Original Paper

Three Decades of Atherosclerotic Renovascular Disease Management – Changing Outcomes in an Observational Study

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Key Words

Atherosclerotic renovascular disease • Chronic Kidney Disease • Epidemiology • Renal revascularization • Vascular protective therapy

Abstract

Background/Aims: Optimized medical therapy has improved cardiovascular outcomes in the general population. To investigate whether changes in the management of atherosclerotic renovascular disease (ARVD) have had an impact on clinical outcomes. **Methods:** Recruitment into this single-center 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. **Conclusions:** Although fewer patients are being investigated for ARVD in our center, 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.

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Introduction

Atherosclerotic renovascular disease (ARVD) frequently co-exists with cardiovascular disease in patients with systemic atherosclerosis [1, 2]. 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 [3]. 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 [4], may improve clinical outcomes in patients with ARVD [5-7]. 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' ($\geq 10\%$ decrease in renal length, $\geq 100\%$ increase in serum creatinine or $\geq 50\%$ decrease in creatinine clearance) during up to 4 years follow-up [8], 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 [9].

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 [10, 11].

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 center database in which the phenotype of ARVD patients has been recorded in detail.

Materials and Methods

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 center (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 ($\mu\text{mol/L}$) 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 [12, 13] at time of entry into the database. Renal revascularization was performed either in accordance with physician preference or after entry into a randomized trial [4,

14]. 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 [15]

(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 [16-18]), 2001-2004 (Group 2; studies advocating benefits of medical therapy [5, 19]), 2005-2008 (Group 3; main ASTRAL recruitment period[14]) and 2009-2014 (Group 4; post-ASTRAL era [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 [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 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, $p = \text{non-significant}$). 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 prescribed >3 anti-hypertensive agents (31% in Group 1 compared to 49% in Group 2, $p < 0.0005$),

Table 1. Baseline characteristics for whole cohort and for the four groups

	All n=872	1986-2000 Group 1 n=265	2001-2004 Group 2 n=235	2005-2008 Group 3 n=287	2009-2014 Group 4 n=85	p-value	Stat test
Median age [IQR] [years]	71.6 [65.6-77.0]	68.3 [61.9-74.2]	72.9 [67.4-77.8]	72.5 [66.9-77.9]	70.4 [63.3-77.8]	<0.0005*	KW
Male [%]	60.0	54.7	65.0	61.1	58.8	0.13	X ²
Diabetic [%]	31.3	21.5	38.3	34.1	32.9	<0.0005*	X ²
CAD [%]	51.3	47.5	53.6	47.7	68.2	0.001^	X ²
CHF [%]	20.0	26.8	19.9	12.0	26.5	0.001^	X ²
FPE [%]	6.8	7.9	6.0	4.9	11.8	0.023^	X ²
PVD [%]	46.2	44.2	52.3	44.9	40.0	0.138	X ²
Median SBP [IQR] [mmHg]	150 [135-170]	160.0 [144.0-190.0]	147.5 [132.0-168.0]	147.0 [128.0-168.0]	158.0 [142.0-180.0]	<0.0005*	KW
Median DBP [IQR] [mmHg]	80.0 [69.0-86.0]	85.0 [80.0-94.9]	80.0 [70.0-87.0]	75.0 [65.0-84.3]	72.0 [62.0-86.0]	<0.0005*	KW
Median Patency Score [IQR]	115.0 [80.0-150.0]	100.0 [90.0-150.0]	110.0 [80.0-150.0]	115.0 [75.0-150.0]	120.0 [60.0-150.0]	0.849	KW
>60% unilat [%]	46.7	49.6	50.5	41.4	45.6	0.147	X ²
>60% bilat [%]	16.7	14.7	14.9	19.5	18.8	0.362	X ²
RAB [%]	49.6	30.8	49.8	61.0	69.4	<0.0005*	X ²
B-blocker [%]	37.0	29.7	38.5	41.0	42.9	0.024	X ²
≥ 3 agents [%]	47.2	31.7	49.4	54.7	64.7	<0.0005*	X ²
Aspirin [%]	54.2	52.1	59.3	53.2	50.0	0.306	X ²
Statin [%]	54.8	20.2	61.9	75.4	74.1	<0.0005*	X ²
Proteinuria [g/24hr] [IQR]	0.5 [0.2-1.0]	0.9 [0.4-1.5]	0.4 [0.2-1.0]	0.6 [0.2-1.1]	0.4 [0.1-1.1]	<0.0005*	KW
Median baseline eGFR [IQR] [ml/min/1.73m ²]	32.7 [23.0-44.7]	27.0 [12.7-43.2]	29.4 [17.6-41.4]	32.8 [22.9-43.9]	34.9 [25.8-50.3]	<0.0005§	KW
Revascularization [%]	17.2	22.6	14.9	13.9	17.6	0.008**	X ²
Median Follow-up [IQR] [months]	54.9 [20.2-96.2]	44.9 [12.9-112.4]	58.4 [22.1-100.0]	68.5 [36.0-97.2]	21.7 [12.1-56.6]	<0.0005	KW

*between Group 1 and Group 2; §between Group 3 and Group 4; ^between Group 1 and Group 3

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 (figure 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 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 ($0.98 \text{ ml/min/1.73 m}^2/\text{year}$ across all four groups, table 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; figure 2). 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 com-

pared 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 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 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

Table 2. Percentage of ARVD patients with and without documented macrovascular disease (MVD) on vascular protective therapy

	Percentage of ARVD patients without confirmed MVD on vascular protective therapy* at baseline	Percentage of ARVD patients with confirmed MVD on vascular protective therapy* at baseline
Group 1	65.91	83.62
Group 2	80.70	90.45
Group 3	90.00	93.91
Group 4	82.35	97.06

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

Fig. 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 3. Rate of eGFR decline calculated from slope of linear regression for the whole cohort and the individual groups

	All n=872	1986-2000 n=265	2001-2004 n=235	2005-2008 n=287	2009-2014 n=85	p- value	Stat test
Median eGFR slope [ml/min/1.73m ² /year] (across all four groups)	-0.98 [-2.60-0.52]	-1.52 [-3.45- -0.03]	-1.00 [-2.44-0.72]	-0.71 [-2.23-0.52]	-1.09 [-3.60-2.20]	0.181*	KW

Table 4. Median time to end-points for each group and for cohort as a whole (in months) obtained from non-adjusted Kaplan-Meier curves

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

* Adjusted for death

Fig. 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).

the post-ASTRAL cohort. However, the proportion of registered ARVD patients who underwent 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).

Table 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.

Group	Death			CVE*			ESKD*			Any		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
2	0.71	0.057-0.89	0.003	1.30	0.94-1.79	0.116	0.81	0.537-1.23	0.327	0.86	0.7-1.08	0.24
3	0.54	0.42-0.69	<0.0005	1.35	0.97-1.87	0.079	0.49	0.30-0.80	0.004	0.84	0.67-1.05	0.127
4	0.84	0.54-1.3	0.432	0.872	0.47-1.62	0.665	0.76	0.32-1.80	0.534	0.76	0.50-1.16	0.209

Fig. 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.

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 center 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. This suggests that in the present era, more 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 [24] or irreversible renal parenchymal injury [25]. 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 led to 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 [26].

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 [27, 28]. 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 center 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-center 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 co-morbidity 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, al-

though we would assume that there was a predominance of cardiovascular deaths in this ARVD population in keeping with evidence from the literature [29]. 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.

Disclosure Statement

None declared.

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