Imaging of vertebral artery stenosis: A systematic review

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TITLE PAGE

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ABSTRACT

Background and purpose: Posterior circulation stroke accounts for 20% of ischaemic strokes. Recent data suggests the early stroke recurrence risk is high, and comparable to carotid artery disease. Vertebral artery stenosis accounts for approximately 20% of posterior circulation stroke and with endovascular treatment available accurate diagnostic imaging is important. We performed a systematic literature review to validate the accuracy of non-invasive imaging techniques: Duplex ultrasound (DUS), Magnetic Resonance Angiography (MRA) and Computed Tomographic Angiography (CTA) in detecting severe vertebral artery stenosis with Intra-arterial angiography (IAA) as the reference standard.

Methods: We identified studies that used non-invasive imaging and IAA as the reference standard to determine vertebral artery stenosis and provided adequate data to calculate sensitivity and specificity. We analysed the quality of these studies, looked for evidence of heterogeneity and performed subgroup analysis for different degrees of stenosis.

Results: 11 studies categorised stenosis into 50-99%. The sensitivity of CTA (single study) and pooled sensitivities of contrast-enhanced MRA (CE-MRA) and colour duplex were 100% (95%CI 15.8-100), 93.9% (79.8-99.3) and 70.2% (54.2-83.3) respectively. The specificities for CTA, CE-MRA and colour duplex were 95.2% (83.8-99.4), 94.8% (91.1-97.3) and 97.7% (95.2-99.1). However, specificities for CE-MRA and colour duplex demonstrated significant heterogeneity p=0.003 and p=0.002, respectively.

Conclusions: CE-MRA and possibly CTA may be more sensitive in diagnosing vertebral artery stenosis than DUS. However, data is limited and further, high quality, studies comparing DUS, MRA and CTA with IAA are required.

INTRODUCTION

Posterior circulation stroke accounts for a fifth of strokes[1, 2], and 20-25% of these are believed to be due to stenosis of a vertebral artery with artery to artery embolism being the likely mechanism[3]. Despite its apparent aetiological importance, optimal management of vertebral artery stenosis remains uncertain. This is in marked contrast to carotid stenosis for which the role of revascularisation with carotid endarterectomy has been established in large randomized controlled trials[4, 5]. Surgical revascularisation for vertebral artery stenosis is more complex due to more difficult surgical access. Angioplasty and stenting is technically feasible, and no more difficult than carotid stenting, although, its role in preventing recurrent posterior circulation stroke is uncertain[6]. Progress in managing vertebral artery stenosis has been hampered by the traditional perception that vertebrobasilar (VB) strokes and transient ischemic attacks (TIAs) have a benign prognosis compared to carotid territory ischemic events. This has have tended to make clinicians reluctant to investigate for vertebral stenosis, particularly when the role of revascularisation is uncertain. However recent data demonstrates that the prognosis is far from benign and a systematic literature review has demonstrated that the risk of subsequent stroke is significantly higher in the acute phase of VB ischaemic events than carotid territory events[7] .

Non-invasive imaging of vertebral stenosis is technically more complex compared with carotid stenosis. On DUS most carotid stenosis can be clearly imaged, while only limited visualisation of the vertebral artery is possible. Until recently, the only alternative was IAA which remains the gold standard but carries a risk of iatrogenic stroke of approximately 1-2%[8]. Non-contrast magnetic resonance angiography allows improved visualisation of the vertebral arteries, and more recently contrast enhanced MRA (CE-MRA) and contrast enhanced CTA have been proposed as alternatives to the gold standard of intra-arterial angiography (figure 1). Many studies have compared these different imaging modalities for carotid artery stenosis. A recent meta-analysis of carotid artery stenosis suggested CE-MRA is more sensitive and specific than ultrasound, non-contrast MRA, and CTA[9]. Fewer studies have compared these imaging modalities in vertebral artery stenosis. Furthermore to extrapolate conclusions drawn for the carotid artery to the vertebral artery might be inappropriate, since the vertebral artery differs significantly anatomically from the internal carotid artery.

The vertebral artery is structurally divided into four sections (figure 2), V_1-V_3 form the extracranial vertebral artery (ECVA) and V_4 forms the intracranial vertebral artery (ICVA). The vertebral artery is much smaller (3-5mm) than the internal carotid artery. It arises at right angles to its feeding vessel whereas the carotid artery arises directly from the common carotid artery. It is asymmetrical with up to 15% of the population having one vertebral artery which is atretic. Approximately 50% have a dominant left vertebral, 25% a dominant right vertebral and 25% have both vertebral arteries of similar calibre[10].

We conducted a systematic review of the literature to determine the diagnostic accuracy of DUS, both contrast and non-contrast enhanced MRA, and CTA, in diagnosing vertebral artery stenosis or occlusion. Previous systematic analyses of carotid artery imaging have highlighted important methodological criteria by which such studies should be assessed[11, 12]. We used these criteria in assessing the quality of the vertebral artery imaging studies.

METHODS

Data sources and study selection

We searched Medline, Embase and Pubmed (final search date: 13 July 2006) for studies that used IAA as the reference standard to validate the accuracy of DUS, MRA and CTA to determine vertebral artery stenosis or occlusion.

The search was limited to studies of humans and articles in English. We combined three search terms: (vertebral OR basilar OR posterior circulation OR vertebrobasilar) AND (magnetic resonance angiogram OR MRA OR magnetic resonance angiography OR computed tomographic angiogram OR computed tomographic angiography OR CTA OR duplex OR Doppler OR ultrasound OR ultrasonography OR angiogram OR angiography) AND (stenosis OR occlusion). Inclusion criteria were: 1) article in English 2) used IAA as reference standard and performed DUS or MRA or CTA and 3) assessed vertebral artery for stenosis or occlusion. Case reports (less than five patients) were excluded. Full text articles of abstracts fulfilling the criteria were reviewed. In addition, the references of articles which fulfilled the inclusion and exclusion criteria were hand searched (figure 3).

All articles which fulfilled the above criteria were independently assessed by two reviewers (G.C.C and S.K.) to identify those which provided sufficient data for inclusion in the analysis. Articles were excluded from the analysis if they 1) did not categorise stenosis into degrees 2) merged vertebral artery data with other vessels 3) provided insufficient data to construct 2x2 contingency tables or 4) provided this data on less than five patients over the age of 18 years. If data was only available for a subset of patients then this subset was included. If articles duplicated data then the article with the greatest amount of useful data was included.

Data extraction

The methodological quality of included articles was independently evaluated by the two reviewers (G.C.C and S.K.) on a standardised form. The criteria for data extraction were formulated from previous review articles[11, 12] and by discussion with a senior neuroradiologist (P.R). The criteria included: demographic information (number of men/women, age - mean and range), methodological quality (prospective, consecutive), patient disease group (posterior circulation stroke/TIA, anterior circulation stroke/TIA, healthy individuals, presumed dissection) number of patients in the study (number having non-invasive imaging, IAA and number for which comparative data is provided), time interval between imaging, existence of verification bias, inclusion criteria for imaging, experience of radiologists reading the scans, blinded assessment, Imaging technique (duplex - with or without colour, MRA – non-contrast or CE-MRA, CTA), scanning machine used (for MRI the TESLA number, for CT the slice scanner used), the method of IAA angiography (selective, aortic arch, the planes imaged e.g. antero-posterior, lateral, oblique etc.) and the method of derivation of stenosis. If it was not stated we assumed that the study was retrospective, non-consecutive and not blinded. Disagreements were resolved by consensus or discussion with a third reviewer (H.S.M).

Analysis methodology

Sensitivity and specificity percentage values were calculated for several categories of stenosis: 50-99% versus <50% and 100%, 50-69/70% (depending on how this group was defined in studies) versus <50% and >70%, 70-99% versus <70% and 100% and 100% (occlusion) versus <100%. Summarising diagnostic accuracy is complex if the studies are heterogeneous; evidence of heterogeneity was sought by plotting diagnostic odds ratio (DOR) for all the stenosis groups and looking for evidence of outliers and performing chi-squared heterogeneity testing. DOR is a measure for the discriminative power of diagnostic test results among diseased to the odds of a positive test results among non diseased. In order to calculate the DOR in studies which had 100% sensitivity or specificity values 0.5 was added to all cells of the 2x2 diagnostic table[13].

$$\text{DOR:} \quad \frac{\text{sensitivity}/(1-\text{sensitivity})}{(1-\text{specificity})/\text{specificity}}$$

Subgroup analysis was performed for the different imaging modalities and degrees of stenosis by pooling data using a fixed effects model and searching for heterogeneity.

RESULTS

3687 articles were identified using Medline, Pubmed and Embase (figure 3). 1023 were duplicate articles, leaving 2664 articles. 2536 articles were excluded based on the inclusion and exclusion criteria. The full text of 128 articles was reviewed and of these 48 fulfilled our criteria. A hand search of references identified a further 31 articles. These 79 articles were reviewed independently by the two reviewers. 27 articles did not categorise data into degrees of stenosis, 8 merged vertebral artery data with other vessels, five did not provide sufficient data to obtain sensitivity and specificity values and 25 articles did not provide comparative data on at least five patients over the age of 18. One article[14] duplicated data from two previous studies[15, 16]. The author was contacted to check that the two studies did not overlap and the original articles, which had the greatest amount of data were included[15, 16]. Two authors were contacted for further information on the number of arteries included in their studies, both had merged data in their articles making it impossible to calculate sensitivity and specificity values for vertebral arteries [17, 18]; only one responded[17].

The methodological quality of studies fulfilling selection criteria was assessed and is presented in table 1.

Author	Year subjects recruited	Disease group*	Imaging modality	No of subjects (arteries)	Prospective	Consecutive	Imaging technique stated	Blind assessment of imaging	Method of derivation of stenosis stated	Vessel compared	Degree of stenosis compared
Ackerstaff 1984[15]	1981-1982	E	Duplex without colour	82 (103)	No	No	Yes	No- Duplex Yes - IAA	Yes	VAO	1-99, 100%
Ackerstaff 1988[16]	1983-1987	E	Duplex without colour	Nm (239)	No	No	Yes	Yes	Yes	VAO & V_1	0-49, 50-99, 100
Visona 1986[25]	1981-1983	B, C & D	Duplex without colour	25 (30)	Yes	No	No	No	Yes Duplex No-IAA	VAO	0, 50-99, 100
De Bray 2001[19]	1996-1998	A, B & D	Colour duplex	158 (316)	Yes	Yes	Yes	Yes	Yes – Duplex No – IAA	ECVA	0, 1-29, 30-49, 50-69, 70-99, 100
Harrer 2004[26]	NM	C & D	2D & 3D Colour duplex	6 (6)	No	No	Yes	Yes	Yes	VAO	<30, 30-69, >70 (raw data)
Wentz 1994[27]	NM	E	Non-contrast MRA	60 (161)	No	No	Yes	Yes	Yes	ICVA & BA Data merged	0, <50, 50-75, >75, 100
Strotzer 1998[23]	NM	E	Non-contrast MRA	40(80)	Yes	Yes	Yes	Yes – MRA No - IAA	No-MRA Yes-IAA	VAO	≥50
Leclerc 1998[20]	1997	A & B	CE-MRA 3D	27 (50)	No	No	Yes	Yes	Yes	ECVA	0, <50, 50-70, >70, 100
Randoux 2003[24]	2000-2001	C	CE-MRA	33 (66)	Yes	Yes	Yes	Yes	Yes	VAO	0,<50, >50, 100
Cosottini 2003[21]	NM	A & B	CE-MRA	48 (89)	Yes	No	Yes-MRA No-IAA	Yes	No	ECVA	0, <30, 30-70, >70, 100
Kim 2004[28]	NM	D & E	CE-MRA	37 (74)	Yes	No	Yes- MRA No-IAA	No	Yes	ECVA	>50, 100
Yang 2005[17]	2001-2002	A, B &E	CE-MRA	40 (Unclear)	No	No	Yes	Yes	Yes	ECVA, ICVA & BA	>50, 100
Farres 1996[22]	NM	A	CTA	24(44 for V_1 & 33 for V_0)	No	No	Yes	No	No	V_0 & V_1 (Incomplete data for V_0)	<50, 50-70, >70, 100

Table 1: Important characteristics of included studies

* Disease group: A=Posterior circulation stroke or TIA probably due to atheromatous disease, B=Stroke or TIA probably due to atheromatous disease (anterior circulation stroke or unspecified territory), C= Risk factors for cerebrovascular disease (CVD), D=healthy individuals. E= Other (including not mentioned, suspected atheromatous disease, neurological symptoms without stating vascular history)

NM= Not mentioned, VAO= Vertebral artery origin, ECVA= Extracranial vertebral artery, ICVA= Intracranial vertebral artery, BA= Basilar artery

Prospective: Prospective recruitment of patients

Consecutive: Patients recruited consecutively into the study

The number of vessels compared excludes the number of vessels not seen

The age of study populations ranged from: 18 – 77. Our inclusion criteria did not stipulate the aetiology of steno-occlusive disease, however we found that studies of dissection did not categorise stenosis into degrees, five of the 13 studies recruited patients with posterior circulation stroke or TIA probably secondary to atheromatous disease[17, 19-22]. Three studies were prospective and consecutive[19, 23, 24] with two of these blindly assessing the imaging[19, 24] and one stating the method of derivation of stenosis for both the intra-arterial angiography and the non-invasive imaging modality[24]. Two studies did not provide details of the number of planes imaged during intra-arterial angiography to decide if accurate diagnosis of stenosis was possible[21, 25]. 11 of the 13 studies provided comparison of 50-99% stenosis, this was analysed in detail and presented below:

50-99% stenosis detection

(a) Ultrasound

Three of the five Ultrasound studies used duplex without colour to assess the vertebral artery origin[15, 16, 25]. The duplex definition of stenosis differed in the three studies: Ackerstaff (1984) used antegrade direction of flow, with peak frequency >4KHz, increased spectral broadening and striking turbulence during systole to define 1-99% stenosis[15]. The same definition in Ackerstaff (1988) was used to define 50-99% stenosis[16] and Visona (1986) defined 50-99% stenosis as high velocity signal >2kHz with a broad spectrum, high pitched and harsh sound[25]. Ackerstaff (1984) was not used for stenosis analysis but results were included for occlusion analysis[15]. One study was prospective[25], one blindly assessed imaging techniques[16] and all three recruited non-consecutive patients. Pooled sensitivity, specificity and DOR were 70.2 %(95% CI 56.6-81.6), 93.4% (95% CI 89.2-96.3) and 37 (95% CI 16-83) respectively for diagnosing 50-99% stenosis on duplex without colour versus diagnosing <50% stenosis or 100% (occlusion).

Two colour duplex studies were included in the analysis[19, 26]. De Bray (2001) was a prospective, consecutive imaging study which blindly assessed the imaging results of 316 arteries[19], while Harrer (2004) was a retrospective, non-consecutive study blindly assessing the imaging of 6 arteries[26]. Pooled sensitivity, specificity and DOR were 70.2% (95% CI 54.2-83.3), 97.7 (95% CI 95.2-99.1) and 75 (95% CI 24-234) respectively for diagnosing 50-99% stenosis versus diagnosing <50% stenosis or 100% (occlusion).

(b) MRA

Two non-contrast MRA studies were identified[23, 27], these provided data for 50-99% stenosis which showed marked heterogeneity for sensitivity, specificity and DOR demonstrating non-overlapping DOR confidence intervals (figure 4) and significant chi-squared heterogeneity p=0.007, p=0.015 and p=0.012, respectively. Wentz retrospectively examined 60 basilar and 106 intracranial vertebral arteries in an unspecified population and did not blindly determine the degree of stenosis[27]. For 50-99% stenosis it demonstrated sensitivity and specificity of 100% (95% CI 63.1-100) and 97.4% (95% CI 93.4-99.3), respectively. Strotzer prospectively recruited 40 consecutive patients and assessed the vertebral artery origin with two imaging techniques, coronal 3D FISP and transverse 3D FISP[23]. Data from the largest study group (3D FISP) was used in the analysis, this had not been blindly analysed. Data was provided for 63 vertebral arteries (17 arteries were not evaluable). It had poor sensitivity and specificity for 50-99% stenosis, 53.8% (95% CI 25.1-80.8) and 88% (95 % CI 75.7-95.5), respectively.

Five CE-MRA studies were identified[17, 20, 21, 24, 28], three examined the extracranial vertebral artery[20, 21, 28], one the vertebral artery origin[24], and one both the vertebral and basilar arteries[17]. Four studies provided data for 50-99% stenosis[17, 20, 24, 28], the largest CE-MRA study categorised stenosis into 0, <30%, 30-70%, >70% and 100% and therefore could not be included in the 50-99% analysis, however, data from this study was used in the 70-99% and 100% (occlusion) analysis[21]. The pooled sensitivity, specificity and DOR were 93.9% (95% CI 79.8-99.3), 94.8% (95% CI 91.1-97.3) and 179 (95% CI 42-765) with heterogeneity testing p values of 0.171, 0.002 and 0.127 respectively.

(c) CTA

One CTA study fulfilling our criteria was identified[22]. This study recruited 24 patients with a clinical diagnosis of vertebro-basilar ischaemia. It examined the vertebral artery origin (V_0 and V_1, separately), categorising stenosis into <50%, 50-70%, >70% and occlusion. For 50-99% stenosis it found sensitivity, specificity and DOR of 100% (95% CI 15.8-100), 95.2% (95% CI 83.8-99.4) and 81 (3-2183.3) respectively.

50-69/70% and 70-99% stenosis

Data on 50-69/70% and 70-99% stenosis was scarce, three and four studies respectively (table 2).

Imaging	No of studies *	No of arteries	Sensitivity (95% CI)	Specificity (95% CI)	DOR (95% CI)
<u>70-99% stenosis</u>					
Colour duplex	1	316	65.2 (42.7-83.6)	99.3 (97.5-99.9)	272.8 (53.2-1398.1)
CE-MRA	2	139	83.3 (35.9-99.6)	98.5 (94.7-99.8)	200 (22-1824)
CTA	1	44	100 (2.5-100)	100 (91.8-100)	261 (3.7-18197)
<u>50-69/70% Stenosis</u>					
Colour duplex (50-69%)	1	316	61.5 (31.6-86.1)	98.7 (96.7-99.6)	119.6 (26.9-531)
CE-MRA (50-70%)	1	50	50 (1.3-98.7)	95.8 (85.7-99.5)	23 (1-517)
CTA (50-70%)	1	44	100 (2.5-100)	95.3 (84.2-99.4)	49.8 (1.69-1562.1)
<u>50-99% Stenosis</u>					
Duplex without colour	2	269	70.2 (56.6-81.6)	93.4 (89.2-96.3)	37 (16 – 83)
Colour Duplex	2	322	70.2 (54.2 – 83.3)	97.7 (95.2 – 99.1)†	75 (24 -234)
TOF MRA	2	224	71.4(47.8-88.7) †	95.1 (91.1-97.6)†	22 (7-64)†
CE-MRA	4	263	93.9 (79.8-99.3)	94.8 (91.1-97.3)†	179 (42 – 765)
CTA	1	44	100 (15.8-100)	95.2(83.8-99.4)	81 (3 – 2183.3)
<u>100% (occlusion)</u>					
Duplex without colour	3	372	98.8 (89.4-100)	90.8 (87.2-93.7)†	211 (38-1172)
Colour Duplex	1	316	83.3 (51.6-97.9)	100 (98.8-100)	2557.8 (115.4-56671)
TOF MRA	1	161	100 (75.3-100)	100 (97.5-100)	8019 (153-420402)
CE-MRA	4	278	89.5 (66.9-98.7)	99.6 (97.9-100)	429.7 (73.9-2498.6)

Table 2: Sensitivity, specificity and diagnostic odds ratio for 70-99% stenosis, 50-59/70% stenosis, 50-99% stenosis and occlusion in all imaging groups

* Where more than one study is available the results have been pooled using the fixed effects model
†Significant heterogeneity (Chi-squared testing, $p<0.05$).
CI = Confidence Interval, DOR = Diagnostic Odds Ratio

For 50-69/70% stenosis colour duplex and CE-MRA had poor sensitivities 61.5 % (95% CI 31.6-86.1) and 50 % (95% CI 1.3-98.7) respectively, with CTA having a high sensitivity but wide 95% confidence intervals 100% (95% CI 2.5-100). The specificities for 50-69/70% were high for all three modalities: colour duplex 98.7% (95% CI 96.7-99.6), CE-MRA 95.8% (95% CI 85.7-99.5) and CTA 95.3% (95% CI 84.2-99.4).
For 70-99% stenosis detection sensitivities were slightly better than for 50-69/70%; colour duplex 65.2% (95% CI 42.7-83.6), CE-MRA (pooled) 83.3% (95% CI 35.9-99.6), and CTA 100% (95% CI 2.5-100). The specificities were also better at 99.3% (95% CI 97.5-99.9), 98.5% (95% CI 94.7-99.8) and 100% (91.8-100) respectively.

Occlusion
Diagnosis of occluded arteries had the highest sensitivity, specificity and DOR. For occluded arteries sensitivity of duplex without colour, colour duplex TOF MRA and CE-MRA were: 98.8% (95% CI 89.4-100), 83.3% (95% CI 51.6-97.9), 100% (95% CI 75.3-100) and 89.5% (95% CI 66.9-98.7). Specificities were: 90.8% (95% CI 87.2-93.7), 100% (95% CI 98.8-100), 100% (95% CI 97.5-100) and 99.6% (95% CI 97.9-100). DOR were: 211 (95% CI 38-1172), 2557.8 (95% CI 115.4-56671), 8019(95% CI 153-420402) and 429.7(95% CI 73.9-2498.6) respectively. The single CTA study did have one occluded artery at the origin but did not comment if this was seen on both CTA and IAA or only on a single imaging modality[22].

Results from CTA studies not fulfilling our inclusion criteria
Several CTA studies were identified which used IAA to validate the accuracy of CTA but did not fulfil all our inclusion criteria. These suggest that CTA may be as accurate[29] or better that TOF MRA in detecting intracranial vertebral artery stenosis and occlusion[18]. These were retrospective studies of 112 and 28 patients respectively; both suggested that CTA might be superior to TOF MRA when slow flow is present. A prospective study in which patients were screened by MRA for >50% stenosis and then had CTA showed that the combination is equivalent to IAA[30].

DISCUSSION
Our systematic review demonstrated a scarcity of good quality studies validating the accuracy of diagnosing vertebral artery stenosis with non-invasive imaging techniques against the gold standard of IAA. Some studies used a cut-off of 70-99%, probably by analogy with carotid stenosis. The vertebral artery is however much smaller (3-5mm) and this has led to many studies using 50-99% as their cut off point. Most data was available for 50-99% stenosis. Identification of the presence or absence of stenosis greater than 50% is important both in identifying vertebral stenosis as a cause of stroke, and in identifying potential stenosis for further intervention. Here the available data suggested that CE-MRA has the highest sensitivity followed by CTA, colour duplex, and duplex without colour. The relevant DORs were 179.4 (95% CI 42 – 765), 81 (95% CI 3-2183), 75 (95% CI 24-234) and 37 (95% CI 16-83), respectively.

For carotid artery stenosis, the risk of stroke and the benefit of surgical intervention has been shown to depend upon the degree of stenosis. Therefore, accurate assessment of the degree of stenosis is important, and 70% has been identified as the cut-off above which patients particularly benefit from endarterectomy. Whether a similar cut-off exists for vertebral artery stenosis, above which the risk of recurrent stroke is particularly high and there is potential benefit from intervention, remains to be determined. However, importantly we identified few studies determining the accuracy of the different imaging modalities in identifying stenoses greater than 70%, and even fewer which determined the accuracy of quantifying the degree of stenosis in patients with stenosis. The limited data available suggested that for 70-99% stenosis CTA and CE-MRA are likely to be the optimal imaging techniques. Although colour duplex had a high DOR this did not take into account false negatives which is important in a screening test. It is important to remember that as the vertebral artery is much smaller than the carotid artery this is likely to reduce the accuracy of stenosis estimation, particularly when determining stenosis to the nearest decile. In addition, when comparing non-invasive techniques with IAA it is important to be aware of the existence of significant inter-observer and intra-observer variability when diagnosing the degree of stenosis. Kappa values of between 0.75-0.88 have been reported for inter-observer agreement in measurement of degree of carotid stenosis.[31] We did not identify similar reproducibility studies for vertebral artery stenosis, but the smaller size of the vertebral artery may result in lower degrees of agreement.

The different imaging modalities offer different logistical advantages. Ultrasound is non-invasive, cheaper, and usually more readily available. Early studies used Doppler ultrasound alone but duplex ultrasound, which appears to have higher sensitivity in detecting vertebral stenosis, is now routine. Three of the five ultrasound studies which we included are over twenty years old and used duplex without colour which can be regarded as historical since it has been replaced with newer machines which use colour and have higher sensitivity and specificity. Our analysis suggests that DUS has a lower sensitivity than CE-MRA and CTA. This is not surprising because ultrasound imaging cannot visualise the full length of the vertebral artery, and therefore detection of stenosis may have to rely on flow disturbance which is only present with more severe stenosis and does not directly show the site of stenosis. A further limitation of ultrasound is the difficulty of differentiating between dissection and atherosclerotic disease. MRA has the advantage that it can be combined with MRI, which has much greater sensitivity for detecting small posterior circulation infarcts. Initial non-contrast MRA techniques offered less good visualisation of the vertebral artery than CE-MRA, and do not always well visualise the origin, a common site of atherosclerosis. CE-MRA has been shown to be more sensitive and specific for investigation of carotid artery stenosis, and, from the limited data available, it appears to have higher sensitivity and specificity than either DUS or non-contrast MRA for extracranial vertebral artery stenosis. It offers the advantage that skilled post processing is not necessary, but has a number of disadvantages including cost, contraindication in patients with metallic devices such as pacemakers, and it is not tolerated due to claustrophobia by a minority of patients. In addition, particularly with the administration of contrast, it is expensive. Multi-slice CT scanning is more widely available and the limited data available suggested it offers a comparable sensitivity and specificity to CE-MRA. It is cheaper and suitable for patients with contraindications to, or intolerance of, MRI. However, it is not without problems involving subjecting patients to radiation, and a potentially nephrotoxic contrast agent as well as being inaccurate for heavily calcified stenoses. Further studies are required to directly compare it with CE-MRA

The two non-contrast MRA studies demonstrated significant heterogeneity in sensitivity (p=0.007) specificity (p=0.015) and DOR (p=0.012) and were excluded from pooled analysis. The increased accuracy for TOF-MRA may be explained by the fact that the TOF study imaged intracranial vessels and the 3D_FISP study imaged vertebral artery origins. Measuring vertebral origins is much more challenging, the origins are often kinked and there is much more unavoidable movement due to pulsation from much larger vessels and breathing. Intracranial vessels are a different shape and apart from slight movement due to arterial pulsation they are static during imaging. Although TOF-MRA had the highest sensitivity, specificity and DOR for intracranial vessels, several studies have suggested that CTA is equivalent or better and recommend it over TOF-MRA[29, 18].

The methodological quality of studies was extremely varied. Whereas some were prospective consecutive studies with a significant number of arteries[19] others were retrospective studies with only 6 arteries[26]. The paucity of data did not allow comparison between the four different segments of the vertebral artery and it is likely that accuracy of the different imaging modalities varies according to the location of the stenosis. We included all the studies and analysed the data. It is also known that not blindly assessing imaging overestimates the accuracy of imaging techniques[11]. There were too few suitable studies to analyse the effect of other important factors such as type of scanning machine used, verification bias or publication bias. Another important factor which we were unable to address, due to lack of data, was the effect vertebral size has on the accuracy of stenosis detection in the different modalities. It is recognised that it can be difficult to differentiate between a severely stenotic and a hypoplastic vessel, although there is no consensus on the definition of a hypoplastic vessel with some studies using 2mm and others 3mm. None of the identified studies provided data for the comparison of more than one non-invasive imaging modality in the same patient population.

In conclusion our systematic review demonstrates a paucity of high quality studies. From the data available CE-MRA appears to offer better sensitivity and specificity than duplex ultrasound for proximal vertebral artery stenosis. Despite CTA increasingly being used as the modality of choice to replace IAA in many centres, this technique still needs validation. Furthermore, no studies have compared the different imaging modalities against intra-arterial angiography in the same cohort of patients. Such studies are essential to determine optimal imaging protocols, particularly if patients with vertebral artery stenosis are to be selected for future randomised controlled trials of angioplasty and stenting.

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FIGURE LEGENDS

Figure 1: IAA, Extracranial CE-MRA and CTA, demonstrating right vertebral artery stenosis in a 64 year old patient who presented with a posterior circulation stroke
a) IAA with right subclavian artery injection
b) Extracranial CE-MRA Maximum Intensity Projection Image
c) Extracranial CTA Sagittal Reformatted Image

Figure 2: Schematic diagram illustrating the four segments of the vertebral artery

Figure 3: Flow diagram showing search methodology for study selection

Figure 4: Sensitivity, specificity and DOR comparing non-invasive imaging techniques with intra-arterial angiography in the diagnosis of 50-99% stenosis

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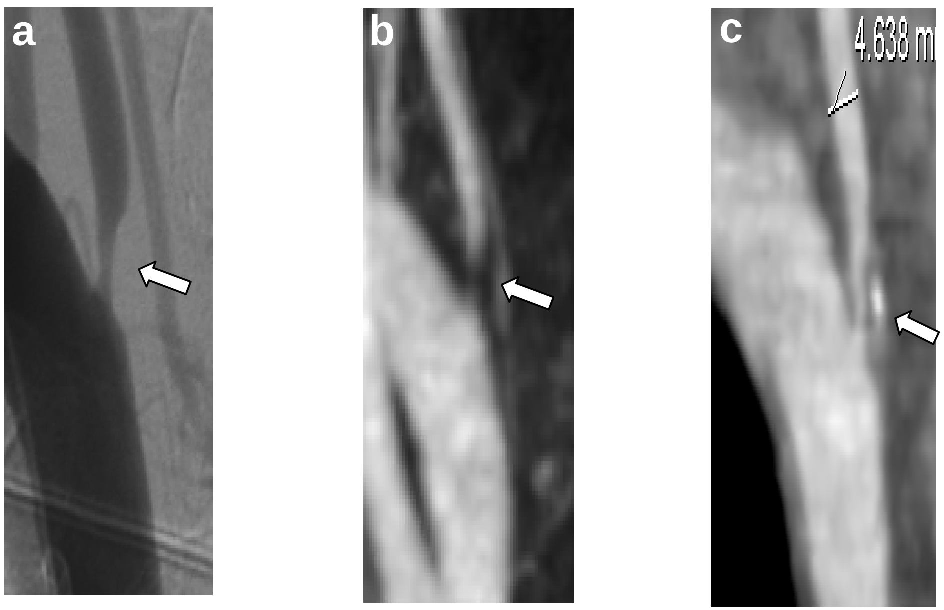

Figure 1: IAA, Extracranial CE-MRA and CTA, demonstrating right vertebral artery stenosis in a 64 year old patient who presented with a posterior circulation stroke. a) IAA with right subclavian artery injection, b) Extracranial CE-MRA Maximum Intensity Projection Image and c) Extracranial CTA Sagittal Reformatted Image.

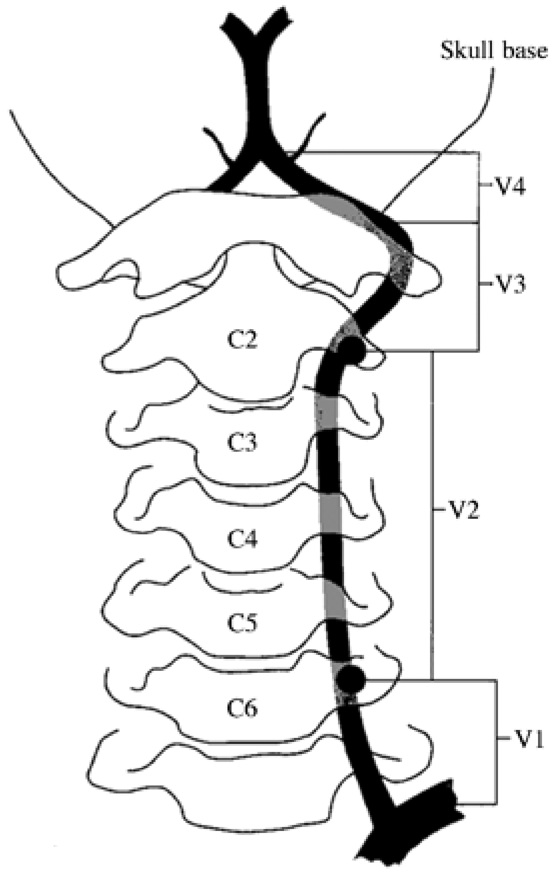

Figure 2: Schematic diagram illustrating the four segments of the vertebral artery

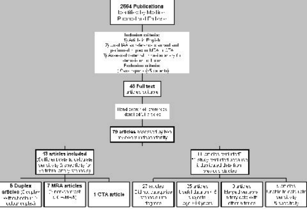

Figure 2: Flow diagram showing search methodology for study selection

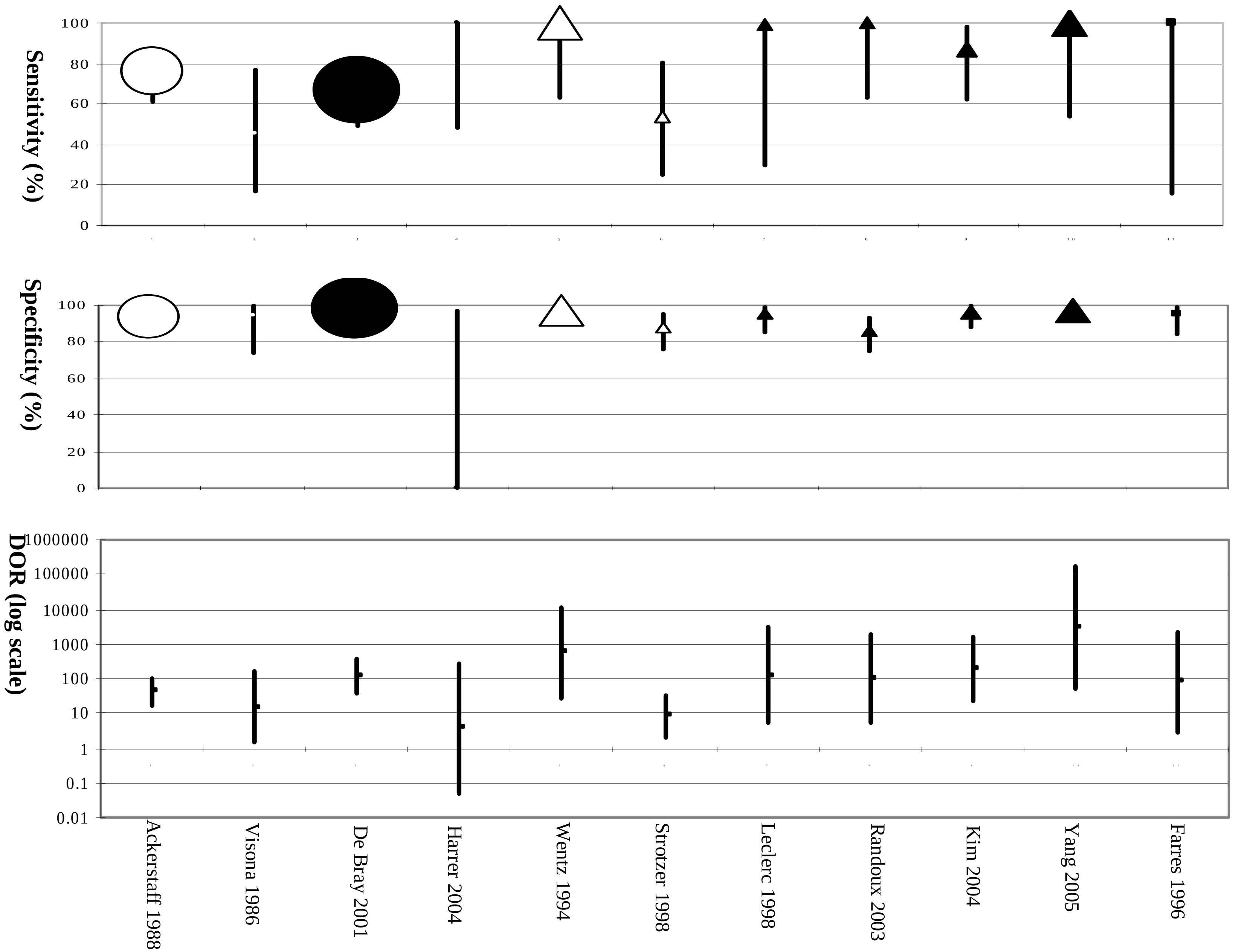

Figure 4: Sensitivity, specificity and DOR comparing non-invasive imaging techniques with Intra-arterial angiography in the diagnosis of 50-99% stenosis

Key:

○ = Duplex without colour △ = TOF MRA ■ = CTA

● = Duplex with colour ▲ = CEMRA

(Symbols are point estimates, their size indicates sample size, Whiskers= 95% CI)