

Accuracy of Computed Tomographic Angiography and Magnetic Resonance Angiography for Diagnosing Renal Artery Stenosis

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Background: Timely, accurate detection of renal artery stenosis is important because this disorder may be a potentially curable cause of hypertension and renal impairment.

Objective: To determine the validity of computed tomographic angiography (CTA) and magnetic resonance angiography (MRA) compared with digital subtraction angiography (DSA) for detection of renal artery stenosis.

Design: Prospective multicenter comparative study conducted from 1998 to 2001. Two panels of 3 observers judged CTA and MRA image data and were blinded to all other results. Digital subtraction angiography images were evaluated by consensus.

Setting: 3 large teaching hospitals and 3 university hospitals in the Netherlands.

Patients: 402 hypertensive patients with suspected renal artery stenosis were included. A group of 356 patients who underwent all 3 diagnostic tests was used for analysis.

Measurements: Reproducibility was assessed by calculating interobserver agreement. Diagnostic performance was evaluated in terms of sensitivity, specificity, and other diagnostic variables. Atherosclerotic stenoses of 50% or greater and fibromuscular dysplasia were considered clinically relevant.

Results: Twenty percent of patients who underwent all 3 tests had clinically relevant renal artery stenosis. Moderate interobserver agreement was found, with κ values ranging from 0.59 to 0.64 for CTA and 0.40 to 0.51 for MRA. The combined sensitivity and specificity were 64% (95% CI, 55% to 73%) and 92% (CI, 90% to 95%) for CTA and 62% (CI, 54% to 71%) and 84% (CI, 81% to 87%) for MRA.

Limitations: Eighteen percent of the patients were included nonconsecutively. Digital subtraction angiography may be an imperfect reference test.

Conclusion: Computed tomographic angiography and MRA are not reproducible or sensitive enough to rule out renal artery stenosis in hypertensive patients. Therefore, DSA remains the diagnostic method of choice.

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*For a list of the other investigators and research coordinators who participated in RADISH, see the Appendix, available at www.annals.org.

See commentary on p 682 and editorial comment on pp 730-731.

Renal artery stenosis may cause renovascular hypertension and renal impairment. Accurate detection and treatment of clinically relevant stenoses may cure or improve hypertension and preserve renal function. Current treatment options include surgery, percutaneous transluminal renal angioplasty with or without stent placement, and medical therapy. Despite the availability of several other diagnostic tests, intra-arterial digital subtraction angiography (DSA) remains the reference standard for anatomic diagnosis of renal artery stenosis. This test, however, is an invasive procedure that carries a risk for serious complications and is burdensome for patients (1, 2). For this reason, less invasive diagnostic alternatives, such as computed tomographic angiography (CTA) and 3-dimensional contrast-enhanced magnetic resonance angiography (MRA), are widely used for diagnostic work-up in patients with suspected renal artery stenosis.

A recent meta-analysis (3) found that CTA and MRA were significantly better than non-contrast-enhanced magnetic resonance angiographic techniques, ultrasonography, captopril renal scintigraphy, and the captopril test at identifying renal artery stenosis when DSA was used as the reference standard. To date, however, only a limited num-

ber of small, well-designed studies have been published on the diagnostic accuracy of either CTA or MRA for detection of renal artery stenosis in patients with suspected renovascular hypertension (4-14). Because CTA and MRA seemed to be promising techniques with the potential to reduce the number of patients requiring conventional angiography, we set up a large-scale multicenter study to investigate the diagnostic performance of these tests, using DSA as reference standard, in hypertensive patients clinically deemed at risk for renal artery stenosis. The purpose of our study was to determine the interobserver agreement and diagnostic accuracy of CTA and MRA in comparison with DSA and to examine whether CTA or MRA can be used as an initial test for detection of renal artery stenosis.

METHODS

We performed a prospective comparative study among CTA, MRA, and the reference standard, DSA, for the detection of renal artery stenosis. Each included patient underwent all 3 diagnostic tests.

Participants

Over a 3-year period, patients were prospectively recruited from the internal medicine outpatient clinics of 3 large teaching hospitals and 3 university hospitals in the Netherlands. The ethical review board of each hospital approved the study, and written informed consent was obtained from all participants. At the 2 hospitals that recruited most of the participating patients, enrollment was consecutive; the other participating hospitals included patients by using nonsystematic convenience samples. At the 6 participating centers, all hypertensive patients between 18 and 75 years of age with a diastolic blood pressure greater than 95 mm Hg were routinely screened for predefined clinical clues indicating renal artery stenosis, as described by the Working Group on Renovascular Hypertension (15) and others (16, 17). Patients were eligible for participation in the study if they exhibited at least 1 clinical clue. Exclusion criteria were known allergy to iodinated contrast agents; pregnancy; contraindications to MRA, CTA, or DSA (18, 19); contraindications to intervention; or previous participation in the study. All included patients were scheduled to have CTA, MRA, and DSA within a 3-month window. At the coordinating center (Maastricht University Hospital), included patients were scheduled to undergo CTA and MRA on the same day, followed by DSA the next day. At the other centers, the tests were performed on the basis of availability. No treatments that could affect the test results were allowed before all tests were completed. The case record forms for all patients were collected at the coordinating center, and the information was entered into a database.

Imaging Techniques

Each participating hospital was equipped with state-of-the-art magnetic resonance scanners (1.0 or 1.5 Tesla), helical computed tomography scanners (single- or multi-detector row systems), and DSA equipment. In addition, hospitals were allowed to optimize scan protocols during the study when new insights emerged or when equipment was upgraded, an approach that conforms to usual clinical practice. Changes in scan protocols occurred twice (**Appendix Table 1**, available at www.annals.org). To ensure state-of-the-art magnetic resonance imaging, all scan protocols had to meet minimal quality standards in terms of spatial resolution and scan duration. The quality standards were defined by the coordinating center and were based on the protocols that were published at the start of the study. During the entire study, the coordinating center continuously monitored the quality of all images.

Information about manufacturers, scan protocols, and contrast agents is shown in **Appendix Table 1** (available at www.annals.org). All imaging was performed or supervised by experienced radiologists and radiologic technologists. Renal CTA, MRA, and DSA had already been part of clinical routine before the start of the study.

Context

Physicians sometimes use computed tomographic angiography (CTA) or magnetic resonance angiography (MRA) to diagnose renal artery stenosis.

Contribution

This prospective multicenter study compared CTA and MRA with digital subtraction angiography (the reference standard) in 402 hypertensive patients with suspected renal artery stenosis. Multiple experienced physicians sometimes disagreed about whether the CTA and MRA tests showed renal artery stenosis. The sensitivity estimates of CTA and MRA for detecting renal artery stenosis were 64% and 62%.

Implications

In this study, even trained physicians had difficulty interpreting some CTA and MRA tests, and neither test was sensitive enough to rule out renal artery stenosis.

—The Editors

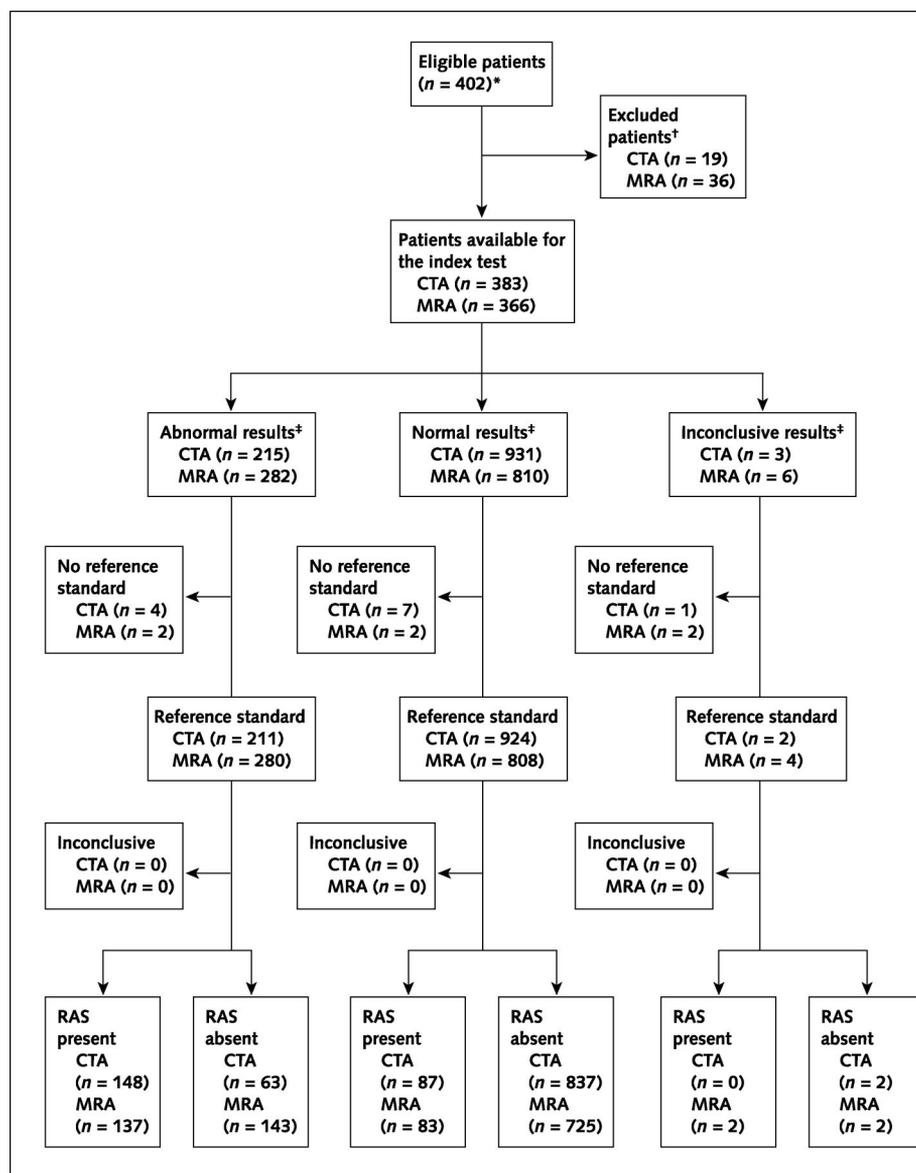
Image Evaluation

At the conclusion of study enrollment, 2 panels of 3 observers evaluated the CTA and MRA image data at the coordinating center. All observers had more than 3 years of experience evaluating such data on a regular basis, and for each method 1 observer had more than 6 years of experience. Each observer independently performed the evaluations and was blinded to all other results, including clinical information and DSA results. Digital image data for all CTA and MRA examinations were evaluated by using a work station equipped with all commonly used image-processing tools (EasyVision, release 4.2.1, Philips Medical Systems, Best, the Netherlands). Source images had to be examined in all cases before a final diagnosis could be made.

The DSA images were evaluated by 4 vascular radiologists, all with more than 10 years of experience in this particular field. The first observer was the radiologist who actually performed the test; the evaluation took place during the DSA procedure. The second and third observers who judged each DSA examination knew the first observer's judgment. If discrepancies existed among the first 3 observers with respect to the number of renal arteries involved or the nature, location, or severity of disease (differences of >10% in the degree of stenosis), a fourth radiologist, who had access to the diagnoses of the other observers, made the final diagnosis. This consensus approach has been used in several other CTA and MRA studies (6, 7, 12–14). All DSA observers were blinded to the results of CTA and MRA.

To determine the degree of stenosis, the diameter of the most severely affected part of a renal artery was measured and related to the reference diameter, which was

Figure 1. Flow of patients through the study.



*The 2 centers that recruited most of the participants included them consecutively. The other centers used nonsystematic convenience samples. Therefore, the exact number of eligible patients is not known. † Reasons for exclusion are given in Appendix Table 2, available at www.annals.org. ‡ The numbers of results presented here are the sum of all computed tomographic angiography (CTA) and magnetic resonance angiography (MRA) observers, respectively. RAS = renal artery stenosis.

defined as the diameter of a representative nonaffected portion of the artery, preferably immediately distal to the stenosis (that is, beyond the site of poststenotic dilatation, if present). Fibromuscular dysplasia was diagnosed when multiple aneurysms separated by focal narrowing (string-of-beads sign) were observed. For CTA, MRA, and DSA, luminal narrowing of at least 50%, as well as all cases of fibromuscular dysplasia, was defined as clinically relevant renal artery stenosis (3).

For each patient, the observers first recorded the number of renal arteries. Subsequently, these arteries were judged with respect to the presence or absence of stenosis (expressed as percentage of luminal narrowing), the nature

of the stenosis (atherosclerotic or fibromuscular dysplasia), the location of the stenosis (ostial or truncal), and the level of confidence in the diagnosis (high, moderate, or poor) (6). Inconclusive examination results were noted on the standardized form used to collect all relevant data.

Statistical Analysis

The severity of the stenoses as seen on CTA and MRA was categorized on a 5-point scale (grade 1, 0% to 19%; grade 2, 20% to 49%; grade 3, 50% to 74% or fibromuscular dysplasia; grade 4, 75% to 99%; and grade 5, total occlusion [100% stenosis]). The Cohen weighted κ analysis was used to test for agreement beyond that of chance

Table 1. Inclusion Criteria for the 356 Patients Who Underwent All 3 Tests*

Inclusion Criterion†	Patients, n (%)
Subcostal bruit present‡	14 (4)
Malignant hypertension‡	20 (6)
Accelerated hypertension‡	49 (14)
Hypertensive retinopathy, grade III or IV‡	22 (6)
Sudden development or worsening of hypertension‡	23 (7)
Signs of atherosclerosis	
In 1 vascular region	25 (7)
In ≥2 vascular regions	42 (12)
Unexplained worsening of renal function (>20- μ mol/L [>0.23 -mg/dL] increase in serum creatinine concentration within 12 mo)‡	38 (11)
Hypertension refractory to appropriate 2-drug regimen	188 (53)
Combination of age <30 y or >60 y and DBP >110 mm Hg	34 (10)
Smoking plus:	
DBP >95 to 110 mm Hg	25 (7)
DBP >110 mm Hg	41 (12)
Impairment of renal function in response to ACE inhibitors‡	20 (6)
Suspicion of restenosis after successful intervention	5 (1)
Unilateral small kidney discovered by ultrasonography (>10% difference in right and left kidney length)‡	7 (2)
Elevated serum cholesterol concentration (>7 mmol/L [>270 mg/dL])	15 (4)
Decreased serum potassium concentration (<3.6 mmol/L) not associated with diuretics	3 (1)
Left ventricular hypertrophy	172 (48)
Captopril renography suggesting renal artery stenosis	2 (1)

* ACE = angiotensin-converting enzyme; DBP = diastolic blood pressure.
 † In addition to the presence of hypertension, patients also had to fulfill at least 1 inclusion criterion to participate in the study. Because of this, the sum of each column exceeds the total number of included patients.
 ‡ Clinical clues as defined by the Working Group on Renovascular Hypertension (15).

among the 3 observers of MRA and among the 3 observers of CTA (20). Unless stated otherwise, all analyses on the diagnostic accuracy of CTA and MRA (sensitivity, specificity, and receiver-operating curve [ROC] analysis) compared with DSA are based on patients as the unit of analysis. In the by-patient analysis, a patient was classified as having positive results if 1 or more renal arteries were found to be stenotic ($\geq 50\%$) on DSA. The most severe stenosis per patient was used for analysis. Inconclusive CTA and MRA results were considered as positive test results because further diagnostic work-up would be required in clinical practice and these patients would be referred for DSA. Exact 2-sided 95% CIs for proportions were calculated by using a binomial distribution. Overall estimates of sensitivity, specificity, positive predictive value, and negative predictive value for all observers per method, including 95% CIs, were calculated by using the cluster option of Stata, version 8.2 (Stata Corp., College Station, Texas) (21). This allowed us to account for the fact that the observations were not independent within each cluster (that is, patient).

The ROC curves, areas under the ROC curves, and standard errors were obtained by assuming a nonparametric distribution. For the construction of ROC curves, the 5-point scale for the severity of stenosis was used. Differ-

ences between areas under the ROC curves were calculated by taking into account the paired nature of the data (22). *P* values less than 0.05 were considered statistically significant.

Additional analyses were performed to determine the influence on test performance of time of data acquisition, location of data acquisition, patient selection, definition of disease, and image evaluation. All data besides clustered data were analyzed by using SPSS (SPSS, Inc., Chicago, Illinois).

Table 2. Demographic and Clinical Characteristics of the 356 Included Patients Who Underwent All 3 Tests*

Characteristic	Value
Mean age \pm SD (range), y	52 \pm 12 (20–75)
Mean systolic blood pressure at baseline \pm SD (range), mm Hg†	183 \pm 25 (128–280)
Mean diastolic blood pressure at baseline \pm SD (range), mm Hg†	107 \pm 15 (40–170)
Mean time with known hypertension \pm SD (range), y‡	8 \pm 9 (0–43)
Mean body mass index \pm SD (range), kg/m ² §	28 \pm 5 (17–46)
Mean creatinine concentration \pm SD (range), μ mol/L [mg/dL]	105 \pm 44 [1.19 \pm 0.50] (51–476 [0.58–5.4])
Mean cholesterol level \pm SD (range), mmol/L [mg/dL]	5.7 \pm 1.1 [220 \pm 42] (2.4–9.1 [93–351 mg/dL])
Women, n (%)	169 (48)
Smokers, n (%)¶	121 (34)
Fundoscopy results, n (%)**	
No retinopathy	19 (14)
Grade I or II	94 (70)
Grade III or IV	22 (16)
Left ventricular hypertrophy on ECG, n (%)††	172 (55)
Intra-arterial DSA results, n (%)	
Renal artery stenosis	72 (20)
Atherosclerotic renal artery stenosis‡‡	45 (63)
Fibromuscular dysplasia	26 (36)
Both atherosclerotic renal artery stenosis and FMD‡‡	1 (1)
Bilateral atherosclerotic renal artery stenosis‡‡	12 (17)
Bilateral FMD‡‡	11 (15)
Distribution of disease on DSA (5-point scale)	
Grade 1 (0%–19% stenosis)	249 (70)
Grade 2 (20%–49% stenosis)	35 (10)
Grade 3 (50%–74% stenosis and all FMD)	49 (14)
Grade 4 (75%–99% stenosis)	10 (3)
Grade 5 (occlusion)	13 (4)

* Clinical data or test results were not available for all patients. DSA = digital subtraction angiography; ECG = electrocardiography; FMD = fibromuscular dysplasia.

† All patients were included on the basis of a mean outpatient diastolic blood pressure greater than 95 mm Hg. Blood pressures presented here were measured under resting conditions in the hospital.

‡ In 348 patients. Criteria for hypertension at the time of initial diagnosis may differ from the criteria currently used.

§ In 347 patients.

|| In 349 patients.

¶ In 353 patients.

** In 135 patients.

†† In 311 patients.

‡‡ Proportion is based on denominator of 72 (that is, the number of patients with renal artery stenosis).

Table 3. Overall Diagnostic Accuracy and Areas under the Receiver-Operating Characteristic Curves for All Observers*

Observer	Sensitivity, %	Specificity, %	Positive Predictive Value, %	Negative Predictive Value, %	AUC
CTA					
A	69	91	67	92	0.84
B	61	89	59	90	0.76†
C	61	97	83	91	0.84
Combined	64 (55–73)	92 (90–95)	68 (59–77)	91 (88–94)	0.85 (0.79–0.91)
MRA					
D	67	77	42	90	0.75
E	63	84	50	90	0.76
F	57	90	59	89	0.81
Combined	62 (54–71)	84 (81–87)	49 (40–58)	90 (87–93)	0.83 (0.77–0.89)

* Values in parentheses are 95% CIs. AUC = area under the receiver-operating characteristic curve; CTA = computed tomographic angiography; MRA = magnetic resonance angiography.

† The AUC for CTA observer B is statistically significantly lower than the AUCs for CTA observers A ($P = 0.03$) and C ($P = 0.05$).

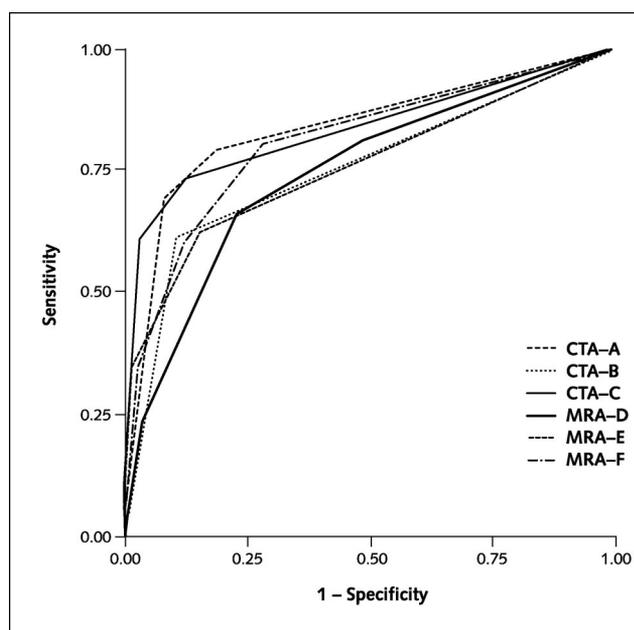
Role of the Funding Source

The Dutch Health Care Insurance Board funded the study after approval of the study protocol. The collection of data and statistical analysis, as well as the reporting of data, were the sole responsibility of the study group. The sponsor did not have an opportunity to comment on the manuscript before submission, and the final version is the sole responsibility of the authors.

RESULTS

Between 28 October 1998 and 30 October 2001, 402 patients met the inclusion criteria and were included in the

Figure 2. Receiver-operating characteristic curves.



Curves are shown for the 3 computed tomographic angiography (CTA) observers (A through C) and the 3 magnetic resonance angiography (MRA) observers (D through F). Areas under the curve are 0.84 for CTA-A, 0.76 for CTA-B, 0.84 for CTA-C, 0.75 for MRA-D, 0.76 for MRA-E, and 0.81 for MRA-F.

study (Figure 1). The distribution of the patients across the participating hospitals is shown in Appendix Table 1 (available at www.annals.org). Forty-six patients were excluded from the analyses because they did not undergo 1 or more of the 3 diagnostic tests. Of these patients, 19 did not undergo CTA and 36 did not undergo MRA; claustrophobia was the most common reason for noncompletion of the latter (Appendix Table 2, available at www.annals.org). For 356 participants, the results of CTA, MRA, and the reference standard, DSA, were available. The median time between performance of DSA and performance of the index tests (CTA and MRA) was 1 day (range, 1 to 60 days).

The distribution of the inclusion criteria for the 356 patients is shown in Table 1. Refractory hypertension and the presence of target organ damage were the most frequently used criteria for inclusion. Multiple clues were present in 126 patients (35%). The distribution of clinical characteristics in the 356 patients is shown in Table 2. There were no statistically significant differences between the characteristics of the 356 patients included in the analysis and the 46 patients who were excluded. In the patients who underwent all 3 tests, DSA showed clinically relevant renal artery stenoses in 72 (96 kidneys), resulting in an overall prevalence of 20%. Twenty-seven patients (38% of all patients with renal artery stenosis) had fibromuscular dysplasia (Table 2). Of the 58 kidneys with atherosclerotic renal artery stenosis, the location of disease was ostial in 35 (60%) and truncal in 23 (40%). Supernumerary (>1 artery per kidney) renal arteries were seen in 140 of 356 patients (39%).

The number of inconclusive examinations ranged from 0 to 2 for the various CTA observers. All 3 MRA observers judged 2 examinations (of the same patients) as inconclusive. Linear weighted κ values indicated moderate interobserver agreement and ranged from 0.59 to 0.64 for CTA and 0.40 to 0.51 for MRA. Diagnostic variables for each observer, including the positive and negative predictive value for a prevalence of 20%, are shown in Table 3. Table 3 also shows the sensitivity and specificity for indi-

vidual observers, which reflect the variation that can occur in clinical practice, and the sensitivity and specificity for CTA and MRA combined for all observers. The combined sensitivity and specificity were 64% (95% CI, 55% to 73%) and 92% (CI, 90% to 95%) for CTA and 62% (CI, 54% to 71%) and 84% (CI, 81% to 87%) for MRA. Receiver-operating characteristic curves for all CTA and MRA observers are shown in **Figure 2**. **Table 4** shows the results of subgroup analyses. The most substantial increase in sensitivity occurred in the subgroup of patients with organ damage who were at least 60 years of age (combined sensitivity, 77% for CTA and 79% for MRA).

DISCUSSION

To our knowledge, this is the largest prospective study comparing the diagnostic performance of CTA and MRA with that of DSA. Our results show that both CTA and MRA have poor sensitivity but adequate specificity for detecting renal artery stenoses. These findings are contrary to the results of nearly all other published studies on the validity of CTA and MRA, which report high estimates for both sensitivity and specificity (up to 100%) (3). Because of the favorable results in the literature, both CTA and MRA are widely used in clinical practice to rule out renal artery disease in hypertensive patients. On the basis of our results, this strategy should be reconsidered. First, however,

potential causes of error in both our study and the other studies in the literature must be considered to find an explanation for the observed discrepancy.

An initial possibility is that diagnostic performance was poor in our study because the technique used to acquire CTA and MRA images was inadequate. However, throughout the study, all participating centers had state-of-the-art equipment and scan protocols. Moreover, when technologic improvements became available, each center was allowed to adjust its scan protocol to take advantage of equipment upgrades. An associated advantage of this protocol flexibility is that it realistically reflected clinical practice and implementation of technologic developments. Subgroup analyses (**Table 4**) showed that neither new technologic developments nor expertise in acquisition of CTA and MRA images resulted in better diagnostic performance. Diagnostic performance in the second half of the study was not better than that in the entire study period and was not higher in the coordinating center, which enrolled 61% of the patients and had more experience with renal CTA and MRA.

Second, it is possible that the discrepancy in diagnostic performance found in our study may be the result of a lack of observer expertise. This explanation, however, does not seem to be well founded; some of the CTA and MRA observers participating in this study have also participated

Table 4. Additional Analyses on Diagnostic Accuracy of Computed Tomographic Angiography and Magnetic Resonance Angiography*

Analysis	Patients, n	Prevalence of Renal Artery Stenosis, %	Overall Estimates for CTA Sensitivity/Specificity, %	Overall Estimates for MRA Sensitivity/Specificity, %
Overall performance	356	20	64 (55–73)/92 (90–95)	62 (54–71)/84 (81–87)
Analyses on time and location of data acquisition				
Only patients included at the coordinating center†	218	23	67 (56–78)/93 (90–96)	67 (57–76)/82 (78–86)
Analyses on patient selection				
Only patients included according to ≥1 criteria of the Working Group on renovascular hypertension	265	22	67 (57–77)/93 (91–96)	68 (60–77)/83 (79–86)
Only patients with organ damage‡	145	26	73 (61–85)/89 (85–93)	77 (67–87)/81 (75–86)
Only patients ≥60 y of age	93	32	77 (64–89)/87 (81–93)	76 (63–88)/75 (67–84)
Only patients ≥60 y of age with organ damage‡	61	36	77 (62–92)/84 (75–93)	79 (66–91)/72 (60–93)
Change in definition of disease				
Only fibromuscular dysplasia considered as disease	356	8	28 (15–52)/99 (98–100)	22 (12–32)/96 (94–97)
Only atherosclerotic renal artery stenosis considered as disease	356	13	77 (67–86)/94 (92–95)	78 (70–87)/88 (86–91)
Definition of clinically relevant renal artery stenosis on DSA ≥70%	356	15	62 (52–72)/90 (86–92)	62 (52–72)/81 (78–92)
Image evaluation				
Defensive approach: defining all diagnoses that were not made with a high level of confidence as positive test results	356	20	83 (76–90)/50 (46–55)	88 (82–93)/50 (46–54)
Only patients without supernumerary arteries	216	21	67 (57–79)/94 (92–97)	67 (57–78)/84 (80–88)

* CTA = computed tomographic angiography; DSA = digital subtraction angiography; MSA = magnetic resonance angiography. Values in parentheses are 95% CIs.

† Maastricht University Hospital.

‡ Inclusion criteria referring to organ damage were subcostal bruit, grade III or IV hypertensive retinopathy, signs of atherosclerosis in ≥1 vascular region, reduced renal function (serum creatinine concentration >133 μmol/L [>1.5 mg/dL]), unilateral small kidney, and left ventricular hypertrophy.

in studies reporting sensitivity and specificity estimates up to 100% (6, 14). Moreover, some of the observers are considered international experts in the field of renal CTA or MRA research, and they all have many years of experience in evaluating such examinations.

Third, the lower sensitivity in our study could be related to patient selection. The construction of a study sample from 6 centers using the same selection criteria but different recruitment methods (consecutive vs. nonconsecutive) may have introduced bias. However, most patients (293 of 356 [82%]) were included consecutively, and within this subgroup the combined sensitivity was still only 67% (CI, 57% to 77%) for CTA and 66% (CI, 57% to 75%) for MRA. Prevalence was 20%, close to that reported by another large study (17). Other studies often reported higher prevalence (up to 70%), suggesting differences in patient selection (4–6, 11, 13). Selection would not be a problem if sensitivity and specificity were invariant variables; it would affect the prevalence but not the sensitivity and specificity. Our study, however, like many other studies, shows that the distribution of the seriousness or grade of disease progression influences these variables. The relatively less restrictive inclusion criteria may explain the lower prevalence and lower sensitivity compared with other studies. The subgroup analysis in patients with higher clinical suspicion, such as patients with organ damage who were at least 60 years of age, showed that the combined sensitivity estimates increased substantially in this group but are still below estimates in previous studies (Table 4).

Fourth, additional analyses with respect to the definition of significant renal artery stenosis showed that the diagnostic accuracy of both CTA and MRA improved when only atherosclerotic renal artery stenoses, usually located in the more proximal part of the renal artery, were considered as disease. This approach excludes fibromuscular dysplasia, which typically affects the more distal renal artery. In the literature, many authors have already indicated that both CTA and MRA have limited ability to visualize disease of the distal (segmental) renal arteries because their spatial resolution is inadequate (5, 11, 23–26).

A striking difference between our study and other studies is the relatively high proportion of patients with fibromuscular dysplasia (38% of all patients with renal artery stenosis). Previous studies reported that the proportion of fibromuscular dysplasia among patients with renal artery stenosis varied between 16% and 40% (27, 28). However, in most studies that reported CTA and MRA sensitivities of up to 100%, the prevalence of fibromuscular dysplasia was low or patients with fibromuscular dysplasia were excluded from analysis (27, 28). It should be noted that in clinical practice it is impossible to exclude patients with fibromuscular dysplasia from the diagnostic work-up because of clinical characteristics. Furthermore, because other studies excluded such patients, their samples are not representative of patients who are referred for diagnosis of renal artery stenosis and excluded those who would benefit most

from intervention (27). The use of another definition of clinically relevant renal artery stenosis (threshold of 70% on DSA) resulted in only a minor increase in sensitivity. The expectation that more severe stenoses are more easily detected was not confirmed (Table 4).

Fifth, with respect to image evaluation, we assessed whether a very defensive approach, defining all diagnoses not made with a high level of confidence as positive test results, might have resulted in an acceptable sensitivity. Sensitivity increased, but not to values exceeding 90%, as were reported elsewhere, and this increase was associated with much lower specificity than in the other studies. Furthermore, whereas many studies analyzed only the main renal arteries and considered all supernumerary (smaller) arteries “accessory” and not clinically relevant, we included such arteries in our baseline analysis (3). One of our subgroup analyses involved patients without supernumerary arteries. No significant changes in diagnostic performance were observed with this approach.

Sixth, it can be argued that DSA is an imperfect reference standard because of its 2-dimensional nature. Reported κ values for DSA indicate that interobserver agreement for the detection of clinically relevant renal artery stenosis is not perfect (range, 0.65 to 0.78), while another study showed that this imperfection was due to variations in estimating both the minimum and reference diameter (29–32). These findings support the notion that DSA is not a perfect reference test. When conditional independence of the reference test and index test (in this case MRA and CTA) is assumed, reference test errors usually result in underestimation of actual test sensitivity, especially when disease prevalence is low (33). Therefore, the imperfection of DSA as a reference standard may partly explain the overall low sensitivity of MRA and CTA in our study and their relatively higher sensitivity in the subgroup of patients with higher clinical suspicion of renal artery stenosis (33).

However, since both the reference test (DSA) and the index tests (MRA and CTA) visualize morphologic changes in arteries, the assumption of conditional independence does not hold. In this situation, reference test errors lead to overestimation of the sensitivity and specificity of the index tests. Given the low sensitivity for MRA and CTA in our study, imperfection of the reference test does not seem to explain the results (34, 35). Moreover, both CTA and MRA showed only moderate interobserver agreements ($\kappa = 0.59$ to 0.64 for CTA and 0.40 to 0.51 for MRA), suggesting that poor reproducibility is a more likely explanation.

Finally, in our study, CTA and MRA images were read by observers who were not involved in clinical work-up. This differs from most other officially blinded studies in which readers were involved in patient care, making some leakage of information almost inevitable. This may also help explain why sensitivity is lower in our study than in previous studies.

Some of the additional analyses presented in Table 4 resulted in higher sensitivity, but estimates still remained well below the 90% to 100% values reported previously. Because of publication bias, studies with favorable results may be overrepresented in the literature. Since this is, to our knowledge, the first large study of both CTA and MRA, publication bias may be an important explanation for the discrepant results.

We conclude that both CTA and MRA are not able to rule out renal artery stenosis in patients whose pretest probability of the disorder is approximately 20%. Even after careful selection of a patient group with a high pretest probability of stenosis, sensitivity remained below 90%. Other authors have emphasized that CTA and MRA are not suitable for identifying fibromuscular dysplasia but suggested that they may be useful for evaluating patients with a high clinical suspicion of atherosclerotic renal artery stenosis (24, 36). Our results do not confirm this hypothesis.

It can be expected that both CTA and MRA will improve with the advent of new technological developments, such as more rapid acquisition by multi-detector row CTA and faster magnetic resonance hardware and software (37, 38). These developments may necessitate new prospective diagnostic studies. Until that time, the moderate interobserver agreements and the low sensitivity of CTA and MRA suggest that DSA is still the method of choice for diagnostic work-up of hypertensive patients with suspected renal artery stenosis.

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COMMENTARY

The principal claim of this carefully done study is that CTA and MRA miss too many cases of renal artery stenosis to be the tests of choice. The purpose of this commentary is to test this claim by translating the sensitivity and specificity into a term that clinicians can use for decision making: the likelihood ratio. Remember that the post-test odds equals the pretest odds times the likelihood ratio. The likelihood ratio, therefore, tells us how much a test result changes the odds of disease. The Table in this commentary shows likelihood ratios calculated from the authors' Table 3.

Often, the physician has decided that the clinical situation (for example, treatment-resistant hypertension) warrants renal artery angioplasty if the patient has renal artery stenosis. The physician then looks to preliminary testing to help decide whether to move on to a more expensive, risky, and invasive definitive test. Given reasonably high clinical suspicion, the question to ask of CTA and MRA is whether a negative result should halt the diagnostic process that could lead to angioplasty. In other words, would the post-test odds after a *negative* CTA or MRA result be so low that a positive result (especially a true-positive result) on DSA would be too unlikely to warrant the risks of DSA?

Given this background, the decision about doing CTA or MRA may depend on the pretest odds. In this study, the average pretest probability was 0.20 (pretest odds, 1:4). Given the negative likelihood ratio of 0.39 for CTA and 0.45 for MRA, the post-test odds would be about 1:10 after negative test results. Is that low enough to stop testing? Physicians may well disagree. Some would do DSA if the chance of a positive result were 10% (this calculation assumes that DSA is a per-

Table. Sensitivity, Specificity, and Likelihood Ratios for Computed Tomographic Angiography and Magnetic Resonance Angiography

Measurement	Computed Tomographic Angiography	Magnetic Resonance Angiography
Sensitivity	0.64	0.625
Specificity	0.92	0.835
Positive likelihood ratio (95% CI)*	7.9 (5.1–12.1)	3.8 (2.8–5.2)
Negative likelihood ratio (95% CI)*	0.39 (0.29–0.53)	0.45 (0.33–0.61)

* Calculated by using data from Table 3 and Stata software, version 8.2 (Stata Corp., College Station, Texas).

fectly accurate test for renal artery stenosis). They should go directly to DSA without doing MRA or CTA, since they would do DSA regardless of the MRA and CTA results. Others would stop the diagnostic process after negative results on MRA or CTA. Since the test results could change their plan, MRA or CTA would be reasonable.

If clinical suspicion were higher than average, the situation would be more clear-cut. Suppose the pretest odds were 1:1. The post-test odds after a negative MRA or CTA result would be about 0.4:1, which corresponds to a probability of 0.29. Most physicians would do a definitive test at this point even after a negative MRA or CTA result, so they should not do MRA or CTA.

This discussion shows that the value of CTA and MRA can depend on the pretest odds of disease.

Harold C. Sox, MD
Editor

Appendix Table 1. Protocols for Computed Tomographic Angiography, Magnetic Resonance Angiography, and Digital Subtraction Angiography*

Variable	Study Center					
	's Hertogenbosch	Maastricht†	Nijmegen†	Tilburg	Utrecht	Veldhoven
Patients included/patients remaining for analysis, <i>n/n</i>	26/21	242/218	89/75	19/16	15/15	11/11
Patients scanned with SENSE MRA/MD-CTA, <i>n/n</i> ‡	0/0	97/0	0/21	0/0	0/0	0/0
CTA						
Scanner manufacturer§	GE	Elscent	Siemens	Philips	Philips	Philips
Collimation, <i>mm/pitch</i>	3/1.5	2.5/0.7	3/1 (4 × 1/1.25)	3/1	3/1	3/1
Contrast agent	Omnipaque 300	Omnipaque 350	Omnipaque 350	Omnipaque 300	Ultravist	Iomeron 300
Amount of contrast agent, <i>mL</i>	120	140	120	120	130	140
Injection rate, <i>mL/s</i>	3.0	4.0	3.0	4.5	3.0	4.0
MRA						
Scanner manufacturer§	GE	Philips	Siemens	Philips	Philips	Philips
Field strength, <i>Tesla</i>	1.5	1.5	1.5	1.0	1.5	1.0
FOV, <i>mm</i>	480 × 288	512 × 302 (400 × 400)	420 × 263	420 × 315	400 × 320	450 × 338
Matrix	512 × 192	512 × 155 (400 × 296)	512 × 192	512 × 163	512 × 196	384 × 160
Acquisition slice thickness, <i>mm</i>	3.0	2.2 (1.9)	2.8	3.0	3.0	2.4
Slices, <i>n</i>	28	29 (35)	32	25	20	28
TR, <i>ms</i>	5.6	5.6 (5.0)	4.6	6.4	7.1	6.3
TE, <i>ms</i>	1.2	1.6 (1.5)	1.8	1.8	1.9	1.7
FA, <i>degrees</i>	40	40 (40)	30	40	45	40
Profile ordering technique	Centric	Centric	Linear	Linear	Centric	Centric
Acquisition voxel size, <i>mm</i> ³	4.2	4.3 (2.6)	3.1	4.7	3.8	5.9
Scan duration, <i>s</i>	30	25 (26)	28	26	28	28
Contrast agent	Magnevist	Magnevist	Magnevist	Omniscan	Magnevist	Prohance
Amount of contrast agent, <i>mL</i>	30	30 (30)	14	20	30	30
Injection rate, <i>mL/s</i>	2.5	3.0 (2.5)	2.5	2.5	2.0	2
DSA						
DSA manufacturer§	GE	Philips	Siemens	Philips	Philips	Philips
Image intensifier, <i>cm</i>	35	38	40	38	38	38
Matrix	1024	1024	1024	512	512	1024
Contrast agent	Omnipaque 300	Omnipaque 300	Omnipaque 240	Omnipaque 300	Ultravist	Iomeron 300
Approximate amount of contrast agent, <i>mL</i>	90	60	160	40	90	60
Injection rate (aorta), <i>mL/s</i>	15	15	20	20	15	10 to 15
Patients with selective renal DSA, <i>n</i>	8	208	3	0	3	2

* CTA = computed tomographic angiography; DSA = digital subtraction angiography; FA = flip angle; FOV = field of view; MD-CTA = multi-detector row CTA; MRA = magnetic resonance angiography; SENSE = SENSitivity Encoding; TE = echo time; TR = repetition time.

† Numbers in parentheses represent the scan variables used for the subgroup of patients who underwent SENSE MRA or 4-row MD-CTA.

‡ SENSE and MD-CTA are recent technologic developments (36, 37). In a subgroup of the included patients (all remaining for analysis), new scan protocols were used; Maastricht used SENSE and Nijmegen used 4-row MD-CTA.

§ Elscint Ltd. is located in Haifa, Israel; GE Medical Systems is located in Milwaukee, Wisconsin; Philips Medical Systems is located in Best, the Netherlands; and Siemens Medical Systems is located in Erlangen, Germany.

|| Omnipaque and Omniscan are products of Nycomed Amersham, Oslo, Norway; Magnevist and Ultravist are products of Schering AG, Berlin, Germany; and Iomeron and Prohance are products of Bracco Byk Gulden, Constanz, Germany.

Appendix Table 2. Unperformed or Incomplete Examinations*

Reason	CTA, <i>n</i>	MRA, <i>n</i>	DSA, <i>n</i>
Death†	0	0	1
Allergic reaction to iodinated contrast agent or gadolinium	0	2	1
Extravasation of contrast agent	1	0	0
Claustrophobia before or during CTA or MRA	1	17	0
Withdrawal from the study‡	4	3	4
Lost to follow-up	3	4	4
Miscellaneous§	5	7	5
Unknown	5	3	0

* Forty-six patients were excluded. Numbers given represent examinations. Since patients could miss more than 1 examination for a specific reason, the sum of unperformed or incomplete examinations exceeds the number of patients. CTA = computed tomographic angiography; DSA = digital subtraction angiography; MRA = magnetic resonance angiography.

† Only deaths that occurred from the time of inclusion to 30 days after the last diagnostic test are reported.

‡ Reasons for withdrawal from the study were unrelated to complications of the studied tests. Informed consent was not withdrawn.

§ In this group, 2 serious adverse events occurred: One patient had a stroke before having any of the studied tests, and another patient had dissection of the left renal artery during DSA (selective catheterization), which resulted in nephrectomy. All other patients in this group did not undergo 1 or more tests because of physical inability (for example, too large, unable to sustain supine position for >5 minutes) or psychological inability (fear of needles).

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