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

Kayria Muttardi[1] • Ali Haydar[2] • Chee Kiang Phua[1] • Neil Chapman[3] • Michael Jenkins[1] • Nicholas JW Cheshire[1] • Colin D Bicknell[1]

[1]Imperial Vascular Unit, Imperial College Healthcare NHS Trust, London, UK; [2]Department of Radiology, Imperial College London, London, UK; [3]International Centre for Circulatory Health, Imperial College London, London, UK
Correspondence to: Colin Bicknell. Email: colin.bicknell@imperial.ac.uk

DECLARATIONS

Competing interests

None declared

Funding

None declared

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,

Summary

Objective: To asses 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

ACEI therapy with appropriate monitoring could be considered for many more patients.

writing, overall responsibility

Acknowledgements
None

Provenance

This article was submitted by the authors and peer reviewed by Eiman Jahangir

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 aneurismal 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 aneurismal disease and indications for ACEI therapy.

Indications for ACEI therapy are listed below and are as determined by the National Institute of Health and Clinical Excellence (NICE) guidance.

- 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 30–40 s.

- 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.

Table 1.
Patient demographics and co-morbidities.

Patient demographics	
Age +xIQ	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.

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

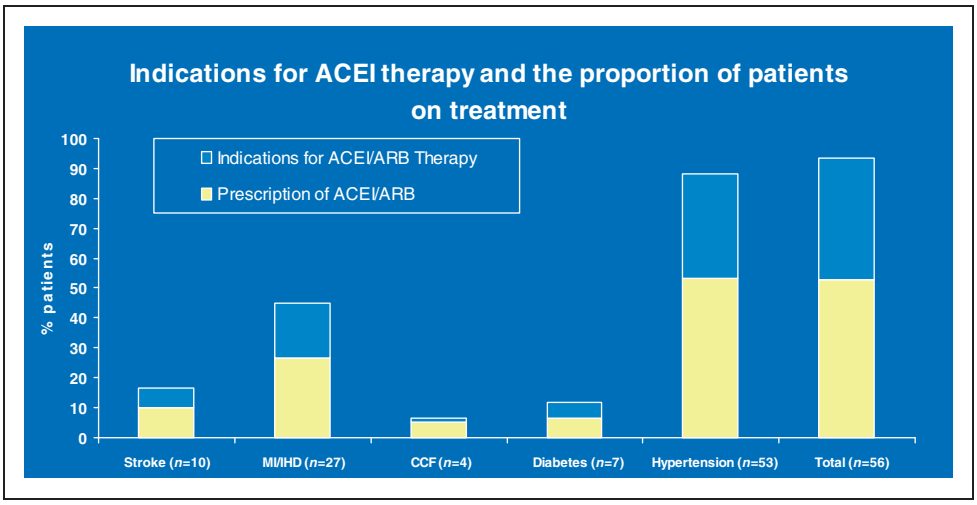

Figure 1. Indications of ACEI therapy in the populations studied and the proportion of these patients who are receiving ACEI therapy. Fifty-six of 60 patients (93%) had at least one indication for ACEI therapy (88% had hypertension, 45% ischaemic heart disease, 16.7% stroke, 11.7% Diabetes mellitus and 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.

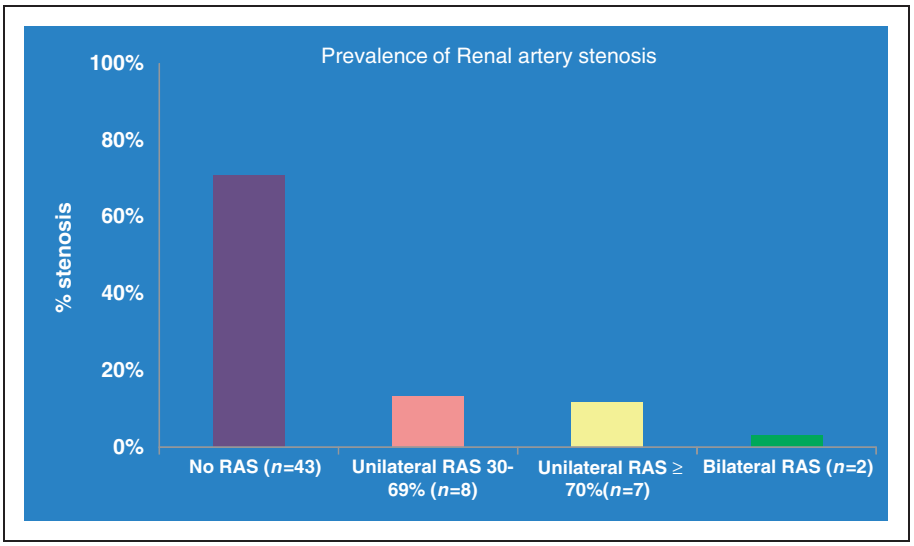

Figure 2. Prevalence of RAS in our population. Forty-three of 60 (72%) had no RAS, 17/60 (28%) patients had RAS of some degree of which 8/60 (13%) had unilateral stenosis of >70% severity and 7/60 (12%) had unilateral flow limiting stenosis. Only 2/60 (3%) patients had bilateral flow limiting RAS. RAS: renal artery stenosis.

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]

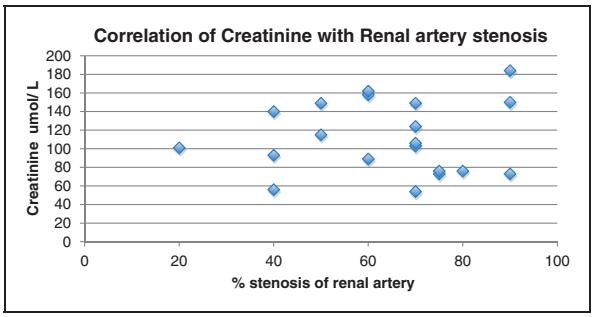

Figure 3. Scatterplot showing correlation between creatinine and RAS. Data based on 17 patients with RAS (15 with unilateral and 2 with bilateral RAS). This demonstrates that there is a poor correlation between creatinine and RAS. Correlation coefficient, 0.07. RAS: renal artery stenosis.

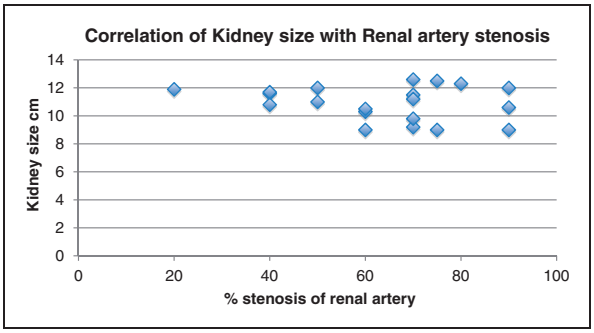

Figure 4. Scatterplot showing correlation between kidney size and RAS. Data based on 17 patients with RAS (15 with unilateral and 2 with bilateral RAS). This demonstrates that there is poor correlation between creatinine and RAS. Correlation coefficient, −0.2. RAS: renal artery stenosis.

Furthermore, there is some evidence to suggest that patients taking ACEI have a reduced risk of rupture from aortic aneurysms, unlike other antihypertensive agents.[7] 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.[8] This is thought to be due to ACEI vascular anti-inflammatory effects and inhibition of matrix metalloproteinases.[7]

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.[2,9] 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,[2] 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 disease[11–14] 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 diagnoses 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 $\geq$20 mmHg or a mean gradient $\geq$10 mmHg or any $\geq$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 aetiologies 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 predates 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.

References

1. Adam DJ, Beard JD, Cleveland T, *et al*. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre randomised controlled trial. *Lancet* 2005;366:1925–34
2. EVAR trial participants. Endovascular aneurysm repair and outcome in patients unfit for open repair of abdominal aortic aneurysm (EVAR trial 2): randomised controlled trial. *Lancet* 2005;365:2187–92
3. Yusuf S, Sleight P, Pogue J, *et al*. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;342:145–53
4. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001;358:1033–41
5. Hirsch AT, Haskal ZJ, Hertzer NR et al. ACC/AHA 2005 Practice Guidelines for the Management of Patients With Peripheral Arterial Disease (Lower Extremity, Renal, Mesenteric, and Abdominal Aortic) : A Collaborative Report from the American Association for Vascular Surgery/Society for Vascular Surgery,* Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation*. 2006;113:e463–e654
6. Stojiljkovic L, Behnia R. Role of renin angiotensin system inhibitors in cardiovascular and renal protection: a lesson from clinical trials. *Curr Pharm Des* 2007;13:1335–45
7. Hackam DG, Thiruchelvam D, Redelmeier DA. Angiotensin-converting enzyme inhibitors and aortic rupture: a population-based case-control study. *Lancet* 2006;368:659–65
8. Moltzer E, Essers J, van Esch JH, Roos-Hesselink JW. The role of the renin-angiotensin system in thoracic aortic aneurysms: clinical implications. *Pharmacol Ther* 2011;131:50–60
9. Greenhalgh RM, Brown LC, Epstein D, *et al*. Endovascular aneurysm repair versus open repair in patients with abdominal aortic aneurysm (EVAR trial 1): randomised controlled trial. *Lancet* 2005;365:2179–86
10. Zoccali C, Mallamaci F, Finocchiaro P. Atherosclerotic renal artery stenosis: epidemiology, cardiovascular outcomes, and clinical prediction rules. *J Am Soc Nephrol* 2002;13:S179–83
11. Valentine RJ, Myers SI, Miller GL, Lopez MA, Clagett GP. Detection of unsuspected renal artery stenosis in patients with abdominal aortic aneurysms: refined indications for preoperative aortography. *Ann Vasc Surg* 1993;7:220–4
12. Olin JW, Melia M, Young JR, Graor RA, Risius B. Prevalence of atherosclerotic renal artery stenosis in patients with atherosclerosis elsewhere. *Am J Med* 1990;88:46N–51N
13. Choudhri AH, Cleland JG, Rowlands PC, Tran TL, McCarthy M, Al-Kutoubi MA. Unsuspected renal artery stenosis in peripheral vascular disease. *BMJ* 1990;301:1197–8
14. Wilms G, Marchal G, Peene P, Baert AL. The angiographic incidence of renal artery stenosis in the arteriosclerotic population. *Eur J Radiol* 1990;10:195–7
15. Leiner T, de Haan MW, Nelema PJ, *et al*. Contemporary imaging techniques for the diagnosis of renal artery stenosis. *Eur Radiol* 2005;15:2219–29
16. Suresh M, Laboi P, Mamtora H, *et al*. Relationship of renal dysfunction to proximal arterial disease severity in atherosclerotic renovascular disease. *Nephrol Dial Transplant* 2000;15:631–6
17. Cheung CM, Wright JR, Shurrab AE, *et al*. Epidemiology of renal dysfunction and patient outcome in atherosclerotic renal artery occlusion. *J Am Soc Nephrol* 2002;13:149–57
18. Farmer CKT, Reidy J, Kalra PA, *et al*. Individual kidney function before and after renal angioplasty. *Lancet* 1998;352:288–9
19. Addad F, Betbout F, Farhat MB, *et al*. Prevalence and predictors of renal artery stenosis in patients with coronary artery disease. *Int J Angiol* 2005;14:81–6
20. Ghaffari S, Sohrabi B, Siahdasht RB, Pourafkari L. Prevalence and predictors of renal artery stenosis in hypertensive patients undergoing coronary angiography. *Hypertension Res* 2009;32:1009–14
21. Guzman R, Zierler R, Isaacson A, O Bergelin R, Strandness D. Renal atrophy and arterial stenosis. A prospective study with duplex ultrasound. *Hypertension* 1994;23:346–50
22. Modrall JG, Timaran CH, Rosero EB, *et al*. Longitudinal changes in kidney parenchymal volume associated with renal artery stenting. *J Vasc Surg* 2012;55:774–80