European Heart Journal (2016) **37**, 3081–3089
doi:10.1093/eurheartj/ehv521

REVIEW

Frontiers in cardiovascular medicine

Catheter-based interventions for acute ischaemic stroke

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Received 4 August 2015; revised 31 August 2015; accepted 14 September 2015; online publish-ahead-of-print 1 October 2015

Catheter-based interventions for acute ischaemic stroke currently include clot removal (usually from the medial cerebral artery) with modern stent-retrievers and in one of five patients (who have simultaneous or stand-alone internal carotid occlusion) also extracranial carotid intervention. Several recently published randomized trials clearly demonstrated superiority of catheter-based interventions (with or without bridging thrombolysis) over best medical therapy alone. The healthcare systems should adopt the new strategies for acute stroke treatment (including fast track to interventional lab) to offer the benefits to all suitable acute stroke patients.

Keywords Acute stroke • Catheter intervention • Thrombectomy • Stent-retriever • Neurologic outcome

Introduction

Acute stroke is one of the leading causes of death worldwide. Over 85% of acute strokes are caused by cerebral ischaemia and <15% by intracranial bleeding. Among the ischaemic strokes not all are suitable for intervention. Only strokes with a large vessel occlusion (~30–40% of all strokes) should be considered. Acute regional ischaemia with progressive necrosis is developing quickly during the initial hours after arterial thromboembolic occlusion in acute ischaemic stroke. Restoration of antegrade blood flow in the acutely occluded artery (i.e. reperfusion of the ischaemic tissue) is the most effective therapy. Timely reperfusion halts the progress of necrosis and preserves viable tissue (cerebral penumbra). The pathophysiology of cerebral infarction is different from myocardial infarction. While myocardial infarction is caused by plaque rupture and *in situ* thrombosis, acute ischaemic stroke is usually caused by embolization from the heart, aorta, or carotid arteries with thromboembolus typically wedged in the medial cerebral artery. There are many similarities, but also many differences between these two potentially fatal diseases.[1]

Evolution of endovascular treatment

The first attempts to treat acute stroke by intravenous thrombolysis were reported in 1976.[2] The first small randomized trial showing potential benefits of thrombolysis when used early in acute stroke was published in 1992[3] and in 1995 the first positive randomized trial of thrombolysis was published.[4] The first official guidelines recommending thrombolysis for acute stroke were published in 2003.[5] Thrombolytic therapy administered within 6 hours after ischaemic stroke onset significantly reduced the proportion of dead or dependent patients (odds ratio, OR, 0.85, 95% CI 0.78–0.93) at the price of increased risk of symptomatic intracranial haemorrhage (OR 3.75, 95% CI 3.11–4.51) and early death (OR 1.69, 95% CI 1.44–1.98). Early death after thrombolysis was mostly attributable to intracranial haemorrhage. Treatment within 3 h of stroke was more effective in reducing death or dependency (OR 0.66, 95% CI 0.56–0.79) without any increase in death. Contemporaneous other antithrombotic drugs increased the risk of death. Participants aged over 80 years benefited equally to those aged under 80 years, particularly if treated within 3 h of stroke.[6]

Intra-arterial thrombolysis—despite its use in interventional practice—was never shown to be clinically superior to best medical care[7,8] and is not approved by FDA.

Direct mechanical reperfusion using catheter-based thrombectomy *without* thrombolysis was first used in 2001[9] and then emerged in the hands of radiologists and neurosurgeons. The first interventional cardiologist reporting experience with acute stroke intervention was Abelson in 2008.[10] Both reperfusion strategies (thrombolysis and catheter-based intervention) are frequently used together and such

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therapy is usually called bridging thrombolysis.[11] The complication rates (device fractures, vessel perforations, new territory embolization, etc.) with the old-generation coil-retrievers were high (7–19%) and the revascularization rates achieved were only moderate.[12–14] The improved technology (specifically the introduction of modern stent-retrievers) significantly improved the results of catheter-based interventions for acute stroke.[15,16] The latest published official guidelines[17] did not yet recognize direct mechanical intervention as the accepted routine therapy for acute stroke. However, this is currently changing: while novel guidelines are being prepared, the European Stroke Organization issued a press release 'Mechanical thrombectomy improves outcomes in acute ischaemic stroke' (http://www.eso-stroke.org/eso-stroke/strokeinformation/press-releases/20-february-2015.html).

Why trials published before 2014 failed to demonstrate the benefit from interventions?

The first three major randomized trials comparing endovascular treatment of acute stroke vs. intravenous thrombolysis were published in March 2013.[18–20] Their results were disappointing due to several important limitations: low (1–13% in different trials) use of stent-retrievers, the absence of treatable arterial occlusion (no pre-intervention vascular imaging) in a significant proportion of patients, long time delays, low number of patients treated per centre per year, etc. (*Table 1*).

2015: The year of change. Why recent trials provided clear evidence favouring interventional treatment?

The recent trials using new-generation stent-retrievers, pre-procedural vascular imaging, and implementing much better design and logistics leading to shortening of time delays[21–25] have demonstrated very clear benefit of catheter-based interventions. Most of these trials used intravenous thrombolysis (whenever indicated) in both study arms and enrolled also thrombolysis ineligible patients, confirming thus superiority of catheter-based interventions + optimal medical therapy over optimal medical therapy alone which might included thrombolysis whenever indicated (*Table 2*).

Current techniques for intracranial and carotid interventions

The following terminology is used in this manuscript: catheter-based interventions (all types of mechanical interventions for acute stroke), catheter-based thrombectomy (specific procedure for clot removal using stent-retrievers and/or aspiration catheters), balloon dilatation, and carotid artery stenting.

The current techniques of catheter-based intervention for acute stroke use guiding catheters (frequently with distal-tip balloons for proximal protection during thrombus retrieval), microcatheters with 0.010″ or 0.014″ guidewires (for selective cannulation of the occluded artery), distal aspiration (distal access) catheters with extremely soft tip (for direct thrombus aspiration), stent-retrievers (for immediate flow restoration and thrombus retrieval), small-size dilatation balloons (for rather rare intracranial stenosis dilatation), carotid dilatation balloons (for internal carotid dilatation—some operators prefer this approach in the acute phase of stroke rather than acute carotid stenting), distal protection devices (during carotid interventions—however, its role in acute stroke setting is not well established), carotid stents (some operators prefer acute carotid stenting over balloon dilatation alone when stroke is caused by extracranial carotid occlusion), coronary stents (in very rare situations of extracranial lesions—e.g. vertebral artery stenosis). Intracranial stenting should be avoided whenever possible. Examples of angiographic findings during acute stroke interventions are in *Figures 1–3*.

The role of imaging in selection of patients for intervention

Recanalization of an occluded artery in acute ischaemic stroke may save patient life and return his/her neurologic functions (when performed early in the course of stroke), but it can also led to intracranial bleeding, progression of neurologic dysfunction and death (when performed too late). The critical period for clinically meaningful and safe recanalization varies from 2 to 3 h in patients with limited collateral flow to >8 h (and in rare cases usually in young patients even over 24 h) in patients with better collaterals. The most important variable is the ratio between penumbra (reversible ischaemia) and ischaemic core (irreversible ischaemia). The size of penumbra is determined by collateral flow and the status of capillaries,[26] by localization and completeness of arterial occlusion and other variables. It is of utmost importance to know the ratio penumbra/ischaemic core prior to the reperfusion treatment (thrombolysis, catheter-based mechanical intervention, or both combined). The possible approaches vary from relatively simple Alberta Stroke Program Early CT score (ASPECTS) to sophisticated methods of quantitative perfusion CT imaging or magnetic resonance diffusion weighted imaging (MRI DWI). The details of these methods are beyond the scope of this article. The key principles are: (i) CT imaging should be followed by intervention as soon as possible, otherwise its conclusion may not be valid anymore at the time of delayed intervention (the ischaemic core may become larger and penumbra smaller during the interval between CT and intervention), (ii) Penumbra imaging is less important in very early presenters (e.g. symptom onset—CT time <2 h) due to the fact that significant penumbra is present in most of them and every minute of time delay (due to sophisticated imaging or interpretation of its results) is extremely critical in these patients (in other words: quick simple CT scan can be sufficient in very early presenters), and (iii) penumbra imaging is critically important in late presenters—it may indicate the intervention in some (usually younger) patients in whom the long (e.g. >6 h) time delay from symptom onset would otherwise lead to conservative therapy (*Figure 4*).

However, penumbra imaging has definite limitations: inherent time delay (performing and interpreting perfusion imaging delays

Table 1 Negative randomized trials comparing endovascular intervention (± thrombolysis) vs. intravenous thrombolysis alone

	IMS III	MR rescue	Synthesis
Baseline			
Total number of patients enrolled	656	118	362
Mean number of enrolled patients per centre per year	2.0	0.8	3.6
Median age	69	65	66
Minimal baseline NIHSS allowed	8	6	2
Median NIHSS at baseline	17	17	13
Confirmation of major artery occlusion by CT-/MR-angiography	No	Yes	No
Penumbra imaging used for patient selection	No	Partly	No
i.v. thrombolysis use in the intervention arm	100%	37%	0%
Time delays			
Time delay as entry criterion	tPA given within <3 h	Enrolment within <8 h	Enrolment within <4.5 h
Stroke onset—tPA start time	122 min		165 min
Stroke onset—reperfusion time in the group with intervention	5.4 h	7 h	3.8 h
Treatment			
Periprocedural anticoagulants/antiplatelets	Heparin 2000 U i.v., followed by 450 U/h during intervention		Heparin 5000 U i.v., followed by 500 U/h during intervention
Stent-retrievers use (intervention group)	1%	0%	12.7%
Procedural complications		26.5%	
Outcomes			
Reperfusion (TICI Grade 2b or 3)	43%	44%	
Favourable neurologic outcome (mRs 0–2 at 90 days) in the intervention group	41%	19%	42%
Favourable neurologic outcome (mRs 0–2 at 90 days) in the i.v. thrombolysis group	39%	20%	46%
Symptomatic intracerebral haemorrhage (intervention group)	6.2%	4.7%	5.5%
Subarachnoid haemorrhage	11.5%		
Asymptomatic intracerebral haemorrhage (intervention group)	27.4%	65.6%	
Early mortality (7 days) in the intervention group	12%		8%
Late mortality (90 days) in the intervention group	19.1%	19%	14.4%

the intervention by ~30 min), difficulties in clear-cut separation between penumbra and ischaemic core, difficulties to distinguish true penumbra from benign oligaemia, etc.

The importance of time

The role of time delay from stroke onset to recanalization is even more critical in acute stroke than in acute myocardial infarction. On the other hand, the rate of necrosis progression in acute stroke is more variable due to variability of collateral flow. One extreme may be a young patient with very good collaterals, who could recover after thrombectomy performed even after 24 h from stroke onset, while the other extreme may be an elderly patient with limited reserve, in whom an angiographically successful thrombectomy done within 2 h after symptom onset may be futile (no neurologic recovery). Nevertheless, the positive results were obtained in the five trials with short onset to recanalization times (median times <6 h). Studies showing the best outcomes were those with the shorter onset recanalization times.

There are several ways how to minimize the delays related to healthcare system: 'double alert system' (preliminary cath-lab alert immediately when a potential stroke patient is on his way to the hospital, followed by a confirmatory cath-lab alert after neurologic examination and brain imaging), bypassing emergency room (direct emergency medical service (EMS) transfer to CT suite in patients with high clinical suspicion for stroke), avoiding sophisticated imaging (CT perfusion or MRI) in early presenters with suitable CT scan or CT angiogram, bypassing intensive care unit (direct transfer from CT suite to cath-lab), short distance from CT to cath-lab. Future technologic improvements could help—e.g. mobile stroke units, rotational flat panel CT angiograms, etc.

However, most delays are patient related. Thus, ongoing public information campaigns about acute stroke symptoms and importance of time are critically important, too.

Table 2 **Positive randomized trials comparing endovascular intervention (± thrombolysis) vs. intravenous thrombolysis (or conservative therapy if thrombolysis contraindicated) alone**

	MR clean	Escape	Extend-IA	Swift prime	Revascat
Baseline					
Total number of patients enrolled	500	315	70	195	206
Mean number of enrolled patients per centre per year	9.6	17.3	3.1	2.5	26
Median age	65	71	68.6	65	66.4
Minimal baseline NIHSS allowed	2	6	No specific limit	8	6
Median NIHSS at baseline	17	16	15	17	17
Confirmation of major artery occlusion by CT-/MR-angiography	Yes	Yes	Yes	Yes	Yes
Penumbra imaging used for patient selection	No	No	Yes (CT perfusion in all points)	Yes (in 81% points)	ASPECTS
i.v. thrombolysis use in the intervention arm	Yes (in 87.1% points)	Yes (in 72.7% points)	Yes (in all points)	Yes (in all points)	Yes (in 68% points)
Number of patients treated by direct intervention (without i.v. thrombolysis)	≤30	≤45	0	0	≤33
Time delays					
Time delay from stroke onset as entry criterion	<6 h to CBI start	<12 h to randomization	6 h	6 h	8 h
Stroke onset—tPA/CBI start time	4.3 h	3.1 h	3.5 h	224 min	269 min
Stroke onset—reperfusion time in the group with intervention	5.5 h	241 min	4.1 h	248 min	355 min
Treatment					
Periprocedural anticoagulants/antiplatelets					
Stent-retrievers use (intervention group)	81%	86.1%	100%	89%	95%
Carotid stenting in the acute phase	12.9%				18.6%
Procedural complications	11.2%	2.4%	11.4%	7.1%	13.7%
General anaesthesia use	37.8%	9.1%	36%	37%	
Outcomes					
Reperfusion (TICI Grade 2b or 3)	58.7%	72.4%	86%	88%	65.7%
Favourable neurologic outcome (mRs 0–2 at 90 days) in the intervention group	32.6%	53%	71.4%	60.2%	43.7%
Favourable neurologic outcome (mRs 0–2 at 90 days) in the i.v. thrombolysis group	19.1%	29.3%	40%	35.3%	28.2%
Symptomatic intracerebral haemorrhage (intervention group)	7.7%	3.6%	5.7%	1%	1.9%
Subarachnoid haemorrhage	0.9%			4.1%	4.9%
Asymptomatic intracerebral haemorrhage (intervention group)				5.1%	16.5%
Early mortality (7 days) in the intervention group	11.6%				9.7%
Late mortality (90 days) in the intervention group	18.9% (30 days)	10.4%	8.6%	9.2%	18.4%

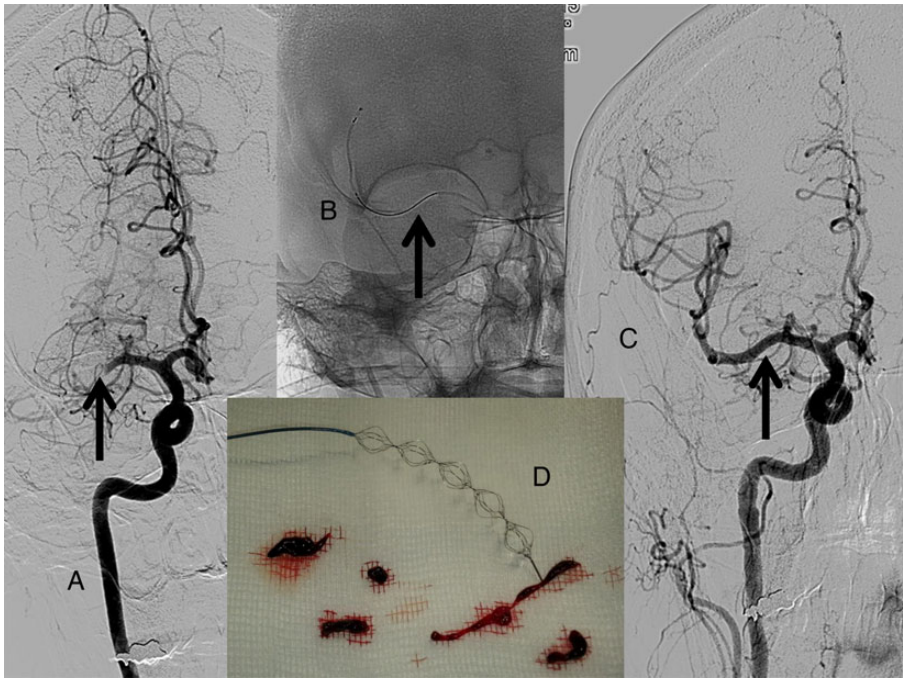

Figure 1 Catheter-based thrombectomy in acute anterior stroke. (*A*) Middle cerebral artery occlusion (arrow) at presentation, (*B*) positioning of the stent-retriever (arrow point to the occlusion site), (*C*) final result after thrombectomy (arrow points to the previously occluded site; note the absence of any underlying stenosis after thrombus extraction), (*D*) fragmented thrombus and the retriever. Patient neurological status normalized.

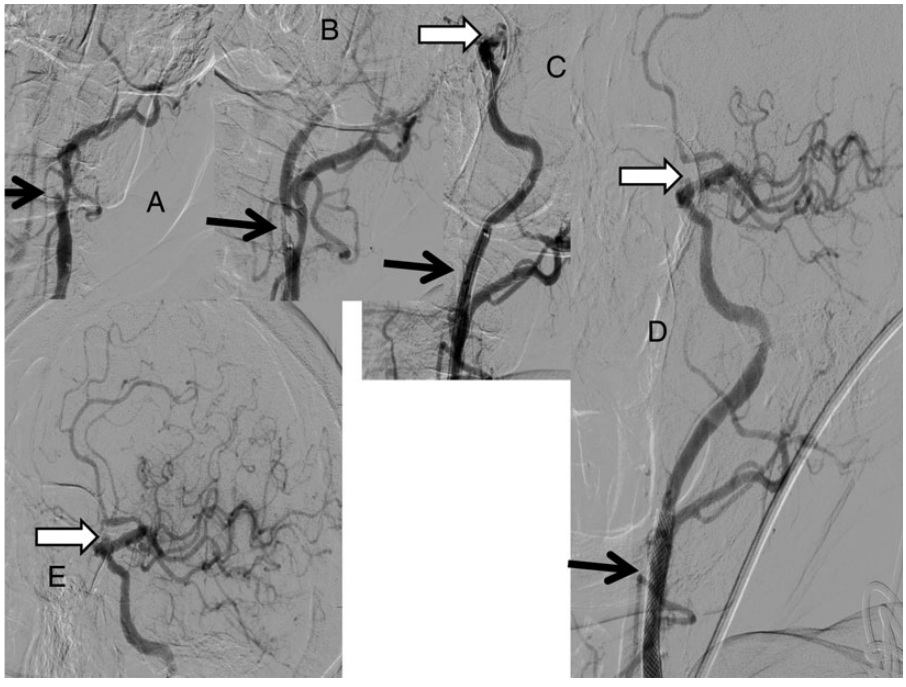

Figure 2 Severe acute anterior stroke due to a tandem occlusion (proximal internal carotid artery occlusion marked with black arrows and distal carotid T-occlusion marked with white arrows). (*A*) Proximal internal carotid artery occlusion, only external carotid artery visualized, (*B*) proximal internal carotid artery faint recanalization after guide wire passage, (*C*) stent placed in proximal internal carotid artery, distal internal carotid artery T-occlusion now fully visualized, (*D* and *E*) complete recanalization after thrombus removal with stent-retriever. Patient improved to final mRS of 2.

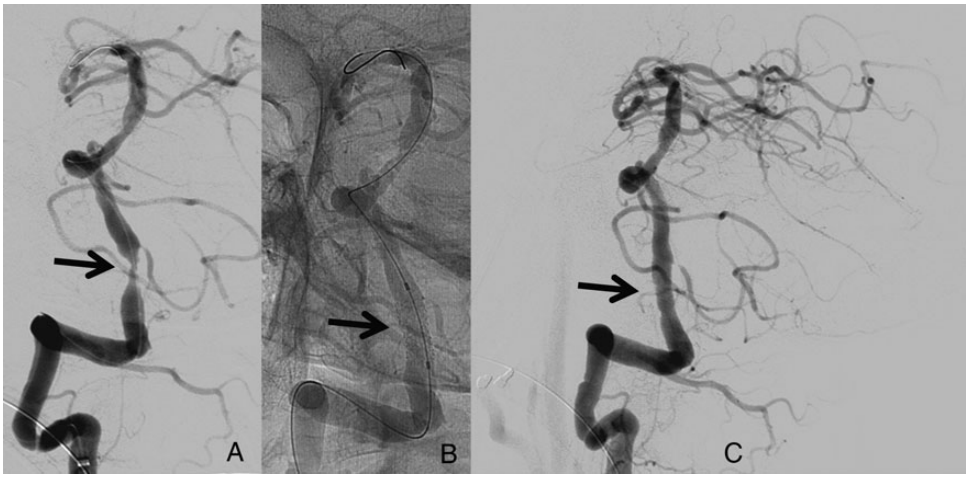

Figure 3 Progressive, stuttering, and posterior stroke. (*A*) Unstable lesion in a large (dominant) vertebral artery with ostial stenosis of the posterior inferior cerebellar artery at the distal end of vertebral artery lesion, (*B*) coronary stent placement with the aim not to cover posterior inferior cerebellar artery ostium, (C) final result—good on vertebral artery, posterior inferior cerebellar artery remained open. Patient neurological status normalized within 24 h.

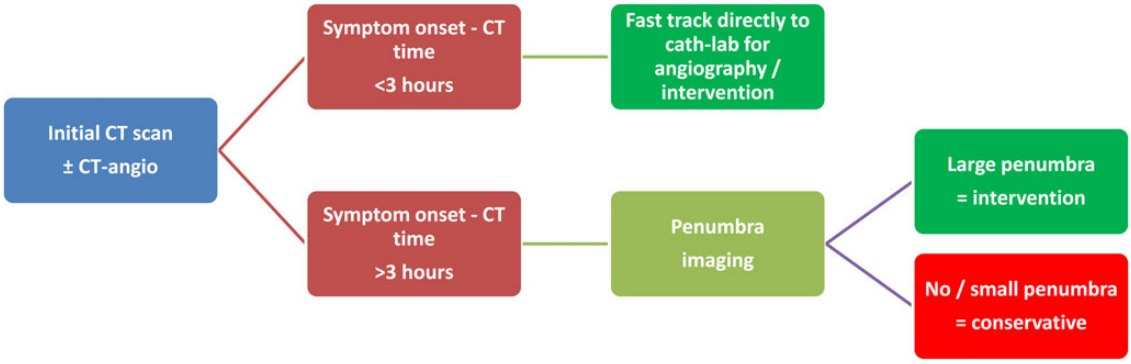

Figure 4 Possible role of penumbra imaging in the decision-making process (for details see the text). This is a suggested possibility, which should be further explored. This figure applies only to <30% of acute stroke patients, in whom intervention might be considered. In majority of strokes, intervention is not indicated due to a different stroke cause (haemorrhagic stroke, lacunar stroke, etc.).

Logistics and workflow

Acute ischaemic stroke should be treated as super-emergency, i.e. similar or even faster than acute myocardial infarction or acute traumatic external bleeding. The suggested optimal logistics and sequence of steps is described in *Figure 5*.

Unresolved questions

The recently published trials and the widespread enthusiasm in favour of acute stroke interventions open many questions, which still wait to be answered:

(1) What is the optimal periprocedural antithrombotic medication? How small dose of antithrombotics is safe to prevent catheter clotting and how big dose of antithrombotics is safe to prevent intracranial bleeding?[27] Possible algorithm for periprocedural antithrombotic therapy is suggested in *Table 3*.

(2) What is the role of thrombolysis in patients who can proceed to angio suite immediately after CT imaging and intervention can start within 30–45 min after CT? Direct catheter-based intervention (without thrombolysis) is used more and more in this situation in many centres despite it is not included in the guidelines. Is such approach right or wrong?

(3) The role of long distance transport: can acute stroke patients transferred for long distances to comprehensive stroke centres derive a real benefit?[28]

(4) Is intubation and general anaesthesia harmful for acute stroke patients and should most interventions be done without general anaesthesia?[29]

(5) What is the role of carotid stenting in acute phase of ischaemic stroke?[30] How should tandem [internal carotid artery

Figure 5 Optimal workflow in acute ischaemic stroke. Direct transfers EMS-to-CT (skipping emergency room) and CT-to-cath-lab (skipping ICU) save ~1 h time! This figure applies only to <30% of acute stroke patients, in whom intervention might be considered. In majority of strokes intervention is not indicated due to a different stroke cause (haemorrhagic stroke, lacunar stroke, etc.).

Table 3 Possible (empirical) algorithm for periprocedural (in-hospital early phase) antithrombotic therapy

	Bridging i.v. thrombolysis	No thrombolysis
No permanent stenting	Periprocedural heparin 0–25 U/kg Aspirin 100 mg/day starting after control CT (within 24 h)	Periprocedural heparin 25–40 U/kg Aspirin 100 mg/day starting after control CT (within 24 h)
Stent implanted in acute phase	Periprocedural heparin 20–30 U/kg Aspirin 200–300 mg just prior to stent implantation, followed by 100 mg/day Clopidogrel 75 mg/day starting after control CT (within 24 h)	Periprocedural heparin 25–40 U/kg Aspirin 200–300 mg just prior to stent implantation, followed by 100 mg/day Clopidogrel 75 mg/day starting after control CT (within 24 h)
Deferred stent implantation	Periprocedural heparin 25–40 U/kg Aspirin 200–300 mg just prior to stent implantation, followed by 100 mg/day Clopidogrel 75 mg/day starting just after stenting	Periprocedural heparin 25–40 U/kg Aspirin 200–300 mg just prior to stent implantation, followed by 100 mg/day Clopidogrel 75 mg/day starting just after stenting

(ICA) + MCA] lesions be treated ? Acute carotid stenting may increase the risk of distal embolization, but its main limitation is the risk of early stent thrombosis. Stent implanted to a thrombus-containing lesion with minimal heparin dose (as full heparin dose in acute stroke increases the risk of intracranial bleeding) and without clopidogrel (P2Y12 inhibitors are usually recommended only 24 h later after control CT excludes secondary bleeding into the ischaemic core), just with aspirin onboard (and usually given just shortly before stent implantation) presents a real risk for early stent thrombosis, what

Table 4 Main angiographic findings and currently used treatment algorithms

Angiographic finding	Typical underlying cause	Interventional technique
MCA occlusion	Thromboembolus (cardioembolic)	Thrombectomy with stent-retriever
Terminal (intracranial) ICA ('T') occlusion	Thromboembolus (cardioembolic)	Thrombectomy with stent-retriever or with distal access aspiration catheter
Extracranial ICA occlusion or >90% stenosis	Atherothrombosis	Balloon dilatation with deferred stenting a few days later (acute phase carotid stenting only as bailout) to postpone dual antiplatelet therapy if possible
Tandem lesion (ICA + MCA)	Atherothrombosis with distal embolization of thrombus fragment	Ballooning ICA + thrombectomy MCA
Intracranial stenosis (stand-alone or residual after thrombectomy)	Atherothrombosis	Balloon dilatation (do not oversize!), avoid stenting unless bailout stent necessary
BA occlusion or subtotal thrombosis	Atherothrombosis	Thrombectomy with stent-retriever
VA occlusion or critical stenosis	Atherothrombosis	Balloon dilatation (or coronary stent?)

MCA, middle cerebral artery; ICA, internal carotid artery; BA, basilar artery; VA, vertebral artery.

may destroy the initial benefit gained by reperfusion. Some centres are moving towards 'deferred stenting strategy': acute ICA occlusion (or critical stenosis) in the acute phase of stroke is treated only by balloon dilatation to allow restoration of flow and access to any possible intracranial emboli in MCA and stent is implanted few days later when bleeding is absent and clopidogrel can be allowed before stenting. Suggested algorithm for interventions is in *Table 4*.

(6) What is better for the patients: fast track to angio suite with simple imaging (CT/computed tomographic angiography) or sophisticated penumbra imaging (MRI or perfusion CT) with inherent delay?

Implications for healthcare systems

The published data suggest that the healthcare systems have to implement acute stroke interventions as integral part of care for patients with this deadly disease.[17,31–33] In principle, there are two ways how to build the system: (i) Highly selective centralized system (comprehensive stroke centres for regions with >1 million citizens or more) including sophisticated penumbra imaging to select patients with the highest likelihood for clinical success of catheter-based interventions or (ii) less selective and partly decentralized system (stroke centres for regions with 0.3–0.5 million citizens—similar density to primary PCI centres for STEMI) with more simple pre-procedural imaging, but with potential to decrease the total ischaemic times by ~1 h or even more (no transport to distant comprehensive stroke centre, no sophisticated imaging). The first option will result in significantly fewer patients treated with significantly better results. The second option will offer this treatment to almost all acute stroke patients at the price of less excellent results.

Another important question is which specialists should perform interventions. The involved specializations include mostly interventional radiologists, but in some areas other specialists are involved: neurosurgeons in the USA, interventional angiologists in Germany and Switzerland, sometimes vascular surgeons, and rarely interventional neurologists or interventional cardiologists. The formal specialization is not important. The involved physicians performing acute stroke interventions should fulfil certain basic requirements: knowledge of acute stroke pathophysiology and of neurovascular anatomy, knowledge of specific problems related to antithrombotic drugs during acute stroke, regular practice in invasive catheter procedures other than just acute strokes, experience with carotid stenting, and of course training in specific acute stroke interventional techniques.

The role of vascular neurologists and the stroke units following the procedures remains an important integral part of patient care, but is beyond the scope of this review article.

Thus, acute stroke interventional treatment is a fascinating, quickly developing field with new publications occurring almost every week. A comprehensive review[34] and a recent meta-analysis[35] being just two examples. There is a reasonable light at the end of the tunnel for most patients with acute ischaemic stroke presenting early to developed healthcare systems.

Authors' contributions

P.W. and L.N.H. drafted the manuscript. P.W. and L.N.H. made critical revision of the manuscript for key intellectual content.

Funding

Funding to pay the Open Access publication charges for this article was provided by the Charles University Prague, research program P35.

Conflict of interest: none declared.

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