal insufficiency.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dzielinska, 2007&lt;sup&gt;34&lt;/sup&gt;</td>
<td>CAG and hypertension (&gt;140/90mmHg or current anti-hypertensive)</td>
<td>59.8 +/- 9.6 (RAS) 56.6 +/- 9.5</td>
<td>Angiography</td>
<td>&gt;50% stenosis</td>
<td>40/333 (12.0%) 8/333 (2.5%) - bilateral &gt;50% Higher carotid intima-media thickness (IMT), more coronary arteries stenosed, higher serum creatinine concentration, lower BMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Study Details</td>
<td>Baseline Data</td>
<td>Procedure</td>
<td>Stenosis Criteria</td>
<td>Findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>---------------</td>
<td>-----------</td>
<td>-------------------</td>
<td>--------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Silva, 2007 &lt;sup&gt;35&lt;/sup&gt;</td>
<td>Chronic heart failure (ejection fraction &lt;40%)</td>
<td>70.0 +/- 1.0</td>
<td>MRA</td>
<td>&gt;50% stenosis</td>
<td>Higher doses of diuretics, lower doses of Angiotensin converting enzyme inhibitors, prolonged hospital admission, admitted with heart failure exacerbations, higher mortality.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohen, 2005 &lt;sup&gt;36&lt;/sup&gt;</td>
<td>Consecutive patients undergoing CAG and abdominal aortography</td>
<td>64 (55-73)</td>
<td>Angiography</td>
<td>≥75% stenosis</td>
<td>Older age, higher creatinine levels, peripheral vascular disease, number of cardiovascular drugs, hypertension, female sex, three-vessel coronary artery disease or previous coronary artery bypass graft.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rigatelli, 2005 &lt;sup&gt;37&lt;/sup&gt;</td>
<td>CAG with one of the following criteria: at least one vessel CAD, severe or resistant HT, abnormal abdominal pulsation or murmur, unexplained kidney dysfunction, flushing pulmonary</td>
<td>67.1 +/- 12.8</td>
<td>Angiography</td>
<td>≥50% stenosis</td>
<td>≥3 vessel coronary artery disease, age &gt;65 years and ≥ 3 cardiac risk factors (hypercholesterolaemia, hypertension, diabetes, smoking)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buller, 2004\textsuperscript{38}</td>
<td>CAG with severe HT and/or unexplained renal dysfunction and/or acute pulmonary edema and/or severe atherosclerosis</td>
<td>67.9 +/- 9.9</td>
<td>Angiography</td>
<td>≥50% stenosis</td>
<td>120/837 (14.3%)</td>
<td>Age, female gender, reduced creatinine clearance, increased systolic blood pressure, and peripheral or carotid artery disease.</td>
<td></td>
</tr>
<tr>
<td>Liu, 2004\textsuperscript{39}</td>
<td>Consecutive patients undergoing CAG</td>
<td>66.4 +/- 7.8 (RAS)</td>
<td>Angiography</td>
<td>≥50% stenosis</td>
<td>24/141 (18.4%)</td>
<td>Three-vessel coronary artery disease, hypertension, renal impairment, hyperlipidaemia, hypokalaemia.</td>
<td></td>
</tr>
<tr>
<td>Park, 2004\textsuperscript{40}</td>
<td>Consecutive patients undergoing CAG</td>
<td>63.2 +/- 8.5 (RAS)</td>
<td>Angiography</td>
<td>≥50% stenosis</td>
<td>158/1459 (10.8%)</td>
<td>Extracranial carotid artery stenosis, peripheral artery disease, renal insufficiency, significant coronary artery disease, hypercholesterolemia,</td>
<td></td>
</tr>
<tr>
<td>Study (Year)</td>
<td>Criteria</td>
<td>Mean Age (SD)</td>
<td>Procedure</td>
<td>Stenosis</td>
<td>Results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>----------</td>
<td>--------------</td>
<td>-----------</td>
<td>----------</td>
<td>---------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Khosla, 2003&lt;sup&gt;41&lt;/sup&gt;</td>
<td>CAG with refractory HT (BP&gt;140/90mmHg on 2 drugs) or flash pulmonary oedema</td>
<td>62.5 +/- 12.1</td>
<td>Angiography</td>
<td>&gt;70% stenosis</td>
<td>101/534 (18.9%) - 26/534 (4.9%) – bilateral &gt;70% stenosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aqel, 2003&lt;sup&gt;42&lt;/sup&gt;</td>
<td>CAG and hypertension (SBP &gt;135mmHg)</td>
<td>65.3 +/- 9.4</td>
<td>Angiography</td>
<td>≥50% stenosis</td>
<td>25/90 (27.8%) - 9/90 (10%) – bilateral ≥50% stenosis - 14/90 (16%) – unilateral ≥70% stenosis - 5/90 (6%) – bilateral ≥70% stenosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang, 2003&lt;sup&gt;43&lt;/sup&gt;</td>
<td>CAG in patients with confirmed coronary artery disease</td>
<td>65.1 +/- 10.2</td>
<td>Angiography</td>
<td>≥50% stenosis</td>
<td>34/230 (14.8%) - 6/230 (2.6%) – bilateral ≥50% stenosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Hypertension, increasing age.**
<table>
<thead>
<tr>
<th>Source</th>
<th>Study Design</th>
<th>Mean Age ± SD</th>
<th>Procedure</th>
<th>&gt;50% Stenosis</th>
<th>&gt;70% Stenosis</th>
<th>Bilateral &gt;50% Stenosis</th>
<th>Unilateral RAS &gt;70%</th>
<th>Additional Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rihal, 2002&lt;sup&gt;44&lt;/sup&gt;</td>
<td>CAG and HT (treatment with ≥1 antihypertensive drug of BP &gt;140/90mmHg)</td>
<td>64.9 ±10.2</td>
<td>Angiography</td>
<td>57/297 (19.2%)</td>
<td>11/297 (3.7%)</td>
<td>21/297 (7.0%)</td>
<td>11/297 (3.7%)</td>
<td>Systolic blood pressure, CVA/TIA, cancer.</td>
</tr>
<tr>
<td>Weber-Mzell, 2002&lt;sup&gt;45&lt;/sup&gt;</td>
<td>Consecutive patients undergoing CAG</td>
<td>67.0 ±8.0 (RAS)</td>
<td>Angiography</td>
<td>19/177 (10.7%)</td>
<td>5/177 (2.8%)</td>
<td>19/177 (10.7%)</td>
<td>5/177 (2.8%)</td>
<td>Low glomerular filtration rate and extent of coronary artery disease.</td>
</tr>
<tr>
<td>Yamashita, 2002&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Consecutive patients undergoing CAG</td>
<td>65.8 ±10.6</td>
<td>Angiography</td>
<td>21/289 (7.3%)</td>
<td>3/289 (1.0%)</td>
<td>21/289 (7.3%)</td>
<td>3/289 (1.0%)</td>
<td>Hypertension and coronary artery disease especially three-vessel disease</td>
</tr>
<tr>
<td>Conlon, 2001&lt;sup&gt;47&lt;/sup&gt;</td>
<td>Consecutive patients undergoing CAG</td>
<td>61 (52-69)</td>
<td>Angiography</td>
<td>362/3987 (9.1%)</td>
<td>33/3987 (0.8%)</td>
<td>362/3987 (9.1%)</td>
<td>33/3987 (0.8%)</td>
<td>Female sex, increasing age, hypertension, CCF, increased creatinine</td>
</tr>
<tr>
<td>Study</td>
<td>Patients Description</td>
<td>Age (Mean ± SD)</td>
<td>Procedure</td>
<td>Stenosis (≥50%)</td>
<td>Events</td>
<td>Risk Factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
<td>--------------------------------------------------------------------------------------</td>
<td>-----------------</td>
<td>------------</td>
<td>-----------------</td>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Song, 2000&lt;sup&gt;48&lt;/sup&gt;</td>
<td>Consecutive patients undergoing CAG</td>
<td>59.2 ±10.3</td>
<td>Angiography</td>
<td>≥50% stenosis</td>
<td>24/427 (5.6%)</td>
<td>Increasing age, hypertension, peripheral vascular disease.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amighi, 2009&lt;sup&gt;49&lt;/sup&gt;</td>
<td>Consecutive patients undergoing revascularization of symptomatic peripheral arterial disease</td>
<td>71 (63-79)</td>
<td>Angiography</td>
<td>≥60% stenosis</td>
<td>76/487 (15.6%)</td>
<td>Increased risk of major adverse events (composite of death, myocardial infarction, stroke, percutaneous coronary intervention, coronary bypass surgery, amputation and kidney failure) and increased risk of death.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Androes, 2007&lt;sup&gt;50&lt;/sup&gt;</td>
<td>Consecutive patients undergoing peripheral angiography for symptomatic PAD.</td>
<td>70.1 ±10.3 (RAS)</td>
<td>Angiography</td>
<td>&gt;50% stenosis</td>
<td>24/200 (12%)</td>
<td>Hypertension, coronary artery disease, female, diabetic, aorto-iliac disease, age, &gt;60 years, multiple levels of PVD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leertouwer, 2001&lt;sup&gt;51&lt;/sup&gt;</td>
<td>Consecutive patients who underwent angiography for suspected ischaemic PAD</td>
<td>68.8 ±9.8 (RAS)</td>
<td>Angiography</td>
<td>≥50% stenosis</td>
<td>126/386 (32.6%)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Population Description</td>
<td>Stenosis Criteria</td>
<td>Imaging Modality</td>
<td>Frequency</td>
<td>Comments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>-------------------</td>
<td>------------------</td>
<td>-----------</td>
<td>----------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iglesias, 2000^2^</td>
<td>Consecutive patients who underwent angiography for aortoiliac disease</td>
<td>&gt;50% stenosis</td>
<td>Angiography</td>
<td>53/201 (26.4%)</td>
<td>History of coronary artery disease.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Ampting, 2003^3^</td>
<td>Consecutive patients starting renal replacement therapy.</td>
<td>≥50% stenosis</td>
<td>CTA</td>
<td>20/49 (40.8%)</td>
<td>6/49 (12.2%) – bilateral ≥50% stenosis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
more recent years\textsuperscript{54}. In contrast, the advent of intensive, multi-targeted vascular protection therapy (e.g. statins, renin-angiotensin blockade) and tight cardiovascular risk factor control (e.g. lower blood pressure targets, smoking cessation campaigns) may have led to a change in the natural history of this condition. A retrospective study performed at our centre based on analysis of at least 2 renal angiograms performed over a 3-year period in 79 patients, showed that the incidence of progression of ARVD over this period of time was around 6\% compared to 30\% in the pre-statin era. Disease regression was also reported in 14 renal arteries from 12 patients (15\%) and a greater proportion of these patients were on a statin (10 patients [83\%] on a statin versus 2 patients [17\%] not on a statin, $p = 0.001$)\textsuperscript{55}. Recent trials also report a lower rate of adverse renal events (16-22\% over 40 months) or progression to ESKD (2-8\% over 40 months) in comparison to much higher rates of adverse renal events (41\% over 44 months) reported in historical literature\textsuperscript{14,15,56}. Nonetheless, the presence of ARVD is still undeniably strongly associated with mortality and this should not be overlooked; the risk of death has indeed been reported to be up to six times that of developing ESKD (incidence of death of 166 per 1000 patient years compared to 29 per 1000 patient years for ESKD)\textsuperscript{22}.

**Histological findings**

Few studies have reported the histological findings that are associated with ARVD given that renal biopsies are seldom performed in these patients. Heterogenous findings have been reported both in the stenosed and the contralateral kidney, in keeping with the complex aetiology and pathogenesis of this condition. These non-specific changes have been termed ‘atherosclerotic nephropathy’ and are characterized by interstitial fibrosis, tubular atrophy, glomerular sclerosis (including focal sclerosing glomerulosclerosis) and arteriolar hylanosis\textsuperscript{57}. Other common histological findings include hypertensive damage, diabetic changes and cholesterol atheroembolism\textsuperscript{58}. Proteinuria has been used as a surrogate marker of the degree of renal parenchymal damage; elevated levels of proteinuria at baseline have been shown to predict adverse outcomes both in revascularized patients and in those managed conservatively\textsuperscript{59}.

**Clinical Presentations**

1. Subclinical

Atherosclerotic renovascular disease is frequently ‘clinically silent’ and may only be diagnosed incidentally during coronary or peripheral angiography. Observational studies have shown that patients with subclinical ARVD have poorer clinical outcomes compared to patients with similar comorbidities but without ARVD\textsuperscript{21}.

2. Renovascular hypertension

It is reported that ARVD accounts for 2\% of all cases of hypertension but is the underlying cause of refractory hypertension (>180mmHg systolic and/or 100mmHg diastolic) in around 8\% of cases\textsuperscript{60}. This could well be an underestimation as patients with treatment resistant
hypertension are not routinely screened for ARVD. The co-existence of ARVD and hypertension does not always indicate causality as these two conditions share common risk factors. Renovascular hypertension refers to hypertension caused by RAS and subsequent activation of the renin-angiotensin system, and it can sometimes resolve with restoration of renal artery patency.

3. Ischaemic nephropathy or deterioration of Renal Function

**Chronic kidney disease (CKD)**
Most patients with ARVD are found to have relatively stable Chronic Kidney Disease (CKD). A recent observational study from our research group has noted that the overall rate of eGFR loss in ARVD is comparable to that in other causes of CKD, around 1-2ml/min/1.73m²/year. However, despite the increased use of multi-targeted vascular protective therapy, 16-22% of patients in the latest large randomized controlled trials still suffered adverse renal events in the form of severe acute kidney injury and rapid loss of renal function.

**Acute Kidney injury (AKI)**
There is little data about the proportion of patients with ARVD who present with AKI; a review of our local renovascular database estimates that less that 2% of patients may present with AKI. Acute kidney injury may develop as a complication of invasive angiography or revascularization through cholesterol embolization or contrast nephropathy, however the commonest cause of AKI in patients with ARVD is use of renin-angiotensin blockade in patients with haemodynamically significant RAS. In this scenario, the decline in glomerular filtration rate is caused by dilatation of the efferent glomerular artery which leads to a marked drop in filtration pressure across the glomerulus. This is usually reversible after stopping the medication. A rise in serum creatinine following initiation of renin-angiotensin blockade was documented in 104 patients (11.9%) out of a total of 872 in our local renal vascular database. Although observational studies have clearly shown that renin-angiotensin blockade is associated with improved survival in patients with ARVD, in line with its positive effects on cardiac outcomes in the cardiovascular population, there is still a degree of reticence amongst clinicians in prescribing these medications in this patient population due to the potential risk of AKI. Renin-angiotensin blockade is considered the anti-hypertensive medication of choice in ARVD however close monitoring of renal function is required after initiation of this medication especially in patients with bilateral severe ARVD or severe RAS affecting a solitary functioning kidney. In general, a rise in creatinine of more than 30% or a decline in glomerular filtration rate of > 25% in the absence of dehydration or concurrent nephrotoxic medication should prompt a decrease in dose of RAB to a previously tolerated level or the RAB should be stopped altogether.

4. Heart Failure
Atherosclerotic renovascular disease and cardiovascular disease frequently co-exist due to shared risk factors. Up to two thirds of patients with atherosclerotic renovascular disease have concurrent coronary artery disease (CAD) while renal artery stenosis has been reported in around 11-20% of patients who have undergone coronary angiography for investigation of CAD. Besides this close association between ARVD and ischaemic heart disease, most patients with ARVD also suffer cardiac dysfunction due to cardiac remodeling. Indeed, in a study looking at echocardiographic characteristics for 79 patients with ARVD, only 5% of patients with ARVD had structurally normal hearts. This cardiac remodeling is driven both by hypertension which is highly prevalent in ARVD patients, and also by the neurohormonal activation which characterizes haemodynamically significant ARVD. Activation of the renin-angiotensin system culminates in production of angiotensin II which besides augmenting hypertension through its potent vasoconstrictive effects and increased reabsorption of salt and water, can stimulate production of pro-fibrotic growth factors within the myocardium. This leads to cardiac remodelling which can present in two different ways:

**Acute pulmonary oedema (Flash pulmonary oedema):**
This is thought to be caused by a rapid increase in end-diastolic left ventricular pressure in patients with poorly-compliant, hypertrophied ventricles. Flash pulmonary oedema can be the presenting feature in up to 10% of patients with ARVD and typically occurs in patients with bilateral severe ARVD or severe ARVD to a single functioning kidney as these patients have impaired pressure natriuresis. As described in more detail below there is observational evidence that these patients may benefit from revascularization and it has attracted the only American Heart Association Class I recommendation for revascularization.

**Chronic heart failure**
Some studies suggest that around half of elderly patients with chronic heart failure have renal artery stenosis >50% while one-third of patients with known ARVD have symptoms of heart failure. Uncontrolled studies and retrospective case series have suggested that revascularization may improve outcomes in these patients, however these results have not been replicated in randomized controlled trials hence the role of revascularization in this patient subset is unclear.

**Diagnosis of ARVD**
Development of new imaging techniques has shifted focus from a two-dimensional evaluation of stenosis severity to a more functional approach which takes the haemodynamic severity of a stenosis and the potential viability of the post-stenotic renal parenchyma into account. None of these novel techniques are yet available in routine clinical practice; however, the final aim is to help identify those patients with critical degrees of stenosis who may benefit from renal revascularization. These different diagnostic modalities are discussed in detail in Chapter 1.3.
Management of ARVD

Medical treatment
Atherosclerotic renovascular disease is invariably associated with systemic atherosclerosis. In view of this, tight atherosclerotic risk factor control, such as smoking cessation and target-level driven control of blood pressure and glycaemic levels in diabetic patients, together with intensive multi-targeted vascular protective therapy should form the mainstay of treatment for all patients with this condition. The role of vascular protective therapy in mitigating adverse outcomes in patients with ARVD is not as well-validated as in the cardiovascular population, but evidence from observational studies has persistently pointed towards important benefits. The pleiotropic effects of statins extend beyond reduction in lipid levels and they have been shown to be associated with better patient survival (HR 0.131 [0.039-0.438], p=0.001) and renal survival (HR 0.211 [0.070-0.637], p=0.006)\textsuperscript{73}, together with reduced risk of disease progression (RR 0.28 [0.10-0.77])\textsuperscript{55}. As mentioned above, concerns about the risk of AKI with use of renin-angiotensin blockade in patients with ARVD has led to underutilization of this important medication in this patient cohort. Evidence from two separate observational studies shows that renin-angiotensin blockade is associated with reduced risk of death (HR 0.61 [0.40-0.91], p=0.02)\textsuperscript{64} and improved survival (HR 0.24 [0.08-0.71], p=0.0098)\textsuperscript{63}. Renin-angiotensin blockade helps mitigate intra-renal parenchymal injury, decrease degree of proteinuria and improve renal outcomes while conferring important cardio-protection in a patient population that is particularly enriched with cardiovascular disease. Data published previously from our Salford Renovascular Study has also revealed a reduced risk of death with anti-platelet agents (RR 0.52 [0.31-0.89], p=0.02) and beta-blockers (RR 0.45 [0.21-0.97], p=0.04)\textsuperscript{80}.

Renal Revascularization
A number of studies have been carried out over the past decades to determine whether restoration of renal artery patency by renal revascularization confers any added benefit to medical therapy. A meta-analysis of 3 small RCTs, included 210 patients randomized to either percutaneous transluminal angioplasty (mostly without stenting) or medical therapy, with change in blood pressure control as the primary end-point. Results showed that revascularization did not improve blood pressure or renal function outcomes, although there was a suggestion that patients with bilateral disease had better blood pressure control post-intervention\textsuperscript{81-83}. Only a minority of these patients underwent stenting, which has en shown to be a technically superior intervention to angioplasty on its own\textsuperscript{84}. A subsequent study, the STAR trial, randomized 140 patients to either medical therapy only or in conjunction with angioplasty and stenting. Primary end-point was change in creatinine clearance over 24 months. This study again showed that revascularization did not exert any further benefit when compared to medical therapy\textsuperscript{18}. It is noteworthy that all these studies highlighted the considerable risks that are associated with revascularization. The STAR trial quoted a
periprocedure mortality rate of 3% and the prevalence of more commonly occurring complications in contemporary clinical practice is around 0.5-10% (Textbox 1.1.1).85

Textbox 1.1.1 Complications post-endovascular renal revascularization85,86

- Groin haematoma
- Renal artery dissection
- Cholesterol embolization
- Renal artery Rupture
- Contrast-medium induced nephropathy
- Aortic dissection

These small studies were followed by two large, landmark RCTs which provide the most robust data regarding the role of renal revascularization in the management of patients with ARVD.

The UK-based Angioplasty and stent for renal artery lesions (ASTRAL) trial randomized 806 patients with ARVD to either medical therapy alone or in conjunction with revascularization. The primary end-point was change in renal function from baseline. Patients were included in the trial if they had ‘substantial’ renal artery stenosis on at least one side and the managing clinician was ‘uncertain’ whether revascularization would provide benefit. This inclusion criterion was the main point of criticism as there were no clear criteria for revascularization and the haemodynamic significance of the stenoses was not assessed. Indeed, out of the study population, 40% were found to have low-grade stenosis (50-70%) at angiography and 17% of patients randomized to stenting did not receive the intervention as there was no identifiable stenosis. After a median follow-up of 34 months, results showed that revascularization had no impact on decline in renal function nor on blood pressure control, incidence of cardiovascular events or mortality (secondary end-points). Revascularization was also associated with a complication rate of 6.8%.14 More recently, the results of a cardiac magnetic resonance sub-study performed in 44 patients recruited into ASTRAL have been published. Cardiac magnetic resonance was performed at recruitment and before revascularization in the intervention group (n=22) and compared with repeat CMR after 12 months. Over this period of time, there was improvement in left ventricular structural parameters in both arms, possibly due to the effect of modern cardioprotective therapy, however there was no significant difference between the two treatment arms.18 These results echo those of a previous Italian study which investigated the effect of revascularization on left ventricular mass index using serial echocardiography in 84 patients with both ARVD and coronary artery disease over the same time period. There was overall improvement in LVMI in both arms, however revascularization did not exert any added benefit77. Patients with severe ARVD or those with acute heart failure were not recruited into either of these studies.
The US-based Cardiovascular outcomes in Renal Atherosclerotic lesions (CORAL) trial randomized 947 patients to either stenting and best medical therapy or best medical therapy alone. The primary end-point was a composite of major cardiovascular events, progressive deterioration in renal function and death from cardiovascular or renal causes. The initial design of CORAL aimed to overcome the flaws that were observed in ASTRAL; only patients with haemodynamically confirmed severe renal artery stenosis and a systolic BP of 155 mmHg or higher despite use of at least 2 antihypertensive agents were originally intended to be recruited. The degree of stenosis was standardized by means of an angiographic ‘core lab’ evaluation and trans-lesional gradient measurement, and severe stenosis was defined as either at least 80% but less than 100% angiographic stenosis or 60-80% stenosis with a trans-lesional systolic pressure gradient of at least 20 mmHg. However, these inclusion criteria had to be relaxed due to slow patient recruitment, but core laboratory criteria were maintained for patient inclusion. By the end of the study average angiographic stenosis was 67%, similar to that in ASTRAL, and only 20% of patients had >80% stenosis. After a median follow-up of 43 months, revascularization did not confer any clinical benefit over medical therapy on its own\(^15\).

**Current Challenges**

*All patients with ARVD should receive adequate multi-targeted vascular protective treatment:* Given the reduction in revascularization procedures performed worldwide following the results of recent RCTs\(^3\), the focus of management of ARVD has shifted onto medical therapy. The multi-targeted treatment regimen used in the CORAL study, consisting of an angiotensin-receptor blocker, statin, antiplatelet agent and goal-oriented treatment of hypertension and diabetes, led to surprisingly good cardiovascular and renal outcomes despite the participants advanced age and significant burden of co-morbidities\(^15\). However, the ‘optimal’ medical therapy regime for patients with ARVD remains to date undefined, and recent data from CORAL confirms that there is still a lot of geographical variability in prescribing tendencies\(^87\). There also appears to be a ‘treatment bias’ as patients who are already known to have documented coronary or cerebrovascular atherosclerotic disease are more likely to be established on adequate vascular protective treatment compared to patients with ARVD who do not have documented extra-renal atherosclerosis. An observational study comparing two prospective cohorts of patients with ARVD, one based in the UK and the other one in Germany, revealed that prescription of statins and renin-angiotensin blockade was much higher in the German cohort, as this cohort was mostly composed of patients who were referred for renal artery imaging following diagnosis of concurrent or suspected coronary artery disease\(^88\). Data from this thesis shows that although there is increased awareness about the importance of vascular protection in patients with systemic atherosclerosis, more effort is required to ensure all patients with ARVD are uniformly prescribed this important therapy.

*Development of non-invasive techniques for risk stratification:*
As explained in Chapter 1.3, the interest in diagnostic imaging in ARVD has shifted from simple anatomical evaluation of stenosis severity to a more functional approach, which aims to determine the haemodynamic significance of a stenosis and the viability of the post-stenotic renal parenchyma. Although none of the randomized controlled trials have shown that revascularization plays a beneficial role in the management of ARVD, these studies have recruited a large proportion of relatively stable patients, many with well-preserved kidney function (e.g., average eGFR at recruitment in CORAL was 58ml/min/1.73m²) leading to an under-representation of patients with uncontrolled hypertension, rapidly deteriorating renal function or recurrent flash pulmonary oedema. Patients with these ‘high-risk’ features are more likely to have underlying ‘critical’ or haemodynamically-significant ARVD. A recent observational retrospective study conducted at our research centre looked at 237 patients with at least 50% RAS and one or more of the above ‘high-risk features. Around one-quarter (24%) of these patients underwent revascularization and clinical outcomes for this subset of patients were compared to those of similar patients who were treated exclusively medically. Results showed that revascularization was associated with improved outcomes in patients with either flash pulmonary oedema or in those with a combination of rapidly declining kidney function and uncontrolled hypertension. Previous work from our research group has forged the concept of ‘hibernating parenchyma’, that is, viable renal parenchyma that has not yet undergone the irreversible changes associated with ARVD and hence retains the possibility to recover function post-revascularization. These kidneys have been shown to exhibit a higher magnetic resonance-measured renal volume to isotopic glomerular filtration rate ratio than kidneys that do not respond positively to revascularization.

The heterogeneous nature of ARVD demands accurate risk stratification of patients to allow a more patient-centred approach to treatment. It is hoped that the novel functional imaging techniques described in Chapter 1.3 will enable characterization of functional significance of RAS and renal parenchyma; however, these modalities are still in an experimental phase, hence there is an urgent need for clinical risk prediction scores based on easily obtainable parameters to help identify patients who may gain benefit from revascularization in a timely manner.

The role of novel therapeutic strategies:

It is important to note that despite the overall improved clinical outcomes in patients with ARVD that have occurred in recent years, probably a product of tighter cardiovascular risk control and optimized medical therapy, 16-22% of patients in both ASTRAL and CORAL still suffered adverse renal end-points irrespective of treatment arm. As explained above, chronic activation of the renin-angiotensin system, oxidative stress and the co-existent atherosclerotic inflammatory milieu that characterize ARVD can overwhelm the kidneys’ adaptive response to hypoperfusion, leading to irreversible endothelial injury, microvascular rarefaction, and renal
fibrosis\textsuperscript{90,91}. In addition, persistent activation of these pro-inflammatory and pro-fibrotic pathways also lead to myocardial injury and remodeling leading to poor cardiovascular outcomes in these patients\textsuperscript{92}.

Besides adding further weight to the importance of administering renin-angiotensin blockade and statins in patients with ARVD, given their potential to attenuate these inflammatory pathways, these research findings highlight the need for development of novel adjuncts to revascularization or conservative medical therapy that may help mitigate irreversible tissue injury and optimize clinical outcomes\textsuperscript{12}. Some experimental strategies include targeting mitochondrial injury, which appears to play a major role in mediating both renal and cardiac remodeling in ARVD, and infusion of vascular growth factors, endothelial progenitor cells or mesenchymal stem cells to stimulate angiogenesis and modulate the inflammatory milieu\textsuperscript{92–95}.

\textit{Creation of an international ARVD registry:}

In light of the neutral results of recent large RCTs, it is unlikely that further RCTs evaluating the role of revascularization in the management of ARVD will be carried out in the near future, exacerbating the declining interest in this intervention. Nonetheless, it is anticipated that the prevalence of ARVD will continue to rise in parallel with the increasing population age and burden of atherosclerotic co-morbidities. While conservative management may be the appropriate approach for the majority of patients with ARVD, reduced interest in establishing the diagnosis of ARVD and referral for revascularization may lead to a risk of missing the opportunity of successful revascularization in the small subgroup of patients who present with the ‘high-risk’ features mentioned above. It is also likely that revascularization may be of benefit in other patients subgroups who were also underrepresented in large RCTs, such as those with chronic heart failure\textsuperscript{72–75} or bilateral severe ARVD\textsuperscript{82,83}.

These issues highlight the need for an international ARVD registry. This would encourage active collaboration between clinicians and researchers to help address important unanswered questions relating to management of ARVD. Patient recruitment onto a registry is not affected by restrictive inclusion or exclusion criteria and clinicians are not bound to adhere to a single treatment protocol, hence a registry would provide an opportunity to evaluate the ‘real-world’ outcomes of an intervention. Indeed, the creation of an international ARVD registry would increase the knowledge base about the natural history of this condition while shedding more light on the clinical and cost-effectiveness of revascularization in specific patient subgroups\textsuperscript{96}.

\textbf{Conclusion}

Atherosclerotic renovascular disease is a heterogenous condition with variable clinical outcomes in different patients. While optimized medical vascular therapy remains the undeniable cornerstone of management of this condition, new information about the complex
pathophysiology of this condition highlights the importance of a more individualized and patient-centred approach. It is hoped that novel diagnostic and risk stratification techniques will help identify patients who may potentially benefit from revascularization whilst avoiding this potentially hazardous intervention in others.
References:


15. Cooper CJ, Murphy TP, Cutlip DE, et al. Stenting and medical therapy for


42. Aqel R a, Zoghbi GJ, Baldwin S a, et al. Prevalence of renal artery stenosis in high-risk


68. Wright JR, Shurrab AE, Cooper A, Kalra PR, Foley RN, Kalra PA. Left Ventricular


1.2 Progress in the treatment of atherosclerotic renovascular disease – the conceptual journey and the unanswered questions

Diana Vassallo, Philip A. Kalra
DOI: 10.1093/ndt/gfv278.

Preface:
This chapter takes a historical perspective and examines how management of ARVD has been influenced by studies published over the past three decades. A review of the English literature was performed by searching the databases of PUBMED, EMBASE, MEDLINE and COCHRANE library from the January 1934 through March 2017 using the Medical Subjects Headings (MeSH) and keywords: ‘atherosclerotic renovascular disease’, ‘atherosclerotic renal artery stenosis’, ‘renal artery stenosis’ and ‘revascularization’. A total of 396 hits were provided through the search engines. A manual search was also performed on the reference lists of all pertinent articles for additional citations that might not have appeared in the initial database search. Case series, observational studies, clinical trials as well as case reports that had an important impact on the history of ARVD management were considered and in total 51 papers were included in this review. The studies included in this review were conducted in different eras, so the methodology employed changed over time. This resulted in significant heterogeneity between studies, with lack of raw data in the older papers, hence it was not possible to use data pooling techniques such as a meta-analysis.

Abstract:
Over the past decades, management of atherosclerotic renovascular disease (ARVD) has undergone significant progress, in parallel with increased knowledge about the complex pathophysiology of this condition. Modern multi-targeted medical management of atherosclerosis has driven a change in both the natural history and the clinical outcomes of ARVD. Progression to total renal artery occlusion is a much less common occurrence and while early studies have reported that up to 41% of patients reached renal end-points over a mean follow-up of 44 months, the latest randomized controlled trials have shown that progressive renal impairment occurs in 16-22% of patients, with less than 8% of patients reaching end-stage kidney disease (ESKD) over a similar time-frame. However, the results of the latest large ARVD trials investigating the effect of renal stenting upon clinical outcomes have been influenced by selection bias as high-risk patients with clinically significant renal artery stenosis (RAS) have largely been excluded from these studies. Although the neutral results of these trials have sown uncertainty about the role of revascularization in the management of patients with ARVD, there is evidence that revascularization can optimize outcomes in selected patients.
with a high-risk clinical phenotype. Future challenges lie in identifying important subgroups of patients with critical RAS and viable kidneys, while continuing to develop strategies to protect the renal parenchyma and hence improve clinical outcomes.

**Introduction:**
The management of atherosclerotic renovascular disease (ARVD) has undergone significant changes over the years, in parallel with increased understanding of this condition. Neutral results of recent large randomized controlled trials (RCTs) have dampened interest in revascularization and there is emerging evidence that contemporary management of atherosclerosis has improved both the natural history and clinical outcomes of ARVD. There is however ample evidence that revascularization still plays an important role in the management of patients with high-risk phenotypes who may not have been adequately represented in RCTs. Accurate identification of these individuals remains a considerable challenge.

Here we critically review selected studies related to management of ARVD that have been performed over the past few decades and illustrate how the clinical outcomes of ARVD have evolved in tandem with significant progress in both the medical treatment of atherosclerosis and revascularization techniques. The progress is depicted with key historic milestones as shown in Table 1.2.1.

**Table 1.2.1 Milestones in the history of management of ARVD.**

<table>
<thead>
<tr>
<th>Era</th>
<th>Management of ARVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1930’s</td>
<td>Experimental RAS caused renal ischaemia and systemic hypertension. Renovascular hypertension was reversed by unilateral nephrectomy.</td>
</tr>
<tr>
<td>1960’s</td>
<td>Complex surgical revascularization techniques were developed to spare renal tissue given that renal angiography showed that ARVD was often a bilateral disease. Surgical revascularization however had limited success and was associated with a high mortality rate while improved pharmacological blood pressure control was noted to correlate with improved survival.</td>
</tr>
<tr>
<td>1980’s-1990’s</td>
<td>Adequate pharmacological blood pressure control did not always prevent loss of renal function and ACEi were associated with AKI especially in patients with bilateral ARVD. Enthusiasm for surgical revascularization increased especially with evidence that it could slow the rate of loss of renal function post-operatively.</td>
</tr>
<tr>
<td>Early 1990’s</td>
<td>Percutaneous angioplasty techniques gained popularity in view of increasing patient age and comorbidity.</td>
</tr>
<tr>
<td>Late 1990’s</td>
<td>PTRAS was shown to be technically superior to PTRA and became the preferred technique for revascularization. There was further evidence that revascularization could improve the rate of decline of renal function post-intervention, but studies were uncontrolled.</td>
</tr>
</tbody>
</table>
Late 1990's to early 2000's
Three small RCTs (EMMA, DRASTIC and Scottish and Newcastle study) showed that PTRA was not associated with any clinical benefit. On the other hand, there was accumulating evidence that enhanced vascular protection, including the use of ACEi could slow the rate of progression of ARVD and improve clinical outcomes.

Current era
Larger RCTs (ASTRAL and CORAL) comparing optimal medical treatment with revascularization confirmed that revascularization does not confer further benefit to multi-targeted medical therapy.

Future directions
Increasing evidence that revascularization may be beneficial in patients with a ‘high-risk’ phenotype who were not adequately represented in clinical trials. Future management of ARVD will rely on modern imaging techniques to establish the haemodynamic significance of RAS and enable accurate identification of patients with a ‘hibernating parenchyma’ (viable parenchyma with potential to recover function), and novel strategies (e.g. cell-based therapies) to protect the renal parenchyma and microvascular architecture.

(ACEi – angiotensin converting enzyme inhibitor; ARVD – atherosclerotic renovascular disease; PTRA – percutaneous transluminal renal angioplasty; PTRAS – percutaneous transluminal renal angioplasty with stenting; RCTs – Randomized controlled trials)

Renovascular hypertension: Surgery and early anti-hypertensive agents (1960’s – 1970’s)
Landmark animal studies performed by Goldblatt in 1934 stimulated interest in the study of hypertension by showing that experimental renal artery stenosis (RAS) in dogs led to systemic hypertension and this could potentially be reversed by removing unilateral diseased kidneys. Almost 3 decades later, pharmacological treatment of hypertension became available but this was fraught with side-effects and hence diagnosing potential surgically correctable forms of hypertension was a priority. Increased use of renal angiography, however, revealed that atherosclerosis often involved both kidneys and could be a multi-organ disease process. In 1968 Wollenweber showed that patients with ARVD had a poor prognosis, with a 5-year survival of 66.7% compared to 91.7% in a normal age-adjusted population. Despite development of complex surgical revascularization techniques to allow sparing of renal tissue, surgery was often hazardous and unsuccessful, especially in patients with long-standing hypertension. On the other hand, anti-hypertensives such as guanethidine, hydralazine and thiazide diuretics improved blood pressure control in up to 65% of patients who were not fit to undergo surgery. Blood pressure targets during this period were higher than current recommendations, a diastolic blood pressure of 100mmHg or less being considered satisfactory, but it was remarkable to note that better blood pressure control was associated with improved survival in this cohort of patients, whereas revascularization generally had no overall effect on survival.
Ischaemic nephropathy – surgery and newer antihypertensive agents (1970’s – 1990’s)

Serial angiographic studies in the 1970-80s shed light on the natural history of ARVD, raising the concern that this disease could progress in up to 44% of affected arteries, especially within the first two years of follow-up and in arteries with more severe stenosis at baseline. Progressively declining renal function in patients with compromised blood flow to either both kidneys or to a solitary functioning kidney was termed ‘ischaemic nephropathy’. This was thought to be the primary cause of end-stage kidney disease (ESKD) in around 14% of all haemodialysis patients and the focus of revascularization shifted from blood pressure control to preservation of functional renal tissue.

Despite development of better antihypertensive agents in the mid-1980s, these were not thought to mitigate ARVD progression. Angiotensin converting enzyme inhibitors (ACEI) were thought to decrease perfusion pressure across a stenosis, precipitating episodes of significant acute kidney injury (AKI) especially in patients with bilateral RAS or RAS in a solitary kidney. A prospective study performed by Dean et al in 1981 looked at 41 patients with presumed renovascular hypertension (RVH) randomly allocated to medical management and showed that 17 patients (41%) had significant deterioration in renal function or loss of renal size that required referral for surgery despite adequate blood pressure control in the majority (88%).

In 1991, the same group looked retrospectively at 58 patients with presumed ‘ischaemic nephropathy’ based on a diagnosis of underlying ARVD and serum creatinine of at least 1.8 mg/dL (158 µmol/l), who underwent renovascular surgery. Pre-operative glomerular filtration rate (GFR) ranged between 0 and 46 mL/minute, and 8 patients were dialysis-dependent at time of surgery. This cohort of patients had rapid loss of renal function pre-operatively which significantly slowed down post-operatively (p=0.0462). The effect of revascularization was heterogeneous but 6 out of the 8 patients on dialysis at time of operation regained independent renal function immediately after revascularization.

Enthusiasm for surgical revascularization continued to increase. An observational study performed by Novick et al looking at revascularization outcomes over an average follow-up of 46 months now showed that surgery could achieve a 5-year survival rate of 96%, almost equivalent to that expected in a normal population. However, these patients were undoubtedly selected as those with symptomatic coronary artery disease or cerebrovascular occlusive disease underwent angiographic screening with pre-emptive correction of vascular occlusive lesions. Novick speculated that although revascularization was ineffective in patients with severe renal impairment and irreversible parenchymal damage, it could potentially improve outcomes in highly-selected patients with viable parenchyma (Table 1.2.2).

Although as a result of improved cardiovascular survival increasingly older patients with more severe renal impairment were now being considered for revascularization, renovascular
Table 1.2.2 Uncontrolled studies of surgery, renal revascularization or medical therapy for ARVD over the past decades

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients (n)</th>
<th>Inclusion Criteria</th>
<th>Follow-up in months</th>
<th>Treatment modality</th>
<th>Primary end-point</th>
<th>Key clinical Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheps et al</td>
<td>1965</td>
<td>54 (22 pts had FMD)</td>
<td>RAS on renal angiography, hypertension</td>
<td>20.3 (mean)</td>
<td>medical</td>
<td>Change in renal function and BP control from baseline and mortality</td>
<td>-32/49 (65%) – controlled BP&lt;br&gt;-5/54 (9%) - died (all had underlying ARVD)</td>
<td>Improved retinal hypertensive changes were used as a correlate of controlled BP.</td>
</tr>
<tr>
<td>Wollenweber et al</td>
<td>1968</td>
<td>109</td>
<td>Unilateral or bilateral renal atherosclerosis</td>
<td>42 (mean)</td>
<td>63 - medical</td>
<td>Change in renal function and BP control from baseline, incidence of cardiovascular events and survival</td>
<td>-Medical group – 18/63 (29%) – controlled BP&lt;br&gt;-Surgical group – 25/46 (54%) – controlled BP&lt;br&gt;-Medical group - 16/63 (25%) – overall deaths&lt;br&gt;-Surgical group - 10/46 (22%) – overall deaths</td>
<td>Advanced ARVD was associated with more severe extrarenal atherosclerosis and a poorer prognosis.</td>
</tr>
<tr>
<td>Dean et al</td>
<td>1981</td>
<td>41</td>
<td>40-65 years, hypertensive, surgically correctable RAS, positive results from RVRA or SRFS</td>
<td>44 (mean)</td>
<td>medical</td>
<td>10% loss in renal length, 100% increase in serum creatinine and 50% decrease in isotopic GFR during follow-up</td>
<td>-12/41 (29%) - Decrease in GFR between 25%-50%.&lt;br&gt;-14/41 (37%) – lost more than 10% renal length</td>
<td>-17/41 (41%) required surgery due to deterioration in renal function or loss of renal length, despite adequate BP control in 15/17 (88%) of patients.</td>
</tr>
<tr>
<td>Novick et al</td>
<td>1984</td>
<td>51</td>
<td>Atherosclerotic renovascular</td>
<td>46 (mean)</td>
<td>surgery</td>
<td>Change in renal function from baseline and mortality</td>
<td>-31/46 (67%) - Improved renal function</td>
<td>In selected patients with ARVD, renal function</td>
</tr>
<tr>
<td>Year</td>
<td>Patients</td>
<td>Disease</td>
<td>Controlled BP</td>
<td>Survival post-surgical revascularization</td>
<td>Deterioration in renal function: 5/51 (10%) died.</td>
<td>Revascularization may improve survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>----------</td>
<td>---------</td>
<td>---------------</td>
<td>----------------------------------------</td>
<td>-----------------------------------------------</td>
<td>----------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1987</td>
<td>29</td>
<td>- RVH</td>
<td>20 (mean)</td>
<td>Change in BP from baseline</td>
<td>Diastolic BP &lt;90mmHg: 4/14 (29%)</td>
<td>25 hypertensive patients without underlying renovascular disease were used as non-randomized 'controls' - 8/25 (32%) had spontaneous improvement in BP.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1991</td>
<td>58</td>
<td>- Ischaemic nephropathy</td>
<td>19.8 (mean)</td>
<td>Surgery</td>
<td>8/53 (15%) - 'cured' hypertension</td>
<td>Patients with bilateral disease had a significant improvement in eGFR after intervention (p=0.0001) unlike patients with unilateral disease.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1995</td>
<td>24</td>
<td>- Ostial ARVD (≥50%) with refractory hypertension or rise in sCr with ACEI</td>
<td>6</td>
<td>Primary/secondary PTRAS (Palmaz)</td>
<td>Diastolic BP &lt;90mmHg with antihypertensive medication: 15/24 (63%) ESKD (cholesterol embolization): 2/24 (8.3%) - Death: 2/24 (8.3%)</td>
<td>ACEI could be restarted without causing deterioration in renal function.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td>32</td>
<td>- Ostial RAS (&gt;50%), failed</td>
<td>17 (mean follow-up)</td>
<td>Primary/Secondary PTRAS</td>
<td>20% change in serum creatinine from baseline, - Improved RF: 11/32 (34%) - Restenosis: 3/24 (12%)</td>
<td>Improved slope of deterioration of renal function.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>Year</td>
<td>N</td>
<td>RAS (%)</td>
<td>Hypertension</td>
<td>Change in renal function and BP from baseline and clinical outcomes at termination</td>
<td>Complications: 6/32 (19%)</td>
<td>Operative mortality: 1/32 (3%)</td>
<td>Function compared to that before stenting.</td>
</tr>
<tr>
<td>---------------</td>
<td>------</td>
<td>-----</td>
<td>---------</td>
<td>--------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>-------------------------</td>
<td>-------------------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Chabova et al</td>
<td>2000</td>
<td>68</td>
<td>&gt;70%</td>
<td>Hypertension</td>
<td>38.9 (mean)</td>
<td></td>
<td></td>
<td>Patients with bilateral renal artery disease had a higher mortality (p=0.07) and a higher risk of deteriorating renal function than patients with unilateral disease.</td>
</tr>
<tr>
<td>Losito et al</td>
<td>2005</td>
<td>195</td>
<td>ARAS &gt;50%</td>
<td></td>
<td>54 (mean)</td>
<td></td>
<td></td>
<td>Intervention had no effect on survival or incidence of ESKD. Baseline creatinine, rather than degree of RAS, was a predictor of reaching ESKD.</td>
</tr>
<tr>
<td>Jaff et al</td>
<td>2012</td>
<td>202</td>
<td>RAS ≥60%</td>
<td></td>
<td>9</td>
<td>9-month binary restenosis rate as determined by duplex ultrasound and/or angiography</td>
<td>Restenosis at 9 months: 22/209 (10.5%)</td>
<td>BP control at 9 months: Statistically significant drop</td>
</tr>
<tr>
<td>-Uncontrolled BP &gt;140/90mmHg despite Rx</td>
<td>in SBP (p&lt;0.0001) with no change in medication 1/202 (0.5%) – died 2/202 (1%) – atheromatous embolization and kidney injury</td>
<td>Revascularization optimized BP control in this selected cohort, and degree of BP reduction correlated with baseline BP. There was no correlation between BP response to revascularization and baseline BNP or BNP reduction.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a* defined as diastolic BP <95 or 90mmHg with no anti-hypertensive medication.

*b* sCr decreased by >20% from baseline

(ACEi – angiotensin-converting enzyme inhibitor; ARAS – atherosclerotic renal artery stenosis; ARB – angiotensin receptor blocker; ARVD – atherosclerotic renovascular disease; BNP – brain natriuretic peptide; BP – blood pressure; eGFR – estimated glomerular filtration rate; ESKD – endstage kidney disease; FMD – Fibromuscular dysplasia; PTRA – percutaneous transluminal renal angioplasty; PTRAS – percutaneous transluminal renal angioplasty and stenting; RAS – renal artery stenosis; RF – renal function; RVH – renovascular hypertension; RVRA – renal vein renin assays; Rx – treatment; sCr – serum creatinine; SRFS – split renal function studies)
surgery in these high-risk populations was more hazardous and had poorer clinical outcomes, with a 30-day mortality of 15.5% compared to 5.6% in lower risk patients, and a 5-year survival of around 64%.

Decreasing surgical morbidity and mortality – percutaneous transluminal angioplasty (1980’s – 1990’s)

Percutaneous transluminal angioplasty (PTRA) was first applied to RAS in 1978, triggering interest in using this non-invasive and inexpensive technique in patients with a high comorbid burden. Mortality rates were documented to be lower than for renovascular surgery, but there was a disappointingly high technical failure rate of around 50% for atherosclerotic RAS lesions due to elastic recoil post-intervention (Table 1.2).22,27, especially following dilatation of ostial lesions. A critical review of studies involving the use of PTRA for the management of RVH concluded that there was no evidence that the procedure was superior to medical therapy in patients with ARVD, given that none of these studies were controlled or randomized.

Improving technical outcomes – percutaneous transluminal angioplasty with stenting (late 1990’s)

The development of balloon-expandable intraluminal stents aimed to overcome the challenges involved in treating ostial atheromatous disease. In a randomized study comparing PTRA against percutaneous transluminal angioplasty with stenting (PTRAS) published in 1999, van de Ven established that PTRAS was technically more successful, with a restenosis rate of 14% compared to 48% for PTRA over 6 months follow-up. Most cases of restenosis were silent and detected only on repeat angiography. The technical success of PTRAS did not necessarily translate into ‘clinical’ superiority (Table 1.2).

Despite this, van de Ven’s study fuelled enthusiasm for PTRAS and several observational case series were carried out throughout the 1990s. Although PTRAS appeared to improve or stabilize the decline in renal function in the short term in around 75%, and also allowed the reintroduction of ACEI 23, a quarter of patients still progressed to ESKD. However, in a small selected population of ARVD patients with pre-procedure decline in renal function, Harden showed that stenting decreased the rate of decline in renal function around four-fold in 18 out of 23 patients studied, even in those with severe, progressive deterioration in renal function.10 Table 1.2.2. Again, in keeping with the contemporary approach to research, no control group was utilized in the study.

Era of the first RCT (late 1990’s to 2000)

At the end of the 1990’s the emergence of evidence-based medicine heralded the era of RCT in ARVD treatment (Table 1.2.3). Two separate small RCT compared PTRA without stenting against medical therapy. The EMMA Study included 49 hypertensive patients with presumed haemodynamically significant unilateral RAS (≥75% or ≥60% stenosis with a positive
### Table 1.2.3 Controlled studies of renal revascularization or medical therapy for ARVD over the past few decades

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients (n)</th>
<th>Inclusion criteria</th>
<th>Follow-up in months</th>
<th>Treatment modality</th>
<th>Primary end-point</th>
<th>Key Clinical outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weibull et al</td>
<td>1993</td>
<td>58</td>
<td>-Non-diabetic&lt;br&gt;-≤70 years&lt;br&gt;-untreated BP ≥160/100mmHg&lt;br&gt;-Significant unilateral RAS&lt;br&gt;-Serum Creat &lt;300umol/L</td>
<td>24</td>
<td>29 - PTRA&lt;br&gt;29 - surgery</td>
<td>Technical success, primary and secondary patency, and changes in BP and renal function from baseline</td>
<td>Diastolic BP &lt;90mmHg – secondary results b:&lt;br&gt;-PTRA 5/29 (17%), Surgery 5/29 (17%)&lt;br&gt;Secondary improved/stable renal function b:&lt;br&gt;-PTRA 83%, Surgery 72% p=0.53&lt;br&gt;Complications:&lt;br&gt;-PTRA 5/29 (17%), Surgery 9/29 (31%) p=0.17&lt;br&gt;Primary Patency rate at 24 months:&lt;br&gt;-PTRA – 75%, Surgery – 96%</td>
<td>Given the tight inclusion criteria and the highly-selected population, it was unclear whether the clinical benefit observed following both interventions could be extrapolated to the general population of patients with ARVD.</td>
</tr>
<tr>
<td>Plouin et al</td>
<td>1998</td>
<td>49</td>
<td>-&lt;75 years of age&lt;br&gt;-Diastolic BP &gt;95mmHg&lt;br&gt;-CrCl ≥50ml/min&lt;br&gt;-Significant unilateral RAS</td>
<td>6</td>
<td>23 - PTRA&lt;br&gt;26 - medical treatment</td>
<td>Blood pressure at 6 months and change from baseline</td>
<td>No statistical difference between mean ambulatory BP at 6 months and average reduction in BP between the two groups.&lt;br&gt;Complications:&lt;br&gt;-PTRA 6/23 (26%), Medical</td>
<td>PTRA resulted in a reduced anti-hypertensive medication use at 6 months, however it was associated with a higher risk of complications</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Age</td>
<td>Criteria</td>
<td>6 months</td>
<td>Change from Baseline</td>
<td>2/25 (8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------</td>
<td>-----</td>
<td>---------------------------------------------------------------------------</td>
<td>----------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Webster et al 30</td>
<td>1998</td>
<td>55</td>
<td>- &lt;75 years</td>
<td>3-54</td>
<td>Blood pressure at 6 months and change from baseline</td>
<td>A statistically significant drop in BP (p&lt;0.05) was detected only in patients with bilateral disease randomized to PTRA. There were no significant differences in renal function or survival between groups.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Diastolic BP ≤ 95mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- ≥50% Unilateral/Bilateral stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- sCr &lt; 500umol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van de Ven et al 9</td>
<td>1999</td>
<td>85</td>
<td>- ≥50% Ostial ARVD</td>
<td>6</td>
<td>Primary success rate and patency rate at 6 months</td>
<td>Primary success rate &lt; : PTRA 24/42 (57%), PTRAS 37/42 (88%) Restenosis at 6 months: PTRA 11/23 (48%), PTRAS 5/35 (14%) Complications: PTRA 18/42 (43%), PTRAS 21/42 (50%) Diastolic BP &lt; 90mmHg: PTRA 2/41 (5%), PTRAS 6/40 (15%) Improved renal function: PTRA 4/41 (10%), PTRAS 5/40 (13%).</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- BP &gt; 160/96mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Positive captopril renography or increase in sCr of ≥20% with ACEi.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>42- PTRA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>43- PTRAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BP fell significantly following the 4 week run-in period with standardized antihypertensives in both groups.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Authors</td>
<td>Year</td>
<td>Sample size</td>
<td>Criteria</td>
<td>Blood pressure at 3 and 12 months after randomization</td>
<td>Differences between the two groups at 12 months, in terms of both renal function and BP control.</td>
<td>PTRAS may only be of benefit in controlling blood pressure in patients with bilateral renal artery disease.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>------</td>
<td>-------------</td>
<td>--------------------------------------------------------------------------</td>
<td>-------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Jaarsveld et al 31</td>
<td>2000</td>
<td>106</td>
<td>-&lt;75 years &lt;sCr ≤200umol/L -Diastolic BP ≥95mmHg -Unilateral or bilateral &gt;50% RAS</td>
<td>Blood pressure at 3 and 12 months after randomization</td>
<td>No significant differences between the two groups at 12 months, in terms of both renal function and BP control.</td>
<td>PTRAS may only be of benefit in controlling blood pressure in patients with bilateral renal artery disease.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bax et al 32 (STAR)</td>
<td>2009</td>
<td>140</td>
<td>-unilateral or bilateral ostial ARAS ≥50% -CrCl &lt;80ml/min -Controlled BP &lt;140/90mmHg for 1 month</td>
<td>&gt;20% decrease in CrCl from baseline: -16/76 (22%) medical Rx, 10/62 (16%) intervention group</td>
<td>Significant number of PTRAS-related complications: -2/62 (3%) – periprocedure mortality -1 death secondary to infected haematoma -ESKD needing dialysis in 1 patient.</td>
<td>Significant number of PTRAS-related complications: -2/62 (3%) – periprocedure mortality -1 death secondary to infected haematoma -ESKD needing dialysis in 1 patient.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wheatley et al (ASTRAL) 12</td>
<td>2009</td>
<td>806</td>
<td>-unilateral or bilateral 'substantial' ARAS -Uncertainty regarding benefit from revascularization</td>
<td>Change in renal function (measured by the mean slope of the reciprocal of serum creatinine) from baseline</td>
<td>Revascularization was associated with serious adverse events in 23/403 (6.7%) patients, including 2 deaths and 3 amputations; revascularization conferred no advantage over optimal medical therapy.</td>
<td>Revascularization was associated with serious adverse events in 23/403 (6.7%) patients, including 2 deaths and 3 amputations; revascularization conferred no advantage over optimal medical therapy.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marcantonio et al 33 (RAS-CAD)</td>
<td>2012</td>
<td>84</td>
<td>Unilateral/bilateral RAS &gt;50%-≤80% - IHD and elective coronary angiography</td>
<td>12</td>
<td>41 – Medical therapy 43 – Medical therapy + PTRAS (intervention group)</td>
<td>Change in echocardiographic LVMI from baseline</td>
<td>Controlled or improved BP control: -75% - Intervention group; 81% - medical Rx</td>
<td>Deaths: -2/43 (4.6%) Intervention group; 2/41 (4.9%) medical Rx</td>
</tr>
<tr>
<td>Cooper et al 13 (CORAL)</td>
<td>2014</td>
<td>947</td>
<td>unilateral or bilateral ARAS ≥60%</td>
<td>43 (median)</td>
<td>480 – medical Rx 467 – medical Rx + PTRAS (95%) or PTRA (intervention group)</td>
<td>Composite end-point of death from cardiovascular or renal causes, myocardial infarction, stroke, hospitalization from congestive heart failure, progressive renal impairment or need for renal replacement therapy</td>
<td>Composite primary end-point -169/472 (35.8%) - medical Rx; 161/459 (35.1%) - intervention group (p=0.58)</td>
<td>Deaths: 63/459 (13.7%) – intervention group 76/472 (16.1%) – medical Rx (p=0.2) ESKD: 16/459 (3.5%) – intervention group 8/472 (1.7%) – medical Rx (p=0.11)</td>
</tr>
<tr>
<td>------------------------</td>
<td>------</td>
<td>-----</td>
<td>---------------------------------</td>
<td>-------------</td>
<td>-------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>a without antihypertensive medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b The results achieved following intervention in the event of restenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c Patency after the first intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d sCr decreased by &gt;20% from baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(ACEi – angiotensin-converting enzyme inhibitor; ARAS – atherosclerotic renal artery stenosis; ARVD – atherosclerotic renovascular disease; BP – blood pressure; ESKD – endstage kidney disease; IHD – ischaemic heart disease; PTRA – percutaneous transluminal renal angioplasty; PTRAS – percutaneous transluminal renal angioplasty and stenting; RAS – renal artery stenosis; RF – renal function; sCr – serum creatinine)
lateralization test) but well-preserved renal function while the Scottish and Newcastle study 30 looked at 55 patients with less severe unilateral or bilateral RAS (≥50% stenosis). Both studies involved a run-in period of standardized antihypertensive treatment for a few weeks prior to randomization. There was no difference in average blood pressure in patients with unilateral RAS at the end of either study, although Webster et al detected improved systolic blood pressure control in patients with bilateral RAS. In the EMMA study, 7 out of 26 patients in the control group crossed over to receive intervention due to refractory hypertension, possibly because ACEI were not permitted in these patients. Both the initial qualifying angiography and subsequent angioplasty were associated with a significant complication rate hence these studies cast doubt on the role of revascularization, although there was no long-term clinical outcome data.

The DRASTIC study was a larger RCT involving 106 hypertensive patients again with well-preserved renal function and either unilateral or bilateral RAS ≥50%. These patients were randomized to antihypertensive medication only or to angioplasty with or without stenting 31. Although DRASTIC showed no significant difference between the interventional and medical arm in terms of blood pressure control, renal function or drug doses at 12 months of follow-up, a significant proportion of patients (44%) failed medical therapy and required angioplasty due to refractory hypertension or deteriorating renal function. It was not specified whether these patients had underlying bilateral ARVD, but it was noteworthy that angioplasty was successful in controlling hypertension or decreasing drug doses in this subset of patients 31.

**Changing natural history and improving clinical outcomes with enhanced vascular protection (1990’s to 2000’s)**

In parallel with progressive improvements in percutaneous techniques, new evidence was emerging about the value of vascular protection using aspirin and statins 34,35. Concurrent development of renal duplex ultrasonography enabled easier follow-up of ARVD progression and there was a suggestion that atherosclerotic RAS was progressing less commonly to total renal artery occlusion. Although earlier angiographic studies had shown a rate of occlusion of up to 39% over around 13 months follow-up in arteries with initial RAS ≥75% 17, RAS assessment using novel Duplex ultrasound criteria, which correlated with renal angiography with an accuracy of around 93% 36, showed a rate of occlusion of 3% over 3 years in renal arteries with baseline RA S ≥60% 37.

The results of two separate observational studies highlighted that ARVD outcomes largely depended on the degree of underlying renal parenchymal damage and overall atherosclerotic burden (Table 1.2.2). Chabova et al retrospectively analysed a cohort of patients with significant ARVD who were treated exclusively medically. The higher average age of this population (71.8 years), compared to that of earlier studies, reflected improved cardiovascular survival. One third of patients were receiving ACEI, and hypertension was successfully controlled in the majority of
patients. There was no information about administration of statins. Only 2 patients out of 68
developed ESKD secondary to progressive vascular disease, while another 2 failed
antihypertensive therapy. This is in sharp contrast with earlier studies in which up to 41% of
patients with ARVD were adjudged as requiring intervention due to progressive deterioration of
renal function or loss of renal mass.

Losito’s group in Italy exploited the state of clinical equipoise between revascularization and
medical treatment to determine long-term outcomes such as cardiovascular mortality in two
comparable patient groups. In this observational non-randomized study, 54 ARVD patients
treated medically and 136 patients who underwent angioplasty were followed-up for an average
of 54.4 months. Statins were only used in patients with high cholesterol levels and around a
third of patients were on ACEI. Interestingly, ACEI did not increase the risk of loss of renal
function but rather, were associated with improved survival in both groups (p=0.002). Renin-
angiotensin blockade became part of the standard of care for ARVD in bilateral as well as
unilateral disease, as it conferred cardiovascular protection to this high-risk population.
Revascularization on the other hand, again appeared to have no impact on survival or
incidence of ESKD.

However, despite lack of conclusive evidence that revascularization improved outcomes in
atherosclerotic RAS, the late 1990s and early 2000s were characterized by the phenomenon of
‘drive-by angioplasty’, where some interventional cardiologists performed routine renal
angiography concurrently with coronary angiography, and carried out PTRAS if RAS was
present, irrespective of its degree or clinical associations. Medicare data suggested that
30,000 plus PTRAS were being performed each year in the US alone in this pro-
revascularization era.


In the wake of this increased interest in revascularization, which admittedly was partly
financially driven, up to 1 in 6 patients with ARVD underwent intervention. However, it was
now established that the majority of patients did not gain benefit from intervention. There was a
need to understand pathogenesis of renal injury in the post-stenotic kidney and how this could
influence outcomes. Multi-targeted atherosclerotic risk factor control using anti-platelet therapy,
renin-angiotensin blockade and statins became a central part of ARVD management, in an
attempt to prevent progression of RAS as well as irreversible renal parenchymal damage.

The contemporary uncertainty paved the way for a head-to-head comparison of optimized
medical therapy with revascularization combined with medical therapy in three RCTs (Table 1.2.3). Novel non-invasive imaging techniques such as computed tomography
angiography (CTA) or magnetic resonance angiography (MRA) were employed together with
conventional angiography to select patients for enrollment in both STAR and ASTRAL.
However, at definitive on-table angiography in patients randomized to stenting, 19% of patients in STAR and 20% of patients in ASTRAL were found to have stenosis <50%, and so did not undergo revascularization. STAR excluded patients with uncontrolled hypertension and ASTRAL specifically excluded patients if the clinician was certain that revascularization would be of benefit, thereby not denying the patient this treatment. Although CORAL investigators attempted to include patients with more significant RAS using a radiology ‘core lab’ to standardize RAS interpretation and severity, inclusion criteria were relaxed due to slow enrollment. In addition, whereas blood pressure was the primary end-point for earlier RCTs, the pre-defined primary outcome measure for ASTRAL and STAR was change in renal function. In ASTRAL, 40% of patients had serum creatinine <150 μmol/l, and hence the likelihood of demonstrating that intervention could exert a beneficial change in renal function was limited. All three RCTs, encompassing almost 1900 randomized patients, demonstrated that revascularization did not confer any added benefit to optimal medical therapy in terms of renal, cardiovascular and mortality outcomes, but lack of selection of the recruited population was actually a major criticism of these studies as patients with ‘high risk’ features were excluded.

Less patients required renal replacement therapy in both arms of each of these 3 RCTs compared to earlier studies, perhaps reflecting the renoprotective action of ACEI and statins. In ASTRAL, 8% of patients, irrespective of randomization arm, reached ESKD over 34 months while less than half this figure reached ESKD in CORAL after 43 months, but patients in CORAL had a higher GFR at baseline (58 ml/min) than patients in ASTRAL (40 ml/min). ASTRAL showed that revascularization may slow the rate of progression of renal impairment but this was not statistically or clinically significant. The much lower crossover rate from medical to interventional arms (e.g. 4.4% in ASTRAL) compared to that seen in DRASTIC (44%) was also a reflection of the efficacy of contemporary medical treatment in achieving target blood pressure control and stable renal function. However, 16-22% of patients in both ASTRAL and CORAL still reached adverse renal end-points (largely AKI or renal death in ASTRAL, doubling of creatinine in CORAL) irrespective of treatment arm, probably due to irreversible renal parenchymal injury.

The RAS-CAD trial provided insights into the cardioprotective effect of modern medical management. The study enrolled patients with underlying coronary artery disease and concomitant RAS to evaluate the effect of revascularization in addition to optimal medical therapy on progression of left ventricular hypertrophy (LVH). Medical therapy decreased the degree of LVH, while revascularization conferred no additional benefit, although again, patients with severe RAS were excluded from this trial. This finding was replicated in the cardiac MR sub-study of ASTRAL which showed no differences in cardiac structure and function at 12 months after randomization in stented versus medically treated patients.
It is noteworthy how historic comparisons can be misleading. The mortality rate reported by ASTRAL (8% per year) was similar to that reported by Wollenweber in 1968. However, the earlier cohort had an average age of 54.5 years compared to 70 years in ASTRAL, and selection bias was manifest by only younger hypertensive patients being referred for angiography and potential surgical revascularization in that era.

**The 2015 view on revascularization**

A recent Cochrane meta-analysis of eight RCTs comparing PTRA or PTRAS and medical therapy for management of ARVD concluded that revascularization had no significant effect on the incidence of cardiovascular or renal adverse events or mortality\(^{42}\). As a result, the number of revascularization procedures performed in the past few years has declined by 50 – 75%\(^{43}\). The American Heart Association guidelines reflect the uncertainty surrounding indications for revascularization; however, despite the lack of robust evidence, they advocate that revascularization may still have a role in ‘high-risk’ situations\(^{44}\).

There has been consistent evidence through the decades of particular subgroups of patients with specific clinical phenotypes who do seem to benefit from revascularization. These patients have tended not to be well-represented in RCTs. As mentioned before, two uncontrolled studies from the 1990’s showed that revascularization improved the rate of decline in renal function particularly in patients with rapidly progressive renal impairment or bilateral RAS\(^7,10\). There were less than 100 patients defined as having prior rapidly declining renal function in ASTRAL, and although there was a signal that revascularization impacted upon this, this was non-significant. In contrast, despite a belief that revascularization may be futile in patients with advanced renal failure\(^{21,45}\), a combined review of two separate UK and German ARVD cohorts showed that revascularization improved GFR in around 50% of patients with CKD stage 4 and 5 and that this was associated with a survival benefit\(^{46}\).

There is also repeated, albeit non-randomized, evidence that revascularization can prevent recurrent flash pulmonary oedema (FPE) in patients with bilateral RAS or significant RAS to a solitary kidney and this is an accepted indication for revascularization\(^{44}\). A recent retrospective single-centre study of 237 patients with underlying ARVD and a high-risk clinical phenotype (i.e. presenting with FPE, refractory hypertension or rapidly declining kidney function), showed that revascularization was associated with improved survival in patients with FPE and in those with the combination of rapidly declining renal function and refractory hypertension\(^1\), but not when the latter conditions presented alone. Other investigators have shown that improved clinical outcomes can be more predictable when the physiological significance of RAS is confirmed by comprehensive ultrasound Doppler studies\(^{47}\).

**Future Directions in management of ARVD**
Establishing a causal relationship between haemodynamically significant ARVD and high-risk clinical phenotypes would enable timely identification of patients likely to gain benefit from revascularization. There is currently controversy regarding whether renal angiography or Doppler ultrasound can identify haemodynamically significant stenosis with high specificity, and conventional cut-offs (50% stenosis for angiography and peak systolic velocities more than 2.0m/s for Doppler ultrasound) overestimate severity of stenosis \(^{48}\). Although evidence is limited, transstenotic pressure gradients may correlate more closely with the physiological significance of RAS \(^{49}\).

Functional characterization of renal parenchyma distal to RAS may help predict revascularization outcomes. High renal resistance indices (RI) (>0.8) obtained on Doppler ultrasound have been suggested to indicate irreversibly damaged renal parenchyma\(^{50}\). However, this has not been confirmed in other studies\(^{51}\) hence RI should not dictate revascularization decisions\(^{48}\). Modern imaging techniques such as blood-oxygen level-dependent magnetic resonance imaging (BOLD-MRI) can identify critically ischaemic kidneys. A high level of hypoxia in relation to the GFR of individual kidneys can predict improvement in renal function post-revascularization and this might represent ‘hibernating parenchyma’ \(^{14}\). Recent research efforts have focused on prevention of irreversible parenchymal injury in order to optimize clinical outcomes. Oxidative stress and ischaemia-reperfusion injury in animal experiments stimulate secretion of an adverse cytokine profile and macrophage infiltration, and eventually lead to loss of renal microvascular architecture. Novel strategies based on cell-based therapies are being explored to target this remodeling process \(^{15,16}\).

Despite the neutral results of the latest RCTs, it is clear that patients with ARVD constitute a very heterogeneous group, and hence indications for revascularization need to be individualized (Table 1.2.4). Multi-targeted treatment for atherosclerosis remains the undeniable cornerstone of ARVD management, but identifying the subset of patients who do respond to revascularization remains a priority. Although ideally another RCT should be performed to help define the role of revascularization in these high-risk subgroups, it seems unlikely that this will occur in the near future. However, an international registry study for patients with ARVD undergoing revascularization should be established to shed light on the responses of individual clinical phenotypes; this would also serve as a powerful research tool.

**Conclusion:**
The past 80 years have witnessed significant progress in our understanding of the natural history, pathophysiology and management of ARVD. Contemporary therapy for atherosclerosis has decreased the rate of RAS progression to total occlusion after initial clinical presentation\(^{20,37}\) and has improved clinical outcomes. The role of revascularization needs to be redefined in light of the neutral results of recent large RCTs. Future research efforts need to focus on timely identification of subgroups of patients who can potentially gain benefit from
revascularization, as well as on controlling the intra-renal inflammatory, fibrotic and microvascular processes which perpetuate ischaemic injury.

**Table 1.2.4** Indications for revascularization in ARVD

<table>
<thead>
<tr>
<th>Definite Indications</th>
<th>Possible Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe or dialysis-dependent AKI</td>
<td>1(^1) Very severe hypertension (e.g. systolic blood pressure &gt;180mmHg on &gt;4 drugs): individual case basis</td>
</tr>
<tr>
<td>Patients who require/would benefit from renin-angiotensin blockade but who are intolerant</td>
<td>- Rapid onset of severe hypertension in patients with previously well-documented normal blood pressure</td>
</tr>
<tr>
<td>Recurrent acute heart failure</td>
<td>- Rapid onset of resistant hypertension in subjects with previously easily controlled hypertension</td>
</tr>
<tr>
<td></td>
<td>1(^1) Rapidly deteriorating renal function: individual case basis</td>
</tr>
<tr>
<td></td>
<td>Concurrent rapidly deteriorating renal function and severe hypertension</td>
</tr>
<tr>
<td></td>
<td>Patients with ‘hibernating renal parenchyma’ (e.g. patients with an elevated MR-measured renal parenchymal volume to isotopic single-kidney GFR ratio (^1))</td>
</tr>
<tr>
<td></td>
<td>Chronic heart failure: uncontrolled case series imply benefit</td>
</tr>
<tr>
<td></td>
<td>Prevention of renal atrophy in the long term: current RCT have only shown short term outcomes</td>
</tr>
</tbody>
</table>

\(^1\)Especially where functionally significant RAS confirmed

(AKI: Acute kidney injury; ARVD: atherosclerotic renovascular disease; GFR – glomerular filtration rate; MR – magnetic resonance; RAS – renal artery stenosis; RCT – randomized controlled trials)
References:


31. Van Jaarsveld BC, Krijnen P, Pieterman H, et al. The effect of balloon angioplasty on...


1.3 From Anatomy to function – diagnosis of atherosclerotic real artery stenosis

Odudu A, Vassallo D, Kalra PA.
DOI: 10.1586/14779072.2015.1100077

Preface:
In this chapter the different imaging modalities that are used to diagnose ARVD are discussed, highlighting the shift in focus from an anatomic assessment of the severity of stenosis to a more functional approach that takes into account the haemodynamic significance of the stenosis and the viability of renal parenchyma. This chapter has been written as a review article in collaboration with a more senior co-author hence the writing style differs from the rest of the thesis. As mentioned above, the following sections have been written by myself and edited by both co-authors:

- Ultrasound
- Novel Ultrasound techniques
- Radionuclide scans
- Computed Tomograph (CT) angiography
- Dynamic Contrast-Enhanced CT
- Serum and Urine Biomarkers
- Clinical Risk scores and phenotypes
- High-risk phenotypes
- Expert Commentary
- Advantages and Disadvantages of Duplex US for diagnosis of renal artery stenosis
- Tables 6 – 10

Abstract
Atherosclerotic renal artery stenosis (ARAS) affects 7% of the over 65s and will be increasingly common with an ageing population. ARAS obstructs normal renal perfusion with adverse renal and cardiovascular consequences. Drug therapy is directed at reducing atherosclerotic risk. Two recent major trials of revascularization for ARAS showed that clinical outcomes were not improved beyond those offered by optimal drug therapy in most patients. This reflects experimental data showing that restoration of blood flow alone may not attenuate a cascade of tissue injury. A shift from anatomic to functional imaging of ARAS coupled to novel therapies might improve clinical outcomes in selected patients. This review outlines the case for separately assessing haemodynamic significance of arterial stenosis and functional reserve of
renal parenchymal tissue. The authors consider current and emerging diagnostic techniques for ARAS and their potential to allow individualized and functionally directed treatments.

Introduction
The prevalence of atherosclerotic renal artery stenosis (ARAS) in a population-based cohort of individuals older than 65 years is around 7%, increasing to 25–50% in comorbid Western populations with high atherosclerotic risk. Study of Medicare claims data revealed a threefold increase in the incidence of ARAS between 1992 and 2004. Whilst this might in part reflect increasing availability of diagnostic imaging, the burden of atherosclerosis in an aging population means that ARAS will be increasingly common.

ARAS is subclinical in the majority, whilst a few individuals have a high-risk phenotype of refractory hypertension, progressive renal functional loss or recurrent flash pulmonary edema. Medical management of ARAS includes optimizing blood pressure control, renin–angiotensin blockade, smoking cessation and lipid-lowering with statin therapy. Despite their individual caveats, recent major randomized controlled trials have shown that restoring vessel patency by angioplasty or stenting does not confer any added benefit beyond that achieved with current optimal medical therapy. This reflects experimental data showing that restoration of blood flow alone may not attenuate a cascade of tissue injury. In light of these data, the number of revascularization procedures performed has declined along with enthusiasm in pursuing the diagnosis. However, these trials still showed that a substantial minority of 16–22% developed substantial renal functional decline or end-stage kidney disease. Furthermore, those with high-risk phenotypes were typically excluded. Emerging novel therapies are directed at attenuating the ischemic injury that persists despite restoring blood flow. It is increasingly important that the diagnosis of ARAS goes beyond assessment of its anatomy and quantifies functional viability. This may allow better selection for novel therapy trials or identification of those patients in whom revascularization will preserve kidney function whilst preventing harm in those who will not. The paradigm shifts in the epidemiology and current management of ARAS have been recently summarized. This review considers current and emerging diagnostic techniques for ARAS and their potential to allow individualized and functionally directed treatments.

Catheter angiography
Catheter angiography (CA) is now a rarely used reference-standard technique for diagnosis of significant ARAS due to its invasive nature. Even with preventative protocols, CA carries a small but important risk of contrast-induced nephropathy, cholesterol embolization, allergic contrast media reactions and arterial dissection. This procedure is now typically reserved for a planned endovascular intervention after non-invasive imaging. Several prospective clinical studies typically used a visually estimated stenosis of greater than 50% or 70% to determine hemodynamic significance. These biologically plausible criteria were supported by data demonstrating that the visually estimated percentage of stenosis was independently associated...
with worse survival. It is now well recognized that such visual estimates have poor interobserver variability with a poor correlation to quantitative methods. Further, even quantitative stenosis grading correlates poorly to functional severity as measured by pressure or flow changes. Studies using latex casts and hemodynamic measurements indicate that measurable reductions in translesional pressures or blood flow only occur at a diameter stenosis of 70–80%. Reasons for such discrepancies include a 2D luminal view that ignores renal blood flow, vessel geometry, radiolucent atherosclerotic plaque, collateral circulation, microvascular resistance and parenchymal injury within the kidney downstream from the ARAS. Subgroup analysis of the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial did not show any benefit in those with >80% stenosis by CA as estimated by individual study centres. The 7% systemic overestimation of diameter stenosis between the core lab using quantitative software and the study centres underscores just one aspect of the fundamental problem of estimating arterial flow based on 2D imaging, an issue not exclusive to the renal vasculature.

Translesional pressure gradients during CA
Indices derived from pressure-transducing guidewires are an established technique for assessing hemodynamic significance of coronary artery stenosis during coronary angiography. These typically use maximal vasodilation with drugs such as adenosine or papaverine to allow a measure of vascular responsiveness independent of autoregulation termed coronary flow reserve. Normal coronary flow reserve is three- to fivefold the resting value. Values < 2 are typically associated with cardiac ischemia. This whole organ flow-derived measure represents the combined effect of contrary artery stenosis and microvascular dysfunction, but cannot distinguish the two. Such studies informed analogous techniques in renal arteries. Manoharan and coworkers measured renal hemodynamics in healthy volunteers modulated by a variety of vasodilators, determining that renal flow reserve was approximately twice the resting value. Lower renal flow reserve compared to the heart is teleological as the kidney aims to maintain filtration pressure across a wide range of renal blood flow, whilst the heart aims to maintain adequate myocardial blood flow across a wide range of perfusion pressures. Under maximal vasodilation, downstream resistance and venous pressure are negligible, and poststenotic blood flow becomes proportional to perfusion pressure and extent of stenosis. Fractional flow reserve (FFR) is a vessel-specific pressure-derived measure defined as the ratio of pressure distal and proximal to a stenosis under maximal vasodilation. Normal maximum blood flow (Qm) is

\[ Q^m = \frac{P_a - P_v}{R} \]

where R is renal microvascular resistance at maximum vasodilation, Pa is mean aortic pressure and Pv is mean central venous pressure. Maximal blood flow (Q) in a stenotic artery can be represented as

\[ Q = P_d - P_v = R \]
where Pd represents pressure distal to the stenosis. Under maximal vasodilation, renal microvascular resistance becomes negligible allowing renal FFR to be defined as

\[
Q/Q^n = (P_d - P_v)/(P_a - P_v)
\]

Assuming the central venous pressure to be negligible, this equation simplifies as

\[
\text{Renal FFR} = P_d/P_a
\]

The renal FFR varies between 0 in a completely occluded artery and 1 in a normal renal artery. Limitations of FFR include the risks of administering vasodilators, assumptions of negligible central venous pressure, as well as the reliance on achieving maximal vasodilation. Failure to achieve maximal vasodilation will overestimate FFR. Several studies measured hemodynamic significance of ARAS using CA with pressure sensing guidewires using a range of translesional pressure gradients Table 1.3.1. These generated a variety of thresholds to predict variably defined reductions in blood pressure with similar diagnostic performance. Using an elegant study design in stented ARAS, De Bruyne and coworkers demonstrated renin release was stimulated when the resting ration between mean pressure distal and proximal to the stenosis (Pd, distal pressure; Pa, aortic pressure) fell below 0.9\(^1\). Thus, resting Pa/Pd ratio < 0.9 was proposed as a physiological definition of significant ARAS. Resting Pa/Pd ratio also did not require testing under vasodilation. Further studies established a poor correlation between 2D angiographic stenosis and translesional pressure gradients. Drieghe and coworkers measured renal artery FFR estimating that a threshold of >50% stenosis by CA, falsely identified hemodynamically significance in 38% of cases (Figure 1.3.1)\(^1\). Expert consensus guidelines summarized these thresholds (Textbox 1.3.1).\(^1\)

Robust validation of translesional gradients in large studies to predict clinical outcomes in ARAS remains an unmet need. The CORAL trial originally had angiographic eligibility criteria of 80–99% stenosis or 60–80% stenosis with a systolic pressure gradient of at least 20 mm Hg\(^6\). Translesional gradients were ultimately used in only 199 of 947 trial participants as the need for this investigation was considered to be a cause of delayed recruitment. Outcomes by FFR categories were not reported. Data on how frequently FFR is currently used in investigation of ARAS are not available. Efforts are being made to develop an international registry of ARAS interventional procedures to capture such data. Sufficient enthusiasm to recruit to an adequately sized FFR-directed clinical trial of revascularization might be unfeasible, unless combined with a novel adjunctive therapy. Whilst an advance from anatomically estimated stenosis, FFR and other pressure gradients focus on arterial hemodynamics ignoring the effects of poststenotic microvascular resistance or the contralateral kidney that may better represent tissue viability.
Table 1.3.1 Studies reporting blood pressure or renal functional response to revascularization by baseline translesional pressure gradient.

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Baseline characteristics</th>
<th>Baseline characteristics</th>
<th>Follow-up (months)</th>
<th>Renal functional change</th>
<th>Definition of BP response</th>
<th>BP Outcome</th>
<th>Authors’ recommended threshold to predict BP response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kądziela 2013 and †Kadziela 2015</td>
<td>35</td>
<td>Visual diameter stenosis (%)</td>
<td>74 (67-80)</td>
<td>0.8 (0.7-1.0)</td>
<td>136 (126–147)</td>
<td>71 (62–79)</td>
<td>Yes</td>
<td>Papaverine</td>
</tr>
<tr>
<td>Protasiewicz 2013</td>
<td>37</td>
<td>Serum creatinine (mg/dL)</td>
<td><strong>85±27</strong></td>
<td><strong>141±14</strong></td>
<td>73±10</td>
<td>Yes</td>
<td>Dopamine</td>
<td>3</td>
</tr>
<tr>
<td>Study</td>
<td>Cohort</td>
<td>Prevalence</td>
<td>DBP (mmHg)</td>
<td>SBP (mmHg)</td>
<td>Success</td>
<td>Treatment</td>
<td>Units</td>
<td>Measure of Response</td>
</tr>
<tr>
<td>---------------------</td>
<td>----------</td>
<td>------------</td>
<td>------------</td>
<td>------------</td>
<td>---------</td>
<td>-----------</td>
<td>-------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Mangiacapra 2010</td>
<td>53</td>
<td>58±16</td>
<td>1.2±0.5</td>
<td>162±24</td>
<td>Yes</td>
<td>Papaverine Dopamine</td>
<td>3</td>
<td>24hr SBP &gt;20mmHg (the mean for the overall group)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dopamine-induced HMG ≥20mmHg was best predictor of 3 month BP response (sensitivity 72%, specificity 82%)</td>
</tr>
<tr>
<td>Leesar 2009</td>
<td>62</td>
<td>50-90%</td>
<td>1.2±0.3</td>
<td>170±12</td>
<td>No</td>
<td>Papaverine</td>
<td>12</td>
<td>DBP &lt;90 mm Hg or reduced by ≥15 mm Hg and/or SBP &lt;140mm Hg on same/reduced medication</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HSG ≥21 mmHg was best predictor of 12 month BP reduction (sensitivity 82%, specificity 84%, and accuracy 84%)</td>
</tr>
<tr>
<td>Mitchell 2007</td>
<td>17</td>
<td>50-90%</td>
<td>57*</td>
<td>174</td>
<td>No</td>
<td>Papaverine</td>
<td>10±2</td>
<td>DBP &lt;90 mm Hg or 3 month BP reduced in</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FFR&lt;0.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Jones 2006&lt;sup&gt;25&lt;/sup&gt;</td>
<td>22</td>
<td>55±17</td>
<td>1.3±0.4</td>
<td>167±24</td>
<td>76±14</td>
<td>No</td>
<td>Acetylcholine</td>
<td>1-5.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>†Kadziela 2013 and Kadziela 2015 report renal and BP outcomes for the same participants. *MDRD estimated GFR ml/min/1.73m&lt;sup&gt;2&lt;/sup&gt;, **Creatinine clearance (ml/min), Abbreviations: ABPM Ambulatory Blood Pressure Monitoring; DBP, Diastolic blood pressure; FFR Fractional Flow Reserve; HMG Hyperemic Mean Gradient; HSG Hyperemic Systolic Gradient; NR, Not Reported; Pd/Pa Ratio of pressure distal (Pd) and proximal (Pa) to a renal artery stenosis; RMG Resting Mean Gradient; SBP, Systolic Blood Pressure;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Figure 1.3.1** Example of angiography, ultrasound measurements and translesional pressure gradient in a right-sided ARAS. Angiography clearly demonstrates >50% stenosis. The left inset shows Doppler signals at the level of the stenosis (300 cm/s). Both suggest “significant” ARAS, while an invasive pressure gradient measurement only documents a very mild gradient (distal pressure/aortic pressure ratio 0.92, hence haemodynamically not significant). ARAS: Atherosclerotic renal artery stenosis. Reproduced from by permission of Oxford University Press.

**Textbox 1.3.1** Tresholds of translesional gradients for haemodynamically significant ARAS by intra-arterial pressure wire.

- Resting mean gradient >10 mm Hg
- Resting Pd/Pa <0.9
- Hyperemic systolic gradient >20 mm Hg
- FFR <0.8

**Ultrasound:**

Duplex ultrasound is an inexpensive, repeatable, non-invasive and widely available technique that can determine the hemodynamic significance of ARAS. Disadvantages include angle dependency, high operator expertise, high interobserver variability and poor reproducibility (Textbox 1.3.2).
Textbox 1.3.2 Advantages and disadvantages of duplex ultrasound for diagnosis of renal artery stenosis

<table>
<thead>
<tr>
<th>Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Inexpensive</td>
</tr>
<tr>
<td>• Non-invasive</td>
</tr>
<tr>
<td>• No contrast</td>
</tr>
<tr>
<td>• No radiation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Time-consuming (&gt;1hr)</td>
</tr>
<tr>
<td>• Operator-dependent</td>
</tr>
<tr>
<td>• Lack of standardization in diagnosis of ARAS</td>
</tr>
<tr>
<td>• Cannot distinguish between 60 and 99% stenosis</td>
</tr>
<tr>
<td>• Limited by abdominal adiposity or overlying gas</td>
</tr>
<tr>
<td>• Limited visualization of distal renal artery and accessory renal arteries</td>
</tr>
<tr>
<td>• Data cannot be acquired in up to 20% of patients</td>
</tr>
</tbody>
</table>

However, in expert hands, it is an excellent rule-out test and received the same Class I, evidence Level B recommendation for diagnostic screening as other established techniques. Studies of duplex ultrasound derived parameters have generated thresholds for significant ARAS with a variable correlation to diameter stenosis by CA (Table 1.3.2). Commonly reported parameters that directly assess the pre-stenotic main renal artery include renal artery peak systolic velocity (PSV) or the renal to aortic ratio (RAR). The latter is the ratio of PSV in the renal artery to the aorta to eliminate the influence of cardiac output. End-diastolic velocities are less commonly reported. Several studies found a PSV > 200 cm/s and RAR > 3.5 corresponded to at least 60% diameter stenosis with sensitivity (71–98%) and specificity (62–98%). A meta-analysis of 88 studies involving 8147 patients determined that PSV was the best predictor of ARAS > 50% by CA, with a sensitivity of 85% and a specificity of 92%.

Comparisons of direct ultrasound parameters to invasively measured translesional pressure gradients suggested that hemodynamically significant ARAS was associated with higher than previously accepted thresholds (PSV > 318 cm/s, RAR > 3.74, Figure 1.3.1). Measuring direct parameters is technically challenging due to overlying bowel gas preventing access to the entire course of the renal artery, a challenge complicated if there are accessory vessels.

Indirect duplex ultrasound parameters assess poststenotic segmental arteries within the renal parenchyma and include the resistance index (RI), acceleration time, acceleration index and the shape of the systolic peak. These parameters are easier to measure and less dependent on optimal Doppler angles. The RI is the most widely reported indirect parameter and is typically taken as a mean of three measurements calculated by \( (1 – \text{end diastolic velocity})/\text{PSV} \times 100 \). The RI is thought to reflect microcirculatory resistance. An RI value of 0.70 is accepted as the upper limit of normal in adults. A study of 58 patients showed that RI ≥ 0.65 is associated with severe interstitial fibrosis and arteriosclerosis. A difference in RI of >0.05 between kidneys correlated with >70% stenosis in a study of unilateral ARAS. A landmark study showed that
Table 1.3.2 Selected studies comparing Duplex ultrasound criteria against catheter angiography

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Duplex Criteria for diagnosis of RAS</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>AUC</th>
<th>Percentage diameter stenosis for catheter angiographic standard</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>AbuRahma 2012</td>
<td>313</td>
<td>PSV &gt;285cm/s</td>
<td>67</td>
<td>90</td>
<td>0.85</td>
<td>&gt;60%</td>
<td>PSV &gt;285cm/s or a RAR of 3.7 were the best parameters to detect RAS &gt;60%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RAR 3.7</td>
<td>69</td>
<td>91</td>
<td>0.82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drieghe 2008</td>
<td>47</td>
<td>PSV &gt;318cm/s</td>
<td>88</td>
<td>77</td>
<td>0.88</td>
<td>&lt;0.90*</td>
<td>RAR had the best AUC in ROC analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EDV &gt;70cm/s</td>
<td>88</td>
<td>77</td>
<td>0.85</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RAR &gt;3.74</td>
<td>75</td>
<td>97</td>
<td>0.94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staub 2007</td>
<td>49</td>
<td>PSV&gt;200cm/s</td>
<td>92</td>
<td>81</td>
<td>NR</td>
<td>&gt;50%</td>
<td>Mean translesional systolic pressure gradient was 24mmHg at 50% diameter stenosis and 23mmHg at PSV&gt;200cm/s. RAR&gt;2.5 and PSV&gt;200cm/s criteria excluding RAS &gt;70% with 100% negative predictive value.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RAR&gt;2.5</td>
<td>92</td>
<td>79</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>dRI&gt;0.05</td>
<td>31</td>
<td>97</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kawarada 2006</td>
<td>60</td>
<td>PSV&gt;219cm/s</td>
<td>89</td>
<td>89</td>
<td>89</td>
<td>&gt;20mmHg**</td>
<td>PSV correlated more strongly with translesional pressure gradients than percentage diameter stenosis, a gradient of 20mmHg corresponded to 47% stenosis.</td>
</tr>
<tr>
<td>Conkbayir 2003</td>
<td>50</td>
<td>PSV180-200cm/s and RAR&gt;3.0</td>
<td>92</td>
<td>88</td>
<td>0.95</td>
<td>&gt;60%</td>
<td>Combination of direct parameters performed best at diagnosing RAS &gt;60%. There was no difference in performance between PSV 180cm/s and 200cm/s.</td>
</tr>
<tr>
<td>Nchimi 2003</td>
<td>91</td>
<td>PSV &gt;180cm/s or</td>
<td>91</td>
<td>97</td>
<td>96</td>
<td>&gt;60%</td>
<td>Duplex ultrasound showed good</td>
</tr>
<tr>
<td>Study</td>
<td>RAR &gt;3.5</td>
<td>PSV &gt;180cm/s and RAR &gt;3.5</td>
<td>50</td>
<td>91</td>
<td>NR</td>
<td>&gt;50%</td>
<td>Interobserver agreement however is unreliable in detection of accessory arteries</td>
</tr>
<tr>
<td>---------------</td>
<td>----------</td>
<td>---------------------------</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>--------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>de Haan 2002</td>
<td>78</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>The authors do not recommend using duplex ultrasound due to a wide range of sensitivities and specificities quoted in different studies</td>
</tr>
<tr>
<td>Zeller 2001</td>
<td>66</td>
<td>RAR &gt;3.5 and dRI &gt;0.05</td>
<td>76</td>
<td>97</td>
<td>NR</td>
<td>&gt;70%</td>
<td>Although RAR detects the presence of RAS, dRI enables the diagnosis of haemodynamically relevant RAS.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RAR &gt;3.5 and dRI &lt;0.05</td>
<td>100</td>
<td>60</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EDV – end-diastolic velocity; dRI – side-to-side difference in Resistance Index; PSV – peak systolic velocity; RAR – renal aortic ratio; RAS – renal artery stenosis; *ratio of post-stenotic renal to aortic pressure <0.9. **translesional systolic pressure gradient
ARAS associated with RI > 0.8 predicted futility of revascularization\textsuperscript{37}. However, increased RI is not specific to ARAS and is increased by other causes of chronic kidney disease (CKD), aging and extremes of heart rate. Other studies showed improved outcomes after revascularization amongst patients with RI > 0.8\textsuperscript{38}. Some data suggest following an algorithm that combines direct and indirect parameters can improve diagnostic sensitivity and specificity (Textbox 1.3.3)\textsuperscript{28}. Table 1.3.3 summarizes studies reporting the predictive ability of ultrasound parameters to predict a clinical response to revascularization.

**Textbox 1.3.3** Diagnostic algorithm for using duplex ultrasound to determine haemodynamically significant ARAS proposed by Zeller and colleagues\textsuperscript{28}

<table>
<thead>
<tr>
<th>Unilateral ARAS</th>
<th>Bilateral ARAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. PSV &gt; 200 and RAR &gt; 3.5</td>
<td>1. PSV &gt; 200 and RAR &gt; 3.5</td>
</tr>
<tr>
<td>2. RI difference between stenotic and contralateral kidney &gt; 0.05</td>
<td>2. Acceleration time &gt; 0.07 s in relevant kidney</td>
</tr>
</tbody>
</table>

ARAS: Atherosclerotic renal artery stenosis; PSV: Peak systolic velocity; RAR: Renal to aortic ratio; RI: Resistance index.

**Novel Ultrasound Techniques**
Contrast-enhanced ultrasound (CEUS) involves slow intravenous injection of 1-3ml of contrast media. The contrast is made of microbubbles with two parts; a biocompatible membrane shell surrounding a gas. The contrast enhancement lasts around 3 minutes after injection. Second-generation microbubbles are licensed that have more persistent contrast. The microbubbles remain in the vascular space and do not undergo glomerular filtration. The added value of contrast enhancement is in improving the proportion of patients with diagnostic images to determine haemodynamic significance as well as using contrast kinetics to quantify regional perfusion. In a study of 120 patients with suspected ARAS, contrast-enhanced ultrasound identified all 38 cases confirmed by CA whilst only 33 were found by conventional duplex ultrasound\textsuperscript{45}. These techniques are not yet widely available.

**Radionuclide scans**
Radioisotope studies remain a reference technique for measurement of glomerular filtration rate (GFR) with excellent correlation to the gold standard of inulin-clearance\textsuperscript{46}. Combining clearance studies with renal scintigraphy generates functional information that might be useful in the assessment of ARAS. The determination of single kidney (SK)-GFR uses \textsuperscript{51}Cr-ethylenediaminetetraacetic acid (\textsuperscript{51}Cr – EDTA) to assess global GFR, and scintigraphy to apportion the filtration of each kidney by uptake of 99mTc-dimercaptosuccinic acid or mercaptoacetyltriglycine (MAG3). Measuring tracer uptake at baseline and after a dose of
### Table 1.3.3: Studies reporting blood pressure or renal functional response to revascularization by baseline Duplex-ultrasound parameters

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Baseline characteristics</th>
<th>Follow-up (months)</th>
<th>Definition of BP response</th>
<th>Renal outcome</th>
<th>Authors’ recommended threshold to predict response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fujihara 2015</td>
<td>49</td>
<td>&gt;60</td>
<td>1.24±0.5</td>
<td>&gt;10mmHg or &gt;15mmHg reduction where pre-procedure SBP is 150-180mmHg or &gt;180mmHg respectively</td>
<td>eGFR increase &gt;10%</td>
<td>RI &lt;0.7 was associated with better response in the CKD group, although there was no overall improvement in renal function post-revascularization</td>
</tr>
<tr>
<td>Bruno 2014</td>
<td>158</td>
<td>&gt;60</td>
<td>67±29*</td>
<td>DBP &lt;90 mm Hg or reduced by ≥15 mm Hg and/or SBP &lt;140mm Hg on same/reduced medication</td>
<td>eGFR increase &gt;20%</td>
<td>RI &gt;0.73 in the contralateral kidney predicts failed renal response but RI did not predict BP outcome</td>
</tr>
<tr>
<td>Ciani 2010</td>
<td>40</td>
<td>&gt;70</td>
<td>2.0±0.9</td>
<td>None</td>
<td>eGFR change &gt;20%</td>
<td>RI&gt;0.83±0.2 averaged from both kidneys predicted renal functional decline and increased proteinuria</td>
</tr>
<tr>
<td>Santos 2010</td>
<td>106</td>
<td>NR</td>
<td>1.5</td>
<td>None</td>
<td>eGFR change &gt;20%</td>
<td>RI &gt;0.8 predicted renal functional decline and death but not BP response.</td>
</tr>
<tr>
<td>Crutchley 2009</td>
<td>86</td>
<td>NR</td>
<td>1.8±1.1</td>
<td>None</td>
<td>eGFR change &gt;20%</td>
<td>RI &gt;0.8 predicted BP response but not renal functional change</td>
</tr>
<tr>
<td>García-Criado</td>
<td>36</td>
<td>&gt;60</td>
<td>NR</td>
<td>&gt;15% reduction in BP on same/reduced medication</td>
<td>&gt;15% reduced</td>
<td>RI&gt;0.8 predicted BP response but not renal functional change</td>
</tr>
<tr>
<td>2005&lt;sup&gt;44&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>serum creatinine</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Zeller 2003&lt;sup&gt;38&lt;/sup&gt;</td>
<td>241</td>
<td>&gt;70</td>
<td>1.6**</td>
<td>NR</td>
<td>NR</td>
<td>yes</td>
</tr>
<tr>
<td>Radermacher 2001&lt;sup&gt;37&lt;/sup&gt;</td>
<td>131</td>
<td>70±13</td>
<td>51±41**</td>
<td>157±22**</td>
<td>86±16**</td>
<td>yes</td>
</tr>
</tbody>
</table>

*creatinine clearance in ml/min; **data was averaged where baseline characteristics were only reported for subgroups.

ABPM: Ambulatory Blood Pressure Monitoring; DBP: Diastolic blood pressure; MAP: Mean arterial pressure; NR: Not Reported; RI: Resistance Index; SBP: Systolic Blood Pressure;
Captopril improves the ability to detect significant unilateral ARAS by an exaggerated transient reduction in GFR in the ipsilateral kidney due to a greater dependence on angiotensin-mediated efferent arteriolar resistance\(^47\). In a multicentre study population with known ARAS detected by other methods, the technique was 83% sensitive and 93% specific for detecting unilateral ARAS >70% by CA\(^48\). Captopril renography is currently rarely used as diagnostic accuracy is limited in bilateral ARAS or patients with CKD\(^47\). Meta-analyses report inferior diagnostic performance to angiography by computed tomography (CT) or magnetic resonance\(^49\).

CT Angiography
In recent years, spiral CT angiography (CTA) has become a standard non-invasive technique for visualization of the renal vasculature. Rapid and accurate images are generated that are suitable for 3D reconstruction (Figure 1.3.2). Compared to magnetic resonance, CTA offers better spatial resolution and shorter exam times. Disadvantages of CTA include ionizing radiation, difficult interpretation in heavily calcified arteries and risk of contrast-induced kidney injury. Although modern non-ionic contrast agents have a lower propensity to cause kidney injury than older ionic agents, the risk is still 2% in the general population and increases with declining GFR and comorbidity such as CKD or diabetes. Patients with a reduced intravascular volume are at a significantly greater risk. International guidelines recommend preventive protocols based on pre-hydration and stopping nephrotoxic drugs\(^50\).

Dynamic contrast enhanced CT
Advances in CT technology allow renal physiological parameters to be derived from kinetic modeling of an injected bolus of iodinated contrast media. Kwon and co-workers recently reported the largest comparison in 96 patients with essential (n=56) or renovascular hypertension (n=40)\(^51\). Multidetector CT decay kinetics were used to derive SK perfusion, volume and GFR and compared to GFR by iothalamate clearance. GFR by CT correlated well with iothalamate GFR \((r = 0.88)\), while Bland-Altman plots showed only moderate agreement with no systemic bias. GFR by CT is at an earlier stage of validation with reports confined to research studies in expert centres. Accuracy remains inferior to reference methods by radioisotope tracers and there is no multi-centre validation\(^38\). A notable disadvantage to the technique is the significant additional dose of ionizing radiation incurred (26-27 mSv)\(^51\).

Magnetic resonance angiography (MRA)
Compared with CA, magnetic resonance angiography (MRA) is noninvasive and with multiplanar acquisition can generate 3D views. A meta-analysis demonstrated CTA and MRA have an almost equivalent performance to CA, with sensitivities and specificities > 90%\(^49\). The spatial resolution of MRA approaches that of CTA. The lack of ionizing radiation or nephrotoxic contrast media makes MRA a good choice both for screening and planning an intervention. MRA is typically performed using gadolinium-based contrast media (Gd). MRA has the ability to be combined with dynamic contrast imaging to determine blood flow, SK-GFR and other
physiological information in a single investigation. Limitations include slower acquisition than CTA, patient intolerance due to claustrophobia, contraindications in patients with implanted ferromagnetic materials, flow-related artifacts and rare risk of nephrogenic systemic fibrosis in patients with advanced CKD. Multiple guidelines now advise avoidance of Gd contrast media in those with estimated GFR < 30 ml/min/1.73 m2 to mitigate this risk, and no cases have been reported since their implementation. Newer noncontrast MRA methods use time-of-flight techniques that are prone to signal loss with historically poor diagnostic accuracy compared to Gd-enhanced MRA. More recent data have demonstrated almost comparable accuracy with a sensitivity of 73–94% and a specificity of 82–98% to determine >50% ARAS by CA. Where MRA was the screening technique for enrollment into the CORAL trial, only patients with specific criteria suggesting a greater likelihood of functionally significant ARAS were allowed to be enrolled. For example, patients with >75% visually estimated stenosis on MRA were enrolled if there was spin dephasing or if the ipsilateral kidney was 1 cm smaller than, enhanced less or showed delayed Gd excretion compared to the contralateral kidney. Although the neutral results of CORAL might argue against the need to evaluate functional significance of ARAS, the above MRA features have not been robustly validated.

**Measuring hemodynamic significance by four-dimensional flow MRI**

Recent advances in MRI hardware and rapid acquisition techniques allow velocity-sensitive image acquisition in three dimensions with cardiac gating. This technique is known as 4D flow MRI. Such acquisitions can provide velocity, flow, shear wall stress and pressure gradients.
without contrast. They have shown excellent agreement with invasive pressure measurements in cardiac studies. Recently, the technique has been developed in renal arteries. Using experimentally induced ARAS in swine, a recent study reported excellent correlation between invasively measured systolic pressure gradient and the 4D-flow MRI estimate (R² = 95%)\(^{54}\). This technique potentially allows noninvasive assessment of translesional pressure gradients to complement routine MRA (Figure 1.3.3).

**Dynamic contrast enhanced MRI (DCE-MRI)**

Gd chelates produce contrast by shortening local T1 relaxation times and are freely filtered at the glomeruli without tubular secretion or reabsorption. After injecting an intravenous bolus of Gd, high-speed repetitive acquisition of T1-weighted images capture the bolus transit from the aorta into the renal arteries, then dispersing into the renal parenchyma and then collecting system. Mathematical modeling of the bolus transit generates estimates of SK-GFR, regional renal blood perfusion and tubular excretion. Dynamic contrast-enhanced (DCE)-MRI-based SK-GFR has a good correlation (r = 0.82–0.92) to isotope based reference methods for SK-GFR using only 3–4 ml of Gd and adding little time to a routine MRA study\(^{55–58}\). Renal DCE-MRI has not yet penetrated into routine clinical practice due to reasons that include variation in the postprocessing, lesser accuracy than reference methods and a lack of multicentre validation\(^{59}\). The authors incorporated DCE-MRI into an investigation of the response to revascularization of ARAS. The authors reported predictors of GFR change in 15 patients with 22 kidneys stented for ARAS with paired assessment of SKGFR by DCE-MRI and radioisotopes at baseline and 4 months post stenting\(^{60}\). Improved GFR was defined as >15% increase from baseline and at least >1 ml/min. DCE-MRI also produced measurements of blood flow, blood volume, extraction fraction, tubular transit time and functional volume (the area of Gd enhancement within the whole renal volume). A good correlation was found between SK-GFR values from DCE-MRI and radioisotopes (r = 0.91). Baseline predictors of GFR increase were lower extraction fraction, higher blood volume, longer tubular transit time and lower SK-GFR, as well as the ratio of renal parenchymal volume to SK-GFR (see below). Revascularization improved blood flow and blood volume in all groups but only increased functional volume in the group with improved GFR. As a result, the authors proposed that well-vascularized RAS kidneys with reduced extraction fractions are those most likely to benefit from revascularization and highlighted DCE-MRI as a complementary technique to routine MRA. The technique requires further refinement and validation before it can be recommended for routine clinical use.

**Figure 1.3.3** Swine model of ARAS with unenhanced 4D flow MRI. (a) Catheter angiography image shows two endovascular pressure-sensing guidewires across a moderate left ARAS (solid arrow). Pressure sensors are located at the end of each wire (open arrows). (B) Reconstruction of the complex difference signal obtained from 4D flow MRI shows stenosis (arrow). (C) Velocity map shows increased velocities (open arrow, color coded in gold and red) distal to ARAS (solid arrow). (D) Corresponding pressure map shows a pressure gradient
Assessing renal functional reserve
One of the recent shifts in the understanding of ARAS is the need to assess the functional viability of the renal parenchyma that lies beyond the stenosis and in the contralateral kidney. This is conceptually equivalent to assessing the ischemic penumbra after a stroke or the area at risk or hibernation after myocardial infarction. These tissue regions are ischemic but not necrosed and retain the potential for restored function consequent to restored perfusion. Further, ARAS is histologically characterized by inflammation, oxidative stress, capillary rarefaction and fibrosis that might persist despite perfusion being restored. Concepts of renal functional reserve have only been sparsely defined. This is in part because advanced imaging techniques have been confined to research settings. However, there is also a more complex relation between perfusion, oxygenation and function in the kidney than other organs. To generate a filtration pressure, renal blood flow is in excess of the metabolic needs of that kidney and there is a steep oxygenation gradient between the cortex and the near hypoxic medulla. Compensatory arteriovenous shunting, tubuloglomerular feedback and neurohormonal inputs form part of complex autoregulatory interplay between perfusion, oxygenation and filtration.

Blood-oxygen level-dependent imaging
In vivo assessment of renal hemodynamics and tissue oxygenation is challenging. Blood-oxygen-level-dependent (BOLD) MRI was first described in human kidneys in 1996 and
remains the most extensively studied noninvasive tool to assess regional renal oxygenation in humans. BOLD imaging exploits the change in the weakly magnetic properties of hemoglobin as it converts from the deoxygenated to the oxygenated form, which in turn alters the magnetic field in the vicinity of adjacent water molecules to increase signal intensity in T2*-weighted images. The relationship between BOLD signal intensity denoted by R2* (R2* = 1/T2*) and renal tissue oxygenation has been validated against implanted oxygen-sensitive microelectrodes in animal studies. However, the nature of the R2* signal is complex as it can be influenced by nonoxygen-related factors including hydration status, sodium avidity, vessel geometry and local temperature. Thus, repeated measures of R2* within patients under physiological challenge are inherently more sensitive to oxygenation changes than single measurements between patients by effectively controlling for confounders. The R2* response to furosemide is most frequently reported. Furosemide inhibits sodium transport in the thick ascending loop of Henle, reducing medullary oxygen consumption with a consequently increased medullary oxygenation and decreased medullary R2*.

Gloviczki and coworkers reported R2* in 24 patients with essential hypertension, 13 with moderate ARAS and preserved renal volume and 17 with severe ARAS and reduced renal volume. Cortical R2* values were increased in severe ARAS but preserved in moderate ARAS. Whilst baseline medullary R2* values did not differ between groups, the medullary R2* response to furosemide was attenuated in moderate and severe ARAS. Textor and coworkers reported R2* response to furosemide in 25 subjects with suspected ARAS. Furosemide induced a normal decrease in R2* in 21 kidneys without ARAS. In kidneys with severe ARAS but preserved volume, R2* was elevated at baseline with the R2* response to furosemide maintained. In kidneys with severe ARAS and reduced volume, the basal R2* was paradoxically low (reflecting increased oxygenation) but with no change in response to furosemide. Gloviczki and coworkers reported R2*, blood flow and SK-GFR in 14 patients with unilateral ARAS and 14 control patients with essential hypertension. Within the ARAS group, stenosed kidneys had increased renal vein renin levels, reduced blood flow, reduced GFR but preserved oxygenation by basal R2* compared to contralateral kidneys. The stenosed kidneys had an attenuated R2* response to furosemide compared to the hypertensive group. Increased renal venous oxygenation invasively sampled from stenosed kidneys was interpreted as an adaptive reduction in oxygen consumption.

In summary, basal cortical R2* may be increased in severe ARAS. The lack of a medullary R2* decrease in response to furosemide might reflect adaptive reduction in oxygenation consumption or reduced renal oxygenation reserve. Quantifying the magnitude of the furosemide R2* response to predict clinical outcomes showed promise in a swine model of ARAS, but to date there are no data in humans.

**Combining renal volume with functional measurements**
The length of a kidney has long been used as a surrogate to predict functional severity of ARAS, with a severe unilateral ARAS being classically associated with a small atrophied kidney. ARAS may also cause glomerular microangiopathy in the contralateral kidney. This results in reduced volume in the stenotic kidney, with the contralateral kidney showing early compensatory hypertrophy then late volume loss. In 65 patients with ARAS, we showed that 3D renal volume measured by MRI was better correlated to isotopic SK-GFR ($r = 0.86; p < 0.001$) than 2D measures including length and cortical thickness ($r = 0.6 – 0.78; p < 0.001$). We also found a greater ratio of volume to SK-GFR in the kidneys with the largest increases in GFR following revascularization, proposing the ratio as a measure of functional reserve or “hibernation” in ARAS. The concept of assessing functional reserve to predict treatment response was evolved in a pilot study of 28 patients investigated for ARAS (16 with ARAS > 50% and 12 controls). We showed that whilst $R2^*$ alone had only 40% sensitivity, the ratio of $R2^*$ to isotopic SK-GFR was 67% sensitive and 86% specific in predicting a 15% increase in GFR four months after stenting of ARAS.

**Other non-invasive MRI tissue characterization techniques**

Other noninvasive MRI-based techniques might hold promise in assessment of renal functional reserve. Magnetic resonance elastography uses an external mechanical vibration source and velocity-encoded MRI to characterize wave propagation. Stiffer tissues generate higher wavelengths allowing 3D maps of tissue stiffness that showed good correlation to fibrosis in a swine model of ARAS.

Diffusion tensor imaging can describe tissue microstructure by quantifying the degree of restriction of water molecule diffusion by cell membranes in multiple directions. Preliminary studies in the setting of CKD and renal allografts have shown diffusion measures correlate to histopathological fibrosis scores, but there are no data in the context of ARAS.

Arterial spin labeling uses magnetic labeling of water in blood across an artery as an endogenous tracer to generate perfusion maps by kinetic modeling. Fenchel and coworkers reported promising initial data in 18 patients; severe ARAS > 70% showed reduced perfusion values (Figure 1.3.4). Combining arterial spin labeling with BOLD to estimate blood flow and oxygenation would have advantages in the assessment of ARAS, allowing serial studies and obviating the need for exogenous contrast or ionizing radiation.

**Figure 1.3.4** Arterial –spin labeling magnetic resonance showing mild (30%) left RAS and severe (90%) right RAS in a 70-year-old man. Perfusion-weighted map shows differences in perfusion between right (191ml/100g/min) and left (270ml/100g/min) kidneys. Color bar represents perfusion, in milliliters per 100g per minute. RAS: renal artery stenosis. Reproduced with permission from.
Serum and Urine Biomarkers

A few studies have reported inflammatory and cardiovascular biomarkers for ARAS. Studies using nonspecific inflammatory or cardiovascular biomarkers such as C-reactive protein have limited value as levels correlate to general atherosclerotic risk and comorbidities that are associated with ARAS. Another nonspecific marker is the level of urinary protein that reflects parenchymal microangiopathy and was correlated to poor renal functional and blood pressure outcomes after revascularization. Plasma renin activity is a marker for activation of the renin-angiotensin-aldosterone system and was historically used to identify patients with renovascular hypertension that would benefit from surgical revascularization. However, serum values showed poor sensitivity and specificity and studies were prone to reporting bias. A recent study explored potential novel biomarkers sampled peripherally and from renal veins in matched groups with ARAS and essential hypertension. Higher systemic and stenotic renal vein levels of neutrophil gelatinase-associated lipocalin, plasminogen activator inhibitor-1 and soluble urokinase-type plasminogen activator receptor were noted in ARAS. Metabolite profiling by liquid chromatography-mass spectrometry (LC-MS) on renal venous samples from 16 patients with ARAS and 16 with essential hypertension demonstrated a clear separation of profiles between groups but not between stenotic and contralateral kidneys. These findings are consistent with the kidney’s ability to adapt to ARAS but also reflect that the contralateral kidney is subject to similar inflammatory and pressor responses initiated in the stenotic kidney. Currently, these biomarkers lack the specificity required to inform clinical practice.

Clinical risk scores and phenotypes

ARAS frequently coexists with extrarenal atherosclerosis and is a common incidental finding during coronary angiographic procedures. Many of the diagnostic techniques we have outlined have small but important hazards, and there has been interest in developing clinical
risk scores that improve the pretest probability or diagnostic yield of such tests. A summary of these studies is outlined in Table 1.3.4. As a practical illustration, Cohen and coworkers described a clinical risk score predicting that a 56-year-old man with hypertension, treated with two cardiovascular drugs, a creatinine level of 1.4 mg/dl and three-vessel coronary disease has an estimated 19% probability of ARAS with >75% stenosis by CA80. A valid critique of such scores is that they merely capture general atherosclerotic risk and lack the specificity to inform clinical decisions.

A recent single-centre study described 237 patients with >50% ARAS and one or more high-risk phenotypes including flash pulmonary edema, rapid decline in kidney function and refractory hypertension (Table 1.3.2). This study showed that revascularization was associated with improved outcomes in patients with flash pulmonary edema or a combination of rapid decline in kidney function and refractory hypertension. Crucially, it is these high risk patient subgroups that are emphasized in consensus guidelines (Table 1.3.5) and scarcely represented in major randomized trials. Identification of high-risk phenotypes might inform shared decision-making around the investigation and management of ARAS.

**Expert Commentary**

In view of neutral results of randomized controlled trials, the value of screening for ARAS is less clear. An important subgroup of patients with high-risk clinical features that will benefit from revascularization remains and the challenge lies in identifying patients with functionally significant stenosis and viable renal tissue. Advances in imaging techniques have shifted the focus from anatomical towards functional imaging. CA and captopril renography are no longer recommended for diagnosis, but CA with translesional pressures can determine hemodynamic significance. Duplex ultrasound shows promise for non-invasive measurement of hemodynamic significance, but remains limited by operator dependency and the inability to distinguish stenosis beyond 60%. It is likely best used in conjunction with CTA or MRA. Although we have summarized small observational cohorts using functional measures to determine hemodynamic significance of ARAS, no randomized trials selecting only by these criteria have been successfully conducted.

The most commonly used diagnostic techniques are CTA and MRA with similar diagnostic accuracy (Table 1.3.6). Their use is limited in patients with estimated GFR < 30 ml/min due to the respective risks of contrast-induced nephropathy and nephrogenic systemic fibrosis. However risks are acceptable by following preventive protocols. As it does not require ionizing radiation, functional MRI with techniques such as velocity encoded and BOLD imaging show the greatest promise for characterizing functionally viable tissue. Their combination with MRA allows a single visit assessment of vascular anatomy, functional significance of ARAS and viability of parenchymal tissue. Whilst pilot studies show promise, they remain at the early phase of validation that would be required to justify adoption in routine practice.
Table 1.3.4 Sensitivity and specificity of putative diagnostic risk prediction scores for significant unilateral ARAS.

<table>
<thead>
<tr>
<th>Study</th>
<th>Derivation cohort</th>
<th>Validation cohort</th>
<th>Factors contributing to score</th>
<th>Reference standard ARAS by CA (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>AUC</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ma 2015&lt;sup&gt;81&lt;/sup&gt;</td>
<td>257 Coronary angiography for myocardial infarction, concurrent renal angiography</td>
<td>98 Ischemic heart failure* ARAS&gt;60% by Duplex ultrasound</td>
<td>Age, hypertension, stroke, intermittent claudication, serum creatinine</td>
<td>&gt;60</td>
<td>85</td>
<td>31</td>
<td>0.72</td>
<td>The score predominantly predicts atherosclerotic risk rather than ARAS per se</td>
</tr>
<tr>
<td>Cohen 2005&lt;sup&gt;80&lt;/sup&gt;</td>
<td>843 Coronary angiography, concurrent abdominal aortography, 10% unilateral ARAS</td>
<td>843 The derivation cohort was internally validated by bootstrapping</td>
<td>Age, sex, serum creatinine, peripheral vascular disease, number of cardiovascular drugs, hypertension, three-vessel coronary artery disease or previous coronary bypass surgery</td>
<td>&gt;75</td>
<td>76</td>
<td>71</td>
<td>0.80**</td>
<td>The score predominantly predicts atherosclerotic risk rather than ARAS per se. Using a score of ≥11 in clinical practice could reduce the proportion of patients receiving abdominal aortography to 34%.</td>
</tr>
<tr>
<td>Krijnen 2005&lt;sup&gt;82&lt;/sup&gt;</td>
<td>460 Refractory hypertension despite a standardized two-drug regime or</td>
<td>180 Refractory hypertension, serum creatinine &lt;200umol/L</td>
<td>Age, sex, vascular disease, recent onset of hypertension, smoking, body mass index, abdominal</td>
<td>&gt;50</td>
<td>91</td>
<td>NR</td>
<td>0.71</td>
<td>Discriminative ability was limited by a high-proportion of non-atherosclerotic stenosis due to 37% fibromuscular dysplasia in</td>
</tr>
</tbody>
</table>
significant rise in creatinine on commencing ACE-inhibitor, serum creatinine \(<200\text{umol/L}\)
bruit, serum creatinine, and hypercholesterolemia

the derivation cohort. The score would reduce imaging referrals by 20% at the expense of 9% false negatives

*New York Heart Classification stage II-IV due to coronary artery disease and Left ventricular ejection fraction <50%. **Concordance index (equivalent to AUC for dichotomous variables)

ACE: Angiotensin Converting Enzyme; ARAS: atherosclerotic renal artery stenosis; AUC: area under receiver-operator characteristic curve; CA: catheter angiography.
Table 1.3.5 Reasonable Indications for Percutaneous revascularization of ARAS from ACCF/AHA Guidelines. Reproduced with permission from 83.

<table>
<thead>
<tr>
<th>Class I</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hemodynamically significant ARAS with unexplained recurrent Congestive heart failure or flash pulmonary edema</td>
</tr>
<tr>
<td>2. Stent placement for ostial ARAS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class IIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hemodynamically significant ARAS with accelerated/resistant/malignant hypertension</td>
</tr>
<tr>
<td>2. Hemodynamically significant ARAS with unstable angina</td>
</tr>
<tr>
<td>3. ARAS and progressive CKD with bilateral stenosis or a solitary functioning kidney</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class IIb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hemodynamically significant ARAS with asymptomatic bilateral stenosis or a solitary functioning kidney</td>
</tr>
<tr>
<td>2. Unilateral ARAS with CKD</td>
</tr>
</tbody>
</table>

ACCF: American College of Cardiology Foundation; AHA: American Heart Association; ARAS: Atherosclerotic Renal Artery Stenosis; CKD: Chronic Kidney Disease

Although serum and urine biomarkers have been investigated in ARAS, data are sparse and are presently of limited diagnostic value. Few studies have described risk prediction scores that might prevent unnecessary investigation particularly in patients who do not align to high-risk phenotypes. These scores are currently too crude to recommend for use.

**Five year view**

After the initial enthusiasm for revascularization of ARAS, recent neutral trial outcomes have shown that restoring vessel patency alone does not recover kidney function in most patients selected by conventional criteria84. There are novel cellular protective treatments on the horizon that are natural adjuncts to revascularization85. Thus, the imperative is greater than ever for diagnostic methods in ARAS that can identify those who might benefit from targeted therapies whilst avoiding harm in those who will not. When benchmarked to a developmental pathway of
comprehensive validation\textsuperscript{86}, even established techniques such as CTA and MRA are inadequate for the purpose of improving patient outcomes (Textbox 1.3.4). Therefore, we believe that the shift from anatomical to functional or physiological imaging will continue to occur. A clear separation should be made between assessing hemodynamic significance of arterial stenosis and functional reserve of renal parenchymal tissue. MRI has advantages over CT with unrealized potential for assessing both hemodynamic significance and tissue viability, mostly without using Gd contrast media. Some MRI techniques such as BOLD imaging are technically established but not validated. A recent study proposed a method of BOLD R2* values to determine fractional tissue hypoxia, a measure that is reproducible and that might form a surrogate outcome or selection criteria for a future clinical trial\textsuperscript{87}. A recent proof-of-concept study reported that arterial-spin labeling might allow measurement of SK-GFR without contrast media and further developments in this area are expected\textsuperscript{88}. 4D flow MRI will allow noninvasive measures of translesional gradients to complement anatomical MRA. SK-GFR with DCE-MRI and low-dose Gd is being developed to further improve accuracy against reference standards. The experience in functional brain imaging has demonstrated that a coordinated research effort to harmonize protocols between research centres and MRI vendors can accelerate technique development and validation\textsuperscript{89}. Efforts are being made to establish a similar international network in renal functional MRI. CT perfusion and GFR measurements will continue to develop with methods to reduce the radiation burden. A current phase 2a clinical trial is assessing the effects of a cell-based therapy as an adjunct to renal revascularization to minimize ischemia reperfusion injury (ClinicalTrials.gov identifier: NCT01755858). This study uses iothalamate GFR as the primary outcome complemented by SK-GFR, perfusion by CT and inflammatory biomarkers. Duplex ultrasound techniques continue to improve and the wider use of microbubble contrast enhancement may start to bridge the gap to CTA and MRA at least in research settings. Recent advances may see microbubbles used not for diagnosis but as targeted delivery of novel cellular protective therapies for ARAS\textsuperscript{90}. The imperative to deliver individualized and functionally directed treatments whilst avoiding harms will accelerate development and validation of these diagnostic techniques.

Table 1.3.6 Prospective studies comparing different imaging modalities performed over the past 10 years.

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Reference standard ARAS (%)</th>
<th>Modalities studied</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eriksson 2010\textsuperscript{91}</td>
<td>47</td>
<td>&gt;50% by CTA</td>
<td>MRA</td>
<td>81</td>
<td>79</td>
<td>CTA and MRA are superior to DUS and CR in diagnosing ARAS but DUS suits patient screening</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DUS</td>
<td>70</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CR</td>
<td>40</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Rountas</td>
<td>58</td>
<td>&gt;50% by CA</td>
<td>CTA</td>
<td>94</td>
<td>93</td>
<td>Authors suggest</td>
</tr>
</tbody>
</table>
individualized algorithms involving use of DUS screening, especially in younger patients, followed by CTA/MRA

Standard US cut-off criteria do not correlate well with hemodynamic significance. CR is not recommended for evaluating ARAS.

**Abbreviations:** ARAS, atherosclerotic renal artery stenosis; CA, catheter angiography; CR, captopril renography; CTA, computed tomographic angiography; DUS, duplex ultrasound; MRA, magnetic resonance angiography

**Textbox 1.3.4 Developmental framework of incremental steps required for comprehensive validation of diagnostic methods of ARAS**

Each step is harder to fulfil. No current test in development achieves more than 7 of these 15 steps and many whole imaging modalities have never achieved the final step.

- Technical development and theoretical basis of test.
- Direct comparison (animal models and then human autopsy material).
- Detection of changes in established disease compared with normal subjects.
- Correlation with known markers of impaired perfusion (eg, reduced glomerular filtration).
- Correlation with known biomarkers of reduced perfusion or filtration (eg, cystatin).
- Demonstration of the test in more than one clinical scenario.
- Demonstration of test sensitivity (early disease or with age).
- Demonstration of the ability to track change (with time, after treatment).
- Demonstration of predictive or prognostic value of the test.
- Standardization of the test (reproducibility, different equipment, non-research settings, quality control, limitations of test).
- Development of robust age/ethnic normal reference ranges.
- Changes in biomarker remain tied to the disease after treatment.
- Demonstration of the test as a surrogate trial endpoint.
- Clinical use and regulatory approval of the test.
- Proof test use improves clinical outcome.
Key issues

- Two recent major trials of angioplasty and stenting for ARAS did not show improved clinical outcomes compared to optimal drug therapy. However, the trials were limited by visually estimated disease severity and a lack of higher-risk patients.
- There has been a shift in focus from anatomical to functional imaging of ARAS to assess hemodynamic significance and the functional reserve of the renal parenchyma.
- ARAS can be diagnosed by several techniques. None are perfect, with a balance of accuracy versus risk.
- Catheter angiography with translesional pressures is the reference standard technique but invasive and reserved for planned intervention.
- Duplex ultrasound is inexpensive, repeatable and non-invasive with potential to determine hemodynamic significance. However it is the least accurate and most operator-dependent. Advances in contrast-enhanced ultrasound may improve accuracy but only preliminary data is available.
- CTA and MRA are the current mainstay of diagnostic techniques with equivalent accuracy.
- Renal functional MRI shows great promise. Techniques such as velocity-encoding, BOLD-imaging, volumetry and single-kidney GFR allow a comprehensive evaluation of stenosis and tissue viability. However standardized protocols in multi-centre studies are required to enable the evidence base to mature.
- In research centres, novel CT methods allow single-kidney GFR and perfusion with the tradeoff of greater ionizing radiation exposure.
- Captopril renography is rarely used but radionuclide studies to determine single-kidney GFR remain the reference standard for measured GFR.
- Soluble biomarkers and clinical prediction scores, currently add little to diagnostic imaging.
References:


assessment of renal artery stenosis--correlation with intra-arterial pressure gradient. 


58. Tofts PS, Cutajar M, Mendichovszky IA, Peters AM, Gordon I. Precise measurement of


Chapter 2 - Aims and Objectives
Preface:
This chapter summarizes the main aims and objectives of the thesis and of each individual results chapter.

Increased understanding of the pathophysiology and molecular biology of many diseases has fuelled interest in the development of ‘precision medicine’ in healthcare, to help identify the subset of patients at higher risk of suffering adverse events. This would help tailor investigations and allocate therapeutic interventions and limited resources more effectively, however this concept has not yet been applied to atherosclerotic renovascular disease (ARVD). Indeed, ARVD is a complex, heterogenous condition that can lead to variable outcomes in different patients. While contemporary multi-targeted medical therapy is the mainstay of treatment in all patients with ARVD, there is observational evidence that renal revascularization can confer added benefit to a small subgroup of patients who present with ‘high-risk’ features such as cardiovascular instability or rapidly deteriorating renal function and expert consensus statements still recommend consideration of revascularization in specific situations. The overall aims of this epidemiological project were to explore the main determinants of adverse outcomes in patients with ARVD, to identify the specific patient sub-groups who may gain benefit from revascularization and to develop a risk stratification model that can facilitate a more patient-specific therapeutic approach. Long-term end-points considered for this research project included death, progression to end-stage kidney disease, cardiovascular event and a composite end-point composed of the first of any of these events.

The following is a brief summary of the aims of each results chapter and the research questions that each study addressed.

The first results chapter is based on the timeline discussed in Chapter 1.2 and aims to explore how management of this condition has been influenced by important studies published in this field over 3 decades.

Chapter 4.1 Research Questions:
1. Has the clinical phenotype of patients with ARVD changed over the past three decades?
2. Has management of ARVD changed over the past three decades?
3. Do changes in clinical management of ARVD correlate with improved clinical outcomes?

The subsequent chapter aims to identify the baseline features that may predict worse clinical outcomes in an unselected cohort of patients with ARVD.
In Chapter 4.3, we tested our hypothesis that outcomes post-revascularization are more likely to be positive in patients who have at least one ‘high-risk’ clinical presentation (rapidly declining renal function, flash pulmonary oedema and/or uncontrolled hypertension) together with anatomically severe stenosis, suggestive of haemodynamic significance, and without significant proteinuria, which is a surrogate of potentially viable renal parenchyma.

Chapter 4.3 Research Questions:
1. What is the effect of revascularization on patients with high-risk clinical presentations, bilateral severe renal artery stenosis and proteinuria, on important long-term clinical end-points?
2. What are the physical characteristics of patients who may gain benefit from revascularization?

In Chapter 4.4 we explored the prognostic value of novel biomarkers in patients with ARVD. The biomarkers selected for this study were those that have been shown to be relevant in patients with chronic kidney disease and cardiovascular disease, conditions that are ubiquitous in patients with ARVD. These novel biomarkers include fibroblast growth factor-23 (FGF-23), cystatin C, kidney injury molecule-1 (KIM-1), myeloperoxidase (MPO), neutrophil gelatinase-associated lipocalin (NGAL), N-terminal prohormone of brain natriuretic peptide (NT-proBNP), high-sensitivity cardiac troponin T (hs-cTNT), anti-apolipoprotein A1 Immunoglobulin G (anti-apo-A1 IgG).

Chapter 4.4 Research Questions:
1. Are novel biomarkers associated with long-term adverse outcomes in patients with ARVD?
2. Can novel biomarkers improve risk prediction when used in conjunction with traditional cardiovascular and renal risk factors?
3. Can novel biomarkers identify patients who respond positively to revascularization?

Finally we selected a small number of variables that were closely associated with long-term end-points and used these to design a simple clinical risk calculator that can aid risk stratification and patient selection for revascularization.
Chapter 4.5 Research Questions:
1. How can we design a risk calculator that can assist clinicians with risk stratification and outcome prediction?
Chapter 3 - Methodology
Preface:
This chapter describes the methodology used for the results section. Given the alternative format of this thesis, there is overlap between the contents of this chapter and the methods section of each results chapter. An overview of the statistical analyses employed in this research project is provided in this chapter, while the method sections of the results chapters provide a more detailed description of the specific analyses used for individual studies.
3.1 Ethical Approval

This observational research study has received approval from the Wrightington Wigan and Leigh Research Ethics Committee (REC 07/Q1410/33) and the Salford Royal NHS Foundation Trust Research and Development Office. Individual patient consent was not required due to the retrospective nature of the studies performed. Funding support has been provided by the Salford Royal NHS Foundation Trust Renal Research Fund.
3.2 Study Design

The Salford Renovascular Study is an observational, longitudinal cohort study that was first established in 1986. Patients recruited into this observational study included all those adults diagnosed with atherosclerotic renovascular disease (ARVD) on renal artery imaging (renal digital subtraction angiography in the early years, computed tomography angiography [CTA] and magnetic resonance angiography [MRA] more recently), either at Salford Royal Hospital or elsewhere, and referred to the Salford renal department (catchment population 1.5 million).

Data was collected anonymously and retrospectively for most patients and only a proportion of patients who were recruited into other studies were consented. Patients with a different aetiology for their renal artery stenosis (e.g. fibromuscular dysplasia, vasculitis) were excluded from this study.

Successive clinical research fellows updated data on an annual basis over a thirty-year period from hospital records; each fellow was trained by their predecessor to ensure systematic and uniform data collection. Data was stored in Microsoft Excel format and was password protected.

New patients were entered into the database up until 31st August 2014 and data censoring was performed at the earliest of 11th May 2015, death, or last patient encounter if discharged or lost to follow-up.
3.3 Data collection

The following data was collected from patient hospital records:

Demographics:
- Date of diagnosis of ARVD
- Age at date of diagnosis of ARVD
- Gender

Renovascular details:
- Stenosis severity - Visual percentage diameter stenosis obtained from cross-sectional angiography (intravenous digital subtraction angiography [IVDSA], intra-arterial digital subtraction angiography [IADSA], computed tomographic [CT] or magnetic resonance [MR] angiography), reported by just two specialist radiologists over a thirty year period
- Patency score – An arbitrary measure of stenosis severity, calculated as: 100 - (Percentage Left renal artery stenosis [RAS] + percentage Right RAS)
- Revascularization – date, indication, outcome

Baseline comorbidities:
This information was collected at time of enrollment into the study:
- Hypertension – defined as blood pressure >140/90mmHg, or patient on anti-hypertensive medication at time of ARVD diagnosis.
- Myocardial infarction and date of event
- Congestive heart failure (CHF) – defined as documented symptoms of orthopnea, paroxysmal nocturnal dyspnea, clinical evidence of CHF on examination and/or echocardiographic left ventricular ejection fraction <40%.
- Flash pulmonary oedema (FPE) – defined as acute decompensated heart failure in the absence of a documented precipitating cardiac event or known reduced ejection fraction (<40%).
- Peripheral vascular disease – defined by symptoms of intermittent claudication, presence of ischaemic ulcers or previous vascular intervention.
- Abdominal aortic aneurysm
- Diabetes – Type 1, Type 2, and microvascular organ damage

Medication:
Prescription of the following medication was documented as recorded on medical correspondence. Follow-up medication data was updated at 12-monthly intervals (+/- 4 months) from date of diagnosis until censoring:
• Angiotensin converting enzyme inhibitor [ACEI]/angiotensin receptor blocker [ARB]/Renin inhibitors and intolerances – documented acute kidney injury (severity undefined) or deterioration in renal function, hyperkalaemia, cough
• Beta-blockers
• Calcium channel blockers
• Alpha-blockers (unless prescribed for prostatic/urologic indications)
• Any diuretics (either loop or thiazide diuretics)
• Total number of antihypertensive agents (including diuretics)
• Aspirin or other anti-platelets (e.g. clopidogrel, ticagrelor)
• Anti-coagulation (e.g. warfarin)
• Statins

**Blood pressure Data:**
Data was collected from office readings as documented on medical correspondence. Follow-up blood pressure data was updated at 12-monthly intervals (+/- 4 months) from date of diagnosis until censoring:
• Systolic and diastolic blood pressure
• Pulse pressure - systolic blood pressure minus diastolic blood pressure
• Mean arterial pressure – diastolic pressure + 1/3 (pulse pressure)

**Laboratory Data:**
Standard biochemical and haematological parameters were recorded from samples obtained during routine clinic visits. Follow-up laboratory data was updated at 12 monthly intervals (+/- 4 months) from date of diagnosis until censoring. No extra visits for venepuncture were scheduled.
• Serum creatinine concentration (µmol/L) – Prior to 12th June 2007, serum creatinine measurements were made using an uncompensated kinetic Jaffé method on Roche Integra and Modular P analyzers. Since this date, all serum creatinine measurements have been performed in a standardized manner on a Roche Modular P analyzer using a blank rated and compensated Jaffé reaction. Results are aligned to the Isotope Dilution Mass Spectrometry (IDMS) method. A correction factor of -18µmol/L was applied to the older measurements to standardize creatinine values between the two time periods¹.
• Serum cholesterol concentration (mmol/L)
• Serum high-density lipoprotein (HDL) cholesterol concentration (mmol/L)
• Haemoglobin (g/L)
• Glycated haemoglobin (HbA1c) (mmol/mol)
• Proteinuria/day (g/day) (24-hour urine collection or spot urine protein-creatinine ratio [PCR]) - measurement of proteinuria evolved over the three decades that span the Salford Renovascular Study. Since October 2006, proteinuria has been measured from spot urine
protein creatinine ratios and reported in mg/mmol, while prior to this date, this was measured in g/day using 24-hour urine collections. These two different methods were standardized by approximating spot PCR to g/day; this was done by dividing urine PCR by 100. Protein creatinine ratios correlate well with 24-hour urine protein, assuming an estimated creatinine excretion of 10 mmol/day².

- Estimated glomerular filtration rate (eGFR) (ml/min/1.73m²): Calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) (Textbox 3.3.1)³. The CKD-EPI formula was chosen in preference to the 4-variable Modification of Diet in Renal Disease (MDRD) equation as the majority of patients in the Salford Renovascular Study had an eGFR > 30ml/min/1.73m² at baseline and the CKD-EPI formula has been shown less likely to misclassify patients with higher measured GFR values as having low eGFR values⁴.

**Textbox 3.3.1 Chronic Kidney Disease Collaboration Equation (CKD-EPI)³**

\[
GFR = 141 \times \min \left( \frac{S_{cr}}{\kappa}, 1 \right)^{\alpha} \times \max \left( \frac{S_{cr}}{\kappa}, 1 \right)^{1.209} \times 0.993^{\text{Age}} \times 1.018 \times 1.159 \times 1.018 \\
\text{if female} \times 1.159 \times 1.018 \text{[if black]}
\]

where:

\[S_{cr}\] is serum creatinine in mg/dL,
\[\kappa\] is 0.7 for females and 0.9 for males,
\[\alpha\] is -0.329 for females and -0.411 for males,
\[\min\] indicates the minimum of \(S_{cr}/\kappa\) or 1, and
\[\max\] indicates the maximum of \(S_{cr}/\kappa\) or 1.
3.4 Biomarker Analysis

A proportion of patients recruited into the Salford Renovascular Study were also enrolled into the Salford Kidney Study, previously known as the Chronic Renal Insufficiency Standards Implementation Study (CRISIS). This is a prospective observational study that aims to investigate clinical outcomes in non-dialysis CKD patients referred to the Salford Renal Department. CRISIS was established in 2002 and recruitment is still ongoing (>3000 patients recruited as of January 2017). In this study, blood and urine samples are taken at baseline and at annual follow-up visits both for routine biochemical and haematological investigations and also for storage to permit subsequent biomarker and genetic analyses. Samples are transferred to the Clinical Sciences Building at Salford Royal Hospital NHS Foundation Trust within four hours of being taken and centrifuged at 1400g for 11 minutes. Plasma and sera are then divided into 0.5ml aliquots and stored at -75°C in the Salford Biological Repository.

In addition to routine biochemical analyses, patients recruited into the Salford Kidney Study had the following novel biomarker analyses performed on stored samples, with the aim of investigating the association between these biomarkers and adverse outcomes in the CKD population: fibroblast growth factor-23 (FGF-23) (RU/ml), Cystatin C (mg/L), kidney injury molecule-1 (KIM-1) (pg/ml), myeloperoxidase (MPO) (pg/ml), neutrophil gelatinase-associated lipocalin (NGAL) (pg/ml), N-terminal prohormone of brain natriuretic peptide (NT-proBNP) (pg/ml), high-sensitivity cardiac troponin T (hs-cTNT) (ng/L), and anti-apolipoprotein A-1 Immunoglobulin G (anti-Apo-A-1 IgG)\(^5,6\). These biomarkers have been analysed through collaborations with the Karolinska institute in Sweden, and the division of Genetics and Laboratory medicine at the Geneva University hospital in Geneva, Switzerland. Samples were transferred to overseas research laboratories in appropriate containers on dry ice. A temperature probe was included in the container and this was returned by the receiving laboratory to confirm that the samples remained at the appropriate temperature throughout transfer. I have not been involved in the laboratory analysis of these biomarkers and the detailed analytical methodology that follows has been provided by the laboratories that performed these analyses.

\textit{Fibroblast Growth Factor-23 (FGF-23):}

FGF-23 was measured on lithium-heparin plasma samples in collaboration with the Karolinska Institute, Stockholm, Sweden, using a second-generation, two-site enzyme linked immunosorbent assay (ELISA) by Immutopics (San Clemente, CA, USA).

The assay used two affinity purified goat polyclonal antibodies selected to detect epitopes within the carboxy-terminal (C-Terminal) of FGF23. The ‘capture’ antibody was biotinylated and the ‘detection’ antibody was conjugated with the enzyme horseradish peroxidase (HRP). These antibodies bound to both the intact FGF-23 molecule and large carboxyl terminal fragments of
human FGF-23. A test sample containing human FGF-23 was incubated with both the capture and the detection antibodies in a streptavidin coated microtiter well. FGF-23 contained within the plasma sample was immunologically bound by the capture and detection antibodies in a ‘sandwich’ complex.

After 30 minutes of incubation, the well was washed to remove any unbound antibody or other components. The enzyme bound to the well was incubated with a substrate solution in a timed reaction and then measured in a spectrophotometric microtiter plate reader. The enzymatic activity of the antibody complex bound to the well was directly proportional to the amount of FGF-23 in the sample. A standard curve was generated by plotting the absorbance versus the respective FGF-23 concentration for each standard on linear or logarithmic scales. The concentration of FGF23 in the samples was determined directly from the standard curve. The assay lowest limit of detection was 1.5 RU/ml, the highest concentration measurable without dilution was the value of the highest standard. Samples reading higher than the highest sample could be diluted as required to obtain a result. The manufacturer-quoted intra and inter-assay coefficient of variation (VC) were <5%. Parallelism on dilution was quoted as 74 and 114% and recoveries varied from 91-116% for samples with low (375 RU/ml) to high (1125 RU/ml) concentrations.

Kidney Injury Molecule-1 (KIM-1), Neutrophil gelatinase-associated lipocalin (NGAL) and Myeloperoxidase (MPO):
Analyses were carried out at the laboratories of the division of Genetics and Laboratory medicine at Geneva University hospital, Geneva, Switzerland.

These biomarkers were measured on citrated plasma by electrochemiluminescence, using the MESO QuickPlex SQ 120 automate from Mesoscale Discovery Systems (Rockville, Maryland, USA). The assays used involved an electrochemiluminescence immunoassay (ELICA). The plasma sample was added to a plate that had been pre-coated with immobilized capture antibodies and incubated for 2 hours. After washing, a solution containing detection antibodies conjugated with electrochemiluminescent labels was added to the plate and incubated for a further 2 hours. The biomarker analyte bound to the immobilized capture antibodies; the detection antibodies were recruited by the bound analytes completing the sandwich. The buffer was added after a further washing, thereby providing the appropriate chemical environment for electrochemiluminescence. The plate was immediately loaded into the imager where a voltage was applied to the plate electrodes, causing capture labels to emit light. The intensity of light emitted provided a quantative measure of analytes in the sample. The standard curve was produced by the automate software from which biomarker concentrations were determined.

The lower limit of detection for the KIM-1 assay was 0.49 pg/ml. Measured intra-assay variation coefficients (VC) were 3.0% and 2.5% for KIM-1 concentrations of 78.1 and 312.5 pg/ml,
respectively (n=34).

The lower limit of detection for the NGAL assay was 2.85 pg/ml. Measured Intra-assay VC were 5.60% and 3.90% for NGAL concentrations of 625 and 2500 pg/ml, respectively (n=34). The lower limit of detection for the MPO assay was 7.46 pg/ml. Measured Intra-assay VC were 6.08% and 7.75% for MPO concentrations of 3125 and 781 pg/ml, respectively (n=34).

*N-terminal pro-brain-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac Troponin T (hs-cTNT):*

Analysis of neutrophil N-terminal pro-brain-type natriuretic peptide (NT-proBNP) and High-sensitivity cardiac Troponin T (hs-cTNT) was carried out at the laboratories of the division of Genetics and Laboratory medicine at the Geneva University hospital, Geneva, Switzerland.

Both biomarkers were measured on citrated plasma by electrochemiluminescence, using an assay supplied by Roche Diagnostics (Indianapolis, USA). The analysis was performed on the Cobas e601 systems automate.

The assays involved a sandwich electrochemiluminescence immunoassay (ELICA). In the case of NT-proBNP, the capture and detection antibodies were polyclonal sheep antibodies, the capture antibody directed towards the N-terminal and the detection antibody to the central molecule. For hs-cTNT, the capture and detection antibodies were monoclonal mouse antibodies that recognized epitopes on the central part of the cTnT molecule. To perform the assay the sample was first incubated with the capture and detection antibodies.

Streptavidin-coated beads were then added so that the immune complexes bind to the microparticles. The reaction mixture was then transferred into the measuring cell of the automate and the beads were captured on to the electrode surface by a magnet. The measuring cell was washed to remove unbound antibody and filled with a detection buffer. Voltage was applied to the electrode and emitted chemiluminescence light detected by a photomultiplier. Results were determined via an instrument specific calibration curve.

The lower limit of detection for the NT-proBNP assay was 0.60 pmol/L and the upper limit of detection 4130 pmol/L. The manufacturer quoted inter-assay VC at 7.00 pmol/L was 3.5% and at 62.60 pmol/L 1.8%.

The lower limit of detection for the hs-cTNT assay was 0.01 ng/mL and the maximum measured value was 25.00 ng/mL. The manufacturer’s quoted inter-assay VC for concentrations of 0.04 ng/mL and 0.65 ng/mL were 3.4 and 1.6% respectively.

*Anti-Apolipoprotein Immunoglobulin G (Anti-ApoA-1 IgG):*

The analysis of Anti-Apolipoprotein Immunoglobulin G (Anti-apoA-1 IgG) was carried out at the
laboratories of the division of Genetics and Laboratory medicine at the Geneva University hospital, Geneva, Switzerland

Anti-ApoA-1 IgG levels were quantified using an ELISA technique. Antibodies were measured on citrated plasma samples. Each sample was tested in duplicate according to the following laboratory methods.

Maxi-sorb plates (Nunc™ from Thermo Scientific, Waltham, MA, USA) were coated with purified human-derived delipidated apoA-1 (20 μg/ml; 50 μl/well) for 1 hour at 37°C. The plates were then washed 3 times with phosphate buffered saline (PBS)-2% bovine serum albumin (BSA; 100 μl/well) and then blocked for 1 hour with 2% BSA at 37°C.

Patient samples were then diluted to 1:50 in PBS-2% BSA, added to the wells and incubated for 60 minutes. Additional patient samples at the same dilution were also added to an uncoated well to assess individual nonspecific binding. After 6 further washes, 50 μl/well of signal antibody (alkaline phosphatase conjugated antihuman IgG; Sigma-Aldrich, Saint Louis MO) diluted to 1:1000 in PBS-2% BSA solution was incubated for 1 hour at 37°C. After 6 more washes (150 μl/well) with PBS-2% BSA solution, the phosphatase substrate p-nitrophenyl phosphate disodium (50 μl/well; Sigma -Aldrich) dissolved in diethanolamine buffer (pH 9.8) was added.

Absorbance was determined as the optical density at 405 nm (OD 405 nm) after 30 minutes of incubation at 37°C (VersaMax, Molecular Devices, Sunnyvale, CA, U.S.). The corresponding non-specific binding value was subtracted from the mean absorbance value for each sample. Anti-apoA-1 IgG were expressed as arbitrary units (optic density (OD) 405 nm) and expressed as a percentage of the positive control.

For this analysis the positivity cut-off was predefined, it was set at an OD value of 0.6 and 37% of the positive control value, which corresponds to the 97.5th percentile of normal distribution assessed in 140 healthy blood donors7. This method has been prospectively validated in rheumatoid arthritis and maintenance haemodialysis populations8,9. The positive control sample was a myocardial infarction patient who tested positive for anti-apoA-1 IgG and negative for anti-phospholipid, antinuclear and anti- cytoplasmic antibodies, as well as negative for anti- heat-shock protein 60 antibodies, displaying an OD value of 2.0.
3.5 Key end-points and verification

Case notes for all patients on the database, including for existing patients that had already been enrolled by previous investigators, were reviewed to verify documented end-points and to capture any new end-points that may have occurred before censoring,

- **Death**: Data was collected from electronic hospital records or through contact with primary care physician. Cause of death was not available for all patients.
  - Date of death
  - Cause of Death (where available)

- **Progression to end-stage kidney disease**: Case notes for each patient were reviewed and the date of starting chronic renal replacement therapy or date of transplantation were recorded. Episodes of acute dialysis were not taken into account. For patients treated conservatively, this time point coincided with the date when eGFR first reached <10ml/min/1.73m², (which is close to the average eGFR at which RRT is started in the UK \(^{10}\)), and remained at this level for the remainder of the follow-up period, to exclude transient episodes of AKI.
  - Date of start of renal replacement therapy including transplantation or
  - Date of reaching sustained eGFR <10ml/min/1.73m²

- **Cardiovascular Events** - Date of first cardiovascular event after recruitment into the study was recorded following review of hospital records. These include:
  - Cardiac
    - Any acute coronary syndrome e.g. new or unstable angina, Myocardial infarction
    - New Arrhythmias (including atrial fibrillation)
    - Cardiac arrest
    - Acute decompensated heart failure

  - Cerebrovascular
    - Transient Ischaemic Attack
    - Stroke

  - Peripheral vascular disease
    - Ischaemic ulceration
    - Gangrene
    - Intermittent claudication
    - Amputation
- Vascular surgery ex Bypass interventions
- Ischaemic bowel

- Abdominal Aortic Aneurysm
  - New Diagnosis
  - Rupture

Date and details of these events were verified either from medical correspondence if the event was managed at a different hospital or by review of hospital notes and confirmation of raised cardiac enzymes, electrocardiogram or chest X-ray changes for cardiac events, neurological imaging or abnormal neurological examination findings for cerebrovascular events, and vascular imaging or procedures for peripheral vascular disease and abdominal aortic aneurysms.

- Any event – A composite end-point composed of the first of any of the above events
3.6 Patient management

All patients were managed in accordance with the contemporary vascular protective advice and UK Renal Association blood pressure targets \(^{11,12}\) at time of entry into the database. Renal revascularization was performed either in accordance with physician preference or after entry into a randomized trial \(^{13,14}\). All revascularization procedures involved percutaneous transluminal angioplasty, with deployment of bare-metal stents since 1998; no embolic protection devices were used.
3.7 Statistical Analysis - overview

All data were analyzed using SPSS version 22.0, RStudio version 1.0.44, SAS version 9.4 (SAS Institute Inc., Cary, NC) or Microsoft Excel 2011.

Categorical variables were expressed both as a number and a percentage and were compared using the Chi-square test. Non-parametrically distributed continuous variables were expressed as median (interquartile range) and compared using Mann-Whitney U test (2 groups) or Kruskal-Wallis (>2 groups). Parametrically distributed continuous variables were expressed as median +/- interquartile range and compared using student t-test (2 groups) or ANOVA (>2 groups). Survival analyses were performed using Kaplan-Meier curves and the log rank test was used to compare event rates. The number of clinical end-points and unadjusted incidence rates per 100 patient years were calculated using the following equation: (total number of events/total number of follow-time) x 100.

The rate of change of eGFR over time, or eGFR slope, was calculated by fitting an ordinary least-squares regression line, using linear regression, to all compiled eGFR measurements for each patient collected from time zero to end of study. As described in previous studies, the slope of the regression line is equivalent to the rate of change in eGFR over time\textsuperscript{15-17}. Blood results taken during in-patient episodes, patients who reached RRT, and patients with less than one year of follow-up or those with less than 3 data points were excluded from this analysis. For revascularized patients, at least 3 data points pre-revascularization and another 3 data points post-revascularization were used to calculate eGFR slope pre- and post-revascularization respectively.

Univariate and multivariate Cox regression analyses were used to determine the Hazard ratio and 95% confidence interval for the association between individual baseline variables and clinical end-points. Progression to ESKD and CVE end-points were both censored for death. Continuous variables were scaled where clinically appropriate (e.g. systolic/diastolic blood pressure was scaled per 10 mmHg increase in blood pressure, age was scaled per 10 year increase, proteinuria was scaled per 1g/day increase). Non-adjusted univariate variables were entered into the multivariate model according to clinical plausibility and statistical significance in the univariate analysis as specified in the individual studies. A p value <0.05 was considered statistically significant for all analyses. In Chapter 4.5, a stepwise regression model was used to select the best predictor variables, that is those with the most significant hazard ratio for each clinical end-point. Although stepwise regression methods have limitations such as exclusion of potentially relevant variables due to lack of correlation with dependent variables or due to strong correlation with other independent variables\textsuperscript{18}, this automated method was employed to give an objective selection of the smallest number of variables that could be used to construct our predictive model.
The incremental risk prediction value of novel biomarkers was assessed using two different methods: receiver operating characteristic (ROC) analyses and continuous or three-category Net Reclassification Index (NRI)\(^1\). ROC analyses provide a measure of model performance and show how well a model is able to classify individuals as cases or controls. The area under the curve (AUC) or c-statistic represents the compromise between sensitivity and specificity that is required for a model to predict an event. However, ROC analyses have limitations and the numeric AUC is not always clinically relevant\(^1\). Indeed, the incremental predictive effect provided by a biomarker-enhanced model is strongly influenced by the AUC of the baseline model and any improvement in AUC should be reported in the context of the AUC of the baseline model\(^2\). The AUC has been shown to be an insensitive measure of the incremental predictive power of an individual biomarker and the contribution of an individual biomarker could still be clinically relevant despite a minimal increase in AUC\(^2\).

The Net reclassification index (NRI) is a measure of the effect of a new model on patient risk reclassification compared to an older model. There are two types of NRI; category-based NRI which is based on pre-defined population based risk categories, and continuous NRI which is not based on risk categorization and considers all changes in predicted risk for both events (cases) and non-events (controls)\(^2\). In situations where there are established risk categories, category-based NRI can provide clinically meaningful results. One example of a significant change in patient risk reclassification that has been incorporated into clinical guidelines is the effect of high-density lipoprotein cholesterol, when used in addition to traditional risk factors, on the Framingham 10-year risk of coronary heart disease, in the absence of a corresponding meaningful change in AUC\(^2\). There are however no comparable established risk categories in the ARVD population, hence the risk cut-offs used in Chapter 4.4 were arbitrarily based on the yearly event rates reported in Chapter 4.2. This limits the application of category-based NRI in ARVD populations and implies that our results require further validation in larger studies. The category-free or continuous NRI was developed to circumvent this issue. In this model, the reclassification effect of a biomarker depends only on the strength of its association with the outcome event and is not influenced by performance of the baseline model\(^2\). This model tends to produce positive results even for weak biomarkers hence results can be misleading and any improvement in risk reclassification obtained from the analysis may be devoid of clinical relevance\(^1,2\). Given that these different statistical approaches provide complementary information, in Chapter 4.4 we presented results for both ROC analyses and reclassification statistics to enhance the interpretation of the incremental predictive value of biomarkers. As advised in the literature, we only presented confidence interval values as opposed to p values for NRI results and we calculated NRI event and non-event rates from reclassification tables\(^2\).

In Chapter 4.5, dynamic Excel sheets were used to compute survival and CVE-free survival estimates at 1, 5 and 10 years for patients with different risk profiles. This was done by adding
the coefficients for models showing the best performance index (as interpreted by Harrell c-index) and dividing them into tertiles. The interactive risk calculator was constructed using Hypertext Markup language (HTML) and this can also be used offline. The Javascript used is shown in Appendix 1.
References:


Chapter 4 - Results
4.1 Three decades of atherosclerotic renovascular disease management – changing outcomes in an observational study

DOI: 10.1159/000443434

Preface:
The literature suggests that both management of ARVD and patient outcomes have evolved over the past decades, as discussed in Chapter 1.3, however no observational study had previously confirmed this hypothesis. This chapter is based on an observational study with up to thirty years of patient recruitment and prolonged follow-up and it is designed around the timeline of studies that have driven important paradigm shifts in ARVD management.

Abstract
Background: Optimized medical therapy has improved cardiovascular outcomes in the general population.

Aim: To investigate whether changes in the management of atherosclerotic renovascular disease (ARVD) have had an impact on clinical outcomes.

Method: Recruitment into this single-centre prospective cohort study started in 1986. Data was analyzed retrospectively. Patients were divided into four groups based on relationship of diagnosis year to landmark randomized controlled trials (RCT); group 1 – pre-large RCT data (1986-2000); group 2 – post-early RCT (2001-2004); group 3 – ASTRAL study recruitment era (2004-2009); group 4 – post-ASTRAL (2009-2014).

Results: In total, 872 patients were followed for a median 54.9 months (IQR 20.2-96.2). Over successive time-periods, there was an increase in baseline utilization of renin angiotensin blockade (RAB) (group 4: 69% vs. group 1: 31%, p<0.001), statins (74% vs 20%, p<0.001) and beta-blockers (43% vs 30%, p=0.024). Median time to death, end-stage kidney disease and cardiovascular events improved except in group 4, which displayed more baseline cardiovascular comorbidities. The number of investigative angiograms performed decreased from 139 per year between 2006 and 2008 to 74 per year in group 4.

Conclusion: Although fewer patients are being investigated for ARVD in our centre, these have more cardiovascular comorbidities. Nonetheless, optimized medical therapy may have contributed towards improved proteinuria, renal function and clinical outcomes in patients diagnosed with ARVD.
Introduction
Atherosclerotic renovascular disease (ARVD) frequently co-exists with cardiovascular disease in patients with systemic atherosclerosis. Increased awareness of cardiovascular risk factors and progress in therapeutic options for both primary and secondary prevention of cardiovascular disease have reduced the number of cardiovascular deaths per year in the general population by 16.7% over a ten-year period between 2000 and 2010. Despite the lack of conclusive evidence as to what constitutes optimal medical therapy for patients with ARVD, observational studies have shown that the use of renin-angiotensin blockade (RAB) and statin therapy, as specified in the CORAL protocol, may improve clinical outcomes in patients with ARVD. However, it is not clear whether these changes in clinical practice have translated into improvement in clinical cardiovascular outcomes specifically in ARVD as is the case in other cardiovascular disease settings.

There is also evidence that fewer patients with ARVD are progressing to end-stage kidney disease (ESKD); while more than three decades ago up to 41% of patients with ARVD suffered significant renal ‘failure events’ (≥10% decrease in renal length, ≥100% increase in serum creatinine or ≥50% decrease in creatinine clearance) during up to 4 years follow-up, the latest trials report that half as many patients (16-22%) reached adverse renal end-points (acute kidney injury or renal death in ASTRAL; doubling of serum creatinine in CORAL) over a similar follow-up period. A further reason why ARVD outcomes may have improved independent of better therapeutic options in cardiovascular disease is earlier diagnosis due to more widespread use of non-invasive imaging techniques.

The aim of this study is twofold; first, we aim to illustrate how clinical phenotype and management of ARVD have evolved over the past three decades and second, we aim to investigate whether changes in clinical management of ARVD correlate with improved clinical outcomes, utilizing the resource of a single renal centre database in which the phenotype of ARVD patients has been recorded in detail.

Method
This study involved retrospective analysis of an observational study first started in 1986. Information on all patients with ARVD referred to or diagnosed at our tertiary renal centre (catchment population of 1.55 million) since this time was entered into a local renovascular database. Ethical approval was granted from the local ethics committee. Data were collected on each patient annually, using hospital patient records. Data collected include presenting features of ARVD, baseline demographics (age at diagnosis, gender), co-morbid conditions (diabetes, macrovascular disease), renal imaging results including angiography, annualized prescribed medications, blood pressure, serum creatinine (umol/L) and proteinuria (g/24h), together with clinical outcome data. The degree of renal artery stenosis (RAS) was obtained from biplane angiography (intravenous digital subtraction angiography (IVDSA) or intra-arterial digital
subtraction angiography (IADSA) in earlier studies, computed tomographic (CT) or magnetic resonance (MR) angiography) and reported by two specialist radiologists over the 30 year period. The reported severity of the RAS was then recorded in the database in a standardized manner using a ‘patency score’; a score of 200 was equivalent to 0% bilateral stenosis while a score of 0 meant 100% bilateral occlusion. Flash pulmonary oedema (FPE) was defined as acute decompensated heart failure in the absence of a documented precipitating cardiac event or known reduced left ventricular ejection fraction (<40%). Estimated glomerular filtration rate (eGFR) was calculated using the CKD Epidemiology Collaboration equation (CKD-EPI). Patients with incomplete baseline information were excluded from this analysis. The date of diagnostic imaging was considered as time zero. New patients were entered into the database up until 31st August 2014 and data was censored at the earliest of death or 11th May 2015 if still known to our services or last patient encounter if discharged or lost to follow-up.

All patients were managed in accordance with the contemporary vascular protective advice and UK Renal Association blood pressure targets at time of entry into the database. Renal revascularization was performed either in accordance with physician preference or after entry into a randomized trial. All revascularization procedures involved percutaneous transluminal angioplasty, with deployment of bare-metal stents since 1998; no embolic protection devices were used.

Predefined primary clinical end-points included:

(1) Date of death
(2) Date of first cardiovascular event after enrollment, a composite of acute coronary syndrome or myocardial infarction, new arrhythmias, pulmonary oedema or decompensated heart failure, cerebrovascular events including transient ischaemic attacks, peripheral vascular disease including peripheral revascularization and abdominal aortic aneurysm repair, and mesenteric ischaemia.
(3) Date of reaching ESKD defined as the earliest of the following events: initiation of renal replacement therapy [RRT] [including renal transplantation] or reaching eGFR <10ml/min/1.73m² which is the average eGFR at which RRT is started in the UK
(4) A composite end-point composed of the first of any of the above events.

A secondary clinical end-point was rate of change of eGFR from time zero to end of study calculated from slope of linear regression, excluding blood results taken during in-patient stay, patients who presented requiring RRT, or those who had less than one year follow-up or less than 3 data points.

**Statistical Analysis**

Patients were divided into four groups based on the relationship of their diagnosis year to that of publication of landmark studies related to management of ARVD: 1986-2000 (Group 1; early studies up until publication of three small RCTs), 2001-2004 (Group 2; studies advocating
benefits of medical therapy\textsuperscript{5,19}, 2005-2008 (Group 3; main ASTRAL recruitment period\textsuperscript{14}) and 2009-2014 (Group 4; post-ASTRAL era\textsuperscript{4,14}). Baseline characteristics were compared across these four groups; categorical data were compared using Chi-squared tests while Kruskal-Wallis was used to compare continuous variables, as these were all non-parametrically distributed on the Shapiro-Wilk test. These non-parametric continuous variables were described using median (interquartile range). Pairwise analyses were performed using post-hoc tests for Kruskal-Wallis and Chi-squared test\textsuperscript{20}. Kaplan-Meier curves were constructed for outcomes in each group and used to estimate the median times to event for each outcome. Incidence rates per 100 patient years were calculated manually for each group. A Cox proportional hazards regression model was used to evaluate the effect of successive time periods on the primary end-point; this was adjusted for baseline age, gender, blood pressure, eGFR and proteinuria.

Results
A total of 894 patient records were reviewed; 22 patients were excluded due to incomplete baseline data (missing date of imaging study, imaging results, comorbidities or baseline medications). Data from 872 patients were analysed, with a median follow-up of 54.9 months (IQR 20.2-96.2). There were 265 patients in Group 1, 235 patients in Group 2, 287 patients in Group 3 and 85 patients in Group 4 (Table 4.1.1).

There was a predominance of male patients in all four groups and the median age of patients diagnosed with ARVD increased significantly after 2000 (72.9 years after 2000 compared to 68.3 years for Group 1, $p<0.0005$), although this was lower in Group 4 (Group 1 vs Group 4, $p=$ non-significant). Results showed a rise in prevalence of diabetes in patients recruited after 2000 (from 21.5% for Group 1 to 38.3% for Group 2, $p<0.0005$). A higher proportion of patients recruited after 2009 had a greater burden of symptomatic coronary artery disease (68.2% in Group 4 vs 47.7% in Group 3, $p=0.001$), congestive heart failure (26.5% in Group 4 vs 12.0% in Group 3, $p=0.001$) and flash pulmonary oedema (11.8% in Group 4 vs 4.9% in Group 3, $p=0.023$) when compared to earlier groups.

Blood pressure control at time of diagnosis improved after 2000, although average blood pressure readings for Group 4 were more elevated than for preceding years. The decrease in average blood pressure after 2000 occurred in parallel with an increase in the number of antihypertensive agents used; a greater proportion of patients diagnosed after 2000 were
Table 4.1.1 Baseline characteristics for whole cohort and for the four groups

<table>
<thead>
<tr>
<th>Table 4.1.1 Baseline characteristics for whole cohort and for the four groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>--------------------------------</td>
</tr>
<tr>
<td>Male [%]</td>
</tr>
<tr>
<td>Diabetic [%]</td>
</tr>
<tr>
<td>CAD [%]</td>
</tr>
<tr>
<td>CHF [%]</td>
</tr>
<tr>
<td>FPE [%]</td>
</tr>
<tr>
<td>PVD [%]</td>
</tr>
<tr>
<td><strong>Median age [IQR] [years]</strong></td>
</tr>
<tr>
<td><strong>Male [%]</strong></td>
</tr>
<tr>
<td><strong>Diabetic [%]</strong></td>
</tr>
<tr>
<td><strong>CAD [%]</strong></td>
</tr>
<tr>
<td><strong>CHF [%]</strong></td>
</tr>
<tr>
<td><strong>FPE [%]</strong></td>
</tr>
<tr>
<td><strong>PVD [%]</strong></td>
</tr>
<tr>
<td><strong>Median SBP [IQR] [mmHg]</strong></td>
</tr>
<tr>
<td><strong>Median DBP [IQR] [mmHg]</strong></td>
</tr>
<tr>
<td><strong>Median Patency Score [IQR]</strong></td>
</tr>
<tr>
<td><strong>&gt;60% unilateral RAS [%]</strong></td>
</tr>
<tr>
<td><strong>&gt;60% bilateral RAS [%]</strong></td>
</tr>
<tr>
<td><strong>RAB [%]</strong></td>
</tr>
<tr>
<td><strong>B-blocker [%]</strong></td>
</tr>
<tr>
<td><strong>≥ 3 agents [%]</strong></td>
</tr>
<tr>
<td><strong>Aspirin [%]</strong></td>
</tr>
<tr>
<td><strong>Statin [%]</strong></td>
</tr>
<tr>
<td><strong>Proteinuria [g/24hr] [IQR]</strong></td>
</tr>
<tr>
<td><strong>Median baseline eGFR [IQR] [ml/min/1.73m²]</strong></td>
</tr>
<tr>
<td><strong>Revascularization [%]</strong></td>
</tr>
<tr>
<td><strong>Median Follow-up [IQR][months]</strong></td>
</tr>
</tbody>
</table>

B-blocker – beta-blocker; CAD – Coronary artery disease; CHF – Congestive heart failure; DBP – diastolic blood pressure; eGFR – estimated glomerular filtration rate; FPE – Flash pulmonary oedema; IQR – interquartile range; KW – Kruskal Wallis; PVD – peripheral vascular disease; RAB – renin angiotensin blockade; RAS – renal artery stenosis; SBP – systolic blood pressure; X² – Chi-square test. *between Group 1 and Group 2; †between Group 3 and Group 4; ‡between Group 1 and Group 4; §between Group 1 and Group 3
prescribed >3 anti-hypertensive agents (31% in Group 1 compared to 49% in Group 2, p<0.0005), a finding which persisted throughout all groups.

The most important change in prescribing practice was the sharp increase in the proportion of patients treated with RAB (30.8% in Group 1 compared to 69.4% Group 4, p<0.0005), beta-blockers (29.7% in Group 1 compared to 42.9% in Group 4, p=0.024) and statins (20.2% in Group 1 compared to 74.1% in Group 4, p<0.0005) at time of diagnosis over successive time periods (Table 4.1.1). Following the year 2000 there was an increase in the proportion of ARVD patients without confirmed macrovascular disease (MVD) established on at least one vascular protective agent (RAB, statin, beta-blocker or Aspirin) at baseline (Table 4.1.2), although overall, less patients without documented MVD were on vascular protective therapy at time of diagnosis of ARVD than those known to have MVD.

There was a parallel significant decline in baseline proteinuria between Group 1 and Group 2 (from 0.9g/day to 0.4g/day, p<0.0005), which then plateaued in the subsequent time periods, and this was in keeping with the fact that baseline renal function (eGFR) was progressively better with each subsequent cohort (p<0.0005 between Group 1 and Group 4). However, overall there was no significant change in the rate of eGFR decline over follow-up time (0.98ml/min/1.73m²/year across all four groups, Table 4.1.3). Patients in the latest cohort were noted to have a slightly higher patency score, although this was not statistically significant.

Survival curves revealed an improvement in the median time to clinical end-points over successive time periods, with the exception of Group 4, which was characterized by a higher burden of coronary artery disease and heart failure at baseline (Table 4.1.4; Figure 4.1.2[a-d]). An analysis of the incidence of combined primary end-points per 100 patient years revealed that Group 3 had the lowest incidence of adverse events compared to the other groups (26.32 for Group 1; 28.34 for Group 2; 20.11 for Group 3 and 23.67 for Group 4). This was also shown in the Cox regression model where Group 1 was used as a referent group. Hazard ratios for Group 4 were non-significant (Table 4.1.5).

An analysis of the annual number of patients diagnosed with ARVD and the number of revascularization procedures performed annually over the past three decades revealed a biphasic pattern; there was a decline in both the number of revascularizations performed and the number of patients diagnosed with ARVD in 2001-2004 and 2009-2014 (Figure 4.1.3). Data on the total number of CTAs and MRAs performed to investigate the presence of ARVD was only available from 2006 onwards; there was a corresponding decline in the total number of CTAs and MRAs performed in the latest cohort. For example, 277 investigations were performed over a two-year period between 2006 and 2008, while 297 investigations were performed over 4 years between 2009 and 2014. An analysis of the rate of revascularization procedures revealed an increase from the earliest to middle two cohorts, with annual figures of 4 in cohort 1, 9 and 10 in cohorts 2 and 3, respectively, falling to 3 procedures per year in the post-ASTRAL cohort. However, the proportion of registered ARVD patients who underwent
Figure 4.1.1 Proportion of patients in each group receiving specific vascular protective agents (renin angiotensin blockade, beta-blockers, statins or aspirin) at time of diagnosis.

Table 4.1.2 Percentage of ARVD patients with and without documented macrovascular disease (MVD) on vascular protective therapy.

<table>
<thead>
<tr>
<th>Group</th>
<th>Percentage of ARVD patients without confirmed MVD on vascular protective therapy* at baseline</th>
<th>Percentage of ARVD patients with confirmed MVD on vascular protective therapy* at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>65.91</td>
<td>83.62</td>
</tr>
<tr>
<td>Group 2</td>
<td>80.70</td>
<td>90.45</td>
</tr>
<tr>
<td>Group 3</td>
<td>90.00</td>
<td>93.91</td>
</tr>
<tr>
<td>Group 4</td>
<td>82.35</td>
<td>97.06</td>
</tr>
</tbody>
</table>

* any of aspirin, statin, renin-angiotensin blockade or beta-blocker.

Table 4.1.3 Rate of eGFR decline calculated from slope of linear regression for the whole cohort and the individual groups

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Median eGFR slope [ml/min/1.73m^2/year]</td>
<td>-0.98 [-2.60-0.52]</td>
<td>-1.52 [-3.45-0.03]</td>
<td>-1.00 [2.44-0.72]</td>
<td>-0.71 [-2.23-0.52]</td>
<td>-1.09 [-3.60-2.20]</td>
<td>0.181*</td>
<td>KW</td>
</tr>
</tbody>
</table>

*across all four groups
Table 4.1.4 Median time to end-points for each group and for cohort as a whole (in months) obtained from non-adjusted Kaplan-Meier curves

<table>
<thead>
<tr>
<th>Group</th>
<th>Death</th>
<th>CVE*</th>
<th>ESKD*</th>
<th>Any</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>45.1 [35.0-55.2]</td>
<td>40.4 [32.9-48.0]</td>
<td>35.2 [26.2-44.2]</td>
<td>34.4 [26.9-41.9]</td>
</tr>
<tr>
<td>Group 2</td>
<td>58.9 [49.9-68.0]</td>
<td>42.8 [34.6-51.1]</td>
<td>49.7 [41.7-57.8]</td>
<td>36.8 [28.6-44.9]</td>
</tr>
<tr>
<td>Group 3</td>
<td>81.6 [68.8-94.5]</td>
<td>47.5 [40.8-78.3]</td>
<td>70.2 [57.9-82.4]</td>
<td>42.4 [36.1-48.7]</td>
</tr>
<tr>
<td>Group 4</td>
<td>65.4 [53.4-77.3]</td>
<td>59.5 [40.8-78.3]</td>
<td>60.8 [43.2-78.4]</td>
<td>55.9 [37.7-74.1]</td>
</tr>
<tr>
<td>All</td>
<td>63.0 [57.0-69.1]</td>
<td>43.8 [39.8-47.8]</td>
<td>54.9 [49.0-60.7]</td>
<td>39.5 [35.2-43.7]</td>
</tr>
</tbody>
</table>

* Adjusted for death

Figure 4.1.2(a-d) Kaplan-Meier curves for time to (a) Death, (b) ESKD, (c) CVE and (d) any event for each group (adjusted for age, gender, macrovascular disease, flash pulmonary oedema, diabetes and baseline eGFR and proteinuria)
Table 4.1.5 Hazard ratio for endpoints in each time period compared to 1986-2000 (reference group), adjusted for age, gender, blood pressure, comorbidities (Macrovascular disease, diabetes, congestive heart failure and flash pulmonary oedema) eGFR and degree of proteinuria at baseline.

<table>
<thead>
<tr>
<th>Group</th>
<th>Death</th>
<th>CVE*</th>
<th>ESKD*</th>
<th>Any</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95%</td>
<td>p value</td>
<td>HR</td>
</tr>
<tr>
<td>2</td>
<td>0.71</td>
<td>0.57-0.94</td>
<td>0.003</td>
<td>1.30</td>
</tr>
<tr>
<td>3</td>
<td>0.54</td>
<td>0.42-0.97</td>
<td>&lt;0.0005</td>
<td>1.35</td>
</tr>
<tr>
<td>4</td>
<td>0.84</td>
<td>0.54-0.87</td>
<td>0.432</td>
<td>1.62</td>
</tr>
</tbody>
</table>

Figure 4.1.3 Number of patients diagnosed with ARVD and number of revascularization procedures performed each year in relation to important events and turning points in the history of management of ARVD.

Revascularization was greatest in the latest cohort (Group 1, 3.88 revascularizations per 100 patient years, Group 4, 6.46 revascularizations per 100 patient years).
Discussion
To our knowledge, this database is the largest observational study of ARVD given its size, length of follow-up and comprehensive data collection. These results provide unique insight into how treatment practices and outcomes of this condition have evolved over the years. Our study suggests that enthusiasm for diagnosing and treating ARVD has been clearly influenced by publication of major studies performed in this field. Despite early enthusiasm for revascularization both for preservation of renal function and treatment of flash pulmonary oedema 21–23, concerns regarding the potential hazards of this intervention and the absence of benefit over medical treatment in unselected populations, as shown in both the small early studies 16–18 and the more recent and far larger ASTRAL and CORAL studies, have led to a decline in revascularization rates 4,14. There was a corresponding sharp decrease in the number of patients diagnosed with ARVD in the post-ASTRAL period and we feel that this was because fewer angiographic investigations were being performed, as these declined from around 139 CTA/MRA investigations per year almost a decade ago to around 74 investigations per year in our centre in the post-ASTRAL cohort. These figures may reflect both a reduced interest in actively investigating for ARVD, and also that during the ‘ASTRAL recruitment period’ there was heightened interest in investigating for underlying ARVD.

Patients in Group 4 were fewer in number and older with a higher burden of comorbidities compared to earlier groups. Increased awareness of potential hazards associated with CTA and MRA, namely contrast-induced nephropathy and nephrogenic systemic fibrosis respectively, may have contributed to a reduction in the number of patients investigated for ARVD24,25. However, this decline in numbers may also suggest that in the present era, only patients with certain high-risk features are being referred for radiological investigations; such patients were underrepresented in ASTRAL and CORAL. Indeed, although less revascularization procedures have been performed per year in the post-ASTRAL period compared to earlier years, the percentage of newly diagnosed ARVD patients who undergo revascularization is significantly higher in this last cohort, reflecting a selected population. Forgoing investigations for ARVD may be the correct option in the large majority of patients in whom revascularization will not lead to benefit, either due to functionally insignificant RAS 26 or irreversible renal parenchymal injury 27. However, there is a concern that reduced enthusiasm for investigation may lead to missed opportunities for timely diagnosis of ARVD 9. There is evidence that this intervention may improve clinical outcomes in patients with clinical features suggestive of critical RAS and viable renal parenchyma. A recent observational study from our group analyzed clinical outcomes for 237 patients with at least 50% RAS and one or more ‘high-risk’ features (uncontrolled hypertension, rapidly deteriorating renal function or flash pulmonary oedema); around a quarter of these patients underwent revascularization either as part of a research study (ASTRAL or CORAL) or if thought to be clinically indicated, while the rest were treated medically as per contemporary guidelines. Revascularization was associated with improved clinical outcomes in patients with either flash pulmonary oedema or in those with combined
rapidly declining renal function and uncontrolled hypertension hence this intervention may benefit carefully selected patients 28.

Our results highlight how increased emphasis on cardiovascular risk reduction in patients with systemic atherosclerosis has driven increased utilization of statins, RAB, and beta-blockers in patients with ARVD, although there is still room for improvement especially when compared to patients with established cardiovascular disease. This change in prescribing practice appeared to be associated with improved blood pressure control, lower proteinuria and a higher baseline eGFR over the years; these are all well-established independent predictors of better renal and patient survival 29,30. It is however difficult to interpret causal associations from such a retrospective study. Although group 4 was noted to have a similar incidence of end-points and rate of decline of eGFR to Group 1 despite a worse cardiovascular risk profile at diagnosis, the better baseline eGFR and proteinuria in recent years could well be the result of earlier diagnosis of ARVD due to more widespread use of non-invasive angiographic investigations. Any detectable long-term benefit of intensified vascular protective therapy could have been offset by selection bias, as the post-ASTRAL period was characterized by patients with a higher comorbid burden. Conversely, the apparent improved outcomes that characterized group 3 could reflect the fact that this period coincided with the major phase of ASTRAL recruitment; indeed, our renal department was a major recruitment centre for ASTRAL and 74 patients were recruited between 2002 and 2008. Recruitment of lower risk patients may have confounded our results, and this was an effect seen in ASTRAL. However a separate analysis comparing baseline characteristics of all Group 3 patients against Group 3 patients excluding those recruited into ASTRAL, revealed no significant difference between the two groups.

This large observational single-centre study has several limitations due to its retrospective nature. Data collection was performed in a standardized manner but by different individuals over almost three decades thus possibly introducing assignment bias. As described above, selection bias in diagnosing ARVD has clearly influenced results, with an over-representation of low-risk patients in Group 3 and evidence that Group 4 includes patients with greater comorbidity burden. Although adjusted for baseline comorbidities, renal function and proteinuria, the Cox model was not adjusted for medications. This is because longitudinal data on the administration of cardioprotective medication was not available and for the purpose of this analysis it was assumed that these were continued for the duration of the follow-up period. In addition, a number of important variables, which would have been relevant to clinical outcomes, were not included due to missing or unreliable data. Amongst these are BMI, smoking status and drug dosage. Cause of death was also not available, although we would assume that there was a predominance of cardiovascular deaths in this ARVD population in keeping with evidence from the literature 31. Blood pressure was documented from the single office reading taken at time of diagnosis. The degree of stenosis was determined by a single radiologist viewing each scan, based on biplanar imaging studies (CTA or MRA), without confirmation of haemodynamic significance of the stenosis. Lastly, the last cohort depicting the post-ASTRAL era was smaller
in size and had a significantly shorter follow-up time compared to the other cohorts, potentially confounding results.

Conclusion:
This study illustrates how management of ARVD has evolved over the years. Our results suggest that the advent of enhanced vascular protective therapy after 2000 may have contributed towards improved baseline proteinuria and eGFR in newly diagnosed ARVD patients however selection bias has affected interpretation of our results. In the wake of neutral results of the ASTRAL and CORAL trials, fewer patients, but a greater proportion with more cardiovascular comorbidities are being referred for investigation of ARVD, and this is likely to explain the apparent worse outcomes in the latest cohort. Timely revascularization may be beneficial in selected individuals hence it is imperative that renal physicians maintain a high index of clinical suspicion for ARVD. Further studies are required to help define this important sub-group and target revascularization more appropriately.
References:


4.2 The importance of proteinuria and prior cardiovascular disease in all major clinical outcomes of atherosclerotic renovascular disease – a single-centre observational study

DOI: 10.1186/s12882-016-0409-1
Creative Commons Attribution 4.0 International License:
http://creativecommons.org/licenses/by/4.0/

Preface
Recent large randomized controlled trials have shown that although optimal multi-targeted medical therapy can improve clinical outcomes in patients with ARVD, a significant proportion can still develop adverse end-points. ARVD is clearly a complex and heterogeneous condition hence identification of patients harbouring features that are more likely to predispose to adverse events would enable intensification of medical therapy and potential consideration of revascularization. The previous study showed that the improvement in the degree of baseline proteinuria noted in recent years, possibly a reflection of increased use of renin-angiotensin blockade in these patients, is contributing to the perceived improvement in clinical outcomes in these patients. There is increasing interest in the relationship between proteinuria and clinical outcomes in both revascularized and non-revascularized ARVD patients. This observational study provides real world data about the longterm effects of proteinuria on important clinical end-points.

Abstract
**Background:** Identification of patients at risk of developing adverse events would enable aggressive medical therapy and possibly targeted revascularization. The aim of this study is to characterize the determinants of long-term outcomes in atherosclerotic renovascular disease (ARVD)

**Methods:** Patients with a radiological diagnosis of ARVD were recruited into this single-centre prospective cohort study between 1986 and 2014. Data collected included baseline co-morbid conditions, annualized prescribed medications and laboratory data (serum creatinine [umol/L], proteinuria [g/24h]). Multivariable Cox regression analysis was used to explore association with these end-points: death, end-stage kidney disease (ESKD), cardiovascular event (CVE) and the first of any of these events.

**Results:** A total of 872 patients were recruited into this study. However, 42 patients were excluded due to missing baseline data and hence case records for 830 patients were reviewed.
Over median follow-up of 57.1 months (interquartile range: 21.7-96.9), incidence per 100 patient years of death, ESKD, CVE and any event was 13.5, 4.2, 8.9 and 21.0 respectively. Macrovascular disease (MVD), congestive heart failure (CHF), flash pulmonary oedema (FPE) and greater proteinuria at baseline were individually associated with increased risk for all endpoints in multivariable analysis (Death: MVD – HR 1.24 [95% CI 1.02-1.50]; CHF – HR 1.33 [95% CI 1.08-1.64]; FPE – HR 2.10 [95% CI 1.50-2.92]; proteinuria – HR 1.14 [95% CI 1.08-1.20]). Higher estimated glomerular filtration rate at time of diagnosis was significantly associated with reduced risk of all end-points (Death: HR 0.92 [95% CI 0.89-0.94]). Administration of statins and renin angiotensin blockade (RAB) at baseline were also associated with reduced adverse events, especially death (RAB: HR 0.83 [95% CI 0.70-0.98]; statins: HR 0.79 [95% CI 0.66-0.94]) and ESKD (RAB: HR 0.84 [95% CI 0.71-1.00]; statins: HR 0.79 [95% CI 0.66-0.93]). Revascularization was associated with reduced risk of death (HR 0.65 [95% CI 0.51-0.83]) and ESKD (HR 0.59 [95% CI 0.46-0.76]).

**Conclusion:** All patients with ARVD require intensive vascular protection therapy to help mitigate systemic atherosclerosis, optimize cardiovascular risk and improve clinical outcomes. More effort is required to identify the minority of patients who may benefit from revascularization.

**Introduction:**
With an increasingly aging population and a rising burden of atherosclerotic risk factors\(^1\), there is a suggestion that atherosclerotic renovascular disease (ARVD) is becoming more prevalent both in the general population and in patients with chronic kidney disease (CKD)\(^2\). This has important implications because although ARVD is clinically silent in the majority of patients, its presence is independently associated with increased mortality when compared to patients with similar risk factors but no significant renal artery stenosis (hazard ratio 2.9 [risk ratio 1.7-7.0] p<0.0001)\(^3\) or non-ARVD CKD (hazard ratio 1.5 [95% confidence interval 1.2-1.8] p<0.0001)\(^4\). Only a minority of patients with haemodynamically–significant ARVD present with a ‘high-risk’ clinical phenotype characterized by one or more of uncontrolled hypertension, rapid decline in renal function, and recurrent heart failure\(^5\).

Management of ARVD has been a contentious subject for many years; recent large randomized controlled trials (RCT) have shown that revascularization does not confer added benefit to optimal medical treatment and atherosclerotic risk factor control, the accepted cornerstones of ARVD management \(^6,7\). However, as with any RCT, these findings only apply to the type of patients included in the trials; those ARVD patients with high-risk features were seldom recruited into these studies. Anectodal evidence from case reports \(^8,9\) and more recently, data from an observational single-centre study performed by our research group comparing medical treatment with revascularization in 237 patients with a high-risk phenotype, support the role of revascularization in specific clinical situations. In this study we found that revascularization
reduced the risk of death in patients presenting with flash pulmonary oedema (hazard ratio 0.4, p=0.01) and was associated with reduced risk of death (hazard ratio 0.15, p=0.04) and cardiovascular events (hazard ratio 0.23, p=0.02) in patients with the combination of refractory hypertension and rapidly declining renal function\textsuperscript{10}.

Accurate identification of patients with ARVD who are at risk of suffering adverse events would allow a patient-specific therapeutic approach with targeted, intense medical therapy and the possibility of timely revascularization. In this study we utilized clinical and laboratory data acquired over almost 3 decades to characterize the phenotype of patients who reached important clinical end-points, to determine the impact of risk factors on long-term outcomes and assess the effect of revascularization in a large unselected population of patients with ARVD.

**Materials and methods:**

*Patient Population and Data Collection:*

All patients with ARVD presenting to our regional renal centre since 1986 have been recruited into this observational epidemiological study. Data were collected on an annual basis from hospital records, in line with ethical approval granted by the local ethics committee and the declaration of Helsinki. Data collection includes baseline demographics (age at diagnosis, gender), co-morbid conditions (diabetes, macrovascular disease [MVD], congestive heart failure [CHF]), presence of flash pulmonary oedema (FPE), and annualized prescribed medications, blood pressure, and laboratory data including serum creatinine (\mu mol/L) and proteinuria (g/24h), together with clinical outcome data. The degree of renal artery stenosis (RAS) was obtained from cross-sectional angiography (intravenous digital subtraction angiography [IVDSA] and intra-arterial digital subtraction angiography [IADSA] in earlier studies, computed tomographic [CT] or magnetic resonance [MR] angiography in later studies), reported largely by two specialist radiologists over a thirty year period, and recorded using a ‘patency score’; a score of 200 was equivalent to 0% bilateral stenosis while a score of 0 meant 100% bilateral occlusion. The date of diagnostic imaging was considered as time zero for study entry. Sequential patients were entered into the database up until 31\textsuperscript{st} August 2014 and data censoring was performed at the earliest of 11\textsuperscript{th} May 2015, death, or last patient encounter if discharged or lost to follow-up.

*Definitions:*

Previous MVD was defined as a composite of documented coronary artery disease (symptomatic angina, previous myocardial infarction or coronary artery bypass grafting, positive coronary angiography or exercise stress test result), peripheral vascular disease (symptomatic intermittent claudication, previous peripheral revascularization, amputation due to limb ischaemia, evidence of ischaemic ulcers or gangrene) and aortic abdominal aneurysms (AAA) confirmed on imaging or previous AAA repair. CHF was defined as documented symptoms of orthopneoa, paroxysmal nocturnal dyspnea, clinical evidence of CHF on examination and/or
echocardiographic left ventricular ejection fraction <40%. FPE was defined as acute
decompensated heart failure in the absence of a documented precipitating cardiac event or
known reduced ejection fraction (<40%). Estimated glomerular filtration rate (eGFR) was
calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI)\textsuperscript{11}. Patient management:

Patients were managed in accordance with the contemporary vascular protective advice and
UK Renal Association blood pressure targets\textsuperscript{12,13}. Renal revascularization was performed in
accordance with physician preference or after entry into a randomized trial\textsuperscript{6,7}. All
revascularization procedures involved percutaneous transluminal angioplasty with or without
deployment of bare-metal stents; no embolic protection devices were used.

\textit{Clinical End-points:}

Predefined primary clinical end-points include:

(1) Date of death as documented on hospital records. This included all causes of death.
(2) Date of first cardiovascular event (CVE) after enrollment, a composite of acute coronary
syndrome or myocardial infarction, new arrhythmias, pulmonary oedema or decompensated
heart failure, cerebrovascular events including transient ischaemic attacks, peripheral vascular
disease including peripheral revascularization and abdominal aortic aneurysm repair, and
mesenteric ischaemia.
(3) Date of reaching ESKD defined as the earliest of the following events: initiation of renal
replacement therapy (RRT) (including renal transplantation) or reaching eGFR
\textless 10ml/min/1.73m\textsuperscript{2} which is the average eGFR at which RRT is started in the UK\textsuperscript{14}
(4) A composite end-point composed of the first of any of the above events.

\textit{Statistical Analysis:}
Demographic features, imaging characteristics of ARVD, comorbid conditions, baseline
medications, blood pressure, eGFR, proteinuria and rate of eGFR change were compared
between patients who reached clinical end-points (death, ESKD, CVE or any event) and those
who did not suffer these adverse events. Non-parametric continuous variables are presented
as median (interquartile range). Chi-squared test was used to compare categorical data
between the two groups while Mann-Whitney-U was used for non-parametric continuous data.
The rate of change of eGFR or eGFR slope from time zero to end of study was calculated from
slope of linear regression, using serial serum creatinine measurements. Patients who had blood
results taken during in-patient stay, patients who reached RRT, and patients with less than one
year follow-up or less than 3 serum creatinine measurements were excluded from the analysis.
For revascularized patients, the rate of change of eGFR or eGFR slope was calculated from at
least three pre-revascularization serum creatinine values only. Unadjusted incidence rates per
100 patient years were calculated manually using the following equation: (total number of
events/total follow-up time) x 100. Baseline variables were entered into a univariable and
multivariable Cox Proportional Hazards model to determine hazard ratios and 95% confidence intervals; variables were entered into the multivariable model depending on clinical plausibility of causal association with outcome and non-adjusted statistical significance. A P-value <0.05 was considered to be statistically significant. Continuous variables were centred around the mean and scaled where clinically appropriate. These analyses were performed using SPSS (version 22.0).

**Results:**
A total of 872 patients were recruited into this observational study; 42 (4.8%) patients were excluded due to one or more missing key baseline parameters (medications [n=4], blood pressure [n=15], eGFR [n=5] and proteinuria [n=25]), leaving a study population of 830 patients with complete datasets. Median age was 71.0 years (interquartile range: 64.8-76.7). Unilateral ≥70% RAS with contralateral <70% RAS was present in 338 patients (39.5%) while 88 patients (10.6%) had ≥70% RAS bilaterally. At time of ARVD diagnosis, 71.8% of patients had evidence of extra-renal atherosclerosis, 50.0% were receiving an angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) 37.1% a beta blocker, 54.5% aspirin and 55.9% a statin (Table 4.2.1).

Over a median follow-up of 57.1 months (interquartile range: 21.7-96.9 months), 604 (72.8%) patients died, 172 (20.7%) reached ESKD (of whom 128 [15.4%] were treated with RRT), 310 (37.3%) suffered a CVE (of whom 46 [14.8%] suffered a fatal CVE) and 682 (82.2%) experienced any of the previous events. In total, 145 (17.5%) patients underwent renal revascularization. The incidence per 100 patient years of death, ESKD, CVE and any event was 13.5, 4.3, 8.9 and 21.0 respectively.

Patients who died were older than surviving patients (72.1 versus 68.6 years, p<0.0001), had higher prevalence of MVD (75.0% versus 63.3%, p=0.001) and CHF (22.5% versus 11.1%, p<0.0001) at baseline, and were less likely to be receiving renin-angiotensin blockade (RAB) (43.9% versus 66.4%, p<0.0001), more than 3 anti-hypertensive agents (45.5% versus 54.9%, p=0.017) or statins (50.7% versus 69.9%, p<0.0001) at time of diagnosis. These patients were also noted to have lower patency score (100.0 versus 120.0, p=0.007), greater degree of proteinuria (0.6 versus 0.3 g/day, p<0.0001) and a lower eGFR (27.3 versus 36.8 ml/min/1.73m², p<0.0001) at baseline. Patients who reached ESKD similarly had more proteinuria (1.0 versus 0.4 g/day, p<0.0001) and worse CKD (eGFR 17.4 versus 33.4 ml/min/1.73m², p<0.0001) at time of diagnosis. Comorbidities and baseline medications were similar between patients who reached ESKD and those who did not, although a higher proportion of patients who suffered ESKD were receiving calcium channel blockers at time of diagnosis (65.7% versus 52.7%, p=0.002) and conversely, less patients who reached ESKD were established on an ACEi or an ARB (41.9% versus 52.1%, p=0.02) (Table 4.2.1).
Patients who suffered a CVE were more likely to have had revascularization compared to patients who remained CVE-free (21.9% versus 14.8%, p=0.009), and they were more likely to be established on Aspirin at time of diagnosis (61.0% versus 50.6%, p=0.004). Patients who reached the composite end-point of any of ESKD, CVE events or mortality were enriched with extra-renal atherosclerosis and cardiovascular disease at baseline, and a fewer proportion were established on vasculoprotective therapy. Degree of stenosis, CKD and proteinuria were significantly worse when compared to those who did not achieve these end-points. Rate of loss of eGFR was also significantly faster in patients who reached ESKD (-2.0 versus -0.6 ml/min/1.73m²/year, p <0.0001), suffered a CVE (-1.2 versus -0.7 ml/min/1.73m²/year, p = 0.02) or any event (-1.0 versus -0.4 ml/min/1.73m²/year, p = 0.01) (Table 4.2.2).

Table 4.2.3 compares baseline characteristics between patients who underwent revascularization and those who were treated exclusively medically; as expected, overall, revascularized patients had more severe stenosis with more frequent bilateral severe disease. A higher proportion of these patients also had documented cardiovascular disease and evidence of heart failure at time of diagnosis. Baseline renal function, degree of proteinuria and rate of eGFR decline (Table 4.2.2) did not differ between revascularized and non-revascularized patients.

Both univariable and multivariable analysis revealed that MVD, CHF, FPE and higher proteinuria at baseline contributed to increased risk for all four end-points (Table 4.2.4). Conversely, better eGFR at time of diagnosis, higher patency score, use of vascular protection therapy and revascularization were associated with reduced risk of adverse events. In the adjusted multivariable analysis, administration of statins and renin angiotensin blockade (RAB) at time of diagnosis was associated with reduced risk of death (RAB: hazard ration 0.83 [95% CI 0.70-0.98]; statins: hazard ratio 0.79 [95% CI 0.66-0.94]) and ESKD (RAB: hazard ratio 0.84 [95% CI 0.71-1.00]; statins: hazard ratio 0.79 [95% confidence interval 0.66-0.93]). Renin angiotensin blockade was associated with reduced risk of CVE and any event in univariable analysis but lost significance in multivariable analysis. Similarly, beta-blocker administration at baseline was associated with reduced hazard ratios for adverse events in the univariable analysis, but did not reach statistical significance in the adjusted analysis. Revascularization appeared to be significantly associated with reduced risk of both death (hazard ratio 0.65 [95% confidence interval 0.51-0.83]) and ESKD (hazard ratio 0.59 [95% confidence interval 0.46-0.76]) (Table 4.2.4).
**Table 4.2.1** Baseline characteristics for entire cohort and for patients who reached and did not reach end-points.

<table>
<thead>
<tr>
<th></th>
<th>All n=830</th>
<th>Died (n=226)</th>
<th>Yes (n=604)</th>
<th>p</th>
<th>ESKD No (n=658)</th>
<th>Yes (n=172)</th>
<th>p</th>
<th>CVE No (n=520)</th>
<th>Yes (n=310)</th>
<th>p</th>
<th>Any No (n=148)</th>
<th>Yes (n=682)</th>
<th>p</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>71.0 (64.8-76.7)</td>
<td>68.6 (68-72)</td>
<td>72.1 &lt;0.0001</td>
<td>71.5</td>
<td>70.2</td>
<td>0.1</td>
<td>71.4</td>
<td>70.4</td>
<td>0.1</td>
<td>69.1</td>
<td>71.4</td>
<td>0.01</td>
<td>MWU</td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>59.9</td>
<td>59.3</td>
<td>60.1</td>
<td>0.8</td>
<td>59</td>
<td>63.4</td>
<td>0.3</td>
<td>58.1</td>
<td>62.9</td>
<td>0.2</td>
<td>57.4</td>
<td>60.4</td>
<td>0.5</td>
<td>X²</td>
</tr>
<tr>
<td>RAS &gt;70% unilateral (%)</td>
<td>39.5</td>
<td>35.0</td>
<td>41.2</td>
<td>0.1</td>
<td>38.8</td>
<td>42.4</td>
<td>0.4</td>
<td>41.5</td>
<td>36.1</td>
<td>0.1</td>
<td>35.1</td>
<td>40.5</td>
<td>0.2</td>
<td>X²</td>
</tr>
<tr>
<td>RAS &gt;70% Bilateral (%)</td>
<td>10.6</td>
<td>9.3</td>
<td>11.1</td>
<td>0.5</td>
<td>10.3</td>
<td>11.6</td>
<td>0.6</td>
<td>10.6</td>
<td>10.6</td>
<td>0.9</td>
<td>6.8</td>
<td>11.4</td>
<td>0.09</td>
<td>X²</td>
</tr>
<tr>
<td>Median patency score</td>
<td>105.0 (70.0-150.0)</td>
<td>120.0</td>
<td>100.0</td>
<td>0.007</td>
<td>110.0</td>
<td>100.0</td>
<td>0.1</td>
<td>105.0</td>
<td>107.5</td>
<td>0.9</td>
<td>130.0</td>
<td>100.0</td>
<td>&lt;0.0001</td>
<td>MWU</td>
</tr>
<tr>
<td>Median SBP mmHg</td>
<td>152.0 (135.0-175.3)</td>
<td>152.0</td>
<td>152.0</td>
<td>154.0</td>
<td>150.0</td>
<td>0.2</td>
<td>150.0</td>
<td>153.5</td>
<td>0.6</td>
<td>150.0</td>
<td>152.5</td>
<td>0.6</td>
<td>MWU</td>
<td></td>
</tr>
<tr>
<td>Median DBP mmHg</td>
<td>80.0 (70.0-90.0)</td>
<td>79.0</td>
<td>80.0</td>
<td>0.3</td>
<td>80.0</td>
<td>80.0</td>
<td>0.9</td>
<td>80.0</td>
<td>80.0</td>
<td>0.9</td>
<td>79.0</td>
<td>80.0</td>
<td>0.2</td>
<td>MWU</td>
</tr>
<tr>
<td>Median MAP mmHg</td>
<td>103.3 (93.3-115.3)</td>
<td>101.8</td>
<td>103.3</td>
<td>0.5</td>
<td>103.3</td>
<td>101.4</td>
<td>0.5</td>
<td>102.8</td>
<td>103.3</td>
<td>0.8</td>
<td>100.7</td>
<td>103.3</td>
<td>0.3</td>
<td>MWU</td>
</tr>
<tr>
<td>MVD (%)</td>
<td>71.8</td>
<td>63.3</td>
<td>75.0</td>
<td>0.001</td>
<td>71.7</td>
<td>72.1</td>
<td>0.9</td>
<td>68.5</td>
<td>77.4</td>
<td>0.006</td>
<td>60.1</td>
<td>74.3</td>
<td>&lt;0.0001</td>
<td>X²</td>
</tr>
<tr>
<td>CHF (%)</td>
<td>19.4</td>
<td>11.1</td>
<td>22.5</td>
<td>&lt;0.0001</td>
<td>19.0</td>
<td>20.9</td>
<td>0.6</td>
<td>17.3</td>
<td>22.9</td>
<td>0.05</td>
<td>8.1</td>
<td>21.8</td>
<td>&lt;0.0001</td>
<td>X²</td>
</tr>
<tr>
<td>FPE (%)</td>
<td>6.4</td>
<td>4.4</td>
<td>7.1</td>
<td>0.2</td>
<td>6.2</td>
<td>7.0</td>
<td>0.7</td>
<td>5.6</td>
<td>7.7</td>
<td>0.2</td>
<td>4.1</td>
<td>6.9</td>
<td>0.2</td>
<td>X²</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>31.3</td>
<td>28.3</td>
<td>32.5</td>
<td>0.2</td>
<td>30.5</td>
<td>34.3</td>
<td>0.3</td>
<td>30.2</td>
<td>33.2</td>
<td>0.4</td>
<td>29.1</td>
<td>31.8</td>
<td>0.5</td>
<td>X²</td>
</tr>
<tr>
<td>RAB (%)</td>
<td>50.0</td>
<td>66.4</td>
<td>43.9</td>
<td>&lt;0.0001</td>
<td>52.1</td>
<td>41.9</td>
<td>0.02</td>
<td>49.6</td>
<td>50.6</td>
<td>0.8</td>
<td>64.9</td>
<td>46.8</td>
<td>&lt;0.0001</td>
<td>X²</td>
</tr>
<tr>
<td>BB (%)</td>
<td>37.1</td>
<td>43.4</td>
<td>34.8</td>
<td>0.02</td>
<td>35.9</td>
<td>41.9</td>
<td>0.1</td>
<td>37.5</td>
<td>36.5</td>
<td>0.8</td>
<td>44.6</td>
<td>35.5</td>
<td>0.04</td>
<td>X²</td>
</tr>
<tr>
<td>CaB (%)</td>
<td>55.4</td>
<td>52.7</td>
<td>56.5</td>
<td>0.3</td>
<td>52.7</td>
<td>65.7</td>
<td>0.002</td>
<td>54.4</td>
<td>57.1</td>
<td>0.5</td>
<td>48.6</td>
<td>56.9</td>
<td>0.07</td>
<td>X²</td>
</tr>
<tr>
<td>&gt;3 anti-hypertensives (%)</td>
<td>48.1</td>
<td>54.9</td>
<td>45.5</td>
<td>0.02</td>
<td>47.6</td>
<td>50.0</td>
<td>0.6</td>
<td>45.8</td>
<td>51.9</td>
<td>0.09</td>
<td>53.4</td>
<td>46.9</td>
<td>0.2</td>
<td>X²</td>
</tr>
<tr>
<td>Aspirin (%)</td>
<td>54.5</td>
<td>54.9</td>
<td>54.3</td>
<td>0.9</td>
<td>54.0</td>
<td>56.4</td>
<td>0.6</td>
<td>50.6</td>
<td>61.0</td>
<td>0.004</td>
<td>52.0</td>
<td>55.0</td>
<td>0.5</td>
<td>X²</td>
</tr>
<tr>
<td>Statin (%)</td>
<td>55.9</td>
<td>69.9</td>
<td>50.7</td>
<td>&lt;0.0001</td>
<td>56.1</td>
<td>55.2</td>
<td>0.8</td>
<td>54.8</td>
<td>57.7</td>
<td>0.4</td>
<td>68.2</td>
<td>53.2</td>
<td>0.001</td>
<td>X²</td>
</tr>
<tr>
<td>Median Proteinuria</td>
<td>0.6 (0.2-1.2)</td>
<td>0.3</td>
<td>0.6</td>
<td>&lt;0.0001</td>
<td>0.4</td>
<td>1.0</td>
<td>&lt;0.0001</td>
<td>0.5</td>
<td>0.6</td>
<td>0.2</td>
<td>0.2</td>
<td>0.6</td>
<td>&lt;0.0001</td>
<td>MWU</td>
</tr>
</tbody>
</table>
Table 4.2.2 Rate of eGFR decline per year for patients who reached clinical end-points and those who remained event-free.

<table>
<thead>
<tr>
<th>Revascularization status</th>
<th>Median eGFR slope* (ml/min/1.73m²/year)</th>
<th>Died</th>
<th>ESKD</th>
<th>CVE</th>
<th>Any</th>
</tr>
</thead>
<tbody>
<tr>
<td>NR</td>
<td>-0.8 (-2.6 - 0.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>-1.7 (-9.8 - 6.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.3 (-1.1 - 1.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bold data indicates a statistically significant difference with a p value less than 0.05.

CVE – cardiovascular event; eGFR – estimated glomerular filtration rate; ESKD – end-stage kidney disease; MWU – Mann Whitney U Test; n = number of patients who met criteria for calculation of eGFR slope; NR – non-revascularized; R – revascularized.

* Representing rate of eGFR decline per year. This was calculated from slope of linear regression, excluding blood results taken during in-patient stay, patients who reached RRT, and patients with less than one year follow-up or less than 3 data points. For revascularized patients, only pre-revascularization serum creatinine values were entered into the analysis.
Table 4.2.3 Comparison of baseline characteristics between revascularized (R) and non-revascularized (NR) patients.

<table>
<thead>
<tr>
<th></th>
<th>All (n=830)</th>
<th>Death (n=604)</th>
<th>ESKD (n=172)</th>
<th>CVE (n=310)</th>
<th>Any (n=682)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NR (n=685)</td>
<td>R (n=145)</td>
<td>p</td>
<td>NR (n=504)</td>
<td>R (n=100)</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>71.6 (65.1-</td>
<td>69.2 (63.3-</td>
<td>0.001</td>
<td>72.1 (67.1-</td>
<td>69.5 (65.2-</td>
</tr>
<tr>
<td></td>
<td>77.3)</td>
<td>74.6)</td>
<td></td>
<td>78.1)</td>
<td>75.1)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>61.2 (53.8-</td>
<td>53.8 (45.5-</td>
<td>0.1</td>
<td>61.5 (40.5-</td>
<td>53.0 (45.0-</td>
</tr>
<tr>
<td>RAS &gt;70% unilateral</td>
<td>38.2 (45.5-</td>
<td>45.5 (40.5-</td>
<td>0.1</td>
<td>40.5 (40.0-</td>
<td>45.0 (40.0-</td>
</tr>
<tr>
<td>RAS &gt;70% bilateral</td>
<td>6.6 (29.7-</td>
<td>29.7 &lt;0.0001</td>
<td></td>
<td>7.3 (30.0-</td>
<td>30.0 &lt;0.0001</td>
</tr>
<tr>
<td>Median patency score</td>
<td>110.0 (90.0-</td>
<td>75.0 (40.0-</td>
<td>&lt;0.0001</td>
<td>100.0 (80.0-</td>
<td>72.5 (40.0-</td>
</tr>
<tr>
<td></td>
<td>150.0)</td>
<td>120.0)</td>
<td></td>
<td>150.0)</td>
<td>115.0)</td>
</tr>
<tr>
<td>Median SBP (mmHg)</td>
<td>150.0 (133.5-</td>
<td>160.0 (139.0-</td>
<td>0.003</td>
<td>150.0 (132.3-</td>
<td>160.0 (139.0-</td>
</tr>
<tr>
<td></td>
<td>172.0)</td>
<td>186.0)</td>
<td></td>
<td>174.5)</td>
<td>185.8)</td>
</tr>
<tr>
<td>Median DBP (mmHg)</td>
<td>80.0 (70.0-</td>
<td>80.0 (72.0-</td>
<td>0.06</td>
<td>80.0 (70.0-</td>
<td>80.0 (72.0-</td>
</tr>
<tr>
<td></td>
<td>90.0)</td>
<td>90.0)</td>
<td></td>
<td>90.0)</td>
<td>89.5)</td>
</tr>
<tr>
<td>Median MAP (mmHg)</td>
<td>102.3 (93.0-</td>
<td>106.7 (96.7-</td>
<td>0.007</td>
<td>103.3 (92.7-</td>
<td>106.7 (96.7-</td>
</tr>
<tr>
<td></td>
<td>114.3)</td>
<td>118.0)</td>
<td></td>
<td>116.6)</td>
<td>118.1)</td>
</tr>
<tr>
<td>MVD (%)</td>
<td>70.4 (73.6-</td>
<td>78.6 (72.7-</td>
<td>0.05</td>
<td>73.6 (73.6-</td>
<td>82.0 (72.7-</td>
</tr>
<tr>
<td>CHF (%)</td>
<td>17.4 (27.6-</td>
<td>29.7 (32.0-</td>
<td>0.001</td>
<td>20.6 (27.6-</td>
<td>32.0 (32.0-</td>
</tr>
<tr>
<td>FPE (%)</td>
<td>5.4 (6.3-</td>
<td>11.0 (6.3-</td>
<td>0.01</td>
<td>6.3 (6.3-</td>
<td>11.0 (6.3-</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>31.4 (32.3-</td>
<td>31.0 (33.0-</td>
<td>0.09</td>
<td>32.3 (33.0-</td>
<td>33.0 (33.0-</td>
</tr>
<tr>
<td>RAB (%)</td>
<td>49.9 (43.5-</td>
<td>50.3 (46.0-</td>
<td>0.9</td>
<td>43.5 (46.0-</td>
<td>46.0 (46.0-</td>
</tr>
<tr>
<td>Variable</td>
<td>Death Univariable</td>
<td>Death Multivariable</td>
<td>ESKD Univariable</td>
<td>ESKD Multivariable</td>
<td>CVE Univariable</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-------------------</td>
<td>---------------------</td>
<td>------------------</td>
<td>-------------------</td>
<td>----------------</td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>HR</td>
<td>95% CI</td>
<td>HR</td>
</tr>
<tr>
<td>Age[^a]</td>
<td>1.48</td>
<td>(1.34-1.63)</td>
<td>1.38 (1.24-1.54)</td>
<td>1.36 (1.23-1.50)</td>
<td>1.17 (1.06-1.31)</td>
</tr>
<tr>
<td>Patency score[^b]</td>
<td>0.95 (0.90-0.99)</td>
<td>0.95 (0.90-0.98)</td>
<td>0.95 (0.90-0.98)</td>
<td>0.95 (0.90-0.98)</td>
<td>0.93 (0.90-0.98)</td>
</tr>
<tr>
<td>Revascularization</td>
<td>0.72 (0.58-0.90)</td>
<td>0.65 (0.51-0.83)</td>
<td>0.70 (0.57-0.87)</td>
<td>0.59 (0.46-0.76)</td>
<td>0.89 (0.73-1.09)</td>
</tr>
<tr>
<td>MVD</td>
<td>1.44 (1.20-1.73)</td>
<td>1.24 (1.02-1.50)</td>
<td>1.37 (1.15-1.65)</td>
<td>1.17 (0.97-1.42)</td>
<td>1.61 (1.35-1.91)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.17 (0.99-1.39)</td>
<td>1.07 (0.89-1.28)</td>
<td>1.09 (0.92-1.30)</td>
<td>0.98 (0.81-1.17)</td>
<td>1.20 (1.02-1.41)</td>
</tr>
</tbody>
</table>

Bold data indicates a statistically significant difference with a p value less than 0.05.

BB – beta blocker; CaB – calcium channel blocker; CHF – Congestive heart failure; CVE – cardiovascular event; DBP – Diastolic Blood pressure; eGFR – estimated glomerular filtration rate; ESKD – End-stage kidney disease; FPE – flash pulmonary oedema; MAP – Mean arterial pressure; MVD – macrovascular disease; MWU – Mann Whitney U test; n – number of patients; RAB – renal artery stenosis; SBP – systolic blood pressure; X² – Chi-square test

[^a]: Calculated using Chronic Kidney Disease Epidemiology collaboration equation (CKD-EPI)^[11]

**Table 4.2.4 Univariable and multivariable association between baseline variable and clinical end-points.**
<table>
<thead>
<tr>
<th></th>
<th>CHF</th>
<th>FPE</th>
<th>RAB</th>
<th>BB</th>
<th>Statin</th>
<th>MAP</th>
<th>Proteinuria (g/day)</th>
<th>eGFR (ml/min/1.73m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.74 (1.43-2.11)</td>
<td><strong>2.10 (1.50-2.92)</strong></td>
<td>0.76 (0.65-0.89)</td>
<td>0.84 (0.71-0.99)</td>
<td>0.80 (0.68-0.95)</td>
<td>0.94 (0.90-0.98)</td>
<td>1.12 (1.07-1.18)</td>
<td>0.89 (0.87-0.91)</td>
</tr>
<tr>
<td></td>
<td>1.33 (1.08-1.64)</td>
<td><strong>2.10 (1.50-2.92)</strong></td>
<td><strong>0.83 (0.70-0.98)</strong></td>
<td>0.93 (0.78-1.10)</td>
<td><strong>0.79 (0.66-0.94)</strong></td>
<td><strong>0.97 (0.92-1.02)</strong></td>
<td><strong>1.14 (1.08-1.20)</strong></td>
<td><strong>0.92 (0.89-0.94)</strong></td>
</tr>
<tr>
<td></td>
<td>1.77 (1.46-2.14)</td>
<td><strong>2.01 (1.48-2.73)</strong></td>
<td>0.78 (0.66-0.92)</td>
<td>0.85 (0.72-1.00)</td>
<td>0.81 (0.69-0.95)</td>
<td>0.93 (0.92-1.02)</td>
<td><strong>1.13 (1.08-1.18)</strong></td>
<td><strong>0.86 (0.84-0.89)</strong></td>
</tr>
<tr>
<td></td>
<td>1.39 (1.13-1.71)</td>
<td><strong>1.82 (1.31-2.51)</strong></td>
<td><strong>0.84 (0.71-1.00)</strong></td>
<td>0.89 (0.75-1.05)</td>
<td><strong>0.79 (0.66-0.93)</strong></td>
<td>0.95 (0.90-1.00)</td>
<td><strong>1.14 (1.09-1.20)</strong></td>
<td><strong>0.89 (0.86-0.91)</strong></td>
</tr>
<tr>
<td></td>
<td>1.84 (1.53-2.21)</td>
<td><strong>2.12 (1.56-2.88)</strong></td>
<td>0.85 (0.73-0.99)</td>
<td>0.84 (0.72-0.99)</td>
<td>0.93 (0.80-1.08)</td>
<td>0.93 (0.90-0.98)</td>
<td><strong>1.09 (1.04-1.14)</strong></td>
<td><strong>0.92 (0.89-0.94)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>1.37 (1.11-1.68)</strong></td>
<td><strong>1.88 (1.36-2.60)</strong></td>
<td>0.88 (0.75-1.03)</td>
<td>0.90 (0.76-1.06)</td>
<td>0.92 (0.78-1.08)</td>
<td>0.95 (0.91-1.00)</td>
<td><strong>1.10 (1.05-1.16)</strong></td>
<td><strong>0.94 (0.92-0.97)</strong></td>
</tr>
<tr>
<td></td>
<td>1.89 1.57-2.27</td>
<td>2.05 1.51-2.77</td>
<td>0.83 0.71-0.96</td>
<td>0.88 0.75-1.03</td>
<td>0.91 0.78-1.06</td>
<td>0.94 0.90-0.98</td>
<td><strong>1.11 1.06-1.16</strong></td>
<td>0.90 0.88-0.92</td>
</tr>
<tr>
<td></td>
<td><strong>1.42 (1.16-1.75)</strong></td>
<td><strong>1.72 (1.24-2.38)</strong></td>
<td><strong>0.85 (0.73-1.00)</strong></td>
<td><strong>0.92 (0.78-1.08)</strong></td>
<td><strong>0.90 (0.76-1.06)</strong></td>
<td><strong>0.94 (0.90-0.98)</strong></td>
<td><strong>1.12 (1.07-1.18)</strong></td>
<td><strong>0.92 (0.89-0.94)</strong></td>
</tr>
</tbody>
</table>

Bold data indicates a statistically significant difference with a p value less than 0.05.

BB – beta blocker; CHF – Congestive heart failure; CI – confidence interval; CVE – cardiovascular event; eGFR – estimated glomerular filtration rate; ESKD – End-stage kidney disease; FPE – flash pulmonary oedema; HR – hazard ratio; MAP – Mean arterial pressure; MVD – macrovascular disease; RAB – renin-angiotensin blockade;

*Adjusted for death

Per 10 year increase

Per 25 unit increase in patency score

Per 10mmHg increase in MAP

Per 1g/day increase in proteinuria

Per 5 ml/min/1.73m² increase in eGFR, calculated using the Chronic Kidney Disease Epidemiology collaboration equation (CKD-EPI)¹¹
Discussion
This observational study is characterized by the longest follow-up on the largest cohort of patients with ARVD to date, thus providing important insight into the determinants of long-term outcomes.

ARVD occurs as part of systemic atherosclerosis hence, as expected, the phenotype of patients who reached clinical end-points is enriched with typical cardiovascular risk factors such as older age, co-existing macrovascular disease and congestive heart failure. In spite of this, in our centre only around half of patients were established on vascular protective therapy at time of diagnosis; this proportion appears to be less than recent data published by the Cardiovascular outcomes in renal atherosclerotic lesions (CORAL) study group, showing that in recruiting centres outside the US, up to 75% of patients were established on statins, and 62% were receiving RAB at baseline. However, our study includes data from a minority of patients recruited before the emergence of evidence on the benefits of vascular protection and tight cardiovascular risk factor control in patients with systemic atherosclerosis. Data from retrospective observational studies has consistently shown that RAB, statins, and more recently, anti-platelet therapy and beta-blockers, offer a similar prognostic benefit to patients with ARVD. Although adoption of this multi-targeted therapeutic approach in treating patients with ARVD has increased in recent years, more effort is required to ensure that this becomes standard care for all patients with ARVD.

While our results suggest that patients who reached adverse end-points were less likely to be receiving vascular protective medication, in multivariable analysis only baseline administration of statins was shown to be associated with an independent mortality benefit. Contrary to expectations, statins had no impact on risk of CVE either in univariable or multivariable analysis and neither RAB nor beta-blockers were significantly associated with benefit in the adjusted analysis. This lack of perceived benefit is probably due to both immortal time bias, as the duration of time patients were receiving the baseline drugs before recruitment into the study was not considered, and the absence of longitudinal drug data. Selection bias may also account for the larger proportion of patients who suffered a CVE that were administered aspirin at baseline due to their higher cardiovascular risk, and the frequent use of calcium channel blockers in patients progressing to ESKD. Indeed, patients who died or reached ESKD had significantly lower renal function at time of diagnosis, hence they were less likely to receive renin-angiotensin blockade for blood pressure control or amelioration of proteinuria.

Although this study suggests that vascular protective therapy may modulate adverse outcomes in ARVD, our results clearly show that these are strongly dictated by the presence of greater degrees of proteinuria and lower GFR, markers of prior renal intrarenal injury. This is in keeping with results published previously by our study group showing that relative risk of declining renal function was 1.23 for every 1g/24h increase in baseline proteinuria, and patients with >0.6g/24h proteinuria at time of diagnosis experienced poor renal outcomes even after
revascularization\textsuperscript{27}. Low eGFR at baseline was also associated with poor survival\textsuperscript{26,28}. Our study provides further support to this data by showing that patients with greater degrees of baseline proteinuria were at greater risk of suffering all adverse events, while patients with better preserved renal function at time of diagnosis had better outcomes. Although diabetics have been included in the analysis and diabetic nephropathy is also associated with proteinuria, the presence of diabetes did not enhance the risk of adverse clinical outcomes. A recent observational study from Taiwan has reported that diabetes increased the risk of ESKD in ARVD around 1.55-fold\textsuperscript{29} while another study from the UK has highlighted increased mortality in diabetic patients with ARVD compared to their non-diabetic counterparts\textsuperscript{30}. Potential reasons for our conflicting results are the uniform distribution of diabetics between groups, and selection bias; patients with rapidly declining renal function or severe proteinuria in the context of presumed significant diabetic nephropathy are unlikely to be referred for investigation of ARVD, despite the known close association between diabetes and the development of systemic and renal atherosclerosis\textsuperscript{31,32}.

The clinical significance of renal vascular anatomy is unclear. Several studies, including publications from this same dataset, demonstrated that severity of stenosis correlates inversely with long-term patient survival\textsuperscript{15,26,30}, but has no bearing on degree of renal dysfunction at presentation and renal functional outcome. This is dependent on the degree of parenchymal disease, which is related to the actual ‘haemodynamic significance’ of a stenosis rather than its ‘severity’ on cross-sectional imaging studies \textsuperscript{26,28,33}. In addition, patients with severe stenosis invariably have widespread systemic atherosclerosis and significant cardiovascular comorbidities, hence most die before progressing to ESKD. Our results point towards a trend between higher patency score and better long-term clinical outcomes, suggesting that in this complex, heterogenous condition, outcomes are influenced by both parenchymal damage and the ‘haemodynamic significance’ of stenosis. However, the patency score used in this analysis does not distinguish between unilateral severe stenosis and bilateral less haemodynamically significant disease, hence results probably reflect the effect of overall atherosclerotic burden rather than specific haemodynamic compromise.

Nonetheless, revascularization was noted to be associated with a significant beneficial effect on long-term survival and progression to ESKD even after adjusting for confounders including age, macrovascular disease, congestive heart failure, flash pulmonary oedema, medications, and baseline blood pressure, proteinuria and renal function. Revascularization contributed to a 33\% reduction in risk for death (hazard ratio 0.67 [95\% confidence interval 0.52-0.87] p=0.003) and a 32\% reduction in risk for ESKD (hazard ratio 0.68 [95\% confidence interval 0.53-0.88] p=0.003); this is similar to the risk reduction noted in a recent observational study performed using administrative claims in Taiwan (adjusted odds ratio 0.64 [95\% confidence interval 0.50-0.84] p<0.01)\textsuperscript{29}. It is however difficult to interpret the effect of revascularization on long-term outcomes in unselected patients with ARVD from observational or retrospective studies as...
these do not take into account hidden confounders or selection bias.

In addition to potential sources of bias already mentioned above, this study has other important limitations. Only patients with complete datasets were included in this analysis. The number of patients excluded from analysis due to missing data was small in comparison to the study population, and so we feel it unlikely that this would introduce potential bias in our study. Data was collected in a standardized manner from patient records, but this was performed by different individuals over three decades, thus introducing assignment bias. Variables such as body mass index, smoking status and drug dosage were not included due to missing or unreliable data. Cause of death data was also not available but for the purposes of our discussion, it was assumed that there was a predominance of cardiovascular deaths in this ARVD population, in keeping with evidence from the literature\textsuperscript{34}. Our analyses are based on ‘all-cause’ death and no imputed outcome data was used in the analyses. Blood pressure was documented from office readings taken at time of diagnosis, which has limitations. The degree of stenosis was determined by a single observer and based on biplanar imaging studies without confirmation of haemodynamic significance of the stenosis. It is hoped that continued prospective data collection coupled with the application of novel non-invasive imaging techniques\textsuperscript{35} and specific serum biomarkers\textsuperscript{36}, to determine the haemodynamic significance of a stenosis and the viability of renal parenchyma, can help overcome these limitations.

**Conclusion:**
The main determinants of adverse clinical outcomes in ARVD are prior cardiovascular disease and intra-renal parenchymal damage manifest by greater proteinuria and reduced renal function. Our results indicate that more effort is required to optimize medical management of ARVD using multi-targeted vascular protection therapy to help improve cardiovascular risk and decrease overall atherosclerotic burden while mitigating intra-renal parenchymal injury. Revascularization may have a beneficial effect on long-term outcomes in certain patients, however, more research is required to help characterize this patient sub-group further.
References:


4.3 The effect of revascularization in patients with anatomically-significant atherosclerotic renovascular disease presenting with high-risk clinical features.

DOI: 10.1093/ndt/gfx025.

Preface:
Atherosclerotic renovascular disease (ARVD) is a heterogenous condition; while the majority of patients have clinically ‘silent’ disease and remain clinically stable on medical therapy alone, a percentage present with flash pulmonary edema, uncontrolled hypertension or rapidly deteriorating renal function. There is observational evidence that revascularization may be of benefit in patients with these ‘high-risk’ clinical features. Moreover, current guidelines suggest that revascularization may be appropriate in patients with ‘global ischaemia’ due to bilateral haemodynamically significant disease, and clinical outcomes post-revascularization may be better in patients with lower degrees of proteinuria at presentation, as these reflect potentially viable renal parenchyma. In this study we investigated the effect of revascularization on long-term clinical end-points such as death, progression to end-stage kidney disease and cardiovascular events in ARVD patients with high-risk clinical presentations, and in those with bilateral severe renal artery stenosis and different degrees of proteinuria at time of diagnosis, to help further characterize the phenotype of patients who may gain benefit from revascularization.

Abstract:
Background: Patients with atherosclerotic renovascular disease (ARVD) and high-risk clinical presentations have been largely been excluded from randomized controlled trials comparing renal revascularization and optimal medical therapy. Here, we explore the effect of revascularization on death, progression to end-stage kidney disease (ESKD) and cardiovascular events (CVE) in a highly selected cohort of patients with ARVD.

Method: All patients with a radiological diagnosis of ARVD referred to our tertiary centre have been recruited into a single-centre cohort study between 1986 and 2014. Patients with ≥70% unilateral or bilateral ARVD together with one or more of the following putative high-risk presentations were designated ‘high-risk’: flash pulmonary edema (FPE), severe hypertension, rapidly deteriorating renal function. The effect of revascularization on clinical outcomes in high-risk patients, patients with bilateral severe ARVD and those with <1g proteinuria at baseline was compared to ‘control’ patients who had the same degree of renal artery stenosis but did not exhibit these features.
**Results:** Median follow-up was 58.4 months (Interquartile range (IQR) 25.4-97.3). Revascularization was associated with a reduced risk of progression to ESKD, CVE and all combined events in patients with rapidly deteriorating renal function (ESKD: HR 0.47 [95% CI 0.25-0.85], p=0.01; CVE: HR 0.51 [95% CI 0.29-0.91], p=0.02; Any: HR 0.51 [95% CI 0.29-0.90], p=0.02). High-risk patients with bilateral ≥70% RAS and those with <1g/day baseline proteinuria also had significantly better renal and cardiovascular outcomes post revascularization when compared to controls.

**Conclusion:** Our results indicate that revascularization may be of benefit in patients with anatomically significant RAS who present with rapidly deteriorating renal function, especially in the presence of severe bilateral ARVD or <1g/day proteinuria.

**Introduction:**
Randomized controlled trials (RCT) and meta-analyses 1–4 of revascularization versus medical therapy in patients with atherosclerotic renovascular disease (ARVD) have shown that revascularization does not confer added benefit to medical therapy in unselected patients, resulting in reduced enthusiasm for revascularization 5.

These studies have been criticized for enrolling a large proportion of stable patients with low risk features6–7. Whilst most ARVD patients have ‘incidental’ disease and remain stable on medical therapy alone, some present with ‘high-risk’ clinical phenotypes that are refractory to medical therapy. These include uncontrolled hypertension, rapid deterioration of renal function, or recurrent episodes of acute heart failure8.

There is consistent, albeit non-randomized, evidence that revascularization may be of benefit in these subgroups. Observational studies have shown that revascularization can stabilize or improve renal function, delaying the need for renal replacement therapy (RRT), in selected patients with ARVD and either rapidly deteriorating or advanced renal impairment 9–12, and case reports support revascularization in patients with recurrent acute pulmonary edema13,14. While revascularization did not improve blood pressure control in RCTs, a more recent prospective but uncontrolled study of the effects of a new renal stent has shown that patients with poorly controlled hypertension at recruitment had a greater reduction in blood pressure post-revascularization compared to those with better blood pressure control 15. In addition, our recent observational study indicates that revascularization is associated with survival benefit in patients presenting with flash pulmonary edema (HR 0.4, 95% CI 0.2-0.9, p=0.01) or rapidly declining renal function and refractory hypertension in combination (HR 0.15, 95% CI 0.02-0.9, p=0.04)16. We have also previously shown that severity of ARVD and proteinuria also correlate with adverse outcomes in ARVD in unselected cohorts17,18.
Despite the lack of RCT evidence, societal guidelines still recommend revascularization in specific clinical scenarios\textsuperscript{19,20}. Patient selection for renal revascularization is complex and challenging, and the lack of benefit from revascularization noted in RCTs is likely due to non-targeted patient selection\textsuperscript{21}. We hypothesized that outcomes post-revascularization are more likely to be positive in ‘high-risk’ patients with anatomically severe stenosis and without significant proteinuria (a surrogate of potentially viable renal parenchyma\textsuperscript{22}). This would potentially aid in characterizing the specific phenotype of patients who would gain benefit from revascularization, even within those sub-groups of ARVD who already meet current criteria for revascularization\textsuperscript{19,20}.

**Method:**

**Patient Population and Data Collection:**
The observational Salford ARVD study was established in 1986. Approval was granted by the local ethics committee. Patients with ARVD were recruited and data updated annually from hospital records. Data include age, gender, co-morbidities (diabetes, macrovascular disease [MVD], congestive heart failure [CHF]), flash pulmonary edema (FPE)), prescribed medications, blood pressure, creatinine (\textit{\textmu}mol/L), proteinuria (g/24h), and clinical outcomes. The degree of renal artery stenosis (RAS) was obtained from cross-sectional angiography (intravenous digital subtraction angiography [IVDSA], intra-arterial digital subtraction angiography [IADSA], computed tomographic [CT] or magnetic resonance [MR] angiography), and recorded using a renal artery ‘patency score’; a score of 200 was equivalent to 0% bilateral stenosis while a score of 0 meant 100% bilateral occlusion. Estimated glomerular filtration rate (eGFR) was calculated using CKD-EPI\textsuperscript{23}.

The date of diagnostic imaging was considered as time zero. New patients were entered into the database up until 31st August 2014 and data censoring was performed at the earliest of 11th May 2015, death, or last patient encounter.

**Study population:**
Our definition of ‘high-risk’ was based on expert consensus statements\textsuperscript{20,21}, and patients were identified by retrospective review of the database. The definition was: \textgreater=70\% unilateral or bilateral angiographic RAS with at least one of:

1. Flash pulmonary edema (FPE) or acute decompensated heart failure in the absence of a documented precipitating cardiac event or known reduced ejection fraction (<40\%) or documented congestive heart failure (CHF)
2. Stage 2 hypertension (systolic \textgreater=160mmHg and/or diastolic \textgreater=100mmHg) despite three or more anti-hypertensives of which one is a diuretic \textsuperscript{24}.
3. Rapidly deteriorating renal function following diagnosis of ARVD, defined as an eGFR slope less than -3.0ml/min/1.73m\textsuperscript{2}/year, this being the 25\% percentile of the eGFR slope
of all ARVD patients on the database (Median eGFR slope: -0.9 ml/min/1.73m²/year [Interquartile range: -3.0 to +0.9]).

Patients with bilateral renal artery occlusion or unilateral occlusion and contralateral RAS <70% were excluded, as these patients are considered less likely to be candidates for revascularization. Patients who met the same inclusion criteria for RAS severity, but did not have any of these three clinical presentations were designated ‘control’. Diabetic patients with retinopathy and ≥1g/day proteinuria were excluded from both groups as they were considered to have underlying diabetic nephropathy.

Patient management:
Patients were managed in accordance with contemporary vascular protective advice and UK Renal Association blood pressure targets. Renal revascularization was performed in accordance with physician preference or after entry into an RCT. All revascularization procedures involved percutaneous transluminal angioplasty; bare-metal stents were deployed in all procedures apart from interventions performed in the 1980s and early 1990s (n=20 [21.1%]); no embolic protection devices were used.

Clinical End-points:
Predefined primary clinical end-points for this study were:

1. Date of death
2. Date of first cardiovascular event (CVE) after enrollment (acute coronary syndrome, myocardial infarction, new arrhythmias, pulmonary edema, decompensated heart failure, cerebrovascular accident, transient ischaemic attack).
3. Date of reaching end-stage kidney disease (ESKD), defined as the earliest of the following events: initiation of renal replacement therapy (RRT, including renal transplantation) or eGFR <10ml/min/1.73m², the average eGFR at which RRT is started in the UK.
4. A composite end-point of the first of any of the above events.

Statistical Analysis:
Patients with missing baseline data were excluded. Baseline characteristics and eGFR slope were compared between control and high-risk patients, and between high-risk revascularized and high-risk non-revascularized patients. Non-parametrically distributed continuous data is presented as median (interquartile range). The Chi-squared test was used to compare categorical data between the two groups while the Mann-Whitney-U was used for non-parametric continuous data. The rate of change of eGFR or eGFR slope from time zero to end of study was calculated from the slope of linear regression, excluding blood results taken during in-patient stays, patients who reached RRT, and patients with less than one year follow-up or less than 3 data points. For revascularized patients, at least 3 data points pre-revascularization were used to calculate the eGFR slope. The number of clinical end-points and unadjusted
incidence rates per 100 patient years were calculated manually. Kaplan-Meier curves were constructed and the log rank test used to compare event rates between groups. Survival analyses were performed using the Cox Proportional Hazards model to determine hazard ratios and 95% confidence intervals for the effect of individual high-risk features, bilateral renal artery disease, proteinuria <1g/day, and revascularization on clinical end-points. These analyses were adjusted for related comorbidities, age, baseline proteinuria and eGFR. ESKD and CVE endpoints were also adjusted for death in survival analyses. Data analyses were performed using SPSS (version 22.0) and a p-value <0.05 was considered statistically significant.

Results:

Patient Characteristics:
Hospital records for 872 patients were screened; 593 (68%) patients were excluded, as they did not have severe RAS or were not candidates for revascularization (bilateral <70% RAS [n=435], unilateral occlusion and contralateral <70% RAS [n=142], bilateral occlusion [n=16]). 4 patients were excluded due to presumed diabetic nephropathy and 12 patients due to missing baseline data (eGFR [n=1], proteinuria [n=8], blood pressure [n=3]). This gave a study population of 263 patients. One hundred and twenty-seven patients (14.6% of 872) met criteria for the ‘high-risk’ category; 44 (5.1%) presented with FPE, 65 (7.5%) presented with severe hypertension, 61 (7.0%) had rapidly deteriorating renal function and 47 (5.4%) had more than one high-risk presentation. 136 patients (15.6%) were designated as ‘control’ (≥70% unilateral or bilateral RAS but no high-risk clinical presentation, Figure 4.3.1). Of the study population 75 had bilateral ≥70% RAS (41 high-risk patients, 34 controls) and 189 had proteinuria <1g/day at baseline (99 high-risk patients, 90 controls). 55 high-risk patients (43.3%) were revascularized compared to 40 (29.4%) control patients (p=0.019, Table 4.3.1). Median follow-up time was 58.4 months (IQR 25.4-97.3) for the whole study population.

The high-risk and control groups were well matched for age, gender, patency score, bilateral disease, eGFR, and proteinuria. However high-risk patients were more likely to have diabetes (37.8% vs. 19.9%, p=0.001) and CHF (33.1% vs. 11.0%, p<0.0005) (Table 4.3.1). As expected, high-risk patients had higher blood pressure, and a greater proportion were receiving ≥3 antihypertensive agents. Revascularized patients had more severe anatomical stenosis than non-revascularized patients in both the high-risk and control groups. Revascularized control patients had a faster rate of loss of eGFR than non-revascularized controls, while revascularized high-risk patients were younger than those treated medically (69.2 vs. 74.0 years, p=0.02) (Table 4.3.1). Similar trends were noticed when examining the baseline characteristics for each individual high-risk presentation (Table 4.3.2).
**Figure 4.3.1** Flowchart illustrating selection of study population.

- Analysis of hospital records (n=872)
- Excluded as:
  - Missing baseline data (n=12)
  - Bilateral renal artery stenosis (RAS) <70% (n=435)
  - Unilateral occlusion and contralateral <70% RAS (n=142)
- Included in study (n=263) ≥70% unilateral or bilateral RAS
- Controls (n=136)
  - No high-risk clinical presentations
- High-risk (n=127)
  - Flash pulmonary edema (n=44)
  - Severe hypertension (n=65)
  - Rapidly deteriorating renal function (n=61)
- Total number of high-risk presentations
  - Single High-Risk presentation
    - Flash pulmonary edema (n=19)
    - Severe hypertension (n=41)
    - Rapidly deteriorating renal function (n=26)
Table 4.3.1 Comparison of baseline characteristics and estimated glomerular filtration rate (eGFR) slope between control and high-risk patients and between high-risk revascularized and high-risk non-revascularized patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall Study Population</th>
<th>Control</th>
<th>Combined High-risk*</th>
<th>Control</th>
<th>Combined High-Risk*</th>
<th>Control</th>
<th>Combined High-Risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) [Median, (IQR)]</td>
<td>72.5 (66.8-77.4)</td>
<td>72.3 (67.1-77.7)</td>
<td>72.6 (65.6-76.6)</td>
<td>0.5</td>
<td>72.9 (67.2-78.6)</td>
<td>70.7 (66.6-75.8)</td>
<td>0.1</td>
</tr>
<tr>
<td>Male [n (%)]</td>
<td>144 (54.8)</td>
<td>77 (56.6)</td>
<td>67 (52.8)</td>
<td>0.5</td>
<td>56 (58.3)</td>
<td>21 (52.5)</td>
<td>0.5</td>
</tr>
<tr>
<td>RAS ≥70% unilateral [n (%)]</td>
<td>185 (70.3)</td>
<td>99 (72.8)</td>
<td>86 (67.7)</td>
<td>0.4</td>
<td>76 (79.2)</td>
<td>23 (57.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>RAS ≥70% Bilateral [n (%)]</td>
<td>75 (28.5)</td>
<td>34 (25.0)</td>
<td>41 (32.3)</td>
<td>0.2</td>
<td>17 (17.7)</td>
<td>17 (42.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>Patency score [Median, (IQR)]</td>
<td>70.0 (40.0-115.0)</td>
<td>80.0 (50.0-110.0)</td>
<td>70.0 (40.0-115.0)</td>
<td>0.4</td>
<td>90.0 (57.0-113.8)</td>
<td>60.0 (20.0-110.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>SBP (mmHg) [Median, (IQR)]</td>
<td>155.0 (134.0-180.0)</td>
<td>148.0 (130.0-164.3)</td>
<td>165.0 (147.0-190.0)</td>
<td>&lt;0.000</td>
<td>145.0 (129.3-159.0)</td>
<td>150.0 (132.3-170.0)</td>
<td>0.2</td>
</tr>
<tr>
<td>DBP (mmHg) [Median, (IQR)]</td>
<td>80.0 (69.0-88.0)</td>
<td>78 (68.3-85.0)</td>
<td>80.0 (69.0-90.0)</td>
<td>0.1</td>
<td>75.0 (65.0-85.8)</td>
<td>80.0 (75.0-85.0)</td>
<td>0.1</td>
</tr>
<tr>
<td>MAP (mmHg) [Median, (IQR)]</td>
<td>103.3 (92.7-115.3)</td>
<td>99.8 (90.2-111.8)</td>
<td>106.7 (96.7-123.0)</td>
<td>&lt;0.000</td>
<td>98.2 (89.0-110.0)</td>
<td>103.2 (96.1-113.3)</td>
<td>0.07</td>
</tr>
<tr>
<td>Macrovascular Disease [n (%)]</td>
<td>203 (77.2)</td>
<td>101 (74.3)</td>
<td>102 (80.3)</td>
<td>0.2</td>
<td>72 (75.0)</td>
<td>29 (72.5)</td>
<td>0.8</td>
</tr>
<tr>
<td>Congestive Heart Failure [n (%)]</td>
<td>57 (21.7)</td>
<td>15 (11.0)</td>
<td>42 (33.1)</td>
<td>&lt;0.000</td>
<td>10 (10.4)</td>
<td>5 (12.5)</td>
<td>0.7</td>
</tr>
<tr>
<td>Flash Pulmonary Edema [n (%)]</td>
<td>44 (16.7)</td>
<td>-</td>
<td>44 (34.6)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Condition</td>
<td>Values</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-----------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes [n (%)]</strong></td>
<td>75 (28.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Renin Angiotensin blockade [n (%)]</strong></td>
<td>144 (54.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Beta Blocker [n (%)]</strong></td>
<td>107 (40.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Calcium channel Blocker [n (%)]</strong></td>
<td>162 (61.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>More than 3 BP agents [n (%)]</strong></td>
<td>143 (54.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Aspirin [n (%)]</strong></td>
<td>152 (57.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Statin [n (%)]</strong></td>
<td>167 (63.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Proteinuria (g/day) [Median, (IQR)]</strong></td>
<td>0.4 (0.1-1.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>eGFR (ml/min/1.73m^2) [Median, (IQR)]</strong></td>
<td>29.5 (20.4-41.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Revascularized [n (%)]</strong></td>
<td>95 (36.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>eGFR slope (ml/min/1.73m^2/year) [Median, (IQR)]</strong></td>
<td>-0.8 (-3.6 to 1.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Bold data indicates a statistically significant difference with a p value less than 0.05.**

BP – blood pressure; DBP – diastolic blood pressure; eGFR – estimated glomerular filtration rate; MAP – mean arterial pressure; RAS – renal artery stenosis; SBP – systolic blood pressure;

*All patients with at least one of flash pulmonary edema, deteriorating renal function or severe hypertension.

*Calculated by the Chronic Kidney Disease Epidemiological Collaboration Equation (CKD-EPI)*

1 Calculated from the slope of linear regression, excluding blood results taken during in-patient stay, patients who were on renal replacement therapy, and patients with less than one year follow-up or less than 3 data points. For revascularized patients, at least 3 pre-revascularization serum creatinine values were entered into the analysis.

2 Number of patients who met criteria for eGFR slope calculation (n)=206;

3 n=96;

4 n=110;

5 n=78;

6 n=18
Table 4.3.2 Comparison of baseline characteristics and estimated glomerular filtration rate (eGFR) slope between revascularized and non-revascularized high-risk patients, patients with bilateral ≥70% renal artery stenosis (RAS) and patients with <1g/day baseline proteinuria.

<table>
<thead>
<tr>
<th></th>
<th>Flash pulmonary edema (n=44)</th>
<th>Severe Hypertension (n=65)</th>
<th>Deteriorating renal function (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-revascularized (n=23)</td>
<td>Revascularized (n=21)</td>
<td>p</td>
</tr>
<tr>
<td>Median Age (years)</td>
<td>75.4 (69.4-79.4)</td>
<td>68.5 (63.2-75.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>Male (%)</td>
<td>16 (69.6)</td>
<td>8 (38.1)</td>
<td>0.04</td>
</tr>
<tr>
<td>RAS ≥70% unilateral (%)</td>
<td>15 (65.2)</td>
<td>8 (38.1)</td>
<td>0.07</td>
</tr>
<tr>
<td>RAS ≥70% Bilateral (%)</td>
<td>8 (34.8)</td>
<td>13 (61.9)</td>
<td>0.07</td>
</tr>
<tr>
<td>Median Patency score</td>
<td>70.0 (30.0-115.0)</td>
<td>40.0 (20.0-100.0)</td>
<td>0.1</td>
</tr>
<tr>
<td>Mean SBP mmHg</td>
<td>150.0 (123.0-155.0)</td>
<td>150.0 (130.5-188.0)</td>
<td>0.2</td>
</tr>
<tr>
<td>Mean DBP mmHg</td>
<td>70.0 (60.0-80.0)</td>
<td>80.0 (70.0-91.5)</td>
<td>0.04</td>
</tr>
<tr>
<td>Mean MAP mmHg</td>
<td>96.7 (83.3-103.3)</td>
<td>103.3 (92.5-121.7)</td>
<td>0.06</td>
</tr>
<tr>
<td>Macrovascular disease (%)</td>
<td>18 (78.3)</td>
<td>17 (81.0)</td>
<td>0.8</td>
</tr>
<tr>
<td>Congestive heart failure (%)</td>
<td>21 (91.3)</td>
<td>17 (81.0)</td>
<td>0.3</td>
</tr>
<tr>
<td>Flash pulmonary edema (%)</td>
<td>8 (34.8)</td>
<td>8 (38.1)</td>
<td>0.8</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>8 (34.8)</td>
<td>10 (47.6)</td>
<td>0.4</td>
</tr>
<tr>
<td>Renin angiotensin blockade (%)</td>
<td>10 (43.5)</td>
<td>8 (38.1)</td>
<td>0.7</td>
</tr>
<tr>
<td>Beta blocker (%)</td>
<td>7 (30.5)</td>
<td>11 (52.4)</td>
<td>0.1</td>
</tr>
<tr>
<td>Calcium channel blocker (%)</td>
<td>12 (52.2)</td>
<td>11 (52.4)</td>
<td>0.9</td>
</tr>
</tbody>
</table>
Table 4.3.2 (continued) Comparison of baseline characteristics and estimated glomerular filtration rate (eGFR) slope between revascularized and non-revascularized high-risk patients, patients with severe bilateral renal artery disease and patients with <1g/day baseline proteinuria.
<table>
<thead>
<tr>
<th></th>
<th>Mean DBP mmHg</th>
<th>Mean MAP mmHg</th>
<th>MVD (%)</th>
<th>CHF (%)</th>
<th>FPE (%)</th>
<th>DM (%)</th>
<th>RAB (%)</th>
<th>BB (%)</th>
<th>CaB (%)</th>
<th>&gt;3 agents (%)</th>
<th>Aspirin (%)</th>
<th>Statin (%)</th>
<th>Median Proteinuria (g/day)</th>
<th>Median eGFR (ml/min/1.73m²)</th>
<th>Median eGFR slope (ml/min/1.73m²/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>73.0 (67.0-88.0)</td>
<td>83.0 (72.0-94.3)</td>
<td>0.02</td>
<td>7.0 (67.0-88.0)</td>
<td>8.0 (72.0-93.3)</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean MAP mmHg</td>
<td>98.3 (90.3-106.7)</td>
<td>113.3 (98.2-128.3)</td>
<td>0.001</td>
<td>100.7 (90.0-113.3)</td>
<td>109.5 (96.6-123.8)</td>
<td>0.007</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVD (%)</td>
<td>27 (81.8)</td>
<td>35 (83.3)</td>
<td>0.9</td>
<td>87 (73.1)</td>
<td>54 (77.1)</td>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF (%)</td>
<td>12 (36.4)</td>
<td>15 (35.7)</td>
<td>0.9</td>
<td>23 (19.3)</td>
<td>20 (28.6)</td>
<td>0.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPE (%)</td>
<td>2 (6.1)</td>
<td>6 (14.3)</td>
<td>0.3</td>
<td>8 (6.7)</td>
<td>9 (12.9)</td>
<td>0.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM (%)</td>
<td>4 (12.1)</td>
<td>11 (26.2)</td>
<td>0.1</td>
<td>36 (30.3)</td>
<td>22 (31.4)</td>
<td>0.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAB (%)</td>
<td>19 (57.6)</td>
<td>23 (54.8)</td>
<td>0.8</td>
<td>63 (52.9)</td>
<td>37 (52.9)</td>
<td>0.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BB (%)</td>
<td>13 (39.4)</td>
<td>22 (52.4)</td>
<td>0.3</td>
<td>45 (37.8)</td>
<td>36 (51.4)</td>
<td>0.07</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CaB (%)</td>
<td>17 (51.5)</td>
<td>25 (59.5)</td>
<td>0.5</td>
<td>71 (59.7)</td>
<td>39 (55.7)</td>
<td>0.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3 agents (%)</td>
<td>20 (60.6)</td>
<td>24 (57.1)</td>
<td>0.8</td>
<td>68 (57.1)</td>
<td>35 (50.0)</td>
<td>0.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin (%)</td>
<td>21 (63.6)</td>
<td>27 (64.3)</td>
<td>0.9</td>
<td>65 (54.6)</td>
<td>43 (61.4)</td>
<td>0.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin (%)</td>
<td>22 (66.7)</td>
<td>24 (57.1)</td>
<td>0.4</td>
<td>76 (63.9)</td>
<td>42 (62.0)</td>
<td>0.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Proteinuria (g/day)</td>
<td>0.4 (0.2-1.3)</td>
<td>0.2 (0.1-0.4)</td>
<td>0.02</td>
<td>0.2 (0.1-0.5)</td>
<td>0.2 (0.1-0.4)</td>
<td>0.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median eGFR (ml/min/1.73m²)</td>
<td>25.3 (15.9-37.5)</td>
<td>28.2 (22.6-35.6)</td>
<td>0.4</td>
<td>31.1 (23.3-43.8)</td>
<td>29.1 (20.5-38.5)</td>
<td>0.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median eGFR slope (ml/min/1.73m²/year)</td>
<td>-0.9 (-3.7 - 2.0)</td>
<td>-1.7 (-9.5 – 8.2)</td>
<td>0.6</td>
<td>-0.6 (-2.8 – 1.1)</td>
<td>-1.7 (-12.1 – 6.8)</td>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n=26; n=24; n=104; n=49.
Impact of high-risk features, bilateral renal artery disease and baseline proteinuria on clinical end-points:

Overall annual mortality was 12.8% for control and 12.4% for high-risk patients, with ESKD occurring in 3.7% and 3.6%, and CVE in 7.7% and 12.0%, per year, respectively (Table 4.3.3).

Table 4.3.3 Incidence rate per 100 patient years of clinical end-points in study population

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Combined High-risk*</th>
<th>Proteinuria &lt;1g/day</th>
<th>Bilateral ≥70% RAS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Combined High-risk*</td>
<td>Proteinuria &lt;1g/day</td>
<td>Bilateral ≥70% RAS</td>
</tr>
<tr>
<td>Died</td>
<td>12.8</td>
<td>14.0</td>
<td>10.5</td>
<td>15.1</td>
</tr>
<tr>
<td></td>
<td>12.4</td>
<td>15.1</td>
<td>9.8</td>
<td>12.3</td>
</tr>
<tr>
<td></td>
<td>12.3</td>
<td>13.9</td>
<td>10.1</td>
<td>13.9</td>
</tr>
<tr>
<td></td>
<td>13.9</td>
<td>22.5</td>
<td>10.4</td>
<td></td>
</tr>
<tr>
<td>ESKD</td>
<td>3.7</td>
<td>3.2</td>
<td>4.6</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td>3.6</td>
<td>4.4</td>
<td>2.8</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td>2.9</td>
<td>2.4</td>
<td>3.5</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>5.0</td>
<td>8.3</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>CVE</td>
<td>7.7</td>
<td>7.1</td>
<td>8.8</td>
<td>9.5</td>
</tr>
<tr>
<td></td>
<td>12.0</td>
<td>14.9</td>
<td>9.5</td>
<td>9.2</td>
</tr>
<tr>
<td></td>
<td>9.2</td>
<td>9.9</td>
<td>8.4</td>
<td>10.5</td>
</tr>
<tr>
<td></td>
<td>10.5</td>
<td>15.4</td>
<td>8.5</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>18.6</td>
<td>19.3</td>
<td>17.4</td>
<td>22.7</td>
</tr>
<tr>
<td></td>
<td>22.7</td>
<td>27.1</td>
<td>17.7</td>
<td>19.4</td>
</tr>
<tr>
<td></td>
<td>19.4</td>
<td>21.3</td>
<td>17.0</td>
<td>23.7</td>
</tr>
<tr>
<td></td>
<td>23.7</td>
<td>37.8</td>
<td>17.9</td>
<td></td>
</tr>
</tbody>
</table>

ARVD – atherosclerotic renovascular disease; CVE – cardiovascular event; ESKD – end-stage kidney disease; NR – non-revascularized; R – revascularized; RAS – renal artery stenosis

*All patients with at least one of flash pulmonary edema, deteriorating renal function or severe hypertension.

Development of ESKD was low overall (2.9% per year) in patients with < 1g/day of proteinuria. Table 4.3.4 shows absolute patient numbers for each end-point. An adjusted analysis showed that there was an increased risk for all four end-points in patients with bilateral disease, and for every g/day increase in baseline proteinuria within the overall study population, and in high-risk patients presenting with rapidly deteriorating renal function (Table 4.3.5). Presentation with FPE significantly increased the risk for the composite end point (HR 1.54 [95% CI 1.04-2.30] p=0.03) while patients with severe hypertension at time of diagnosis had a reduced hazard ratio for death (HR 0.69 [95% CI 0.48-0.99] p=0.04) when compared to patients without these clinical presentations (Table 4.3.5).

**Effect of revascularization on patients with high-risk features, bilateral renal artery disease, <1g proteinuria at baseline and controls:**

Kaplan-Meier survival curves are shown for high-risk patients and controls in Figure 4.3.2 (a) to (h), demonstrating the beneficial effect of revascularization in the former sub-group. Another Kaplan-Meier analysis also showed a benefit of revascularization on time to all outcomes in control patients with bilateral ≥70% RAS, but revascularization was only significantly associated with reduced time to CVE in high-risk patients with <1g proteinuria (Table 4.3.6).

On analyzing the effect of revascularization in overall aggregated high-risk categories and control patients adjusted for age, comorbidities, number of anti-hypertensives, statin use, baseline proteinuria, eGFR and blood pressure control, revascularization was significantly associated with reduced risk of ESKD (HR 0.59 [95% CI 0.37-0.93], p=0.02) in high-risk patients. When the effect of revascularization was analyzed in the individual clinical phenotype sub-groups, revascularization was non-significantly associated with reduced adjusted hazard.
ratios for adverse events in patients presenting with FPE and severe hypertension. In patients with rapidly declining renal function, revascularization was significantly associated with reduced risk of ESKD (HR 0.47 [95% CI 0.25-0.85], p=0.01), CVE (HR 0.51 [95% CI 0.29-0.91], p=0.02) and all combined events (HR 0.51 [95% CI 0.29-0.90], p=0.02) (Table 4.3.7).

Revascularization was associated with reduced risk of progression to ESKD in high-risk patients with bilateral ≥70% RAS (HR 0.35 [95% CI 0.15-0.84], p=0.02), but not in controls with the same degree of RAS. In patients with <1g/day proteinuria at baseline and any high-risk clinical presentation, revascularization was associated with reduced risk of ESKD (HR 0.52 [95% CI 0.32-0.86], p=0.01), CVE (HR 0.52 [95% CI 0.32-0.83], p=0.006) and all combined events (HR 0.57 [95% CI 0.36-0.90], p=0.02). In high-risk patients with both bilateral ≥70% RAS and <1g/day proteinuria at baseline, revascularization was significantly associated with reduced risk of ESKD (HR 0.38 [95% CI 0.16-0.88], p=0.03) (Table 4.3.8). There was no association between revascularization and improved outcomes in patients with ≥1g/day baseline proteinuria (Table 4.3.9).

Discussion:
Our results concur with our previous finding that revascularization may confer benefit to patients with ‘high-risk’ clinical presentations\textsuperscript{16}. Uniquely, we show here that even within this group, further stratification for likelihood of benefit can be achieved by considering bilateral severe RAS and low levels of proteinuria at time of diagnosis.

In patients with haemodynamically significant ARVD, activation of the renin-angiotensin system (RAAS) leads to secondary hypertension and triggers an inflammatory cascade that leads to renal parenchymal damage and loss of function\textsuperscript{8,28}. Patients are also at risk of developing cardiac disturbance syndromes such as acute decompensated heart failure or ischaemic events due to impaired pressure natriuresis. Observational studies have shown that timely revascularization can reduce activation of RAAS and improve renal perfusion, leading to reduction in arterial pressure, improvement in fluid overload, and stabilization of the cardiac disturbance syndrome\textsuperscript{8,29}.

Such patients have been under-represented in clinical trials; mortality in our study population was higher than in major clinical trials (12% per year compared to 4-8%)\textsuperscript{1,2}. This probably acted as a competing risk for progression to ESKD; the trajectory of eGFR decline in our overall study population is similar to that reported in age-matched ARVD and non-ARVD CKD cohorts, although the ‘high-risk subgroup had around a three-fold higher rate of eGFR loss per year\textsuperscript{30,31}. Also, in the Cardiovascular Outcomes in Renal Atherosclerotic lesions (CORAL) study the mean eGFR of the patients was 59 ml/min, which was substantially higher than in our study (31 ml/min).
**Table 4.3.4** Summary of clinical end-points in study population.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Combined High-Risk*</th>
<th>Proteinuria &lt;1g/day</th>
<th>Bilateral &gt;70% RAS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n=136)</td>
<td>NR (n=96)</td>
<td>R (n=40)</td>
<td>All (n=127)</td>
</tr>
<tr>
<td>Died (%)</td>
<td>95 (69.9)</td>
<td>68 (70.8)</td>
<td>27 (67.5)</td>
<td>89 (70.1)</td>
</tr>
<tr>
<td>ESKD (%)</td>
<td>25 (18.4)</td>
<td>14 (14.6)</td>
<td>11 (27.5)</td>
<td>24 (18.9)</td>
</tr>
<tr>
<td>CVE (%)</td>
<td>46 (33.8)</td>
<td>28 (29.2)</td>
<td>18 (45.0)</td>
<td>60 (47.2)</td>
</tr>
<tr>
<td>Any (%)</td>
<td>107 (78.7)</td>
<td>74 (77.1)</td>
<td>33 (82.5)</td>
<td>107 (84.3)</td>
</tr>
</tbody>
</table>

CVE – cardiovascular event; ESKD – end-stage kidney disease; NR – non-RAS – renal artery stenosis
*All patients with at least one of flash pulmonary edema, deteriorating renal function or severe hypertension.

**Table 4.3.5** Effect of high-risk features, bilateral renal artery disease and proteinuria on clinical end-points in study population (n= 275)

<table>
<thead>
<tr>
<th></th>
<th>Flash pulmonary edema*</th>
<th>Severe Hypertensionb</th>
<th>Deteriorating renal functionc</th>
<th>Bilateral ≥70% RASd</th>
<th>Baseline Proteinuria (g/day)e,f</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>p</td>
<td>HR</td>
<td>p</td>
<td>HR</td>
</tr>
<tr>
<td>Death</td>
<td>1.54 (1.01-2.36)</td>
<td>0.05</td>
<td>0.69 (0.48-0.99)</td>
<td>0.04</td>
<td>1.74 (1.21-2.51)</td>
</tr>
<tr>
<td>ESKD*</td>
<td>1.37 (0.90-2.07)</td>
<td>0.1</td>
<td>0.71 (0.50-1.01)</td>
<td>0.06</td>
<td>1.90 (1.32-2.74)</td>
</tr>
<tr>
<td>CVEg</td>
<td>1.47 (0.98-2.21)</td>
<td>0.06</td>
<td>0.83 (0.60-1.16)</td>
<td>0.3</td>
<td>1.93 (1.36-2.75)</td>
</tr>
<tr>
<td>Any</td>
<td>1.54 (1.04-2.30)</td>
<td>0.03</td>
<td>0.84 (0.61-1.16)</td>
<td>0.3</td>
<td>1.91 (1.35-2.71)</td>
</tr>
</tbody>
</table>

**Bold data indicates a statistically significant difference with a p value less than 0.05.**

CVE – cardiovascular event; ESKD – end-stage kidney disease; RAS – renal artery stenosis
*Adjusted for severe hypertension, deteriorating renal function, bilateral disease, age, diabetes, baseline proteinuria, estimated glomerular filtration rate (eGFR) and revascularization.

bAdjusted for flash pulmonary edema (FPE), deteriorating renal function, bilateral disease, age, diabetes, baseline proteinuria, eGFR and revascularization.

cAdjusted for FPE, severe hypertension, bilateral disease, age, diabetes, baseline proteinuria, eGFR and revascularization.

dAdjusted for FPE, severe hypertension, deteriorating renal function, age, diabetes, baseline proteinuria, eGFR and revascularization.

fAdjusted for FPE, severe hypertension, deteriorating renal function, bilateral disease, age, diabetes, eGFR and revascularization.

Hazard ratio calculated for every 1g/day increase in baseline proteinuria
*Adjusted for death
Figure 4.3.2 (a – h) Kaplan-Meier curves showing time to death for revascularized and non-revascularized combined high-risk (patients with at least one of flash pulmonary edema, deteriorating renal function or severe hypertension) and control patients.
Table 4.3.6 Effect of revascularization on median time to clinical outcomes (in months) in patients with bilateral ≥70% RAS and in those with <1g/day baseline proteinuria.

<table>
<thead>
<tr>
<th>Patients with bilateral ≥70% RAS (n=75)</th>
<th>Non-revascularized (n=33)</th>
<th>Revascularized (n=42)</th>
<th>Log-rank test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median time (months) (95% Confidence Interval)</td>
<td>Median time (months) (95% Confidence Interval)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Death Overall 28.6 (23.5-33.8) 88.9 (65.8-111.9) 0.0008</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High-risk 29.1 (1.0-57.3) 94.6 (63.1-126.0) 0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control 25.3 (1.8-48.9) 57.2 (19.1-95.3) 0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ESKD Overall 25.3 (11.6-39.1) 72.2 (48.2-96.2) 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High-risk 26.0 (17.6-34.4) 83.1 (54.4-111.7) 0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control 13.1 (0.0-35.1) 57.2 (1.6-112.8) 0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CVE Overall 24.7 (8.2-41.3) 54.2 (38.6-69.8) 0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High-risk 24.7 (14.1-35.4) 52.4 (27.3-77.5) 0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control 13.1 (0.0-35.1) 54.2 (19.5-92.3) 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any Overall 15.8 (1.3-30.3) 49.6 (21.1-78.2) 0.009</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High-risk 22.4 (6.6-38.3) 49.6 (11.6-87.5) 0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control 9.9 (4.2-15.5) 53.7 (0.0-109.3) 0.002</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patients with <1g/day baseline proteinuria (n=189)

<table>
<thead>
<tr>
<th>Patients with &lt;1g/day baseline proteinuria (n=189)</th>
<th>Non-revascularized (n=119)</th>
<th>Revascularized (n=70)</th>
<th>Log-rank test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median time (months) (95% Confidence Interval)</td>
<td>Median time (months) (95% Confidence Interval)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Death Overall 63.3 (48.7-77.9) 84.2 (62.2-106.2) 0.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High-risk 56.0 (45.8-66.2) 74.5 (43.3-105.7) 0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control 81.8 (47.8-115.8) 88.9 (51.3-126.5) 0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ESKD Overall 55.4 (47.6-63.1) 71.6 (49.3-93.8) 0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High-risk 51.7 (44.5-58.9) 71.6 (55.2-88.0) 0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control 61.7 (29.8-93.6) 70.5 (34.6-106.3) 0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CVE Overall 46.9 (32.0-61.7) 52.3 (45.0-59.7) 0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High-risk 29.1 (12.2-46.0) 56.2 (41.0-71.5) 0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control 53.3 (41.5-65.0) 52.3 (43.7-61.0) 0.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any Overall 46.9 (31.2-62.5) 49.4 (38.9-59.9) 0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control (n=136)</td>
<td>Combined High-risk (n=127)</td>
<td>Flash pulmonary edema (n=44)</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------</td>
<td>---------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td></td>
<td>HR p</td>
<td>HR p</td>
<td>HR p</td>
</tr>
<tr>
<td>Death</td>
<td>0.84 (0.52-1.37)</td>
<td>0.5</td>
<td>0.69 (0.43-1.09)</td>
</tr>
<tr>
<td>ESKD</td>
<td>0.86 (0.53-1.39)</td>
<td>0.5</td>
<td>0.59 (0.37-0.93)</td>
</tr>
<tr>
<td>CVE</td>
<td>0.96 (0.61-1.51)</td>
<td>0.9</td>
<td>0.65 (0.42-1.00)</td>
</tr>
<tr>
<td>Any</td>
<td>1.00 (0.63-1.57)</td>
<td>0.9</td>
<td>0.67 (0.44-1.02)</td>
</tr>
</tbody>
</table>

Bold data indicates a statistically significant difference with a p value less than 0.05.

CVE – cardiovascular event; ESKD – end-stage kidney disease;

* All patients with at least one of flash pulmonary edema, deteriorating renal function or severe hypertension.

* Adjusted for age, congestive heart failure, flash pulmonary edema, diabetes mellitus, three or more antihypertensive agents at baseline, statin, baseline proteinuria and estimated glomerular filtration rate (eGFR), and mean arterial pressure (MAP)

* Adjusted for age, baseline proteinuria, MAP and eGFR

* Adjusted for death
Table 4.3.8 Effect of revascularization on clinical end-points in patients with bilateral renal artery disease and patients with proteinuria <1g/day

<table>
<thead>
<tr>
<th></th>
<th>Bilateral ≥70% RAS (study population) (n=75)</th>
<th>Bilateral ≥70% RAS (high-risk)(^a) (n=41)</th>
<th>Bilateral ≥70% RAS (control) (^a) (n=34)</th>
<th>Proteinuria &lt;1g/day (study population)(^b) (n=189)</th>
<th>Proteinuria &lt;1g/day (high-risk) (^b) (n=99)</th>
<th>Proteinuria &lt;1g/day (control) (^b) (n=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR p</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0.71 (0.38-1.32) 0.3</td>
<td>0.59 (0.25-1.38) 0.2</td>
<td>0.80 (0.30-2.13) 0.6</td>
<td>0.76 (0.52-1.10) 0.1</td>
<td>0.64 (0.38-1.05) 0.08</td>
<td>0.87 (0.48-1.56) 0.6</td>
</tr>
<tr>
<td>ESKD(^c)</td>
<td>0.53 (0.29-0.98) 0.04</td>
<td>0.35 (0.15-0.84) 0.02</td>
<td>0.72 (0.28-1.84) 0.5</td>
<td>0.69 (0.48-0.99) 0.04</td>
<td>0.52 (0.32-0.86) 0.01</td>
<td>0.87 (0.48-1.57) 0.6</td>
</tr>
<tr>
<td>CVE(^c)</td>
<td>0.55 (0.31-0.99) 0.05</td>
<td>0.54 (0.24-1.20) 0.1</td>
<td>0.40 (0.15-1.08) 0.07</td>
<td>0.79 (0.56-1.12) 0.2</td>
<td>0.52 (0.32-0.83) 0.006</td>
<td>1.17 (0.68-2.00) 0.6</td>
</tr>
<tr>
<td>Any</td>
<td>0.60 (0.34-1.06) 0.08</td>
<td>0.50 (0.23-1.10) 0.08</td>
<td>0.51 (0.19-1.36) 0.2</td>
<td>0.85 (0.61-1.20) 0.4</td>
<td>0.57 (0.36-0.90) 0.02</td>
<td>1.28 (0.75-2.19) 0.4</td>
</tr>
</tbody>
</table>

Bold data indicates a statistically significant difference with a p value less than 0.05.

CVE – cardiovascular event; ESKD – end-stage kidney disease; RAS – renal artery stenosis

\(^a\)Adjusted for age, baseline proteinuria and estimated glomerular filtration rate (eGFR)

\(^b\)Adjusted for age and baseline eGFR

\(^c\)Adjusted for death

---

Table 4.3.8 (continued) Effect of revascularization on clinical end-points in patients with bilateral renal artery disease and patients with proteinuria <1g/day

<table>
<thead>
<tr>
<th></th>
<th>Bilateral ≥ 70% RAS and Proteinuria &lt;1g/day (study population) (n=59)(^b)</th>
<th>Bilateral ≥ 70% RAS and Proteinuria &lt;1g/day (high-risk) (n=36)(^b)</th>
<th>Bilateral ≥ 70% RAS and Proteinuria &lt;1g/day (control) (n=23)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR p</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0.52 (0.28-0.99) 0.05</td>
<td>0.56 (0.24-1.31) 0.2</td>
<td>0.37 (0.12-1.19) 0.09</td>
</tr>
<tr>
<td>ESKD(^c)</td>
<td>0.46 (0.25-0.86) 0.02</td>
<td>0.38 (0.16-0.88) 0.03</td>
<td>0.50 (0.16-1.57) 0.2</td>
</tr>
<tr>
<td>CVE(^c)</td>
<td>0.46 (0.25-0.86) 0.02</td>
<td>0.48 (0.22-1.07) 0.07</td>
<td>0.35 (0.11-1.09) 0.07</td>
</tr>
<tr>
<td>Any</td>
<td>0.53 (0.29-0.97) 0.04</td>
<td>0.51 (0.23-1.10) 0.09</td>
<td>0.50 (0.16-1.54) 0.2</td>
</tr>
</tbody>
</table>

Bold data indicates a statistically significant difference with a p value less than 0.05.

\(^b\)Adjusted for age and baseline eGFR

\(^c\)Adjusted for death
Table 4.3.9 Effect of revascularization on clinical end-points in patients with ≥1g/day proteinuria at baseline.

<table>
<thead>
<tr>
<th></th>
<th>Proteinuria ≥1g/day (study population) (n=74)</th>
<th>Proteinuria ≥1g/day (high-risk) (n=28)</th>
<th>Proteinuria ≥1g/day (control) (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR p</td>
<td>HR p</td>
<td>HR p</td>
</tr>
<tr>
<td>Death</td>
<td>0.84 (0.44-1.6)</td>
<td>0.6</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.85 (0.23-3.11)</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.06 (0.48-2.33)</td>
<td>0.9</td>
</tr>
<tr>
<td>ESKD</td>
<td>0.74 (0.39-1.41)</td>
<td>0.4</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.82 (0.23-2.99)</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.03 (0.47-2.23)</td>
<td>0.9</td>
</tr>
<tr>
<td>CVE</td>
<td>0.98 (0.55-1.75)</td>
<td>0.9</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.51 (0.50-4.56)</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.86 (0.40-1.85)</td>
<td>0.7</td>
</tr>
<tr>
<td>Any</td>
<td>0.93 (0.52-1.66)</td>
<td>0.8</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.42 (0.47-4.24)</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.99 (0.97-1.01)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Accurate identification of haemodynamic significance is difficult in clinical practice. Selection of ‘high-risk’ patients needs to be based on both the ‘anatomical severity’ of ARVD and the clinical phenotype of the patient. The degree of cross-sectional stenosis correlates poorly with fractional flow reserve or translesional pressure gradients, and indeed, a lower cut-off of >50% on catheter angiography has been found to falsely identify haemodynamically significant stenosis in 38% of cases. We found no difference in patency score or bilateral disease between control and high-risk patients. In contrast to our earlier study, we have used ≥70% RAS as indicating severe stenosis in keeping with current recommendations. We also increased the threshold for definition of uncontrolled or severe hypertension to reflect current guidance and focused on patients with a rate of negative eGFR slope below the 25th percentile for all ARVD patients within our database. As a result of these ‘tighter’ selection criteria, only 15% of the total ARVD population met our definition of ‘high-risk’ compared to 28% reported in the earlier study, and a larger proportion of ‘high-risk’ patients in our study underwent revascularization (43% compared to 24%).

Our results confirm that bilateral severe RAS is associated with an increased risk of adverse events, as are deteriorating renal function and greater baseline proteinuria. This highlights the complex interplay between intrarenal damage, haemodynamic compromise, and overall atherosclerotic burden in determining clinical outcomes in ARVD. As in our earlier study, presentation with FPE increased the risk of adverse events, although the smaller numbers in the current study had an impact on the strength of the statistical association.

Severe hypertension was associated with reduced hazard ratios for all end points. Longitudinal change in blood pressure was not included in this analysis hence successful response to medical therapy may account for improved long-term outcomes. Alternatively, this effect may reflect the J-shaped relationship that has been observed between lower blood pressures and adverse outcomes especially in higher-risk patients.
Revascularization appears to be associated with reduced risk of adverse outcomes in high-risk patients, but not in controls, despite the presence of more severe RAS and bilateral disease in the high-risk group. This survival benefit was predominantly in patients with rapidly deteriorating renal function. This finding is replicated elsewhere. Although a small number of prospective, non-randomized studies have shown that revascularization may be appropriate in patients with severe hypertension, this has never been correlated to long-term hard outcomes. In contrast to our previous findings, revascularization was not statistically associated with improved outcomes in patients with FPE although hazard ratios were reduced, and this is probably due to sample size. We believe that revascularization should still be considered in patients presenting with FPE.

Our results suggest that revascularization is more frequently performed in patients with bilateral severe RAS i.e. that clinicians may base revascularization decisions on anatomical stenosis severity. Revascularization may reduce the risk of both death and progression to ESKD in patients who have high-risk clinical presentation in addition to bilateral severe RAS, but not severe RAS alone. Consistent with this, one meta-analysis did not find any differences in response to revascularization between patients with unilateral or bilateral RAS while a second meta-analysis found insufficient data to allow for subgroup analysis between unilateral and bilateral disease. A small RCT did show that revascularization can be associated with improved blood pressure control in patients with bilateral >50% RAS and a diastolic blood pressure >95mmHg.

The haemodynamic compromise triggered by ARVD leads to an inflammatory cascade culminating in renal microvascular remodeling and fibrosis. In this context, restoration of renal artery patency may fail to improve renal clearance. We have used proteinuria as a surrogate marker of irreversible renal parenchymal injury, although proteinuria is also associated with general upregulation of systemic inflammation and vascular endothelial dysfunction. In keeping with our previous findings, we have shown that outcomes post-revascularization are better in patients with lower degrees of proteinuria at time of diagnosis, emphasizing the importance of timely revascularization before the development of irreversible parenchymal damage.

Although numbers were limited, there was reduced progression to ESKD in high-risk patients with both bilateral severe stenosis and <1g/day proteinuria. These patients may represent an important sub-group with haemodynamically significant stenosis but preserved renal parenchyma. We have previously shown that kidneys with a high renal volume to GFR ratio functionally do better post-revascularization; these kidneys presumably have viable, ‘hibernating’ parenchyma. Current research efforts are focusing on development of non-invasive magnetic-resonance-based techniques that can help characterize both the...
haemodynamic significance of a stenosis and the viability of the post-stenotic renal parenchyma\textsuperscript{46}.

The main limitation of this study is that it is retrospective, and that patients were not randomized to revascularization, hence selection bias and hidden confounders potentially affect the results. The study has included patients who were recruited over three decades. During this time interval, the approach to ARVD has evolved significantly. A larger proportion of patients are now established on multi-targeted medical therapy while those with more cardiovascular comorbidities tend to be selectively referred for revascularization, potentially underestimating the benefit gained from revascularization\textsuperscript{5}. Study patient numbers were small and this restricted the extent of adjusting within Cox regression models. The definitions used for some high-risk presentations are arbitrary and potentially imprecise. For example, the lack of uniform echocardiographic data did not permit accurate confirmation of FPE. Blood pressure was documented from office readings taken at time of diagnosis, and medication dosage and longitudinal change were not included in the analyses. While RAS $\geq 70\%$ was considered ‘severe’ stenosis for the purpose of this study in line with current recommendations\textsuperscript{19}, the actual haemodynamic significance of RAS was not evaluated or confirmed and the degree of stenosis was determined by a single observer and based on biplanar imaging studies only; it is known that the severity of RAS is frequently over-estimated on angiography\textsuperscript{2}.

Nonetheless, data were meticulously collected in a standardized manner on an annual basis from patient records throughout the three decades. The size of our overall study population, approaching 900 patients, has enabled an insightful analysis of patients that are under-represented in RCTs.

**Conclusion**

Our study confirms that flash pulmonary edema, rapidly deteriorating renal function, greater baseline proteinuria and severe bilateral renal artery disease are adverse prognostic features in patients with ARVD. We also provide further evidence that revascularization appears to be of benefit in high-risk patients especially those presenting with rapidly deteriorating renal function and concurrent bilateral $\geq 70\%$ RAS and/or $<1\text{g/day}$ baseline proteinuria.
References


4.4 Association of novel biomarkers with major clinical outcomes in atherosclerotic renovascular disease.

Vassallo D, Alderson HV, Vuilleumier N, Ritchie J, Green D, Pagano S, Virzi J, Chrysochou C, Kalra PA

Preface
Atherosclerotic renovascular disease (ARVD) is a complex heterogeneous condition, hence risk prediction and stratification are difficult. While large randomized controlled trials have shown that revascularization does not confer added benefit beyond that provided by optimal medial therapy in the populations studied, observational studies have shown that a subgroup of patients with certain ‘high-risk’ clinical features can benefit from revascularization. Novel biomarkers have been shown to be associated with adverse events in patients with chronic kidney disease (CKD) and may facilitate risk stratification; however, their risk predictive value in ARVD has to date not yet been investigated. In this paper we investigate whether novel biomarkers improve risk prediction and selection for revascularization in patients with ARVD.

Abstract
The value of novel biomarkers in atherosclerotic renovascular disease (ARVD) has not yet been investigated. In this study we investigate whether the addition of novel biomarkers to a model based on traditional risk factors improves risk prediction. Patients recruited to the Salford Renovascular Study who had the following biomarkers analyzed on a baseline sample were included in this study: fibroblast growth factor-23 (FGF-23), cystatin C, kidney injury molecule-1 (KIM-1), myeloperoxidase, neutrophil gelatinase-associated lipocalin (NGAL), N-terminal prohormone of brain natriuretic peptide (NT-proBNP), high-sensitivity Troponin T and anti-apolipoprotein A1 IgG. Cox proportional hazards models and net reclassification index were used to study the effects of either individual or a panel of novel biomarkers on predicting these end-points: death, end-stage kidney disease (ESKD), cardiovascular events (CVE) and the first of any of these events.

In total, 112 patients were followed-up for a median of 59.9 months (IQR 33.6-86.9). Only NT-proBNP maintained a statistically significant association with all end-points (Death: HR 1.62 [95% CI 1.26-2.10], p<0.0005; ESKD: HR 1.51 [95% 1.19-1.91], p=0.001; CVE: HR 1.56 [95% CI 1.23-1.97], p<0.0005; any event: HR 1.48 [95% CI 1.19-1.84], p<0.0005). Risk reclassification of all end-points improved with addition of all biomarkers as a panel to the base model. The individual incremental value of NT-proBNP was limited to prediction of death. Patients with NT-proBNP levels above standard cutoff (300pg/ml) gained benefit from revascularization with regards to all adverse end-points compared to medically managed
patients, whereas this effect was not evident in revascularized patients with lower levels of NT-proBNP.

**Introduction:**
Atherosclerotic renovascular disease (ARVD) typically exists in the context of systemic atherosclerosis-related cardiovascular disease (CVD), as well as in chronic kidney disease, and these accumulative risks factors are usually the principal determinants of adverse outcomes in ARVD patients. Most patients with ARVD have silent disease and only a small proportion develop high-risk features such as uncontrolled blood pressure, rapid deterioration in renal function or flash pulmonary oedema. It is often difficult to confirm the haemodynamic and functional significance of ARVD but even clinically silent disease has prognostic significance, with a four-fold increased risk of cardiovascular events and a three-fold increased risk of death. Indeed, global risk stratification in this heterogeneous condition is complex and still remains an unmet clinical need. It is hoped that early identification of patients at higher-risk would not only encourage intensification of medical management, but also optimize patient selection for revascularization, enhancing ARVD treatment efficacy. Large randomized controlled trials showed that renal revascularization in ARVD patients does not provide overall clinical benefit in the populations studied. Although debated, this could be partly due to selection bias related to under-representation of “high-risk” ARVD patients who have been shown to gain benefit from revascularization in observational studies.

Traditional cardiovascular risk factors and routine laboratory parameters have been shown to correlate with adverse events in the chronic kidney disease (CKD) population and have been used to create risk stratification tools to facilitate individualized clinical decision-making with regards to renal replacement therapy planning. As expected, similar risk factors are associated with adverse outcomes in patients with ARVD although to date, there are no equivalent risk stratification tools for this specific patient group. In addition, the only conventional cardiovascular risk factor that has been shown to potentially predict outcomes post-revascularization is baseline proteinuria. Several novel biomarkers related to important biological processes that underpin cardiac, renal and vascular injury have recently been shown to be independently associated with adverse outcomes in patients with CKD; however, their value in risk prediction in ARVD patients is unclear. Only a few studies have investigated the pathogenic role of some of these biomarkers in the context of ARVD and their validity for long-term risk prediction in patients with this specific condition has not yet been evaluated.

The biomarkers chosen for analysis were those with high clinical justification in patients with CKD. We aimed to determine whether these biomarkers, when considered individually, were associated with long-term adverse outcomes in a population of patients with ARVD and whether their addition to a conventional model based on traditional cardiovascular and renal risk factors...
could aid risk prediction in this specific patient cohort. Finally we explored whether any of these biomarkers can help identify patients who respond beneficially to revascularization.

**Materials and Methods:**

Patients diagnosed with ARVD on radiological imaging and referred to the Salford renal department have been recruited into the Salford Renovascular Study for several decades\(^{19}\). Ethical approval for this observational study was granted from the local ethics committee. The study database is updated on an annual basis from hospital records. Data collection has been described elsewhere\(^{19}\). In brief, data include baseline demographics, co-morbid conditions (diabetes, macrovascular disease [MVD], congestive heart failure [CHF]), presence of flash pulmonary oedema [FPE]), annualized prescribed medications, blood pressure, routine baseline biochemistry including serum creatinine (\(\mu\)mol/L) and parathryoid hormone levels (pg/mL), baseline proteinuria (g/24h), and clinical outcome data. The degree of renal artery stenosis (RAS) is obtained from cross-sectional angiography (intra-arterial digital subtraction angiography [IADSA], computed tomographic [CT] or magnetic resonance [MR] angiography), reported by only two specialist radiologists over the study period so facilitating repeatability, and quantified using a ‘patency score’. A score of 200 was equivalent to 0% bilateral stenosis while a score of 0 meant 100% bilateral occlusion. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI)\(^{20}\). Patients recruited into the Salford Renovascular Study have been managed in accordance with contemporary vascular protective advice and UK Renal Association blood pressure targets\(^{21}\).

Renal revascularization has been performed in accordance with physician preference or after entry into a RCT\(^4,5\). All revascularization procedures involved percutaneous transluminal angioplasty. Bare-metal stents were deployed in all procedures and no embolic protection devices were used.

Since 2005 we have been collecting plasma samples in unselected patients entering the cohort, and these are the patients included in the current study. The following biomarkers were analysed: fibroblast growth factor-23 (FGF-23) (RU/ml), Cystatin C (mg/L), kidney injury molecule-1 (KIM-1) (pg/ml), myeloperoxidase (MPO) (pg/ml), neutrophil gelatinase-associated lipocalin (NGAL) (pg/ml), N-terminal prohormone of brain natriuretic peptide (NT-proBNP) (pg/ml), high-sensitivity cardiac Troponin T (hs-cTNT) (ng/L),\(^{15,16}\) and anti-apolipoproteinA-1 Immunoglobulin G (anti-apoA-1 IgG) (optical density [OD])\(^{22-26}\). Patients with missing baseline data were excluded from analysis. The date of sampling was considered as time zero for clinical event analysis. New patients were entered into the database up until 31\(^{st}\) August 2014 and data censoring was performed at the earliest of 11\(^{th}\) May 2015, death, or last patient encounter if discharged or lost to follow-up.

**Biomarker analysis:**

FGF-23 was measured using a second-generation, two-site enzyme linked immunosorbent assay (ELISA) supplied by Immutopics (San Clemente, CA, USA) detecting both intact FGF-23
and its carboxyl-terminal fragments. KIM-1, NGAL and MPO were quantified with the MESO QuickPlex SQ 120 Automate using immuno-electrochemiluminescence from Mesoscale Discovery Systems (Rockville, MD, USA). The lower limits of detection in pg/ml were 0.49, 2.85 and 7.46 for KIM-1 NGAL and MPO, respectively. The intra-assay variation coefficients (VC) were as follows: For KIM-1, 3.04 % (n=34) at 312.5pg/ml, and 2.5% at 78.1 pg/ml (n=34). For NGAL, 5.57 % (n=34) at 2500pg/ml, and 3.87% at 625 pg/ml (n=34). For MPO, intra-assay VCs were 6.08 % (n=34) at 3125pg/ml, and 7.75% at 781 pg/ml (n=34).

The inter-assay VCs were as follows: For KIM-1, VCs were 5.45% (n=17) and 3.02 % (n=17) at concentrations of 312.5 and 78.1pg/ml, respectively. For NGAL, VCs were 5.77% (n=17) and 8.52 % (n=17) at concentration of 2500 and 625pg/ml, respectively. For MPO, VCs were 8.17% (n=17) and 8.52 % (n=17) at concentration of 3125 and 781.25pg/ml, respectively.

NT-proBNP and hs-cTNT were measured on citrated plasma by electrochemiluminescence, using an assay supplied by Roche Diagnostics (Indianapolis, USA). Cystatin C was measured by the turbidimetric method (Gentian, Moss, Norway). Anti-apoA-1 IgG levels were quantified on citrated plasma samples, using an ELISA technique as described in previous studies24–26.

Clinical End-points:
Predefined primary clinical end-points for this study include:

(1) Date of ‘all-cause’ death as recorded in the hospital records
(2) Date of first cardiovascular event (CVE) after enrollment, defined as a composite of acute coronary syndrome or myocardial infarction, new arrhythmias, pulmonary oedema or decompensated heart failure, cerebrovascular events including transient ischaemic attacks.
(3) Date of patient reaching end-stage kidney disease (ESKD) defined as the earliest of the following events: initiation of renal replacement therapy (RRT) (including renal transplantation) or reaching eGFR <10ml/min/1.73m², which is the approximate average eGFR at which RRT is commenced in the UK27.
(4) A composite end-point composed of the first of any of the above events.

Statistical analysis:
Baseline characteristics were compared between the study population and patients in the Salford Renovascular study who did not undergo biomarker analysis. Comparison of baseline characteristics and biomarker levels was then performed for patients in the study population with CKD stage 3, 4 and 5, and for patients with different severity of RAS. Categorical data is presented as a number and percentage, normally distributed continuous data as mean +/- standard deviation and non-parametric continuous data as median (interquartile range). Chi-
square test was used to compare categorical data, Kruskal-Wallis or Mann-Whitney U tests were used to compare non-parametric continuous data and Student T test or ANOVA was used for parametric data. The number of clinical end-points and unadjusted incidence rates per 100 patient years were calculated manually.

The association of traditional risk factors and novel biomarkers with each of the clinical end-points was explored using Cox Proportional Hazards regression. Hazard ratios (HR) for age and eGFR were scaled by exponentiation of the HR to 10 years and 5ml/min/1.73m² respectively to aid clinical interpretation. All biomarkers had a skewed distribution; as frequently observed for inflammatory and cardiac-related biomarkers and were accordingly logarithmic transformed before analyses. Biomarkers values were graded into quartiles and hazard ratios are reported per quartile increase in biomarker level or per values above vs below the predefined NT-proBNP cutoff. Assuming a conservative survival rate difference of 20% between patients with high vs low NT-proBNP values previously reported in CKD patients, post-hoc power calculation showed that our sample size of 112 patients displayed a power of 86% at the alpha level of 5%.

A baseline multivariable model consisting of traditional risk factors associated with adverse events in patients with CKD and ARVD was created for each of the four clinical end-points. These variables were selected based on established clinical significance and the same variables were retained for all end-points irrespective of statistical significance. Each novel biomarker was then added individually to each of the four base models to obtain adjusted hazard ratios for each quartile increase in biomarker level; the additional predictive value for each biomarker, adjusted for traditional risk factors, was illustrated on Forest plots. Biomarkers that were individually significant in this analysis were then added as a panel to the baseline model to investigate the association between this combination of biomarkers and individual end-points.

Receiver operator characteristic analyses were used to determine whether the addition of novel biomarkers, either individually or as a group, to the base model, improved risk discrimination, which was quantified using the area under the curve (AUC). Goodness of model fit was assessed using Akaike Information Criterion (AIC). Net reclassification index (NRI) was used to quantify any improvement in risk discrimination; biomarkers were again analyzed as quartiles. Both continuous and three-category NRI results are presented and NRI event and non-event rates were calculated from reclassification tables. Risk categories for categorical NRI were arbitrarily based on yearly event rates reported previously in an unselected ARVD population, given the lack of established risk categories in the ARVD population. Integration discrimination improvement (IDI) results are also presented. Given the small patient numbers, for the purposes of this analysis, progression to ESKD and CVE end-points were considered composite with death. Kaplan-Meier curves were used to analyse the effect of revascularization on time to end-points in patients with different levels of those biomarkers that were most
strongly associated with adverse events on multivariate analyses. Patients were dichotomized either according to previously validated cut-off levels or according to the median biomarker level observed in the current study; the latter was used if standard cutoffs were not applicable to our study population or if the number of events in groups resulting from standard cutoffs was too small.

All analysis have been performed using SPSS version 22.0, Microsoft Excel and RStudio version 1.0.44, and a p value <0.05 was considered statistically significant.

Results:
Out of a total of 830 patients recruited into the Salford Renovascular study, 170 patients had biomarker analyses performed on a baseline plasma sample as part of another study. Only 112 patients had complete laboratory datasets and these comprised the study population (Figure 4.4.1). Median follow-up was 59.9 months (33.6-86.9). Median age was 71.1 years (66.7-76.9), 66.1% were male and median baseline eGFR was 27.4ml/min/1.73m² (18.8-39.0). Table 4.4.1 shows that patients in the Salford Renovascular study who did not have biomarker analyses performed had similar characteristics to the 112 patients in this analysis, with the exceptions that the latter had a lower degree of proteinuria at baseline (0.3 vs 0.6 g/24hr, p<0.0005) and were more frequently established on a statin at time of diagnosis (71.4% vs 51.7%, p<0.0005). In addition, the study population had a comparatively lower incidence of adverse events per 100 patient years. In total, 75 (67.0%) patients died, 21 (18.8%) reached ESKD or started RRT, 36 (32.1%) suffered a CVE and 87 (77.7%) patients had any of these events (Table 4.4.2).

Levels of PTH, Cystatin-C, KIM-1, NGAL and NT-proBNP increased with declining renal function, while the remaining biomarkers, including FGF-23, did not show any statistically significant change with progression from CKD stage 3 to stage 5. Of note, the number of patients who had CKD stage 5 at baseline was much smaller compared to the other two groups (Table 4.4.2). Patients with more severe RAS had similar baseline characteristics, including renal function and blood pressure control, to patients with less severe disease. The only statistically significant differences between these two groups of patients were NT-proBNP (706.3 pg/ml versus 370.5 pg/ml, p=0.02) and PTH (87.0 pg/ml versus 57.0 pg/ml, p=0.002; Table 4.4.2).

Baseline multivariable models for death, progression to ESKD, CVE and the first of any of these events are shown in Table 4.4.3. Older age at time of diagnosis was associated with increased risk of death (HR 1.76 [95% CI 1.22-2.52], p=0.003) and CVE (HR 1.55 [95% CI 1.10-2.18], p=0.01) while higher degree of baseline proteinuria was associated with increased risk of progression to ESKD (HR 1.30 [95% CI 1.01-1.67], p=0.04). Macrovascular disease and cardiovascular comorbidities such as CHF and FPE at time of diagnosis were not found to
Figure 4.4.1 Flowchart describing selection of study population

Hospital records screened (n=872)

Excluded due to:
- Missing baseline proteinuria (n=21)
- Missing baseline blood pressure (n=8)
- Missing baseline eGFR (n=1)
- Missing baseline medications (n=3)
- Missing baseline proteinuria, eGFR and blood pressure (n=1)
- Missing baseline proteinuria and eGFR (n=1)
- Missing baseline proteinuria and blood pressure (n=3)

42 patients enrolled in Salford Renovascular Study (n=830)

Patients who had biomarker analyses performed on baseline plasma sample as part of another study\textsuperscript{11,12} (n=170)

Study population: patients who had results available for all of the following biomarkers: FGF-23, Cystatin C, KIM-1, MPO, NGAL, NT-proBNP, hs-cTNT and anti-apoA-1 IgG. (n=112)

Patients with no biomarker analyses performed on baseline plasma sample (n=660)

Excluded due to:
- Missing FGF-23 result (n=55)
- Missing KIM-1 result (n=3)

58 patients with no biomarker analyses performed on baseline plasma sample (n=660)

Table 4.4.1 Comparison between study population and patients recruited into the Salford Renovascular Study who had no biomarker data available

<table>
<thead>
<tr>
<th></th>
<th>Study Population</th>
<th>Salford Renovascular Study patients with no available biomarker data</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>112</td>
<td>660</td>
<td></td>
</tr>
</tbody>
</table>

Demographics, baseline characteristics and co-morbidities

<table>
<thead>
<tr>
<th></th>
<th>Study Population</th>
<th>Salford Renovascular Study patients with no available biomarker data</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) [median (IQR)]</td>
<td>71.1 (66.7-76.9)</td>
<td>71.2 (65.1-76.8)</td>
<td>0.7</td>
</tr>
<tr>
<td>Male [n (%)]</td>
<td>74 (66.1)</td>
<td>380 (57.6)</td>
<td>0.09</td>
</tr>
<tr>
<td>MVD [n (%)]</td>
<td>81 (72.3)</td>
<td>471 (71.4)</td>
<td>0.8</td>
</tr>
<tr>
<td>CHF [n (%)]</td>
<td>15 (13.4)</td>
<td>140 (21.2)</td>
<td>0.06</td>
</tr>
<tr>
<td>FPE [n (%)]</td>
<td>6 (5.4)</td>
<td>46 (7.0)</td>
<td>0.5</td>
</tr>
<tr>
<td>DM [n (%)]</td>
<td>41 (36.6)</td>
<td>204 (30.9)</td>
<td>0.2</td>
</tr>
<tr>
<td>RAB [n (%)]</td>
<td>64 (57.1)</td>
<td>321 (48.6)</td>
<td>0.1</td>
</tr>
<tr>
<td>Beta-blocker [n (%)]</td>
<td>46 (41.1)</td>
<td>236 (35.8)</td>
<td>0.3</td>
</tr>
<tr>
<td>CCB [n (%)]</td>
<td>71 (63.4)</td>
<td>357 (54.1)</td>
<td>0.07</td>
</tr>
<tr>
<td>Statin [n (%)]</td>
<td>80 (71.4)</td>
<td>341 (51.7)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Baseline Proteinuria (g/day) [median (IQR)]</td>
<td>0.3 (0.1-0.7)</td>
<td>0.6 (0.2-1.2)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Baseline eGFR (ml/min/1.73m²) [Median (IQR)]</td>
<td>27.4 (18.8-39.0)</td>
<td>30.8 (18.9-44.4)</td>
<td>0.1</td>
</tr>
<tr>
<td>MAP (mmHg) [median (IQR)]</td>
<td>102.0 (90.5-112.5)</td>
<td>103.3 (93.7-115.9)</td>
<td>0.1</td>
</tr>
<tr>
<td>SBP (mmHg) [median (IQR)]</td>
<td>150.0 (132.0-168.0)</td>
<td>153.0 (136.0-177.8)</td>
<td>0.2</td>
</tr>
<tr>
<td>DBP (mmHg) [median (IQR)]</td>
<td>79.8 (68.3-84.0)</td>
<td>80.0 (70.0-90.0)</td>
<td>0.1</td>
</tr>
<tr>
<td>≥70% Unilateral RAS [n (%)]</td>
<td>44 (39.3)</td>
<td>269 (40.8)</td>
<td>0.8</td>
</tr>
<tr>
<td>≥70% Bilateral RAS [n (%)]</td>
<td>8 (7.1)</td>
<td>74 (12.1)</td>
<td>0.2</td>
</tr>
<tr>
<td>Patency Score [median (IQR)]</td>
<td>105.0 (80.0-140.0)</td>
<td>110.0 (70.0-150.0)</td>
<td>0.9</td>
</tr>
<tr>
<td>Revascularized [n (%)]</td>
<td>19 (17.0)</td>
<td>111 (16.8)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Routine Biomarkers

<table>
<thead>
<tr>
<th></th>
<th>Study Population</th>
<th>Salford Renovascular Study patients with no available biomarker data</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH (pg/mL) [median (IQR)]</td>
<td>70.0 (39.5-129.0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CRP (mg/L) [median (IQR)]</td>
<td>4.6 (2.2-10.0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hb (g/dL) [median (IQR)]</td>
<td>126.0 (117.5-133.5)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Albumin (g/dL) [mean +/- SD]</td>
<td>43.7 +/- 3.3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Phosphate (mg/dL) [median (IQR)]</td>
<td>1.1 (1.0-1.3)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Calcium (mg/dL) [mean +/- SD]</td>
<td>2.2 +/- 0.1</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Novel Biomarkers

<table>
<thead>
<tr>
<th></th>
<th>Study Population</th>
<th>Salford Renovascular Study patients with no available biomarker data</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGF-23 (RU/mL) [median (IQR)]</td>
<td>185.0 (125.5-324.0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cystatin-C (mg/L) [median (IQR)]</td>
<td>2.6 (1.9-3.2)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>KIM-1 (pg/mL) [median (IQR)]</td>
<td>276.0 (219.2-387.2)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MPO (pg/mL) [median (IQR)]</td>
<td>54.4 (32.2-80.0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NGAL (pg/mL) [median (IQR)]</td>
<td>204.7 (148.5-277.3)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL) [median (IQR)]</td>
<td>521.2 (201.2-1511.0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hs-cTNT (ng/L) [median (IQR)]</td>
<td>16.0 (11.4-27.1)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anti-apoA-1 IgG (OD) [median (IQR)]</td>
<td>0.5 (0.3-0.8)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Clinical Outcomes per 100 patient years

<table>
<thead>
<tr>
<th></th>
<th>Study Population</th>
<th>Salford Renovascular Study patients with no available biomarker data</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>12.9</td>
<td>15.4</td>
<td>-</td>
</tr>
<tr>
<td>ESKD</td>
<td>4.1</td>
<td>4.8</td>
<td>-</td>
</tr>
<tr>
<td>CVE</td>
<td>7.5</td>
<td>10.5</td>
<td>-</td>
</tr>
<tr>
<td>Any</td>
<td>18.9</td>
<td>25.1</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 4.4.2 Baseline characteristics, serum biomarkers and clinical outcomes subdivided by chronic kidney disease (CKD) Stage and renal artery stenosis (RAS) severity. Bold data indicates a statistically significant difference with a p value less than 0.05.

<table>
<thead>
<tr>
<th>Demographics, baseline characteristics and co-morbidities</th>
<th>Study Population</th>
<th>CKD Stage</th>
<th>RAS severity</th>
<th>p</th>
<th>&lt; 70% Bilaterally</th>
<th>≥70% Unilaterally or Bilaterally</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) [median (IQR)]</td>
<td>71.1 (66.7-76.9)</td>
<td>68.9 (65.3-74.5)</td>
<td>73.6 (67.7-78.4)</td>
<td>72.7 (69.7-78.2)</td>
<td>0.04</td>
<td>70.5 (64.2-76.0)</td>
<td>72.2 (67.9-78.4)</td>
</tr>
<tr>
<td>Male [n (%)]</td>
<td>74 (66.1)</td>
<td>34 (70.8)</td>
<td>32 (62.7)</td>
<td>8 (61.5)</td>
<td>0.7</td>
<td>43 (71.7)</td>
<td>31 (59.6)</td>
</tr>
<tr>
<td>MVD [n (%)]</td>
<td>81 (72.3)</td>
<td>33 (68.8)</td>
<td>36 (70.6)</td>
<td>12 (92.3)</td>
<td>0.2</td>
<td>43 (71.7)</td>
<td>38 (73.1)</td>
</tr>
<tr>
<td>CHF [n (%)]</td>
<td>15 (13.4)</td>
<td>4 (8.3)</td>
<td>8 (15.7)</td>
<td>3 (23.1)</td>
<td>0.3</td>
<td>7 (11.7)</td>
<td>8 (15.4)</td>
</tr>
<tr>
<td>FPE [n (%)]</td>
<td>6 (5.4)</td>
<td>1 (2.1)</td>
<td>2 (3.9)</td>
<td>3 (23.1)</td>
<td>0.01</td>
<td>3 (5.0)</td>
<td>3 (5.8)</td>
</tr>
<tr>
<td>DM [n (%)]</td>
<td>41 (36.6)</td>
<td>18 (37.5)</td>
<td>16 (31.4)</td>
<td>7 (53.8)</td>
<td>0.3</td>
<td>25 (41.7)</td>
<td>16 (30.8)</td>
</tr>
<tr>
<td>RAB [n (%)]</td>
<td>64 (57.1)</td>
<td>29 (60.4)</td>
<td>30 (58.8)</td>
<td>5 (38.5)</td>
<td>0.3</td>
<td>33 (55.0)</td>
<td>31 (59.6)</td>
</tr>
<tr>
<td>Beta-blocker [n (%)]</td>
<td>46 (41.1)</td>
<td>16 (33.3)</td>
<td>27 (52.9)</td>
<td>3 (23.1)</td>
<td>0.05</td>
<td>21 (35.0)</td>
<td>25 (48.1)</td>
</tr>
<tr>
<td>CCB [n (%)]</td>
<td>71 (63.4)</td>
<td>29 (60.4)</td>
<td>35 (68.6)</td>
<td>7 (53.8)</td>
<td>0.5</td>
<td>35 (58.3)</td>
<td>36 (69.2)</td>
</tr>
<tr>
<td>Statin [n (%)]</td>
<td>80 (71.4)</td>
<td>37 (77.1)</td>
<td>33 (64.7)</td>
<td>10 (76.9)</td>
<td>0.4</td>
<td>42 (70.0)</td>
<td>38 (73.1)</td>
</tr>
<tr>
<td>Baseline Proteinuria (g/day) [median (IQR)]</td>
<td>0.3 (0.1-0.7)</td>
<td>0.2 (0.1-0.7)</td>
<td>0.4 (0.1-1.0)</td>
<td>0.3 (0.1-0.6)</td>
<td>0.7</td>
<td>0.3 (0.2-0.7)</td>
<td>0.2 (0.1-0.7)</td>
</tr>
<tr>
<td>Baseline eGFR (ml/min/1.73m²) [Median (IQR)]</td>
<td>27.4 (18.8-39.0)</td>
<td>40.8 (33.8-45.9)</td>
<td>23.0 (18.2-26.6)</td>
<td>11.7 (7.7-14.5)</td>
<td>-</td>
<td>27.4 (17.8-35.9)</td>
<td>27.6 (20.1-41.6)</td>
</tr>
<tr>
<td>MAP (mmHg) [median (IQR)]</td>
<td>102.0 (90.5-112.5)</td>
<td>104.7 (97.2-116.3)</td>
<td>96.7 (86.7-106.7)</td>
<td>100.0 (95.8-117.5)</td>
<td>0.01</td>
<td>101.7 (90.5-110.5)</td>
<td>103.3 (90.9-113.3)</td>
</tr>
<tr>
<td>SBP (mmHg) [median (IQR)]</td>
<td>150.0 (132.0-168.0)</td>
<td>160.0 (132.5-179.3)</td>
<td>145.0 (123.0-160.0)</td>
<td>155.0 (140.0-187.5)</td>
<td>0.02</td>
<td>149.8 (132.3-167.9)</td>
<td>154.0 (130.5-176.0)</td>
</tr>
<tr>
<td>DBP (mmHg) [median (IQR)]</td>
<td>79.8 (68.3-84.0)</td>
<td>80.0 (71.5-85.0)</td>
<td>72.0 (66.0-81.0)</td>
<td>80.0 (67.5-85.0)</td>
<td>0.03</td>
<td>80.0 (68.3-85.0)</td>
<td>78.8 (67.5-83.8)</td>
</tr>
<tr>
<td>≥70% Unilateral RAS [n (%)]</td>
<td>44 (39.3)</td>
<td>21 (43.8)</td>
<td>19 (37.3)</td>
<td>4 (30.8)</td>
<td>0.6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Biomarker</td>
<td>Median (IQR)</td>
<td>Mean ± SD</td>
<td>Median (IQR)</td>
<td>Mean ± SD</td>
<td>Median (IQR)</td>
<td>Mean ± SD</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-------------------------</td>
<td>-------------</td>
<td>-------------------------</td>
<td>-------------</td>
<td>-------------------------</td>
<td>-------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>≥70% Bilateral RAS [n (%)]</td>
<td>8 (7.1)</td>
<td></td>
<td>1 (2.1)</td>
<td></td>
<td>6 (11.8)</td>
<td></td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>Patency Score [median (IQR)]</td>
<td>105.0 (80.0-140.0)</td>
<td>82.0 (44.0-156.5)</td>
<td>120.0 (81.3-143.8)</td>
<td>95.0 (80.0-107.5)</td>
<td>0.1</td>
<td>140.0 (96.3-150.0)</td>
<td>100.0 (55.0-105.0)</td>
</tr>
<tr>
<td>Revascularized [n (%)]</td>
<td>19 (17.0)</td>
<td>7 (13.7)</td>
<td>8 (16.7)</td>
<td>4 (30.8)</td>
<td>0.3</td>
<td>9 (15.0)</td>
<td>10 (19.2)</td>
</tr>
<tr>
<td><strong>Routine Biomarkers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTH (pg/mL) [median (IQR)]</td>
<td>70.0 (39.5-129.0)</td>
<td></td>
<td>57.0 (35.0-87.8)</td>
<td></td>
<td>82.0 (44.0-156.5)</td>
<td></td>
<td>101.0 (54.0-157.8)</td>
</tr>
<tr>
<td>CRP (mg/L) [median (IQR)]</td>
<td>4.6 (2.2-10.0)</td>
<td></td>
<td>5.4 (2.2-9.6)</td>
<td></td>
<td>3.9 (1.6-10.0)</td>
<td></td>
<td>3.0 (2.0-12.3)</td>
</tr>
<tr>
<td>Hb (g/dL) [median (IQR)]</td>
<td>126.0 (117.5-133.5)</td>
<td></td>
<td>128.0 (120.8-137.0)</td>
<td></td>
<td>126.0 (116.0-130.0)</td>
<td></td>
<td>124.5 (113.5-131.3)</td>
</tr>
<tr>
<td>Albumin (g/dL) [mean +/- SD]</td>
<td>43.7 +/- 3.3</td>
<td></td>
<td>43.9 +/- 2.9</td>
<td></td>
<td>43.3 +/- 3.7</td>
<td></td>
<td>42.7 +/- 3.0</td>
</tr>
<tr>
<td>Phosphate (mg/dL) [median (IQR)]</td>
<td>1.1 (1.0-1.3)</td>
<td></td>
<td>1.1 (1.0-1.3)</td>
<td></td>
<td>1.2 (1.0-1.4)</td>
<td></td>
<td>1.1 (1.0-1.4)</td>
</tr>
<tr>
<td>Calcium (mg/dL) [mean +/- SD]</td>
<td>2.2 +/- 0.1</td>
<td></td>
<td>2.2 +/- 0.1</td>
<td></td>
<td>2.2 +/- 0.1</td>
<td></td>
<td>2.2 +/- 0.1</td>
</tr>
<tr>
<td><strong>Novel Biomarkers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FGF-23 (RU/mL) [median (IQR)]</td>
<td>185.0 (125.5-324.0)</td>
<td></td>
<td>160.0 (119.8-287.3)</td>
<td></td>
<td>229.0 (130.5-390.0)</td>
<td></td>
<td>184.0 (114.3-596.2)</td>
</tr>
<tr>
<td>Cystatin-C (mg/L) [median (IQR)]</td>
<td>2.6 (1.9-3.2)</td>
<td></td>
<td>2.2 (1.9-2.8)</td>
<td></td>
<td>3.0 (2.4-3.4)</td>
<td></td>
<td>3.1 (2.2-3.6)</td>
</tr>
<tr>
<td>KIM-1 (pg/mL) [median (IQR)]</td>
<td>276.0 (219.2-387.2)</td>
<td></td>
<td>255.4 (181.2-322.4)</td>
<td></td>
<td>305.3 (222.3-481.6)</td>
<td></td>
<td>323.7 (265.1-680.8)</td>
</tr>
<tr>
<td>MPO (pg/mL) [median (IQR)]</td>
<td>54.4 (32.2-80.0)</td>
<td></td>
<td>47.4 (31.1-83.7)</td>
<td></td>
<td>53.0 (29.1-74.9)</td>
<td></td>
<td>73.5 (50.8-177.2)</td>
</tr>
<tr>
<td>NGAL (pg/mL) [median (IQR)]</td>
<td>204.7 (148.5-277.3)</td>
<td></td>
<td>185.7 (143.9-228.1)</td>
<td></td>
<td>230.4 (154.4-322.5)</td>
<td></td>
<td>211.3 (136.2-279.9)</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL) [median (IQR)]</td>
<td>521.2 (201.2-1511.0)</td>
<td></td>
<td>283.0 (133.8-749.5)</td>
<td></td>
<td>901.0 (344.7-1959.0)</td>
<td></td>
<td>590.2 (226.6-3697.8)</td>
</tr>
<tr>
<td>Hs-cTNT (ng/L) [median (IQR)]</td>
<td>16.0 (11.4-27.1)</td>
<td></td>
<td>15.9 (10.0-27.0)</td>
<td></td>
<td>16.0 (11.4-26.5)</td>
<td></td>
<td>19.7 (14.2-37.3)</td>
</tr>
<tr>
<td>Anti-aPO-A1 IgG (OD) [median (IQR)]</td>
<td>0.5 (0.3-0.8)</td>
<td></td>
<td>0.5 (0.3-0.7)</td>
<td></td>
<td>0.5 (0.3-0.8)</td>
<td></td>
<td>0.5 (0.3-0.8)</td>
</tr>
<tr>
<td>Clinical Outcomes per 100 patient years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESKD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4.4.3: Multivariable model based on base model (shaded area) and combination of those biomarkers that are individually statistically significant when adjusted for base model. Bold data indicates a statistically significant difference with a p value less than 0.05. The empty boxes represent variables (biomarkers) that were not significant on univariable analysis, hence were not included in multivariable analysis.

<table>
<thead>
<tr>
<th></th>
<th>Death HR 95% CI</th>
<th>ESKD HR 95% CI</th>
<th>CVE HR 95% CI</th>
<th>Any HR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>1.41 (1.01-1.99)</td>
<td>0.96 (0.69-1.34)</td>
<td>1.27 (0.90-1.79)</td>
<td>0.87 (0.62-1.22)</td>
</tr>
<tr>
<td><strong>MVD</strong></td>
<td>1.91 (0.94-3.88)</td>
<td>1.24 (0.67-2.29)</td>
<td>1.42 (0.77-2.62)</td>
<td>1.14 (0.64-2.03)</td>
</tr>
<tr>
<td><strong>CHF</strong></td>
<td>0.41 (0.18-0.93)</td>
<td>0.56 (0.25-1.24)</td>
<td>0.92 (0.43-1.94)</td>
<td>0.77 (0.35-1.67)</td>
</tr>
<tr>
<td><strong>FPE</strong></td>
<td>2.25 (0.79-6.39)</td>
<td>1.43 (0.50-4.13)</td>
<td>1.05 (0.39-2.88)</td>
<td>0.90 (0.32-2.53)</td>
</tr>
<tr>
<td><strong>Baseline Proteinuria</strong></td>
<td>1.10 (0.82-1.47)</td>
<td>1.06 (0.82-1.38)</td>
<td>1.08 (0.82-1.42)</td>
<td>1.03 (0.80-1.34)</td>
</tr>
<tr>
<td><strong>Baseline eGFR</strong></td>
<td>1.06 (0.95-1.18)</td>
<td>1.07 (0.96-1.19)</td>
<td>1.05 (0.95-1.16)</td>
<td>1.03 (0.93-1.14)</td>
</tr>
<tr>
<td><strong>PTH</strong></td>
<td>0.86 (0.64-1.14)</td>
<td>0.98 (0.75-1.29)</td>
<td>0.89 (0.68-1.16)</td>
<td>0.84 (0.65-1.09)</td>
</tr>
<tr>
<td><strong>Calcium</strong></td>
<td>0.81 (0.63-1.04)</td>
<td>0.87 (0.68-1.12)</td>
<td>0.77 (0.60-0.98)</td>
<td>0.79 (0.62-1.01)</td>
</tr>
<tr>
<td><strong>Phosphate</strong></td>
<td>0.95 (0.74-1.23)</td>
<td>1.03 (0.80-1.31)</td>
<td>1.10 (0.87-1.38)</td>
<td>1.05 (0.83-1.34)</td>
</tr>
<tr>
<td><strong>FGF-23</strong></td>
<td>1.18 (0.90-1.55)</td>
<td>1.19 (0.92-1.55)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Cystatin C</strong></td>
<td>1.29 (0.90-1.84)</td>
<td>1.36 (0.96-1.93)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>KIM-1</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>MPO</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>NGAL</strong></td>
<td>1.20 (0.85-1.69)</td>
<td>1.23 (0.89-1.71)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>NT-proBNP</strong></td>
<td>1.62 (1.26-2.10)</td>
<td>1.51 (1.19-1.91)</td>
<td>1.56 (1.23-1.97)</td>
<td>1.48 (1.19-1.84)</td>
</tr>
<tr>
<td><strong>Hs-cTNT</strong></td>
<td>-</td>
<td>-</td>
<td>1.26 (0.99-1.62)</td>
<td>1.25 (0.96-1.63)</td>
</tr>
<tr>
<td><strong>Anti-apoA-1 IgG</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Anti-apoA-1 IgG – anti-apolipoprotein A-1 immunoglobulin G; CHF – congestive heart failure; CI – Confidence interval; CVE – cardiovascular event; eGFR – estimated glomerular filtration rate; ESKD – end-stage kidney disease; FGF-23 – fibroblast growth factor-23; FPE – flash pulmonary edema; HR – hazard ratio; Hs-cTNT – high-sensitivity cardiac troponin T; KIM-1 – kidney injury molecule-1; MPO – myeloperoxidase; MVD – macrovascular disease; NGAL – neutrophil gelatinase-associated lipocalin; NT-proBNP – N-terminal prohormone of brain natriuretic peptide; PTH – parathyroid hormone. *Adjusted for death; †hazard ratio reported per 1g/day increase in baseline proteinuria; ‡hazard ratio reported per 5ml/min/1.73m²; §hazard ratio reported per quartile increase in biomarker level; ††correlation coefficient between eGFR and NT-proBNP is -0.288 (p=0.002).
predict any adverse events. Renal function at time of diagnosis did not appear to have a strong statistical impact on clinical outcomes, while hazard ratios for all adverse events increased for every quartile increase in baseline PTH and phosphate levels. Higher calcium levels at time of diagnosis were associated with reduced hazard ratios for clinical end-points.

Figures 4.4.2 (a-d) show the effect of each quartile increase in individual biomarker level when added separately to the baseline multivariable models for each of the 4 end-points. Biomarkers that were individually statistically significant after adjusting for traditional risk factors were then added as a panel to each of the four base models. Table 4.4.3 shows that NT-proBNP was the only biomarker to remain strongly associated with all adverse events after adjusting for traditional risk factors and other biomarkers in the panel (Death: HR 1.62 [95% CI 1.26-2.10] p<0.0005; ESKD: HR 1.51 [95% CI 1.19-1.91] p=0.001; CVE: HR 1.56 [95% CI 1.23-1.97] p<0.0005; Any: HR 1.48 [95% CI 1.19-1.84] p<0.0005).

Table 4.4.4 shows that the addition of all biomarkers as a panel to the base model improved model discrimination and net reclassification performance for all end-points; continuous NRI showed the strongest effect size. Despite the strong association between NT-proBNP and adverse events noted on multivariable analysis, this biomarker only exerted an intermediate prognostic effect on mortality when added individually to the base model (continuous NRI 0.42, 95% CI [0.03-0.8], p=0.04). Table 4.4.5 shows the event and non-event NRI components for the extended model composed of base model and the complete panel of biomarkers.

Figure 4.4.3 (a-h) show that revascularization may have a beneficial effect on time to all adverse end-points compared to medical management in patients with NT-proBNP level above the validated cut-off value of 300pg/ml [31] at time of diagnosis. This effect was not seen in patients with NT-proBNP below this cut-off level. This is despite the former patients having older age (median age 73.7 years versus 68.8 years, p=0.001), increased cardiovascular disease burden (CHF: 20.0% versus 2.4%, p=0.008), lower baseline eGFR (24.4ml/min/1.73m^2 versus 33.6 ml/min/1.73m^2 p=0.002) and more severe degree of stenosis (patency score 100.0 versus 132.5, p=0.02) Table 4.4.6. Revascularization had no effect on time to clinical end-points when the study population was divided according to hs-cTNT and Cystatin C median levels Table 4.4.7.

Discussion:
To our knowledge this is the first study that has analyzed a diverse panel of serum biomarkers in relation to long-term outcomes in a population of patients with ARVD. Given our relatively small sample size, our findings require confirmation in larger cohorts; however, it appears that the use of an extensive panel of novel biomarkers in conjunction with more traditional risk factors can strongly improve risk prediction of adverse events. While NT-proBNP was the most strongly associated with increased risk for all adverse events, its value in individual incremental prediction was limited to prediction of death according to reclassification statistics.
Figures 4.4.2 (a – d) Effect of individual biomarkers upon hazard ratio for death, progression to end-stage kidney disease (ESKD), cardiovascular events (CVE) and any event when added to baseline model.

Table 4.4.4 Model fit and overall net reclassification index for base model, the base model in combination with all biomarkers, and base model with N-terminal prohormone of brain natriuretic peptide (NT-proBNP) only, for each clinical end-point. Bold data indicates a statistically significant association with a p value less than 0.05.

<table>
<thead>
<tr>
<th></th>
<th>Base model only</th>
<th>Base model + all biomarkers</th>
<th>Base model + NT-proBNP only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>AUC 0.90 (0.84-0.96)</td>
<td>0.95 (0.92-0.99)</td>
<td>0.91 (0.85-0.96)</td>
</tr>
<tr>
<td></td>
<td>AIC 110.42</td>
<td>134.13</td>
<td>115.9</td>
</tr>
<tr>
<td>NRI continuous</td>
<td>-</td>
<td>1.06 (0.72-1.40)</td>
<td>0.42 (0.03-0.81)</td>
</tr>
<tr>
<td>NRI categorical</td>
<td>(0-15%; 15-30%); ≥30%)</td>
<td>-</td>
<td>0.27 (0.09-0.46)</td>
</tr>
<tr>
<td>IDI</td>
<td>-</td>
<td>0.17 (0.08-0.25)</td>
<td>0.01 (-0.01-0.02)</td>
</tr>
<tr>
<td>ESKD*</td>
<td>AUC 0.87 (0.80-0.94)</td>
<td>0.94 (0.91-0.98)</td>
<td>0.88 (0.81-0.94)</td>
</tr>
<tr>
<td></td>
<td>AIC 114.72</td>
<td>136.08</td>
<td>120.04</td>
</tr>
<tr>
<td>NRI continuous</td>
<td>-</td>
<td>0.99 (0.62-1.37)</td>
<td>0.21 (-0.21-0.62)</td>
</tr>
<tr>
<td>NRI categorical</td>
<td>(0-5%; 5-10%; ≥10%)</td>
<td>-</td>
<td>0.27 (0.11-0.43)</td>
</tr>
<tr>
<td>IDI</td>
<td>-</td>
<td>0.20 (0.11-0.30)</td>
<td>0.004 (-0.01-0.021)</td>
</tr>
<tr>
<td>CVE*</td>
<td>AUC 0.87 (0.79-0.94)</td>
<td>0.93 (0.88-0.98)</td>
<td>0.87 (0.80-0.94)</td>
</tr>
<tr>
<td></td>
<td>AIC 113.9</td>
<td>143.16</td>
<td>118.51</td>
</tr>
<tr>
<td>NRI continuous</td>
<td>-</td>
<td>0.96 (0.58-1.34)</td>
<td>0.21 (-0.22-0.63)</td>
</tr>
<tr>
<td>NRI categorical</td>
<td>(0-10%; 10-20%; ≥20%)</td>
<td>-</td>
<td>0.20 (0.02-0.39)</td>
</tr>
<tr>
<td>IDI</td>
<td>-</td>
<td>0.15 (0.07-0.24)</td>
<td>0.01 (-0.02-0.03)</td>
</tr>
<tr>
<td>Any</td>
<td>AUC 0.84 (0.77-0.92)</td>
<td>0.91 (0.86-0.97)</td>
<td>0.84 (0.77-0.92)</td>
</tr>
<tr>
<td></td>
<td>AIC 114.6</td>
<td>143.85</td>
<td>119.84</td>
</tr>
<tr>
<td>NRI continuous</td>
<td>-</td>
<td>0.64 (0.20-1.07)</td>
<td>0.18 (-0.27-0.63)</td>
</tr>
<tr>
<td>NRI categorical</td>
<td>(0-20%; 20-40%; ≥40%)</td>
<td>-</td>
<td>0.32 (0.10-0.55)</td>
</tr>
<tr>
<td>IDI</td>
<td>-</td>
<td>0.18 (0.09-0.27)</td>
<td>0.01 (-0.01-0.03)</td>
</tr>
</tbody>
</table>

AIC – Akaike information criterion; AUC – area under the curve; CVE – cardiovascular event; ESKD – end-stage kidney disease; IDI – Integration discrimination improvement; NRI – net reclassification index. NT-proBNP – C-terminal of prohormone of brain natriuretic peptide

*Assessed as a composite end-point with Death; †Assessed as quartiles
Table 4.4.5 Reclassification table showing event and non-event NRI for prediction of all end-points

<table>
<thead>
<tr>
<th>Event</th>
<th>Baseline model only</th>
<th>Controls</th>
<th>Baseline model + all Biomarkers*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0-15%</td>
<td>&gt;15-≤30%</td>
<td>&gt;30% Total</td>
</tr>
<tr>
<td></td>
<td>0-15%</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;15-≤30%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt;30%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>1</td>
<td>71</td>
</tr>
<tr>
<td>ESKDb</td>
<td>0-5%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt;5-≤10%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt;10%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>0</td>
<td>0</td>
<td>79</td>
</tr>
<tr>
<td>CVEb</td>
<td>0-10%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt;10-≤20%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt;20%</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>0</td>
<td>1</td>
<td>80</td>
</tr>
<tr>
<td>Any</td>
<td>0-20%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt;20-≤40%</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;40%</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>0</td>
<td>4</td>
<td>81</td>
</tr>
</tbody>
</table>

CVE – cardiovascular event; ESKD – end-stage kidney disease; NRI – net reclassification index.

*Assessed as quartiles; bAssessed as a composite end-point with death.
**Figure 4.4.3** Kaplan-Meier curves showing the effect of revascularization on death, progression to end-stage kidney disease (ESKD), cardiovascular events (CVE) and any event in patients with serum N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels and below standard cut-off of 300pg/ml.
Table 4.4.6 Comparison of baseline characteristics and serum biomarkers for revascularized and non-revascularized patients. Bold data indicates a statistically significant association with a p value less than 0.05.

<table>
<thead>
<tr>
<th>Demographics, co-morbidities and characteristics</th>
<th>NT-proBNP &lt;300pg/ml</th>
<th>NT-proBNP ≥300pg/ml</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) [median (IQR)]</td>
<td>68.8 (62.3-73.6)</td>
<td>73.7 (68.9-78.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Male [n (%)]</td>
<td>29 (69.0)</td>
<td>45 (64.3)</td>
<td>0.6</td>
</tr>
<tr>
<td>MVD [n (%)]</td>
<td>29 (69.0)</td>
<td>52 (74.3)</td>
<td>0.6</td>
</tr>
<tr>
<td>CHF [n (%)]</td>
<td>1 (2.4)</td>
<td>12 (20.0)</td>
<td>0.008</td>
</tr>
<tr>
<td>FPE [n (%)]</td>
<td>1 (2.4)</td>
<td>5 (7.1)</td>
<td>0.3</td>
</tr>
<tr>
<td>DM [n (%)]</td>
<td>11 (26.2)</td>
<td>30 (42.9)</td>
<td>0.08</td>
</tr>
<tr>
<td>Baseline Proteinuria (g/day) [median (IQR)]</td>
<td>0.2 (0.1-0.7)</td>
<td>0.3 (0.1-0.9)</td>
<td>0.3</td>
</tr>
<tr>
<td>Baseline eGFR (ml/min/1.73m²) [median (IQR)]</td>
<td>33.6 (25.1-43.2)</td>
<td>24.4 (18.0-33.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>MAP (mmHg) [median (IQR)]</td>
<td>102.5 (89.8-115.8)</td>
<td>102.0 (92.3-109.3)</td>
<td>0.6</td>
</tr>
<tr>
<td>SBP (mmHg) [median (IQR)]</td>
<td>147.5 (129.5-168.0)</td>
<td>150.0 (132.0-170.5)</td>
<td>0.8</td>
</tr>
<tr>
<td>DBP (mmHg) [median (IQR)]</td>
<td>80.0 (68.8-90.5)</td>
<td>76.0 (67.8-82.3)</td>
<td>0.1</td>
</tr>
<tr>
<td>≥70% Unilateral RAS [n (%)]</td>
<td>12 (28.6)</td>
<td>32 (45.7)</td>
<td>0.07</td>
</tr>
<tr>
<td>≥70% Bilateral RAS [n (%)]</td>
<td>2 (4.8)</td>
<td>6 (8.6)</td>
<td>0.5</td>
</tr>
<tr>
<td>Patency Score [median (IQR)]</td>
<td>132.5 (90.0-150.0)</td>
<td>100 (73.8-122.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Revascularized [n (%)]</td>
<td>5 (11.9)</td>
<td>14 (20.0)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

CHF - congestive heart failure; DBP – diastolic blood pressure; DM – diabetes mellitus; eGFR – estimated glomerular filtration rate; FGF-23 – fibroblast growth factor-23; FPE – flash pulmonary edema; Hb – haemoglobin; Hs-cTNT – high-sensitivity cardiac troponin T; IQR – interquartile range; MAP – mean arterial pressure; MPO – myeloperoxidase; MVD – macrovascular disease; NT-proBNP – N-terminal prohormone of brain natriuretic peptide; RAS – renal artery stenosis; SBP – systolic blood pressure

Table 4.4.7 Median time to end-points in months for revascularized and non-revascularized patients with high-sensitivity cardiac Troponin T (hs-cTNT) and Cystatin C levels below and above median.

<table>
<thead>
<tr>
<th>Hs-cTNT &lt;16ng/L</th>
<th>Hs-cTNT ≥16ng/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-revascularized</td>
<td>Revascularized</td>
</tr>
<tr>
<td>Death</td>
<td>91.5 (80.4-102.6)</td>
</tr>
<tr>
<td>ESKD*</td>
<td>87.9 (62.3-113.4)</td>
</tr>
<tr>
<td>CVE*</td>
<td>69.0 (25.3-112.6)</td>
</tr>
<tr>
<td>Any</td>
<td>69.0 (33.2-104.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hs-cTNT &lt;2.6mg/L</th>
<th>Hs-cTNT ≥2.6mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-revascularized</td>
<td>Revascularized</td>
</tr>
<tr>
<td>Death</td>
<td>85.3 (57.0-113.6)</td>
</tr>
<tr>
<td>ESKD*</td>
<td>72.8 (56.6-89.0)</td>
</tr>
<tr>
<td>CVE*</td>
<td>69.5 (43.5-95.4)</td>
</tr>
<tr>
<td>Any</td>
<td>72.3 (39.7-104.9)</td>
</tr>
</tbody>
</table>
CVE – cardiovascular event; ESKD – end-stage kidney disease; hs-cTNT – high-sensitivity cardiac Troponin T

*Adjusted for death

Nevertheless, Kaplan-Meier analyses performed on patients subgroups according NT-proBNP levels, showed that patients with NT-proBNP level above the standard cut-off level (≥300 pg/ml) significantly benefited from revascularization in relation to all adverse end-points during follow-up, whereas such benefit was not observed in patients with NT-proBNP below cut-off. Furthermore, such effect was not observed when dichotomizing patients according to other biomarkers values.

These results extend the limited evidence in the literature suggesting that BNP could help select ARVD patients for revascularization. In a small study of 27 patients with refractory hypertension and ≥70% RAS, there was a significant reduction in BNP levels post-revascularization and hypertension improved in 17 out of 22 patients (77%) with baseline BNP levels >80 pg/ml. In a similar study performed in 120 patients with confirmed haemodynamically significant RAS, revascularization in patients with a baseline BNP cutoff of >50 pg/ml was associated with improved 24 hour ambulatory blood pressure control at 6 months follow-up. In contrast, in a third study, revascularization did not significantly affect levels of BNP or NT-proBNP post-revascularization and baseline levels of these biomarkers did not correlate with blood pressure response post-revascularization. There was no difference in NT-proBNP levels between hypertensive patients with ARVD (n=47) and those without ARVD (n=44) at baseline although average RAS severity is not quoted in this study and inclusion criteria suggest that ARVD was less haemodynamically significant. An earlier study published by our group, also did not show any correlation between NT-proBNP levels and RAS severity, but patient numbers were very small.

Our results suggest that patients with more severe RAS may have a characteristic biomarker profile. As expected, levels of PTH and NT-proBNP were higher in patients with poor renal function, but they were also more elevated in those with anatomically more severe ARVD despite equivalent baseline renal function to those with less severe disease. Severe ARVD typically exists in the context of widespread vascular disease; elevated PTH levels represent disordered calcium and phosphate metabolism and may be a surrogate marker of reduced arterial compliance, which in turn can increase cardiac afterload, leading to left ventricular dilatation and elevated NT-proBNP levels. Renin-angiotensin system activation can also directly lead to elevated NT-proBNP levels; angiotensin II can cause increased synthesis and release of BNP independent of myocardial stretch.

Observational evidence has consistently shown that ‘high-risk’ patients characterized by haemodynamically significant RAS, neurohormonal activation or cardiac instability are those most likely to benefit from revascularization. Despite the contradictory findings of previous studies, the present data indicates that stable ARVD patients with no overt signs of cardiac...
impairment but with biochemical evidences of myocardial strain warrant investigation for the presence of underlying haemodynamically significant disease with consideration for revascularization. Further risk stratification based upon NT-proBNP values could allow the selection of apparently low-risk patients who could benefit from more aggressive management when compared to medical treatment alone. These findings could represent a simple way to foster precision medicine in this disease. It is nonetheless unclear whether our study findings are generalizable to the general ARVD population given the lower level of proteinuria, higher administration of statins at time of diagnosis and lower incidence of clinical outcomes in this study population.

The small sample size may explain the lack of association between cardiovascular comorbidities and adverse events noted in this study. The limited number of patients with CKD Stage 5 may have also masked differences between groups and may partly explain why, contrary to findings in general CKD populations, there was no significant differences in FGF-23 levels between successive CKD stages\textsuperscript{14,15}. Moreover, there was no difference in FGF-23 levels between patients with different RAS severity but similar baseline renal function; similarly, an observational study reported equivalent FGF-23 levels between healthy volunteers, patients with essential hypertension (EH) and those with renovascular hypertension (RVH, defined as defined as unilateral $\geq$60\% RAS or renal artery Doppler peak systolic velocity $>$200cm/s)\textsuperscript{18}. Levels of KIM-1 and NGAL were higher in patients with lower eGFR; again RAS severity did not influence levels. Systemic and renal levels of NGAL were however shown to be higher in RVH patients compared to EH patients or healthy volunteers while KIM-1 levels were equally elevated in RVH and EH patients, suggesting that NGAL may be a marker of upregulated intrarenal and systemic inflammation. \textsuperscript{17}

We did not observe any significant associations between MPO and anti-apoA-1 IgG with any of the study endpoints in ARVD patients despite the fact that both these molecules have been proposed to be promising markers and mediators of atherogenesis in different settings. MPO, a heme-containing enzyme produced by monocytes and neutrophils catalyzing the production of a broad range of reactive oxygen species and protein carbamylation, is involved in the initiation and development of atherosclerosis by promoting oxidative stress, lipid peroxidation and HDL dysfunction\textsuperscript{40}. In haemodialysis patients, higher serum MPO levels were associated with inflammation, advanced atherosclerosis, and poorer prognosis\textsuperscript{41,42} suggesting that MPO could be of relevance in ARVD too. Anti-apoA-1 IgGs have been associated with adverse cardiovascular risk factors and outcomes in different populations, and were shown to represent active mediators of atherogenesis\textsuperscript{22-28}. Nevertheless, their existence and possible prognostic value in ARVD has been unexplored so far. Reasons underlying the lack of association with study end-points are still elusive but could be due either to a power issue or to the fact that these molecules may not be relevant as prognostic biomarkers in ARVD patients.

Important limitations of this study include the small sample size despite its adequate power of 86\% derived from post-hoc analyses, and its retrospective and observational nature which
make it prone to selection bias and hidden confounders. As discussed above, our results may not be directly applicable to all patients with ARVD and mechanistic insights are at present unclear. To this respect it would have been insightful to have other phenotypic cardiovascular-related data such as ankle-brachial index, pulse wave velocity, or carotid intima-media thickness assessment, but these investigations were not systematically performed upon patient’s inclusion. Blood pressure was documented from office readings taken at time of diagnosis and baseline vitamin D levels were not available. Finally, given the short half-lives of the current biomarkers tested presently (NT-proBNP especially) and the study design, we were not able to assess biomarker fluctuations over time or levels immediately preceding clinical events. Therefore, we could not explore the possible incremental prognostic value of temporal changes versus single time measurement to predict long-term clinical outcomes. However, we do not think that temporal profiling would have provided clinical relevant information especially in the context of biomarkers with a short half-life. Optimal time windows for repeat biomarker investigations are unclear and may be variable due to influences from renal clearance or concurrent treatment, and may introduce delays in patient management.

**Conclusion:**

Despite the limited sample size of our study, our results suggest that NT-proBNP is independently associated with an increased risk for all adverse events in ARVD patients. Novel biomarkers, especially NT-proBNP, may have an incremental risk predictive value when used in combination with traditional risk factors, but larger multicentre studies are now required to confirm that NT-proBNP measurements provide added value for risk stratification and patient selection for revascularization.
References:


12. Murphy TP, Cooper CJ, Pencina KM, et al. Relationship of Albuminuria and Renal Artery Stent Outcomes: Results From the CORAL Randomized Clinical Trial (Cardiovascular Outcomes With Renal Artery Lesions). *Hypertension.* 2016;68(5):1145-1152.


42. Al-hweish A, Sultan SS, Mogazi K, Elsammak MY. Plasma myeloperoxidase, NT-proBNP, and troponin-I in patients on CAPD compared with those on regular
4.5 Design of a clinical risk calculator for major clinical outcomes in patients with atherosclerotic renovascular disease.

Vassallo D, Foley R, Kalra PA

Preface
Many medical fields have embraced the concept of ‘precision medicine’ to tailor treatment for a condition to the individual characteristics of a patient or a particular patient subgroup. It reflects increased understanding of heterogeneity both in the pathogenesis of disease and response to treatment. Although, as highlighted in the previous chapters, atherosclerotic renovascular disease (ARVD) is clearly a heterogenous condition, this concept has not yet been applied to this field. In this study, we collaborated with an expert renal epidemiologist to help create a simple risk score that can aid clinicians with risk stratification and potentially patient selection for revascularization.

Abstract:
Background:
Risk stratification in atherosclerotic renovascular disease (ARVD) can influence treatment decisions and facilitate patient selection for revascularization. In this study, we aim to use variables with the best predictive value to design a risk calculator that can assist clinicians with risk stratification and outcome prediction.

Method:
Patients with a radiological diagnosis of ARVD referred to our tertiary renal centre were recruited into this prospective cohort study between 1986 and 2014. Primary clinical end-points included: death, progression to end-stage kidney disease (ESKD) and cardiovascular events (CVE). A stepwise regression model was used to select variables with the most significant hazard ratio for each clinical end-point. The risk calculator was designed using HyperText Markup language (HTML). Survival and CVE-free survival were estimated at 1, 5 and 10 years.

Results:
In total 872 patients were recruited into the Salford ARVD study with a median follow-up period of 54.9 months (20.2-96.0). Only models predicting death and CVE showed good performance (c-index >0.80). Survival probabilities obtained from the risk calculator show that most patients with ARVD have reduced long-term survival. Revascularization improved outcomes in patients with higher baseline eGFR and lower proteinuria but not in those with co-existing comorbidities and higher levels of baseline proteinuria.
Conclusion:
Although this risk calculator requires further independent validation in other ARVD cohorts, this study shows that a small number of easily obtained variables can help predict clinical outcomes and encourage a patient-specific therapeutic approach.

Introduction
The majority of patients with atherosclerotic renovascular disease (ARVD) typically have silent disease that is discovered incidentally during investigation for extra-renal atherosclerosis. Studies have shown that even clinically unsuspected disease can be a strong independent predictor of adverse events. Potential reasons include the greater atherosclerotic burden that usually accompanies ARVD and the associated upregulation of inflammatory markers that can accelerate cardiovascular morbidity and mortality. While contemporary intensive multi-targeted therapy can achieve stable long-term renal function and blood pressure control, together with improved cardiovascular outcomes in most patients, numerous case studies describe a subgroup of patients who develop adverse events despite adequate medical therapy. Increasingly, non-randomized data suggests that revascularization can optimize clinical outcomes in specific ‘high-risk’ patient subgroups, such as those presenting with poor blood pressure control, rapid loss of renal function or syndromes of cardiac dysfunction. The heterogenous nature of ARVD and the complexity of co-existing comorbidities make accurate risk stratification difficult, but this remains a clinical priority as it may influence treatment decisions and may improve patient selection for revascularization.

In recent years there has been an increased interest in developing a more personalized therapeutic approach based on patient risk stratification. Simple clinical risk scores based on easily obtainable variables are widely used for prognostication and therapeutic decision-making both in the general population and in patient cohorts with established disease. The existing clinical risk prediction scores that have been developed in the context of ARVD are however limited to merely predicting the presence of significant renal arterial disease in patients being investigated for extra-renal atherosclerosis or suspected ARVD, with the aim of targeting costly and potentially hazardous imaging techniques more effectively. None of these scores evaluate the long-term clinical implications of a stenosis or the risk status of individual patients.

This study is based on a large epidemiological ARVD database with three decades of longitudinal data collection. We aimed to identify the variables that had the best predictive value for long-term adverse outcomes and to then use these to design a risk calculator that can assist clinicians with risk stratification and outcome prediction. The information provided by the risk calculator could facilitate shared decision-making, by enabling clinicians to discuss the long-term risk of important clinical end-points with patients and also whether revascularization could potentially modulate outcomes.
Methods

Patient Population and Data Collection:
The observational Salford ARVD study was established in 1986. All patients with radiologically-diagnosed ARVD who presented or were referred to our regional renal centre have systematically been recruited into the study. Approval was granted by the local ethics committee. Data collection has been described elsewhere and in brief, it includes age, gender, co-morbidities (diabetes, hypertension, coronary artery disease [CAD], congestive heart failure [CHF], peripheral vascular disease [PVD], flash pulmonary edema [FPE]), prescribed medications, blood pressure, creatinine (umol/L), proteinuria (g/24h), and clinical outcomes. Data was updated annually from hospital records. The degree of renal artery stenosis (RAS) was obtained from cross-sectional angiography (historically, intravenous digital subtraction angiography [IVDSA], intra-arterial digital subtraction angiography [IADSA], and for the last 2 decades, computed tomographic [CT] or magnetic resonance [MR] angiography), as reported by two specialist radiologists over a thirty year period, and recorded using a renal artery ‘patency score’; a score of 200 was equivalent to 0% bilateral stenosis while a score of 0 meant 100% bilateral occlusion. Estimated glomerular filtration rate (eGFR) was calculated using CKD-EPI[27]. The date of diagnostic imaging was considered as time zero. New patients were entered into the database up until 31st August 2014 and data censoring was performed at the earliest of 11th May 2015, death, or last patient encounter.

Patient management:
Patients were managed in accordance with contemporary vascular protective advice and UK Renal Association blood pressure targets[28,29]. Renal revascularization was performed in accordance with physician preference or after entry into a RCT[7,8]. All revascularization procedures involved percutaneous transluminal angioplasty; bare-metal stents were deployed in all procedures apart from 20 interventions performed in the 1980s and early 1990s. No embolic protection devices were used.

Clinical End-points:
Predefined primary clinical end-points for this study were:

(1) Date of all-cause mortality
(2) Date of first cardiovascular event (CVE) after enrollment (acute coronary syndrome, myocardial infarction, new arrhythmias, pulmonary edema, decompensated heart failure, cerebrovascular accident, transient ischaemic attack).
(3) Date of reaching end-stage kidney disease (ESKD), defined as the earliest of the following events: initiation of renal replacement therapy (RRT, including renal transplantation) or eGFR <10ml/min/1.73m², reflecting the average eGFR at which RRT is started in the UK[30]
Statistical Analysis:
All patients in the database were included in the analyses however patients with >20% missing data were not considered. Non-parametrically distributed continuous data is presented as median (interquartile range) while categorical variables were expressed both as a number and as a percentage. Candidate variables were selected using a stepwise proportional hazards regression model; variables with p<0.05 were selected and maintained in the model. This was performed for each end-point separately. Variables considered included age, number of blood pressure medications, systolic blood pressure, diastolic blood pressure, baseline eGFR, baseline proteinuria, gender, revascularization, hypertension, history of coronary artery bypass grafting, myocardial infarction, angina, coronary artery disease, left ventricular failure, peripheral vascular disease, abdominal aortic aneurysm and diabetes mellitus. A stepwise regression model was used to select the subset of variables with the most significant hazard ratio for each clinical end-point and the Harrell C-index was used to assess the discrimination performance of the final models. Death was a censoring event for both ESKD and CVE end-points. Hazard ratios for continuous variables are for a one-unit change. Dynamic Excel sheets were used to compute survival and CVE-free survival estimates at 1, 5 and 10 years for patients with different risk profiles, by adding the model coefficients and dividing them into tertiles. The risk calculator was designed as a standalone application using Hypertext Mark-up Language (HTML). The text script used is shown in Appendix 1; this can be downloaded and saved as a text file with '.html' as file extension. An interactive version is found in Appendix 2. All data analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results:
In total, 872 patients were recruited into the Salford ARVD study and they were followed-up for a median period of 54.9 months (20.2-96.0). Their baseline characteristics have already been described elsewhere. In summary, median (inter-quartile range, IQR) age at time of diagnosis was 71.1 (64.7-76.7) years while median baseline eGFR was 30 (19.5-43.3) ml/min/1.73m² and baseline proteinuria was 0.6 (0.2-1.2) g/day. The majority of patients had a history of hypertension (93.1%) and around half had documented coronary artery disease (51.3%). Symptoms of angina or peripheral vascular disease were present in more than one-third of patients at time of recruitment into the study (Table 4.5.1).

Death
Out of 872 patients, 641 (73.5%) have died, giving an incidence per 100 patient years of 13.9. Median age at death was 76.5 (70.8-81.6) years. Increased risk of mortality was associated with older age at time of diagnosis (HR 1.04 [95% CI 1.03-1.05], p<0.0001), greater baseline proteinuria (HR 1.13 [95% CI 1.06-1.19], p<0.0001), history of congestive heart failure (HR 1.61 [95% CI 1.30-1.98], p<0.0001), co-existing peripheral vascular disease (HR 1.35 [95% CI 1.14-1.60], p=0.0007) but not with either systolic or diastolic blood pressure. Conversely, better survival was associated with higher eGFR at time of diagnosis (HR 0.98 [95% CI 0.98-0.99),
p<0.0001) and renal revascularization (HR 0.68 [95% CI 0.53-0.85]). Overall, this model showed good discrimination performance with a c-index of 0.80 (Table 4.5.2).

**Table 4.5.1 Baseline characteristics of study population**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (IQR) or n (%)</th>
<th>Number of patients included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) [median (IQR)]</td>
<td>71.1 (64.7-76.7)</td>
<td>872</td>
</tr>
<tr>
<td>Patency score [median (IQR)]</td>
<td>105.0 (70.0-147.5)</td>
<td>872</td>
</tr>
<tr>
<td>Number of blood pressure agents</td>
<td>2 (2 – 3)</td>
<td>863</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg) [median (IQR)]</td>
<td>152.0 (135.0-175.0)</td>
<td>857</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg) [median (IQR)]</td>
<td>80.0 (70.0-90.0)</td>
<td>857</td>
</tr>
<tr>
<td>Baseline eGFR (ml/min/1.73m²) [median (IQR)]</td>
<td>30.0 (19.5-43.3)</td>
<td>867</td>
</tr>
<tr>
<td>Baseline Proteinuria (g/day) [median (IQR)]</td>
<td>0.8 (0.2-1.2)</td>
<td>847</td>
</tr>
<tr>
<td>Male gender [n, (%)]</td>
<td>523 (60)</td>
<td>872</td>
</tr>
<tr>
<td>Revascularization [n, (%)]</td>
<td>150 (17.2)</td>
<td>872</td>
</tr>
<tr>
<td>Hypertension [n, (%)]</td>
<td>765 (93.1)</td>
<td>822</td>
</tr>
<tr>
<td>Coronary artery bypass grafting [n, (%)]</td>
<td>142 (16.3)</td>
<td>872</td>
</tr>
<tr>
<td>Angina [n, (%)]</td>
<td>294 (33.9)</td>
<td>868</td>
</tr>
<tr>
<td>Myocardial infarction [n, (%)]</td>
<td>247 (28.4)</td>
<td>869</td>
</tr>
<tr>
<td>Coronary artery disease [n, (%)]</td>
<td>447 (51.3)</td>
<td>872</td>
</tr>
<tr>
<td>Left ventricular failure [n, (%)]</td>
<td>173 (19.8)</td>
<td>872</td>
</tr>
<tr>
<td>Peripheral vascular disease [n, (%)]</td>
<td>319 (36.7)</td>
<td>869</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm [n, (%)]</td>
<td>132 (15.4)</td>
<td>859</td>
</tr>
<tr>
<td>Diabetes mellitus [n, (%)]</td>
<td>273 (31.3)</td>
<td>872</td>
</tr>
</tbody>
</table>

eGFR – estimated glomerular filtration rate; IQR – interquartile range

**Table 4.5.2 Risk factors for long-term clinical end-points**

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Median follow-up (months) (IQR)</th>
<th>Risk Factor</th>
<th>HR (95% CI)</th>
<th>P value</th>
<th>C-index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (n=641)</td>
<td>54.9 (20.2-96.0)</td>
<td>Age at Diagnosis</td>
<td>1.04 (1.03-1.05)</td>
<td>&lt;0.0001</td>
<td>0.80 (0.73-0.86)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Baseline eGFR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.98 (0.98-0.99)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Baseline proteinuria&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.13 (1.06-1.19)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Revascularization</td>
<td>0.68 (0.53-0.85)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Congestive heart failure</td>
<td>1.61 (1.30-1.98)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peripheral vascular disease</td>
<td>1.35 (1.14-1.60)</td>
<td>0.0007</td>
<td></td>
</tr>
<tr>
<td>CVE (n=319)</td>
<td>38.5 (14.8-75.8)</td>
<td>Baseline eGFR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.99 (0.99-0.99)</td>
<td>0.03</td>
<td>0.85 (0.76-0.92)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myocardial infarction</td>
<td>1.71 (1.33-2.20)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Congestive heart failure</td>
<td>1.57 (1.17-2.10)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peripheral vascular disease</td>
<td>Baseline eGFR*</td>
<td>Baseline proteinuria*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td>-----------------------------</td>
<td>---------------</td>
<td>----------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESKD (n=177)</td>
<td>46.0 (14.1-89.4)</td>
<td>0.93 (0.92-0.95)</td>
<td>1.20 (1.12-1.29)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CVE – cardiovascular event; eGFR – estimated glomerular filtration rate; ESKD – end stage kidney disease; HR – hazard ratio; IQR – interquartile range
*Per 1 unit increment (eGFR – per 1ml/min/1.73m²; proteinuria – per 1g/day)

Cardiovascular events

Out of the study population, 319 (36.6%) patients suffered a CVE, and 52 (6%) were fatal events. The incidence of CVE was 8.8 per 100 patient years. Median age of patients suffering their first CVE was 74.2 (68.4-79.2) years. Previous myocardial events and episodes of congestive heart failure were both strongly associated with CVE (MI: HR 1.71 [95% CI 1.33-2.20], p<0.0001; CHF: HR 1.57 [95% 1.17-2.10], p=0.003). Concurrent PVD also increased the risk of CVE (HR 1.28 [95% CI 1.01-1.62], p=0.04), but again there was no negative association with blood pressure. Conversely, better baseline renal function was protective against development of CVE (HR 0.99 [95% CI 0.99-0.99], p=0.03). This model showed a good discrimination performance with a c-index of 0.85 (Table 4.5.2).

End-stage kidney disease

In total, 177 (20.3%) patients reached ESKD, out of whom 131 (15.0%) started RRT while the remainder were managed conservatively. Incidence of ESKD was 4.2 per 100 patient years. Median age at reaching ESKD was 72.9 (66.4-78.5) years. Better baseline renal function was associated with reduced risk of progression to ESKD (HR 0.93 [95% CI 0.92-0.95], p<0.0001) while greater baseline proteinuria increased risk of ESKD (HR 1.2 [95% CI 1.12-1.29], p<0.0001). However, the c-index of this model was only 0.57, hence this model was not considered further (Table 4.5.2).

Individual Risk Calculator

The risk calculator depicted in Figure 4.5.1 computes overall and CVE-free survival at 1, 5 and 10-year intervals for patients utilizing the values of the variables that were significantly associated with study end-points (Table 4.5.3). As an example, an average patient on our database (Patient A: 70 years old, baseline eGFR 30 ml/min/1.73m², baseline proteinuria 0.5 g/day, past history of MI, CHF and PVD, non-revascularized) would have an overall 1-year survival of 75%, 5-year survival of 36% and 10-year survival of 8%. CVE-free survival would be 75% at 1 year, 48% at 5 years, and 20% at 10 years. Revascularization would change the overall survival to 89% at 1 year, 48% at 5 years and 17% at 10 years, while CVE-free survival would remain the same. A patient identical to our average patient but without any documented comorbidities (MI/CHF/PVD) (Patient B) was still observed to suffer a significant reduction of their overall long-term survival with equivalent results to revascularized Patient A: 1-year
survival 89%, 5-year survival 48%, 10-year survival 17%. However, in a 70-year old patient with a baseline eGFR of 20 ml/min/1.73m² and proteinuria of 1.0 g/day and with a past history of MI, CHF and PVD (Patient C), revascularization is seen not to exert any difference in overall or CVE-free survival (Overall survival: 1-year 75%, 5-year 36%, 10-year 8%; CVE-free survival: 1-year 75%, 5-year 48%, 10-year 20%).

Discussion:
To our knowledge this is the first study that illustrates how important long-term end-points in patients with ARVD can be predicted using a small number of easily obtainable variables. The risk calculator can be used as a bedside tool that can help clinicians evaluate the risk of mortality and CVE for individual patients, while inviting patients to participate in discussions about their care. As previously reported, the main determinants of long-term outcomes are traditional risk factors such as increasing age and cardiovascular comorbidities, together with eGFR and proteinuria, which act as surrogate markers of renal parenchymal viability and independent predictors of adverse events. Hence, strategies to optimize cardiovascular risk, mitigate systemic atherosclerosis and protect the renal parenchyma are of paramount importance in this patient population. These include multi-targeted medical therapy, smoking cessation, weight loss and optimal glycaemic control. The ‘optimal’ medical therapy regime for these patients remains undefined, but observational data supports the use of renin-angiotensin blockade, statins and antiplatelet therapy. Our risk calculator highlights that all patients with ARVD are at risk of significantly reduced long-term survival, even in the absence of confirmed extrarenal atherosclerosis. However, studies have indicated that ARVD patients without documented evidence of extra-renal atherosclerosis tend to be established less often on adequate vascular protective therapy than patients with documented co-existing coronary or cerebrovascular atherosclerosis. Risk quantification using this bedside tool may emphasize the importance of intensified multi-targeted vascular protective therapy in all patients with ARVD.

Our results demonstrate that revascularization could modulate long-term outcomes in certain patient phenotypes in this ARVD cohort; the unselected nature of our cohort makes our results more likely to be representative of ‘real world’ outcomes and as opposed to the results of randomized controlled trials. Indeed, both the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) and the Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trials have shown that revascularization does not confer any added benefit to optimal medical therapy in patients with ARVD who were recruited into these studies. These studies included few patients presenting with ‘high-risk’ features such as rapidly deteriorating renal function, flash pulmonary oedema or uncontrolled blood pressure. However, if patients with high-risk features are specifically studied, revascularization appears to confer benefit. A retrospective study conducted at our research centre looked at 237 patients extracted from the Salford Renovascular database with at least 50% RAS and one or more of the above ‘high-risk
Figure 4.5.1 Atherosclerotic renovascular disease risk calculator

![Risk Calculator for ARVD](image)

**Instructions**

Enter the following information. When you press the Calculate Risks button, the data you entered will be displayed in a pop-up window. Age and eGFR must be entered for other variables, enter values that are not '0'. Calculations are based on a 2-level risk hierarchy.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>eGFR (mL/min/1.73m²)</th>
<th>eGFR</th>
<th>Proteinuria (g/day)</th>
<th>Proteinuria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Revascularization (y/n if absent, t if present) Revasc: Myocardial infarction (y/n if absent, t if present) MI

Left ventricular failure (y/n if absent, t if present) LVF: Peripheral arterial disease (y/n if absent, t if present) PAD

Calculate Risks

Table 4.5.3 Predicted survival probabilities for revascularized and non-revascularized patients with different clinical phenotypes obtained using risk calculator.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>0.75</td>
<td>0.89</td>
<td>0.89</td>
<td>0.89</td>
<td>0.75</td>
<td>0.75</td>
</tr>
<tr>
<td>5 years</td>
<td>0.35</td>
<td>0.48</td>
<td>0.48</td>
<td>0.48</td>
<td>0.36</td>
<td>0.36</td>
</tr>
<tr>
<td>10 years</td>
<td>0.08</td>
<td>0.17</td>
<td>0.17</td>
<td>0.17</td>
<td>0.08</td>
<td>0.08</td>
</tr>
<tr>
<td>CVE-free Survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>0.75</td>
<td>0.75</td>
<td>0.89</td>
<td>0.89</td>
<td>0.75</td>
<td>0.75</td>
</tr>
<tr>
<td>5 years</td>
<td>0.48</td>
<td>0.48</td>
<td>0.65</td>
<td>0.65</td>
<td>0.48</td>
<td>0.48</td>
</tr>
<tr>
<td>10 years</td>
<td>0.20</td>
<td>0.20</td>
<td>0.39</td>
<td>0.39</td>
<td>0.20</td>
<td>0.20</td>
</tr>
</tbody>
</table>

*Patient A – 70 years old, baseline eGFR 30ml/min/1.73m², baseline proteinuria 0.5g/day, past medical history significant for myocardial infarction, congestive heart failure and peripheral vascular disease.

*Patient B – 70 years old, baseline eGFR 30ml/min/1.73m², baseline proteinuria 0.5g/day, with no past history of myocardial infarction, congestive heart failure or peripheral vascular disease.

*Patient C – 70 years old, baseline eGFR 20ml/min/1.73m², baseline proteinuria 1.0g/day, past medical history significant for myocardial infarction, congestive heart failure and peripheral vascular disease.
features. Around one-quarter (24%) of these patients were revascularized and clinical outcomes for these patients were compared to those of patients with high-risk features who were treated exclusively medically. Revascularization was associated with improved outcomes in patients with flash pulmonary oedema and in those with a combination of rapidly declining kidney function and uncontrolled hypertension. Another study from the same database investigated the effect of revascularization on 127 patients with more severe anatomical RAS (at least 70% RAS unilaterally or bilaterally) and similar high-risk presenting features. Results showed that ‘high-risk’ patients with rapidly deteriorating renal function, severe bilateral RAS and lower levels of baseline proteinuria gained benefit from revascularization.

With the declining interest in revascularization that followed publication of ASTRAL and CORAL, there is a real risk that opportunities for timely revascularization are being missed. This concern has fuelled research efforts to attempt to identify the subgroup of patients who are likely to respond positively to revascularization. Advanced non-invasive imaging techniques have been proposed as viable methods to determine the haemodynamic significance of a stenosis and the functional integrity of renal parenchyma. Studies have used the blood oxygen level dependent magnetic resonance imaging (BOLD-MRI) signal as a surrogate of renal cortical deoxyhaemoglobin or degree of tissue oxygenation (R*), and the magnitude of the response of medullary R* to a furosemide challenge has been suggested to reflect the degree of adaptive attenuation of oxygen consumption in viable renal parenchyma. A higher ratio of magnetic resonance imaging (MRI)-derived R* or three-dimensional parenchymal renal volume to isotopic single-kidney GFR has been found to be indicative of kidneys that show improvement in function post-revascularization. These studies forged the concept of ‘hibernating parenchyma’, viable renal parenchyma that has not yet undergone the irreversible changes associated with ARVD and prolonged ischaemia; consequently, the stenotic kidney maintains a normal volume, and retains the possibility to recover function post-revascularization. Other studies have suggested that novel biomarkers such as N-terminal pro-brain natriuretic peptide (NT-proBNP) can also help discriminate those patients who benefit from revascularization.

However none of these pilot studies have been validated in large trials and the techniques are not yet applicable to routine clinical practice. In addition, imaging techniques that are solely focused on the kidneys do not take the burden of extra-renal comorbidities into account. In view of this, there is an urgent need for a simple bedside tool that can simultaneously evaluate the viability of renal parenchyma and risk stratify patients according to extra-renal comorbidities. Our risk calculator in fact shows that revascularization can potentially modulate outcomes in patients with presumed better preserved renal parenchyma, as suggested by a higher baseline eGFR and lower proteinuria, in keeping with the ‘hibernating parenchyma’ hypothesis. Conversely, as expected, both co-existing extrarenal atherosclerosis and higher levels of proteinuria at baseline appear to eliminate any benefit derived from revascularization.
In our study there was no relationship between the severity of renal artery stenosis and clinical outcomes. A previous study carried out in the same unselected ARVD population also showed that patency score was not associated with mortality or CVE but was only associated with progression to ESKD (HR 0.95 [95% CI 0.90-0.98])\textsuperscript{31}. In contrast, a strong inverse relationship between stenosis severity and survival has been previously described, with a 4-year adjusted survival of 70% in patients with 50% RAS and 48% in those with ≥95% RAS\textsuperscript{1}. In a study mentioned above, bilateral ≥70% RAS was associated with increased risk of progression to ESKD and CVE\textsuperscript{16}. This apparently conflicting data highlights the fact that angiographic stenosis is a poor correlate of true haemodynamic significance and only very severe cross-sectional RAS of >70-80% have been shown to consistently be associated with reduced translesional pressure gradients or renal blood flow\textsuperscript{41}. Given that the median degree of RAS in our study population was 50% with a median patency score of 110, cardiovascular comorbidities and extent of renal parenchymal damage were of over-riding importance than RAS burden in determining long-term outcomes\textsuperscript{31}. It is noteworthy that neither systolic nor diastolic blood pressure were found to be important for any major outcome in the risk calculator. We believe that this is because our study cohort was based at a tertiary renal centre, the majority of cases having been referred primarily with CKD rather than for hypertension. We accept that the risk calculator might contain different variables if used to calculate risk in a population of ARVD patients derived from a specialist hypertension clinic.

Although both baseline renal function and degree of proteinuria were associated with progression to ESKD, the resulting model had a low predictive value. The yearly rate of progression to ESKD in our study was only around 4%, similar to that reported in ASTRAL. Indeed, it has been shown that while patients with ARVD have an increased risk of mortality and CVE\textsuperscript{3}, the average rate of loss of eGFR in an unselected ARVD population is equivalent to that reported in a non-ARVD CKD population, at around 1-2 ml/min/1.72m\textsuperscript{2}/year\textsuperscript{48}.

The Salford ARVD study recruited all unselected patients presenting with ARVD to a single centre over many years, with no exclusions, which is a strength, increasing the likelihood of generalizability of the study findings to other ARVD cohorts managed by renal centres. However, there are several limitations. Our findings are unlikely to be generalizable to primarily hypertensive (non-CKD) populations, and this was emphasized by the lack of importance of either systolic or diastolic blood pressure in any risk prediction model. Data collection was performed by different research fellows over three decades, thus introducing assignment bias. In addition, previous data has shown that both the therapeutic approach and the clinical phenotype of patients recruited into the study understandably changed over this lengthy time interval. Patients recruited into the study in recent years were more likely to be established on optimal medical therapy but concurrently, those referred for revascularization within the last few years tended to have more significant cardiovascular comorbidities\textsuperscript{39} and a greater likelihood of being ‘higher risk’ phenotypes. These changes may have introduced bias in the reported
incidence of adverse events in these patients, hence our ARVD calculator has a role in preventing potential underestimation of the beneficial effect of revascularization. As discussed above, the degree of stenosis reported in the database was determined by biplanar imaging studies without confirmation of haemodynamic significance of the stenosis. Variables that may have a role in risk prediction such as body mass index, smoking status, or kidney size were not included due to missing or unreliable data and it is possible that the addition of these variables could improve the predictive power of our risk calculator. A stepwise regression model was used in this analysis to objectively select the smallest useful number of variables that could be used to design the risk calculator. This method however may result in loss of important predictive information and potentially creates a biased multivariable model as it excludes potentially relevant but only marginally significant variables. There is now a need to externally validate the risk calculator in other data sets.

Despite these limitations this study illustrates how a small number of predictors of long-term outcomes in ARVD can be used to design a personalized clinical risk profile to help develop a more patient-centred approach to treatment. In addition, this risk calculator also has important implications for future research as it could be refined by future imaging techniques or novel biomarkers as they become available to help improve risk stratification in this heterogenous condition. It could also improve the design of future clinical trials by allowing selection of higher-risk patients for enrollment into studies.

**Conclusion:**

In this study a small number of variables were used to design a simple risk calculator to help predict long-term outcomes in patients with ARVD. This tool highlights the fact that most patients are at risk of reduced long-term survival, advocating the need for multi-targeted medical vascular protective therapy in all patients with ARVD. It may also help predict outcomes post-revascularization, thus encouraging a more individualized therapeutic approach and potentially facilitating patient selection for revascularization. This risk calculator requires further independent validation in other ARVD datasets.
References:


47. Murphy TP, Cooper CJ, Pencina KM, et al. Relationship of Albuminuria and Renal Artery Stent Outcomes: Results From the CORAL Randomized Clinical Trial (Cardiovascular Outcomes With Renal Artery Lesions). *Hypertension.* 2016;68(5):1145-1152.


Chapter 5 - Conclusion
5.1 Key results

Results Chapter 4.1: Three decades of atherosclerotic renovascular disease management – changing outcomes in an observational study

Following publication of ASTRAL and CORAL, fewer patients are being investigated for ARVD in our centre but these patients have more cardiovascular comorbidities.

This study investigated how landmark studies published in the field of ARVD have influenced management of this condition over a thirty-year period and explored whether these changes have been translated into measurable improvement in patient outcomes. The neutral results of recent large randomized controlled trials have led to a worldwide decline in both the number of renal artery imaging investigations performed and the number of patients referred for renal revascularization\(^1\)–\(^4\). Nonetheless, our results showed that there is a trend towards increased patient selection for revascularization, in light of observational evidence showing that revascularization may be of benefit in specific ‘high-risk’ subgroups\(^5\). Indeed, patients referred for revascularization at our centre post-publication of ASTRAL and CORAL tended to have a greater cardiovascular and comorbid burden than patients referred during earlier eras. There was a suggestion that improvements in medical therapy over the years may correlate with optimized baseline proteinuria, renal function and clinical outcomes, but this was less evident in the post-ASTRAL era due to the selection bias that characterizes this group. The results of this study emphasize the importance of vascular protective therapy as the mainstay of ARVD management and although it is clear that this has improved over the past three decades, there is still scope for improvement as all patients with ARVD should be administered adequate multi-targeted medical therapy.

Results Chapter 4.2: The importance of proteinuria and prior cardiovascular disease in all major clinical outcomes of atherosclerotic renovascular disease – a single-centre observational study

The main determinants of adverse clinical outcomes in ARVD are prior cardiovascular disease and intra-renal parenchymal damage manifest by greater proteinuria and reduced renal function.

This study provided unique insight into the determinants of long-term clinical end-points in patients with ARVD as it was based on our cohort of ARVD patients, perhaps the largest international cohort, and involved the longest follow-up of patients. Our results reinforced the fact that traditional cardiovascular risk factors such as older age, extra-renal atherosclerosis and congestive heart failure all contribute to adverse outcomes in ARVD. In addition, in line with results from other studies, markers of irreversible renal parenchymal injury such as higher degrees of baseline proteinuria and lower eGFR were also associated with adverse end-points\(^6\),\(^7\). Our results confirmed findings from earlier studies showing that patients established
on renin-angiotensin blockade and statins at time of diagnosis have a reduced long-term risk of death and progression to ESKD. Indeed, multi-targeted vascular protective therapy should be standard therapy in all patients with ARVD as it helps decrease systemic atherosclerotic burden and improve cardiovascular risk while mitigating intra-renal parenchymal injury. Our results however also showed that revascularization was associated with reduced risk of death and progression to ESKD in this unselected population of patients with ARVD, suggesting that intervention may have a therapeutic role alongside standard vascular protective therapy. This study highlighted the need to characterize the clinical phenotype of patients who may gain benefit from revascularization further.

Results Chapter 4.3: The effect of revascularization in patients with anatomically-significant atherosclerotic renovascular disease presenting with high-risk clinical features.

Revascularization may be of benefit in patients with anatomically significant RAS who present with rapidly deteriorating renal function, especially in the presence of severe bilateral ARVD or <1g/day proteinuria. In this study we discriminated further the clinical phenotype of the patient subgroup that had previously been shown to gain benefit form revascularization, by uniquely applying tighter selection criteria for our definition of ‘high-risk’. Indeed, using a more stringent definition only 15% of all patients with ARVD recruited onto the Salford ARVD study met our definition of ‘high-risk’ compared to 28% in the earlier study. Whilst the limited number of patients included in this study had an impact on the strength of statistical associations, our results suggested that patients with presumed haemodynamically-significant ARVD in the context of well-preserved renal parenchyma (as represented by low-level proteinuria) may gain benefit from revascularization.

Our study strengthened the hypothesis that clinical outcomes post-revascularization are highly dependent on the degree of irreversible damage within the renal parenchyma. A previous observational study showed that in patients with at least 50% unilateral or bilateral RAS, a high baseline three-dimensional parenchymal renal volume (PV) (measured by magnetic resonance imaging) to single-kidney isotopic GFR (isoSK-GFR) (measured by standard radioisotopic methodology) ratio was predictive of improved renal function post-revascularization (eGFR increasing by 6.3 +/-2.0 ml/min in high PV:isoSK-GFR ratio patients versus -0.9 +/-0.4 ml/min in low or normal PV:iso-SKGFR ratio patients, p=0.002). Both low levels of proteinuria and a high three-dimensional parenchymal renal volume are considered surrogate markers of well-preserved, less irreversibly damaged renal parenchyma. This concept was subsequently investigated in a prospective pilot study that looked at the ratio of the severity of ischaemia within a stenotic kidney, an adaptive response to reduced renal blood flow and thus a marker of metabolically active renal tissue (measured by BOLD-MRI, quantified as R2*), to isoSK-GFR.
Results showed that those kidneys that improved post-revascularization had higher R2*:isoSK-GFR ratio compared to kidneys that remained stable, those that deteriorated or controls (p=0.003). This ratio reflects hypoxic but well-preserved renal tissue distal to a haemodynamically-significant stenosis that is potentially salvageable post-revascularization. Recently published data has similarly showed that kidneys with improved function post-revascularization had a three-fold higher PV:isoSK-GFR ratio compared to kidneys that deteriorated or showed no change in function, and again a high PV:isoSK-GFR ratio was predictive of an improvement in function post-revascularization. Interestingly this effect was even seen in kidneys with very low isoSK-GFR (<10ml/min); a similar improvement in renal function in patients with advanced CKD was previously noted in an observational study.

Clinical presentation with flash pulmonary oedema (FPE) is at present the only Class I indication for revascularization, and it has previously been shown that patients presenting with FPE demonstrated improved survival post-revascularization compared to medically-managed patients (HR 0.43, 95% Confidence interval 0.20-0.91, p=0.01). Whilst the association between revascularization and clinical end-points did not reach statistical significance in our study, hazard ratios were still <1.0 and this is probably an effect of the small sample size. We still recommend that revascularization should be considered in patients with ARVD presenting with FPE.

Results Chapter 4.4: Association of novel biomarkers with major clinical outcomes in atherosclerotic renovascular disease.

A panel of novel biomarkers may have an incremental risk predictive value when used in combination with traditional risk factors and patients with NT-proBNP levels ≥300pg/ml may gain benefit from revascularization.

Novel biomarkers have been shown to be independently associated with adverse outcomes in CKD. Several studies have investigated their incremental risk predictive value when used in combination with traditional risk factors to evaluate whether they enhance existing risk stratification tools. However the value of novel biomarkers in the context of ARVD is relatively unexplored. This study was the first to analyze the correlation between novel biomarkers and long-term adverse outcomes in a population of patients with ARVD and their additive risk predictive value. Results showed that the use of an extensive panel of diverse biomarkers (fibroblast growth factor-23 [FGF-23], Cystatin C, myeloperoxidase [MPO], kidney injury molecule-1 [KIM-1], neutrophil gelatinase-associated lipocalin [NGAL], high-sensitivity cardiac troponin T [hs-cTNT], N-terminal pro-brain natriuretic peptide [NT-proBNP] and anti-apolipoprotein A-1 Immunoglobulin G [anti-ApoA-1 IgG]) in conjunction with traditional risk factors such as cardiovascular comorbidities, baseline renal function and proteinuria, can improve risk prediction. In addition, results also suggest a potential role for novel biomarkers in patient selection for revascularization, as patients with NT-proBNP levels above the standard
A cutoff of 300 pg/ml had a reduced risk of all adverse events post-revascularization. Given the limited sample size, these results require confirmation in larger multi-centre trials.

**Results Chapter 4.5: Design of a clinical risk calculator for major clinical outcomes in atherosclerotic renovascular disease.**

**A small number of readily available variables can be used to design a simple risk calculator that can help predict clinical outcomes and encourage a patient-specific therapeutic approach.**

In an era characterized by increasing interest in ‘precision medicine’ and patient risk stratification, accurate prognostication and outcome prediction in the context of ARVD remain an unmet clinical challenge. Literature suggests that individualized risk prediction improves patient outcomes due to a combination of improved adherence to treatment guidelines, and increased shared decision-making. Advances in information technology have enabled easy access to a number of risk calculator tools\(^{21-23}\). Whilst the principal determinants of adverse outcomes in ARVD have already been described, this was the first study that combined them all into a simple risk calculator. This tool can also be used to explore how revascularization can modulate outcomes, thus potentially facilitating patient selection for revascularization. This risk calculator requires external validation in other ARVD datasets.
5.2 Limitations

Limitations pertaining to each study have been discussed individually in the respective results chapters hence this section will acknowledge other general limitations of this research project.

Although data collection for the Salford ARVD Study has been performed longitudinally, all the analyses included in this thesis have been designed retrospectively. As a result, variables that would have been of interest in this thesis but which were not included in the original database were not available for analysis. These variables include kidney size, body mass index, smoking status and echocardiographic data. The retrospective nature of the analyses also means that no sample size calculations were performed as eligible patients were identified from the existing database. This limited the number of patients that could be recruited into the studies and potentially underpowered the analyses.

Patients were recruited into the database from Salford Royal NHS Foundation Trust and affiliated district general hospitals and hence these studies are all single-centre analyses. Salford Royal NHS Foundation Trust was a major recruiting site for important RCTs and as a result there is an inherent interest in this condition amongst clinicians working in this hospital. This may have introduced referral bias as consultant practice in referring for investigation of ARVD varies between different hospitals, hence the patients recruited onto the database may not be representative of the generalized ARVD population. Disease severity was reported by two specialist radiologists over the entire follow-up period, however inter-observer and intra-observer variability were not assessed and these may have changed over this prolonged period. Moreover, diagnosis of ARVD was established using three different imaging techniques throughout the whole study; renal digital subtraction angiography was used in the early years, while computed tomography angiography (CTA) and magnetic resonance angiography (MRA) were used in more recent years. Neither did the analyses statistically adjust for longitudinal fluctuations in medication and blood pressure control. Other potential hidden confounders include alternative primary causes of renal disease, although patients with documented glomerular diseases were eliminated from the database at the outset and diabetic patients with ≥1g/day proteinuria and diabetic retinopathy were excluded from analyses. While a number of potential clinically relevant associations between risk factors or variables and clinical end-points were identified in this thesis, the retrospective analyses presented in this thesis do not explore the aetiology or causal effect of these associations24.

Specific aspects of the statistical methodology are also prone to potential shortcomings. Simple linear regression was used to calculate eGFR slope; while this method is considered a valid method for estimating eGFR slope it can be relatively insensitive and can overestimate the proportion of patients with true positive slopes25. Other more accurate tests, such as Bayesian
linear mixed effect models, were not used in this thesis\textsuperscript{25,26}. Laboratory methods for estimation of proteinuria changed over the study follow-up period. Although contemporary spot urine protein : creatinine ratios correlated well with the gold standard 24 hour urine protein excretion the strength of this correlation is influenced by the timing of the spot urine collection, as well as by the degree of proteinuria and creatinine clearance\textsuperscript{27}. Only patients with complete datasets were included in analyses. Given the small number of patients with missing data, sensitivity analyses to determine whether data was missing at random were not performed, providing another potential source of bias.
5.3 Strengths

Despite the limitations described above, the Salford ARVD database is one of the largest international non-RCT ARVD populations with the longest follow-up reported in the literature. The single-centre design enabled accurate verification of clinical end-points thus creating a robust dataset. The cohort studies described in this thesis provide a feasible way of investigating the association between multiple risk factors and long-term clinical end-points. Where appropriate, we considered clinical relevance of these associations by exploring improvements in risk discrimination and risk reclassification, and by designing a simple risk calculator tool that can be easily used at the bedside. The lack of those tight inclusion and exclusion criteria typically associated with clinical trials facilitates extrapolation of these results to the general population of patients with ARVD and thus enhances applicability to routine clinical practice.
References:


Chapter 6 - Suggestions for future work
The results of this thesis have the potential to impact current routine clinical practice, but there are also clear opportunities for further research.

**National and International ARVD Registries**
The data presented in this thesis provide evidence that revascularization can be of benefit in subgroups of ARVD patients presenting with ‘high-risk’ clinical features. These results require validation in larger multi-centre studies together with the need to further research the underlying pathophysiology and mechanistic details. Given that only a small proportion of patients with ARVD present with such ‘high-risk’ features, a protocol driven study is unlikely to recruit enough patients over a realistic timeframe. Hence there is a need for both national and international prospective ARVD registries; this would allow time-efficient and cost-effective data collection and analyses across multiple sites. Health registries are strong epidemiological tools that can facilitate both prospective and retrospective research and which have led to significant improvements in other medical and surgical fields\(^1\)–\(^4\).

We suggest that a select group of ‘high-risk’ patients with ARVD with a clinical phenotype as described in Chapter 4.3 could be feasibly recruited onto the national RareRenal registry (RaDAR). This would incorporate a ‘high-risk ARVD’ registry into the NIHR Clinical Research Network Portfolio, stimulate interest about this reasonably rare clinical phenotype and facilitate sharing of knowledge at a national level.

**The role of a panel of novel biomarkers in risk prediction in ARVD – translation into clinical practice.**
We demonstrated that a panel of novel biomarkers could potentially improve risk prediction in our ARVD population. Before these findings can be translated into clinical practice, well-powered prospective studies need to be performed to confirm how these investigations influence treatment decisions and patient outcomes. A cost-effectiveness analysis may also be necessary; all patients with a diagnosis of ARVD warrant multi-targeted medical treatment hence it needs to be established whether these costly investigations can help identify those patients who benefit from more intensive monitoring, and whether this can prevent adverse outcomes.

**Use of NT-proBNP levels to predict outcome post-revascularization**
In chapter 4.4 we showed that revascularized patients with a baseline NT-proBNP level \(\geq 300\) pg/ml appeared to have better clinical outcomes compared to patients with lower levels of this biomarker. The number of patients recruited into this specific study was limited and hence further work is needed to validate our results, ideally in larger multi-centre trials. A cost-benefit analysis may be less relevant if these validated studies confirm that revascularization, a costly and potentially hazardous intervention, can be avoided in patients with low levels of NT-proBNP but targeted for use in those with higher biomarker levels.
Neither the RAS-CAD study nor the cardiac MRI sub-study of ASTRAL have confirmed that revascularization exerts an impact on cardiac structure, but both of these studies have been performed in predominantly low-risk populations\(^5,6\). Nonetheless, there are reports of dramatic improvement in echocardiographic parameters following revascularization in patients presenting with acute flash pulmonary oedema\(^7\). In view of this, a prospective study design that includes recording of serial echocardiographic data could strengthen the findings presented in our study while providing more insight into the pathophysiology of this association.

**External validation of ARVD risk calculator**

In Chapter 4.5 we proposed that a novel ARVD risk calculator based on a small number of easily obtainable variables could help predict long-term clinical outcomes for patients with ARVD, potentially facilitating the selection of patients who gain benefit from revascularization. This risk calculator has been developed in a single-centre population of ARVD patients and so it requires external validation in other datasets. At present hope is to undertake external validation in the ASTRAL trial dataset. Introduction of this risk calculator into clinical practice would provide data on whether better risk stratification in ARVD impacts positively on patient management and clinical outcomes.

**Design of a randomized controlled trial investigation the effect of revascularization in ARVD patients with severe anatomical disease and high-risk clinical features**

A posthoc analysis of the ASTRAL trial showed that there was no significant difference in primary outcome between 163 patients with severe anatomical disease defined as at least 70% renal artery stenosis bilaterally or unilaterally to a single functioning kidney, and patients with less severe degrees of stenosis (\(p=0.23\))\(^8\). On the other hand, results from our observational study described in chapter 4.3 suggest that revascularization may be associated with reduced progression to ESKD in patients with bilateral \(\geq 70\%\) RAS and at least one co-existing high-risk clinical feature such as uncontrolled hypertension, flash pulmonary oedema and rapidly deteriorating renal function (HR 0.35 [0.15-0.84], \(p=0.02\)). The beneficial impact of revascularization appeared enhanced in patients who in addition to this high-risk clinical phenotype also had \(<1\text{g/day} \) proteinuria at time of diagnosis. Conversely, there was no statistically significant association between revascularization and outcomes in control patients who had the same severity of RAS but who were otherwise clinically stable\(^9\). These results probably mirror the under-representation of truly ‘high-risk’ risk patients in the ASTRAL trial. We propose that results from our observational study highlight the need for a randomized controlled trial investigating the role of revascularization in a selected group of ‘high-risk ARVD patients’ with anatomically severe disease. Inclusion criteria would be as described above in our study while patients with bilateral renal artery occlusion or unilateral occlusion and contralateral RAS \(<70\%\) would be excluded. The study population would be randomized to revascularization or conservative treatment however both study arms would receive intensive vascular protective
therapy. Primary end-points would be mortality, progression to ESKD, cardiovascular events or a composite of these events. Although results of such as RCT would be highly desirable, we foresee difficulties with ethical approval and recruitment. Randomization of an ARVD with flash pulmonary oedema to conservative management may not be ethically appropriate given that revascularization carries a Class I recommendation in this clinical scenario. In addition, the neutral results of ASTRAL and CORAL have tempered enthusiasm for revascularization thus limiting the academic or industry interest that such a study would attract. Nonetheless we hope that our results in conjunction with future epidemiological analyses derived from registry data continue to fuel interest for further research in this field.
References


Appendix 1

Instructions: Copy the following script into a textfile and save with the '.html' file extension.

```html
<html>
<meta name="viewport" content="width=device-width, initial-scale=1">
<link rel="stylesheet" href="https://www.w3schools.com/w3css/4/w3.css">
<link rel="stylesheet" href="https://fonts.googleapis.com/css?family=Raleway">
<link rel="stylesheet" href="https://cdnjs.cloudflare.com/ajax/libs/font-awesome/4.7.0/css/font-awesome.min.css">

<head>
<title>Form Example</title>
<style>
body,h1 {font-family: "Raleway", Arial, sans-serif; margin:12px;}
h1 {letter-spacing: 6px}
.w3-row-padding img {margin-bottom: 12px}
input[type=text], select {
  width: 10%;
  padding: 12px 12px;
  margin: 12px 4;
  display: inline-block;
  border: 1px solid #ccc;
  border-radius: 4px;
  box-sizing: border-box;
}
input[type=submit] {
  width: 100%;
  background-color: #4CAF50;
  color: white;
  padding: 14px 20px;
  margin: 8px 0;
  border: none;
  border-radius: 4px;
  cursor: pointer;
}
```
function display() {
    var a = (parseInt(document.form1.age.value)) ;
    var b = parseInt(document.form1.egfr.value);
    var c = parseInt(document.form1.proteinuria.value);
    var d = parseInt(document.form1.revascularization.value);
    var e = parseInt(document.form1.mi.value);
    var f = parseInt(document.form1.lvf.value);
    var g = parseInt(document.form1.pad.value);

    A = a;
    B = b;
    var C = 0; if (c > 0) C = c;
    var D = 0; if (d > 0) D = d;
    var E = 0; if (e > 0) E = e;
    var F = 0; if (f > 0) F = f;
    var G = 0; if (g > 0) G = g;

    survScore = 0.03569*A - 0.01767*B + 0.11832*C - 0.39351*D + 0.47349*F + 0.30001*G;
    if (survScore >= 2.4648) surv1 = 0.75;
    else if (survScore < 2.4648) surv1 = 0.89;
    else if (survScore < 1.9628) surv1 = 0.96;
    if (survScore >= 2.4648) surv5 = 0.36;
    else if (survScore < 2.4648) surv5 = 0.48;
    else if (survScore < 1.9628) surv5 = 0.71;
    if (survScore >= 2.4648) surv10 = 0.08;
    else if (survScore < 2.4648) surv10 = 0.17;
else if (survScore < 1.9628) surv10 = 0.5;

var cveScore = 0.53452*E + 0.44827*F + 0.24749*G - 0.00721*B;
if (cveScore >= 0.228) cvefree1 = 0.75;
else if (cveScore < 0.228) cvefree1 = 0.89;
else if (cveScore < -0.14875) cvefree1 = 0.96;
if (cveScore >= 0.228) cvefree5 = 0.48;
else if (cveScore < 0.228) cvefree5 = 0.65;
else if (cveScore < -0.14875) cvefree5 = 0.75;
if (cveScore >= 0.228) cvefree10 = 0.2;
else if (cveScore < 0.228) cvefree10 = 0.39;
else if (cveScore < -0.14875) cvefree10 = 0.54;

DispWin = window.open("','NewWin', 'toolbar=no,status=no,width=400,height=200')
message = "<ul><li>Overall Survival at 1 Year: " + surv1;
message += "<li> Overall Survival at 5 Years: " + surv5;
message += "<li>Overall Survival at 10 Years: " + surv10;
message += "<li> " + ";
message += "<li>CV Event-Free Survival at 1 Year: " + cvefree1;
message += "<li>CV Event-Free Survival at 5 Years: " + cvefree5;
message += "<li>CV Event-Free Survival at 10 Years: " + cvefree10 + "</ul>";
DispWin.document.write(message);
}
</script>
</head>
<body>
<header class="w3-container w3-teal">
  <h1>Risk Calculator for ARVD</h1>
</header>

<h1>Instructions</h1>
Enter the following information. When you press the Calculate Risks button, the data you entered will be displayed in a pop-up window. Age and eGFR must be entered; for other variables, enter values that are not '0'. Calculations are based on a 3-level risk hierarchy.
<form name="form1">
  <p>
    <b>Age</b> (years) <input TYPE="TEXT" NAME="age" placeholder="Age">
<b>eGFR</b> (mL/min/1.73m<sup>2</sup>) <input TYPE="TEXT" NAME="egfr" placeholder="eGFR">

<b>Proteinuria</b> (g/day) <input TYPE="TEXT" NAME="proteinuria" placeholder="Proteinuria">

<b>Revascularization</b> (0 if absent, 1 if present) <input TYPE="TEXT" NAME="revascularization" placeholder="Revasc.">

<b>Myocardial Infarction</b> (0 if absent, 1 if present) <input TYPE="TEXT" NAME="mi" placeholder="MI">

<b>Left ventricular failure</b> (0 if absent, 1 if present) <input TYPE="TEXT" NAME="lvf" placeholder="LVF">

<b>Peripheral arterial disease</b> (0 if absent, 1 if present) <input TYPE="TEXT" SIZE="20" NAME="pad" placeholder="PAD">

<input TYPE="BUTTON" VALUE="Calculate Risks" onClick="display();"></p>
</form>
</body>
</html>
Appendix 2

Please refer to the enclosed USB flash drive