Question 4 evidence tables

Question 4: Which diagnostic investigations such as CT Angiography (CTA), MRI, MR Angiography (MRA) and Digital Subtraction Angiography (DSA), should be used and when in patients with acute intracerebral haemorrhage to detect a macrovascular abnormality?

NB Any discrepancies between reviewers in evidence quality and comment were discussed at the corresponding evidence review meeting

dAVF = dural arteriovenous fistulas, INR = international normalised ratio, CTA = computed tomography angiography, DSA = digital subtraction angiography, MRI = magnetic resonance imaging, MRA = magnetic resonance angiography, CT = computed tomography, AHA = American Heart Association, bAVM = brain arteriovenous malformation, CSF = cerebrospinal fluid, SVD = small vessel disease, SR = systematic review, MA = meta-analysis, RCT = randomised controlled trial, IPDMA = individual patient data meta-analysis, MDT = multidisciplinary team, PICO = patient/population, intervention, comparison and outcomes, OR = odds ratio, CI = confidence interval, QoL = quality of life, ADL = activities of daily living, OR = odds ratio, RR = relative risk, aOR = adjusted odds ratio, cOR = crude odds ratio, CI = confidence interval, RoB = risk of bias, I2 = heterogeneity statistic.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
592	Van Asch et al (2015). Diagnostic yield and accuracy of CT angiography, MR angiography, and digital subtraction angiography for detection of macrovascular causes of intracerebral haemorrhage: Prospective, multicentre cohort study. The BMJ. 351: h5762.	Prospective diagnostic study, 22 hospitals in the Netherlands over 6 years (Jul 2008 – Jun 2014). Inclusion: 18-70 years old, premorbid mRS < 3. Exclusion: >45 years old with hypertension and deep/post fossa ICH. On oral anticoagulation and INR>2.5.	CTA within 7 days of onset, preferably < 48 h IF CTA -ive, MRI/MRA 4-8 weeks after onset DSA if above investigations inconclusive or negative. Also had DSA if prior imaging suggested AVM or dAVF, to plan treatment.	Followed for at least 1 year – telephone interviews at 4 weeks, 3 months, 12 months. Main outcome: presence of a macrovascular cause (AVM, dAVF, DVA, CVST, cavernoma).	A macrovascular cause was identified in 69 patients (23%). 291 patients (98%) underwent CT angiography; 214 underwent additional MRI/MRA and 97 underwent DSA. Early CTA detected 51 macrovascular causes (yield 17%, 95% CI: 13% to 22%). CTA with MRI/MRA identified two additional macrovascular causes (18%, 14% to 23%) and DSA another 15 (23%, 18% to 28%). PPV of CT angiography was 72% (60% to 82%), of MRI/MRA 35% (14%	Good quality, prospective study, testing an investigation strategy. Potential for missed macrovascular causes in excluded patients: >70, >45 with hypertension and post fossa / deep bleed, on anticoagulant.

					to 62%), and of DSA was 100% (75% to 100%). 0.6% of patients who underwent DSA experienced permanent sequelae.	
592	Van Asch et al (2015). Diagnostic yield and accuracy of CT angiography, MR angiography, and digital subtraction angiography for detection of macrovascular causes of intracerebral haemorrhage: Prospective, multicentre cohort study. The BMJ. 351: h5762.	Prospective, multi-centre study, 18 Dutch hospitals 2008-2014. Age 18-70, independent pre-ICH (mRS<3) Excluded: age > 45 with hypertension and ICH in basal ganglia, thalamus and posterior fossa. Also excluded if known cancer pre-ICH, known macrovascular pathology or if INR > 2.5 in patient on oral anticoagulant.	CTA within 7 days of ICH, preferably within 48 hours. If CTA neg, then MRI/MRA within 4-8 weeks or earlier if indicated. DSA if CT/CTA/MRI/MRA negative or inconclusive OR if AVM/dAVF found on CT/MRI. All subjects followed up to at least 1 year. Patients followed > 1 year as part of clinical practice had recording of recurrent ICH/aetiology if known of same. Neuroradiology assessments all blinded to patient clinical features.	Primary outcome- presence of macrovascular cause of ICH including AVM, aneurysm, dAVF, cavernoma, venous sinus thrombosis or DVA. Diagnostic yield of CTA alone, CTA + MRI/MRA and of CTA + MRI/MRA + DSA was calculated.	N=302 subjects, 4 imaging protocol violations excluded Mean age 53 yrs, median ICH vol 11 ml (IQR 4-26 ml) Median f/u 450 days (IQR 371-1150 days) 23% (n=69) macrovascular cause found: AVM (n=34, 11%), dAVF (n=13, 4%), cavernoma (n=10, 3%), VST (n=4, 1%), aneurysm (n=7, 2%) and DVA (n=1, 0.3%) Other causes: probable CAA (n=18, 6%),hypertensive (n=36, 12% neoplasm (n=3, 1%), cocaine n=1, 0.3%) Unknown cause n=169, 57%. Median interval from non-contrast CT to CTA 1 day (IQR 0-2 days), from CTA to MRI/MRA 46 days (IQR 32-64 days) and from MRI/MRA to DSA was 33 days (IQR 3-60 days). CTA diagnostic yield 17% (13-22%) CTA + MRI/MRA diagnostic yield 18% (14-23%)	Excluded patients > 45 yrs with hypertension and ICH in basal ganglia, thalamus or posterior fossa. Excluded patients > 70 yrs 'as little chance of finding macrovascular cause'

			Reference standard was the best available evidence from all test results during 1 year of f/u.		CTA+MRI/MRA + DSA diagnostic yield 23% (18-28%). In 59 of 230 subjects (26%) without a macrovascular cause an alternative cause was found, mainly on MRI 0.6% of DSA patients had permanent sequelae as complication. Independent predictors of macrovascular cause detection were posterior fossa ICH OR 13.0 (3.7-46.5), small vessel disease on CT OR 8.5 (2.9-25.3), lobar ICH OR 5.5 (2.0-15.3) and age OR 0.96 (0.93-0.99).	
581	C. P. Derdeyn et al (2017). Management of Brain Arteriovenous Malformations: A Scientific Statement for Healthcare Professionals from the American Heart Association/American Stroke Association. Stroke. 48: 8. e200-224.	A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association	N/A	N/A	N/A	- Non-systematic narrative review without a proper consensus process.

581	C. P. Derdeyn et al (2017). Management of Brain Arteriovenous Malformations: A Scientific Statement for Healthcare Professionals from the American Heart Association/American Stroke Association. Stroke. 48: 8. e200-224.	AHA scientific statement Non-conflicted experts formed a Writing Group. 2-3 authors per subcategory including Diagnosis (of brain AVMs, bAVMs). Other sections included natural history and outcome, and management aspects of bAVMs. Purpose of statement= to increase knowledge and awareness of health professionals	Literature searched for ability of CT, MRI and DSA to detect bAVMs.	Narrative synthesis of a selection papers covering the category topics.	Most bAVMs occurred in those with indeterminate findings on plain CT. CTA compares well with DSA for detection bAVM MRA approaches the accuracy of CTA but more limited in detecting smaller anomalies. DSA is the reference standard and is often performed after negative CTA/MRA. Risk of thromboembolic stroke but this is low. Very occasionally even DSA can miss a AVM nidus (e.g. compression by adjacent haematoma) so follow up imaging sometimes needed.	Followed AHA Task Force Guidelines for Literature Searches. However, this is a consensus statement of experts summarising medical literature.
582	J. Ding et al (2022). Acceleration of Brain Susceptibility-Weighted Imaging with Compressed Sensitivity Encoding: A Prospective Multicenter Study. AJNR. American journal of neuroradiology.	Ninety-nine subjects, prospectively enrolled from 5 centers, underwent 8 brain SWI sequences: 5 different folds of compressed sensitivity encoding acceleration (CS2, CS4, CS6, CS8, and CS10), 2 different folds of sensitivity encoding acceleration (SF2 and SF4), and 1 without acceleration. Images were assessed quantitatively on both the SNR of the red nucleus and its contrast ratio to the CSF and, subjectively, with scoring on overall image quality; visibility of	N/A	SNR of the red nucleus and its contrast ratio to the CSF and, subjectively, with scoring on overall image quality; visibility of the substantia nigra–red nucleus, basilar artery, and internal cerebral vein; and diagnostic confidence of the cerebral microbleeds and other intracranial diseases.	Compressed sensitivity encoding showed a promising ability to reduce the acquisition time (from 202 to 41 seconds) of SWI while increasing the acceleration factor from 2 to 10, though at the cost of decreasing the SNR, contrast ratio, and the scores of visual assessments. The visibility of the substantia nigra–red nucleus and internal cerebral vein became unacceptable in CS6 to CS10. The basilar artery was well-	N/A

		the substantia nigra–red nucleus, basilar artery, and internal cerebral vein; and diagnostic confidence of the cerebral microbleeds and other intracranial diseases.			distinguished, and diseases including cerebral microbleeds, cavernous angiomas, intracranial gliomas, venous malformations, and subacute hemorrhage were well-diagnosed in all compressed sensitivity encoding sequences.	
584	J. Hebert at al (2016). 320-Row Multidetector CT Angiography in the Detection of Critical Cerebrovascular Anomalies. Canadian Journal of Neurological Sciences. 43: 4. 543-548.	Retrospective single-centre cohort assessing pathway of 320-row multidetector CTA in the detection of cerebrovascular abnormalities. 82 subjects with 102 abnormalities detected. Reports of CTA and DSA compared to determine the diagnostic accuracy of CTA.	320-row multidetector CTA + DSA	Vascular abnormality on CTA/DSA. Sensitivity and specificity of 320-row multidetector CTA.	The overall sensitivity and specificity of 320-row multidetector CTA for detecting cerebrovascular abnormalities were, respectively, 97.60% and 63.20%. For 'unusual ICH': sensitivity 94.1%; specificity 63.4%	+
584	J. Hebert at al (2016). 320-Row Multidetector CT Angiography in the Detection of Critical Cerebrovascular Anomalies. Canadian Journal of Neurological Sciences. 43: 4. 543-548.	Retrospective convenience sample of 82 consecutive patients who underwent a 320-row multidetector CTA followed by cerebral angiography from February 2010 to February 2014. Mean age 56y. 67% female. Not restricted to ICH.	320-row multidetector CTA Vs DSA reference standard.	Detection of intracranial vascular malformations.	The overall sensitivity and specificity of 320-row multidetector CTA for detecting cerebrovascular abnormalities were, respectively, 97.60% and 63.20%.	– At risk of partial verification bias (only those with a positive test receive the reference standard) given this was retrospective sample of clinical practice.

585	N. A. Hilkens et al (2018). Predicting the presence of macrovascular causes in non-traumatic intracerebral haemorrhage: The DIAGRAM prediction score. Journal of Neurology, Neurosurgery and Psychiatry. 89: 7 . 674-679.	Secondary analysis of DIAGRAM study (Ref 3) to derive a statistical prediction model for a macrovascular cause and then validate in an independent cohort. Second cohort was 173 consecutive ICH patients from NHNN who underwent DSA as part of clinical care, as decided at a weekly MDT (no specific criteria)	N/A	Detection of a macrovascular cause on DSA.	Independent predictors were age, lobar or posterior fossa location, absence of SVD. Regression model performance: c-statistic 0.83, 95% CI 0.78-0.88 in derivation cohort and 0.66 95% CI 0.58-0.74 in validation cohort. When CTA results added, this improved to 0.91 and 0.88 respectively.	Selection bias is an issue with both cohorts, perhaps less so the DIAGRAM cohort. This makes estimation of the performance of this model in an unselected group of ICH patients unknown.
585	N. A. Hilkens et al (2018). Predicting the presence of macrovascular causes in non-traumatic intracerebral haemorrhage: The DIAGRAM prediction score. Journal of Neurology, Neurosurgery and Psychiatry. 89: 7 . 674-679.	DIAGRAM score development with external validation. The DIAGRAM study (N=298; 69 macrovascular cause; 23%) is a prospective, multicentre study, assessing yield and accuracy of CTA, MRI/MRA and intra-arterial catheter angiography in diagnosing macrovascular causes in patients with non-traumatic ICH. We considered pre-specified patient and ICH characteristics in multivariable logistic regression analyses as predictors for a macrovascular cause. We combined independent predictors in a model, which we validated in an external cohort of 173 ICH	N/A	Diagnostic accuracy	Independent predictors of macrovascular cause were younger age, lobar or posterior fossa (versus deep) location of ICH and absence of small vessel disease (SVD). A model that combined these predictors showed good performance in the development data (c-statistic 0.83; 95% CI 0.78-0.88) and moderate performance in external validation (c-statistic 0.66; 0.58-0.74). When CTA results were added, the c-statistic was excellent (0.91; 0.88-0.94), and good after external validation (0.88; 0.83-0.94). Predicted probabilities varied from 1%	**++**

		patients (78 macrovascular cause, 45%).			in patients aged 51-70 years with deep ICH and SVD, to more than 50% in patients aged 18-50 years with lobar or posterior fossa ICH without SVD.	
586	C. B. Josephson et al (2015). Computed tomographic angiography or magnetic resonance angiography for detection of intracranial vascular malformations in patients with intracerebral hemorrhage. Stroke. 46: 1. e2-e3	DTA systematic review of studies reporting data that compared CTA or MRA, or both, with IADSA in the same patients for the detection of IVMs after ICH. Methodological quality varied considerably, with partial verification bias and retrospective designs being particularly prominent.	8 [n=526] compared CTA with IADSA and 3 [n=401] compared MRA with IADSA	Intracranial vascular malformations.	The pooled estimate of sensitivity and specificity was 0.95 (95% CI 0.90–0.97) and 0.99 (95% CI 0.95–1.00), respectively, for CTA and 0.98 (95% CI 0.80–1.00) and 0.99 (95% CI 0.97– 1.00), respectively, for MRA.	**+** Cochrane systematic review
586	C. B. Josephson et al (2015). Computed tomographic angiography or magnetic resonance angiography for detection of intracranial vascular malformations in patients with intracerebral hemorrhage.	Cochrane Corner (section of Stroke). Summary of a Cochrane Systematic review and meta-analysis Full paper published in Cochrane Database of Syst Rev Subjects in studies were post ICH and were undergoing CTA or MRA and DSA for detection of intravascular malformations (IVMs)	CTA vs DSA MRA vs DSA	Sensitivity and specificity of imaging modality for detection of intracranial vascular malformations against DSA as gold standard	Overall : 11 studies, 927 participants, 8 studies (n=526) compared CTA vs DSA 3 studies (n=401) compared MRA vs DSA CTA : sens 0.95, spec 0.99 MRA sens 0.98, spec 0.99 No significant difference in sensitivity/specificity CTA versus MRA	**++** Cochrane methods QUADAS tool to evaluate quality of included studies

	Stroke. 46: 1. e2-e3					
589	P. Schuss et al (2021). Mr-imaging and histopathological diagnostic work-up of patients with spontaneous lobar intracerebral hemorrhage: Results of an institutional prospective registry study. Diagnostics. 11: 2. 368.	Single centre prospective registry study of consecutive ICH patients admitted to a neurosurgical centre. 198 patients with ICH, 131 deep-seated ICH patients excluded, leaving 67 patients with lobar ICH. Further 15 excluded due to end-of-life/palliation, leaving 52 patients with diagnostic work-up data.	Nil		Lobar ICH associated with a variety of aetiologies. Authors suggest a thorough work-up.	0 Although prospective, this a single centre study with significant selection bias.
589	P. Schuss et al (2021). Mr-imaging and histopathological diagnostic work-up of patients with spontaneous lobar intracerebral hemorrhage: Results of an institutional prospective registry study. Diagnostics. 11: 2. 368.	52 patients with lobar ICH undergoing neurosurgical intervention at one institution.	MRI n=40, histopathology n=9 No comparator. Not DTA.	Detection of underlying cause of ICH.	Macrovascular disease was detected in 14 patients with lobar ICH (27%). In 11 patients, diagnostic workup identified cerebral amyloid angiopathy-related ICH (21%). In addition, five patients with tumor-related ICH (10%) and six patients with ICH based on infectious pathologies (11%) were identified. In four patients, the cause of bleeding remained unknown despite extensive diagnostic workup (8%).	– Hospital-based registry case series.
590	D. Wilson et al (2017). Developing an algorithm to identify	Retrospective review of consecutive ICH cases who underwent DSA at Queen's	Decision about DSA taken at weekly MDT. No age limit applied.	Univariate odds ratios, sensitivity and specificity generated for age, ICH	N=78 had macrovascular cause on DSA.	ICH cases selected for DSA at MDT based upon age, ICH location and vascular risk

	patients with intracerebral haemorrhage secondary to a macrovascular cause. European Stroke Journal. 2: 4. 369-376.	Square, London Jan 2010-April 2014. Inclusion: non-traumatic ICH with available CT/CTA and DSA. N=204 ICH cases had DSA, 54% male, median age 49 (IQR 18-86) Met all inclusion criteria n=173	Neuroradiology Vascular Fellow reviewed each CTA for macrovascular cause, blinded to DSA result. Same compared with Consultant Neuroradiology report. Disagreement adjudicated by Prof Of Vascular Neuroradiology. Small vessel disease (WMD simplified Fazekas Scale, lacunes) on CT graded by Clin research Fellow in the contralateral hemisphere to ICH.	location, pre-ICH hypertension, SVD on CT and CTA result against reference standard DSA detected macrovascular causes. Logistic regression model generated coefficients. Model fit compared with observed outcomes. Internal validation assessed using bootstrap validation with 1000 samples. Discrimination quantified using ROC area and calibration assessed using Cox-Millar calibration slope.	AVM 68, dAVF 7, aneurysms 2, 1 carotid cavernous fistula. Median CTA to DSA time 2 days (IQR 1-11). 3 AVMs only detected on repeat DSA done median of 264 days post CTA (IQR 78-314 days). ICH locations: lobar 83, deep 60, cerebellar 21 and pure IVH 9. CTA identified 85 with definite or possible macrovascular cause. 67/67 definite CTA cases were also positive on DSA Logistic regression analysis predictors of macrovascular cause of ICH were: Abnormal CTA OR 67.4 (21.3-213.1) Absence of SVD OR 5.0 (1.3-19.6) Absence of pre-ICH hypertension OR 3.4 (1.0-11.4) Age and ICH location were ns.	factors introduces selection bias. Young median age of included subjects. Higher proportion of macrovascular causes found vs routine clinical practice Findings mainly apply to younger ICH cases ICH volumes not recorded Many patients did not have MRI. External validation of model is required.

					CTA sensitivity for macrovascular cause 82% (Final simplified model using these 3 variables showed excellent agreement with patient actual DSA findings. Bootstrap validation excellent (ROC area 0.919). Good calibration shown by Cox-Millar slope of 0.949. Using these 3 variables generated a suggest spontaneous ICH imaging algorithm.	
590	D. Wilson et al (2017). Developing an algorithm to identify patients with intracerebral haemorrhage secondary to a macrovascular cause. European Stroke Journal. 2: 4. 369-376.	Square, London). We identified patients with acute spontaneous ICH who underwent acute non-contrast CT, CTangiography (CTA) and intra-arterial digital subtraction angiography (IADSA) at our institution from January 2010 to April 2014	N/A	Yield of AVM on IADSA.	A combination of CTA, SVD and pre-ICH hypertension predict the likelihood of finding a macrovascular cause in patients with acute spontaneous ICH, allowing informed decisions regarding the likely benefit and risk of IADSA. 73 patients (46% female, median age 49) of whom 78 had a macrovascular cause on IADSA were included. Predictors of a macrovascular cause were: abnormal CTA (OR 67.4; p<0.001); absence	++

					of SVD (OR 5.0; p¼0.019); and absence of pre-ICH hypertension (OR 3.4; p¼0.05). In our internally derived prediction model, the combination of CTA, SVD and pre-ICH hypertension predicted the likelihood of an underlying macrovascular cause (optimism-adjusted ROC area 0.919). Patients with negative CTA, SVD and pre-ICH hypertension have a low likelihood of an underlying macrovascular cause (1.8%).	
591	C. E. Denby et al (2020). Is four-dimensional CT angiography as effective as digital subtraction angiography in the detection of the underlying causes of intracerebral haemorrhage: a systematic review. Neuroradiology. 62: 3. 273-281.	Systematic review and meta-analysis. Subjects in studies had ICH and used 4D CTA and DSA as part of patients investigations.	4D CTA versus reference standard DSA to detect vascular abnormalities. (4D combines the traditional 3-D CTA with time-resolved techniques that show AVM vessels at different blood flow phases.	Sensitivity and specificity of 4D CTA	Only 4 studies identified, small number of patients 3 studies reported 100% sensitivity and/or specificity with DSA therefore no meaningful meta-analysis possible. Instead- qualitative analysis undertaken.	+ Followed PRISMA and Cochrane guidelines. Unclear whether 1 or 2 authors performed literature search.
591	C. E. Denby et al (2020). Is four-dimensional CT angiography as	SR of of studies comparing 4-D CTA vs DSA in detection of underlying structural cause of ICH published 1998-2019.	4 D CTA vs DSA. Median time from 4 D CTA to DSA (3	Primary outcome – correct detection by 4 D CTA of vascular	237 studies identified. Upon review of same, only 4 potential studies for meta-analysis, n=91 subjects.	4 D CTA requires at least 256 detector row CT hardware. Small sample size of included studies, young patient age.

	effective as digital subtraction angiography in the detection of the underlying causes of intracerebral haemorrhage: a systematic review. Neuroradiology. 62: 3. 273-281.	Cochrane Database of Systematic Reviews Guidelines used. PRISMA guidelines used for study selection. Age range 20-80 yrs Mean age (3 studies) varied between 24.8-38 yrs.	studies) varied between 4-11 hours to10 days.	abnormality/lesion cause of ICH.	Meta-analysis not performed due to limited variability of sensitivity and specificity of 4 D CTA and DSA Summary statistics only reported for each of the 4 included studies. Sensitivity of 4 D CTA vs DSA varied between 70-100%. Specificity 100% in each study.	Further work required.