NEPHROLOGY

NEPHROLOGY 2010; **15**, S218–S226 doi:10.1111/j.1440-1797.2009.01244.x

Screening tests for diagnosis of renal artery stenosis

Date written: December 2008
Final submission: June 2009
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[Correction added after online publication on 1 April 2010: Authors' names added.]

GUIDELINES

No recommendations possible based on Level I or II evidence

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based primarily on Level III and IV evidence)

- Gadolinium-enhanced magnetic resonance angiography (MRA) is highly sensitive in detecting atherosclerotic renal artery stenosis (RAS) and is significantly more accurate in excluding the disease. Gadolinium-based imaging should be avoided in patients with glomerular filtration <30 mL/min per 1.73 m^2 because of the risk of nephrogenic systemic fibrosis.
- Spiral computed tomography angiography (CTA) is an accurate, minimally invasive screening test especially suited to diagnosis of RAS due to fibromuscular dysplasia (FMD).
- In an optimal sonographic setting, duplex ultrasonography (DU) is a useful non-invasive screening test in patients with renal insufficiency.

IMPLEMENTATION AND AUDIT

Screening tests of diagnosis of RAS will depend on the availability and institutional expertise with a particular modality. Given the difficulties in conducting research in this area, which is subject to continual technological development, an audit of cases that progress to intra-arterial digital subtraction angiography (IA-DSA) could be undertaken to provide ongoing evidence of diagnostic techniques.

BACKGROUND

Renovascular hypertension (RVHT) is systemic hypertension due to haemodynamically significant RAS of the main renal artery or its proximal branches.[1] From a haemodynamic point of view, a stenosis is significant when there is a demonstrable pressure gradient. The pressure drop beyond the stenosis triggers intrarenal adaptive mechanisms leading to renal ischaemia and hypertension.[2] At least a 50% narrowing is necessary to produce such a pressure gradient, as shown by a study combining three-dimensional MRA and direct measurements across a stenotic lesion.[3] Therefore, despite lack of consensus, most authors use a reduction in luminal diameter of 50% as a cut-off point, to define the presence of haemodynamically significant RAS.[4]

Atherosclerosis accounts for 70–90% of cases of RAS and usually involves the ostium and proximal third of the main renal artery.[5,6] FMD is a collection of vascular diseases that affects either intima, media or adventitia and is responsible for 10–30% of cases of RAS.[5,7] The prevalence of RAS in an unselected hypertensive population varies between 1% and 5%.[8] This increases to 20–40% in patients who exhibit specific clinical symptoms or signs of RVHT.[6]

The IA-DSA is regarded as the gold standard for diagnosis of RAS. However, it is invasive, does not establish the functional nature of the stenotic lesion and is subject to substantial inter-observer variations.[9,10] Conventional IA-DSA is hazardous, especially in those patients most likely to be studied, where co-existing aortic disease may result in athero-embolic complications and therefore clinicians will continue to rely on non-invasive methods as initial diagnostic steps.[11]

These guidelines are an attempt to provide an overview of diagnostic accuracy and reproducibility of three contemporary imaging modalities: duplex ultrasound, CTA and contrast-enhanced magnetic resonance angiography (CE-MRA) for the detection of RAS in patients with clinically suspected RVHT. Functional tests of the renin-angiotensin system, including captopril renography, are not included in these guidelines. They are not recommended in elderly atherosclerotic patients because hypertension in these patients is not renin-dependent and the results do not reliably predict the course of hypertension after revascularization.[5]

SEARCH STRATEGY

Databases searched: The terms used to define arteriosclerotic renovascular disease were 'renal artery obstruction' (as a MeSH term and text word) and 'renal artery stenosis', 'renovascular disease$' and 'renal artery occlusion$' as text words were combined with relevant MeSH terms and text words for diagnosis. The search was performed in Medline (1950 to April 2009). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline. **Date of searches:** 2 April 2009.

WHAT IS THE EVIDENCE?

Anatomical diagnosis

During the past few decades, several studies of non-invasive or minimally invasive tests for the diagnosis of RAS have reported broad ranges of sensitivities and specificities for each test. There is also a significant degree of overlap among the reported diagnostic accuracies of tests. Studies differ in case mix, specific test characteristics and cut-off points of positive test results, all of which may affect estimates of test performance. There are no randomized controlled trials reported in this area. There are three meta-analyses[4,12,13] and two prospective comparative studies.[14,15] These studies fulfilled the following predefined criteria to allow assessment of comparative test performance:

1. suspected RVHT was the indication
2. IA-DSA was used as the gold standard
3. a cut-off point for a positive test was clearly defined
4. absolute number of true positive, false negative, true negative and false positive results were available or could be derived from the presented data
5. clear description of imaging techniques, and
6. blinded comparison with IA-DSA.

These studies form the basis for the formulation of this subtopic.

Duplex ultrasound

A high quality meta-analysis by Williams *et al.*[13] examined 88 studies involving 9974 arteries in 8147 patients. The data were analysed according to a hierarchical summary receiver-operating characteristic (ROC) curve model (Tables 1,2). Heterogeneity in test performance relating to population and design features were also investigated. The following four parameters were evaluated – peak systolic velocity (21 studies), acceleration time (13 studies), acceleration index (13 studies) and renal aortic ratio (13 studies). It was concluded that duplex sonography is a moderately accurate test for RAS and that single peak systolic velocity has the highest performance characteristics, with expected sensitivity of 85% and specificity of 92%. Additional measurements did not increase accuracy.

Computed tomographic angiogram

The meta-analysis performed by Vasbinder *et al.*[4] included five studies[16–20] that met the predefined inclusion criteria. In three studies, the assessment was blinded. Overall sensitivities and specificities ranged from 94% to 100% and 92–99%, respectively. The area under the ROC curve for CTA was 0.99 (Table 3).

Magnetic resonance angiography

The meta-analysis by Tan *et al.*[12] identified 39 studies, of which 25 met inclusion criteria. The number of patients included in the meta-analysis was 998: 499 with non-enhanced MRA and 499 with gadolinium-enhanced MRA. The sensitivity and specificity of non-enhanced MRA were 94% (95% confidence interval (CI): 90–97%) and 85% (95% CI: 82–87%), respectively. For gadolinium-enhanced MRA sensitivity was 97% (95% CI: 93–98%) and specificity was 93% (95% CI: 91–95%). Thus, specificity and positive predictive value were significantly better for gadolinium-enhanced MRA ($P < 0.001$). Accessory renal arteries were depicted better by gadolinium-enhanced MRA (82%; 95% CI: 75–87%) than non-gadolinium MRA (49%; 95% CI: 42–60%) ($P < 0.001$). It was concluded that MRA with gadolinium enhancement is highly sensitive and specific for diagnosis of RAS (Table 4).

Vasbinder *et al.*[4] in their meta-analysis involving 16 studies on MRA demonstrated that gadolinium-enhanced MRA had the highest diagnostic performance. The area under the summary ROC curve for gadolinium-enhanced MRA was 0.99 and for non-gadolinium-enhanced MRA was 0.97 (Figs 1,2).

Assessment of functional significance of renal artery stenosis

Many researchers are attempting to determine whether anatomical lesions are functionally significant using MRI, MD CTA (multi detector system) and DU.

Duplex ultrasonography

The most widely used ultrasonographic parameter to assess the functional significance of RAS is the resistive index (RI). The RI can be calculated from a spectral Doppler and is defined as 1 – (minimum diastolic velocity divided by maximum systolic velocity) × 100.

Radermacher *et al.*[21] have shown that in patients with at least 50% stenosis in at least one renal artery RI values above 80 are highly sensitive and specific to identifying patients in whom angioplasty or surgery will not improve renal function, blood pressure or kidney survival. However, a potential source of bias in this study is that revascularization was considered only in patients with ≥50% stenosis on duplex ultrasound.

Computed tomography angiography

In clinical practice, the assessment of the functional significance of RAS with CT is performed by measuring morphological parameters such as cortical thickness and area, medullary length and area[22,23] and by analysis of renal time attenuation curves after contrast injection as a measure of renal perfusion.

Monier-Vehier *et al.*[23] found a mean cortical thickness of 6.6 mm in post-stenotic kidneys and 7.9 mm in normal contralateral kidneys. A cortical thickness threshold of 8 mm identified significant RAS with a sensitivity of 73% and specificity of 93%. Further work by the same group demonstrated that renal length and cortical thickness increased

6 months after angioplasty for atherosclerotic RAS.[24] The drawback of CT assessment is the additional contrast and radiation dose.

Magnetic resonance angiography/imaging

There are several functional parameters such as renal perfusion, glomerular filtration rate, tubular concentration and transit, diffusion and oxygenation that can be assessed using MRI.[25,26]

Prince *et al.*[27] have demonstrated that the defacing artefact due to turbulent flow distal to RAS as measured with 3D phase contrast MRA is correlated with the presence of haemodynamically significant stenosis. Haemodynamic significance was defined as a decrease in serum creatinine level of 30 µmol/L or a reduction in the number of medications required for blood pressure control after renal artery PTA or surgery. In addition, the study showed that the ischaemic kidney length and mean parenchymal thickness were reduced in unilateral haemodynamically significant lesions.

Schoenberg *et al.*[28,29] demonstrated that the post-gadolinium two-dimensional cine phase contrast flow measurements profile had a sensitivity of 90% and specificity of 94% for the presence of haemodynamically significant stenosis. Characteristic changes in significant RAS include delay and complete loss of the early systolic peak.

Binkert *et al.*[30] investigated the utility of MR-based renal artery flow and volume measurements to predict functional recovery (defined as more than a 15% drop in diastolic BP or more than a 20% reduction in serum creatinine) at 24 h after percutaneous renal angioplasty. They found that the combination of normal renal volume and a renal flow index (renal flow divided by renal volume) below 1.5 mL/min per cm^3 identifies PTA responders with the sensitivity of 91% and specificity of 67%.

Relative merits and shortcomings

Duplex ultrasonography

Duplex ultrasound has several advantages: it is widely available, non-invasive and inexpensive. The drawbacks are: requirement of optimal sonographic test conditions, it is time-consuming, highly operator-dependent, limited by obesity and overlying intestinal gas and inconsistent in identifying accessory and aberrant renal arteries.[31]

Computed tomography angiography

Spiral CT angiography can reliably visualise accessory renal arteries and in this regard it is equal to conventional IA-DSA.[17,18] It also provides better visualization of distal parts of renal arteries than does MRA and hence it is more accurate in the detection of RAS due to FMD.[32] The diagnostic accuracy is reduced to some extent in patients with impaired renal function.[33] The risk of contrast nephropathy seems to be the same with spiral CTA and conventional angiography.[17] An important aspect of spiral CTA is the ability to visualize both arterial lumen and arterial wall (which may contain calcified plaques). It also allows three-dimensional reconstruction, thus allowing spatial assessment of severity of stenosis.[34,35]

Magnetic resonance angiography

The major limitations of CE-MRA are overestimation of significance of moderate lesions and inter-observer variability. This is because the accuracy of interpretation depends on the sophistication of image reconstruction software and radiologists' skill in manipulating images using that software.[36]

At present there are no published studies that specifically investigate the utility of gadolinium-enhanced MRA for detection of FMD and there is little more than anecdotal data available from other studies. Although overt cases of FMD can be diagnosed with gadolinium-enhanced MRA, the general opinion is that we currently not able to detect FMD with high accuracy in the presence of only subtle anatomic changes.[9] MRA, however, can be a useful procedure in patients with compromised renal function.[37] It is contraindicated in patients with claustrophobia and metallic implants. In addition, among patients with moderate to severe renal disease (glomerular filtration rate <30 mL/min per 1.73 m^2), and those requiring dialysis, administration of gadolinium has been strongly linked to nephrogenic systemic fibrosis.[38,39]

Two studies – RADISH[14] (Renal Artery Diagnostic Imaging Study in Hypertension) and the diagnostic phase of DRASTIC[40] (Dutch Renal Artery Stenosis Intervention Cooperative) study illustrate the pitfalls of diagnostic tests for RAS. In the RADISH study, the reported results of validity of CE-MRA and CTA were neither sufficiently reproducible nor sensitive enough to exclude RAS. The possible explanations for these discrepant findings were suboptimal technique, low overall disease prevalence, a high proportion of patients with FMD and imperfect standard of reference.

On the other hand, the authors of the DRASTIC study developed a clinical prediction rule with a reported diagnostic accuracy similar to renal scintigraphy with a sensitivity of 72% and specificity of 90%. The authors concluded that in the diagnostic work up of patients suspected of having RAS, the clinical prediction rule can help select patients for renal angiography in an efficient manner by reducing the number of angiographic procedures without the risk of missing many true RAS.

SUMMARY OF THE EVIDENCE

The search for ideal non-invasive or minimally invasive tests for the screening and diagnosis of RAS is incomplete. Most of the evidence cited in the meta-analyses of published trials suggests superiority of CE-MRA and CTA for screening atherosclerotic RAS.

The imaging modalities used in any particular situation are going to be a combination of what best suits the patient as well as available infrastructure and expertise.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: Guideline 4.1

For patients in whom there is suspicion of renal artery disease (RAD), the clinician should:

1. Estimate the probability of RAD using a predictive index derived from clinical characteristics.
2. Obtain a non-invasive screening test for RAD.
3. Refer to a kidney specialist for evaluation.

UK Renal Association: No recommendation.
Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines: No recommendation.
International Guidelines: No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

Future research in this area is fraught with uncertainties as a result of lack of definitive proof of benefit of endovascular intervention, and rapidly evolving technological innovations designed to improve visualization of renal arteries.

CONFLICT OF INTEREST

Murty Mantha has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

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APPENDICES

Table 1 Summary of population and design characteristics of studies of the accuracy of sonography in the diagnosis of renal artery stenosis

Characteristic	Frequency	
	n	%
Articles reporting number of patients undergoing both duplex sonography and angiography	87	99
Articles reporting number of failed sonographic examinations	77	88
Sonographic method described	76	86
Analysis of occlusion		
Excluded	57	65
Included	21	24
Unclear	5	6
No occlusions in study	5	6
Severity of renal artery stenosis		
50%	54	61
60%	27	31
Other (e.g. 20%, 75%)	6	7
Sonographer blinded to angiographic findings	53	60
Analysis of sonographic failures		
Excluded	44	50
No failures	20	23
Not stated	17	19
Included	7	8
Angiographic method adequately described	43	49
Interpreter of angiograms blinded to sonographic findings	36	41
Angiographic views specified	35	40
Accessory arteries		
Not stated	34	39
Excluded from analyses	30	34
None reported	16	18
Included by two-by-two table data	8	9
Prospective	32	36
Vessel diameter measured during angiography	25	28
Consecutive enrollment	22	25
Clinical spectrum		
Hypertension and other features†	21	24
Hypertension with or without chronic renal failure	21	24
Hypertension moderate or unspecified	18	21
Hypertension and peripheral vascular disease	15	17
Transplant recipient	6	7
Peripheral vascular disease	2	2
No details stated	5	6
Two independent reviewers of angiographic results	13	15
Angiography operator specified	10	11
Performers of both tests blinded to clinical information about patient	7	8

†Other features include bruit, resistance to medications, deterioration and young age. Adapted from Williams *et al.*[13]

Table 2 Estimated Sensitivity, 1 – Specificity, and Likelihood Ratios for diagnosis by duplex ultrasonography

	Peak systolic velocity ($n = 21$)	Acceleration time ($n = 13$)	Acceleration index ($n = 13$)	Renal-aortic ratio ($n = 13$)
Sensitivity	0.85 (0.76–0.90)	0.80 (0.62–0.91)	0.74 (0.55–0.87)	0.78 (0.67–0.86)
1 – Specificity	0.08 (0.05–0.13)	0.12 (0.05–0.25)	0.15 (0.07–0.29)	0.11 (0.06–0.17)
Positive likelihood ratio	10.2 (6.3–16.5)	6.6 (2.8–15.2)	4.8 (2.4–9.9)	7.3 (4.3–12.3)
Negative likelihood ratio	0.2 (0.1–0.3)	0.2 (0.1–0.5)	0.3 (0.2–0.6)	0.2 (0.2–0.4)

Values in parentheses are 95% confidence interval. Adapted from Williams *et al.*[13]

Table 3 Diagnostic tests in renovascular hypertension

Study (reference)	Year	Test	Patients (*n*)	Definition of haemodynamically significant stenosis† %	Blinded review‡	Accessory arteries included	Missing observations§	Unit of analysis	True positive results	False negative results	True negative results *n*	False positive results	Sum¶	Sensitivity %	Specificity %	Area under the receiver-operating characteristic curve††
Equine *et al.*[19]	1999	CTA	50	50	Not mentioned	No	None	Artery	53	0	65	6	124	100	92	1.00
Galanski *et al.*[16]	1994	CTA	52	50	Yes	Yes	None	Artery	91	5	68	2	166	95	97	0.99
Kaatee *et al.*[18]	1997	CTA	71	50	Yes	Yes	Excluded	Artery	60	1	89	6	156	98	94	0.99
Olbricht *et al.*[17]	1995	CTA	62	50	Yes	Yes	None	Artery	23	1	172	1	197	96	99	0.99
Wittenberg *et al.*[20]	1999	CTA	82	50	No	Yes	None	Patient	26	7	15	1	49	79	94	0.95

†Cut-off value for a positive result on the gold standard test. ‡The index test and conventional angiography were judged without knowledge of the outcome of the opposite test. §Missing observations or technical failures were included in analysis. ¶Total of true positive results, false positive results, false negative results and true negative results. ††Areas for individual studies are computed by assuming logistically distributed data for healthy and diseased persons with equal variances. Adapted from Vasbinder *et al.*[4] CTA, computed tomography angiography.

Table 4 Extracted data from studies that met the inclusion criteria

Study (reference)	Year	Test	Patients	Definition of haemodynamically significant stenosis† %	Blinded review‡	Accessory arteries included	Missing observations§	Unit of analysis	True positive results *n*	False negative results *n*	True negative results *n*	False positive results *n*	Sum¶ *n*	Sensitivity %	Specificity %	Area under the receiver-operating characteristic curve††
Bongers *et al.*	2000	Gadolinium-enhanced MRA	43	50	Yes	No	None	Patient	29	0	14	0	43	100	100	1.00
De Cobelli *et al.*	2000	Gadolinium-enhanced MRA	45	50	Yes	Yes	Excluded	Artery	32	0	65	5	102	100	93	1.00
Korst *et al.*	2000	Gadolinium-enhanced MRA	88	50	Yes	Yes	Excluded	Artery	36	0	57	5	88	100	92	1.00
Leung *et al.*	1998	Gadolinium-enhanced MRA	20	60	Not mentioned	No	None	Artery	8	0	31	1	40	100	97	1.00
Reiumont *et al.*	1997	Gadolinium-enhanced MRA	30	50	Yes	Yes	Excluded	Artery	46	0	15	5	66	100	75	1.00
Thornton *et al.*	1999	Gadolinium-enhanced MRA	62	50	Yes	Yes	Excluded	Artery	23	3	101	2	129	88	98	0.99
Arlart *et al.*	1992	2-D time-of-flight MRA**	41	50	Yes	No	Excluded	Artery	23	3	28	5	59	88	85	0.93
Fellner *et al.*	1995	2-D time-of-flight MRA**	46	60	Yes	No	Included	Artery	7	0	71	14	92	100	84	1.00
Laissy *et al.*	1996	2-D time-of-flight MRA**	36	50	Yes	Yes	None	Artery	15	1	60	1	77	94	98	0.99
Arlart *et al.*	1992	3-D time-of-flight MRA**	41	50	Yes	Yes	None	Artery	18	2	24	9	53	90	73	0.90
Borrello *et al.*	1995	3-D time-of-flight MRA**	15	50	Yes	No	None	Artery	7	6	20	1	34	54	95	0.89
Fellner *et al.*	1995	3-D time-of-flight MRA**	46	60	Yes	No	Included	Artery	7	0	76	9	92	100	89	1.00
Postma *et al.*	1997	3-D time-of-flight MRA**	37	50	Yes	No	None	Patient	12	0	24	1	37	100	96	1.00
Smith and Bakke	1993	3-D time-of-flight MRA**	12	75	Yes	Yes	None	Artery	7	0	18	1	26	100	95	1.00
Strotzer *et al.*	1995	3-D time-of-flight MRA**	55	60	Not mentioned	No	Included	Artery	10	0	90	10	110	100	90	1.00
De Cobelli *et al.*	1996	Phase-contrast MRA**	50	50	Yes	Yes	Excluded	Artery	18	2	80	1	101	90	99	0.99
De Haan *et al.*	1996	Phase-contrast MRA**	33	50	Yes	Yes	Excluded	Patient	6	0	26	1	33	100	96	1.00
Loubeyre *et al.*	1996	Phase-contrast MRA**	46	50	Yes	No	None	Artery	11	0	55	29	95	100	65	1.00

**Included in the non-gadolinium-enhanced MRA subgroup. †Cut-off value for a positive result on the gold standard test. ‡The index test and conventional angiography were judged without knowledge of the outcome of the opposite test. §Missing observations or technical failures were included in analysis. ¶Total of true positive results, false positive results, false negative results and true negative results. ††Areas for individual studies are computed by assuming logistically distributed data for healthy and diseased persons with equal variances. Adapted from Vasbinder *et al.*[4] 2-D, two-dimensional; 3-D, three-dimensional; MRA, magnetic resonance angiography.

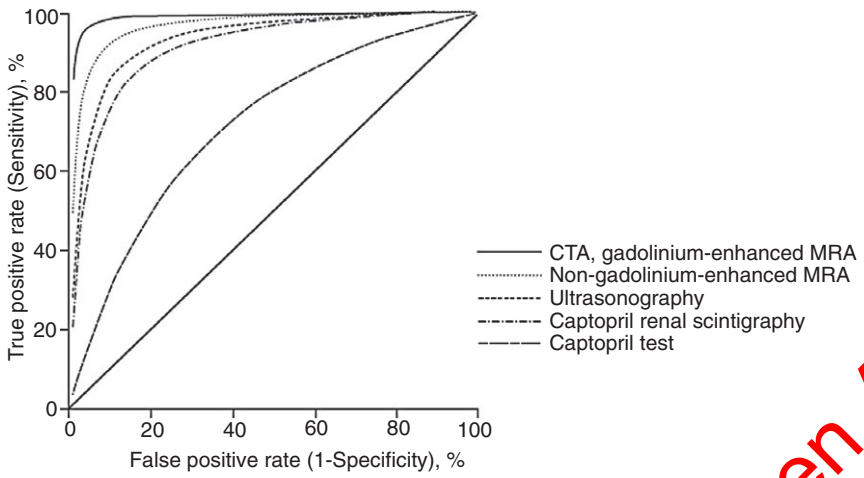

Fig. 1 Summary receiver-operating characteristic (ROC) curves. For each diagnostic technique, the current summary ROC curve is shown. The boldface, diagonal line indicates the point at which sensitivity equals 1 − specificity. Because data for computed tomography angiography (CTA) and gadolinium-enhanced magnetic resonance angiography (MRA) were nearly identical, both tests are represented by the same line pattern. Reproduced from Vasbinder *et al.*[4]

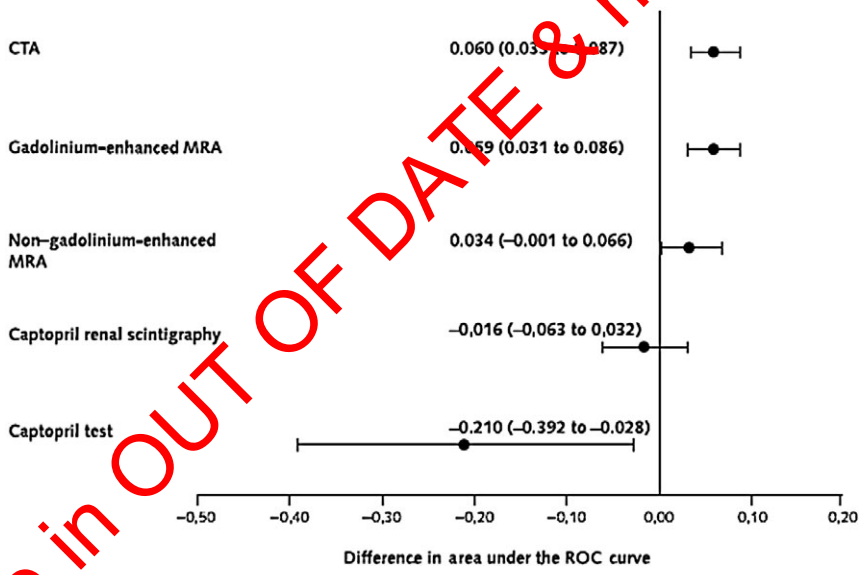

Fig. 2 Difference between the areas under the summary receiver-operating characteristic (ROC) curve for a particular test and the area under the summary ROC curve for the reference test (ultrasonography). Values in parentheses are 95% confidence intervals. CTA, computed tomography angiography; MRA, magnetic resonance angiography. Reproduced from Vasbinder *et al.*[4]