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Non-invasive investigations of potential renal artery stenosis in renal insufficiency

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Abstract

Background The diagnostic value of non-invasive methods for diagnosing renal artery stenosis in patients with renal insufficiency is incompletely known.

Methods Forty-seven consecutive patients with moderately impaired renal function and a clinical suspicion of renal artery stenosis were investigated with CT Angiography (CTA), gadolinium-enhanced MR angiography (MRA), contrast-enhanced Doppler ultrasound, and captopril renography. The primary reference standard was stenosis reducing the vessel diameter by at least 50% on CTA, and an alternative reference standard ("morphological and functional stenosis") was defined as at least 50% diameter reduction on CTA or MRA, combined with a positive finding from ultrasound or captopril renography.

Results The frequency of positive findings, calculated on the basis of individual patients, was 70% for CTA, 60% for MRA, 53% for ultrasound, and 30% for captopril renography. Counting kidneys rather than patients, corresponding frequencies were 53%, 41%, 29%, and 15%, respectively. In relation to the CTA standard, the sensitivity (and specificity) at the patient level was 0.81 (0.79) for MRA, 0.70 (0.89) for ultrasound, and 0.42 (1.00) for captopril renography, and at the kidney level 0.76 (0.82), 0.53 (0.81), and 0.30 (0.86), respectively. Relative to the alternative reference standard, corresponding values at the patient level were 1.00 (0.62) for CTA, 0.90 (0.69) for MRA, 0.91 (1.00) for ultrasound, and 0.67 (1.00) for captopril renography, and at the kidney level 0.96 (0.76), 0.85 (0.79), 0.71 (0.97), and 0.50 (0.97), respectively.

Conclusions CTA and MRA are superior to ultrasound and captopril renography at diagnosing morphological stenosis, but ultrasound may be useful as a screening method and captopril renography for verifying renin-dependent hypertension.

Key words

Computed tomography angiography, magnetic resonance angiography, renal artery stenosis, renal failure, renography, ultrasound.

Introduction

There is debate over how to investigate renal artery stenosis (RAS), in particular how to determine whether, and to what extent, this contributes to renovascular hypertension. Presently, there is not much data that speak in favor of a liberal use of percutaneous transluminal renal angioplasty (PTRA) in uncomplicated cases of renal artery stenosis [1] Even less is known about how to investigate and treat patients with renal failure and suspected renal artery stenosis. Ischemic nephropathy has been defined as "impairment of renal function beyond occlusive disease of the main renal arteries" [2], stressing that reduced blood flow may not be the sole or even the major contributor to reduced renal function. Angiotensin II, endothelin-1, TGF-β, and PDGF-β are some of the actors that may participate in the process of building extracellular matrix and collagen IV in the renal interstitium [3]. In one study, the 2-year cumulative incidence of renal atrophy assessed with duplex ultrasound scanning was 6% in patients with normal renal arteries, 12% if <60% stenosis, and 21% if at least 60% stenosis [4]. Using duplex ultrasonography and renal scintigraphy in all patients, renal biopsy in 40% and renal angiography in 25%, a carefully performed study of 56 consecutive patients with a presumed diagnosis of nephrosclerosis found atheromatous renovascular disease in 34% of cases and "true" hypertensive nephrosclerosis in only 46% [5]. The intensity and mode of lipid lowering therapy may influence intima-media thickness in atherosclerosis [6–9], and more accurate diagnosis of ischemic nephropathy, distinguishing between small vessel and large vessel disease, would hopefully stimulate development of new medical strategies against atherosclerotic and fibrotic mechanisms in the kidney. Furthermore, a convenient and inexpensive method for diagnosing ischemic nephropathy could also prevent other diagnostic procedures with potential risks, e.g. renal biopsy in patients with proteinuria. The point of detecting RAS is thus not only to find patients suitable for PTRA, but also to characterize the nature of kidney disease eventually facilitating medical therapy. In the former situation, the specificity of the method is important, whereas higher sensitivity may be preferred on other occasions.

Renography has long been a useful tool in the functional evaluation of RAS [10]. However, the method is said to be less accurate when used in patients with impaired renal function. The other major technique to functionally evaluate renal artery stenosis is to use ultrasound with Doppler analysis of the blood flow in the artery, where stenosis is typically accompanied by an increase in peak systolic velocity (PSV) [11, 12]. This method has become more feasible since non-toxic contrast media that increase the sensitivity have emerged [13]. For non-invasive morphological imaging of the vasculature, the clinician can choose between CT angiography [14] and MR angiography [15], both of which give high-resolution images but also involve the use of contrast media.

The question of "gold standard" for assessment of arterial stenoses is complicated. Invasive catheter angiography has been used for a long time and can be combined with measurement of the pressure drop across the stenosis [16–20], but these measurements are disturbed by the presence of a catheter in the narrow lumen [20–24]. In this study we tested different approaches to defining the reference method using CT angiography alone or combined with functional methods, and also using varying thresholds for measured quantities such as PSV and diameter reduction.

To evaluate and compare the four non-invasive techniques used to diagnose RAS, we therefore recruited 47 non-diabetic patients with moderately reduced kidney function and clinical suspicion of RAS. The studied diagnostic methods were CT angiography, MR angiography, renography and contrast-enhanced ultrasound. Our main aim was to evaluate

feasibility and usability of these techniques and to make an evaluation of their relationship to one another.

Subjects and Methods

Patients

Forty-seven patients of both genders, 18–80 years of age, with a screening serum creatinine 150–300 μmol/L living in the catchment area of Linköping University Hospital in southeastern Sweden were consecutively recruited for the study. Eligible patients had to have a resting blood pressure >160 systolic and/or >90 diastolic mmHg or treatment with antihypertensive medication, and suspicion of renovascular hypertension defined as at least one of: 1. general atherosclerotic disease in coronary arteries, cerebrovascular or peripheral arterial disease according to patient file reviews, 2. hypertension that developed or worsened suddenly, 3. poorly controlled hypertension (>160/90 mmHg) despite use of three antihypertensive agents [25], 4. malignant hypertension with retinopathy, fundus grade III or IV, 5. increase in serum creatinine >20 μmol/L induced by ACE- inhibitors or angiotensin II receptor antagonists [26]. Exclusion criteria included diabetes, other kidney disease than presumed nephrosclerosis, hypersensitivity to radiologic contrast agents, pregnancy/lactation, use of pacemaker, contagious diseases, and known malignancy. Patients judged not to tolerate withdrawal of ACE inhibitors or angiotensin II receptor antagonists for seven days prior to the investigations and/or unable to hold their breath for 15 seconds were also not eligible for the study.

The patients all started the investigations at about 9.00 a.m. on day 1 by blood sampling for analysis of routine laboratory parameters and a check by the responsible physician. They proceeded by undergoing baseline renography, after initiation of intravenous infusion of 0.9% NaCl. Ultrasound and MRI examination were performed immediately after the renography, and the administration of NaCl continued until the patient was provided with lunch. Then, CT angiography was performed and intravenous saline infusion continued during another 12 hours. Day 2 began with drawing of blood in the fasting state and included re-analysis of serum creatinine. The patients then underwent the second renographic examination after pre-treatment with captopril. Patients in whom the serum creatinine had not increased more than 15% were allowed to return home after lunch on day two after a final check-up by the responsible physician.

Investigations

CT Angiography (CTA)

During the time period Dec. 2004–Oct. 2006, 27 patients were examined with a multidetector-row CT scanner (Somatom Sensation16; Siemens Medical Systems, Forcheim, Germany) by injecting 50 ml iodixanol 320 mg I/ml (Visipaque®, GE Healthcare, Princeton, NJ, USA) at 5.5 ml/sec, followed by a saline bolus (70 ml, 5.5 ml/sec). Automatic bolus triggering was used. An early arterial phase (16×0.75 mm collimation, slice width 1.0 mm, reconstruction interval 0.4 mm, mean 120 mAs, 120 kV) was acquired. During the time-period Nov. 2006–Febr. 2008, 20 patients were examined with a dual source multidetector-row CT scanner (Somatom Definition; Siemens Medical Systems, Forcheim, Germany) with contrast injection as described above. An early arterial phase (64×0.65 mm collimation, slice width 0.75 mm, reconstruction interval 0.3 mm, mean 170 mAs, 120 kV) was acquired. The field of view for the acquired datasets from the two scanners was the same: 256 mm × 256

mm with 512×512 matrix, resulting in an identical in-plane voxel size of 0.5 mm × 0.5 mm. All patients were scanned with single-breath-hold technique in the cranio-caudal direction through the kidneys. Images were transferred over the network to a PACS system (SECTRA, IDS5, Linköping, Sweden).

MR Angiography (MRA)

MRI examination was carried out on a 1.5 T scanner (Philips Achieva, Philips Healthcare, Best, the Netherlands) with an effective gradient strength of 114 mT/m, using a SENSE Body coil. The protocol included axial steady state free precession (Balanced Turbo Field Echo) images as well as coronal 3D gradient echo (Fast Field Echo) images (TE=1.54 ms, TR=5.4 ms, 3 dynamic phases, voxel size $0.7 \times 0.7 \times 1.0$ mm^3, covering the abdominal aorta and renal arteries, after injection of gadodiamide (Omniscan®, GE Healthcare, Oslo, Norway) or Gd-DTPA (Magnevist®, Schering AG, Berlin, Germany) in a dose of 30 ml in a rate of 2.5 ml/sec followed by 25 ml saline. In accordance with the initial protocol, gadodiamide was used in 34 patients, but after the publication of several reports concerning the association between nephrogenic systemic fibrosis and certain gadolinium agents [27], it was decided (in January 2007) to continue the study using Gd-DTPA (given in 13 patients) restricted to patients with glomerular filtration rate > 30 ml/min per 1.73 m^2. Synchronization between injection and acquisition was achieved with real-time imaging of the abdominal aorta during the injection.

Morphological image assessment

Images from CT were reviewed as original slices as well as with multiplanar reformat (MPR) and Volume Rendering Technique (VRT) by one observer, blinded for the other modalities. Images from MRI were viewed as original slices, MPR and with Maximum Intensity Projection (MIP) by a different observer, blinded for the other modalities. Analyses included an assessment of the main renal arteries and of the accessory arteries. With access to the original slices and MPR reformats, as well as digital measurement tools, the observers made a decision on the presence of morphological stenosis exceeding 50% diameter reduction (in any direction) on a 5-grade scale: 1 = definitely absent, 2 = probably absent, 3 = inconclusive, 4 = probably present and 5 = definitely present. In comparisons with other methods, 1–2 were considered negative findings, and 4–5 positive findings. The degree of stenosis was estimated on a 6-grade scale: normal, diameter reduction >10% but ≤30%, diameter reduction >30% but ≤50%, diameter reduction >50% but ≤70%, diameter reduction >70%, and occlusion.

Ultrasound

Ultrasound was not part of the original protocol but was added later and carried out, according to a standardized protocol, in 36 patients. The ultrasound examinations were performed using a Siemens ACUSON Sequoia C512 with a 4C2 probe (Siemens Medical Systems, Forcheim, Germany) with pulsed wave Doppler at 2 Mhz, imaging at 2–4 MHz and high pulse repetition frequency mode, using a flank approach and an intravenous contrast agent. The number of examiners involved in the study was limited to two, and they were blinded to other modalities.

The contrast agent Sonovue (Bracco Imaging SpA, Milan, Italy) was given as a 2.4 ml bolus dose, or as a dose of 2.4 ml mixed with 10 ml of saline (NaCl 0.9%), producing approximately 12.4 ml of contrast mixture, which was infused at a rate of 2 ml/min using a syringe pump (Bracco VueJect BR-INF 100). Contrast administration was repeated when deemed necessary.

During the exam, color Doppler imaging was used to identify the renal arteries, and pulsed wave Doppler to measure the blood flow velocity. Measurements were made in the proximal, intermediate and distal renal artery. Post-examination evaluation was performed on the Siemens ACUSON KinetDx workstation.

The diagnosis was based on the peak systolic velocity (PSV) [27]. A positive finding was defined as a PSV value of at least 1.8 m/s [29]. In those cases where no reliable velocity measurement was obtained, the examination was considered inconclusive. The frequency of positive findings was also calculated with an alternative PSV threshold of 2.5 m/s.

Captopril renography

Renography was exclusively performed as ACE inhibition renography [10] including a two-day protocol with a baseline renogram day 1 and a captopril stimulated renogram the following day. ACE-inhibitors and angiotensin II-blockers were discontinued 7 days before the baseline examination.

One hour before the renographic study day 2, the patient received 25 mg of captopril (Capoten®, Bristol-Myers Squibb AB) orally. For renin analysis, blood samples were collected after 60 min rest with the patient in supine position before and one hour after the administration of captopril. The analytical method used measures the concentration of active renin by an immunoradiometric assay (IRMA Cisbio Bioassays). Reference values are 3-20 ng/L.

A dual-head large field of view gamma camera (GE XRT, Entegra, GE Medical, Milwaukee, WI, USA), equipped with a general-purpose parallel-hole collimator, was used and images were collected in a 128 × 128 matrix. Starting immediately after the intravenous injection of 70 MBq 99mTc-MAG3 (Mallinckrodt Ltd.), serial 10 second per frame images were obtained for 16-20 minutes.

Subsequent analysis was made using in-house software for renal scintigraphy, including calculation of relative renal function as well as absolute function (camera-based MAG3-clearance in ml/min) [30].

The interpretation of the ACE inhibitor renography was based on the criteria in [10]. In cases of an intermediate test result, the final interpretation was resolved by adding the result of the renin analysis. A positive result was defined as an absolute P-renin level after stimulation exceeding 50 ng/L and at least twice the basal level. Two out of totally six intermediate renography results were thus turned into positive, and four into negative tests.

Ethics

The study was approved by the Regional Ethics Committee of Linköping and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participating subjects.

Methodological standards

Using CTA-demonstrated stenosis reducing the vessel diameter by more than 50% as the reference method, sensitivity and specificity of each diagnostic method was calculated. In addition, a combined criterion representing morphological as well as functional evidence of renal artery stenosis was defined in the following way: if at least one of CTA and MRA indicated a diameter reduction exceeding 50% *and* at least one of the two functional methods ultrasound and captopril renography supplemented by renin analysis indicated the presence of

significant stenosis, then “morphological and functional stenosis” was considered to be positive.

Statistics

Descriptive statistics are given as mean ± standard deviation (SD) and number (percent), respectively. Confidence limits for sensitivity and specificity were obtained by exact calculation from the binomial distribution. The agreement between ultrasound and renography, as well as between CTA and MRA with respect to degree of stenosis, was evaluated as percent agreement and with the (linearly weighted) kappa coefficient (with 95% confidence interval) [32].

Results

Clinical background variables are summarized in Table 1, and results of standard laboratory tests in Table 2. The laboratory tests confirmed that the patients had moderate renal failure. All patients included in the study were treated with antihypertensive drugs.

The diagnostic procedures were carried out without complications. In none of the patients was there a rise in plasma creatinine by more than 12 μmol/L; in fact, there was a mean decrease of 13 μmol/L. No patient showed signs of nephrogenic systemic fibrosis at follow-up. Two patients declined MRI examination due to claustrophobia. The test material for the captopril test was lost in three cases. There was a blood pressure drop before the renin blood sample in one patient, most likely causing a false positive captopril test.

Accessory arteries were seen with CTA and MRA in 16 patients (11 had 3 arteries, 4 had 4 arteries and one had 5 arteries), whereas 31 patients (66%) had one artery to each kidney.

Frequency of pathological findings

When the data were analyzed at the individual level, so that presence of arterial stenosis was defined for each patient, the frequency ranged between 30% for captopril renography and 70% for CTA with stenosis defined as 50% diameter reduction (Table 3). When defined as 70% diameter reduction, the frequency of stenosis with CTA and MRA decreased, approaching the number of positive findings obtained with renography.

When each kidney was evaluated separately, the frequency figures were consistently lower, ranging between 15% for captopril renography and 53% for CTA (with 50% diameter reduction). When defined at the artery level, the prevalence as detected by CTA and MRA became even lower.

Agreement between methods

When the degree of stenosis in individual arteries was compared between CTA and MRA, the agreement was moderate with no tendency to systematic over- or underestimation with MRA relative to CTA (Table 4). If only the presence or absence of stenosis exceeding 50% diameter reduction was considered, the observed agreement was 52.8% and kappa 0.576 (0.419–0.734).

When ultrasound was related to renography, both methods agreed on a positive finding in 12 patients and on a negative finding in 13 patients. A positive ultrasound finding was combined

with a negative renography finding in 7 patients, and the converse in 1 patient (observed agreement 75.8%; kappa = 0.530 (0.247–0.814)). When evaluated separately for each kidney, concordant positive findings were obtained for 6 kidneys, concordant negative findings for 32 kidneys, and discordant findings for 14 kidneys, 6 of which with negative ultrasound and positive renography result. In 20 cases, either method was inconclusive. The observed agreement was 73.1% and kappa 0.284 (0–0.604).

Evaluation using CTA as reference standard

CTA-verified stenosis with more than 50% diameter reduction was present in 52 renal arteries, representing 50 kidneys in 33 patients. Using this criterion as the reference method (Table 5), the highest sensitivity was found for MRA, both at patient and kidney level. However, at the patient level, the sensitivity of ultrasound was only slightly lower. When evaluated for each kidney, captopril renography had considerably lower sensitivity values. The highest specificity, on the other hand, was found for captopril renography when evaluated at the patient level, whereas comparable specificity figures were found for all the tested methods at the kidney level.

Evaluation using the combined reference standard

Summarizing the diagnostic findings to the combined criterion "morphological and functional stenosis" resulted in a positive diagnosis in 21 patients, a negative diagnosis in 13 patients, and inconclusive results in 13 patients. Relating each diagnostic method to this reference variable (Table 6), the highest sensitivity was found for CTA, and the highest specificity for ultrasound and captopril renography, regardless of whether the analysis was carried out at the patient, kidney or artery level. Raising the stenosis threshold for CTA and MRA to 70% diameter reduction resulted in markedly lower sensitivity values, in particular for MRA. Captopril renography had lower sensitivity than ultrasound.

Post-study arterial angiography and renal artery dilatation

Although not a part of the study, catheter arteriography was eventually performed in 17 patients with a positive diagnosis according to the combined reference method and in 5 patients with CTA and MRA-verified stenosis exceeding 50% diameter reduction but inconclusive functional data. These 22 patients had uncontrolled hypertension and/or threat to substantial parts of the renal parenchyma as well as renal stenosis qualifying for dilatation, and all of them underwent PTRA.

Discussion

As our findings show, all studied methods for diagnosis of renal artery stenosis may be used in patients with moderately impaired renal function. This is of particular interest, as most previous studies have not comprised this group of patients. Also, ultrasound contrast agents do not seem to have been frequently used in earlier studies.

The absence of an undisputable "gold standard" is problematic; although invasive angiography has a strong tradition as reference method, it relies only on morphologic information obtained from one or a few projections, thus ignoring much of the spatial information in CTA and MRA as well as the functional information from Doppler ultrasound and renography. Ideally, methods for diagnosing renal artery stenosis should be evaluated against the outcome of interventions such as PTRA. In clinical routine, however, the decision to undertake such an intervention in a patient with renal failure is not based on a single

diagnostic procedure, and evaluating its effect is confounded by the effects of concurrent medical therapy, patient-related preferences, and costs. We therefore judged it impractical to use therapeutic outcome as reference method in this group of patients.

An alternative might be to base the reference diagnosis on invasive measurement of the pressure drop across the stenosis [16–20]. In a semi-experimental study, the pressure drop was shown to be related to the release of renin behind the stenosed artery [33]. The obvious drawback is that this diagnostic procedure requires the introduction of a catheter for pressure measurements into the arterial system of the patient, with known complication risks. Hence, we considered it ethically unacceptable to carry out catheterization in those of our patients where non-invasive diagnostic methods did not indicate any stenosis. Furthermore, the presence of the catheter itself may influence the pressure measurements [21–24]. It may also be difficult to apply and interpret pressure measurements to tandem stenoses.

Considering these difficulties in establishing a suitable reference method, we decided to use CTA, the morphological technique offering the highest spatial resolution, as our primary reference method. We then found MRA to have superior sensitivity compared to ultrasound and captopril renography, regardless of whether patients, kidneys or arteries were considered. MRA is also the only of the studied methods, in addition to CTA, that can reliably distinguish between several arteries supplying the same kidney. Specificity, on the other hand, was higher for captopril renography and Doppler ultrasound at the patient level. At the kidney level, all three methods had comparable specificity.

The alternative criterion, “functional and morphological stenosis” (Table 6), was an attempt to include functional as well as morphological information in the reference method. The effect was only a moderate reduction of the proportion of positive cases from 70% to 62%. The high sensitivity of CTA against this standard comes as no surprise, but its remarkably low specificity raises the suspicion that CTA may identify morphological stenoses even in the absence of substantial effects on the blood flow through the vessel. The specificity of ultrasound and captopril renography was in general higher than that of the morphological methods, unless the stenosis thresholds were raised to 70%. The sensitivity for ultrasound was higher than that for captopril renography. A related issue, not addressed in this study, is whether the functional information present in ultrasound and captopril renography can be replaced by quantitative MRI phase-contrast velocity measurements [34–36]. Regardless of which method is used for functional assessment, it seems that combining morphological and functional data in a strictly defined variable might be useful in future studies of renal artery stenoses.

In general, the frequency of renal artery stenosis was higher than we had expected in this population. The large differences in frequency of pathological findings between methods revealed by Table 3 are remarkable. The findings also illustrate the fact that prevalence figures referring to subjects must not be compared with figures referring to separate kidneys or individual arteries. The prevalence of renovascular hypertension in the general hypertensive population has been reported to be <1%, but as high as 20–40% in highly selected materials [37]. One might consider whether the low frequency of positive renography findings could reflect the frequency of critical stenosis more appropriate than stenosis defined by 50% diameter reduction at CTA. Studying this problem is difficult without recourse to selective catheterization methods.

In our material, the agreement between the two morphological methods CTA and MRA was moderate, and a limited agreement between ultrasound and captopril renography at the kidney level was also found. Renography is a method for detecting renovascular hypertension and not primarily RAS. The method is based on activation of the renin–angiotensin–aldosterone

system in the affected kidney, due to a substantial reduction in post-stenotic perfusion pressure and a suppression of contralateral renin secretion [31]. The fact that captopril renography cannot give useful information on the contralateral side in positive cases is reflected in the present study as lower sensitivity and specificity at the kidney level, as all contralateral findings have been defined as inconclusive.

For the clinical situation, it should be specified whether we want a method with high specificity for selection of patients suitable for PTRA or a method with high sensitivity suitable for screening of renovascular disease (ischemic nephropathy). Only identifying severe stenosis may be insufficient if we want to treat renovascular disease aggressively with anti-hypertensive and lipid-lowering therapy, a strategy that recently has been shown to decrease intima-media thickness in atherosclerosis [6]. Potential risks of the diagnostic methods used here mainly relate to the injected contrast media, as the radiation dose is a minor concern in the current age group. Both iodine (for CTA) and gadolinium (for MRA) are problematic in this type of patients [27, 38]. However, we observed no cases of either contrast-induced nephropathy or nephrogenic systemic fibrosis in our limited group of patients. The ultrasound protocol we have used included the use of a contrast agent with a very good safety profile [39].

In conclusion, in our material consisting of hypertensive non-diabetic patients with moderate renal insufficiency, CTA and MRA both seem apt to diagnose stenosis in the renal artery with a diameter reduction of 50% or more, whereas ultrasound and, in particular, renography were less sensitive in this respect. In the clinical work-flow, however, ultrasound and renography may have complementary roles, where the high-sensitivity method ultrasound may be useful in screening before morphological stenosis has been diagnosed, and the more restrictive captopril renography by confirming the effect on renin secretion of a morphological stenosis whose hemodynamic consequences are otherwise unclear.

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Table 1. Clinical characteristics of the 47 patients at inclusion

Variable	Mean ± SD / *n* (%)
Age	67.6 ± 10.6
Male sex	35 (74.5%)
Systolic BP, day 1 (mm Hg)	166 ± 28
Diastolic BP, day 1 (mm Hg)	88 ± 13
Number of anti-hypertensive drugs, 1 week before study	3.0 ± 1.1
Treatment with ACE or AII-inhibitors (except the week immediately preceding investigations)	22 (46.8%)
Atherosclerotic heart disease	20 (42.6%)
Cerebrovascular disease	14 (29.8%)
Atherosclerotic limb disease	6 (12.8%)
Smoking previous ongoing never	 22 (46.8%) 12 (27.7%) 13 (25.5%)
Lipid-lowering therapy	24 (51.1%)
Inclusion criterion “rising plasma creatinine on ACE- or AII-inhibition”	12 (25.5%)
Inclusion criterion “at least 3 antihypertensive drugs”	20 (42.6%)
Inclusion criterion “known atherosclerotic disease”	33 (70.2%)
Inclusion criterion “sudden onset of or worsening of hypertension”	9 (19.1%)

Table 2. Laboratory values day 1 and day 2

Laboratory value	Mean ± SD
Blood hemoglobin, day 1 (g/l)	132 ± 14
Plasma hsCRP, day 1 (mg/l)	10 ± 11
Plasma creatinine, day 1 (μmol/l)	180 ± 40
Plasma creatinine, day 2 (μmol/l)	167 ± 41
Plasma urea, day 1 (mmol/l)	12.6 ± 5.0
Plasma urea, day 2 (mmol/l)	10.5 ± 5.5
Iohexol clearance (ml/min and 1.73 m^2 body area)	30.6 ± 13.7
Plasma triglycerides, fasting, day 2 (mmol/l)	1.8 ± 1.4
Plasma cholesterol, fasting, day 2 (mmol/l)	4.7 ± 1.1
Plasma HDL cholesterol, fasting, day 2 (mmol/l)	1.2 ± 0.3
Plasma LDL cholesterol, fasting, day 2 (mmol/l)	2.6 ± 0.8
Plasma LDL/HDL ratio	2.3 ± 0.8
Fasting plasma glucose, day 2 (mmol/l)	5.9 ± 1.2

Table 3. Frequency of pathological findings with different diagnostic methods

Evaluated at patient level (*n*=47)

	Positive	Inconclusive	Negative	Total
CTA (>50% diameter reduction)	33 (70%)	—	14 (30%)	47
CTA (>70% diameter reduction)	21 (45%)	—	26 (55%)	47
MRA (>50% diameter reduction)	27 (60%)	1 (2%)	17 (38%)	45
MRA (>70% diameter reduction)	16 (36%)	—	29 (64%)	45
Ultrasound (PSV≥1.8 m/s)	19 (53%)	3 (8%)	14 (42%)	36
Ultrasound (PSV≥2.5 m/s)	12 (33%)	3 (8%)	21 (58%)	36
Captopril renography	12 (25%)	6 (13%)	29 (62%)	47
Captopril renography + renin analysis	14 (30%)	—	33 (70%)	47

Evaluated at kidney level (*n*=94)

	Positive	Inconclusive	Negative	Total
CTA (>50% diameter reduction)	50 (53%)	—	44 (47%)	94
CTA (>70% diameter reduction)	24 (25%)	—	70 (74%)	94
MRA (>50% diameter reduction)	37 (41%)	3 (3%)	50 (56%)	90
MRA (>70% diameter reduction)	18 (20%)	—	72 (80%)	90
Ultrasound (PSV≥1.8 m/s)	21 (29%)	8 (11%)	43 (60%)	72
Ultrasound (PSV≥2.5 m/s)	12 (17%)	8 (11%)	52 (72%)	72
Captopril renography	12 (13%)	18 (19%)*	64 (68%)	94
Captopril renography + renin analysis	14 (15%)	14 (15%)*	66 (70%)	94

*) Including inconclusive findings in 14 kidneys contralateral to a kidney with positive finding

Evaluated at artery level (*n*=116)

	Positive	Inconclusive	Negative	Total
CTA (>50% diameter reduction)	52 (45%)	1 (1%)	63 (55%)	116
CTA (>70% diameter reduction)	25 (22%)	1 (1%)	90 (78%)	116
MRA (>50% diameter reduction)	39 (35%)	6 (5%)	67 (60%)	112
MRA (>70% diameter reduction)	19 (17%)	1 (1%)	92 (82%)	112

Table 4. Degree of stenosis in individual arteries with CT Angiography and MR Angiography

	Diameter reduction by CTA						
Diameter reduction by MRA	≤10%	10–30%	30–50%	50–70%	>70%	Occlu-sion	Total
≤10%	16	7	1	0	0	0	**24**
10–30%	10	4	2	6	0	0	**22**
30–50%	7	1	9	4	1	0	**22**
50–70%	4	1	2	8	8	0	**23**
>70%	1	1	1	2	10	2	**17**
Occlusion	1	0	0	0	0	1	**2**
Total	**39**	**14**	**15**	**20**	**19**	**3**	**110**

Agreement = 49.1% (= 54/110); linearly weighted kappa = 0.497 (0.386–0.608); McNemar: $p = 1.000$

Table 5. Sensitivity and specificity of diagnostic methods relative to the presence of diameter reduction exceeding 50% according to CTA.
TP= true positive; FP=false positive; TN=true negative; FN=false negative.

Evaluated at patient level (*n*=47)

Method	*n*	TP	FP	TN	FN	Incon-clusive	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)
MRA (>50% diameter reduction)	45	25	2	11	6	1	0.806 (0.625–0.925)	0.786 (0.492–0.953)
Ultrasound (PSV≥1.8 m/s)	36	19	0	8	7	2	0.704 (0.498–0.862)	0.889 (0.518–0.997)
Captopril renography + renin analysis	47	14	0	14	19	0	0.424 (0.255–0.608)	1.000 (0.807–1.000)

Evaluated at kidney level (*n*=94)

Method	*n*	TP	FP	TN	FN	Incon-clusive	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)
MRA (>50% diameter reduction)	90	31	6	40	10	3	0.756 (0.597–0.876)	0.816 (0.680–0.912)
Ultrasound (PSV≥1.8 m/s)	72	19	2	29	14	8	0.528 (0.355–0.696)	0.806 (0.640–0.918)
Captopril renography + renin analysis	94	13	1	43	23	14	0.295 (0.168–0.452)	0.860 (0.733–0.942)

Evaluated at artery level (*n*=116)

Method	*n*	TP	FP	TN	FN	Incon-clusive	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)
MRA (>50% diameter reduction)	111	29	9	54	13	6	0.674 (0.515–0.809)	0.794 (0.679–0.883)

Table 6. Sensitivity and specificity of diagnostic methods relative to the provisional reference method ”functional and morphological stenosis” with PSV threshold 1.8 m/s. TP= true positive; FP=false positive; TN=true negative; FN=false negative.

Evaluated at patient level (*n*=34; reference method missing in 13 cases)

Method	*n*	TP	FP	TN	FN	Incon-clusive	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)
CTA (>50% diameter reduction)	34	21	5	8	0	–	1.000 (0.867–1.000)	0.615 (0.316–0.861)
CTA (>70% diameter reduction)	34	17	0	13	4	–	0.810 (0.581–0.946)	1.000 (0.794–1.000)
MRA (>50% diameter reduction)	33	18	3	9	2	1	0.900 (0.683–0.988)	0.692 (0.386–0.909)
MRA (>70% diameter reduction)	33	12	2	11	8	–	0.600 (0.361–0.809)	0.846 (0.546–0.981)
Ultrasound (PSV≥1.8 m/s)	34	19	0	13	1	1	0.905 (0.696–0.988)	1.000 (0.794–1.000)
Captopril renography + renin analysis	34	14	0	13	7	–	0.667 (0.430–0.854)	1.000 (0.794–1.000)

Evaluated at kidney level (*n*=61; reference method missing in 33 cases)

Method	*n*	TP	FP	TN	FN	Incon-clusive	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)
CTA (>50% diameter reduction)	61	27	8	25	1	–	0.964 (0.817–0.999)	0.758 (0.577–0.889)
CTA (>70% diameter reduction)	61	18	2	31	10	–	0.643 (0.441–0.814)	0.939 (0.798–0.993)
MRA (>50% diameter reduction)	60	23	4	26	4	3	0.852 (0.663–0.958)	0.788 (0.611–0.910)
MRA (>70% diameter reduction)	60	12	3	30	15	–	0.444 (0.255–0.647)	0.909 (0.757–0.981)
Ultrasound (PSV≥1.8 m/s)	61	14	0	32	6	2	0.714 (0.513–0.868)	0.970 (0.842–0.999)
Captopril renography + renin analysis	61	14	0	32	8	7	0.500 (0.306–0.694)	0.970 (0.842–0.999)

Evaluated at artery level (*n*=74; reference method missing in 42 cases)

Method	*n*	TP	FP	TN	FN	Incon-clusive	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)
CTA (>50% diameter reduction)	74	29	9	34	2	–	0.935 (0.786–0.992)	0.791 (0.640–0.900)
CTA (>70% diameter reduction)	74	18	2	41	13	–	0.581 (0.391–0.755)	0.953 (0.842–0.994)
MRA (>50% diameter reduction)	72	22	5	33	7	5	0.733 (0.541–0.877)	0.786 (0.632–0.897)
MRA (>70% diameter reduction)	72	12	3	39	17	1	0.400 (0.227–0.594)	0.929 (0.805–0.985)