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Dispelling the myth: the use of renin–angiotensin blockade in atheromatous renovascular disease

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Abstract

Background. Many physicians retain reservations regarding the routine prescription of renin–angiotensin blockade (RAB) in patients with atheromatous renovascular disease (ARVD). Conversely, these patients are in most need of the cardio- and renal protection offered by RAB. This reservation is mostly because of fear of precipitating acute renal deterioration. We aimed to study whether RAB can be used safely in ARVD patients and whether it altered their outcome.

Methods. Prospective observational study of all ARVD patients presenting to our tertiary referral centre from 1999–2009. Data capture included usage and tolerability of RAB, and correlation with endpoints of cardiovascular events, dialysis or death.

Results. Six hundred and twenty-one subjects were available for analysis. Mean age (SD) of the cohort was 71.3 (8.8) years, median (interquartile range) follow-up 3.1 (2.1, 4.8), range 0.2–10.61 years. Seventy-four patients had an intolerance to RAB at study entry. When utilized prospectively, RAB was tolerated in 357 of 378 patients (92%), and this was even seen in 54/69 (78.3%) patients with bilateral >60% renal artery stenosis (RAS) or occlusion. Patients (4/21) who were intolerant of RAB during follow-up (and 12 retrospectively intolerant), underwent renal revascularization which facilitated safe use of these medications post-procedure. On multivariate time-adjusted analysis, patients receiving RAB were significantly less likely to die ($P = 0.02$).

Conclusion. RAB is well tolerated even in patients with bilateral severe RAS and reduced mortality in a large group of ARVD patients. We recommend all ARVD patients be considered for RAB therapy unless an absolute contra-indication exists. Intolerance of these agents due to renal dysfunction should be considered an emerging indication for renal revascularization to facilitate their re-introduction.

Keywords: angiotensin-converting enzyme inhibitors; angiotensin receptor blockers; atheromatous renovascular disease; cardiovascular events; dialysis

Introduction

Atheromatous renovascular disease (ARVD) is a common condition, associated with ageing and other vascular risk factors with an incidence of 3.09 cases per thousand patient-years in elderly US citizens [1]. It is frequently associated with hypertension and chronic kidney disease (CKD) [2, 3] and is characterized by the presence of other extra-renal atheromatous disease. As a result of this atherosclerotic burden and associated co-morbidities, patient prognosis can be poor. Medicare data shows that ARVD patients have a three times greater risk of mortality than non-ARVD counterparts [1], and ARVD patients on dialysis programmes have an annual mortality rate of 36% [2].

There is robust evidence that renin–angiotensin blockade (RAB) with angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) is invaluable in CKD [4]. There is consensus that ACE-Is/ARBs have specific renoprotective effects, and guidelines endorse the view that these are the drugs of choice for the treatment of hypertension in renal disease [5]. Randomized control trials (RCTs) of patients with CKD, particularly those with proteinuria, provide evidence that ACE-I/ARB treatment offers significant renal protection in addition to attributable blood pressure lowering [6, 7]. American, British and European guidelines [6, 8-11] all encourage the use of ACE-I/ARB as first line therapy to reduce proteinuria and retard the progression of CKD in both diabetic and non-diabetic patients as Level 1 evidence.

Priorities in the management of ARVD are to halt the progression of renal impairment, control hypertension and reduce cardiovascular risk. As patients with ARVD often have cardiac structural abnormalities [12], coronary artery disease [13], congestive cardiac failure (CCF) [14] and proteinuria [15], there are multiple reasons in which CKD patients can benefit from RAB as shown in the HOPE [16], EUROPA [17] and PEACE [18] studies. These agents can

improve blood pressure in ARVD after several other classes of anti-hypertensives have failed [19], and this benefit is noticed even at low doses. ACE-I/ARB may even be better tolerated than other anti-hypertensives [20, 21] in this patient group. Sub-group analyses of the HOPE [22, 23] and EUROPA [24] studies have shown that ACE-Is are effective in preventing cardiovascular events (CVEs) in individuals with estimated glomerular filtration rate (eGFR) <60 mL/min, without an increased risk of precipitating acute kidney injury.

However, evidence points to under-utilization of ACE-I/ARB in patients with ARVD because of concerns regarding their safety in respect to renal complications (deteriorating renal function and/or hyperkalaemia) [25, 26]. The summary of product characteristics (SPCs) for ACE-I and ARBs states that they are contra-indicated in bilateral significant renal artery stenosis (RAS) or significant RAS in a solitary kidney [27]. As such, we believe that ACE-I and ARBs may be under-prescribed in a group of patients who may benefit most from the cardiac and renal protection conferred.

Aims

Firstly, we wished to determine the use and tolerance of ACE-I/ARB therapy in a large prospective cohort of ARVD patients with CKD and hypertension.

Secondly, we aimed to analyse the outcomes of new CVEs, progression to dialysis and death according to whether patients received RAB therapy or not.

Materials and methods

Data from all patients with ARVD presenting to our renal centre (catchment population for renal referrals 1.55 million) have been prospectively entered into a renovascular database since 1999. We analysed the data collected from 1999 to February 2009. All severities of ARVD have been included, those with RAS <60%, significant RAS >60% and unilateral or bilateral renovascular disease. The baseline date was taken as the date of the initial angiographic study confirming ARVD. Baseline clinical data (e.g. smoking status, previous CVE), laboratory values (e.g. creatinine, eGFR, proteinuria) and medication were recorded. If patients were previously on RAB but not on it at baseline due to intolerance, this was recorded as a retrospective intolerance to RAB.

Follow-up was conducted on an annual basis, as part of the patient's routine clinical visit to the renal outpatients and interrogating the electronic records for any hospital admissions in the interim. The majority of patients were seen in a dedicated renovascular clinic, but others were seen regularly in general nephrology clinics. Data were inputted annually on the database to update cardiovascular and renal outcome. Where applicable, outpatient notes from the surrounding hospitals were obtained.

Annual follow-up data included any usage of ACE-I/ARB, intolerance of these drugs and recording endpoints of CVEs, dialysis or mortality.

eGFR was calculated with the Modification of Diet in Renal Disease formula and proteinuria values were expressed in grams per day as the majority of proteinuria values were recorded as such. In more recent patients, proteinuria values were converted from Urine protein creatinine ratios (g/mol) to grams per day to enable comparability of data. The severity of proximal renovascular lesions was estimated by a residual patency score of the proximal renal arteries whereby normal = 2.0; unilateral occlusion = 1.0, with degrees of stenosis ranging between 0 and 2 [28]. The lower the score, the worse the degree of stenosis.

Hypertension was defined as a blood pressure >140/90 on two or more occasions and needing anti-hypertensive medication to obtain better control. A new CVE was defined as new onset angina, ischaemic heart disease (IHD), myocardial infarction, coronary or peripheral revascularization, hospitalization for congestive cardiac failure (CCF), peripheral vascular disease (PVD) or cerebrovascular accident/transient ischaemic attack in the study period.

Where an intolerance or side effect to ACE-I/ARB was noted, the case records were interrogated to assess the nature of the intolerance (e.g. acute deterioration of renal function).

The STROBE recommendations for reporting of observational studies were adhered to when preparing this paper [29].

Statistics

The results are expressed as mean and SD for normally distributed, and median and interquartile range (IQR) for non-normally distributed data. Categorical data are expressed as a number with the percentage of the total complete entries in that group. Differences in clinical and biochemical risk factors of a continuous nature were tested with analysis of variance when the mean and median were similar or by the non-parametric Mann–Whitney *U*-test in the case of non-normally distributed variables. Quantitative variables were compared using the χ^2 test.

The chief outcomes of CVE, progression to dialysis and mortality were analysed in relation to baseline ACE-I/ARB usage and also considering ACE-I/ARB use as a time-varying covariate. For adjustment, a propensity score was made for being on ACE-I/ARB at baseline from a logistic regression model. This methodology is described in detail in the footnote to Table 4. A P-value <0.05 was considered statistically significant; SAS 7 and SPSS version 15 were used for analysis.

Results

Of the 634 patients who were recorded in the database during 1999 to early 2009, near complete follow-up information was available on 621 subjects.

Baseline demographics

Mean age (SD) of the cohort was 71.3 (8.8) [range 40.0–92.0] years. Median follow-up (IQR) was 3.1 (2.1, 4.8), range (0.2–10.6) years representing 2184 patient-years of follow-up. Three hundred and ninety-five (63.6%) subjects were male, 226 (36. 4%) female. Patients (84.1%) had hypertension at baseline, with a high prevalence of PVD (32.5%), Type 2 diabetes (33.2%), IHD (43.8%) and abdominal aortic aneurysm (19.7%). Three hundred and sixty-seven (72%) patients had previously suffered at least one CVE by the time of baseline enrolment. Three hundred and thirty-eight (54.4%) patients were on RAB therapy at the start of the study and a further 40 commenced therapy during the study. A total of 37.8% of patients had unilateral significant RAS ≥60%, and 10.5% had bilateral RAS ≥60% or renal artery occlusion (RAO). Baseline demographics are given in Table 1. Table 2 subdivides patients by whether they received an ACE-I or ARB during the study period. Patients who received RAB tended to be younger, have hypertension, diabetes, fewer strokes, better eGFR and be on concomitant aspirin and a statin. There was no association between severity of RAS and likelihood of being on RAB.

ACE-I/ARB use and tolerance

Three hundred and thirty-eight (54.4%) patients were on RAB therapy at the start of the study. Of the remaining 283 patients, 74 patients had a pre-study entry record of intolerance to RAB therapy and were not on RAB at the start of the study (Table 3). Thirty-nine of the 74 (52.7%) patients had baseline unilateral RAS ≥60%, 19 (25.7%) bilateral RAS ≥60% and 16 (21.6%) RAS <60%. In 71 of these 74,

Table 1. Baseline characteristics of all patients at study entry ($n = 621$)

	Mean (SD) [min–max] or %
ACE-I/ARB (%)	
None	45.6
ACE-I or ARB	54.4
Age (years)	71.3 (8.8) [40.0–92.0]
Female (%)	36.4
RAS > 60% (%)	
None	51.7
One vessel	37.8
Both vessels	10.5
Patency score	0.9 (0.44) [0.10–2.00]
Hypertension (%)	84.1
IHD (%)	43.8
CCF (%)	14.0
Flash pulmonary oedema (%)	3.7
Cerebrovascular accident (%)	19.0
PVD (%)	32.5
Abdominal aortic aneurysm (%)	19.7
Diabetes (%)	33.2
Smoking (%)	
Non-smoker	11.8
Ex-smoker	24.2
Current smoker	13.0
Number of anti-hypertensive drugs	2.4 (1.5) [0.0–7.0]
Aspirin therapy (%)	51.9
Statin therapy (%)	62.3
Creatinine (μmol/L)	202.1 (119.7), 39.0–853.0
eGFR (mL/min/1.73 m^2)	35.7 (18.2) [5.0–120.0]
Urinary protein excretion (g/day)	0.7 (1.4) [0.0–15.0]
Systolic blood pressure (mmHg)	150.4 (27.2) [75.0–220.0]
Diastolic blood pressure (mmHg)	77.8 (14.2) [33.0–130.0]

this intolerance was a documented deterioration of renal function, which prompted investigation of RAS. The other three were recorded as having a cough following ACE-I use. During prospective follow-up, 40 of these 74 patients were restarted on RAB therapy. Of 378 patients either on RAB at baseline or started during the study, only 21 (5.6%) patients had a documented side effect or intolerance to RAB therapy during the prospective follow-up. The reasons for RAB discontinuation during follow-up were acute kidney injury $n = 4$, deterioration of renal function $n = 11$, hyperkalaemia $n = 2$, cough $n = 1$, angioedema $n = 1$, allergic rash $n = 1$ and worsened psoriasis $n = 1$.

RAB was tolerated even in those with significant ARVD as 54 of 69 (78.3%) patients with bilateral RAS ≥60% who were treated with ACE-I/ARB tolerated the drugs. Two of these patients had bilateral RAO, and seven had near complete RAO (i.e. RAS 100% and contralateral RAS ≥90%) and tolerated RAB. Four patients had RAS in a solitary kidney. Of these, two patients with significant RAS (65 and 75%, respectively) tolerated RAB without side effects, but another with 95% RAS experienced renal functional deterioration and had the medication discontinued.

Of the 74 patients who were RAB intolerant prior to inclusion in the database, 13 underwent revascularization and 12 had RAB therapy safely re-introduced post-procedure. The one patient unable to commence RAB had a recorded allergic rash following ACE-I therapy. A further 4 of the 21 patients recorded prospectively as intolerant to RABs underwent percutaneous renal revascularization, following which RAB was safely re-introduced.

Table 2. Associations of ACE-I/ARB use ($n = 621$)

	No ACE-I No ARB, $n = 243$ (39.1%)	ACE-I or ARB, $n = 378$ (60.9%)	Dual therapy ACE-I +ARB, $n = 17$ (2.7%)	P	AOR ACE-I or ARB[a,b]	P
Age (years)	72.4 (0.5)	70.5 (0.5)	65.6 (2.1)	**0.0007**	1.027 (1.001, 1.053)	**0.04**
Female (%)	37.7	34.7	41.2	0.7	1.164 (0.760, 1.784)	
RAS > 60% (%)				0.08		
None	53.5	50.7	35.3		1 (ref.)	
One vessel	38.0	37.9	35.3		1.038 (0.681, 1.582)	0.4
Both vessels	8.5	11.5	29.4		0.745 (0.366, 1.515)	0.4
Patency score	0.89 (2.6)	0.89 (2.6)	1.08 (10.7)	0.2	1.001 (0.996, 1.006)	0.7
Hypertension (%)	80.4	87.2	100.0	**0.02**	1.852 (0.999, 3.436)	0.05
IHD (%)	43.4	44.8	35.3	0.7	1.442 (0.937, 2.217)	0.1
CCF (%)	13.3	15.6	0.0	0.2	0.985 (0.560, 1.733)	1.0
Flash pulmonary oedema (%)	4.8	2.4	5.9	0.3	2.883 (0.913, 9.104)	0.07
Cerebrovascular accident (%)	19.9	17.7	23.5	0.7	1.747 (1.061, 2.875)	**0.03**
PVD (%)	30.7	33.0	58.8	0.05	1.321 (0.863, 2.023)	0.2
Abdominal aortic aneurysm (%)	21.5	18.4	5.9	0.2	1.081 (0.655,1.785)	0.8
Diabetes (%)	27.5	37.5	64.7	**0.0007**	0.744 (0.483, 1.146)	0.2
Number of anti-hypertensive drugs	1.7 (0.1)	3.1 (0.1)	4.6 (0.3)	**<0.0001**	0.409 (0.339, 0.494)	**<0.0001**
Aspirin therapy (%)	44.9	59.7	47.1	**0.001**	0.870 (0.569, 1.332)	0.5
Statin therapy (%)	50.6	75.0	64.7	**<0.0001**	0.545 (0.352, 0.843)	**0.006**
Creatinine (μmol/L)	207.3 (122.4)	196.6 (107.5)	178.9 (96.7)	**0.6**	1.001 (0.997, 1.004)	**0.6**
eGFR	34.8 (1.1)	36.4 (1.1)	41.1 (4.5)	0.3	0.986 (0.975, 0.997)	**0.02**
Proteinuria	0.8 (0.1)	0.6 (0.1)	0.4 (0.4)	0.4	1.077 (0.900, 1.288)	0.4
Systolic blood pressure	150.2 (1.8)	148.7 (1.7)	161.4 (7.1)	0.2	1.001 (0.991, 1.01)	0.9
Diastolic blood pressure	78.6 (1.0)	76.2 (0.9)	78.1 (3.8)	0.2	1.081 (0.655, 1.785)	0.8
					Model[a], P < 0.0001, C = 0.80	

[a]Figures in parentheses represent standard errors or 95% confidence intervals. The values in bold represent p<0.05.
[b]From a logistic regression model. Adjustment was made for all variables except patency score and proteinuria for most of variables. For patency score, adjustment is made for all variables except RAS >60 and proteinuria.

Table 3. Number of patients exposed to RAB therapy including tolerability on retrospective and prospective follow-up

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

There were no significant differences in age, sex nor most baseline co-morbid parameters between patients who had previously had or later developed renal impairment in association with RAB. However, patients who experienced renal deterioration were more likely to have suffered a previous CVE (14.7 versus 4.2%, $P < 0.0001$). Of the 86 (71 retrospectively and 15 prospectively) patients with acute renal deterioration associated with ACE-I/ARB use, all except one recovered renal function once the drugs were withdrawn. This patient died from multiple co-morbidities.

Major outcomes

Table 4 shows the risk of the major outcomes according to whether patients were treated with RAB at baseline and considering RAB therapy as a time-adjusted variable, and propensity scores are provided for each.

There were 73 (11.8%) new CVEs in the study period, this corresponded to a rate of 2.7 per 100 patient-years.

Fifty (8%) patients went on to require renal replacement therapy (RRT), i.e. 2 per 100 patient-years. Patients who were not receiving RAB at baseline were more likely to require RRT, but this did not reach significance with time-adjusted modelling.

Two hundred and twelve (34.1%) people died during the study period. This corresponded to a rate of 9.7 per 100 patient-years. One hundred and six of these patients had not received RAB therapy. Patients receiving RABs were significantly less likely to die than patients who did not receive RAB ($P = 0.001$). This relationship persisted after adjustment for RAB usage over time [hazard ratio (HR) 0.61 (0.40–0.91), $P = 0.02$]. The median survival was 73 months for patients receiving RAB, as compared to 65 months for those not receiving them. Aggregating the endpoints of CVEs, dialysis or death into one composite endpoint, analysis showed an HR of 1.72 for those not receiving ACE-I/ARBs ($P < 0.0001$). With multivariate adjustment, this relationship retained significance (HR 1.636, confidence interval 1.200–2.232, $P = 0.002$).

Discussion

In this study of 621 patients with ARVD, treatment with ACE-I and ARBs was associated with the following effects:

(1) Patients with bilateral and significant RAS were able to tolerate these medications safely in most cases. Fifty-four of 69 patients with bilateral RAS ≥60% tolerated the medications on prospective follow-up.

(2) Patients receiving RAB were proportionately more likely to have CVEs on follow-up than patients not on RAB.

(3) Proportionately, patients who received RAB were less likely to progress to RRT, although this did not retain significance on multivariate time adjusted modelling.

(4) ACE-I or ARBs conferred a survival benefit. This retained significance and corresponded to an adjusted HR of 0.61 on time adjusted modelling.

(5) In a small sub-group of patients who were unable to tolerate RAB, renal artery revascularization enabled safe re-commencement of these drugs.

Tolerability of RAB

Patients with ARVD are particularly likely to have hypertension, which is difficult to control [30], abnormal cardiac morphology [12] and proteinuria [15], all compelling indications for RAB therapy. In addition, as pointed out in the UK CKD guidelines, concomitant ARVD is common among patients with extra-renal vascular disease [13, 31, 32], so it is likely that many patients included in trials that demonstrated survival advantage resulting from ACE-I treatment would have had RAS. Despite this evidence, many physicians retain reservations to prescribe RAB therapy in patients with ARVD.

Our data shows that RAB was well tolerated by the majority of our ARVD patients in whom RAB was prescribed. This included 54/69 (78.3%) patients with bilateral significant RAS and 2/3 patients with a unilateral RAS >60% (both groups of patients are usually considered contra-indicated for this therapy). At study baseline, 84.1% of patients had hypertension, and significant numbers had IHD, diabetes, PVD, CCF and proteinuria. As less than 50% of the patients were receiving RAB at baseline, it can be inferred that RABs were under-prescribed in this unselected group of ARVD patients, who had a high incidence of cardiovascular disease, proteinuria and left ventricular hypertrophy.

A meta-analysis of trials involving ACE-I and ARB usage [33] noted that there is often a paucity of reported information regarding side effects of these medications. Many such studies have reported a lower risk for younger patients who are less likely to have co-morbid diseases. Our study demonstrates the outcome benefits of RAB in ARVD patients, who are characteristically an older and higher risk group of patients, and also emphasizes the safety and tolerance of these agents. The latter is very important as many clinicians would wish to avoid using RAB in patients with significant anatomical RAS [34], a group who are probably most likely to benefit from these drugs given the increased likelihood of vascular co-mordities [16].

Table 4. ACE-I/ARB: HRs for death, RRT, CVE and a composite of any of these events

ACE-I/ARB at baseline					ACE-I/ARB as time-varying covariate[a]			
Unadjusted			Propensity score—adjusted[b]		Unadjusted		Propensity score—adjusted	
% With event ±[c]	HR	P	HR	P	HR	P	HR	P
Death (212 events, rate 9.7 per 100 patients-years)								
63.7/36.3	0.58 (0.44–0.77)	0.0002	0.64 (0.46–0.89)	0.008	0.56 (0.38–0.82)	0.003	0.61 (0.40–0.91)	0.02
RRT (50 events, rate 2.0 per 100 patients-years)								
72.0/28.0	0.37 (0.20–0.71)	0.0003	0.26 (0.12–0.54)	0.0003	0.48 (0.21–1.09)	0.08	0.50 (0.21–1.16)	0.1
CVE (73 events, rate 2.7 per 100 patients-years)								
46.6/53.4	1.29 (0.81–2.05)	0.3	1.57 (0.92–2.71)	0.1	1.00 (0.54–1.88)	1.0	1.22 (0.64–2.32)	0.6
Composite event (259 events, rate 13.0 per 100 patients-years)								
59.9/40.2	0.66 (0.52–0.85)	0.001	0.71 (0.53–0.96)	0.03	0.71 (0.51–1.00)	0.05	0.79 (0.56–1.12)	0.2

[a]Based on ACE-I/ARB status at years 0 through 10 of the study.
[b]From the logistic regression model of ACE-I/ARB use at baseline shown in Table 2. For each subject, the propensity for ACE-I/ARB use at baseline was calculated as $1/(1 + e^{-z})$, where $z = -0.9909 + 0.0265(\times \text{age}) + 0.1521$ (if female) $+ 0.123$ (if RAS $> 60\%$ in one vessels) $- 0.2087$ (if RAS $> 60\%$ in two vessels) RAS $+ 0.6164$ (if hypertension) $+ 0.3659$(if IHD) -0.0152(if left ventricular failure) $+1.0588$ (if flash left ventricular failure) $+0.5578$ (if cerebrovascular accident) $+ 0.2785$ (if peripheral vascular disease) $+0.0782$ (if abdominal aortic aneurysm) -0.296 (if diabetes mellitus) -0.052 (if ex-smoker) -0.0161 (if current smoker) -0.8933 (number of blood pressure drugs) $- 0.1387$(if on aspirin) $- 0.6073$ (if on statin) $- 0.0142$ (eGFR) $+ 0.000596$ (systolic blood pressure) $+0.0144$.
[c]± denote non-exposed/exposed to ACE-I/ARB.

Current UK guidelines advocate cessation of treatment when serum creatinine rises to 20–30% above baseline [35], but these data are extrapolated from trials in selected groups of patients and may not apply to the unselected ARVD population. A review of 12 RCTs concluded that a creatinine rise >30% [36] should be the cut-off for discontinuation of RAB. Reassuringly, rises in serum creatinine usually return to baseline upon drug cessation [37] and this was confirmed in all but one of our ARVD population. Interestingly, an inverse correlation has been described between the initial fall in GFR and the subsequent rate of renal functional decline over time [38]. This was not analysed in our group.

In this study, patients with prior CVEs at baseline were more likely to develop an intolerance to RAB. Possible explanations can only be speculative and include greater likelihood of multiple drug combinations, more severe RAS or a poorer cardiac output. These patients are those most likely to be considered for introduction of RAB and this association suggests that close monitoring is required when initiating ACE-I/ARB in this sub-group. The safe use of RAB entails checking renal function at baseline and shortly after initiation. Caution is advised in those taking concomitant diuretics or using non-steroidal anti-inflammatory drugs and also particularly at times of inter-current illness that will lead to hypovolaemic stress (e.g. dehydration associated with diarrhoea and vomiting). In the latter cases, there is a case for temporary discontinuation of the RAB at the commencement of the illness, with early re-introduction once the patient has recovered.

Cardiovascular morbidity, dialysis and RAB use

In our study, 11.8% of patients suffered a new CVE during follow-up; patients receiving RAB were more likely to suffer a future CVE. This appears surprising as there is abundant data supporting the benefit of RABs in reducing cardiovascular morbidity and mortality [16, 17], reversing left ventricular hypertrophy [36, 39], with fewer hospital admissions for CCF [40]. Nonetheless, fewer patients in our study actually suffered CVE than has been observed in other large studies (30.4% per year [30]). Interestingly, a recent meta-analysis of haemodialysis patients found similar results to our ARVD population, in that that those who received RAB had a statistically significant reduction in left ventricular mass, although their use was not associated with a reduction in the risk of fatal and non-fatal CVEs [41].

The Mayo group examined the impact of >25% worsening renal failure in patients who were prescribed RAB therapy in a small prospective study of 26 patients with haemodynamically significant RAS [42]. RAB therapy was discontinued in these patients and long-term renal function studied. Five patients progressed to end-stage renal disease (ESRD), and 19 patients experienced an improvement in eGFR. A lower eGFR predicted ESRD, but they concluded that a larger study was warranted to understand the long-term impact of RAB therapy in elderly patients. In our study, use of ACE-I/ARB was associated with reduced risk of subsequent dialysis need, although this did not reach significance on time-dependent multivariate modelling. As the population group were unselected, multiple causes of renal impairment may have been responsible for this decline. Nonetheless, RAB therapy may have reverted some modifiable risk factors, e.g. proteinuria. A number of RCTs in CKD patients show this to be the case, with demonstration that RAB can slow progressive functional decline [43-45].

Mortality and RAB use

In our study, the chief benefit to receiving RAB therapy was the survival advantage conferred. Patients who received RAB were 44% more likely to survive than those who had not received these drugs. On multivariate

time-adjusted propensity scoring analysis, this benefit was retained at 39%. Notwithstanding the limitations to the study (which was an observational study, not an RCT), we feel that this is an important finding especially due to the large population size. The survival advantage of RAB therapy in ARVD was also shown in an observational outcome study by Losito *et al.* [43] in which factors affecting survival and renal function were investigated in 195 ARVD patients treated invasively or with medical therapy alone. The only factor contributing towards a longer survival in both groups was the use of ACE-I ($P = 0.002$).

Revascularization to facilitate use of RAB

Although not routinely performed for this indication, timely intervention with revascularization can allow safe re-introduction of RAB in the many ARVD patients in whom these agents are strongly indicated. This was the case for 16 patients in our study and has been shown in other small studies [19, 46]. Due to the multiple benefits of RAB, revascularization of those with worsening renal function associated with therapy can be considered an emerging indication for revascularization.

We acknowledge that our study has several shortcomings, which include the fact that there was no analysis of drug dosage. Nevertheless, time-adjusted modelling with multivariate analysis showed a benefit from any dose of RAB on survival. Secondly, because of the observational study design, it is possible that particular patients may have been selected for RAB therapy (e.g. younger patients, higher eGFR, cardiovascular disease or proteinuria) although the baseline co-morbidity data was similar in both those receiving or not receiving RAB. It was also surprising that only 37.2% of patients were active or previous smokers, given that the ASTRAL data showed 72% of patients were current or ex-smokers. It may be that our local policies concerning smoking cessation were important.

Recognition of drug intolerances and CVEs was dependent upon whether such data had been in the electronic patient records. Thus, it is possible that more patients were intolerant of the RAB and stopped by their general practitioners in the interval between annual follow-up appointments. In addition, we did not analyse more modest changes in GFR as this was an epidemiological study with acute kidney injury as an endpoint. Our study is strengthened by the inclusion of a large number of unselected ARVD patients, who had varying degrees of RAS, and also by use of the time adjusted propensity-scoring analysis.

Provided due caution is adhered to and the serum biochemistry appropriately monitored, we recommend that all patients with ARVD be considered for ACE-I/ARB therapy. In the future, intolerance of RAB due to acute renal dysfunction could be considered a major indication for selecting patients for renal revascularization.

Conflict of interest statement. None declared.

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