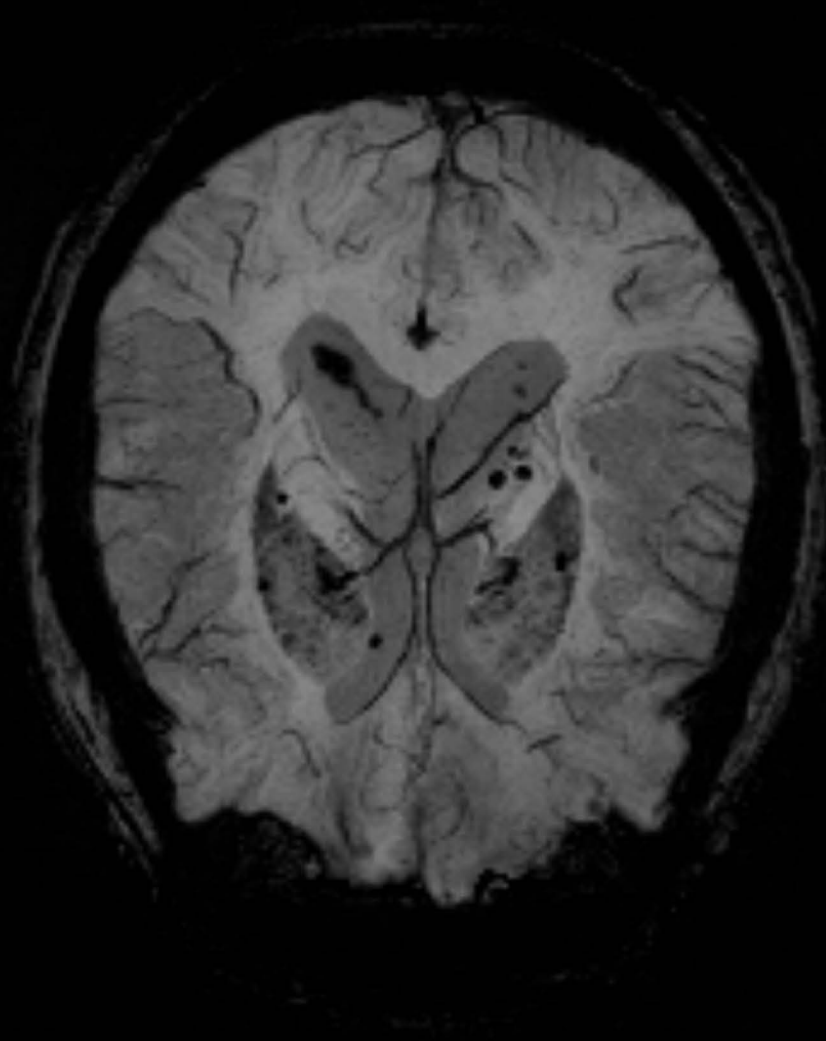


# IMAGING IN ACUTE STROKE – NEW OPTIONS AND STATE OF THE ART

EDITED BY: Anders Fogh Christensen and Hanne Christensen  
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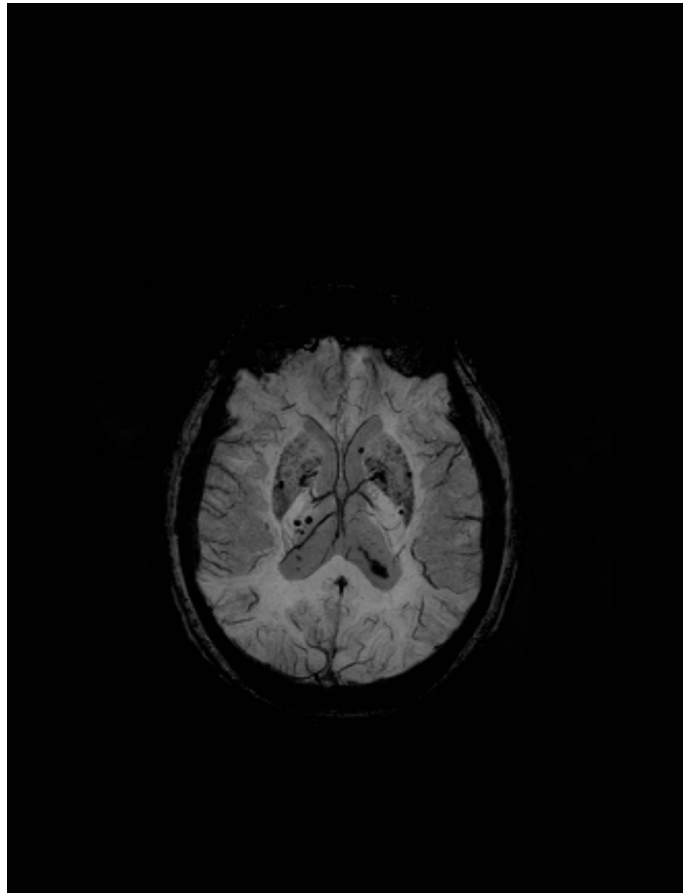
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# IMAGING IN ACUTE STROKE – NEW OPTIONS AND STATE OF THE ART

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SWI mIP sequences in a hypertensive patient admitted with TIA documenting microbleeds in the basal ganglia area; DWI confirmed an acute ischemic lacunar lesion.

Image from Røntgenafdelingen, Bispebjerg Hospital, Copenhagen, Denmark.

One in six adults suffer a stroke during their lifetime and stroke remains the major cause of new onset disability in adulthood. The worldwide burden of stroke is increasing due to an ageing population, however, globally half of stroke victims are young. Stroke is the clinical diagnosis of an acute vascular incident and covers a multitude of pathophysiological causes. The clinician needs imaging to make decisions on acute treatment as well as to plan a secondary prevention strategy: a non-contrast CT and a Duplex of the carotids followed by an aspirin as a one-size-fits-all strategy does not always provide sufficient support for those decisions.

Presently, fast, generally available, and non-invasive imaging provides new possibilities of establishing a cause of stroke, and provides specific information on the brain parenchyma – including possibly salvageable tissue and micro-bleeds – as well as allowing for more specific prognostication in acute stroke.

This eBook covers both ischemic and haemorrhagic stroke and includes hot topics such as micro-bleeds, salvageable tissue and spot-sign, clinically challenging issues including movement artefacts in MRI as well as an overview of present options including pragmatic and feasible suggestions for an approach to state of the art acute imaging.

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# Editorial: Imaging in Acute Stroke—New Options and State of the Art

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## Editorial on the Research Topic

### Imaging in Acute Stroke—New Options and State of the Art

During the last two decades, the state of art imaging in acute stroke has developed from non-contrast CT performed within 7 days to including hyperacute imaging including both angiographic and perfusion imaging. This includes using both new techniques but also using new ways to combine long existing modalities in daily practice. The increasing focus on the importance of both swift and reliable diagnostics combined with an improved scanner accessibility has fueled this development.

This development in imaging has answered to the needs of the introduction of acute vascular recanalization treatments in ischemic stroke, which has revolutionized the area. I.V. thrombolysis has been increasingly used since the end of the 1990s and is now considered a standard treatment, while mechanical thrombectomy has been accepted as a standard procedure following randomized controlled trials documenting its efficacy within the last 5 years. Further, efficacious treatment options in acute ICH are sought, including thrombostatics to reduce final hematoma volume leading to increased activity in this area also.

The imaging modalities, which are in widespread use in primary stroke imaging—at least in tertiary centers, include CT, MRI, and sonography. These methods are complementary in clinical practice with their different strengths. In the following, we will discuss generally available methods to image brain parenchyma, cerebral, and pre-cerebral vasculature and cerebral perfusion in acute stroke.

## IMAGING THE BRAIN PARENCHYMA

Time is of the essence in the diagnosis and treatment of acute ischemic stroke (1). It has been shown that by using a CT-based set-up for IV thrombolysis, a door to needle time around 20 min is achievable based on admitting patients directly to hospital units providing imaging facilities including radiology department, emergency rooms, or trauma centers (2).

CT has a high sensitivity in detecting blood and thereby identifying a bleeding in the brain parenchyma, which is the major contraindication in IV thrombolysis as well as identifying, e.g., neoplasms. Consequently, IV thrombolysis can be initiated safely based on a non-contrast-CT of the brain as only brain imaging (3).

It has been reported that dual-energy CT (DECT-CT) should improve detection of underlying causes for ICH as well as the differentiation between blood and leaked iodine contrast after endovascular procedures compared to standard non-contrast CT.

Trans cranial Doppler (TCD) has little use in visualizing brain parenchyma but can be used to measure the size of an intracerebral hemorrhage and thus visualize an eventual expansion in size (4);

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however, the sensitivity for, e.g., hemorrhage in proximity to the skull base does not allow for this modality as only imaging before revascularisation treatment.

MRI is superior to CT in showing acute ischemic changes in the brain parenchyma (5). Diffusion-weighted imaging shows the ischemic lesion in 80–90% of cases in acute stroke but, in the remaining patients, there will not be DWI-positivity, i.e., the DWI-negative stroke (6). Consequently, a reliable diagnosis of stroke cannot be made based on only MRI conformation if ischemia, clinical diagnosis is still needed.

The ability to detect ischemic lesions is, however, also valuable in transient ischemic attack (TIA). This diagnosis is in Europe based on clinical definitions, but severity scores are used in combination with DWI-positivity in the identification of high-risk patients who have a substantial risk of a subsequently ischemic stroke (7). An unexplained sevenfold variation exists in the frequency of DWI lesions between TIA cohorts, and a DWI-negative scan is very far from ruling out a true ischemic event in these patients (8). MRI is also superior in identifying the underlying cause of stroke based on examination of the brain parenchyma: the pattern of DWI lesions helps to differentiate between large vessel disease and cardiac emboli where, in the latter, several vascular territories are often affected. Microvascular changes in small vessel disease can be diagnosed and quantified, not only forming the basis of a diagnosis of small vessel disease but also in differencing between probable cerebral amyloid angiopathy and deep perforator angiopathy. MRI allows for identifying location and number of micro bleeds, lacunar infarcts, unspecific vascular gliosis, and enhanced perivascular space.

Substantial leukoariosis predict a higher risk of both symptomatic and asymptomatic hemorrhage after IV thrombolysis treatment and independent of this was evaluated by MRI or CT (9). The presence of cerebral micro-bleeds before IV thrombolysis treatment predicts and increased risk of new micro-bleeds after treatment. Further, patients with new micro-bleeds were more likely to develop symptomatic remote hemorrhage, but no increase in rate of hemorrhagic transformation was observed, consequently, this is of minor clinical importance (10).

Using MRI in the work-up of hyperacute stroke increases the door to needle time with about 10 min even in a well-organized setting. This is due to MRI safety issues as well as longer scan-time compared to CT (11). A protocol used for evaluating acute ischemia must include T2 flair and a hemo-sequence in order to exclude intracerebral bleeding. MRI is not possible in a substantial number of acute stroke patients due to either safety issues, being unable to cooperate, or in need of close monitoring. The number of patients falling into this category has been reported as high as 20–40% (12) MRI is performed without applying any radiation to the patient in comparison with CT, which makes it safer to use regarding younger patients.

## IMAGING THE ARTERIAL VESSELS OF THE HEAD AND NECK

By adding CT-angiography (CTA) to an nc-CT, the vessels from the aortic arch to the vertex can be visualized with a resolution

of 0.5 mm iso voxel corresponding to a vessel size of 1 mm. This reveals vessel occlusion down to vessel sized too small for mechanical thrombectomy, thereby allowing for precise identification of patients for this procedure. CTA is also reliable in evaluation for underlying pathologies such as dissection and arteriosclerotic disease (13, 14).

CT-angiography in combination with cerebral post-contrast CT is not only a strong tool in identification of neoplasms but also other underlying causes in patients with intracerebral hemorrhage, including some vascular malformations (15). In addition, the presence of arterial and/or venous extravasation of contrast, the so-called spot-sign, is a strong predictor for hematoma expansion with resulting poorer outcome (16). This may be of use in selecting patients for experimental treatment with pro-thrombotic drugs in order to reduce hematoma expansion (16).

Dual-energy CT improves the diagnostic accuracy of CTA in areas close to bone (17), which is clinically highly relevant in patients with posterior circulation stroke.

Sonography can be performed in the stroke unit and, since it involves no radiation exposure, patient safety issues will not limit the number of examinations. It is possible to evaluate both arterial vessels of the neck as well as intracranial vessels—the latter only as a flow examination whereas the vessel wall of the arteries of the neck can be examined with a resolution of 0.2 mm. This allows the detection of occlusions and stenosis as by CTA but with a greater possibility of a non-conclusive examination based on the possible lack of a temporal sonar window or other bone disturbances of the sonar signal. TCD allows for documentation of reperfusion after IV thrombolysis treatment (18) as well as for quantification of collateral status in middle cerebral artery occlusion by measuring the flow in the anterior cerebral arteries (19). This allows for close observation of this critical patient group.

Sonography has the ability to verify vessel wall changes in cervical arteries including dissection, plaque characterization, and detection of unstable thrombi; however, the clinical implications of especially plaque characterization remain uncertain. Likewise, it is standard practice to use Duplex in the preoperative evaluation of carotid stenosis for thrombectomy using flow measurements to quantify the degree of a stenosis even if CTA has documented a reduction in vessel lumen (20). By using ultrasound contrast media, it is possible to diagnose the presence of persistent foramen ovale or a pulmonary fistula if contrast media is detected in the intracerebral circulation after Valsalva (21).

Further, continuous sonographic input on the acute thrombolysis increases the thrombolytic effects of rTPA (22).

MR angiography may be performed without contrast as Time of Flight sequences, i.e., arterial TOF, which is more time consuming compared to CT angiography as the scan time is several minutes just to visualize the intracranial arteries and longer if the cervical arteries are also included. The longer the scan time the higher the risk of impairing movement artifacts, which are more prevalent in MRI in an acute setting in comparison to planned examinations (Havsteen et al.).

Contrast-enhanced arterial TOF-sequences improve detection of pathology in the vessel lumen in comparison to non-contrast-enhanced TOF sequences. Contrast-enhanced TOF

can be augmented to a resolution down to 0.5 mm isovoxel—the same level as CTA—when using 3-T MRI, but at the expense of prolonged scan time.

Comparative studies show no difference in the sensitivity for detection small aneurisms in comparison to CTA, but the specificity seems to be lower (23). High resolution MRI (HR-MRI) can characterize arteriosclerotic plaques often using contrast-enhanced series, which is reported to give prognostic information about the risk of subsequent vascular events. HR-MRI can also verify dissection changes in small intracranial arteries and visualize reperfusion of such vessels. Vessel wall imaging may be improved by using higher field strength, i.e., 7T MRI (24).

CT-perfusion can be added to the imaging protocol at the price of 5 min more scan-time and an extra 3–5 ms radiation dose. Whole-brain CT-perfusion, i.e., 16 cm coverage has been introduced and has the ability to show areas with low perfusion anywhere in the brain and not restricted to a 4–8 cm slab. This can be useful to both quantify the area with perfusion below which brain parenchyma is lost, i.e., infarct core as well as surrounding salvageable areas with less degree of decreased perfusion, i.e., penumbra. Recently, results from the DAWN study (25) were presented at the ESOC 2017 conference indicating that CT-perfusion—or MR-DWI—can be used to select patients for thrombectomy up to 24 h after ictus, increasing the clinical interest in CTP. The DAWN study was set up to address the issue of wake up and late presenting strokes and neurointervention based on CT-perfusion or DWI-FLAIR mismatch: imaging markers of salvageable tissue. In order to differentiate between ischemic stroke and stroke mimics, perfusion CT may also be helpful and thus compensate for the low visibility of acute ischemia in the brain parenchyma on non-contrast CT alone (26).

An additional feature of whole brain perfusion is the possibility to extract a 4-D angiogram from the perfusion image data without having to perform an angiography; these images show the filling of the intracranial vessels from the early arterial to the late venous phase, which adds a dynamic perspective in the evaluation of acute ischemia improving the visualization of collateral filling (27). The lack of visualization of the vessels of the neck using this method alone can hinder the diagnosis of the underlying cause of stroke.

MRI perfusion is able to show the same findings as CT-perfusion and when it is based on the use of contrast MRI perfusion has considerable advantages especially in obtaining absolute measures of perfusion. It is also possible to apply perfusion sequences without the use of contrast, i.e., arterial spin labeling techniques

ASL. ASL has proven as reliable as contrast-enhanced perfusion techniques in detecting areas with reduced perfusion in acute brain ischemia (28) and with the more extensive use of 3T MRI technology, the resolution has improved. It is reported that adding ASL to a DWI-based TIA protocol increases correct detection of ischemic lesions by 5%. This is primarily the case when the DWI lesion is very small and, therefore, doubtful but with a simultaneous area of hypo perfusion surrounding it clarifying the ischemic diagnosis (29).

Perfusion MRI, in combination with DWI, may also guide the decision of mechanical thrombectomy in large vessel occlusion with unknown time of onset based on the mismatch of the infarct core and the surrounding penumbra on CT perfusion (29), but is more time-consuming than the approach used in the DAWN study.

## CONCLUSION

Combining several image techniques offers several opportunities and advantages. Modern ultrasound apparatus thus offers real-time image fusion so that sonography of the intracranial vessels can be performed using an already performed CTA as anatomical guide. The CTA images can be viewed simultaneously with the live images from TCD and thus assist in the evaluation of intracranial stenosis. Likewise, it is possible in a modern PACS system to co-evaluate all three modalities and thus extract the needed information. This can combine information from a MRI perfusion investigation with CTA visualization of the vessel and Doppler measurements in order to assess the impact of the changes. The information of flow direction and speed from sonography in combination with perfusion measurements and images of the vessel wall can help to explain the extent and location of ischemic lesions and help to decide the treatment options. In acute stroke, the access to all these modalities help to ensure the correct action needed; however, this requires a neuroradiologist on call in collaboration with specialized stroke neurologists. Often in our experience from a tertiary centre, a good strategy is to combine a CTA with an MRI of the brain (DWI, FLAIR, GE/SWI, ASL) to diagnose the cause of stroke and to rule out stroke mimics.

## AUTHOR CONTRIBUTIONS

This editorial was written with equal participation from the authors.

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# A Critical Review of Alberta Stroke Program Early CT Score for Evaluation of Acute Stroke Imaging

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Assessment of ischemic stroke lesions on computed tomography (CT) or MRI using the Alberta Stroke Program Early CT Score (ASPECTS) is widely used to guide acute stroke treatment. We aimed to review the current evidence on ASPECTS. Originally, the score was developed for standardized lesion assessment on non-contrast CT (NCCT). Early studies described ASPECTS as a predictor of functional outcome and symptomatic intracranial hemorrhage after iv-thrombolysis with a threshold of  $\leq 7$  suggested to identify patients at high risk. Following studies rather pointed toward a linear relationship between ASPECTS and functional outcome. ASPECTS has also been applied to assess perfusion CT and diffusion-weighted MRI (DWI). Cerebral blood volume ASPECTS proved to be the best predictor of outcome, outperforming NCCT-ASPECTS in some studies. For DWI-ASPECTS varying thresholds to identify patients at risk for poor outcome were reported. ASPECTS has been used for patient selection in three of the five groundbreaking trials proving efficacy of mechanical thrombectomy published in 2015. ASPECTS values predict functional outcome after thrombectomy. Moreover, treatment effect of thrombectomy appears to depend on ASPECTS values being smaller or not present in low ASPECTS, while patients with ASPECTS 5–10 do clearly benefit from mechanical thrombectomy. However, as patients with low ASPECTS values were excluded from recent trials data on this subgroup is limited. There are several limitations to ASPECTS addressed in a growing number of studies. The score is limited to the anterior circulation, the template is unequally weighed and correlation with lesion volume depends on lesion location. Overall ASPECTS is a useful and easily applicable tool for assessment of prognosis in acute stroke treatment and to help guide acute treatment decisions regardless whether MRI or CT is used. Patients with low ASPECTS values are unlikely to achieve good outcome. However, methodological constraints of ASPECTS have to be considered, and based on present data, a clear cutoff value to define “low ASPECTS values” cannot be given.

**Keywords:** stroke, acute stroke treatment, computed tomography, magnetic resonance imaging, Alberta Stroke Program Early CT Score

## INTRODUCTION

The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) is widely used in clinical practice to assess the extent of early ischemic changes on brain imaging for acute stroke treatment. ASPECTS has been applied to various imaging modalities in acute stroke imaging since its introduction in 2000. ASPECTS is a 10-point scoring system with anatomical regions distributed over the MCA territory (1).

It was designed as a robust imaging measure to predict outcome in intravenous thrombolysis. ASPECTS has drawn a lot of attention due to its use for patient exclusion in the 2015 trials demonstrating efficacy of mechanical thrombectomy (2–4).

Due to high efficacy, we will see an increase of mechanical thrombectomy over the course of the next years and with it probably an increasing use of ASPECTS in routine clinical practice, as patient stratification is key in this time-dependent treatment. There are also a rapidly growing number of scientific studies using ASPECTS in stroke research or addressing methodological questions concerning ASPECTS (please see **Figure 1** for an overview of the number of studies published per year over the last 10 years). This article aims to summarize the current evidence on ASPECTS in a topical and selective review and to explain its applications in clinical practice and trials.

## ORIGINAL CT SCORE

The ECASS-1 trial first established the relevance of early ischemic signs on non-contrast CT scans prior to intravenous thrombolysis (5). Von Kummer et al. showed in 1997 that patients with early ischemic changes in over one-third of the MCA territory had a lower chance of good outcome after ivrtPA (6). However, identification of patients following the 1/3 of the MCA territory paradigm proved to be unreliable in clinical practice (7).

Given these limitations to the 1/3 rule and the necessity to assess early ischemic changes in a reliable way, Barber et al. developed ASPECTS. The score was intended as a pragmatic, reliable,

and easily applicable scoring template for early ischemic changes on CT (1).

The template consists of 10 anatomically defined regions, 4 for subcortical structures [caudate (C); lentiform (L); internal capsule (IC); insular ribbon (I)] and 6 for cortical structures in the MCA territory, labeled M1–M6 (1, 8) (**Figure 2**).

The MCA territory is assessed on all axial CT cuts in two distinct levels, the “ganglionic” and “supraganglionic” level. All axial cuts on the level of the caudate head or below are hereby allotted to the ganglionic level, all above to the supraganglionic. The caudate nucleus is part of both layers, the head belonging to the ganglionic, body, and tail to the supraganglionic level (8).

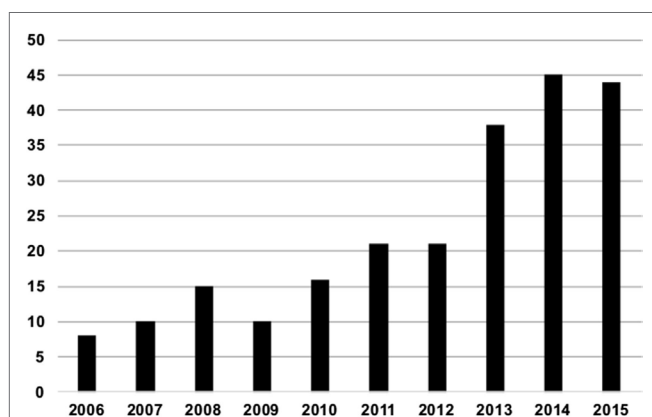
Early ischemic changes on CT were originally defined as intraparenchymal hypoattenuation (loss of gray–white matter distinction) and focal swelling. For each ASPECTS region that presents with early ischemic changes on at least two consecutive cuts, the overall score of 10 is reduced by 1. Thus, a score of 0 would indicate infarction of all 10 regions.

Despite relatively vague definition of the individual regions interrater agreement for dichotomized ASPECTS has been described as good (1, 9, 10) with some studies reporting moderate agreement (11–13).

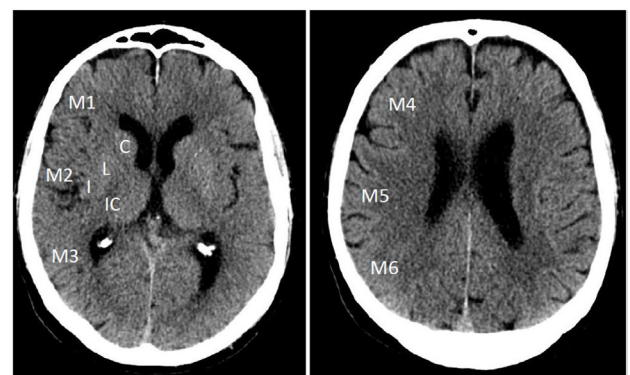
## ASPECTS AS PREDICTOR OF STROKE OUTCOME

The original publication proposed a cutoff of  $\leq 7$  on the initial non-contrast CT (NCCT) as it predicted functional dependence in patients who underwent thrombolysis within 3 h from symptom onset (1).

A larger Canadian study of 936 patients treated with iv-thrombolysis in 3 h time window between 1999 and 2001 demonstrated a near linear inverse relationship between ASPECTS on baseline NCCT and functional outcome (14). However, in 2012, González et al. reported no significant prediction of MRS  $>2$  after 6 months by ASPECTS on initial NCCT performed within 24 h from symptom onset in 649 patients diagnosed with ischemic stroke (15).



**FIGURE 1 |** Number of publications indexed in MedLine for the search term “Alberta Stroke Program early CT Score” per year since 2006.



**FIGURE 2 |** Alberta Stroke Program Early Computed Tomography Score template on non-contrast CT with 10 regions distributed over the MCA territory in ganglionic and supraganglionic levels.

For iv-thrombolysis a modification of treatment effect by ASPECTS could not be proven in 3 or 6 h time windows (16, 17). Still, in the NINDS rtPA Stroke Study higher ASPECTS values were associated with a greater benefit from iv treatment with rtPA (16).

## ASPECTS AS PREDICTOR OF SYMPTOMATIC INTRACRANIAL HEMORRHAGE AFTER THROMBOLYSIS

Barber et al. originally described ASPECTS as a significant predictor of symptomatic intracranial hemorrhage after thrombolysis within 3 h from symptom onset (1). This could not be reproduced based on data from the ECASS-II or NINDS-stroke trials (16, 17).

In 2009, Puetz et al. published a comprehensive review focusing mainly on NCCT-ASPECTS. As isolated cortical swelling can occur in penumbra and infarct core, they proposed the removal of isolated focal swelling without hypoattenuation from the early ischemic changes relevant for scoring (18).

## USE OF ASPECTS WITH PERFUSION-CT AND DIFFUSION-WEIGHTED MRI

There have been numerous publications assessing the applicability of ASPECTS to multiparametric CT and MRI. One prominent focus has been the evaluation of different CT Perfusion measures using ASPECTS.

Parsons et al. described cerebral blood volume (CBV) ASPECTS within 6 h from symptom onset as a more accurate predictor of irreversibly damaged tissue when compared with NCCT ASPECTS in 2007 (19). Lin et al. identified a MTT/CBV ASPECTS mismatch of  $\geq 1$  within 6 h as the optimal cutoff to identify a volumetric mismatch of  $\geq 20\%$  (20). MTT/CBV ASPECTS mismatch within 3 h from symptom onset was also highly correlated with volumetric tissue at risk in a 2011 study by Sillanpää et al.; furthermore, CBV ASPECTS within 8 h from symptom onset was superior to NCCT ASPECTS in discriminating patients with favorable outcome (21, 22). In contrast, a large study with 824 patients from a Dutch stroke registry could not find an additional impact of CBV and MTT ASPECTS compared to only NCCT ASPECTS within 9 h from symptom onset when analyzed in a multivariate model. In the same study, CBV and MTT ASPECTS were significant predictors of poor clinical outcome in univariate analysis (23).

Thus, it is unclear whether CTP ASPECTS offers a clear advantage over NCCT ASPECTS, data at the present state are ambiguous. There have been reports of improved interrater reliability on CBV ASPECTS within 4.5 and 9 h from stroke onset compared to NCCT ASPECTS (13, 24).

ASPECTS has also been used to assess lesion extent on diffusion-weighted MRI (DWI), usually labeled “DWI-ASPECTS.” DWI-ASPECTS within 3 h after symptom onset has been proven to predict functional outcome (MRS) and mortality after 3 months in patients undergoing iv-thrombolysis. As a cutoff to identify patients at risk for poor outcome DWI-ASPECTS  $> 6$  was proposed, though specificity was low at 33% (25). Another study

identified DWI-ASPECTS  $> 5$  within 3 h after onset as a cutoff to identify patients with good functional outcome 7 days after iv-thrombolysis (26). Based on a cohort of patients with imaging between 3 and 24 h after onset, Tei et al. proposed a cutoff of DWI-ASPECTS  $> 7$  to predict MRS  $\geq 3$  after 3 months in 2011 (27). In all three studies, DWI-ASPECTS was an independent predictor of functional outcome. Nezu et al. found DWI-ASPECTS to be approximately 1 point lower than NCCT-ASPECTS within 3 h from symptom onset in 360 patients, who underwent both imaging modalities. In the same study, there was no significant difference in area under the receiver operating characteristic (ROC) curve of DWI- and NCCT-ASPECTS for prediction of MRS 0–2 at 90 days. Interrater agreement was higher for DWI-ASPECTS (28).

Overall due to the higher sensitivity of DWI (29), DWI-ASPECTS is more sensitive for the detection of early ischemic changes than NCCT ASPECTS (30). After endovascular therapy within 12 h from symptom onset DWI-ASPECTS had higher interrater agreement and according to ROC analysis outperformed NCCT ASPECTS in predicting good functional outcome at 90 days poststroke (9).

There have been multiple attempts to use ASPECTS as a surrogate marker for DWI lesion volume and a threshold of  $< 4$  has been proposed to identify patients with DWI volume  $> 100$  ml (31, 32). We could show that depending on lesion location estimation of DWI lesion volume by DWI-ASPECTS is unreliable (see below) (33).

## ASPECTS FOR USE WITH MECHANICAL THROMBECTOMY

Identification of a clearly defined treatable lesion was highlighted as a key issue (34, 35) after three endovascular trials published in 2013 (36–38) failed to prove a significant additional benefit of endovascular stroke treatment over standard iv treatment. As the acute stroke setting comes along with restrictions for time consuming post processing of CT or MRI data, ASPECTS among other techniques has been proposed as a fast and easy method to identify patients suitable for endovascular reperfusion treatment.

There have been several studies suggesting an increased benefit of endovascular treatment for patients with higher ASPECTS values using various imaging modalities.

In the Penumbra Pivotal Stroke (39) trial not a single patient with ASPECTS  $< 5$  on the initial CT scan up to 8 h after symptom onset achieved a favorable outcome (MRS 0–2 after 3 months), good outcome was significantly more frequent in the ASPECTS score  $> 7$  group when compared to the ASPECTS score  $\leq 7$  group [50 vs. 15%; RR, 3.3; 95% confidence interval (CI), 1.6–6.8;  $p < 0.0001$ ].

A further analysis of data from trials using the Penumbra system including 249 patients again showed an increase in favorable outcome with higher ASPECTS values (40). Symptomatic intracranial hemorrhage was more frequent in patients with low ASPECTS scores on initial CT scans. Furthermore, patients with ASPECTS 0–4 had significantly worse outcome than patients with ASPECTS 5–10 and did not benefit from faster treatment,



thus suggesting a cutoff ASPECTS  $\leq 4$  to identify patients with poor response to intravascular treatment (40).

In a study of 51 patients undergoing aspiration thrombectomy with a median onset to recanalization time of 292 (IQR 246–357) min, patients with good outcome (MRS 0–2) had significantly higher CBV ASPECTS (CBV ASPECTS 8 vs. 6,  $p = 0.0007$ ), CBV ASPECTS  $> 7$  was identified as optimal cutoff with a positive predictive value of 65% (41). This was reproduced by Lum et al. in a collective of 46 patients within 6 h from symptom onset (42).

Soize et al. reported an independent prediction of outcome and of symptomatic intracranial hemorrhage by DWI-ASPECTS in 59 patients after mechanical thrombectomy (mean time from symptom onset to recanalization 296 min) (43). Inoue et al. identified DWI-ASPECTS  $\geq 5$  as the optimal predictor of favorable outcome after 90 days following intra-arterial treatment in a collective of 210 patients [median time from onset to MRI 105 (IQR 75–178) min] (44).

In the IMS-III trial (656 subjects randomized), patients with ASPECTS 8–10 on initial NCCT up to 3 h after symptom onset were almost twice as likely (relative risk, 1.8; 99% CI, 1.4–2.4) to achieve a favorable outcome. However, there was no significant treatment by ASPECTS interaction (45).

## ASPECTS IN THE LARGE STENT-TRIEVER THROMBECTOMY TRIALS

In 2015, five randomized-controlled trials demonstrated a strong positive effect of mechanical thrombectomy using stent-trieter devices on patient outcome when compared with standard iv treatment alone. Most of these trials used NCCT-ASPECTS for patient selection based on the experience of the studies cited above.

The first new generation thrombectomy trial published, MR CLEAN did not use an ASPECTS threshold for patient exclusion. Patients were included up to 6 h after symptom onset. There was a consistent additional effect of intra-arterial treatment over all ASPECTS ranges analyzed (0–4, 5–7, 8–10). Intra-arterial treatment caused no increase of symptomatic intracranial hemorrhage in any of the ASPECTS groups compared iv treatment only. However, only 30 patients with ASPECTS 0–4 were analyzed and only one of those achieved MRS 2 (46, 47).

Based on the findings of Inoue et al. (44), the SWIFT-PRIME study used NCCT- or DWI-ASPECTS  $\leq 5$  within 6 h after symptom onset as an exclusion threshold. There was no difference in outcome between patients with ASPECTS 6–7 and 8–10 (4). Investigators in the ESCAPE study also applied an ASPECTS threshold of  $\leq 5$  up to 12 h after symptom onset to exclude patients. Again, there was no heterogeneity of effect between patients with ASPECTS 6–7 and 8–10 (2).

The only study to use DWI-ASPECTS and NCCT-ASPECTS in a time window up to 8 h after symptom onset was REVASCAT. To account for the different sensitivities of DWI and NCCT-imaging a threshold of  $< 7$  was applied to CT and  $< 6$  to DWI for patient exclusion. The difference of 1 point between DWI- and NCCT-ASPECTS was chosen based on earlier findings by

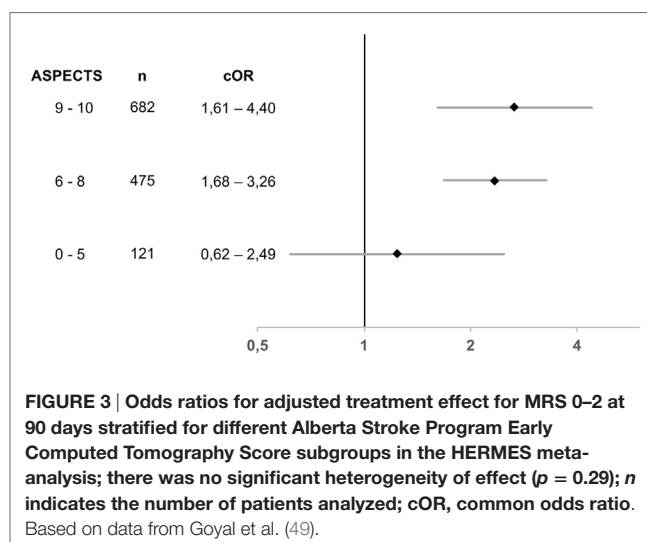
Nezu et al. (28). There was no significant difference in outcome for patients with ASPECTS  $\leq 7$  and above (3). In EXTEND-IA, patient selection was not based on ASPECTS but on volumetric infarct core to perfusion lesion mismatch (48).

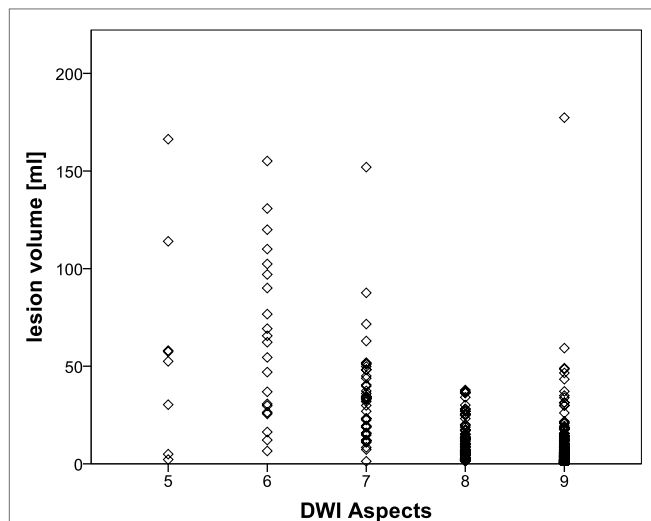
A recent meta-analysis performed a central reading of all pre-treatment scans from the five thrombectomy trials and found a clear benefit of thrombectomy in patients with ASPECTS  $> 5$  (49). Of note, in the pooled data, median ASPECTS was 9 for both the treatment (IQR 7–10) and control (IQR 8–10) groups. Treatment effect was analyzed for three ASPECTS strata: 0–5, 6–8, and 9–10. While there was a strong and consistent treatment effect for both ASPECTS 6–8 and 9–10 with an adjusted odds ratio of OR 2.36 (95% CI 1.68–3.26) and 2.66 (1.61–4.40), no clear benefit was observed for 121 patients with ASPECT 0–5 with an OR of 1.24 (0.62–2.42). **Figure 3** illustrates the odds ratios for the different ASPECTS subgroups.

## METHODOLOGICAL ISSUES AND LIMITATIONS OF ASPECTS

Despite its broad application ASPECTS has limitations. First of all, the original ASPECTS score is limited to the anterior circulation only (1). Second, ASPECTS shows an unequal weighing of brain regions, as first described in 2006 by Phan et al. (50). The template is based on anatomical structures, and thus, the individual regions cover different amounts of brain tissue. Additionally, the exact extent of each region or how much damaged tissue is required to render a region affected has never been defined (1).

In a study of 496 patients, we could show that correlation of ASPECTS with DWI lesion volume varied considerably depending on lesion location (33). **Figure 4** shows the distribution of lesion volumes for ASPECTS values  $> 4$ . Two patients with the same ASPECTS score do not necessarily have similar lesion volumes. As lesion volume is a strong predictor of functional outcome (51–53), the template's unequal weighing could compromise clinical decisions. If decision making is based solely on an ASPECTS threshold this might lead to unjustified exclusion





**FIGURE 4 |** Distribution of lesion volumes in patients with diffusion-weighted MRI (DWI)-Alberta Stroke Program Early Computed Tomography Score (ASPECTS)  $\geq 5$ , these patients were shown to benefit from mechanical thrombectomy in the recent HERMES meta-analysis (49). Lesion volumes varied considerably in patients with the same DWI ASPECTS. Based on data from Schröder et al. (33).

of patients from clinical trials or even treatment when lesion location is not considered.

Depending on analyzed sample, treatment, and imaging modality applied, various cutoffs to identify patients at risk of poor outcome have been suggested (1, 14, 20, 25–27, 47). Furthermore, large studies suggested a linear relationship or even no significant outcome prediction by ASPECTS at all (14, 15). Thus, recommendation of one single threshold to identify patients with poor outcome based on the available data seems hardly justifiable.

Another issue confined to the widely used NCCT ASPECTS is the poor sensitivity in the early period after stroke (29).

## CONCLUSION

ASPECTS is a useful and easily applicable tool for standardized evaluation of the extent of acute ischemic lesions that may help in the assessment of prognosis in acute stroke treatment regardless

whether MRI or CT is used. Patients with low ASPECTS values are unlikely to achieve good outcome. However, based on present data, a clear cutoff value to define “low ASPECTS values” cannot be given.

A clear advantage of CT perfusion ASPECTS over NCCT ASPECTS has not been established, both could be shown to predict poor functional outcome as assessed by the MRS after 90 days. CBV ASPECTS may offer slightly improved interrater reliability.

Due to DWI’s high sensitivity, a key issue of DWI-ASPECTS is the definition how much lesioned tissue is required for a region to be counted as affected. Formal instructions are lacking. This could explain at least part of the variance in the proposed cutoff values. There are contradicting reports comparing the performances of DWI-ASPECTS and NCCT-ASPECTS for outcome prediction. Interrater agreement was improved for DWI-ASPECTS compared to NCCT-ASPECTS.

ASPECTS may further help in guiding patient selection for enrollment in clinical trials as well as for reperfusion treatment. For mechanical thrombectomy, a clear benefit over iv treatment alone has been proven for patients with NCCT ASPECTS 6–10, while for ASPECTS values 0–5 treatment effect is not clear.

However, when applying ASPECTS cutoffs methodological limitations have to be considered resulting from the unequal weighing of different brain regions by ASPECTS. As a consequence, stroke lesions with the same ASPECTS rating may have quite different lesion extent depending on their location. Thus, we do not recommend to stick to strict NCCT- or DWI-ASPECTS values for exclusion of patients from treatment but rather consider ASPECTS as a helpful of diagnostic tools that should be looked at in the broader perspective including other imaging and clinical features.

## AUTHOR CONTRIBUTIONS

Both JS and GT made substantial contributions to the conception, the acquisition, analysis, and interpretation of data for the work; drafted the work and/or revised it critically for important intellectual content; approved the final version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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# Are Movement Artifacts in Magnetic Resonance Imaging a Real Problem?—A Narrative Review

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Movement artifacts compromise image quality and may interfere with interpretation, especially in magnetic resonance imaging (MRI) applications with low signal-to-noise ratio such as functional MRI or diffusion tensor imaging, and when imaging small lesions. High image resolution has high sensitivity to motion artifacts and often prolongs scan time that again aggravates movement artifacts. During the scan fast imaging techniques and sequences, optimal receiver coils, careful patient positioning, and instruction may minimize movement artifacts. Physiological noise sources are motion from respiration, flow and pulse coupled to cardiac cycles, from the swallowing reflex and small spontaneous head movements. Par example, in resting-state functional MRI spontaneous neuronal activity adds 1–2% of signal change, even under optimal conditions signal contributions from physiological noise remain a considerable fraction hereof. Movement tracking during imaging may allow for prospective correction or postprocessing steps separating signal and noise.

**Keywords:** acute stroke imaging, dynamic magnetic resonance imaging, motion artifacts, noise reduction, motion tracking

## BACKGROUND

Movement artifacts are an inherent problem to magnetic resonance imaging (MRI) technology where low signal and sensitivity to motion are obstacles driving the development of ever faster sequences, e.g., gradient echo, and finer detection equipment, e.g., multichannel phased array coils, since the very beginning of nuclear magnetic resonance (NMR) imaging (1). A brief history of medical imaging may be found in Ref. (2).

## Why Is Movement a Problem?

Movement artifacts in MRI degrade image quality and may lead to misinterpretation especially in MRI acquisitions with low signal-to-noise ratios (SNRs), or for small lesion pathology. In MRI sequences with robust visual interpretation, simple motion artifacts can be identified as, e.g., ghosting or blurring. In dynamic MRI scans, motion artifacts can cause signal changes that may severely confound statistical analysis rendering results unreliable (3, 4).

## Movement Artifacts Interfere with Image Interpretation in Dynamic and Static MRI Functional MRI (fMRI)

Functional MRI measures subtle changes in local blood oxygenation and flow related to neural activity. Head motion artifacts can cause signal changes, **Figure 1**. In the worst case, motion-related signal changes may be correlated with activation of interest in task-based fMRI rendering results difficult to interpret or in resting-state where motion-related signal changes may be confused with correlations between regions when measuring functional connectivity (3–6). By carefully mapping isolated head movement artifacts, spatial patterns resembling the default mode network were found (3). Also movement induced signal changes introduce spatiotemporal structured noise that invalidate the typical assumptions of independent and identically distributed Gaussian noise in the statistical analysis (7).

### Diffusion-Weighted Imaging (DWI)

Diffusion-weighted imaging shows directional variation of diffusion restriction in diffusion-weighted images. Movement artifacts cause misalignment of data and introduce noise in the images rendering results unreliable (8). The main compromise usually stands between resolution and acquisition time. DWI has long acquisition times with repetition times up to 10 s which increases sensitivity to motion artifacts. For detection of focal diffusion restriction, one usually uses three orthogonal diffusion directions only, with usual 1–2 mm axial resolution and acquisition

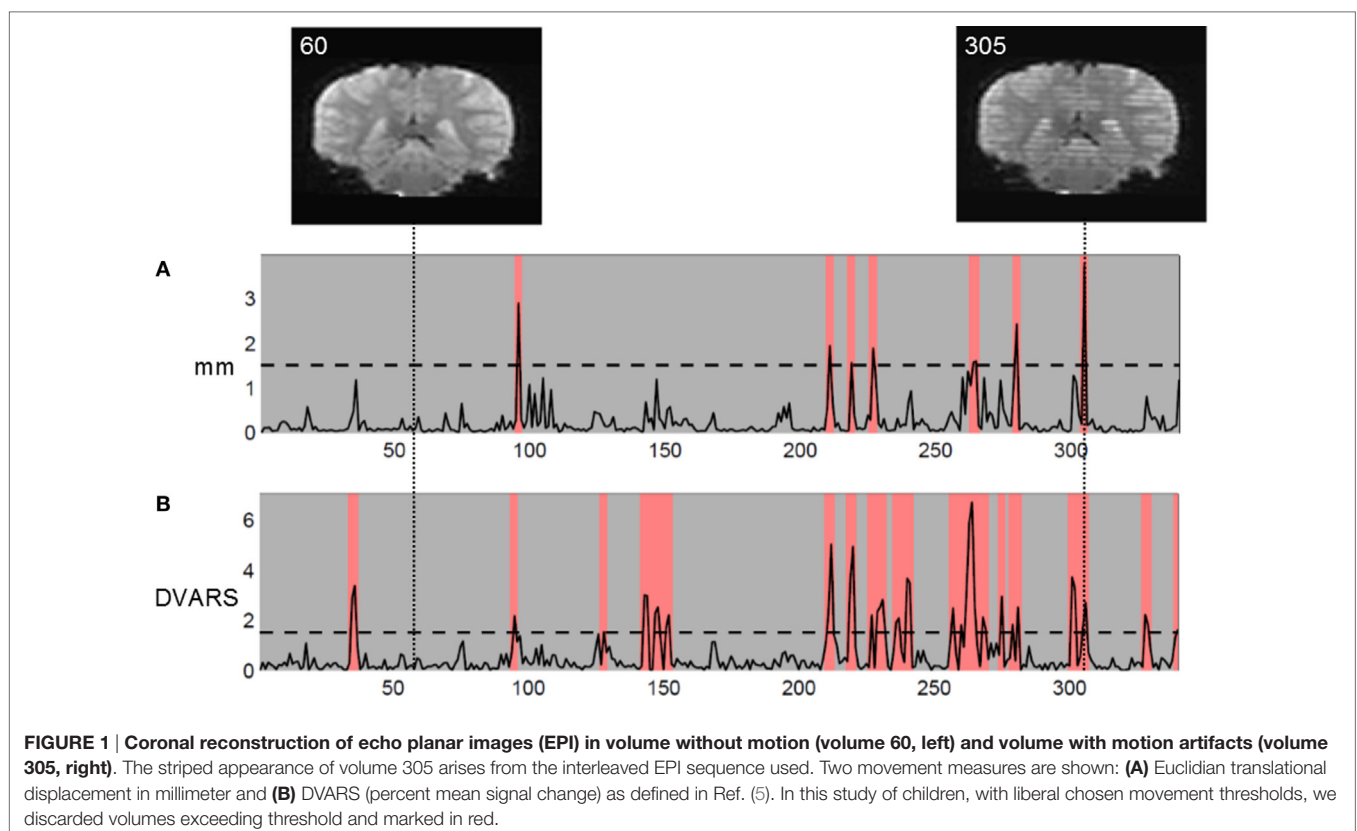
times around 2 min. Diffusion tensor imaging (DTI) used for, e.g., fiber tracking and determination of white matter integrity needs imaging along at least six gradient directions, usually 20–60. DTI has longer acquisition times, usually 4–5 min, rendering it more susceptible to motion artifacts than 3-gradient direction DWI, **Figure 2**. In DWI, artifacts due to physiological noise are usually minor and can be handled by gating (9–11).

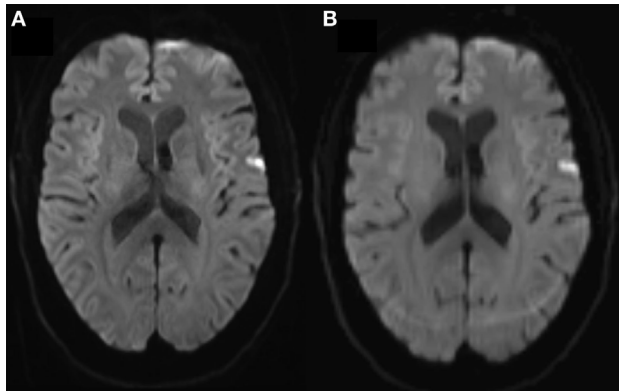
### Arterial Spin Labeling (ASL)

Arterial spin labeling is a perfusion imaging technique that uses endogenous blood water labeled as “paramagnetic tracer” to estimate cerebral blood flow. One labels blood water prior to inflow into the imaging region and subtracts labeled images from control images to find a measure proportional with cerebral blood flow. Bulk motion during free breathing introduces additional blurring. Breath-hold timing and background suppression schemes enhance image quality using series of additional saturation and inversion pulses (12).

### Structural Images

In structural images movement, artifacts are a smaller problem, here the strong SNR enables visual acuity to robustly differentiate between anatomical structure and artifact. Yet, challenges remain especially in areas with high intrinsic motion, e.g., cardiac MRI encounters both cardiac pumping and respiration. Head motion has been shown to compromise T1-derived volumetric measurements of cortical thickness, where a seeming reduction imitates cortical atrophy (13).





**FIGURE 2 | (A)** Three and **(B)** 20-gradient direction diffusion-weighted imaging (DWI) images of 68 years female with 2 h lasting transient ischemic attack symptoms including right hand paresis and slurred speech. In **(B)**, note the occipital ring artifact, blurred contours of the right-sided cortical diffusion lesion and blurred cortex outline due to motion. Three-gradient direction DWI had acquisition time 2 min and 7 s and 20-gradient direction DWI had 4 min and 39 s, both were standard vendor protocols.

### Small Lesions

Small lesions, 3 mm or below, are challenging to image with high fidelity and to confidently categorize (14, 15), yet evidence grows of their clinical importance as, e.g., small stroke suspect lesion presence is associated with increased mortality and morbidity (16). Intra- and interrater agreement show deviations <5% and 2 ml for acute ischemic DWI lesions over 15 ml (17). For smaller lesions in a combined minor stroke and TIA cohort with mean DWI lesion volume 3.4 ml, measurement intra- and interrater agreement were very good (ICC 0.96 and 0.94) (18). Still, 3.4 ml corresponds to 1.5 cm lesion length using simple cubic calculation. While these results are excellent, there still is a way to lesions around 3 mm, the usual cutoff value for ischemic lesion inclusion (19), these would have volumes of 0.027 ml. Only recently, the Standards for Reporting Vascular Changes on Neuroimaging group has included lesions below 3 mm as potential signs of small vessel disease (14). The goal is to image structures with enough detail and minimal distortion to achieve proper identification. One path is noise reduction.

### Higher Field Strengths Yield Higher Resolution and Higher Sensitivity to Motion Artifacts

There is a general trend toward higher magnetic field strengths (1). At 7 T, angiographic MRI studies using susceptibility-weighted imaging (20) or Time Of Flight (21) achieve resolutions similar to CT (about 0.4 mm in-plane) without contrast agents or ionizing radiation. The increase in imaging sensitivity at higher field strengths comes with an increase in sensitivity to physiological noise and motion, i.e., the proportion of noise increases even without increasing resolution. Higher B fields allow higher resolution, where even smaller movement artifacts compromise image quality. Also high resolution demands long acquisition

times and motion artifacts worsen with longer acquisition times. The problem remains in future.

### Aim

This text aims to assess if subject-related movement artifacts in MRI are problematic, i.e., interfere with interpretation, to identify where this is the case, investigate the magnitude of movement artifacts compared with MR signal and other noise sources, and to explore strategies to attenuate or circumvent movement artifacts.

This review is rooted in neuroimaging in a clinical context but extends into the realm of research, as many clinicians are involved in research budding from clinics striving to improve current practice. The intended audience is the interested neurologist in the interface between clinics and neuroscientific research. The review's scope is introductory, to provide a background for understanding the underlying causes of motion artifacts and strategies for their mitigation. This is a narrative review based on a practical approach; a systematic literature review is beyond the scope of this text.

## THE SIGNAL AND THE NOISE

### Outlining the Problem: Accurate Imaging at High Resolution

Small objects are most susceptible to motion artifacts. If the resolution, voxel size, is near or larger than the imaged objects, their contours appear smeared or blurred and the effect is called partial volume. Similarly, movement artifacts degrade image quality, because some voxels will be moved to another part of the object that may have different signal intensity, e.g., in the brain a white matter voxel is moved into gray matter or cerebrospinal fluid filled cavities as the lateral ventricles. Thus, motion artifacts are most prominent at contrast edges (22), i.e., the border between the brain and the skull or air-filled sinuses, borders between gray and white matter and around the lateral ventricles.

In image acquisition, in-plane acceleration schemes (23–25) are attractive as they allow decreasing the length of readout trains. This greatly reduces distortions allowing shorter echo times and higher resolutions to be achieved. However, in this context, it is important to note that these acceleration schemes come at the price of reduced SNR (25–27) and importantly can lead to increased motion sensitivity, in particular if motion occurs during the reference/auto-calibrating signal scans. Furthermore, accelerated imaging may cause complicated motion artifacts that are more difficult to identify. Simultaneous multislice (SMS) acquisition schemes (28, 29) allow speeding up echo planar imaging (EPI) acquisition with little or no penalty in the SNR for moderate acceleration factors. When compared to in-place acceleration schemes, SMS is typically considered to increase motion sensitivity to a lesser extent; however, it should be noted that SMS can also complicate the identification of motion artifacts as they will affect several slices simultaneously and may lead to reconstruction artifacts.

One may attempt to correct for motion artifacts, i.e., motion-induced voxel misplacement relative to adjacent structures,

by retrograde realignment of the acquired image slices. The procedure is called six parameter rigid body transformation and mitigates motion-related noise (30, 31). One assumes that the imaged volume, i.e., the head, is a rigid body and that its movements can be described with six vectors, three translational along orthogonal axes, and three rotational. Retrograde calculations of translational and rotational movements are based on the assumption that motion happens only between volumes. In reality, most sequences use most of the time for either magnetization or readout. Also the method does not account for non-linear motion effects or movements in previous scans and their effects on field inhomogeneity and spin history (32). Motion artifacts, here mostly head motion, cause local changes in the magnetic field showing for echo planar sequences as warping in the phase encoding direction and for spiral acquisition as blur (22). Yet, the six-parameter rigid body transformation greatly reduces motion effects and is a common preprocessing step in fMRI.

## Scaling the Signal and the Noise Back to Basics—How Are MR Images Made?

When an object is within a strong magnetic field, one may send in a radio wave and receive an echo (the MR signal). The echo is determined by two physical constants, T1 and T2. Each tissue has unique T1 and T2 relaxation curves.

The MRI signal is created by a strong static magnetic field ( $B_0$ ) formed by a superconductive coil combined with one or more radiofrequency (RF) fields ( $B_1$ ) created through the application of RF pulses and several weak magnetic fields generated by gradient coils.

For anatomic MR signal (echo) localization in voxels, one forms a grid with three orthogonal directions: the RF excitation pulse creates a weaker  $B_1$  field. A slice-selective gradient cuts the  $B_1$  field into two-dimensional (2D) slices, and in each 2D slice magnetic field gradients encode phase and frequency forming cubes (voxels) with unique anatomic localization. The RF pulse is tuned to the NMR frequency of hydrogen, which is determined by the strength of the  $B_0$  field and the gyromagnetic ratio of hydrogen. When a patient enters the scanner, the magnetic moments of protons in the body tend to align with the  $B_0$  field. The RF pulse is applied and forces the magnetic moments to precess at their resonant frequency creating the  $B_1$  field. This precession and its decay after the RF pulse is switched off (the echo) are detected by one or more receive coils as the signal. For more details, see, e.g., Ref. (2, 33).

Hydrogen (1H) is the most abundant and commonly used. 19F, 31P, 7Li, 129Xe, 23Na, 13C, and 17O are examples of other nuclei that possess the required spin property, and each requires its own RF pulse tuned to its frequency.

## How Does the MR Signal Relate to Field Strength?

Higher magnetic field strengths improve image SNR and contrast-to-noise ratio (CNR) yielding higher resolution. Images with higher resolution are more sensitive to motion artifacts. **Table 1** shows that higher spatial resolution is achievable at higher field strength and that the spatial resolution of fMRI is inferior to the anatomical resolution because signal changes are small, only a few percent of the available signal (**Table 2**). All other conditions

**TABLE 1 | Spatial resolution.**

B (T)	Resolution (mm <sup>3</sup> )
3 T anatomical images	1 × 1 × 1
3 T functional MRI (fMRI) and perfusion contrast	2 × 2 × 2 <sup>a</sup>
7 T anatomical images	0.5 × 0.5 × 0.5
7 T fMRI	1 × 1 × 1 <sup>a</sup>

From Ref. (1).

<sup>a</sup>Spatial resolution is inferior to anatomical because the small signal changes, only a few percent of the available signal. The use of higher resolutions generally reduces both image signal-to-noise ratio and contrast-to-noise ratio.

**TABLE 2 | Contributions to rs-fMRI signal change in whole brain gray matter at voxel level in 7 T.**

Low frequency drift due to scanner instability	3.2%
Thermal noise	2.3%
Spontaneous neuronal activity	1.9%
RETROICOR <sup>a</sup>	0.1%
Cardiac rate	0.1%
Respiration volume per unit time	0.1%

From Ref. (34).

<sup>a</sup>Eight regressors correlated with physiological activity.

equal, higher spatial resolution requires longer acquisition times. Presumably, one could obtain higher resolution in the same or shorter time if one increases the SNR/CNR accordingly.

## fMRI Signal

The anatomical basis of the fMRI signal are perfusion and oxygenation-related local changes in venous blood [blood oxygenation level-dependent (BOLD) signal] in the cortex and pial vessels related to local neuronal activity (35, 36). Deoxyhemoglobin is paramagnetic and oxyhemoglobin is diamagnetic. The paramagnetic deoxyhemoglobin causes a focal artifact of signal loss in T2\*-weighted sequences because it causes a focal inhomogeneity in the magnetic field that increases T2\* decay. The metabolic demand of neural activity increases local perfusion and oxygenation, decreasing local deoxyhemoglobin concentration. The relative absence of deoxyhemoglobin and its related signal loss is seen as BOLD signal increase. For more details, see, e.g., Ref. (37). Movement may veil or obliterate these subtle local field homogeneity changes.

The changes in BOLD signal amplitude are only a few percent of the signal and are too small for visual assessment. They require statistical analysis for detection (**Table 2**). fMRI precision estimation depends not only on image SNR but also on the signal stability on repetition of the image acquisition as reflected in the temporal SNR (tSNR) (38).

## Breaking Down the Noise into Its Components—Nuisance Modeling

In fMRI signal, variability may stem from four principal sources as thermal and scanner noise arising from system instabilities, physiological noise of BOLD origin (spontaneous neural activity), and other physiological noise arising from subject motion, cardiac cycles, and respiration (34).

**Table 2** shows noise sources' relative contribution to resting-state fMRI signal changes.



Thermal noise is related to the scanning process and has white noise characteristics (uniform power spectral density) and originates from both the brain tissue and from detector electronics. It can be reduced using high B-fields and multichannel detector array receive coils.

Non-thermal, physiological noise sources generally cause signal fluctuations that scale with the absolute signal strength (39–41). In fMRI, the noise sources, physiological and non-physiological, need to be properly characterized and separated from the signal (34, 42). Otherwise they limit the improvements in detection sensitivity available with high B-fields (27, 43).

### Movement-Related Noise and Its Size

Even healthy and cooperative adults show spontaneous head movements up to a millimeter (32). Friston and colleagues (32) divided movement-related signal components into differences in the position of the object in the scanner and differences due to the history of the position of the object. **Table 3** shows displacement sizes for respiratory, cardiac, and head motion.

### Respiration and Cardiac Cycles

During normal *breathing*, the diaphragm moves several centimeters and the chest wall several millimeters. Most imaging strategies involve tracking of the respiratory cyclic motion and imaging within a chosen interval of the cycle (gating).

*Cardiac motion and arterial pulsation* have implications for imaging, especially for heart and brain studies. Cardiac pumping consists of longitudinal and radial contraction and causes displacements measuring over 1 cm in healthy individuals (44). Also beat-to-beat variations in blood flow may cause artifacts (46). Further reading on motion in cardiovascular imaging can be found in Ref. (47).

Brain pulsation cause non-rigid displacements of up to 0.1 mm in some brain regions (45). Timing the MRI pulse with respiratory and cardiac cycles (gating) may be necessary when imaging at submillimeter resolutions in research settings.

### Other fMRI- and DWI-Relevant Artifacts

#### Susceptibility Artifacts at Tissue Boundaries

The EPI sequence used for fMRI and DWI is vulnerable to susceptibility artifacts. Differences in tissue magnetic susceptibility cause field inhomogeneity at tissue boundaries, which cause spins to dephase faster and frequency shifts that produce low signal areas. Bone and air have much lower magnetic susceptibility than most soft tissues; thus, the signal loss is most pronounced at brain–air or brain–bone interfaces.

## HANDLING THE NOISE

To achieve as good and reliable data as possible to draw valid conclusions from it is an advantage to know if and when motion

has occurred and its extent. Ideally, external motion tracking is preferable to motion estimation from data itself as motion may compromise the acquired data. The effective tracking system aims to provide real-time tracking with subpixel accuracy and must not introduce extra artifacts (48).

### General Strategies to Avoid or Reduce Physiologic Noise—Quick and Snug

The use of fast imaging sequences and optimal receive coils minimizes acquisition times and hence subject motion. One may consider using shorter protocols with for restless patient groups. Usually these protocols have a compromise between resolution and acquisition time, they are useful in, e.g., acute settings where quick information without detail is better than no information. Careful considerations on comfortable positioning of patients in the scanner, instruction and reminding of the importance of staying still during the scan are essential. Sedation or anesthesia may be necessary for difficult cases. **Table 4** summarizes common sources of motion artifacts and practical tips.

### Shielding

Motion artifacts occur in the phase direction. Saturation bands are areas where RF pulses are used to suppress MR signal from moving tissues outside the structure one wants to image, e.g., if on axial spine images the phase direction is anterior–posterior, the saturation band is placed to cover the throat and esophagus to avoid motion artifacts from swallowing on the spine.

### Alternative Acquisition Patterns in k-Space

Motion artifacts on sequences with simple linear data acquisition in k-space result in concentrated motion artifacts in certain areas of the scan according to the time of the motion event, e.g., a single slice becomes unreadable. Alternative, e.g., propeller-shaped data acquisition patterns fill the center of the k-space repeatedly and thereby enabling motion correction between the propeller blades if inconsistencies occur (49, 50).

### Handling Noise from Respiration and Cardiac Cycles in Advanced Neuroimaging

In functional MRI, changes in respiration rate and depth over time cause non-neuronal BOLD signal changes, i.e., the varying

**TABLE 4 | Common sources of motion artifacts and practical tips.**

Motion source	Mitigation strategy
Situational subject motion	Protocol design matches population (e.g., shorter protocols in acute settings)
	Patient preparation including management of pain, claustrophobia, or other discomfort
	Information, scanner familiarization
	Comfortable positioning and optimal head support by padding
	Reminders
	Structural magnetic resonance imaging: sedation, if clinically indicated
Physiological	Functional MRI: task pretraining
	Monitoring
	Imaging in chosen intervals on respiratory/cardiac function curve
	Skip data with motion above predefined threshold
	<i>Post hoc</i> motion correction as estimated from data

**TABLE 3 | Displacement sizes.**

Respiratory motion of the diaphragm	Several cm
Respiratory motion of the chest wall	Several mm
Cardiac motion	>1 cm (44)
Head motion	1 mm (32)
Brain pulsation	0.1 mm (45)

TR due to, e.g., breath hold will cause T1 effects in BOLD imaging that are difficult to handle. The most common approach in neuroimaging is a combination of careful instruction, respiration monitoring, skip-and-redo, and *post hoc* modeling to eliminate respiration-induced signal changes (51). Other specific strategies to handle artifacts from respiration are respiratory gating or triggering, respiratory compensation or phase re-ordering (52) and navigator echoes (53).

Cardiac cycles may be tracked either centrally with ECG nodes or peripherally with pulse oximeters. While traveling in the arteries, the pulse cycle is delayed and deformed with distance to the heart, so the tracking position depends on what one wants to image: imaging the heart will yield the best results by tracking the cardiac motion. Imaging the brain one can use peripheral tracking as the distance between heart and a fingertip is similar to the distance between heart and brain.

Noise from respiratory and cardiac cycles may be removed by regression using the recorded data in a tape-and-filter strategy (7, 51, 54). An alternative strategy is noise removal as estimated from the data itself (6, 55, 56).

## Head Motion

Head motion can be mitigated through careful instruction and comfortable fixating strategies as cushions and straps. Several tracking systems to monitor head motion have been developed and are described below. The main challenge is real-time integration of motion-tracking data and image acquisition.

### The Case for Prospective versus Retrospective Head Motion Correction

Retrospective and intra-image methods for head motion registration perform image acquisition and head position registration in the same data set. Attempts at motion correction within the data cannot correct for through-plane motion (57), and also cannot account for movements in previous scans with effects on field inhomogeneity and spin history (32). The method may introduce blurring artifacts through interpolation.

The solution is image acquisition with simultaneous prospective motion correction (57–60). Thesen and colleagues (58) developed Prospective Acquisition CorrEction (PACE) that acquired images for a volume while monitoring the head position and realigned the 3D grid to the head position before scanning the next volume in a stepwise process with high precision. The main disadvantage is that movements are not corrected until they are detected in the image, so rigid body transformation is still necessary.

### Scanner-External Motion Tracking Strategies

The most common strategy for prospective, slice-by-slice head movement registration is to optically monitor a marker attached to the patient's forehead with one or more video cameras and synchronize data continuously between scanner-external the camera space (where the head is) and the magnet space (where BOLD signals are recorded) (59–61). This requires extra hardware (camera and marker setup), line of sight between camera and head marker, extra software for position registration and regular synchronization with the BOLD signal. In addition,

the initial setup requires time [ca. 30 min (60)] and may be a constraint to the patient flow. If the system requires calibration for individual patients this prolongs the in-bore patient time and worsens motion artifacts akin to prolonged scan time. On the pro side, it is universally applicable to all scanner types and relatively cheap.

## REMAINING CHALLENGES

Power and colleagues (5) have shown that movement artifacts imitating functional connectivity correlations between brain regions persist even after on-line scanner motion corrections as proposed by Thesen and colleagues (58). Here, motion-induced artifacts occurred with movements in the order of a few tenths of a millimeter or less. They propose a skip-and-redo strategy of motion tracking and removal of acquired volumes with tracked movement artifacts over a chosen threshold. tSNR may provide a quality measure of functional connectivity data (3). Further information on postprocessing strategies for noise removal may be found in Ref. (3, 4, 6).

At present, scanner internal and external motion correction solutions exist, and their main application is to find the areas with excessive motion during the scan, so these data can be discarded and reacquired. The remaining problem is to integrate data continuously from a motion correction setup during image acquisition.

## CONCLUSION

In summary, movement artifacts are a problem in applications with low SNR, and they are exacerbated at high resolution and long acquisition times. Basic important strategies for motion reduction are comfortable patient positioning, instruction, and reminding of the importance to keep still during the scan. Fast imaging techniques are essential for short acquisition times. Common preprocessing techniques include realignment and six parameter rigid body transformation, and measures to detect motion, e.g., DVARS (percent mean signal change). Regression of physiological noise from cardiac and respiratory motion is recommended employing a nuisance modeling strategy, alternatively, if former is futile, as estimated from the data itself. External motion tracking yields best control of motion artifacts that may compromise data but requires extra equipment and setup. Its main challenge is real-time data integration. Prospective tracking of cardiac and respiratory cycles and head motion provide possibilities for motion correction. Head motion artifacts are ideally handled by correction using tracked parameters, or combined with a skip-and-redo strategy for movements over a chosen threshold.

## AUTHOR CONTRIBUTIONS

The idea was conceived by IH, HC, and AC. The first draft was written by IH with input from KM, JN, and AO. All authors have contributed to manuscript writing and have read and approved the final manuscript, and have no conflicts of interest.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Wake-up stroke: clinical characteristics, imaging findings, and treatment option – an update

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About 25% of all strokes occur during sleep, i.e., without knowledge of exact time of symptom onset. According to licensing criteria, this large group of patients is excluded from treatment with received tissue-plasminogen activator, the only specific stroke treatment proven effective in large randomized trials. This paper reviews clinical and imaging characteristics of wake-up stroke and gives an update on treatment options for these patients. From clinical and imaging studies, there is evidence suggesting that many wake-up strokes occur close to awakening and thus, patients might be within the approved time-window of thrombolysis when presenting to the emergency department. Several imaging approaches are suggested to identify wake-up stroke patients likely to benefit from thrombolysis, including non-contrast CT, CT-perfusion, penumbral MRI, and the recent concept of diffusion weighted imaging-fluid attenuated inversion recovery (DWI-FLAIR). A number of small case series and observational studies report results of thrombolysis in wake-up stroke, and no safety concerns have occurred, while conclusions on efficacy cannot be drawn from these studies. To this end, there are ongoing clinical trials enrolling wake-up stroke patients based on imaging findings, i.e., the DWI-FLAIR-mismatch (WAKE-UP) or penumbral imaging (EXTEND). The results of these trials will provide evidence to guide thrombolysis in wake-up stroke and thus, expand treatment options for this large group of stroke patients.

**Keywords:** wake-up stroke, acute ischemic stroke, thrombolysis, computed tomography, magnetic resonance imaging, fluid attenuated inversion recovery, DWI-FLAIR-mismatch

## METHODS

The literature used in this review was searched in PUBMED and MEDLINE (1977–2013 October) using the following key words “wake-up stroke,” “stroke on awakening,” “stroke of unknown symptom onset,” “thrombolysis,” “diffusion weighted imaging,” and “fluid attenuated inversion recovery (FLAIR).” The selection was made by the authors evaluating clinical relevance, currentness, and methodical correctness. Our purpose was not to give a general overview of the current state of literature concerning thrombolysis in wake-up stroke in general, but to emphasize the possibilities of treatment for wake-up stroke on the basis of current literature. Therefore, we have done no systematic literature review but one focused on our demand.

## STROKE AND STROKE THROMBOLYSIS

Patients waking-up with symptoms of stroke represent a specific subgroup of stroke patients. In general, stroke is the second most common single cause of death and the most frequent cause of permanent disability in industrialized countries. Based on WHO estimates about 15 million people suffer from stroke each year of whom five million are left permanently disabled (1). As a consequence, stroke carries an enormous social and economic burden both for the individual patients as for society at large. In the EU stroke accounts for just over 500,000 deaths each year with just around 1 in 10 men (9%) and 1 in 8 women (12%) dying from stroke (2).

The demonstration of efficacy and safety of treatment with intravenous tissue plasminogen activator (IV-tPA) (3) has ended an age of therapeutic nihilism and revolutionized stroke care. Together with the establishment of the stroke-unit concept, thrombolysis has motivated the implementation of specialized acute stroke treatment in most developed countries.

In ischemic stroke, the acute occlusion of a brain vessel leads to hypoperfusion of the downstream brain areas resulting in an insufficient supply with oxygen. Within seconds the functional metabolism of brain cells breaks down, and depending on the degree and duration of ischemia, the affected brain areas decay. Thrombolysis aims to reperfuse the brain vessel occlusion by dissolution of the clot. In acute stroke, thrombolysis was proven effective in two randomized controlled trials resulting in a marked increase of the number of patients with a favorable outcome after stroke (3, 4). In large observational trials, this effect was reproduced in the clinical practice (5), and thrombolysis has become a keystone of acute stroke treatment. However, thrombolysis was only proven effective in patients treated within 4.5 h of symptom onset, and is only recommended for patients to be treated within this time-window.

## WAKE-UP STROKE

In a large number of stroke patients, the time point of symptom onset is not known. About 20–25% of stroke patients realize stroke symptoms after waking-up from sleep (6–9) (Table 1).

This subgroup of stroke patients (“wake-up strokes”) differs from stroke patients who suffer from stroke while being awake and pose a specific challenge to stroke physicians. The most relevant difference between both groups is the fact that in wake-up stroke patients, the exact time point of symptom onset is unknown. As a result, according to approval criteria and guideline recommendations, this large group of patients is excluded from thrombolysis (9, 10), thus excluding patients from the only approved specific treatment of acute stroke with proven safety and efficacy.

Within the past years, however, wake-up stroke has come into focus of research activities. Observational studies have brought insights into clinical and imaging characteristics of wake-up stroke; new approaches to guide treatment in wake-up stroke patients have been suggested. Finally, clinical trials are under-way testing intravenous thrombolysis in patients with unknown time of symptom onset including wake-up stroke. We will give an update of the recent insights on wake-up stroke and ongoing developments that are likely to improve the treatment of these patients in the near future.

### CLINICAL AND IMAGING CHARACTERISTICS OF WAKE-UP STROKE

There are observations that point toward strokes during sleep being more severe (15) and having a worse clinical outcome (12). In a recent large analysis of wake-up-stroke as compared to stroke while awake, a smaller initial severity for wake-up-stroke with deterioration to comparable mortality and morbidity was shown (14). Especially, the secondary deterioration underlines the potential responsiveness of wake-up stroke for therapy. In addition, further clinical and imaging observations suggest that in a large number of patients waking-up with stroke symptoms strokes may have occurred in the early morning hours so that they might still be eligible for thrombolysis. There are studies reporting comparable frequency of early ischemic signs on CT (EICs) in wake-up stroke patients as compared to patients studied by CT within 3 (16) or 6 h of symptom recognition (17). Additionally, the equal developmental time pattern of EICs in patients with known and unknown onset in a follow-up from 3 h after recognizing the symptoms to 3 months supports the presumption that wake-up strokes occur close to awakening (18). An MRI-based study reported a similar proportion of wake-up stroke patients showing a perfusion–diffusion-mismatch as compared to patients within 3 h of symptom onset (11). A similar observation was made for the detection of “tissue at risk” by perfusion CT in wake-up stroke patients (18). Together these findings suggest that a large number of patients with wake-up stroke might still be within a time-window for thrombolysis when reaching the hospital.

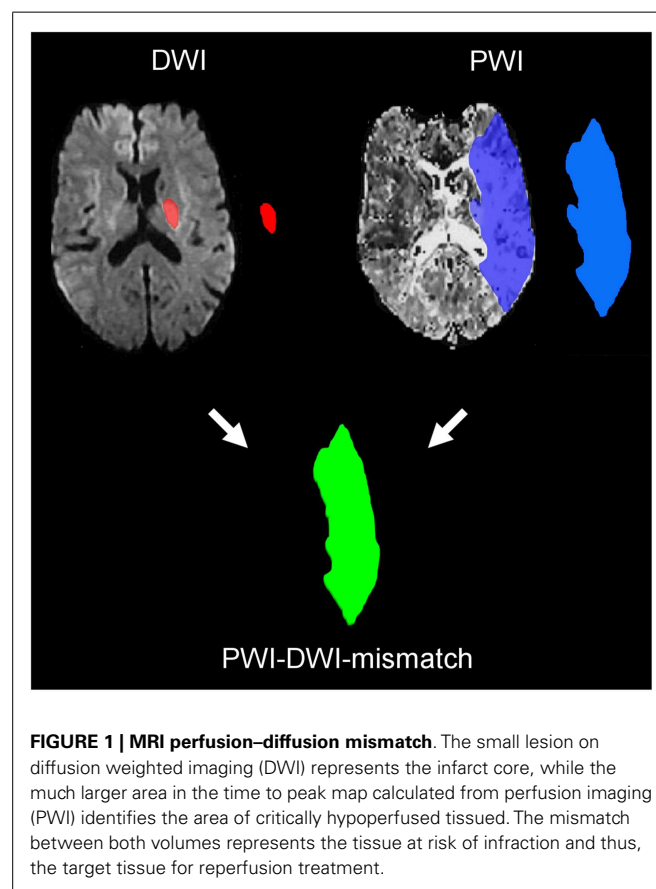
### IMAGING APPROACHES TO GUIDE TREATMENT IN WAKE-UP STROKE

To identify wake-up stroke patients who may benefit from thrombolysis two imaging approaches are set in the focus of investigation. The detection of tissue at risk by penumbral imaging (perfusion–diffusion mismatch, **Figure 1**), and the approach of identifying stroke patients within the 4.5 h-time-window by tissue characteristics in stroke MRI [diffusion weighted imaging (DWI)-FLAIR-mismatch]. Penumbral imaging based on DWI and

**Table 1 | Incidence of wake-up stroke.**

Wake-up strokes (%)	Total	Reference
100 (27)	364	(11)
301 (24)	1.248	(8)
349 (14)	2.585	(12)
48 (18)	263	(13)
273 (14) <sup>a</sup> (+12% “no estimation of onset”)	1.854	(6)
5.152 (30)	17.398	(14)

<sup>a</sup>Of note, according to clinical in- and exclusion criteria 36% of these patients were potentially eligible for thrombolysis according to the authors.



**FIGURE 1 | MRI perfusion–diffusion mismatch.** The small lesion on diffusion weighted imaging (DWI) represents the infarct core, while the much larger area in the time to peak map calculated from perfusion imaging (PWI) identifies the area of critically hypoperfused tissue. The mismatch between both volumes represents the tissue at risk of infarction and thus, the target tissue for reperfusion treatment.

perfusion MRI allows to determine the status of damaged tissue in acute ischemia and to distinguish irreversibly damaged one from critically hypoperfused but potentially salvageable tissue. The mismatch of these was suggested to identify tissue that is tPA-responsive beyond time-window or independent from time (19–21). In observational studies, it was shown that tissue at risk may be saved by reperfusion up to 6 h after symptom onset (22). Secondary analysis of randomized controlled trials with selection by penumbral imaging (23, 24) demonstrated a reduction of final infarct volume (25) and a clinical benefit of thrombolysis in patients with a large perfusion–diffusion mismatch with an odds ratio for good clinical response of 2.83 between desmoteplase and placebo (26). Moreover, large DWI lesion volumes were found to

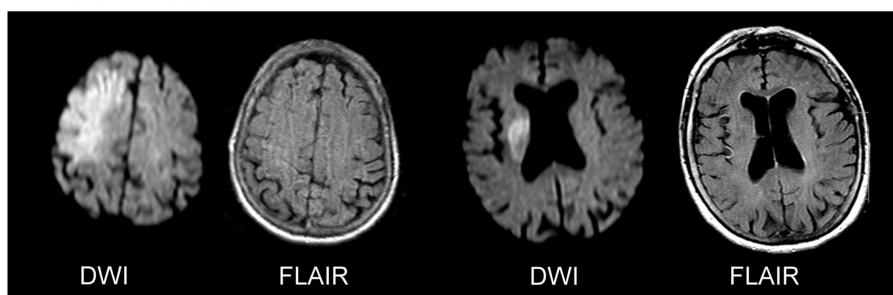
be associated with a higher risk of symptomatic intracranial hemorrhage (SICH) and poor outcome (22, 27, 28). Thus, the exclusion of patients with very large DWI lesion volumes by MRI will likely increase the safety of MRI-based thrombolysis. The re-analysis of EPITHET and DEFUSE resulted in a more restrictive definition of the perfusion lesion (29, 30), which are used in the ongoing Extending the time for Thrombolysis in Emergency Neurological Deficits (EXTEND) trial (31). The detection of treatable wake-up strokes by perfusion–diffusion mismatch has been suggested (32–34) and used in a relatively small non-randomized trial (35). In line with these considerations, the EXTEND trial will allow the randomization of patients with wake-up stroke based penumbral imaging.

The DWI-FLAIR-mismatch (**Figure 2**) concept refers to the time-window. There is a broad and striking evidence for the benefit of intravenous thrombolysis of ischemic stroke within 4.5 h (3, 4, 35). Therefore, it was suggested to use brain imaging to determine stroke age in the case of unknown symptom onset. The chronological evolution of ischemic stroke can be characterized by MRI. A lack of cerebral blood flow with a decreased intracellular energy metabolism causes cytotoxic edema, which can be detected by a reduced apparent diffusion coefficient (ADC) on DWI within minutes of stroke (36, 37). During the following 1–4 h, tissue osmolality increases, accompanied by a net increase of water (38, 39). This absolute increase of water content can be detected by T2-weighted MRI (36, 40). Thus, DWI allows an instant determination of acute ischemic lesions, but gives no evidence of further developmental changes, which may be characterized by T2. Due to artificial limitations of T2 caused by the high signal intensity of

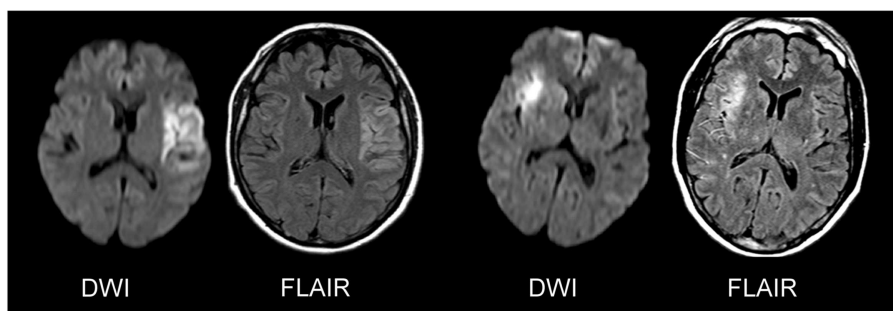
cerebrospinal fluid (CSF) with partial volume effects FLAIR is considered superior and more widely used (41, 42). The pattern of a visible ischemic lesion on DWI together with normal T2-weighted imaging or FLAIR is a typical finding in human stroke if imaging is performed within the first hours of stroke (43–45). These results are also well in line with data from experimental stroke, where T2wI failed to detect acute ischemia until about 2–3 h of stroke (37, 46, 47).

The DWI/FLAIR-mismatch was established (48) to estimate lesion age and identify patients likely to benefit from thrombolysis. It differs from the perfusion–diffusion coefficient by revealing information about the time and not the quality of damage. Single-center studies reported of a 100% visibility of ischemic lesions after 3–6 h (49–51), and the DWI-FLAIR-mismatch was shown to identify patients within 3–4.5 h with high specificity and positive predicted value (PPV) (48–51). These results have been confirmed in large multicenter studies (PRE-FLAIR: Predictive value of FLAIR and DWI for the identification of acute ischemic stroke patients  $\leq 3$  and  $\leq 4.5$  h of symptom onset – a multicenter study including 643 patients) (52). The specificity of the DWI-FLAIR-mismatch to identify patients within the time frame of 4.5 h was in this study 0.81 and the PPV 0.87. The identification within 6 h showed a PPV of 0.95 in PRE-FLAIR (50), and 1 of 0.97 in a Japanese study (49). Concerning the Cochrane analysis indicating a possible beneficial effect of thrombolysis in addition with the absence of an increased risk of SICH up to 6 h of symptom onset (53, 54), these results are of paramount interest for treatment indication. Just recently, an observational study reported of a high frequency (44%) of wake-up strokes

#### DWI-FLAIR-mismatch



#### No DWI-FLAIR-mismatch



**FIGURE 2 | DWI-FLAIR-mismatch.** The upper row gives two examples of a clearly visible acute ischemic lesion on diffusion weighted imaging (DWI), while no marked parenchymal hyperintensity is detected on fluid attenuated

inversion recovery (FLAIR) images indicating DWI-FLAIR-mismatch. In the lower row, a clear hyperintensity can be seen on FLAIR images in the area of the acute DWI lesion (no DWI-FLAIR-mismatch).

showing a DWI-FLAIR-mismatch (55). Based on this evidence, the *Efficacy and safety of MRI-based thrombolysis in wake-up stroke: a randomized, double-blind, placebo-controlled trial (WAKE-UP)* will randomize wake-up stroke patients using the DWI-FLAIR-mismatch as the imaging criterion to identify patients likely to benefit from thrombolysis (56).

## THROMBOLYSIS IN WAKE-UP STROKE: CASE REPORTS AND OBSERVATIONAL STUDIES

Resulting from the dissatisfaction with the lack of any evidence-based treatment recommendations for patients with wake-up stroke, there is a growing number of case reports and case series, which report on thrombolysis in patients with wake-up stroke based on imaging findings (Table 2). These studies used either plain CT (50), multiparametric CT (57–60), or multiparametric stroke MRI (32–35). In a study including 74 patients with an onset time over 4.5 h and 73 patients with an unknown onset no difference in eligibility and response for perfusion CT based thrombolysis was shown (59). Non-contrast CT and clinically indicated thrombolysis for wake-up ischemic stroke in over 80 years old patients was considered to be beneficial concerning the modified Ranking Scale (mRS) after 90 days compared to non-thrombolysed patients (61), and a comparison with initial and follow-up examination (mRS) after 90 days of 68 patients with wake-up ischemic stroke to 326 patients within the time-window of 4.5 h showed equal results after thrombolysis indicated by non-contrast CT scan combined with clinical judgment (62). In a further single-center observational safety study 20 patients were treated with intravenous thrombolysis in the presence of an

arterial occlusion on CT-A and an ASPECTS score of greater than five on baseline CT (60).

RESTORE (reperfusion therapy in unclear-onset stroke based on MRI evaluation) was an observational study in which 83 of 430 patients with an unclear onset of symptoms received tissue-plasminogen activator (rt-PA), intravenously, intra-arterial, or in combination. The decision for applying this therapy was made upon a perfusion–diffusion mismatch of more than 20% and negative or subtle hyperintensities on FLAIR. The clinical outcome determined by the mRS after 3 months was in 44.6% favorable and in 28.9% excellent compared to untreated patients (35). Intracranial hemorrhage with a neurological decline was reported in 6% of the treated patients. Therefore, a distinct benefit for patients being treated with rt-PA due to estimation by MRI could be shown. Restraints of this study are the non-randomized study design, the non-quantitative measurement of FLAIR, and the relatively small number of treated patients with unknown symptom onset.

Finally, there is a single-armed observational US American study of thrombolysis with Alteplase in patients with unknown symptom onset (MR WITNESS: a Study of Intravenous Thrombolysis with Alteplase in MRI-Selected Patients, ClinicalTrials.gov. Identifier: NCT01282242). MR WITNESS will use the concept of DWI-FLAIR-mismatch to identify patients likely to respond to thrombolysis and plans to enroll 80 patients.

In summary, these studies demonstrate the feasibility of imaging guided thrombolysis in wake-up stroke patients while there was no excess in SICH and outcome appeared in large parts similar as compared to thrombolysis in patients treated within 4.5 h of known symptom onset. However, final conclusions to the safety

**Table 2 | Trials with thrombolysis with indication set by imaging in wake-up strokes.**

Sample size wake-up stroke	Imaging method	Main results	Reference
68 Strokes with unknown onset, all received IV-tPA (case–control comparison)	NECT	Similar outcome as treatment within 4.5 h (mRS after 3 months, any ICH, symptomatic ICH)	(61, 62)
73 Strokes with unknown onset, in 32 (44%) of these IV-tPA	Perfusion CT	No SICH, 56% good outcome after 3 months (mRS <2)	(59)
89 Strokes with unknown onset, in 20 (22%) of these thrombolysis	NECT and CT-A/TCD	Two asymptomatic ICH, none symptomatic, two died of massive infarction, two died of stroke complications	(60)
80 Wake-up strokes, 46 received thrombolysis (intra-arterial, IV-tPA, or combined)	NCCT, CT- or MRI-perfusion–diffusion mismatch	Two symptomatic ICH, better clinical outcome (mRS) and higher mortality in treated cohort	(57)
43 Strokes with unknown onset, 10 (22%) received IV-tPA	Perfusion–diffusion mismatch (MRI)	One asymptomatic ICH, no symptomatic ICH	(32)
32 Strokes with unclear onset	Perfusion–diffusion mismatch and FLAIR(non-quantitative)	No difference in frequency of symptomatic ICH and 3 months outcome (mRS after 3 months) to treatment within 4.5 h	(33)
430 Strokes with unknown onset, in 83 (19.3%) of these thrombolysis (10% IV-tPA only)	Perfusion–diffusion mismatch and FLAIR(non-quantitative)	Benefit of treatment (after 3 months: 44.6% mRS 0–2; 28.9% mRS 0–1) with safe MRI-based indication (symptomatic ICH in 6%)	(35)

IV-tPA, intravenous tissue plasminogen activator; NECT, non-enhanced computed tomography; CT-A, CT-angiography; TCD, transcranial Doppler ultrasound; FLAIR, fluid attenuated inversion recovery; ICH, intracranial hemorrhage.



and efficacy of thrombolysis in wake-up stroke can only be drawn from randomized clinical trials.

## RANDOMIZED CONTROLLED CLINICAL TRIALS OF THROMBOLYSIS IN WAKE-UP STROKE

Currently, two randomized controlled trials of intravenous thrombolysis allow the enrollment of patients with wake-up stroke: WAKE-UP and EXTEND.

EXTEND (ClinicalTrials.gov. Identifier: NCT00887328) is a randomized, multicentre, double-blinded, placebo-controlled phase III trial of intravenous thrombolysis with rt-PA in ischemic stroke patients (31). Treatment has to be initiated between 3 h (or 4.5 h depending on local practice) up to 9 h of symptom onset, or in case of wake-up stroke. For wake-up stroke, the midpoint between sleep onset (or last known to be normal) and time of waking-up must not exceed 9 h. Further clinical inclusion criteria include a National Institutes of Health Stroke Scale (NIHSS) score of 4–26. Patients are studied by MRI including diffusion and perfusion MRI or CT including CT-perfusion and randomized to either treatment with placebo or Alteplase (0.6 or 0.9 mg/kg body-weight based on local practice) if they show a penumbral pattern on MRI or CT. Penumbral pattern is defined by infarct core volume <70 ml, perfusion lesion/infarct core mismatch ratio >1.2, and absolute mismatch >10 ml. For definition of the perfusion lesion  $T_{max} > 6$  s for MRI and CT is used, while infarct core is defined using MRI diffusion imaging or CT-CBF imaging. The primary outcome measure is a favorable outcome defined by a score of 0–1 on the mRS at day 90. EXTEND aims to enroll 400 patients in Australia and in an accompanying study in international study sites (EXTEND international). There is a European companion study under preparation (ECASS 4-EXTEND-Europe), which will only use MRI for patient enrollment.

WAKE-UP (ClinicalTrials.gov. Identifier: NCT01525290) is the first clinical trial to use the novel approach of DWI-FLAIR-mismatch to prospectively identify patients for thrombolysis. WAKE-UP is an investigator-initiated, interventional, randomized, double-blind, placebo-controlled, parallel-assignment, international, multi-center efficacy, and safety study (56). The aim of WAKE-UP is to test efficacy and safety of MRI-based intravenous thrombolysis with rt-PA (Alteplase) in patients with unknown symptom onset, e.g., patients waking-up with stroke symptoms who otherwise fulfill the approval criteria for intravenous thrombolysis in acute stroke. Patients fulfilling clinical inclusion and exclusion criteria will undergo MRI including DWI and FLAIR. They will be randomized 1:1 to either treatment or placebo if MRI is indicative of lesion age of less than 4.5 h, i.e., shows a DWI-FLAIR-mismatch. Clinical inclusion criteria include age between 18 and 80 years and a disabling neurological deficit. Primary efficacy endpoint is favorable outcome defined by a score of 0–1 on the mRS 90 days after stroke. Primary safety endpoints are Mortality and death or dependency 90 days after stroke. WAKE-UP plans to enroll 800 patients in 40–60 study sites in six European countries and has started recruitment in October 2012.

## CONCLUSION

Patients waking-up with stroke symptoms represent a large group of stroke patients who are currently excluded from intravenous

thrombolysis based on licensing criteria. Growing evidence from clinical and imaging studies suggests that a relevant proportion of patients with wake-up stroke might benefit from reperfusion treatment and be promising candidates for intravenous thrombolysis. Different imaging approaches have been suggested to select wake-up stroke patients for thrombolysis, including multiparametric CT and MRI. Approaches currently under investigation involve the identification of tissue at risk of infarction independent from time by penumbral imaging and the identification of patients within the approved time-window for thrombolysis by the concept of DWI-FLAIR-mismatch. Both approaches are currently tested in large randomized controlled trials. The results of these trials are expected to change clinical practice by making available effective and safe treatment for a large group of acute stroke patients currently excluded from specific acute treatment.

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# Automated decision-support system for prediction of treatment responders in acute ischemic stroke

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MRI is widely used in the assessment of acute ischemic stroke. In particular, it identifies the mismatch between hypoperfused and the permanently damaged tissue, the PWI-DWI mismatch volume. It is used to help triage patients into active or supportive treatment pathways. COMBAT Stroke is an automated software tool for estimating the mismatch volume and ratio based on MRI. Herein, we validate the decision made by the software with actual clinical decision rendered. Furthermore, we evaluate the association between treatment decisions (both automated and actual) and outcomes. COMBAT Stroke was used to determine PWI-DWI mismatch volume and ratio in 228 patients from two European multi-center stroke databases. We performed confusion matrix analysis to summarize the agreement between the automated selection and the clinical decision. Finally, we evaluated the clinical and imaging outcomes of the patients in the four entries of the confusion matrix (true positive, true negative, false negative, and false positive). About 186 of 228 patients with acute stroke underwent thrombolytic treatment, with the remaining 42 receiving supportive treatment only. Selection based on radiographic criteria using COMBAT Stroke classified 142 patients as potential candidates for thrombolytic treatment and 86 for supportive treatment; 60% sensitivity and 29% specificity. The patients deemed eligible for thrombolytic treatment by COMBAT Stroke demonstrated significantly higher rates of compromised tissue salvage, less neurological deficit, and were more likely to experience thrombus dissolving and reestablishment of normal blood flow at 24 h follow-up compared to those who were treated without substantial PWI-DWI mismatch. These results provide evidence that COMBAT Stroke, in addition to clinical assessment, may offer an optimal framework for a fast, efficient, and standardized clinical support tool to select patients for thrombolysis in acute ischemic stroke.

**Keywords:** stroke, brain edema, magnetic resonance imaging, brain ischemia, decision-support systems, clinical, thrombolytic therapy

## INTRODUCTION

Neuroimaging is valuable to identify acute ischemic stroke patients that may benefit from thrombolysis (1, 2). Magnetic resonance based diffusion- and perfusion-weighted imaging (DWI and PWI) are widely utilized modalities in clinical practice that aid in treatment selection (3). While DWI hyper-intense regions typically indicate cytotoxic edema as a surrogate for permanent tissue injury, delayed PWI regions correspond to tissue with compromised hemodynamics (4, 5).

The ischemic penumbra is defined as tissue that is hypoperfused to such an extent that focal neurological symptoms arise, but where neurological function can be restored and tissue survival is ensured by early reperfusion.

Current PWI techniques are not able to distinguish between critically hypoperfused tissue and benign oligemia. This shortcoming potentially overestimates the actual mismatch volume and is especially noticeable with small lesions (6). Additionally, hyper-intense areas on diffusion-weighted images have shown reversal

following thrombolysis (7, 8). Nevertheless, the PWI-DWI mismatch is recognized as surrogate for risk at tissue that may be viable if perfusion is restored timely (4, 9, 10). Accordingly, the volume of the mismatch and the ratio between the volume of mismatch and volume of permanent injured tissue (PWI-DWI mismatch ratio) are two practical markers that are used to help triage stroke patients into interventional or supportive treatment pathways. For example, when considered along with other parameters, it has been shown that patients with a mismatch volume > 10 mL and a PWI-DWI mismatch ratio > 1.2 have greater benefit from thrombolysis compared to those without a significant mismatch (11–13). The time and expertise required to perform these calculations, along with inter-observer variability are potential factors that may limit their utilization and efficacy. To overcome these factors, automated computer-based algorithms for the determination of PWI-DWI mismatch have been developed (14). The overall aim of this study was to compare the agreement and outcomes between a solely automated computer-based patient triage algorithm and the actual

clinical decision made for thrombolysis. Herein, we tested whether the treatment decisions of an automated patient selection software tool “Computer-Based Decision-Support System for Thrombolysis in Stroke” (COMBAT Stroke), were associated with 24 h clinical and imaging outcomes.

## MATERIALS AND METHODS

### PATIENTS AND DATA ACQUISITION

Following approval from national and regional ethics committees, patients with acute ischemic stroke were identified from the European I-Know consortium (2006–2009) and the Remote Ischemic Perconditioning Study (RIPS, 2009–2011) (15, 16). Clinical information available in the databases includes gender, age, time from symptom onset to treatment initiation, immediate and 24 h and 3 month follow-up National Institutes of Health Stroke Scale (NIHSS) score, lesion laterality, stroke etiology subtype, treatment (i.e., intravenous recombinant tissue plasminogen activator (rt-PA), or supportive treatment), admission blood pressure, presence of intracranial hemorrhage, home medications, platelet count, and MR angiography-based recanalization status at 24 h. Only adult patients (age >18) with acute ischemic stroke in the anterior circulation territory were included. Patients with ischemic strokes of the vertebrobasilar circulation were excluded.

Standard dynamic susceptibility contrast MRI was performed on various scanner types at different field strengths (GE Signa Excite 1.5T, GE Signa Excite 3T, GE Signa HDx 1.5T, GE Signa Horizon 1.5T, Siemens TrioTim 3T, Siemens Avanto 1.5T, Siemens Sonata 1.5T, Philips Gyroscan NT 1.5T, Phillips Achieva 1.5T, and Philips Intera 1.5T). The PWI sequence (TE 30/50 ms for 3 and 1.5 Tesla field strength, TR 1500 ms, FOV 24 cm, matrix 128 × 128, slice thickness 5 mm) was obtained during intravenous injection of Gadolinium based contrast (0.1 mmol/kg) at a rate of 5 mL/s followed by 30 mL of physiological saline at the same injection rate. Echo-planar DWI was obtained at  $b$ -value = 0 s/mm<sup>2</sup> and  $b$ -value = 1.000 s/mm<sup>2</sup>. DWI images were automatically linear co-registered and re-sliced to acute PWI space using SPM8 (Wellcome Trust Centre for Neuroimaging, UCL, UK).

### CLINICAL PRACTICE

Patients from highly specialized stroke centers from Denmark, Germany, United Kingdom, France, and Spain were included in this study. The local rt-PA practices follow the general recommendation from American Heart Association, where patients older than 18 years with no imaging or clinical evidence for hemorrhage who have significant neurological deficit are eligible for treatment within 4.5 h of symptom onset. All centers routinely perform DWI and PWI in clinical practice and use the mismatch information as well as clinical information in treatment decision-making.

### AUTOMATIC MISMATCH ESTIMATION

COMBAT Stroke generates and applies a whole-brain mask to acute images to exclude non-brain structures, e.g., eyes, cerebrospinal fluid etc. Next, the software determines the lesion laterality by analyzing the acute apparent diffusion coefficient map (ADC) and the time-to-peak of the tissue curve map (TTP). The lesion laterality is used to compute a normal tissue reference and subsequently the algorithm outlines the initially injured tissue on DWI. Similarly, the algorithm automatically outlines the

hypoperfused lesion on TTP map, and the mismatch is defined as the part of the hypoperfused lesion that is not contained in the co-registered DWI lesion. We automatically estimated the PWI-DWI mismatch ratio and mismatch volume for all patients in the cohort using COMBAT Stroke.

### MANUAL MISMATCH OUTLINING

Comparing automated delineations of the mismatch to those determined manually by a single expert has the potential to introduce bias, therefore we used four expert raters (neuroradiologists) with extensive clinical experience in stroke diagnosis. The raters manually outlined the hypoperfused lesion on TTP maps and the lesion core on DWI images using in-house developed software. All raters worked individually and were blinded to each other and the remainder of the clinical data. Next, an expert rater consensus mismatch mask was created by summing the ratings (1 = lesion; 0 = normal) in every image voxel for each of the four expert raters. We utilized a cutoff summative score of 3 to create the mask to establish a consensus, consistent with previously described methods (14). The stroke community has been discussing the optimal choice of PWI map in stroke management, however no consensus exists. We chose TTP as the PWI modality because of its perceived superiority in separating normo- and hypoperfused tissue. A recent study demonstrated that TTP performed superior to deconvolved maps (e.g., MTT and Tmax) in terms of predicting tissue fate (17).

### CONFUSION MATRIX MODELING

Initially, all patients were assessed exclusively on imaging criteria alone: thrombolysis could potentially be administered in cases where PWI-DWI mismatch ratio >1.2 and mismatch volume >10 mL. Assessments were made for each patient twice, once with the use of COMBAT Stroke and again by using the data generated by the expert neuroradiologists' consensus. Next, confusion matrices were generated to quantify the performance of (1) COMBAT Stroke versus actual clinical decision and (2) COMBAT Stroke versus human measurement. The four entries of the confusion matrix denote true positive (TP, both clinical decision and COMBAT Stroke agree for thrombolytic therapy), true negative (TN, both clinical decision and COMBAT Stroke agree for supportive treatment), false positive (FP, COMBAT Stroke supports thrombolysis, but the patient was treated supportively), and false negative (FN, COMBAT Stroke advises for supportive treatment, however the patient was treated with thrombolysis).

Mindful that a multitude of factors are used in the actual clinical determination of administering thrombolytic treatment, we analyzed the following presentation variables for the four entries of the confusion matrix: mismatch volume, NIHSS score, and contraindications. The definition of contraindication in this study was based on the American Heart Association's Stroke Guidelines and includes any of the following criteria: systolic blood pressure greater than 185 mmHg, diastolic blood pressure greater than 110 mmHg, evidence of intracranial hemorrhage, use of anticoagulants, international normalized ratio (INR) greater than 1.7, and time for symptom onset to treatment greater than 4.5 h, all of which were available in the database. Subsequently, we analyzed the clinical outcomes, in terms of mismatch salvage, reduction in NIHSS score at 24 h, and vessel recanalization determined by MR



angiography at 24 h, to determine the association between presence/absence of significant acute mismatch and clinical outcome. The acute DWI-PWI mismatch was determined as the fraction of the hypoperfused area, which was not contained in the lesion core (Figure 1). Infarct evolution at 1 month follow-up was evaluated on T2 FLAIR for all patients in the cohort. The mismatch salvage was the portion of the acute mismatch that remained functional at 1 month follow-up. Rank sum-test was conducted to test the difference in median value of acute decision parameters and clinical outcomes between the groups.

To examine the relative importance of the presentation variables (Mismatch volume, NIHSS, and contraindications) in predicting thrombolytic treatment, we also conducted a classification and regression tree (CART) analysis. The best spilled of data at each node was determined by optimization of the Gini's diversity index and the analysis was conducted in MATLAB 2010B (The MathWorks, Inc. Natick, MA, USA).

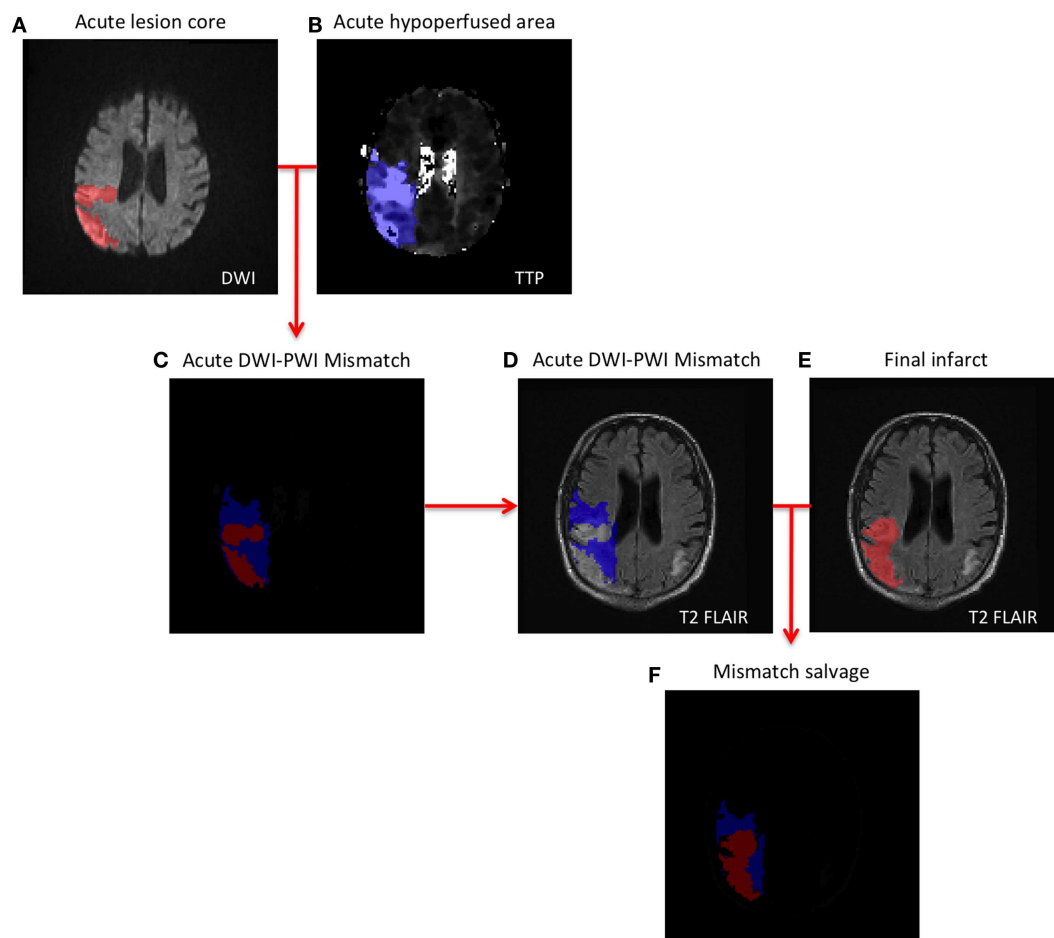
## RESULTS

228 patients (136 males, 92 females) were identified as meeting criteria for analysis from the European I-Know consortium database

and the Remote Ischemic Perconditioning Study. The patient characteristics for the two study populations are shown in Table 1. In comparison with the I-Know cohort the patients in the RIPS study had significantly lower neurological deficit at baseline, 24 h, and 3 month follow-up in terms of NIHSS and modified Rankin Score. No significant difference in the acute mismatch volume between the I-Know patients [56 mL, 25th and 75th percentile = (5, 133)] and RIPS patients [36 mL (1, 105)] was observed. 89% of the patients in the I-Know study were treated actively compared to 100% in the RIPS study. Altogether, 40 patients exceeded the 4.5-h treatment window, of whom 16 were treated actively. The median processing time for automatic PWI-DWI mismatch estimation across all patients was 31 s when processed on an Apple MacBook Pro, 2.6 GHz Intel Core i7.

## CONFUSION MATRIX – COMBAT VERSUS CLINICAL DECISION

186 of 228 patients underwent thrombolytic treatment, with the remaining 42 patients receiving supportive treatment only (Figure 2A, columns). Assessment of the cohort based on mismatch criteria (mismatch > 10 mL and PWI-DWI ratio > 1.2) alone with COMBAT Stroke classified 142 patients as potential



**FIGURE 1 | Schematic illustration of mismatch salvage computation (A,F).** The acute lesions are outlined on DWI and TTP (C). Illustrates the concept of DWI-PWI mismatch (blue region) (D–F). Combining the DWI-PWI mismatch information with the 1-month infarct evolution on T2 FLAIR yields the mismatch salvage (blue region in F).

**Table 1 | Demographic and clinical characteristics of the patient cohort.**

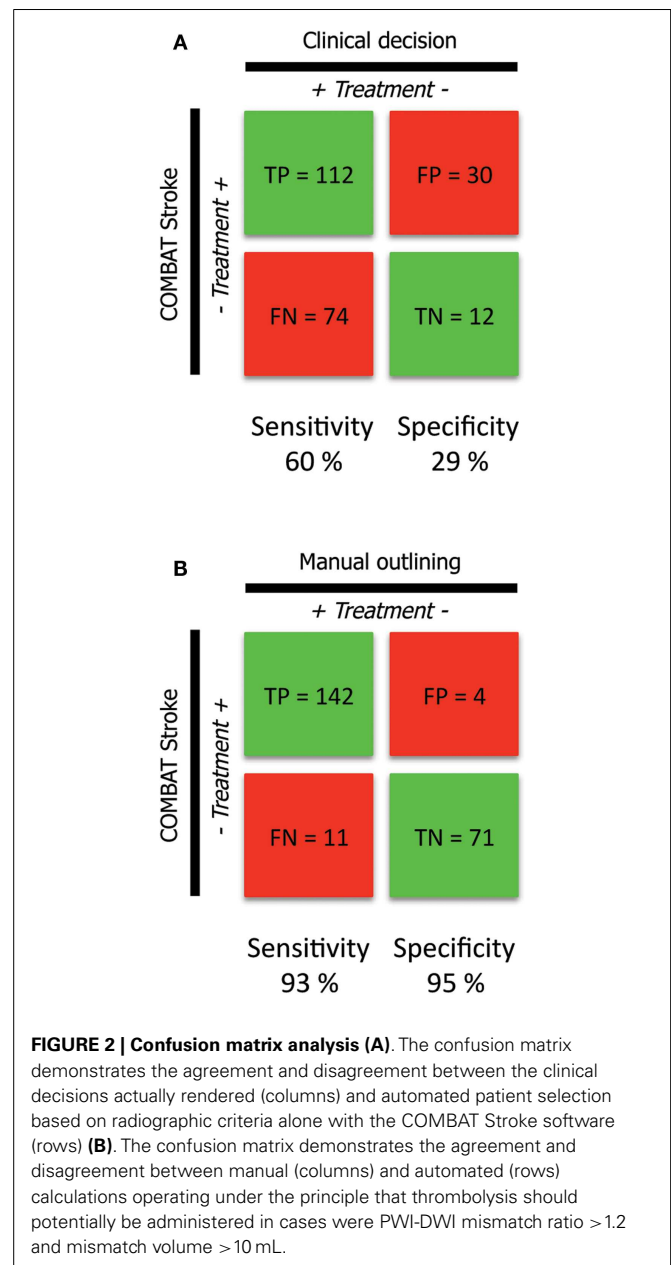
	I-Know	RIPS	<i>p</i>
Patients	129	99	
Male	77 (60%)	59 (60%)	0.108
Median age and IQ range, years	70 (60, 77)	69 (61, 76)	0.922
Left hemisphere stroke	74 (57%)	50 (50%)	<0.001
IV t-PA	89 (69%)	99 (100%)	<0.001
Median time to treatment and IQ range, min	188 (150, 280)	164 (137, 220)	0.006
Time to treatment > 4.5 H	34 (26%)	6 (6%)	<0.001
Treated beyond 4.5 H	10 (29%)	6 (100%)	0.002
Median acute NIHSS and IQ range	11 (6, 16)	6 (4, 10)	<0.001
Median 24 h NIHSS and IQ range	4 (1, 10.25)	2 (1, 6)	<0.001
Median 3 months NIHSS and IQ range	2 (0, 6)	0 (0, 2)	<0.001
Median 3 months mRS and IQ range	2 (0, 3)	1 (0, 3)	<0.001
Median systolic BP and IQ range (mmHg)	145 (130, 158)	150 (140, 165)	0.038
Median diastolic blood pressure	83 (72, 90)	85 (79, 90)	0.406
Anticoagulant therapy	22 (17%)	1 (1%)	<0.001
Clopidogrel therapy	18 (14%)	6 (6%)	0.027
Median mismatch volume (mL)	56 (5, 133)	36 (1, 105)	0.179
Mismatch volume <10 mL	37 (29%)	33 (33%)	0.086
Mismatch volume <10 and > 100 mL	51 (39%)	38 (38%)	0.031
Mismatch volume > 100 mL	41 (32%)	28 (28%)	0.098
<b>STROKE SUB-TYPES</b>			
Cardiac source of emboli	58	36	0.046
Large vessel disease with significant carotid stenosis	22	16	0.140
Large vessel disease, other	12	10	0.174
Small vessel disease (lacunar)	5	24	<0.001
Carotid dissection	6	2	0.172
Other/unusual cause	3	1	0.315
Undetermined	23	10	0.039

Values represented as median with interquartile ranges presented in brackets. Sample size, where appropriate, is represented as numbers and the percentage of the cohort is contained in parentheses.

candidates for thrombolytic treatment and 86 for supportive treatment; 60% sensitivity and 29% specificity, 79% positive predictive value, and 14% negative predictive value (Figure 2A, rows). The comparison of COMBAT Stroke with treatment decision based on manually outlined mismatch statistics demonstrated excellent agreement; 93% sensitivity and 95% specificity, 97% positive predictive value and 87% negative predictive value (Figure 2B).

#### VOLUMETRIC AGREEMENT

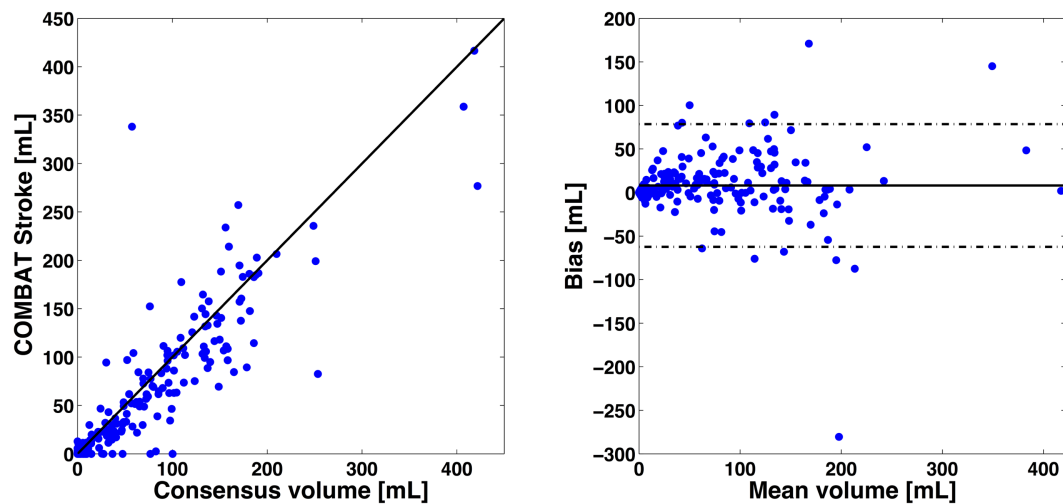
The correlation between PWI-DWI mismatch volumes using the automatic algorithm and manual outlines performed by experts was excellent, with Spearman  $R = 0.89$  [CI: (0.86, 0.91)] (Figure 3). The mean difference in mismatch volume between the



manual and automatic approach was 8 mL (SD: 35 mL), indicating an overall underestimation by COMBAT Stroke (Figure 3). We observed a significant difference in median mismatch volume in the manual outlines estimated by COMBAT Stroke between patients scanned on a 1.5T [median mismatch volume = 80 mL (27, 135),  $p < 0.01$ ] versus 3T [median mismatch volume = 29 mL (1, 95)] MRI. Likewise, this difference was apparent in COMBAT Stroke estimations; 1.5T: median mismatch volume = 62 mL (13, 106),  $p < 0.01$ , 3T: median mismatch volume = 15 mL (0, 102).

#### ACUTE DECISION PARAMETERS

The patients in the TP group (112 patients actually receiving thrombolytic treatment where COMBAT stroke determined them to be potential candidates) had significantly higher median



**FIGURE 3 | Volumetric comparisons of mismatch delineations.**

On left, x-axis represents the expert consensus mismatch volume and y-axis represent the mismatch volume estimates by the automatic approaches. On right, x-axis represents the average mismatch volume between expert consensus and automatic approaches. The y-axis represent the difference in mismatch volume between expert

consensus and automatic approaches. The Spearman correlation was  $R^2 = 0.89$  [CI: (0.88, 0.91)] for COMBAT Stroke compared with the manual outlining. The mean difference in volume between manual and COMBAT Stroke outlining was 8 mL (SD: 35 mL). Solid line indicates the mean between the two compared methods and dashed lines indicate mean difference  $\pm 2$  SD.

mismatch volume [96 mL (48, 144)], compared with TN [12 patients, median = 0 mL (0, 22),  $p < 0.001$ ], FN [74 patients, median = 0 mL (0, 3),  $p < 0.001$ ] and the FP [30 patients, median = 73.4 mL (28, 109),  $p = 0.04$ ] (**Figure 4A**). Additionally, the NIHSS score was significantly higher in the TP group [median = 11 (7, 16)] compared with TN [median = 6 (4.25, 13.5),  $p < 0.001$ ], FN [median = 5 (3, 7.5),  $p < 0.001$ ] and FP [median = 8 (5, 15),  $p < 0.001$ ] (**Figure 4B**). Contraindications to thrombolysis were present in 83% of the patients in the TN group and in 73% in the FP group. Among the patients in the TP and FN groups, contraindications were present in 24 and 23% of cases, respectively (**Figure 4C**). A summary of acute decision parameters statistics and significance levels are given in **Table 2** for TN and FN group.

### CLINICAL OUTCOME

The 112 patients in the TP group demonstrated the largest mismatch salvage [median = 84.8 mL (42, 138)] and significantly greater salvage than in the TN [median = 8.2 mL (1, 34),  $p < 0.001$ ] and FN groups [median = 1.5 mL (0, 7),  $p < 0.001$ ]. No significant difference in the volume of salvaged tissue was observed between the FP group [median = 73.4 mL (44, 109),  $p = 0.05$ ] and TP (**Figure 4D**). The neurological improvement (assessed by reduction in NIHSS score at 24 h) was significantly better for the TP group [median = 5 (2, 9)] compared with each of the other three groups [TN: median = 3 (2, 4),  $p = 0.03$ ; FN: median = 1 (−1, 3),  $p < 0.001$ ; FP: median = 2 (0, 5),  $p = 0.01$ ] (**Figure 4E**). Routine 24 h MR angiography demonstrated recanalization in 42% of the patients in the TP group, 15% of the TN group, 8% of the FN group, and 10% of the patients in the FP group (**Figure 4F**). A summary of 3 month outcomes (mRS and NIHSS score) are given in **Table 2** for TN and FN group.

### CART ANALYSIS

According to CART analysis, clinicians based their treatment decisions on a multitude of factors, but primarily on the presence/absence of a contraindication (**Figure 5**). The majority of the patients who had no contraindications (152 of 228) were treated with thrombolysis ( $n = 142$ ). If the patient had one or more contraindications, the clinician involved the PWI-DWI mismatch ratio and mismatch volume as a secondary parameter in the clinical decision-making. Finally, neurological assessment quantified by NIHSS score appeared to be the least influential parameter in the regression tree.

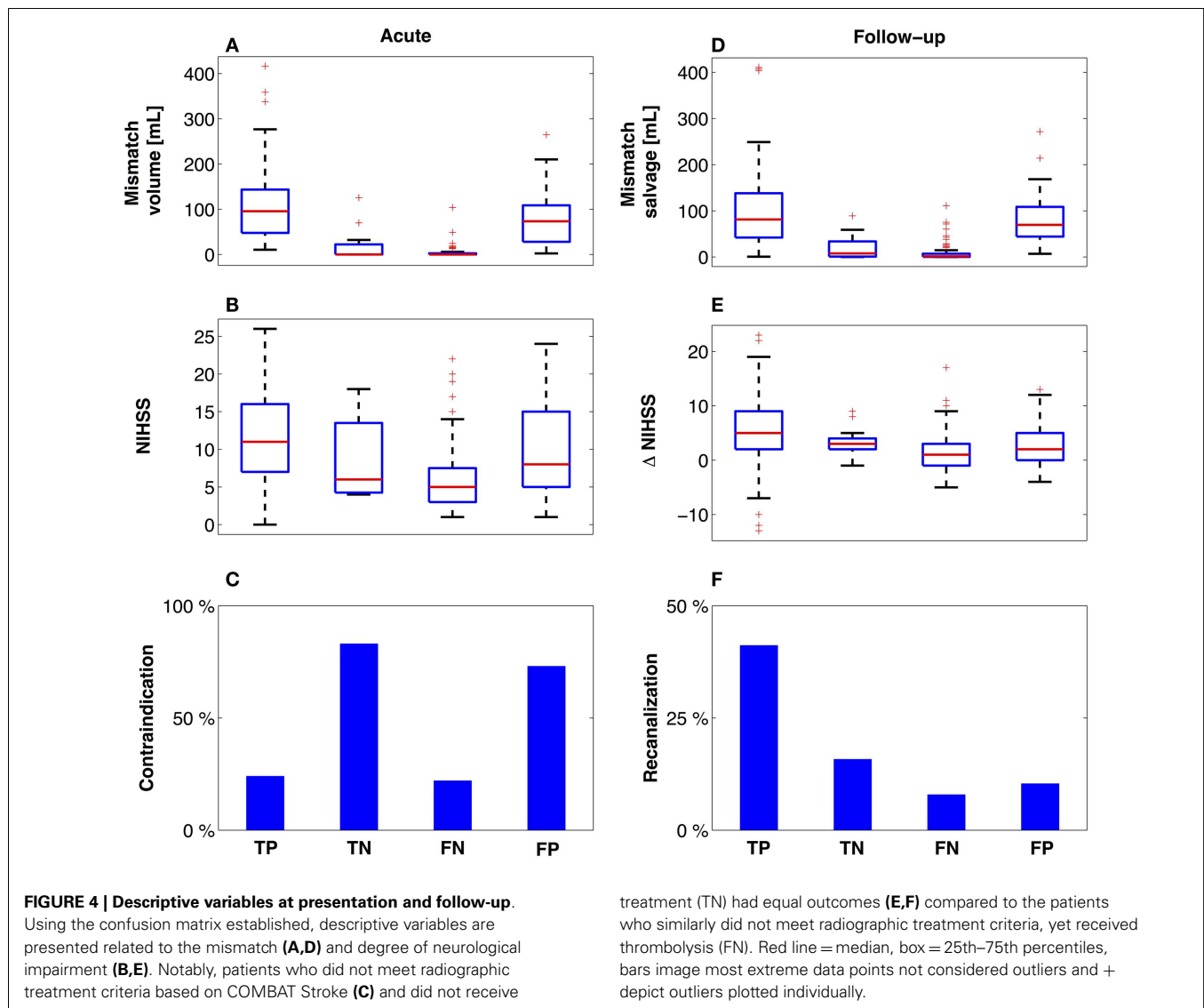
### DISCUSSION

This study reports a 93% sensitivity and 95% specificity between automated patient triaging by COMBAT Stroke and treatment decisions rendered by manually outlined mismatch statistics. Patients with significant mismatch volume and ratio (TP and FP groups) at the time of acute MRI imaging demonstrated higher mismatch salvage compared with those who hadn't significant mismatch, regardless the clinical treatment decision (**Figure 4**).

Not surprisingly, there was a poor agreement between COMBAT Stroke and the actual clinical decision made (**Figure 2A**). This was most notable in patients that did not receive thrombolysis. In that group, there were only 12 cases where there was agreement between clinical and automated decision-making (29% specificity). In contrast, in 74 cases the clinicians decided to administer thrombolysis when COMBAT Stroke decided against (60% sensitivity). This poor correlation reflects the many different variables associated with clinical care and treatment decisions.

Importantly, our results indicate that the patients who did not meet mismatch treatment criteria based on COMBAT Stroke and did not receive treatment (TN) had higher rates of recanalization





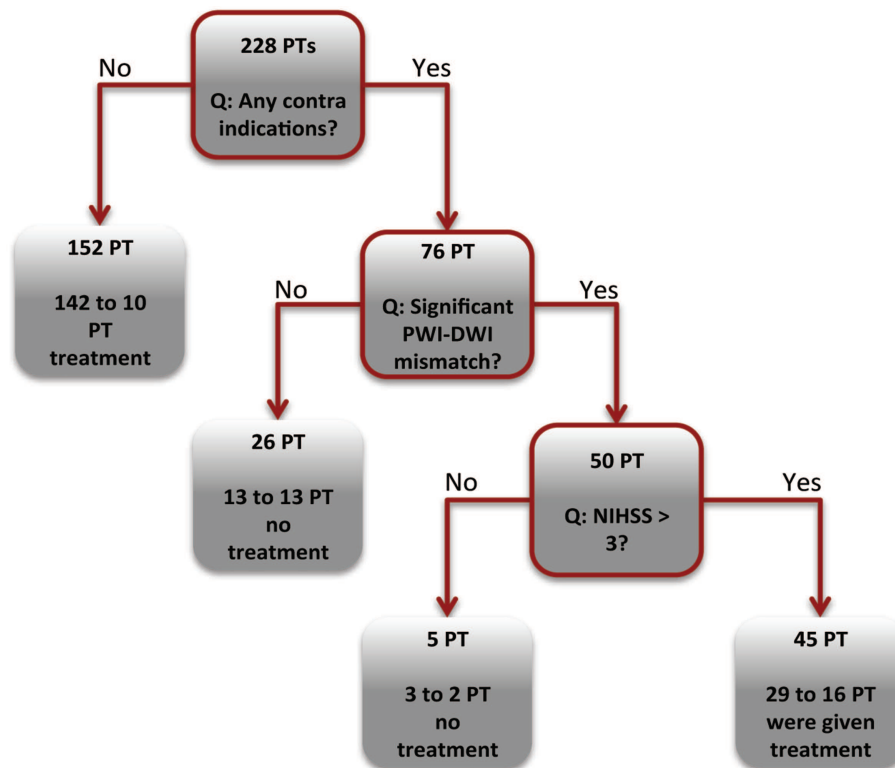
**Table 2 | Summary of acute decision parameters and clinical outcome parameters for TN and FN groups.**

	TN	FN	<i>p</i>
Mismatch	0 mL (0, 22)	0 mL (0, 3)	0.26
Mismatch salvage	8.2 mL (1, 34)	1.5 mL (0, 7)	0.06
Acute NIHSS	6 (4.25, 13.5)	5 (3, 7.5)	0.4
ΔNIHSS	3 (2, 4)	1 (−1, 3)	0.8
Contraindications	83%	23%	N/A
Recanalization	15%	8%	N/A
3-Months mRS	2 (1, 3.75)	1 (0, 1.5)	<0.01
3-Month NIHSS	2 (0.25, 6.5)	0 (0, 1)	<0.01

(15%), larger reduction in NIHSS score (median = 3), and greater mismatch salvage (median = 8.2 mL) compared to the patients who similarly did not meet mismatch treatment criteria, yet received thrombolysis (FN). The analysis of 3 months mRS and

NIHSS score outcomes revealed that patients in FN group had significantly better functional recovery compared to TN group (Table 2). It should be emphasized that the patients in FN group had, in general, the mildest grade of neurological deficit at admission, Figure 4B. Therefore, selection bias may be a confounding factor in the good functional recovery observed in this group. Overall, this data supports a need for greater emphasis on the contribution of strict radiographic criteria in the decision-making process. Use of an automated software system such as COMBAT Stroke may provide rapid and accurate information to objectively contribute to the clinical decision.

In general, the patients COMBAT Stroke identified for potential treatment and were treated had significantly better neurological improvement, mismatch salvage, and higher rates of recanalization compared to the other groups. This indicates the importance of the size of the mismatch and the ratio of the potentially salvageable and infarcted tissue with outcome following thrombolysis (18). Our data suggests that the volumetric assessment of the mismatch



**FIGURE 5 | Decision tree analysis.** The CART tree illustrates the classification of patients (PT) into thrombolysis or supportive treatment. The boxes with red borders indicate a binary question related to the acute clinical or imaging markers. The boxes without red borders denote patient classification into a treatment group.

provided by COMBAT Stroke, in conjunction with the clinical assessment, is potentially a decision-support tool for rapid and standardized stroke management.

To further investigate the factors that influence decision to perform thrombolysis, a CART analysis was performed. About 93% of patients without contraindications were administered thrombolysis (Figure 5). Among the treated patients, 15 and 12% of TP and FN groups had contraindication to treatment, in contrast to the 83 and 78% in the TN and FP groups. It could be suggested that the clinicians in our cohort followed an “aggressive” treatment strategy by administering thrombolysis in the presence of generally accepted contraindications (19, 20). This is not entirely unexpected, as each patient’s care must be individualized, and a risk-benefit ratio of treatment cannot be accurately predicted or captured from our database variables alone (21).

The main limitations of this study are those inherent in any retrospective design. We attempted to overcome selection bias by utilizing a consecutive cohort of ischemic stroke patients from two detailed multi-center databases. Variations in clinical practices between, and even within, different hospitals are not possible to account for and can influence the rates of intervention and clinical outcome (22, 23). Furthermore, individual aspects of patient care such as the patient’s own preexisting wishes regarding treatment are not typically captured in a retrospective analysis. Unfortunately, the balance between actively and supportively

treated patients was highly skewed, thus drawing conclusions by comparing the different groups should be done cautiously. The main technical limitations in this study are the numerous automatic post-processing steps in COMBAT Stroke algorithm. For instance, the co-registration is fully automated and in cases where the co-registration is not optimal, the determination of mismatch volume and mismatch salvage is incorrect. To avoid incorrect estimation of the radiographic parameters, we manually checked all automated steps in the COMBAT Stroke algorithm.

Our study identifies many aspects of investigating an automated clinical decision-support tool that can be further investigated in a prospective fashion. These include any causal effect on neurological outcome, radiographic outcome, and even “door-to-needle” time. The automated process of mismatch volumetric calculation may also prove valuable in the growing population of patients that are treated beyond the typical treatment time window based on dynamic imaging characteristics (24–28).

## CONCLUSION

COMBAT Stroke may help to not only identify patients that are potential candidates for thrombolysis, but also to exclude patients that are unlikely to experience benefit. COMBAT Stroke, in addition to clinical assessment, may provide a decision-support tool for a fast, efficient, and standardized clinical decision-making in acute ischemic stroke.

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# Meta-analysis of Vascular Imaging Features to Predict Outcome Following Intravenous rtPA for Acute Ischemic Stroke

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**Background:** The present review investigated which findings in vascular imaging techniques can be used to predict clinical outcome and the risk of symptomatic intracerebral hemorrhage (sICH) in patients who underwent intravenous thrombolytic treatment.

**Methods:** Publications were searched, and the inclusion criteria were as follows: (1) published manuscripts, (2) patients with acute ischemic stroke managed with intravenous recombinant tissue plasminogen activator (rtPA), and (3) availability of imaging assessment to determine vessel patency or the regulation of cerebral blood flow prior to, during, and/or after thrombolytic treatment. Clinical outcomes were divided into neurological outcome [National Institutes of Health Stroke Scale (NIHSS) within 7 days] and functional outcome (modified Rankin score in 2–3 months). sICH was defined as rtPA-related intracerebral bleeding associated with any worsening of NIHSS.

**Results:** Thirty-nine articles were selected. Recanalization was associated with improved neurological and functional outcomes (OR = 7.83; 95% CI, 3.71–16.53;  $p < 0.001$  and OR = 11.12; 95% CI, 5.85–21.14;  $p < 0.001$ , respectively). Both tandem internal carotid artery/middle cerebral artery (ICA/MCA) occlusions and isolated ICA occlusion had worse functional outcome than isolated MCA occlusion (OR = 0.26, 95% CI, 0.12–0.52;  $p < 0.001$  and OR = 0.24, 95% CI, 0.07–0.77;  $p = 0.016$ , respectively). Reocclusion was associated with neurological deterioration (OR = 6.48, 95% CI, 3.64–11.56;  $p < 0.001$ ), and early recanalization was associated with lower odds of sICH (OR = 0.36, 95% CI, 0.18–0.70;  $p = 0.003$ ).

**Conclusion:** Brain circulation data before, during, and after thrombolysis may be useful for predicting the clinical outcome. Cerebral arterial recanalization, presence and site of occlusion, and reocclusion are all important in predicting the clinical outcome.

**Keywords:** ischemic stroke, clinical outcome, intracerebral hemorrhage, cerebral hemodynamics, intracranial circulation, cerebral autoregulation, rtPA

## INTRODUCTION

A meta-analysis of recombinant tissue plasminogen activator (rtPA) trials suggested that there may be a group of patients who would benefit from thrombolysis within 6 h of symptom onset, if they were carefully selected using advanced imaging modalities (1).

There has been an extensive investigation of prognostic indices of good outcomes that can be applied before, during, and after thrombolysis (2). It is well known that factors, such as age, initial National Institutes of Health Stroke Scale (NIHSS) score, and systolic blood pressure, are of predictive value for clinical outcome and symptomatic intracerebral hemorrhage (sICH) (3). Magnetic resonance imaging (MRI), computed tomography (CT), and transcranial Doppler (TCD) have also been used as possible prognostic determinant tools (4). In particular, arterial occlusion, recanalization, and reocclusion, among other factors, have been investigated in terms of outcome prediction (4). However, there is a gap in the literature about how many methods, which evaluate intracranial circulation, have been used before and after thrombolysis to predict the outcome in a systematic fashion, together with a critical review of the strengths and weaknesses of each method.

The aim of the present review is (1) to undertake a descriptive systematic review of studies that have evaluated the intracranial circulation before, during, and after thrombolysis; (2) to evaluate the parameters that provide prognostic information of clinical outcome and/or sICH; and (3) to perform a meta-analysis of studies that used such parameters.

## MATERIALS AND METHODS

### Search Strategy

A literature search strategy, restricted to publications from January 1994 to January 2015, was designed to identify cerebral hemodynamic studies, which assessed cerebral vessel patency and/or autoregulation in acute ischemic stroke patients treated with intravenous rtPA. Two reviewers (Ricardo C. Nogueira and Nazia P. Saeed) identified studies from PubMed database using the keywords “ischemic stroke” AND “rtPA treatment” OR “thrombolysis” AND “cerebral hemodynamics” OR “cerebral autoregulation” OR “cerebral blood flow control.” Bibliographic references of selected articles were examined for additional suitable studies. The inclusion criteria were (1) published manuscripts in English language, (2) patients (>18 years of age) with acute ischemic stroke treated with intravenous rtPA, and (3) availability of assessment of intracranial circulation to determine vessel patency and/or regulation of cerebral blood flow prior to, during, and/or after thrombolytic treatment. The exclusion criteria were (1) acute ischemic stroke not managed with intravenous rtPA, (2) impossibility to determine the vessel patency or the regulation of cerebral blood flow before, during, and/or after rtPA administration, (3) non-English language publications, (4) non-human models, and (5) case reports. The systematic review followed PRISMA guidelines; quality assessment of articles were used applying the American Academy of Neurology rating system by two raters (Ricardo C. Nogueira and Nazia P. Saeed), reviewed

by a third investigator (Edson Bor-Seng-Shu) in terms of agreement, and this individual resolved any discrepancies. For the meta-analysis, authors of publications with incomplete data were contacted for additional information. Moreover, care was taken to exclude articles with no comparable data (for example: lack of imaging after thrombolysis, lack of clinical outcome measured, etc.) and articles with patients included in other articles from the same institution to avoid biasing the population sample.

### Data Extraction

The following data were extracted from each article: sample size, presence of a control group, type(s) of diagnostic modality used, time delay between assessment and thrombolysis (when stated), time interval between rtPA treatment and monitoring examinations (assessment during and following treatment, when stated), outcomes, conclusions, and study limitations. The articles were grouped according to the method of cerebral hemodynamic assessment. Data from cerebral hemodynamic assessment techniques were compared based on their common aspects, primary contributions, and limitations.

### Outcomes

Clinical outcomes were divided into functional, defined by modified Rankin scale (mRS) in the late post-thrombolytic therapy (2–3 months) with good outcome been considered as mRS  $\leq 2$ , and neurological outcomes, assessed by NIHSS and comprising improvement (reduction of 10 points or final NIHSS  $\leq 3$ ) or deterioration (increase  $\geq 4$  points) in the early post-thrombolytic therapy stage (within 7 days). sICH was defined as rtPA-related intracerebral bleeding detected by CT or MRI associated with any worsening of NIHSS or death. Additional outcome measures were arterial recanalization assessed by different scales [thrombolysis in brain ischemia (TIBI), thrombolysis in myocardial ischemia (TIMI), and partial or full recanalization], reocclusion (within 24 h), and cerebral infarct volume.

### Meta-analysis

The variables related to assessment of intracranial circulation were identified in each retrieved paper and, if they presented in the results a significant correlation with clinical outcome and sICH in a multivariate analysis, they were considered for the meta-analysis. The software used for meta-analysis was the OpenMetaAnalyst (Center for Evidence-based Medicine, Brown University School of Public Health – Providence, RI, USA), the binary random-effect method was applied, and the heterogeneity of studies was evaluated using  $I^2$  statistics. To identify for publication bias, a funnel plot and Egger's test were applied in the analysis of any assessed variable, where information was available from three or more studies.

## RESULTS

### Number of Studies Retrieved

The search in PubMed retrieved 7369 articles. After analyzing the title and abstract, a total of 278 articles were deemed suitable. The inclusion and exclusion criteria were then applied, leaving 39 articles for further analysis (Figure 1). Each article was then grouped



according to the neuroimaging technique performed; 26 studies used TCD ultrasonography, 2 computed tomography angiography (CTA), 10 magnetic resonance imaging angiography (MRA), and 1 either MRA or CTA. TCD ultrasonography was the most used method for cerebral hemodynamic evaluation and was, on average, performed on more patients per study, besides presenting the shortest time interval for follow-up assessment (average 2.4 h).

## Characteristics of the Included Studies

There were 38 observational studies (37 cohort and 1 case-control) and 1 interventional study; no randomized controlled clinical trial was identified (please see Supplementary Material). The majority of the observational studies (36 of 38) used the neuroimaging methods for prognostic purposes, and the remainder used the methods for investigating diagnostic accuracy or causation.

After grouping the articles based on the type of cerebral hemodynamic assessment, common findings were as follows.

### MR/CT Angiography

Thirteen studies using CTA (2 studies), MRA (10 studies), or MRA + CTA (1 study) were included (please see Supplementary Material) (5–17). In two studies (one using MRA and another CTA), neuroimaging assessment was not performed after rtPA treatment. The mean time delay from neuroimaging examination to thrombolytic therapy was 40 min, and the mean time for a second exam following therapy was 19.2 h. One study had an interventional design, and the main outcomes were functional and recanalization (TIMI 1–3). rtPA was associated with higher rates of recanalization and better functional outcomes. Concerning the observational studies, the findings revealed that the presence, site of arterial occlusion [proximal middle cerebral artery (MCA), distal MCA, or tandem internal carotid artery (ICA)–MCA], and the occurrence of partial or full recanalization were related to the clinical outcomes and final infarct size. The limitations included

a small sample size and difficulties in determining the time of arterial recanalization.

### Transcranial Doppler

Twenty-six studies used TCD as a method for cerebral hemodynamic assessment (please see Supplementary Material) (3, 18–42). In 24 studies, cerebral hemodynamic parameters were evaluated prior to and after thrombolytic treatment (range from 2 h to 2 days), while the remaining 2 studies presented only pre-rtPA cerebral hemodynamic data. TCD was the sole method for monitoring the cerebral hemodynamic status during thrombolysis.

These studies revealed that factors, such as pretreatment TIBI classification score, arterial recanalization/reocclusion, and the site of occlusion (tandem occlusions, proximal/distal ICA, or MCA occlusions), were associated with clinical outcome, infarct size, and sICH.

Limitations included the operator-dependence nature of the TCD method, the absence of arterial imaging resources (making it difficult to determine the site of occlusion), and unfavorable cranial windows for ultrasound energy passage.

## Pooled Results

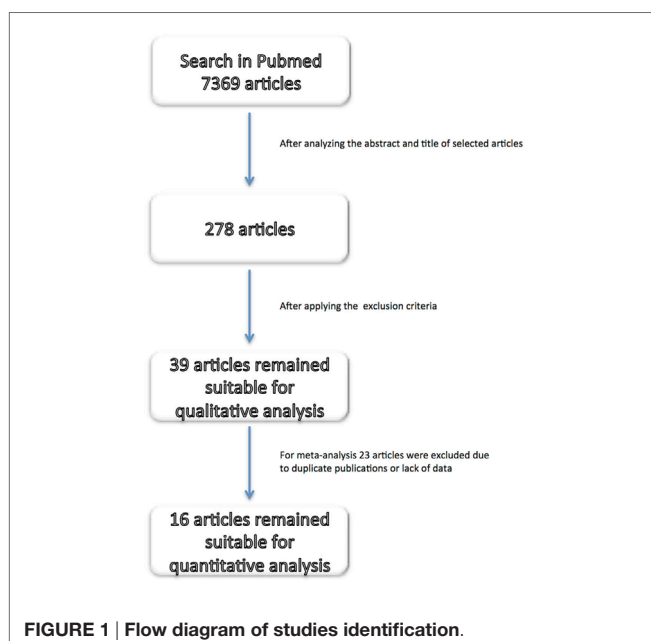
The cerebral circulation variables associated with functional and neurological outcomes or sICH were arterial recanalization/reocclusion, presence/absence of arterial occlusion, and the site of occlusion (Tables 1 and 2). No article regarding cerebral autoregulation (CA) was identified.

For the meta-analysis, 23 out of 39 articles were excluded for the following reasons: possibility of overlapping patients (12 articles, 964 patients), lack of data able to be compared (6 articles, 360 patients), and lack of success in obtaining additional data (5 articles, 129 patients). Arterial recanalization was significantly associated with good functional outcome (OR = 11.12; 95% CI, 5.85–21.14;  $p < 0.001$ ) and neurological improvement (OR = 7.83; 95% CI, 3.71–16.53;  $p < 0.001$ ) (Figures 2A,B). Both tandem ICA/MCA occlusions and isolated ICA occlusion had worse functional outcome than isolated MCA occlusion (OR = 0.26, 95% CI, 0.12–0.52;  $p < 0.001$  and OR = 0.24, 95% CI, 0.07–0.77;  $p = 0.016$ , respectively) (Figures 2C1,C2). Patients with recanalization followed by reocclusion within 24 h of thrombolysis had significant association with neurological deterioration (overall OR: 6.48, 95% CI: 3.64–11.56,  $p < 0.001$ ) (Figure 2D). Early recanalization (up to 2 h after thrombolysis) was associated with lower odds of sICH (overall OR = 0.36, 95% CI, 0.18–0.70;  $p = 0.003$ ) (Figure 3).

The funnel plots of functional outcomes and sICH were suggestive of potential publication bias, which was confirmed by the Egger's test (intercept: 43.65,  $p = 0.046$ ; intercept: 1.97,  $p = 0.003$ ; Figures 4A,B, respectively). However, the funnel plot of neurological improvement did not indicate the publication bias (Egger's test intercept: 1.48,  $p = 0.83$ ; Figure 4C).

## DISCUSSION

In 2003, Schellinger et al. (43) highlighted the importance of various diagnostic modalities, such as brain MRI, CT, and TCD

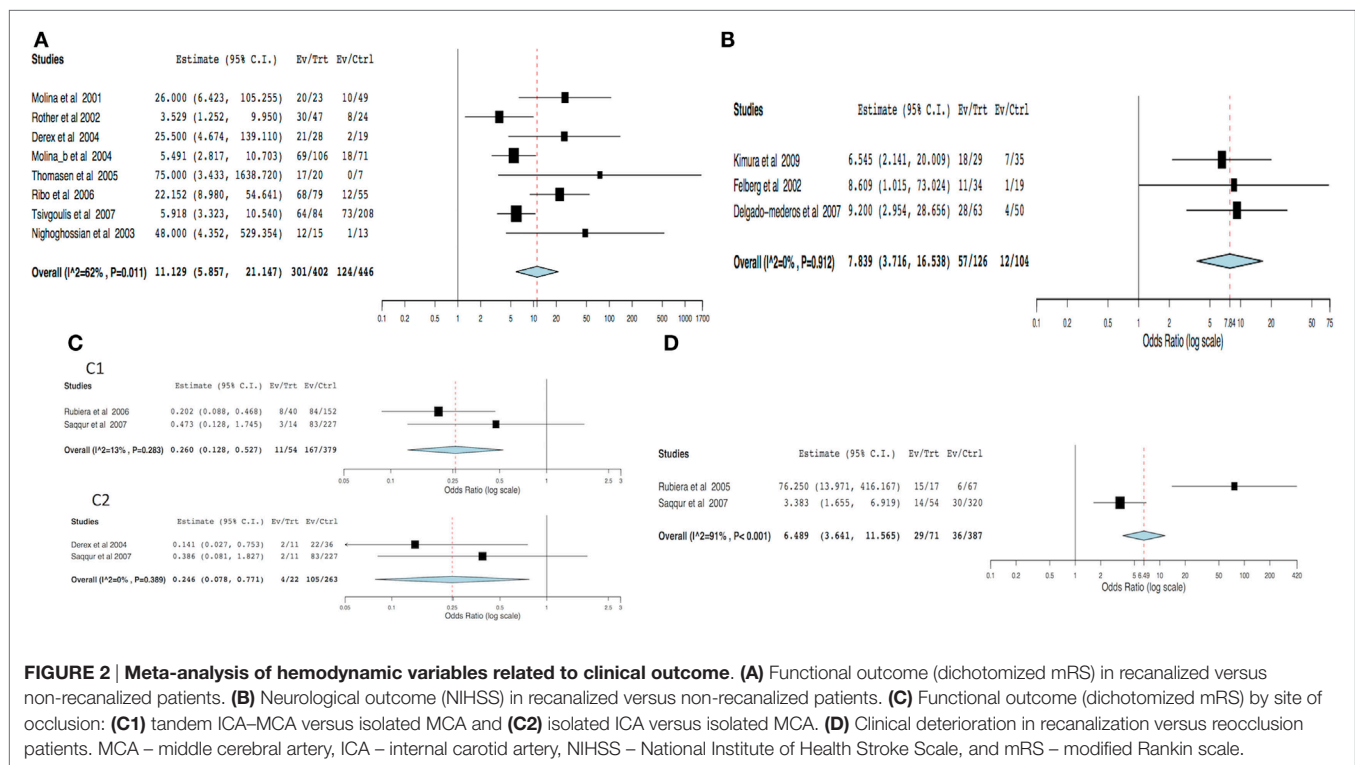


**TABLE 1 | Studies demonstrating association with clinical outcome.**

Article	Method	Variable	Outcome	Result
Molina et al. (19)	TCD	Early recanalization (6 h)	Good outcome (mRS $\leq 2$ ) in 90 days	OR = 23.4 (5.4–96) $p = 0.001$
Nighoghossian et al. (12)	Multiparametric MRI	Recanalization	NIHSS at day 60	Multiple linear regression $p = 0.0001$
Molina et al. (3)	TCD	Proximal occlusion before thrombolysis	Good outcome (mRS $\leq 2$ ) in 90 days	OR = 0.25 (0.10–0.61) $p < 0.001$
Sims et al. (17)	CTA	Absence of occlusion	Early improvement (4 points in NIHSS)	OR = 5.0 (1.1–23.3) $p = 0.04$
Sims et al. (17)	CTA	Absence of occlusion	Good outcome (mRS $\leq 2$ ) in 7 days	OR = 6.8 (1.3–34.6) $p = 0.02$
Saqqur et al. (42)	TCD	Reocclusion	Clinical deterioration (4 points in NIHSS)	OR = 4.9 (1.7–13) $p = 0.002$
Saqqur et al. (41)	TCD	Distal $\times$ proximal MCA occlusion before thrombolysis	Good outcome (mRS $\leq 1$ ) in 90 days	OR = 2.1 (1.1–4) $p = 0.025$
Tsivgoulis et al. (34)	TCD	Recanalization within 2 h	Good outcome (mRS $\leq 2$ ) in 90 days	OR = 5.98 (2.58–13.84) $p < 0.001$

**TABLE 2 | Studies demonstrating association with symptomatic intracerebral hemorrhage.**

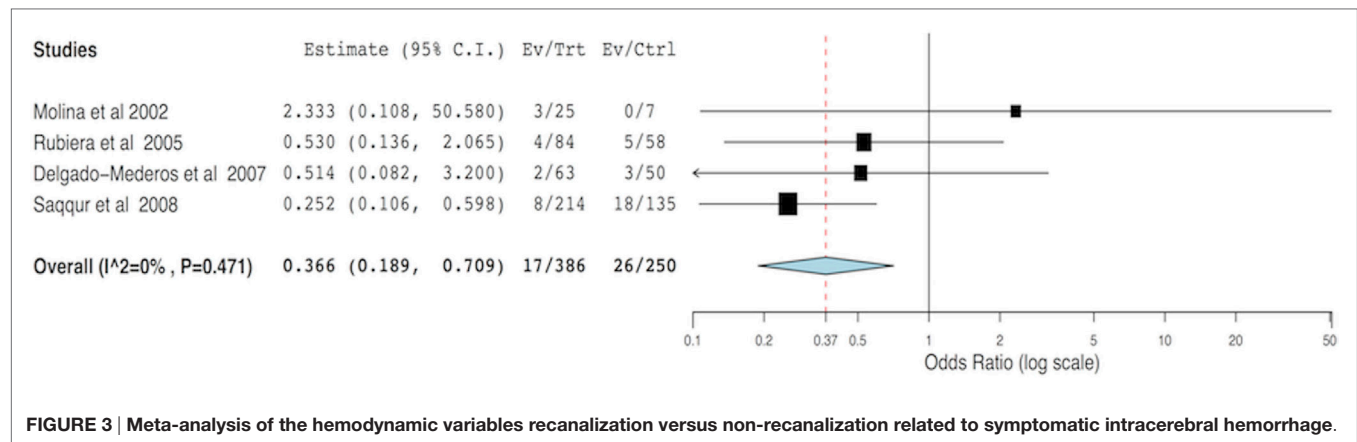
Article	Method	Variable	Outcome	Result
Saqqur et al. (36)	TCD	Persistence of occlusion $\geq 2$ h	sICH	OR = 6 (1.5–21.3) $p = 0.01$
Saqqur et al. (36)	TCD	Recanalization beyond 24 h or persistent occlusion	sICH	OR = 3 (1.1–10) $p = 0.04$
Saqqur et al. (36)	TCD	Persistence of proximal occlusion at 2 h	sICH	OR = 5 (1.5–15) $p = 0.008$
Saqqur et al. (36)	TCD	Persistence of proximal occlusion at 2 h (excluding reocclusion)	sICH	OR = 8 (3–26) $p < 0.001$



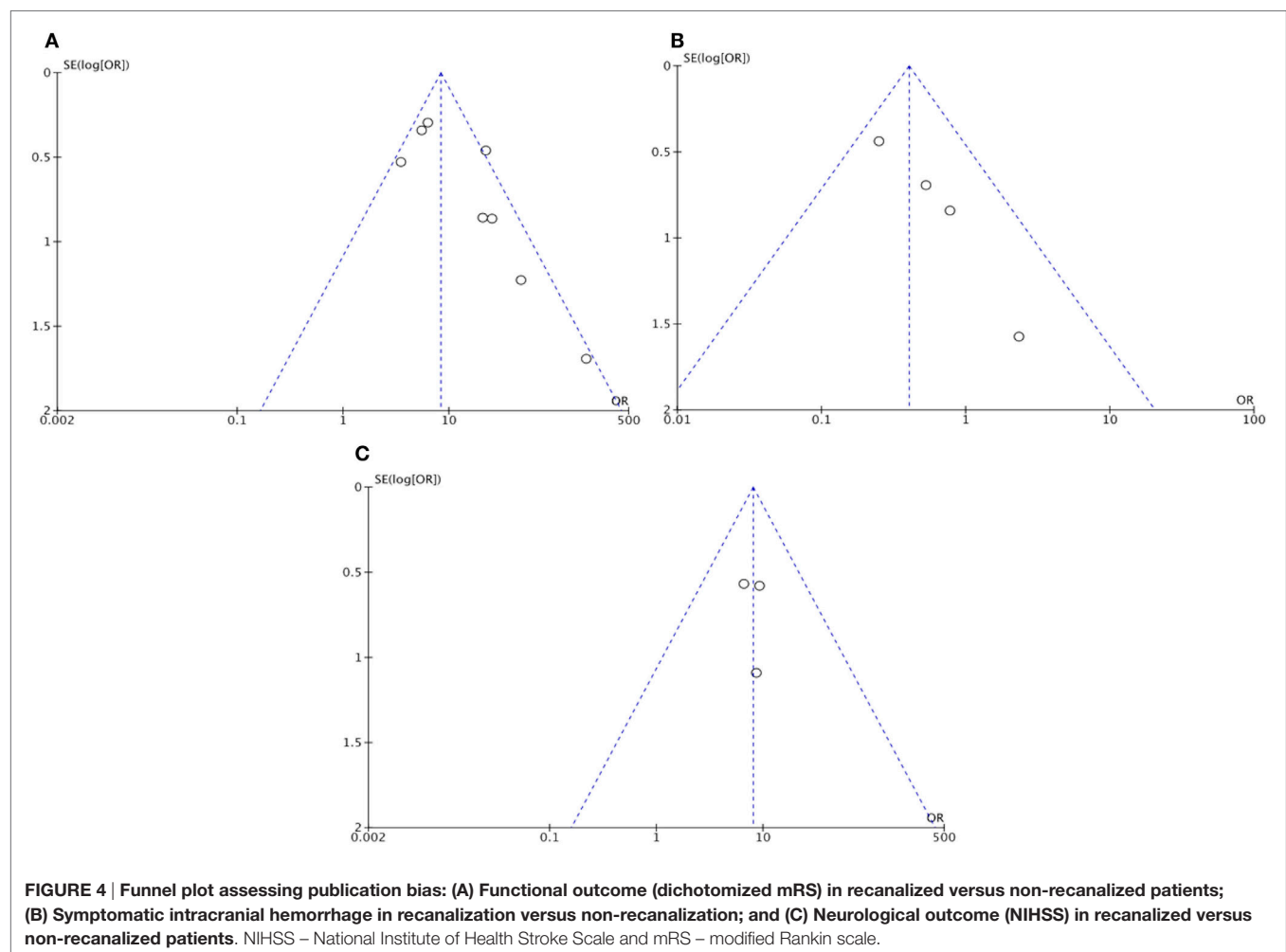
**FIGURE 2 | Meta-analysis of hemodynamic variables related to clinical outcome. (A)** Functional outcome (dichotomized mRS) in recanalized versus non-recanalized patients. **(B)** Neurological outcome (NIHSS) in recanalized versus non-recanalized patients. **(C)** Functional outcome (dichotomized mRS) by site of occlusion: **(C1)** tandem ICA-MCA versus isolated MCA and **(C2)** isolated ICA versus isolated MCA. **(D)** Clinical deterioration in recanalization versus reocclusion patients. MCA – middle cerebral artery, ICA – internal carotid artery, NIHSS – National Institute of Health Stroke Scale, and mRS – modified Rankin scale.

ultrasonography, for the decision-making process regarding thrombolytic therapy for acute ischemic stroke. Furthermore, the assessment of cerebral hemodynamic during and after thrombolytic therapy may be important to determine the parameters that could influence the clinical outcome, especially in the face of new research investigating the aggressive control of ABP in this scenario (44). Finally, with the new guidelines regarding

endovascular treatment (45), the evaluation of cerebral circulation will be useful to determine proximal occlusion and also could select patients who were excluded from endovascular trials, but could benefit from the interventional therapy. To our knowledge, the present paper is the first to use techniques of systematic review and meta-analysis to verify the influence of assessment of intracranial circulation, provided by brain MRI,



**FIGURE 3 |** Meta-analysis of the hemodynamic variables recanalization versus non-recanalization related to symptomatic intracerebral hemorrhage.



**FIGURE 4 |** Funnel plot assessing publication bias: (A) Functional outcome (dichotomized mRS) in recanalized versus non-recanalized patients; (B) Symptomatic intracranial hemorrhage in recanalization versus non-recanalization; and (C) Neurological outcome (NIHSS) in recanalized versus non-recanalized patients. NIHSS – National Institute of Health Stroke Scale and mRS – modified Rankin scale.

CT, and TCD ultrasonography on clinical outcomes and sICH in acute ischemic stroke patients who underwent thrombolytic therapy (46).

Considering the hemodynamic studies reviewed here, the specific details of each study are worth emphasizing. MRA and

CTA represent valuable options for detecting and confirming large vessel occlusion, but cannot identify the timing of recanalization (8, 11, 15, 16, 37, 47–49). Furthermore, early imaging changes are the strong predictors of sICH (50) and could be used in association with cerebral circulation parameters. The primary

limitations of MRA and CTA studies were the time delay in assessment after thrombolytic treatment, the use of intravenous contrast media, and the difficulties in determining the timing of recanalization (6, 9, 12, 48, 49). However, it is well established that the presence and timing of brain arterial recanalization correlates with clinical outcome, hemorrhagic complications, and infarct size (14, 19–22, 25, 29, 31, 36, 37). For this purpose, TCD ultrasonography remains a valuable choice, as this method exhibits the following advantages: (1) device portability, (2) low cost of the method, and (3) real-time monitoring during thrombolysis (3, 18, 20–23, 25, 26, 30, 34, 36, 37). TCD ultrasound may also play a therapeutic role during thrombolysis; a recent systematic review revealing that sonothrombolysis associated with rtPA is a safe procedure that increases recanalization rate in the acute ischemic stroke setting (51, 52). However, TCD is operator-dependent, cannot reliably monitor small brain artery occlusion, and does not determine the exact site of occlusion. Therefore, in the future, a combination of methods may be important.

Only variables that, in the retrieved papers, presented significant correlation with outcome (clinical or sICH) in a multivariate analysis were included in the present review. The main variables associated with clinical outcome or sICH were recanalization, reocclusion, and the presence and site of occlusion. Our meta-analysis showed that recanalization is significantly associated with functional and neurological outcomes, but not with sICH. In fact, some studies have shown that the time of recanalization is associated with neurological recovery (21), and the persistence of occlusion is associated to sICH (36). Our findings are in agreement with a previous meta-analysis, which found significant association between recanalization and clinical outcome (OR: 4.43) and no association between recanalization and sICH, but comparisons should be made with caution because the previous meta-analysis evaluated intravenous, intra-arterial, and mechanical therapies (53).

Most of the conclusions presented in this paper have already been presented in endovascular therapy (EVT) trials. However, some issues, such as reocclusion, are more suitable for investigation by non-invasive imaging techniques. Furthermore, we believe that the information gathered in this paper, reaffirming the conclusions obtained with EVT trials and pointing the positive and negative aspects of other imaging techniques, is important to support the utilization of multimodality imaging in stroke care. A multimodality approach may provide a better understanding of the natural evolution of this pathology, and perhaps better future selection of patients for interventional therapies, who are currently excluded. Finally, strengthening the importance of different imaging modalities in the intravenous therapy setting is important for centers that still do not have access to interventional therapy, especially in low-income countries.

There are few studies concerning CA during acute and subacute ischemic stroke. Existing publications on CA in ischemic stroke reveal a transient impairment of CA during the subacute stages of major ischemic stroke (54–57). Interestingly, using animal models, it has been demonstrated that rtPA displays neurotoxic properties that can disrupt the blood–brain barrier,

damage vessels, and possibly impair the CA (58). To our knowledge, only one study of CA after rtPA treatment in humans is available, which concluded that this treatment does not contribute to impaired CA. However, this study evaluated CA 10–20 h after rtPA treatment; not eliminating the possibility of an initial detrimental effect by rtPA on CA (59).

The limitations of the current review are (1) the search strategy was restricted to just one database, although PubMed comprises a majority of the relevant articles on this topic; (2) the inclusion criteria were limited to research of standard dose of rtPA (0.9 mg/kg) for thrombolysis, although low dose of rtPA (0.6 mg/kg), other thrombolytic drugs (desmoteplase or tenecteplase), or other methods (mechanical thrombectomy, intra-arterial rtPA) have been investigated; (3) lack of analysis concerning the effect of recanalization time on clinical outcome, although the present meta-analysis showed the clinical impact of recanalization at the first 24 h; (4) use of different imaging modalities for detecting arterial occlusion and recanalization; (5) data heterogeneity (especially number of patients included in each study, quality of study, and average stroke severity) from different publications; and (6) potential publication bias of some outcomes' measures confirmed by the funnel plot and Egger's test.

## CONCLUSION

In conclusion, the use of brain assessments of cerebral circulation before, during, and after rtPA thrombolysis is promising, especially, to predict outcome. Arterial recanalization, presence and site of occlusion, and reocclusion relate to clinical outcome. Future studies of prognostic accuracy should investigate these factors, ideally using more than one method of cerebral hemodynamic assessment. In addition, the evaluation of cerebral blood flow regulation mechanisms during and after rtPA treatment should be explored.

## AUTHOR CONTRIBUTIONS

RN contributed to the conception and design of research; acquisition, analysis, and interpretation of data; statistical analysis; drafting of the manuscript; and approved the final version. EB-S-S and NS contributed to the conception and design; interpretation of data; drafting of the manuscript; and approved the final version. MT, RP, and TR contributed to the analysis and interpretation of data; critical revision of the manuscript for important intellectual content; and approved the final version of the manuscript.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at <http://journal.frontiersin.org/article/10.3389/fneur.2016.00077>



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# Thrombolysis-related intracerebral hemorrhage and cerebral amyloid angiopathy: accumulating evidence

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Intracerebral hemorrhage (ICH) is the most feared risk of systemic thrombolysis for ST-elevated myocardial infarction, pulmonary embolism, or acute ischemic stroke. Clinical, radiological, and pathological evidence suggests that cerebral small vessel disease and, in particular, cerebral amyloid angiopathy (CAA) may contribute to or in some cases directly underpin thrombolysis-related intracerebral hemorrhage (TICH) (1). Further developments, particularly in neuroimaging, have strengthened this hypothesis, hinting at the prospect of identifying biomarkers to measure TICH risk for individual patient groups. Emerging biomarkers for CAA such as lobar cerebral microbleeds (2) may become increasingly useful for outcome endpoints in clinical trials and patient risk stratification for TICH (3).

Thrombolysis-related intracerebral hemorrhage is a complex pathophysiological process. For ischemic stroke patients, a key issue is the location of TICH, i.e., hemorrhage into the area of ischemia vs. hemorrhage in a remote non-ischemic site (occurring in about 20% of patients with symptomatic TICH). Classification of TICH has traditionally focused on clinical and radiological features (4), with less emphasis on whether different mechanisms might be implicated in TICH in remote from or within the acute infarcted region (5) or whether pathological assessment has occurred.

Coregistered Pittsburgh compound B positron emission tomography (PiB-PET) imaging has revealed that spontaneous hemorrhage hotspots preferentially occur at locations with increased amyloid  $\beta$ -protein burden (6). In patients treated with recombinant tissue plasminogen activator (rt-PA) for acute ischemic stroke, cerebral amyloid  $\beta$ -protein (as detected with PiB-PET) retention was higher in patients with parenchymal hemorrhage compared to patients without (7). Although PiB-PET has somewhat poor spatial resolution and cannot reliably resolve parenchymal and cerebrovascular amyloid  $\beta$ -protein, the finding is probably one of the strongest pieces of radiological evidence implicating CAA in TICH. Matrix metalloproteinase 9, a zinc-dependent endopeptidase and a marker of hemorrhagic transformation after ischemic stroke, is released from neutrophil granules by rt-PA in humans (8). Amyloid  $\beta$ -protein can also release and activate MMP-9 from mouse endothelial cells (9), suggesting that convergent risk factors may lead to hemorrhage.

Cerebral microbleeds identified on MRI in a lobar distribution are considered a characteristic hemorrhagic marker of a vasculopathy related to CAA (2). It has slowly emerged that multiple microbleeds might increase the risk of symptomatic ICH following thrombolysis treatment, a relationship which increases with increasing numbers of microbleeds (10, 11). In more recent studies with larger groups of ischemic stroke patients receiving intravenous thrombolysis in both European and Chinese populations, multiple cerebral microbleeds were more clearly associated with symptomatic and parenchymal hemorrhage, respectively (12, 13). Future study may provide insights into potential mechanisms, and meta-analyses may highlight the relative importance of lobar and non-lobar cerebral microbleeds in stratifying the intracerebral hemorrhagic risk from thrombolysis.

In a review in 2004 (1), we identified 10 patients with pathological investigation of TICH, 7 of whom had evidence of CAA. All of these patients had been treated for acute myocardial infarction and nine of the patients had multiple hemorrhages in a lobar distribution. With an increasing emphasis on primary percutaneous intervention for ST-elevated myocardial infarction, it may not be surprising that no further TICH cases following thrombolysis for acute myocardial infarction have been reported. However, although thrombolysis rates have increased for acute ischemic stroke patients, in an updated systematic literature search, only two further autopsy TICH cases (multiple and both hemispheres) have been reported in the stroke literature, both of whom had CAA (14). The relative lack of human pathological studies compared to neuroimaging studies hampers further developments in this area. A pathological register

attached to a clinical register would enhance our understanding of TICH, particularly in the older population with acute ischemic stroke.

The known predictors of clinically significant TICH currently include age, clinical stroke severity, high blood pressure, hyperglycemia, early CT ischemic changes, large baseline diffusion lesion volume, leukoaraiosis, and cerebral microbleeds on MRI; the evidence for a role of CAA in TICH continues to accumulate.

## Author Contributions

AC conceived the idea and reviewed the literature and drafts of the paper. JN contributed to the writing, analyzed the literature, and reviewed drafts of the paper. MM wrote the first draft and reviewed drafts of the paper.

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# New cerebral microbleeds and mechanism of post-thrombolysis remote intracerebral hemorrhage: “red meets white” revisited<sup>†</sup>

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<sup>†</sup> The title is inspired by an Editorial,  
published after the first study revealing  
the rapidly evolving nature of cerebral  
microbleeds in the acute phase of  
ischemic stroke was reported.  
See Kidwell and Greenberg (2009),  
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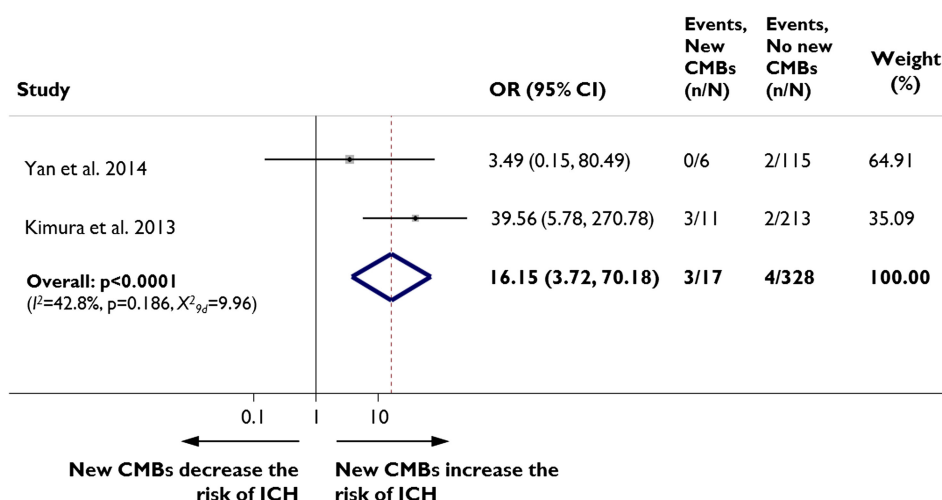
**Keywords:** acute stroke, cerebral microbleeds, cerebral small vessel disease, cerebral amyloid angiopathy, intracerebral hemorrhage, thrombolysis

Intravenous thrombolytic therapy in acute ischemic stroke patients is complicated by intracerebral hemorrhage (ICH) at a site remote from the infarcted area in roughly 2–3% of cases (1, 2). Historically, the etiology underlying these was proposed to be hemorrhagic infarction at a distant unrecognized silent focus of ischemia from multiple emboli. However, the use of diffusion-weighted imaging has demonstrated clear examples of remote intracerebral hemorrhage (rICH) occurring at sites devoid of ischemia, signifying alternate contributory mechanisms (3). Cerebral microbleeds (CMBs) are markers of bleeding-prone microangiopathies – most commonly hypertensive arteriopathy and cerebral amyloid angiopathy (CAA) (4) – that are visualized on T2\*-weighted magnetic resonance imaging (MRI). Pathological studies have demonstrated intact erythrocytes underlying 13% of CMBs (5) implying that a subset of these lesions reflect acute or subacute areas of microhemorrhage. Fittingly, radiographic studies have demonstrated development of new CMBs in 5–13% of acute ischemic stroke patients within the first week after symptom onset (6–8). It is hence biologically plausible that thrombolysis-induced expansion of rapidly appearing CMBs might be the cause underlying a proportion of rICH in acute ischemic stroke patients. In this Opinion piece, we explored this hypothesis by pooling available evidence from relevant MRI patient cohorts with acute ischemic stroke.

Two recent studies from east-Asian centers including a total of 345 patients have assessed the risk of rICH in patients who develop new post-stroke CMBs. Both studies used exclusively intravenous thrombolysis with rtPA: the dose used was 0.6 mg/kg in one study (7) and 0.9 mg/kg in the other (8). Overall, 129 (39%) of the patients had CMBs on pre-treatment baseline MRI and 17 (5%) developed new CMBs at 24 h post-thrombolysis. Post-thrombolysis rICH occurred in 2% ( $n = 7$ ) of the entire population. In fixed effects pooled meta-analysis of the data, patients who developed new CMBs had a significantly increased risk of rICH than patients without new CMBs (odds ratio (OR) 16.15, 95% CI 3.72–70.18,  $p < 0.0001$ ; **Figure 1**). The results were consistent in sensitivity analysis using a random effects model.

These findings, although preliminary, suggest that thrombolysis-induced expansion of new CMBs might account for a proportion of rICH in acute ischemic stroke patients. Post-thrombolysis rICH has been previously documented to occur at a site of CMB (9) and meta-analyses have suggested elevated risk of any post-thrombolysis symptomatic intracerebral hemorrhage in patients with CMBs (10, 11). However, whether these lesions – detected on baseline pre-thrombolysis MRI – were acute CMBs or simply a chronic marker of underlying hemorrhage-prone microangiopathies in the brain is uncertain, as thus far only chronic-subacute CMBs have been proposed to possibly have a distinctive MRI signature (12).





**FIGURE 1 | New cerebral microbleeds and remote (i.e., extra-ischemic) intracerebral hemorrhage.** Meta-analysis of the association between symptomatic remote intracerebral hemorrhage (ICH) risk in patients with acute ischemic stroke treated with intravenous thrombolysis, in relation to the presence of new cerebral microbleeds (CMBs) on MRI. Moderate heterogeneity was detected across the different studies pooled in the meta-analysis. Two authors search PubMed and extracted relevant data for the analysis. We quantified the strength of the association between new CMBs and ICH using odds ratios (OR) and their corresponding 95% CIs, with the inverse variance method for weighting. We assessed statistical heterogeneity using I-squared statistics and also visually through inspection of the forest plot. We repeated all analyses using random effects models. Meta-analyses were performed using Stata 11.2 (StataCorp LP, Texas).

Two cohorts published in the last year have attempted to characterize clinical predictors of rICH (1, 2). In the Safe Implementation of Treatments in Stroke-International Stroke Register (SITS-ISTR) prior stroke and older age were independently associated with rICH. However, the lack of robust associations with traditional ischemic risk factors led the authors to postulate whether another undetected mechanism, including CAA (13), was at play (2). Conversely, prior transient ischemic attack (TIA) was the only clinical predictor of rICH in an Australian cohort (1). Although, this observation could support the notion that rICH occurs from hemorrhagic transformation of unrecognized acute or subacute ischemic infarcts, patients with CAA often experience transient focal neurological episodes that can mimic TIA, and are highly predictive of future lobar ICH (14).

Together, these observations raise the possibility that multiple etiologies (both primary hemorrhagic and primary ischemic) likely contribute to the pathogenesis of post-thrombolysis rICH. They also demonstrate the rapidly evolving nature of

microbleeds in the acute phase of ischemic stroke, suggesting a potential role of an active small vessel microangiopathic process (15). As our pooled analysis is unadjusted, it remains to be determined whether the association between new CMBs and rICH is indeed an independent one or rather simply an indirect association due to common underlying pathophysiology, such as small vessel disease, stroke-induced acute hypertensive response, or neurovascular unit dysfunction from up regulation of inflammatory cascades. Future larger studies that incorporate a comprehensive assessment of both clinical and MRI predictors of rICH, as well as circulating markers of inflammation, would further elucidate this hypothesis.

## Author Contributions

Study Concept: AS and AC. Acquisition of data: AS, SY, and AC. Statistical Analysis: AC. Drafting of the manuscript: AS; Revising the manuscript for content: AC and SY.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Prediction and observation of post-admission hematoma expansion in patients with intracerebral hemorrhage

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Post-admission hematoma expansion in patients with intracerebral hemorrhage (ICH) comprises a simultaneous major clinical problem and a possible target for medical intervention. In any case, the ability to predict and observe hematoma expansion is of great clinical importance. We review radiological concepts in predicting and observing post-admission hematoma expansion. Hematoma expansion can be observed within the first 24 h after symptom onset, but predominantly occurs in the early hours. Thus capturing markers of on-going bleeding on imaging techniques could predict hematoma expansion. The spot sign observed on computed tomography angiography is believed to represent on-going bleeding and is to date the most well investigated and reliable radiological predictor of hematoma expansion as well as functional outcome and mortality. On non-contrast CT, the presence of foci of hypoattenuation within the hematoma along with the hematoma-size is reported to be predictive of hematoma expansion and outcome. Because patients tend to arrive earlier to the hospital, a larger fraction of acute ICH-patients must be expected to undergo hematoma expansion. This renders observation and radiological follow-up investigations increasingly relevant. Transcranial duplex sonography has in recent years proven to be able to estimate hematoma volume with good precision and could be a valuable tool in bedside serial observation of acute ICH-patients. Future studies will elucidate, if better prediction and observation of post-admission hematoma expansion can help select patients, who will benefit from hemostatic treatment.

**Keywords:** intracranial hemorrhage, cerebral hemorrhage, cerebral angiography, X-ray computed tomography, transcranial ultrasonography

## BACKGROUND

Early intervention is today a growing concept in the treatment of stroke patients. Patients arrive in the hospital early after the onset of stroke symptoms as a consequence of treatment options in ischemic stroke. Due to the ultra-early work-up, patients with intracerebral hemorrhages (ICH) will often be diagnosed quickly after symptom onset. ICH presents in general as devastating strokes, and patients are often prone to poor outcome. This is due to the stroke *per se* and the lack of treatment concepts proven to be effective in randomized clinical trials. Recently, both surgical intervention (1) and hemostatic therapy (2) have failed to improve the functional outcome.

As ICH is diagnosed increasingly early, post-admission hematoma expansion will become a more frequent observation. Post-admission hematoma expansion contributes to the clinical instability of the patients, but at the same time it might be a promising target for interventions to limit final hematoma volume, save brain tissue – and improve functional outcome. Thus, being able to predict and dynamically observe post-admission hematoma expansion is of paramount clinical importance. In recent years, several radiological concepts to predict post-admission hematoma expansion have been identified. In this review, we summarize radiological predictors of hematoma expansion in patients with ICH. We further review new imaging concepts in dynamical observation of post-admission hematoma expansion.

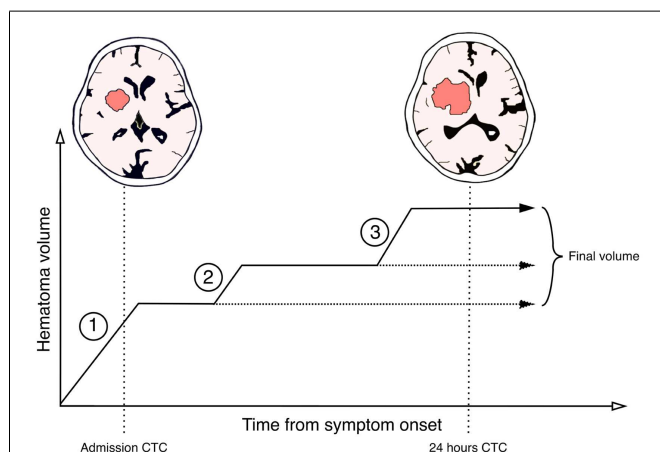
## POST-ADMISSION HEMATOMA EXPANSION

Post-admission hematoma expansion is defined as enlargement of the hematoma volume between the admission imaging procedure and a later imaging procedure. A variety of definitions of significant hematoma expansion have been proposed based on both relative (e.g., 33%) and absolute (e.g., 6 or 12.5 mL) hematoma volume increase. No convincing evidence exists as to which of these definitions best discriminate patients prone to poor functional outcome and all definitions yield equally low sensitivity (3). However, a trend might exist toward definitions based on absolute expansion being slightly more clinically meaningful in terms of outcome compared to definitions based on relative expansion (3).

Studies to determine the time interval of which post-admission hematoma expansion occur have been limited by the fact that serial radiological examinations in order to estimate the hematoma volume are hard to perform in an unstable patient-group and would potentially expose the patients to unacceptable amounts of ionizing radiation. Consequently, most published studies are limited by few prospective measurements or imprecise retrospective methodology. Studies indicate that post-admission hematoma expansion can be observed in up to 40% of patients admitted in an acute fashion (3). In a prospective study conducted on patients admitted within 3 h after symptom onset Brott et al. reported that 26% suffered hematoma expansion within the first

hour after admission and additional 12% suffered expansion within the following 23 h (4). Ovesen et al. reported in another prospective study that active expansion could be observed within the first 8 h after symptom onset in the group of patients, who on 24 h follow-up CT-scan presented a final clinically relevant hematoma expansion ( $>12.5$  mL) (5). Even though the vast majority of the hematoma expansion is observed to occur in the first hours after stroke onset, evidence also indicates that it is possible for hematoma expansion to take place later on and up to 24 h (6, 7). This supports the hypothesis that hematoma expansion (Figure 1) is a dynamic process with intermitting bleeding episodes caused by not only the originally ruptured vessel, but also by secondary rupture of adjacent vessels exposed to pressure and ischemia inflicted by the hematoma mass-effect (8). The secondary vessel rupture in the rim of the hematoma might explain that hematoma expansion does not happen symmetrically around the surface of the hematoma, but is located non-uniformly (9). Further, the secondary vessel rupture and intermitting bleeding episodes might also be the cause of the apparent plateau-phases with constant hematoma volume between active expansion episodes (5).

Post-admission hematoma expansion has been independently associated with early neurological deterioration (4, 10), poor functional outcome, and mortality (11, 12). An almost linear association between hematoma expansion and the probability of poor outcome has been reported – with 1 mL additional expansion yielding a 5% increased risk of death and dependency (12).



**FIGURE 1 | Suggested schematic model for a step-wise hematoma expansion-profile in intracerebral hemorrhages.** Phase 1 represents the initial active bleeding-period most likely caused by the originally ruptured vessel. If patients are admitted within this phase an active hemorrhage will still be occurring post-admission and instant expansion can be observed. After phase 1 a plateau-phase might exist in which the hematoma volume is constant or active bleeding occurs slowly. In some patients, this phase might represent the final hematoma volume (horizontal stippled line). Phase 2 represents a secondary bleeding-period. This is likely due to secondary vessel rupture caused by pressure and ischemia on adjacent tissue structures or by re-bleeding from the originally ruptured vessel. Some patients might have multiple secondary bleeding-periods and some even late (phase 3). Between these periods are interpolated plateau-phases with relative constant hematoma volume or slow active bleeding. This results in the final hematoma volume observed on follow-up imaging.

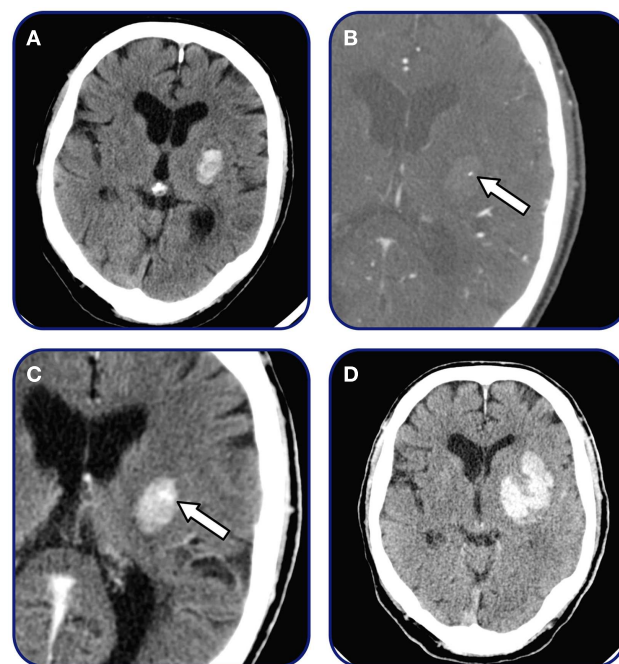
## COMPUTED TOMOGRAPHY ANGIOGRAPHY

Post-admission hematoma expansion occurs due to leakage of blood into an existing hematoma cavity. As previously discussed, this process represents an on-going or intermittingly on-going active bleeding process. Consequently, the ability to visualize this process of on-going bleeding could provide us with excellent prediction of hematoma expansion. It is an alluring thought that this active bleeding process could be visualized using radiographic contrast-agents, because leakage from surrounding vessels would be represented by pooling of contrast-material inside the hematoma. The concept of contrast-leakage into the hematoma in acute ICH-patients undergoing angiography dates back more than 40 years (13). It was originally observed that patients arriving earlier in the hospital more often demonstrated contrast-leakage. In recent years, much attention has been placed on the possibility of visualizing contrast-leakage using computed tomography angiography (CTA).

## CONTRAST-LEAKAGE ON CT-IMAGING

Traditionally, two interrelated marker of contrast-leakage have been defined: the spot sign on CTA source images or maximum intensity projections and pooling of contrast (contrast extravasation) in the hematoma (Figure 2).

One of the first studies on contrast extravasation in patients with spontaneous ICH using CTA was presented by Murai et al. (14) in 1999. The study looked at extravasation of contrast on 3D-CTA images and concluded that extravasation was linked



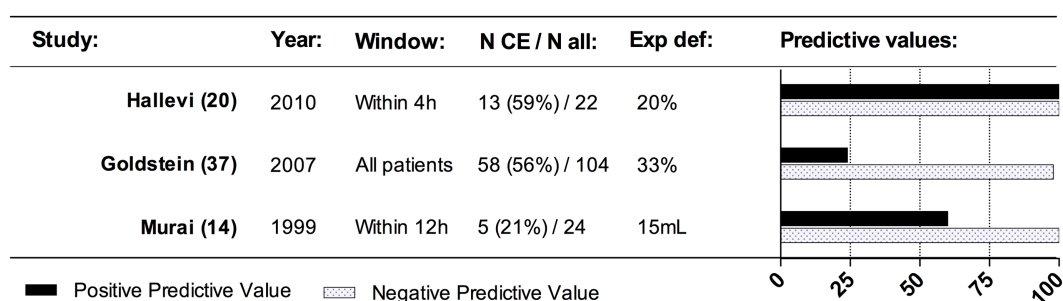
**FIGURE 2 | Spot sign and contrast extravasation.** Patient admitted within 2 h after symptom onset. (A) Initial non-contrast CT demonstrating small basal-ganglia hemorrhage, (B) CTA source image demonstrating single spot sign (arrow), (C) 3-min post-contrast CT-imaging demonstrating contrast extravasation (arrow), and (D) 24 h follow-up CT revealing final hematoma volume.

to hematoma expansion. Other studies have later supported this claim, and excellent negative predictive value in predicting hematoma expansion is indicated across studies performed (Figure 3). The concept of contrast extravasation in general refers to all manners of contrast-leakage into the hematoma. However, in more recent studies, the concept of contrast extravasation refers only to pooling of contrast in the hematoma on post-contrast CT-imaging following CTA (15). In this review, contrast-leakage will be used as an umbrella term for both contrast extravasation and the spot sign.

Wada et al. (16) was the first to describe small enhancing foci on CTA source images – the spot sign – and its ability to predict

hematoma expansion. Ever since, many other studies have focused on the spot sign as a promising biomarker to predict hematoma expansion. Among studies, slightly different definitions of the spot sign have been used, however, many studies use definitions similar to the one proposed by Wada et al.: “one or more, 1–2 mm foci of enhancement within the hematoma on CTA source images” or as proposed by Delgado Almandoz et al. (17): (i)  $1 \geq$  focus of contrast pooling within the ICH; (ii) with an attenuation  $\geq 120$  Hounsfield units; (iii) discontinuous from normal or abnormal vasculature adjacent to the ICH; and (iv) of any size and morphology.

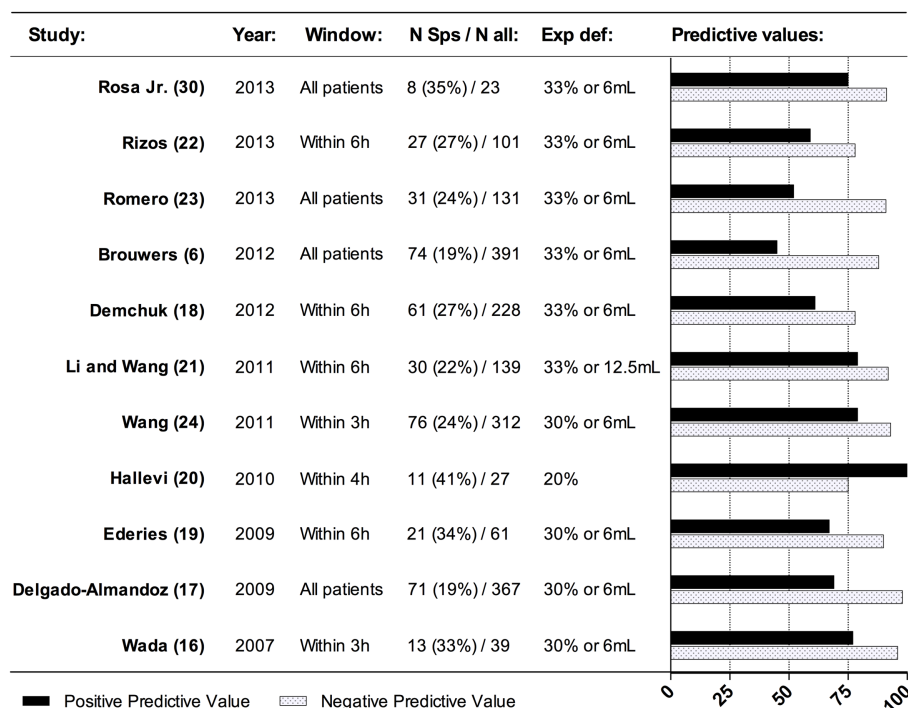
The overall prevalence of the spot sign varies among studies from 19 to 41% (6, 16–24) (Figure 4). This reflects the differences



**FIGURE 3 | Effect of contrast extravasation on hematoma expansion.**

This figure presents the predictive values across studies for contrast extravasation to predict hematoma expansion. The predictive values indicated the independent effect of contrast extravasation and

not the effect of contrast extravasation in addition to spot sign – please see text. N CE, number of patients with contrast extravasation; N all, total number of patients in the population; exp def, definition of hematoma expansion.



**FIGURE 4 | Effect of spot sign on hematoma expansion.** This figure presents the predictive values across studies for spot sign in predicting hematoma expansion. N Sps, number of patients with spot sign; N all, total number of patients in the population; exp def, definition of hematoma expansion.

in the definition used, different scan protocols and the time-window utilized. In patients arriving within 3 h, the prevalence is reported to be as high as 43–60% (6, 17) dropping down to 11% in patients presenting beyond 6 h after onset (6). This is in good accordance with the proposed temporal profile of post-admission hematoma expansion, because it indicates that the majority of expansion happens within the first hours. The spot sign has been shown to be associated with larger hematoma admission volume (17, 18, 22, 25), higher admission National Institute of Health Stroke Scale (NIHSS) value (18), and hypertension on admission (17, 22). Whether use of vitamin-K antagonists and antiplatelet medication is associated with a higher prevalence of the spot sign, varies between study-results (17, 18, 22). It has been observed that the contrast-phase, in which CTA images were acquired, plays a role in the prevalence of the spot sign. The prevalence of the spot sign was highest in the late venous phase. This might reflect the time required for contrast to accumulate in the hematoma (26).

Across studies, the inter-observer agreement for identifying the spot sign is in general reported to range between good and moderate ( $\kappa = 0.60$ – $0.85$ ) (16, 21, 22). In the PREDICT-study, it was observed that even though no definition for the spot sign was selected at the beginning of the study, the agreement in identifying the spot sign between site-investigators and the final expert-adjudication was substantial ( $\kappa = 0.72$ ) (18). Huynh et al. (27) presented a study regarding the accuracy of 131 readers to recognize the spot sign, and it was found that physicians in general showed a good specificity (96%), however, the sensitivity was smaller (78%). This might be due to incorrect perception of spot sign mimic. The study further shows that the identification of spot sign proceeded quickly (27). The spot sign must consequently be seen as a relatively easily recognizable biomarker. However, physicians' ability to recognize it can be improved by simple learning programs (28). This adds greatly to the every-day clinical usefulness of the spot sign in acute ICH-patients.

The spot sign has been proven to be a valid biomarker of hematoma expansion, possibly because of its representation of foci of active bleeding (29). The spot sign in general yields a relatively high negative predictive value (NPV: 0.75–0.98) along with slightly lower positive predictive value (PPV: 0.45–1.00) toward hematoma expansion (Figure 4) (6, 16–24, 30). Sensitivity and specificity are reported to be 0.46–0.91 and 0.84–1.00, respectively (6, 16–24). This is true, even though studies report patients included in different time intervals after ictus. Brouwers et al. (6) found that the positive and negative predictive value remained relatively constant in patients admitted 0–3, 3–6, and >6 h after symptom onset. This indicates the overall ability of the spot sign to predict hematoma expansion across various time-windows. Differences in imaging protocols might also affect the ability of the spot sign to predict hematoma expansion. Spot sign observed in the peak arterial contrast-phase might entail a larger absolute hematoma expansion volume compared to spot sign observed in later venous phases (26). The effect of the spot sign on hematoma expansion is observed to be independent from other predictors of hematoma expansion – especially vitamin-K antagonist use and hematoma volume (16–18, 22) even through the factors might complement each other. In a recently proposed prognostic score, time to initial

CT-scan, initial hematoma-size, CTA spot sign, and pre-stroke warfarin treatment were included in order to enable a better stratification of patients with regard to the likelihood of post-admission hematoma expansion (31).

Different amendments to the spot sign have been proposed to increase its ability to identify patients prone to hematoma expansion. Besides the spot sign observed on CTA source images, delayed post-contrast sequences have been utilized to visualize contrast extravasation. Two small studies indicate that the presence of both spot sign and post-contrast extravasation increases the likelihood of hematoma expansion compared to the spot sign alone (19, 20). Another related add-on to the spot sign is the so-called tail-sign (32). The tail-sign is observed originating from the M1 segment of the middle cerebral artery on coronal CTA images in patients with a basal-ganglia hemorrhage and is thought to represent active bleeding from the striate arteries. Only a single smaller study has elaborated the tail-sign, and additional work is needed to confirm its validity.

### SPOT SIGN SCORE

The spot sign score (SSS) was originally proposed by Delgado Almandoz et al. (17) in an attempt to systematically characterize the spot sign and develop a scale capable of predicting hematoma expansion better than the spot sign *per se* was able to. The resulting SSS is presented in Table 1. In the original study, the score provided excellent discriminative capability, when it comes to hematoma expansion (AUC-ROC 0.93 CI: 0.89–0.95), and the risk of hematoma expansion (>30% or 6 mL) increased from 2% in the group with a SSS of 0 to 100% in patients with a SSS of four. Patients with spot sign on admission that arrived in hospital earlier in general presented with a higher SSS compared to patients, who arrived later. The authors later demonstrated that the SSS independently predicts in-hospital mortality and 3 months outcome in an almost linear manner (when increasing from SSS 0 to 4, in-hospital mortality increased from 24 to 75% – and mean 90 days mRS from 3.2 to mRS 5.4) (33).

Other studies have confirmed the independent capability of SSS to predict hematoma expansion (21, 23, 34), mortality, and poor outcome (21, 23) along with the almost linear increase in risk of poor functional outcome with increasing SSS (23). However, not all studies have confirmed that SSS contained superior predictive

**Table 1 | Spot sign score.**

Spot sign characteristics	Points
Number of spot signs	
1–2	1
≥3	2
Maximal axial dimension	
1–4 mm	0
≥5 mm	1
Maximum attenuation	
120–179 HU	0
≥180 HU	1

Replicated from Delgado Almandoz et al. (17).



capabilities of discriminating patients prone to hematoma expansion and poor outcome compared to the spot sign *per se* (21, 34). This might suggest that much of the predictive capability of the SSS is contained within the demonstration of the spot sign. This was emphasized in a *post hoc* analysis from the PREDICT-study revealing no differences between the discriminative capability toward hematoma expansion of the number of spot signs demonstrated and the SSS (34). It was further demonstrated that the risk of hematoma expansion did not increase significantly with increasing SSS. In contrast to this, the risk of hematoma expansion increased significantly with increasing number of spot signs present. The authors speculate that the reason for these differences is that the attenuation of the spot sign – which was proven to have good discriminative ability, when it comes to hematoma expansion in single center studies – might vary between different CT-scanner manufactures along with differences in contrast administration protocol (34).

All in all, the SSS would – if proven valid – provide a better prediction of hematoma expansion useful in clinical decision-making and clinical trials, but so far, the general validity is questionable. However, due to the relative complexity of obtaining the score compared to the spot sign *per se* or number of spot signs, it might represent a less relevant tool in every-day clinical practice and outside clinical trials.

#### RELATIONSHIP BETWEEN CONTRAST-LEAKAGE AND OUTCOME

Both the spot sign and contrast extravasation have been shown to be associated with poor outcome. The predictive values are presented in **Table 2** for in-hospital mortality, 90 days mortality and 90 days functional outcome.

The presence of contrast-leakage on admission is associated with short-term clinical outcome (**Table 2**). It has been shown that the presence of spot sign on admission CTA is linked to neurological deterioration within the first 24 h after symptom onset (18, 35). Across studies, a clear trend toward high negative predictive values of in-hospital mortality was identified, however, with relatively modest or poor positive predictive values (16, 21–23, 33, 36, 37). All in all, the absence of contrast extravasation or spot sign indicates an overall increased stability of the patient during the acute phase of illness. This might be an important observation, as it appears that the difference in mortality between spot sign positive and negative patients manifests during the initial days after symptom onset. After the initial period, the mortality-rate appears to become even between the two groups (18, 38).

The absence of the spot sign in general is associated with good negative predictive values, when it comes to 3 months mortality (18, 21, 22). The spot sign independently increases the probability of long-term fatality (18, 21, 38) and poor functional outcome 3 months after admission in most studies (21, 23, 33, 38). The patients with spot sign in general present a higher 3-month modified Rankin scale score compared to patients without – indicating poorer functional rehabilitation outcome (18, 38). However, in a recent prospective study, this association could not be replicated (22). This finding could represent local variations in treatment and rehabilitation efforts.

#### NON-CONTRAST COMPUTED TOMOGRAPHY

Non-contrast computed tomography (NC-CT) remains the radiological investigation of choice conducted, when stroke patients are admitted for fibrinolysis work-up. Simple and broadly validated predictors of post-admission hematoma expansion observed on NC-CT are therefore essential, because this can potentially predict clinical instability and poor long-term functional outcome.

#### HEMATOMA-SIZE

For a long period of time, the initial admission hematoma volume has been recognized as a major determinant of outcome in patients with acute ICH. In a classic study elaborated by Broderick et al. (39), it was demonstrated that the 30-day mortality in patients with basal-ganglia hemorrhage and a volume above 60 mL was as high as 93% dropping down to 23% for volumes below 30 mL. A similar pattern was observed for patients with lobar hemorrhages.

Other studies have replicated these findings and added other measurements of outcome to the predictive capability of the initial hematoma volume (e.g., in-hospital mortality (40), functional outcome and mortality (40–44), long-term survival (45)), and initial hematoma volume features in most clinical grading scores concerning ICH-patients (46). Hematoma volume and clinical neurological status score on admission (Glasgow Coma Scale, NIHSS, or Canadian Stroke Scale) in general compete for being among the most powerful predictors of outcome.

In the context of acute demonstration of ICH, the natural questions to be raised are: (1) what volume is the most predictive – the early volume with possible on-going hemorrhage or the final hematoma volume? (2) Is it safe to assume that a patient, who arrives early in the hospital and demonstrates a small hematoma volume, is clinically stable and prone to good outcome? (3) What can the hematoma volume tell us about the expansion-potential of the patient?

In an analysis from the VISTA-database (47) on patients presenting with ICH within 6 h after ictus, it was demonstrated that patients with an initial hematoma volume below 20 mL were significantly less likely to undergo hematoma expansion compared to a hematoma volume above 30 mL (using the 12.5 mL expansion-definition). The observation that smaller hematomas are more stable is supported by data from the Recombinant Activated Factor VII ICH Trial (48, 49) along with other individual publications (50, 51). In addition to a decreased rate of post-admission hematoma expansion, smaller hematomas are in general associated with a lower likelihood of early neurological deterioration – and thus a more stable acute course of illness (35, 47, 52).

In a most interesting study elaborated by Rodriguez-Luna et al. (35), the hematoma volume was divided by the time from ictus to admission, yielding an ultra-early hematoma growth pace. It was demonstrated that a higher growth pace was independently associated with the occurrence of post-admission hematoma expansion, early neurological deterioration and poor long-term functional outcome. The discriminative capability of hematoma growth pace was better compared to absolute volume on admission toward early neurological deterioration and poor long-term functional outcome. This method could potentially solve some of the previously proposed uncertainties on the predictive value of hematoma

**Table 2 | Effect of contrast-leakage in predicting outcome.**

	Design	Extravasation sign	No. contrast-leakage positive (%)	Total number participating	Time-frame	Outcome	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
<b>In-hospital mortality</b>										
Becker et al. (36)	Retrospective	Contrast extravasation	52 (46)	113	All patients	Hospital fatality	77	73	63	84
Goldstein et al. (37)	Retrospective	Contrast extravasation	58 (56)	104	All patients	Hospital fatality	73	50	33	85
Wada et al. (16)	Retrospective	Spot sign	13 (33)	39	All patients	Hospital fatality	43	69	23	85
Delgado Almandoz et al. (33)	Retrospective	Spot sign	133 (23)	573	All patients	Hospital fatality	41	85	56	76
Li and Wang et al. (21)	Prospective	Spot sign	30 (22)	139	Within 6 h	Hospital fatality	60	81	20	96
Romero et al. (23)	Prospective	Spot sign	31 (24)	131	All patients	Hospital fatality	68	88	61	91
Rizos et al. (22)	Prospective	Spot sign	27 (27)	101	Within 6 h	Hospital fatality	47	77	26	89
<b>90-days mortality</b>										
Li and Wang et al. (21)	Prospective	Spot sign	30 (22)	139	Within 6 h	Case fatality	50	82	27	93
Demchuk et al. (18)	Prospective	Spot sign	53 (25)	211	Within 6 h	Case fatality	43	81	43	80
Rizos et al. (22)	Prospective	Spot sign	27 (27)	101	Within 6 h	Case fatality	29	74	26	77
<b>90-days outcome</b>										
Delgado-Almandoz et al. (33)	Retrospective	Spot sign	133 (23)	573	All patients	mRS > 3 <sup>a</sup>	23	89	51	70
Li and Wang et al. (21)	Prospective	Spot sign	30 (22)	139	Within 6 h	mRS > 2	36	94	87	58
Romero et al. (23)	Prospective	Spot sign	31 (24)	131	Within 24 h	mRS > 3 <sup>a</sup>	34	94	90	50
Havsteen and Ovesen et al. (38)	Prospective	Spot sign	37 (29)	128	Within 4.5 h	mRS > 4	60	86	68	81

<sup>a</sup>Based on the surviving patients at 3 months.

volumes in patients with early presentation due to possible on-going hemorrhage, and the method needs validation in broader populations.

### INTRAVENTRICULAR HEMORRHAGIC EXTENSION

Intraventricular hemorrhagic extension is a frequent finding in patients admitted with acute ICH. In patients admitted earlier than 3 h after symptom onset, intraventricular hemorrhagic extension (IVH) is present in 31–48% (22, 35, 38, 53, 54), but delayed IVH can be detected, on follow-up imaging, in up to 20% (53, 54) of the patients without IVH on admission. This is a consequence of post-admission hematoma expansion decompressing into the low resistance ventricular system.

The anatomical location of the intracerebral hematoma is an important determinant for the probability of IVH. Hematomas located in the thalamus or the caudate nucleus will more often extend into the ventricular system due to the proximity (53–57) compared to lobar hematomas. Hallevi et al. (56) calculated for each anatomical position a volume range (decompression range), below which IVH was very unlikely, however, if ICH volume grew above this range, IVH was very likely. This range was very narrow for hematomas located in the thalamus (7.0–12.7 mL) and pons (4.3–11.2 mL) but considerably wider for lobar hematomas (15.4–70.7 mL). This implicates that if a patient with thalamic or pontine hemorrhage without IVH is admitted early after symptom onset or display radiological predictors of active bleeding on admission CT, later re-scan should be considered due to a high probability of delayed IVH. The decompression ranges might also explain the fact that patients with IVH in general present significantly higher admission hematoma volumes compared to patients without (54, 57).

Whether the presence of IVH is associated with hematoma expansion is controversial. Most studies do not find an association between hematoma expansion and IVH, however, one study has shown that lenticular and lobar hematomas with accompanying IVH displayed a higher proportion of hematoma expansion (54). This could be explained by the fact that the expansion-potential is high in a non-periventricular hematoma, if it is able to break through to the ventricles. This finding needs validation in further studies.

Intraventricular hemorrhagic extension may be viewed as a separate hematoma, and expansion of the intraventricular blood volume can occasionally be observed. Steiner et al. (57) reported that 12% of patients with initial IVH suffered enlargement of the IVH volume between baseline and follow-up scan. This expansion was associated with higher baseline ICH hematoma volume, elevated blood-pressure and short time from symptom onset to admission scan. Expansion of the IVH volume was independently associated with poor functional outcome and death.

Intraventricular hemorrhagic extension is reported to be independently associated with both early (<48 h after onset) (10, 35, 58) and late (48 h–1 week after onset) (59) neurological deterioration. There is a high load of evidence indicating that the presence of IVH is independently related to poor clinical outcome and mortality (43, 45, 60–62) mainly due to the obstruction of cerebrospinal fluid flow and hydrocephalus (55, 63), but also by other mechanisms. The association with mortality

and poor outcome is likely related to the severity of the IVH volume (57, 61, 64).

### HEMATOMA HETEROGENICITY (SWIRL-SIGN) AND IRREGULARITY

It is a frequent observation that patients with ICH present hematomas in various shapes and with heterogeneous attenuation on NC-CT. It has for a long period of time been a puzzling hypothesis that this could potentially predict the risk of post-admission hematoma expansion due to the fact that this may signify on-going bleeding.

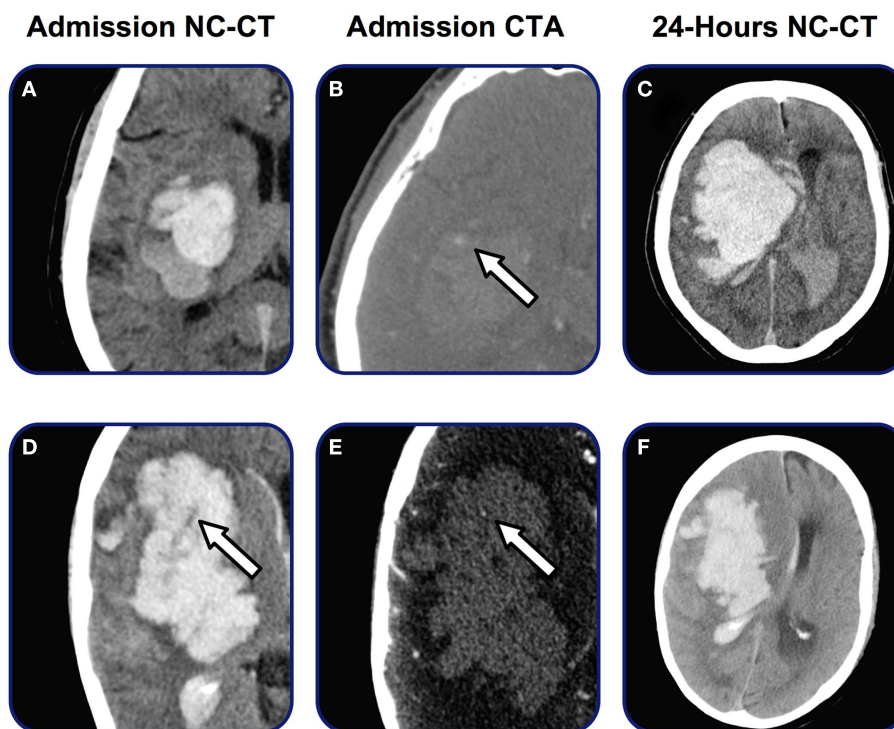
The observation that a heterogenic attenuation of the hematoma on NC-CT represents on-going bleeding originally descends from observations of patients with epidural hematomas (65). It was observed that the finding of a zone of hypoattenuation within the hyperattenuated hematoma – the so-called “Swirl-sign” – correlated to active bleeding (66). The theory that the swirl-sign could represent on-going bleeding was founded on early studies using computed tomography techniques demonstrating that coagulated and retracted blood-clots appear hyperattenuated compared to normal brain tissue. When blood coagulates, it expels low-density serum leaving behind a high concentration of red blood cells – and thus the globin-protein responsible for the high attenuation (67). Consequently, if a hematoma contains a mixture of coagulated (hyperattenuation) and uncoagulated blood (hypo- or isoattenuation), it appears heterogenic on a NC-CT.

A number of studies have applied the same principle on patients with acute ICH. Definitions of a heterogeneous attenuation (swirl-sign) (Figure 5) vary between studies, however, a clinically relevant and potentially every-day useful definition proposed by Selariu et al. yielded good intra- and inter-observer agreement: swirl-sign was defined as regions of hypoattenuation or isoattenuation (compared to the attenuation of surrounding brain-parenchyma) within the hyperattenuated ICH (68).

A study elaborated by Barras et al. on patients included on the placebo arm of the Recombinant Activated Factor VII ICH Trial reported that hypoattenuated foci on the admission scan independently predicted some definitions of hematoma expansion, even after adjustment for other predictors of hematoma expansion (48). Additional studies have later confirmed this observation (51, 69). The presence of heterogeneity is further linked to mortality and poor functional outcome (68).

It has been shown that patients arriving in the hospital early have a higher probability of presenting a heterogeneous attenuation of the hematoma. This fits well with the observations of the timing of post-admission hematoma expansion. In one study, the prevalence dropped from 36% in patients arriving within 2 h to 13% in patients arriving later than 24 h after symptom onset (68). The relationship between the swirl-sign and the spot sign would be of pathophysiological and clinical interest and remains to be investigated.

Another proposed marker of active bleeding is irregular shape of the hematoma. The hypothesis behind this observation is that the irregularity could result from multiple leaking vessels feeding the hematoma and hence a higher probability of hematoma expansion (70). Even though the observation that irregularity of the hematoma shape should facilitate hematoma expansion is validated in a large study elaborated by Fujii et al. (71), other studies



**FIGURE 5 | Heterogeneity on admission NC-CT.** Admission and follow-up radiology on two patients admitted with acute ICH. NC-CT (**A,D**) demonstrates marked heterogenic attenuation in hematoma appearance. Arrow on (**D**) marks swirl-sign. On (**B,E**) both patients present spot sign. After 24 h (**C,F**) both patients present enlargement of the hematoma volume and midline shift.

have not been able to confirm this finding – thus making irregular shaping of the hematoma an uncertain predictor of hematoma expansion (48, 51, 69).

### FOLLOW-UP IMAGING IN PATIENTS WITH INTRACEREBRAL HEMORRHAGE

In relation to the substantial amount of patients undergoing post-admission hematoma expansion and the trend toward shorter interval between symptom onset and admission imaging, the need for follow-up imaging after the acute phase of illness becomes more crucial (72). In general, follow-up NC-CT 24 h post-admission is implemented in many centers to evaluate the final hematoma volume, midline shift, the presence of intraventricular or subarachnoid extension of the hemorrhage, and edema formation. NC-CT is in general viewed as the gold standard, when it comes to demonstrating and measuring the volume of ICH. However, CT is limited by the utility of ionizing radiation making it unsuitable for serial assessments of the hematoma volume. In addition, the patients have to leave the stroke wards in most centers in order to undergo CT-studies.

In recent years, the concept of transcranial duplex sonography (TCDS) has become available to dynamically follow the progression of the intracerebral hematoma on B-mode ultrasound images. The examination is performed through the trans-temporal bone window (Figure 6). On B-mode images, the hematoma is visualized as a hyperechogenic structure compared to surrounding brain-parenchyma. The hematoma is often visualized through the

contralateral bone window in reference to the hematoma location (73) (Figure 7). The volume of the hematoma is obtained by measuring the sagittal, transversal, and coronal diameter of the hematoma and then calculating the volume using the standard formula:  $ABC/2$  (74, 75) (Figure 7). Studies indicate that TCDS is able to identify ICH with good sensitivity (73, 75–79). TCDS is also able to estimate the diameters of the hematoma with systematic deviation close to zero (75, 76) and good volume estimation compared to CT (75–77). Studies further indicate that TCDS is useful in following hematoma expansion (75) and demonstrating the presence of IVH (73, 77). In patients with hematomas that are difficult to visualize on TCDS, the administration of ultrasound contrast might improve precision of the estimated volume (78).

Midline shift can also dynamically be followed using TCDS by measuring the distance from the transducer to the third ventricle bilaterally (77, 80, 81). The third ventricle is normally easily recognized on TCDS (Figure 7). By adding Doppler flow studies of the intracranial vessels, TCDS might also be able to estimate intracranial pressure (82, 83), however, additional work needs to examine this in greater detail.

The major limitation to TCDS in patients with ICH is that not all patients present with trans-temporal acoustical bone windows sufficient to allow penetration of diagnostic ultrasound waves. The proportion of the study populations without an acoustical window varies from 7 to 56% in studies on ICH-patients, even though most studies report approximately 20% failure-rate (73, 75, 76, 78, 81, 83). The most notorious predictors of lack of an acoustical window

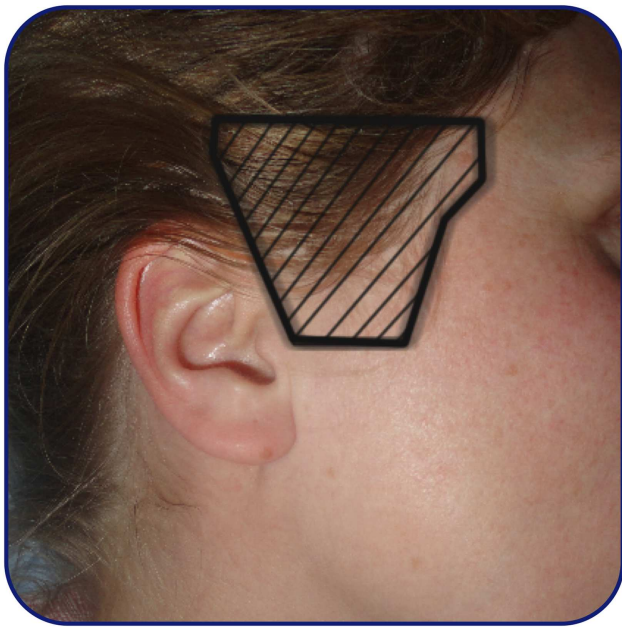
are gender (women in general present poorer acoustical windows), increasing age, and thickness of skull (84, 85). In addition, people of Asian descent in general present with a higher prevalence of inadequate trans-temporal acoustical bone windows compared

to Caucasians (76, 84). TCDS is further limited by the anatomical location of the hematoma. Volume estimation of hematomas located either high cortical or infratentorial can be troublesome due to its position in relation to the trans-temporal bone window (73, 75, 77).

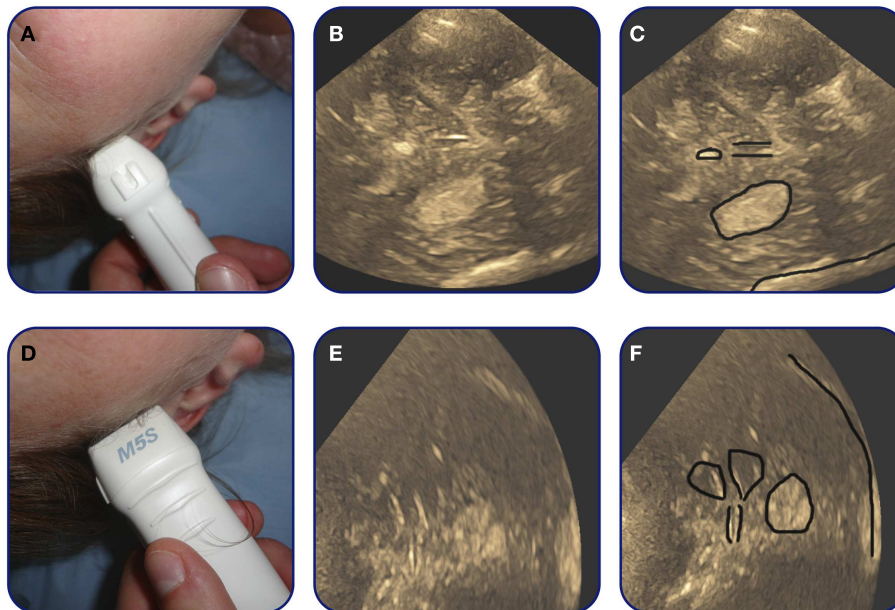
Even with the presented limitations, evidence suggests the usefulness of TCDS in patients with ICH as an add-on to the consecutive clinical surveillance during the acute phase of illness.

## CONCLUSION

Post-admission hematoma expansion in patients with ICH contributes to the clinical deterioration, but may also contain an attractive target for early intervention. CTA for the purpose of evaluating underlying vascular pathology and presence or absence of the spot sign should be considered in all acute ICH-patients. The spot sign has been shown to be a promising biomarker of post-admission hematoma expansion with good predictive capability. In patients with contraindications to CTA predictors of on-going hemorrhage are available for NC-CT. The presence of spot sign, swirl-sign, IVH, or a large hematoma on admission scan marks the patient as potentially clinical unstable and as subject for intensified clinical observation and follow-up imaging. Predictors of hematoma expansion also contain prognostic information toward long-term functional outcome and mortality. TCDS provides a new method to consecutively monitor the development of the hematoma bedside. On-going and future studies will elucidate, if selection of patients for hemostatic therapy based on radiological predictors of post-admission hematoma expansion will finally provide us with an effective treatment-offer for patients with ICH.



**FIGURE 6 | Trans-temporal ultrasound window.** Approximate location of the trans-temporal ultrasound window.



**FIGURE 7 | Transcranial duplex sonography-images of basal-ganglia hemorrhage.** A patient with basal-ganglia ICH. On axial images (A,B) the hematoma can be observed as a hyperechogenic region in the middle of the picture. The rim of the hematoma is marked

by black on (C). In addition on (C) the location of important midline landmark structures as the pineal gland and the third ventricle are marked. (D,E) Are coronal images. On (F) the lateral ventricles, the third ventricle, and the hematoma is marked.



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