RESEARCH

An underused opportunity to introduce ACE inhibitors and influence prognosis: observational study of patients undergoing aortic surgery

Kayria Muttardi1 • Ali Haydar2 • Chee Kiang Phua1 • Neil Chapman3 • Michael Jenkins1 • Nicholas JW Cheshire1 • Colin D Bicknell1

1Imperial Vascular Unit, Imperial College Healthcare NHS Trust, London, UK; 2Department of Radiology, Imperial College London, London, UK; 3International Centre for Circulatory Health, Imperial College London, London, UK

Correspondence to: Colin Bicknell. Email: colin.bicknell@imperial.ac.uk

Summary

Objective: To assess whether Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are underused in patients with aortic disease due to concerns regarding flow limiting (>70%) renal artery stenosis (RAS).

Design: A prospective analysis of patients admitted for aortic surgery was performed (January–July 2009). Co-morbidity, ACEI/ARB use and renal function were recorded. Computerised tomography (CT) angiograms were reviewed by a single blinded radiologist for the presence and severity of RAS.

Setting: St Mary’s Hospital, Vascular Unit, Imperial College Healthcare NHS Trust, London, UK.

Participants: 75 randomly selected patients admitted to our vascular unit including elective and emergency admissions.

Main outcome measures: Indications for ACEI therapy were identified as determined by the National Institute of Health and Clinical Excellence (NICE) guidance. The ratio of the measurement distal to the stenosis and at the area of maximal stenosis on CT angiography were used to calculate the percentage RAS.

Results: 60 patients were identified (15 patients excluded due to previously modified renal vessels). The median age was 73 [interquartile range 68, 77]. Their underlying aortic disease included 52 (87%) aortic aneurysm, 6 (10%) with aortic dissection, 1 (1.7%) patient with occlusive disease and 1 (1.7%) patient with mycotic disease. Overall, 56/60 (93%) patients had at least one indication for ACEI therapy. 33/60 (55%) of patients were already receiving ACEI. CT angiogram examination demonstrated 17/60 (28%) patients have RAS of some degree, of which only 9/60 (15%) have flow limiting RAS.

Conclusion: A large proportion of aortic patients do not receive ACEI/ARB therapy despite definite indications and a low prevalence of flow-limiting RAS is low. After the exclusion of RAS at angiography, careful introduction of

DECLARATIONS

Competing interests None declared

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Ethical approval Advice was sought from the local research and development department and as it is a quality improvement study/audit, no written consent was required.

Guarantor CDB

Contributorship KM: data collection, analysis, writing. AH: data collection, analysis, writing. CKP: data collection, analysis, writing. NC, MJ, NJWC and CB: data analysis.
ACEI therapy with appropriate monitoring could be considered for many more patients.

**Introduction**

Medical therapy is of vital importance for the long-term survival and prognosis of atherosclerotic patients. However, despite there being good evidence to support the use of aspirin and statins in vascular disease, it has been shown that these are often not well utilized in vascular patients. The BASIL trial\(^1\) showed that almost 40% of vascular patients were not receiving antiplatelet therapy and that only a third were taking statins. Similar figures were echoed by the EVAR II trial.\(^2\)

There has also been growing evidence to support the use of angiotensin-converting enzyme inhibitors (ACEI) in patient cohorts similar to those enrolled in the above-mentioned trials. The HOPE study\(^3\) demonstrated a relative risk survival advantage of 22% in patients with cardiovascular risk factors, showing benefits beyond those gained from blood pressure control alone. Analogous findings have been shown in the PROGRESS study\(^4\) with a reduced stroke risk of 28% and a 26% reduction in major coronary events with perindopril. Additional evidence for ACEI benefits in heart failure and diabetes-associated microalbuminuria have also been demonstrated.

The American Heart Association (AHA) guidelines\(^5\) for the management of patients with peripheral arterial disease (PAD) now recommend the use of ACEI in patients with asymptomatic PAD owing to its cardiovascular benefits. Despite this large body of evidence, there still appears to be some reluctance to use ACEI in arterial patients due to the concern over renal artery stenosis (RAS). ACEI are contraindicated in bilateral flow limiting (FL) RAS and unilateral FL RAS with a single functioning kidney. Impaired renal function per se is not a contraindication to the use of ACEI.

Our aim was to determine (1) the number of patients undergoing aortic surgery with an indication for ACEI therapy, (2) the prevalence of RAS in this population and (3) the proportion of patients who were already on ACEI prior to surgery and therefore estimate the percentage of patients who would benefit from introducing ACEI therapy at the time of assessment and treatment of their aortic disease.

**Methods**

**Patient selection**

We prospectively studied 75 randomly selected patients from January 2009 to July 2009 that were admitted to our vascular unit including elective and emergency admissions. The inclusion criteria were anyone admitted with aortic occlusive and aneurismatic disease including infrarenal, juxtarenal and thoracoabdominal aneurysms. Fifteen patients with previous hybrid grafts, branched stents and renal transplants had to be excluded from the trial as the renal vessels in these patients were previously modified.

**Data collection**

Patient demographics were collected for each of these patients including age, sex, ethnicity, type of aneurismatic disease and indications for ACEI therapy.

- Stroke
- Myocardial infarction (MI)/Ischaemic heart disease (IHD)
- Hypertension (HTN)
- Diabetes mellitus (DM)
- Congestive cardiac failure (CCF)

Admission creatinine values were also recorded for each patient as a surrogate for renal function.

**CT angiography interpretation**

In order to assess the presence of RAS, preoperative CT scans were analysed. The CT scans were carried out with Siemens 64-CT scanner by a single radiologist according to the CTA protocol for St Mary’s Hospital, Paddington, UK. The following is a summary of the CTA protocol used:

- To obtain optimal images of the kidney hilum, the patient is required to hold his/her breath for 30-40s.
The region of interest for imaging extends from the suprarenal abdominal aorta to the bifurcation of the iliac artery.

A narrow collimation of 1–3 mm and a pitch up to 2 are used as parameters for helical CT scanning.

For the evaluation of renal hilum in renal stenosis, a 1-mm interscan spacing is ideal. Images are reconstructed equally throughout the data set.

A single-blinded radiologist analysed images. Maximum intensity projection (MIP) and volume rendering techniques were used in the evaluation of RAS. Measurements of the vessel distal to the stenosis and at the area of maximal stenosis were taken. The ratio was obtained and this constituted an estimate measurement of the RAS. We defined flow-limiting RAS as stenosis of 70% or more.

Statistical analysis

Data analyses was performed to determine which patients were already on ACEI/ARBs, how many would benefit from them and how many should be excluded because of RAS. Correlation coefficients were calculated to assess the relationship between kidney size, creatinine and the presence of RAS.

Results

Sixty patients were identified (median age 73 [interquartile range 68, 77]) of which 51 were Caucasian. Their underlying aortic disease included 52 (87%) aortic aneurysm, 6 (10%) with aortic dissection, 1 (1.7%) patient with occlusive disease and 1 (1.7%) patient with mycotic disease (see Table 1).

Analysis of our patient demographic demonstrated that 56 (93%) patients overall had at least one indication for ACEI therapy (see Figure 1). Eighty-eight per cent had HTN, 45% IHD, 16.7% stroke, 11.7% DM and 6.7% with CCF. Furthermore, patients often had more than one indication for being on an ACEI/angiotensin receptor blocker (ARB) with 18.3% of patients having three or more risk factors and 52% having two or more risk factors.

Despite these indications, only 33 (55%) patients were receiving an ACEI (60% of hypertensive patients, 60% of stroke patients, 57% of diabetic patients, 70% of CCF patients and 59% of IHD patients). The superimposed yellow bars in Figure 1 demonstrate this.

Prevalence of RAS

A high proportion of patients do not have RAS. Seventeen of 60 (28%) patients were found to have RAS of some degree, of which 7/60 (11.7%) have FL RAS >70% on one side. Two patients had bilateral FL RAS and therefore these patients had an absolute contraindication to ACEI therapy (see Figure 2).

In patients with no RAS, the median creatinine was 99 μmol/L, the median right kidney size was 10.2 cm and the median left kidney size was 10.5 cm.

We also looked to see whether there is any correlation between renal function, kidney size and

| Table 1. | Patient demographics and co-morbidities. |
|----------|------------------------------------------|
| **Patient demographics** | |
| Age ±iQ | 73 (68, 77) |
| Male | 51/60 (85%) |
| Caucasian | 56/60 (93%) |
| **Aortic disease** | |
| Aortic aneurysm (%) | 52/60 (87%) |
| Aortic dissections (%) | 6/60 (10%) |
| Occlusive disease (%) | 1/60 (1.7%) |
| Mycotic disease (%) | 1/60 (1.7%) |
| **Co-morbidities** | |
| Stroke | 10/60 (16.7%) |
| Myocardial infarction/Ischaemic heart disease | 27/60 (45%) |
| Congestive cardiac failure | 4/60 (6.7%) |
| Diabetes mellitus | 7/60 (11.7%) |
| Hypertension | 53/60 (88%) |
| **Renal function** | |
| Creatinine μmol/litre | Median (interquartile range) |
| | 101 (81, 124) |
| ACEI/ARB on admission | 33/60 (55%) |
| Side effect/intolerance of ACEI | 1/60 (1.7%) |

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.
the presence of RAS. We analysed the data from 19 kidneys (15 kidneys unilateral RAS and four kidneys bilateral RAS) and found that the presence of RAS did not correlate well with simple markers of renal function such as kidney size and creatinine (see Figures 3 and 4).

Discussion

The prognostic effects of ACEI have been credibly demonstrated in patients with IHD, HTN, Stroke, CCF and DM in numerous large outcome studies.6

Figure 1. Indications of ACEI therapy in the populations studied and the proportion of these patients who are receiving ACEI therapy. Fifty-six of 60 patients (93%) had at least one indication for ACEI therapy (88% had hypertension, 45% ischaemic heart disease, 16.7% stroke, 11.7% Diabetes mellitus and 6.7% with congestive cardiac failure). The superimposed bars in yellow represent actual ACEI use on admission of which in total only 33/60 (55%) were receiving it despite one or more indications. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.

Figure 2. Prevalence of RAS in our population. Forty-three of 60 (72%) had no RAS, 17/60 (28%) patients had RAS of some degree of which 8/60 (13%) had unilateral stenosis of >70% severity and 7/60 (12%) had unilateral flow limiting stenosis. Only 2/60 (3%) patients had bilateral flow limiting RAS. RAS: renal artery stenosis.
Furthermore, there is some evidence to suggest that patients taking ACEI have a reduced risk of rupture from aortic aneurysms, unlike other antihypertensive agents. This is supported by studies in both mice models and patients with Marfan’s, which have shown that the use of ACEI slows down the rate of aortic root growth. This is thought to be due to ACEI vascular anti-inflammatory effects and inhibition of matrix metalloproteinases.

Although this study looked at 60 patients, the patient demographic appears to be representative of the population we wish to study. This is backed by the consistency of our demographic data with the EVAR trial baseline characteristics. Our results confirm that a large proportion of patients with aortic disease (93%) have at least one indication for ACEI therapy. This is fully expected due to the well-known strong correlation between aneurysmal aortic disease and vascular risk factors such as HTN, IHD and diabetes. However, despite the indications, only 55% of patients were receiving an ACEI. This raises concern along with data from EVAR II, which showed that only 58% of high-risk aneurysm patients were taking aspirin and 41.8% taking statins. We did not analyse data on statin and aspirin use on admission, which retrospectively would have been useful.

Many factors may influence the underuse of medical therapy in vascular patients including patient autonomy and difficulties with polypharmacy. In addition, the degree of primary care contact with the patient would have a significant effect. There is also the issue of side effects particularly cough with ACEI; however, only one of our patients had a known side effect to ACEI.

Although this does not explain the low rates of aspirin and statin use in vascular patients, one theory for the underuse of ACEI/ARB in these
patients may be the concern over the possible presence of RAS. ACEI are contraindicated in FL bilateral RAS or unilateral RAS with a single functioning kidney. If used in these circumstances, ACEI can cause a reversible rise in creatinine and acute renal failure. However, a baseline raised creatinine alone without RAS is not in itself a contraindication to ACEI therapy.

RAS of which 90% is atherosclerotic is the most common primary disease of the renal arteries.10 There have been no studies looking at the presence of RAS in patients with aortic disease specifically but often patients with risk factors for atherosclerotic disease are studied. However, haemodynamically significant RAS can be present in patients with normal blood pressure and renal function. Studies have demonstrated a varied prevalence of RAS from 14% to 42% in patients with aortic or peripheral vascular disease11–14 as stated in Ref. 10. Our results show that 28% of our patients have some degree of RAS. Seven (11.7%) patients have unilateral FL RAS and 2 (3%) have bilateral FL RAS.

Most would consider intra-arterial digital subtraction angiography as the standard in the diagnosis of RAS. However, it is invasive and subject to high inter-observer variation in assessing severity of lesions.15 Therefore, the AHA guideline 2005 recommends the following screening tests for RAS.

- Duplex ultrasonography
- CT angiography
- MRA
- Catheter angiography as diagnostic test to establish diagnosis of RAS when clinical index of suspicion is high and results of non-invasive tests are inconclusive

CT angiography has been shown to have a sensitivity of 59–96% and specificity of 82–99% for detecting significant RAS when compared to catheter guided angiography.5 In our study, all CT scans were reviewed by a single radiologist to avoid inter-observer bias. Another important reason for the wide prevalence estimate of RAS in atherosclerotic patients is that some studies use 50% as the definition for FL RAS and others use 70%. At least 50% stenosis is required to give a pressure drop in the renal artery; however, the narrower the stenosis the more likely that there is a drop, which is the rationale for using 70% stenosis as the cut off. The AHA guidelines 2005 define haemodynamically significant stenosis as any stenosis of 50–70% associated with a translesional gradient of ≥20 mmHg or a mean gradient ≥10 mmHg or any ≥70% stenosis. As flow cannot be measured on CT, we used 70% stenosis as our cut off for FL disease.

We also looked at renal function and size as predictors of RAS. There was a poor correlation between creatinine and severity of RAS. One explanation is that in this cohort of patients, renal dysfunction is likely to be as a consequence of multiple aetologies including HTN and DM. Nevertheless, similar findings have been reported in several studies.16–18 Both epidemiological studies and single kidney Glomerular filtration rate (GFR) studies found no correlation between RAS severity and degree of renal impairment, apart from kidneys with complete occlusion of the renal artery where an ischaemic nephropathy usually ensues.

However, there is evidence to suggest that age >65 and the presence of HTN are independent predictors of RAS.19,20 Some studies have suggested that renal parenchymal injury in patients with RAS is secondary to long standing HTN. The HTN often predate RAS and is the major factor responsible for raised creatinine in these patients. This is supported by single kidney GFR studies that also demonstrate impaired renal function in the non-affected kidney of patients with single kidney RAS.18

Our results show that kidney size was similar for all patients irrespective of the presence of RAS and its severity. It may be that our sample size is too small or that a natural history study would be more appropriate to examine this as the evidence from several studies has demonstrated decrease in kidney size with FL RAS.21,22

Of the 56 patients with indications for ACEI therapy, three have been excluded (two due to bilateral FL RAS and one due to side effects). This leaves 53 patients of which 33 are already receiving ACEI/ARBs. Therefore, 20 patients (33%) should be on an ACEI but are not currently receiving it. Consequently, we conclude that a large proportion of aortic patients do not receive ACEI/ARB therapy despite definite indications and even though the prevalence of flow-limiting RAS is low. After the exclusion of RAS at CT angiography, careful introduction of ACEI therapy with appropriate
monitoring could be considered for many more patients. We propose that the hospital admission for the treatment of the underlying aortic disease is an ideal point for the introduction of ACEI, statins and aspirin for patients who would benefit from them.

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