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REVIEW

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Reperfusion therapy of acute ischaemic stroke and acute myocardial infarction: similarities and differences

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The evolution of reperfusion therapy in acute myocardial infarction and acute ischaemic stroke has many *similarities*: thrombolysis is superior to placebo, intra-arterial thrombolysis is not superior to intravenous (i.v.), facilitated intervention is of questionable value, and direct mechanical recanalization without thrombolysis is proven (myocardial infarction) or promising (stroke) to be superior to thrombolysis—but only when started with no or minimal delay. However, there are also substantial *differences*. Direct catheter-based thrombectomy in acute ischaemic stroke is more difficult than primary angioplasty (in ST-elevation myocardial infarction [STEMI]) in many ways: complex pre-intervention diagnostic workup, shorter time window for clinically effective reperfusion, need for an emergent multidisciplinary approach from the first medical contact, vessel tortuosity, vessel fragility, no evidence available about dosage and combination of peri-procedural antithrombotic drugs, risk of intracranial bleeding, unclear respective roles of thrombolysis and mechanical intervention, lower number of suitable patients, and thus longer learning curves of the staff. Thus, starting acute stroke interventional programme requires a lot of learning, discipline, and humility. Randomized trials comparing different reperfusion strategies provided similar results in acute ischaemic stroke as in STEMI. Thus, it might be expected that also a future randomized trial comparing direct (primary) catheter-based thrombectomy vs. i.v. thrombolysis could show superiority of the mechanical intervention if it would be initiated without delay. Such randomized trial is needed to define the role of mechanical intervention alone in acute stroke treatment.

Keywords Myocardial infarction • Acute stroke • Reperfusion • Thrombolysis • Primary angioplasty • Catheter intervention • Thrombectomy

Introduction

Acute regional ischaemia with progressive necrosis developing quickly during the initial hours after arterial thrombotic occlusion is a common feature of acute myocardial infarction and acute ischaemic stroke. Both these diseases are leading causes of death worldwide. Restoration of antegrade blood flow in the acutely occluded artery (i.e. reperfusion of the ischaemic tissue) is the most effective therapy in both situations (*Figures 1* and *2*). Timely reperfusion halts the progress of necrosis and preserves viable tissue (myocardium in jeopardy or cerebral penumbra).

The pathophysiology of cerebral infarction is different from myocardial infarction. Whereas in myocardial infarction thrombotic arterial occlusion over the ruptured coronary plaque can be found in 90–95% of patients, acute stroke in many patients cannot be simply attributed to a cerebral vessel occlusion (e.g. lacunar cerebral infarction has completely different aetiology). The differences between these two diseases are at least as important as the similarities, and the treatment should be done by physicians having these differences in mind (*Table 1*).

Reperfusion therapy of acute myocardial infarction using thrombolytic agents was first used by Chazov *et al.*[1] in 1976 and

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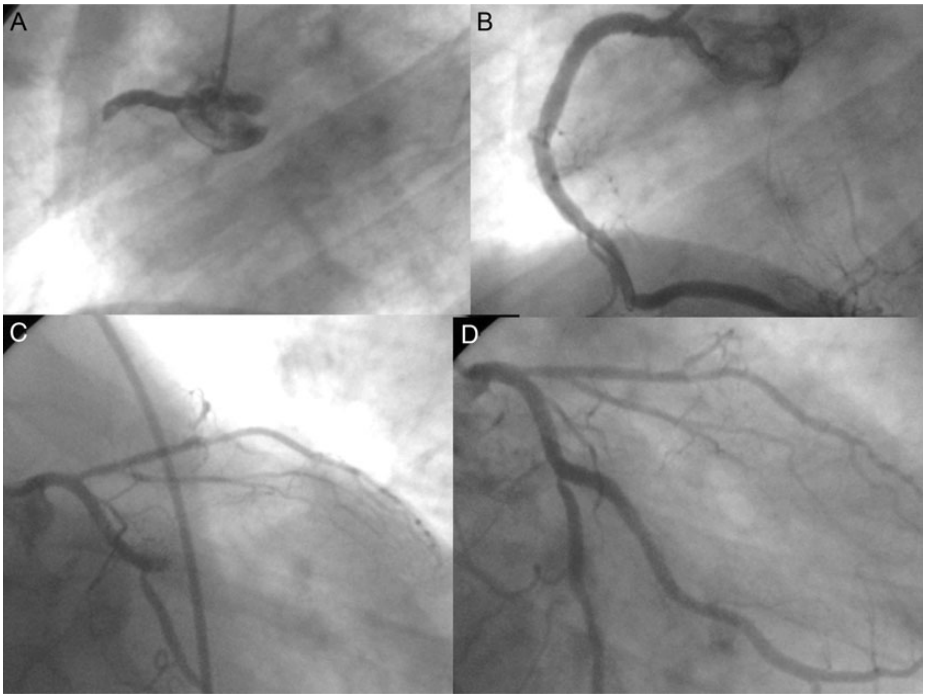

Figure 1 Coronary angiography before and after primary percutaneous coronary intervention in a patient with 'double' ST-elevation myocardial infarction [STEMI] (two acutely occluded coronary arteries). (*A*) Thrombotic occlusion of the proximal right coronary artery on admission. (*B*) Widely patent (near-normal) right coronary artery after stent implantation. (*C*) Thrombotic occlusion of the proximal obtuse marginal branch on admission. (*D*) Widely patent (near-normal) obtuse marginal branch after stent implantation.

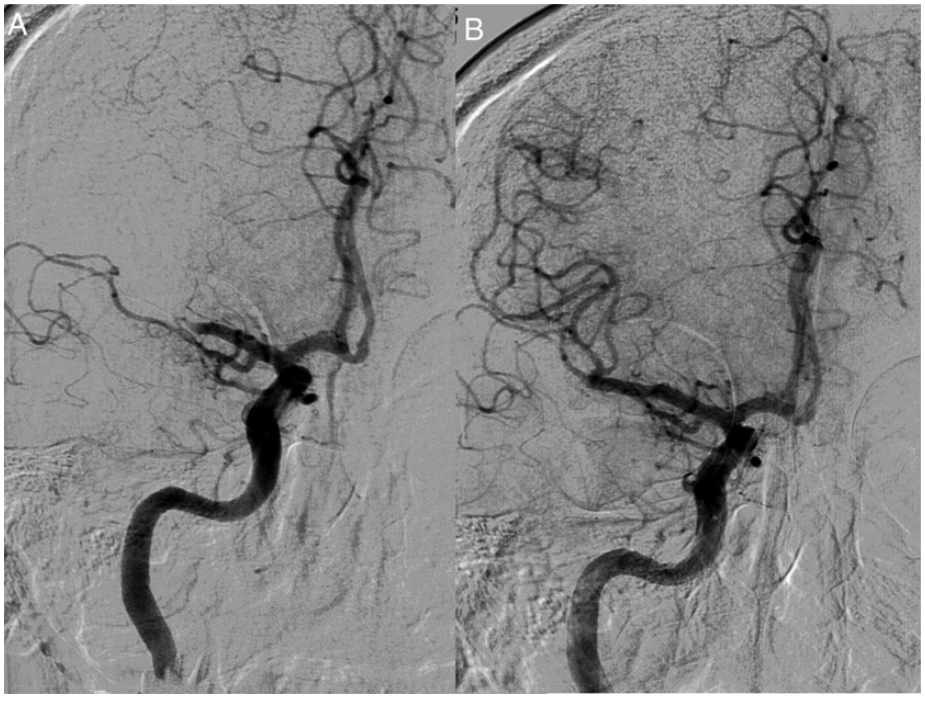

Figure 2 Carotid angiography before and after catheter-based thrombectomy in acute anterior circulation stroke. (*A*) Thrombotic occlusion of the middle cerebral artery on admission. (*B*) Widely patent (near-normal) middle cerebral artery after catheter-based thrombectomy.

Table 1 Similarities and differences between acute myocardial infarction and acute stroke

	Acute myocardial infarction	Acute ischaemic stroke
Similarities		
Pathophysiology	Arterial occlusion + ischaemic necrosis in nearly all cases	Arterial occlusion + ischaemic necrosis in only half of the cases
Clinical picture	Acute onset	Acute onset
Prognosis	High mortality (if untreated by reperfusion)	High mortality and permanent disability
Effective treatment	Reperfusion therapy	Reperfusion therapy
Differences		
Aetiology	Uniform: plaque rupture + thrombosis *in situ* in 90–95%	Multifactorial: cardioembolic, arterioembolic, thrombosis *in situ*, lacunar, cryptogenic
Arterial occlusive thrombus feasible for catheter-based intervention	Found in 90–95% of acute coronary angiograms	Found only in ~40–50% of acute CT-angiograms
Time window symptom onset—intervention start (to offer benefit and not harm)	24 h (48 h in some patients)	3 h (8 h in some patients)
Reperfusion damage	Only theoretically, clinically is reperfusion beneficial	Reperfusion damage (parenchymal bleeding) is a real clinical problem
Clinical picture	Pain (dyspnoea) alerts most patients to call early for help	Neurological dysfunction and absence of pain frequently results in late medical contact
Diagnostic method before reperfusion therapy indication	ECG (fast, simple, cheap, at the site of first medical contact)	CT (takes more time, expensive, in-hospital)
Laboratory diagnostic marker	Troponin (although not needed for the initial decision in ST-elevation myocardial infarction)	Not yet available
Contraindications for catheter-based intervention	None	Intracranial bleeding or advanced ischaemia on CT
Percentage of hospitalized patients who undergo reperfusion therapy in well-functioning health care systems	>90%	<10%

was introduced into broad clinical practice 10 years later after the publication of the pivotal randomized clinical trials GISSI[2] and ISIS-2.[3] Mechanical recanalization by means of primary angioplasty was first used by Meyer *et al.*[4] and Hartzler *et al.*[5] The first three randomized clinical trials showing superiority of primary PTCA over thrombolysis in ST-elevation myocardial infarction [STEMI] were published by Zijlstra *et al.*,[6] Grines *et al.*,[7] and Gibbons *et al.*[8] in 1993. It took another 9 years before the Czech Society of Cardiology published the world's first official guidelines recommending primary angioplasty as the first-choice therapy for STEMI.[9]

The history of reperfusion therapy in acute ischaemic stroke is even more complicated. The first attempts to treat acute stroke by thrombolysis were reported in 1976.[10] The first small randomized trial showing potential benefits of thrombolysis when used early in acute stroke was published in 1992,[11] and in 1995 the first positive randomized trial of thrombolysis was published.[12] The first official guidelines recommending thrombolysis for acute stroke were published in 2003.[13] Direct mechanical reperfusion using catheter-based thrombectomy *without* thrombolysis was first used in 2001,[14] and there is yet no randomized trial completed to date comparing mechanical reperfusion (without thrombolysis) vs. intravenous (i.v.) thrombolysis. Thus, the latest official guidelines[15] do not yet recognize direct mechanical intervention as the accepted routine therapy for acute stroke.

There is a marked difference in the use of reperfusion therapy for acute myocardial infarction and for acute ischaemic stroke. In the USA during 2009, only 4.5% of ischaemic strokes were treated by i.v. thrombolysis.[16] The situation is similar in Europe. In the Czech Republic, 4% of all hospitalized strokes are treated by thrombolysis and 0.3% by the combination of thrombolysis with mechanical intervention. On the other hand, nearly all STEMI patients are treated by primary percutaneous coronary intervention (PCI) in many European countries—e.g. the Czech Republic, The Netherlands, Sweden, Germany, Poland, and many others as was shown by the Stent for Life initiative.[17] This initiative helped to improve STEMI treatment in many European countries during the last few years.[18] In other countries (e.g. UK, Slovakia, and others) similar improvement was achieved by the joint initiative of cardiologists and local governments.

Although cardiologists succeeded to decrease the in-hospital case fatality of unselected acute myocardial infarction to current 5–8% during the last 20 years, case fatality of acute stroke in many countries remained almost unchanged. In the USA, the population mortality of stroke decreased (from #3 cause of death to #4 cause of death), and much of this improvement is attributed to care in primary stroke centres and in specialized stroke units. Thrombolysis has not been associated with reductions in case fatality due to acute ischaemic stroke. Many cardiologists worldwide (after having fully developed STEMI networks in their regions) are increasingly interested in

acute stroke treatment. The interventional treatment of acute stroke (unlike acute myocardial infarction) requires effective cooperation between several medical specialities. The leading neurologists, neurosurgeons, and neuroradiologists recognize the possibilities of effective regional STEMI networks (enabling 24/7 service for acute interventions) and are opening their minds to future cooperation with cardiologists to improve the patient access to this modern therapy. However, there remain many obstacles, including resistance of neurosciences specialists to the concept of non-neurosciences-trained physicians caring for and performing interventions on patients with stroke. These attitudes are due to typical issues such as 'turf battles', financial concerns, as well as the relatively small number of patients who may be eligible for treatment, but also important and relevant concerns regarding knowledge of cerebral physiology, anatomy, and stroke management.

Of course, this review article reflects the point of view of the authors—two cardiologists and one neurologist. The authors recognize that others might have somewhat different views. The aim of this contribution is not to give recommendations, but rather to stimulate interdisciplinary discussion.

Intravenous thrombolysis vs. conservative treatment

Many randomized clinical trials confirmed superiority of i.v. thrombolysis over placebo in STEMI when used early after symptom onset (*Figure 3*). The rate of intracranial bleeding was 0.5–1.4% in a meta-analysis.[19]

In acute stroke, one of the two most positive thrombolytic trials[12] did not show significant mortality benefit (17.3% 3-month mortality after thrombolysis vs. 20.5% mortality after placebo, $P = 0.30$), but found a significant decrease in overall unfavourable outcome (death or severe disability defined as modified Rankin Scale (mRS) > 2 was found in 57% after thrombolysis vs. 73% after placebo)—the difference caused by 13% absolute reduction in permanent disability. Symptomatic intracranial (6.4% thrombolysis vs. 0.6% placebo) as well as overall fatal (2.9% thrombolysis vs. 0.3% placebo) bleeding was significantly higher after recombinant tissue plasminogen activator (rt-PA).

The ECASS-III trial[20] enrolled 821 patients treated between 3 and 4.5 h after the onset of a stroke. Fewer patients had an unfavourable

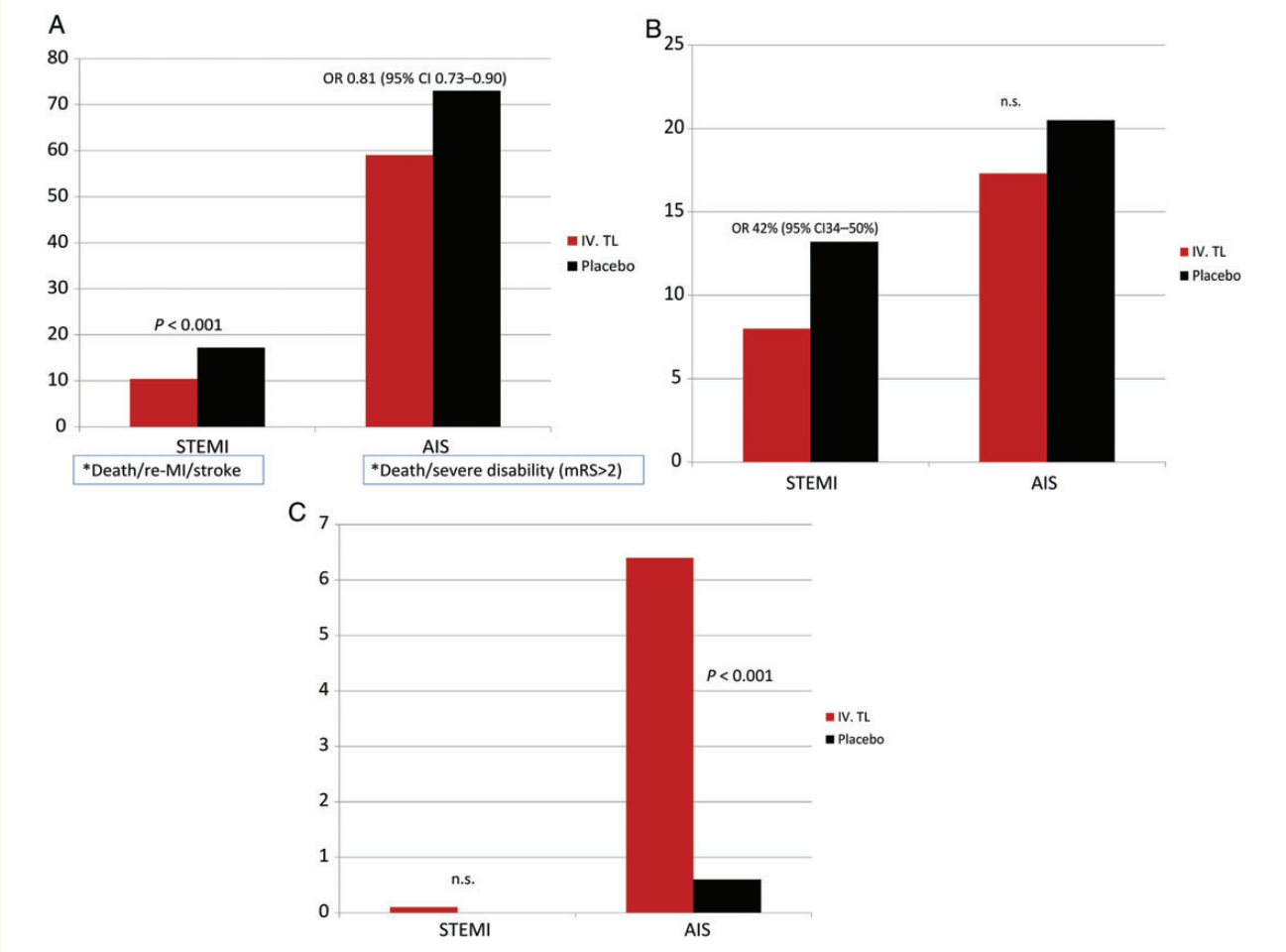

Figure 3 Comparison of intravenous thrombolysis vs. placebo in acute myocardial infarction and acute stroke. (*A*) 'Hard' clinical endpoints, i.e. death/re-infarction/stroke for STEMI patients and death/severe disability (modified Rankin Scale [mRS] > 2) for stroke patients. (*B*) All-cause mortality. (*C*) Symptomatic intracranial haemorrhage. Adopted from references 3,12, and 22.

outcome (death or severe disability) with alteplase over placebo (48 vs. 55%; $P = 0.04$). The incidence of symptomatic intracranial haemorrhage (sICH) was higher with alteplase than with placebo (2.4 vs. 0.2%; $P = 0.008$). Mortality did not differ significantly between the alteplase and placebo groups (7.7 and 8.4%, respectively; $P = 0.68$).

The Third International Stroke Trial (IST-3[21]) randomized 3035 elderly (53% were >80 years) patients with acute ischaemic stroke <6 h from symptom onset in two groups: (i) i.v. rt-PA or (ii) control treatment. Unfavourable outcome (death or disability by Oxford Handicap Score >2) at 6 months was found in 63% (rt-PA) vs. 65% (control, $P = 0.181$). Fatal or non-fatal sICH within 7 days occurred in 7% after rt-PA vs. 1% in the control group. Early mortality was 11% (rt-PA) vs. 7% (control group, $P = 0.001$)—total 6-month mortality was equal in both groups (27%).

A comprehensive meta-analysis comparing i.v. thrombolysis vs. conservative therapy for acute stroke[22] included 26 trials involving 7152 patients. Thrombolytic therapy within 6 h from symptom onset increased the risk of sICH (OR 3.49, 95% CI 2.81–4.33) and death (OR 1.31, 95% CI 1.14–1.50) at 3–6 months post-stroke. However, the proportion of patients who were dead or dependent (modified Rankin 3–6) at 3–6 months after stroke was reduced (odds ratio 0.81, 95% confidence interval 0.73–0.90). Treatment within 3 h was more effective at reducing the combined endpoint of death or dependency (OR 0.71, 95% CI 0.52–0.96) but had no effect on mortality (OR 1.13, 95% CI 0.86–1.48).

Another meta-analysis[23] included 3670 patients from eight trials using rt-PA (ECASS-III, EPITHET, and six older trials) and was focused on the time window between symptom onset and start of thrombolysis. Favourable 3-month outcome (defined as modified Rankin score 0–1) increased as time delay decreased ($P = 0.0269$) and there was no benefit of rt-PA treatment beyond 270 min. Benefit was greater the earlier patients were treated: adjusted odds of a favourable 3-month outcome were 2.55 (95% CI 1.44–4.52) for 0–90 min, 1.64 (1.12–2.40) for 91–180 min, 1.34 (1.06–1.68) for 181–270 min, and 1.22 (0.92–1.61) for 271–360 min. Large ICH occurred in 5.2% of patients assigned to alteplase and 1.0% of controls, with no relationship to time delays. However, mortality increased with time delay [$P = 0.0444$: adjusted odds were 0.78 (0.41–1.48) for 0–90 min, 1.13 (0.70–1.82) for 91–180 min, 1.22 (0.87–1.71) for 181–270 min, and 1.49 (1.00–2.21] for 271–360 min.

Thus, i.v. thrombolysis is superior to placebo for both diseases (acute myocardial infarction and acute stroke) provided it is used timely: within <12 h in STEMI (with maximum benefit within <6 h) and within <4.5 h in acute stroke (with mortality benefit only within <90 min).

Intravenous plus/vs. intra-arterial thrombolysis

Historically, thrombolysis was introduced to STEMI treatment as *intracoronary* infusion (*Figure 4*).[1,24–26] However, it was soon recognized that i.v. infusion of a fibrinolytic agent is able to achieve the same clinical benefit with the same (or even lower—due to lack of arterial punctures and lack of mechanical manipulations in a 'hypocoagulable state') bleeding risk.[27,28] The slightly higher recanalization rates (50–60%) achieved with intracoronary thrombolysis over i.v. route (40–45%) did not result in improved clinical outcomes. Thus, the intracoronary administration of thrombolytic agents was completely abandoned >20 years ago.

Meta-analysis of 15 studies[29] on combined i.v. + intra-arterial (i.a.) thrombolytic therapy in acute stroke found 35.1% complete recanalization rate, 17.9% mortality, 51.1% unfavourable outcome (death or disability mRs > 2 at 90 days), and 8.6% sICH (proven haemorrhage with an increase of National Institute of Health Stroke Scale (NIHSS) by ≥4 points). Neither mortality difference nor difference in sICH was found when combined lytic therapy was compared with i.v. thrombolysis alone.

The PROACT-II trial randomized 180 patients with angiographically proven middle cerebral artery occlusion treated within 6 h of stroke onset to either i.a. thrombolysis or placebo. Mechanical manipulation of the thrombus was not permitted. The study showed clinical superiority of thrombolysis (40% good neurological outcomes—mRS ≤ 2) over placebo (25% mRS ≤ 2). The rate of sICH was 10.9% with thrombolysis and 2% with placebo. There was no difference in 90-day mortality.[30]

The Japanese MELT trial used i.a. urokinase in patients with M1 or M2 MCA occlusions of <6 h duration.[31] The trial was stopped after enrolling 114 patients because of Japanese approval of IV tPA. The primary endpoint (mRS ≤ 2) was not significantly different compared with placebo, and the rate of sICH was 9%. However, a preplanned secondary analysis showed that the rate of recovery to normal or near normal (mRS ≤ 1) was higher in the treatment group (42.1 vs. 22.8%, $P = 0.045$).

The data from these two trials show the efficacy of IAT compared with placebo in the treatment of patients with angiographically proven MCA occlusion. Although there has been no direct, pure comparison of IA thrombolysis vs. i.v. thrombolysis, it is known[32–35] that recanalization rates for large-vessel occlusion are generally poor with i.v. tPA (e.g. MCA recanalization rate is ~33%, ICA recanalization is ~8%, and patients with thrombi >8 mm do not recanalize with i.v. tPA). Unfortunately, the initiation of IAT is much more time-consuming than i.v. tPA; therefore, the potential benefit may be lost due to the delay in treatment onset. Furthermore, the sICH rates ~10%[31,32] after i.a. thrombolysis are rather high.

Thus, there is no direct evidence (neither for acute myocardial infarction nor for acute stroke) that i.a. administration of a fibrinolytic agent is of any superior clinical value over simple i.v. thrombolysis alone.

Facilitated intervention (thrombolysis + mechanical intervention)

Many randomized trials in STEMI[36–39] and others tested the attractive hypothesis: to use i.v. thrombolysis at the time of first medical contact (to save time), followed by coronary angiography and angioplasty (to maximize the recanalization rates) (*Figures 5* and *6*). However, all these trials failed to show benefit of this approach over direct angioplasty alone. The results of most trials almost copied the two similarly designed three-arm trials[28,36]: facilitated angioplasty was slightly superior to i.v. thrombolysis alone, but was far less effective than primary angioplasty alone. The explanation is complex, but most important are two differences favouring

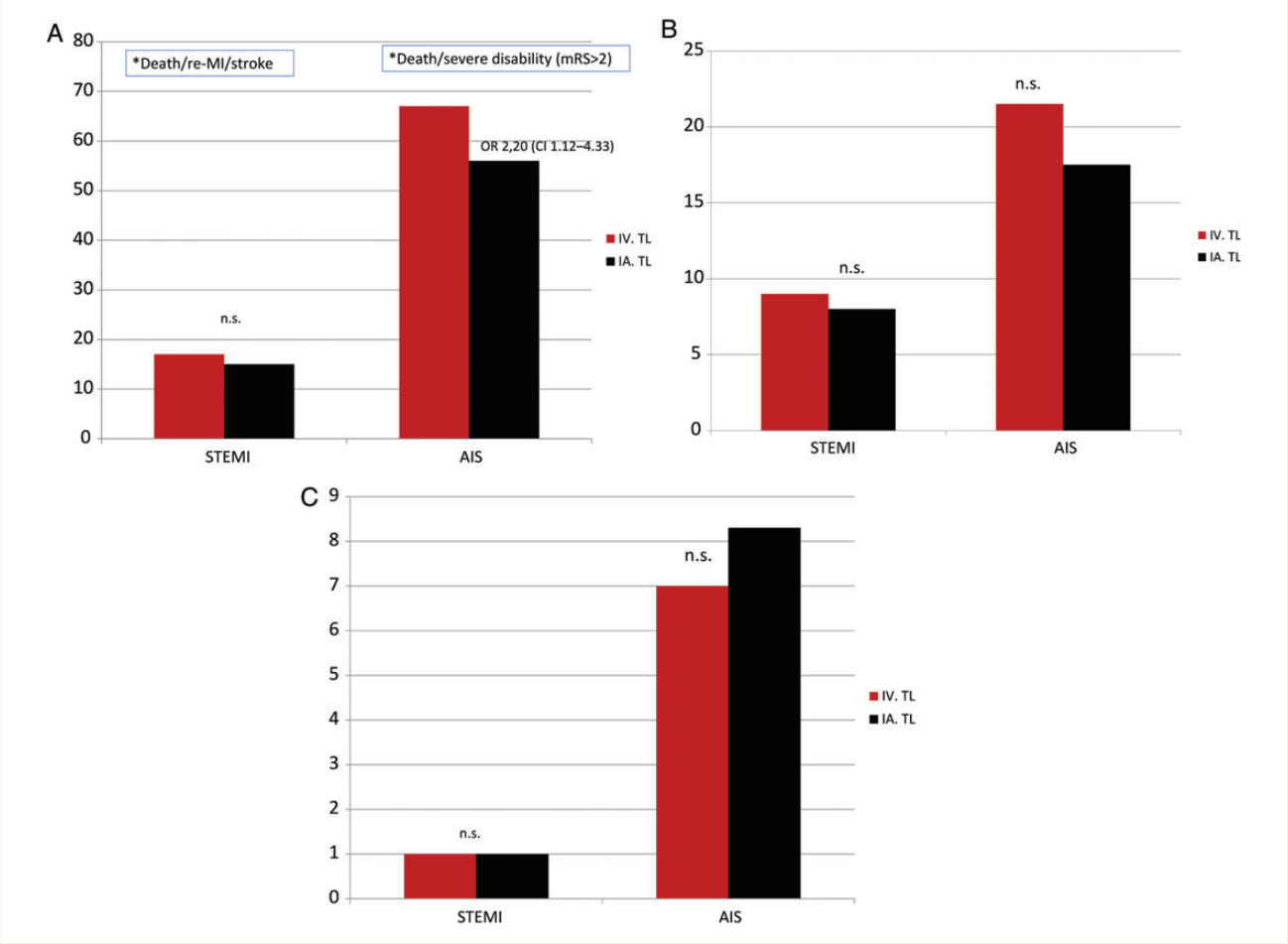

Figure 4 Comparison of intra-arterial vs. intravenous thrombolysis in acute myocardial infarction and acute stroke. (*A*) 'Hard' clinical endpoints, i.e. death/re-infarction/stroke for STEMI patients and death/severe disability (mRS > 2) for stroke patients. (*B*) All-cause mortality. (*C*) Symptomatic intracranial haemorrhage. Adopted from references 24–26 and 29.

primary over facilitated PCI: higher rates of re-infarction (including stent thrombosis) and higher rates of bleeding complications (including cardiac tamponade) after facilitated PCI.

The recently published STREAM trial randomized selected patients (unable to undergo primary PCI within 1 h from the first medical contact) to either pre-hospital fibrinolysis with subsequent coronary angiography (± PCI) or primary PCI. The trial found similar outcomes in both groups. However, fibrinolysis was associated with a slightly increased risk of intracranial bleeding.[39]

The Interventional Management of Stroke (IMS 3) trial[40] compared i.v. thrombolysis (tPA) alone vs. facilitated intervention (i.v. tPA + i.a. tPA or mechanical thrombectomy). The trial has suspended enrolment for futility. A major limitation of the IMS III trial was that patients were selected upon clinical grounds and only 47% had a CT angiogram (CTA). In a pre-planned analysis of the patients with a documented arterial occlusion by CTA, there was a significant benefit in favour of facilitated intervention ($P = 0.01$).

These data on combined therapy demonstrate that there is *no benefit from facilitated intervention (i.v. thrombolysis followed by i.a. thrombolysis ± catheter intervention) over i.v. thrombolysis alone in acute stroke* patients when used as a primary strategy. However, in patients with failed i.v. thrombolysis and in some selected patients with a large thrombus burden, IAT can be considered for rescue therapy. This is very similar to the situation in acute myocardial infarction 25 years ago (intracoronary thrombolysis was not superior to i.v. thrombolysis) or more recently (facilitated PCI was not shown to be superior in several trials).

Primary catheter-based intervention (primary percutaneous coronary intervention, direct catheter-based thrombectomy)

The benefits of primary PCI over thrombolysis in STEMI were clearly demonstrated 20 years ago (*Figure 7*).[6–8] These benefits are present even when patients require transportation from the first medical contact site to the nearest PCI-capable hospital.[41,42] A large meta-analysis has demonstrated this benefit unequivocally.[43]

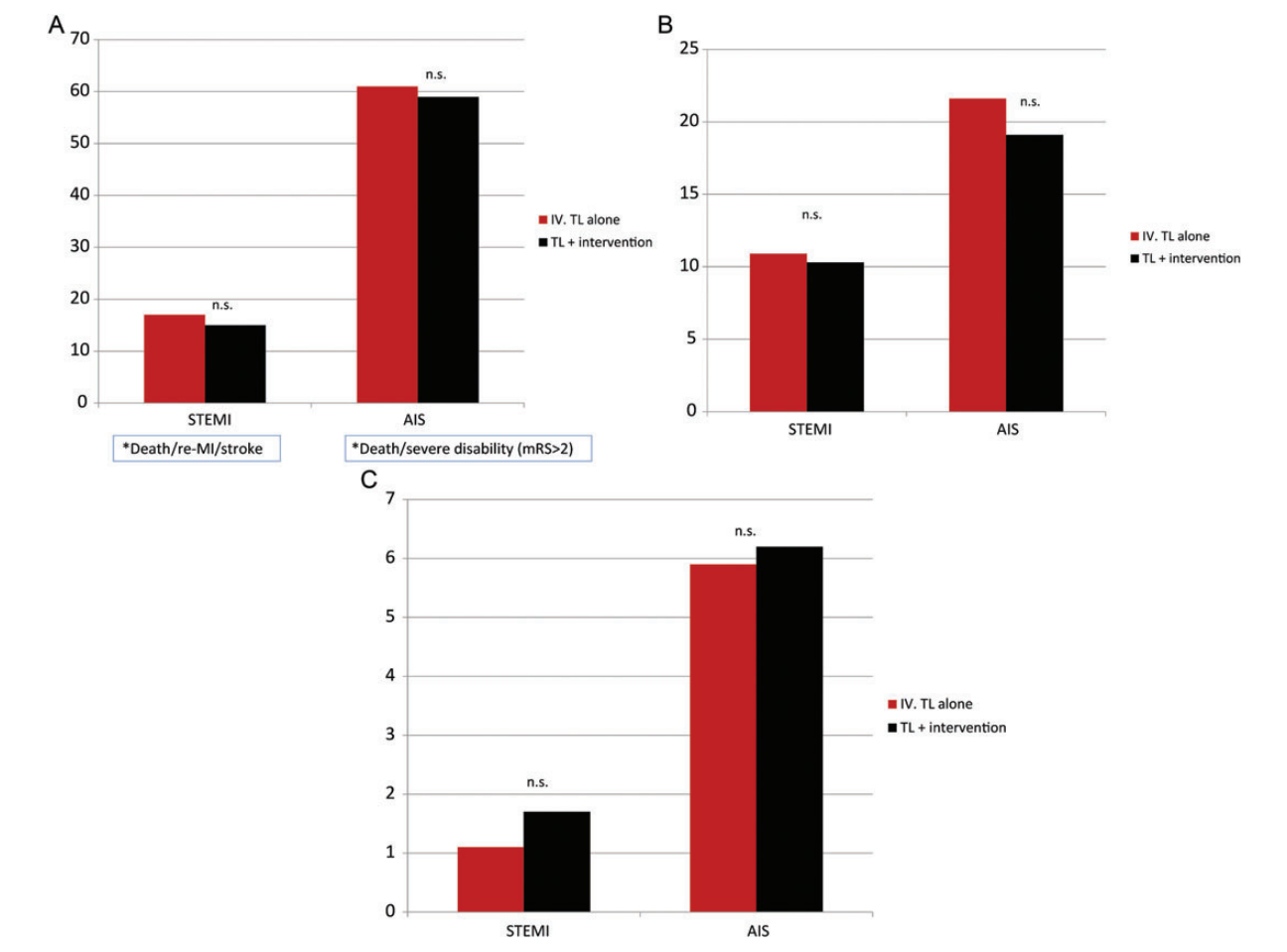

Figure 5 Comparison of intravenous thrombolysis vs. lysis-facilitated intervention in acute myocardial infarction and acute stroke. (*A*) 'Hard' clinical endpoints, i.e. death/re-infarction/stroke for STEMI patients and death/severe disability (mRS $>$ 2) for stroke patients. (*B*) All-cause mortality. (*C*) Symptomatic intracranial haemorrhage. Adopted from references 28,36, and 40.

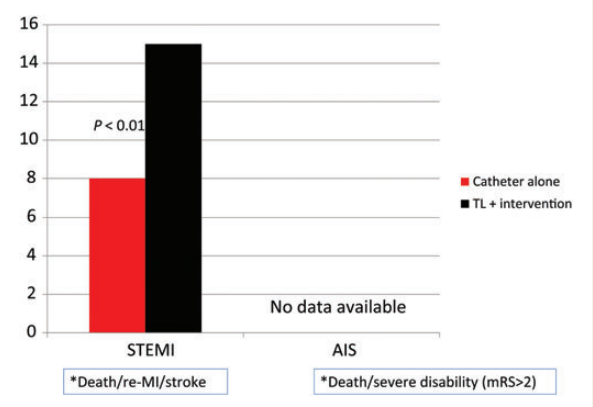

Figure 6 Comparison of facilitated intervention vs. catheter intervention alone in acute myocardial infarction and acute stroke. Adopted from references 28 and 36 (STEMI); no randomized trials available for acute stroke.

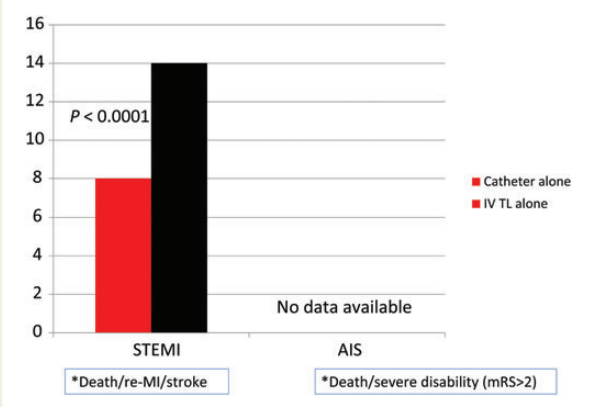

Figure 7 Comparison of catheter intervention alone vs. intravenous thrombolysis alone in acute myocardial infarction and acute stroke. Adopted from reference 43 (STEMI); no randomized trials available for acute stroke.

Similar evidence from randomized trials is lacking in acute ischaemic stroke. A few years ago, CBT was performed with bulky devices, and a significant risk of complications was present. In the last 3–5 years, several new clot retrieval devices (stent retrievers) have been introduced and received CE mark for the use in European patients. These devices (e.g. Solitaire® or Trevo®) are something between a tiny self-expanding stent and a soft 'spider-web-like' basket for clot removal, and the risks of complications with this latest generation stent retrievers are much smaller, whereas their success rates are higher. Detailed information about CBT was published in the *JACC* white paper.[44]

The Penumbra Pivotal Stroke Trial[45] included 125 patients, mostly pre-treated by thrombolysis, with a mean NIHSS of 17.6, and demonstrated an 81.6% of recanalization rate. However, clinical outcomes were not different (or were even worse) from previous thrombolytic trials: 32.8% 90-day mortality, 75% unfavourable outcome (death or disability), and 11.2% sICH.

The Solitaire With the Intention For Thrombectomy (SWIFT) trial[46] tested the Solitaire® stent retriever against the Merci Retriever® in patients within 8 h of stroke onset but was stopped early after the randomization of 113 patients because an interim analysis showed that the primary efficacy outcome (TIMI 2 or 3 flow) was achieved more often with Solitaire® (61 vs. 24%, OR 4.87, $P < 0.0001$).[46] Importantly, good neurological outcome (58 vs. 33%, OR 2.78, $P = 0.0001$) and 90-day mortality (17 vs. 38%, OR 0.34, $P = 0.0001$) were more favourable in the Solitaire® group with a markedly lower rate of sICH (2 vs. 11%, OR 0.14, $P = 0.057$).

The TREVO 2 trial[47] was similar to SWIFT and tested the Trevo® stent retriever vs. The Merci Retriever®. Recanalization (TICI 2 or greater) was higher with Trevo® than with Merci® (86 vs. 60%, OR 4.22, $P < 0.0001$) as was good clinical outcome (40 vs. 22%, OR 2.39, $P = 0.013$). There were no differences in the risk of sICH (7 vs. 9%, OR 0.75, $P = 0.78$) or 90-day mortality (33 vs. 24%, OR 1.61, $P = 0.18$). An important finding from the SWIFT trial was that the speed of recanalization with the stent retrievers was significantly lower (36 min with Solitaire® vs. 52 min with Merci®, $P = 0.038$). Several other devices with varying designs are currently being tested.

A recently published single-centre experience[48] with 104 patients treated with the Solitaire® stent retrieval, 75% of them received also thrombolysis. The recanalization rate was 78%. The mean NIHSS decreased from 15.3 (before) to 7.8 (after treatment). Mortality was 16% (anterior circulation) and 47.8% (posterior circulation). Intracranial bleeding occurred in 8%.

Another recent multicentre retrospective review[49] included 237 patients (mean age 64 years; mean baseline NIHSS 15) with acute proximal intracranial anterior circulation occlusion—endovascular treatment was initiated >8 h (mean 15 h) from time last seen well. The treatment selection was strictly based on MRI or CT perfusion imaging. Successful revascularization was achieved in 74%. Parenchymal haematoma occurred in 9%. The 90-day mortality rate was 21.5% and unfavourable outcome was in 55%.

The most recent meta-analysis[50] of CBT registries identified 16 eligible published studies: 4 on the Merci device ($n = 357$), 8 on the Penumbra system ($n = 455$), and 4 on stent retrievers Solitaire® or Trevo® ($n = 113$). The mean procedural duration for Merci was 120 min. The mean puncture-to-recanalization time for Penumbra was 64.6 min, and for stent retrievers, 54.7 min. Successful recanalization was achieved in 59.1% (Merci), 86.6% (Penumbra), and 92.9% (stent retrievers). Functional independence (mRS ≤ 2) was achieved in 31.5% (Merci), 36.6% (Penumbra), and 46.9% (stent retrievers). The 3-month mortality rate was 37.8% in the Merci studies, 20.7% in the Penumbra studies, and 12.3% in stent retriever studies. This study demonstrated improved outcomes after CBT when performed with the latest generation of stent retrievers. Major limitations of this and any other meta-analysis or comparison between stroke trials are the heterogeneity of the stroke patients enrolled and the criteria for patient selection. This heterogeneity stems from the multitude of causes of ischaemic stroke (e.g. atherosclerotic occlusion, cardioembolism, spontaneous dissection, etc.) as well as the variable sizes and locations of thrombi and occlusions. In addition, the status of collaterals, the severity of the ischaemic penumbra, and the size of the ischaemic core pre-treatment all have an effect on prognosis and outcomes.

The interventional techniques and peri-procedural management are highly variable. Patients undergoing catheter-based interventions for acute ischaemic stroke receive either general anaesthesia (GA) or conscious sedation. General anaesthesia may delay time to treatment, whereas conscious sedation may result in patient movement and compromise the safety of the procedure. Analysis of 980 patients who underwent intervention for acute anterior circulation stroke at 12 stroke centres between 2005 and 2009 found an overall recanalization rate of 68% and a symptomatic haemorrhage rate of 9.2%. General anaesthesia was used in 44% of patients with no differences in intracranial haemorrhage rates when compared with the conscious sedation group. The use of GA was associated with poorer neurological outcome at 90 days (odds ratio = 2.33; 95% CI 1.63–3.44; $P < 0.0001$) and higher mortality (odds ratio = 1.68; 95% CI 1.23–2.30; $P < 0.0001$) compared with conscious sedation. For example, it is becoming increasingly more likely that the use of GA has a significant deleterious effect on outcomes and increased mortality.[51]

A recent study[52] demonstrated that even stroke caused by the acute occlusion of the internal carotid artery (with only 8–17% recanalization rate and 55% mortality rate when treated by thrombolysis) can be effectively treated by CBT: successful revascularization of extracranial internal carotid artery with acute stent implantation was achieved in 95% of patients. The intracranial recanalization was achieved in 61% of patients, who had simultaneous intracranial artery occlusion. The mortality rate was 13.6% at 90 days and the favourable outcome (mRS ≤ 2) was 41%.

These data show that the latest generation of stent retrievers is able to recanalize 80–90% of occluded intracranial arteries—three times more compared with thrombolysis. However, it is not yet known whether this translates to better clinical outcomes. The sufficient data on outcomes after primary CBT (without thrombolysis) are still missing and trials comparing i.v. thrombolysis vs. primary CBT are urgently needed and are being planned and initiated.

Adjuvant antithrombotic therapy before/after reperfusion

One of the major differences between acute MI and acute stroke lies in the intensity of adjuvant antithrombotic therapy connected to any reperfusion strategy. Although antithrombotic therapy in acute MI is

usually based on full-dose parenteral anticoagulation plus dual (or sometimes even triple) antiplatelet therapy, such multidrug strategy in acute stroke would be disastrous and cause many intracranial bleedings. Antithrombotic therapy in acute stroke, especially when treated by thrombolysis, should be cautious, low dose, usually with a single agent. There are no trials at all assessing adjuvant antithrombotic therapies during/after direct catheter-based interventions in acute stroke. This important topic is, however, beyond the scope of this review.

Future: how to improve acute stroke outcomes?

Facing the above-mentioned minimal benefits from i.v. thrombolysis (vs. conservative treatment) in acute stroke and absence of any benefits from i.a. thrombolysis (vs. i.v. lysis alone), the future trials in acute stroke must follow the way paved by acute myocardial infarction trials: the future trials should compare i.v. thrombolysis alone vs. catheter-based mechanical intervention alone (without lytics) for the occlusion of major cerebral arteries. If such trials would demonstrate superiority of catheter-based thrombectomy, we can face in future similar revolution in acute stroke treatment as we have been facing in acute MI treatment in the past years.

Nevertheless, irrespective of the trial results, the most important is to prevent acute strokes—and this field is much more successful already today. When the acute stroke occurs despite the preventive measures, the critical value of every minute shortening the delay to reperfusion therapy is essential. The continuous education should be focused on both—the wide population knowledge of stroke symptoms and the critical role of time and also to health care professionals, who must change their passive attitude to stroke treatment.

Summary

The evolution of reperfusion therapy in acute myocardial infarction and acute ischaemic stroke has many *similarities*: thrombolysis is superior to placebo, i.a. thrombolysis is not superior to i.v., facilitated intervention (thrombolysis followed by mechanical intervention) is of questionable value, and direct mechanical recanalization without thrombolysis clearly is (myocardial infarction) or possibly will be (stroke) superior to thrombolysis—but only when started with no or minimal delay (*Table 2*).

However, there are also substantial *differences*. Direct catheter-based thrombectomy in acute ischaemic stroke is more difficult than primary angioplasty (in STEMI) in many ways: complex pre-intervention diagnostic workup, shorter time window for clinically effective reperfusion, need for an emergent multidisciplinary approach from the first medical contact, vessel tortuosity, vessel fragility, no evidence available about dosage and combination of peri-procedural antithrombotic drugs, risk of intracranial bleeding, unclear respective roles of thrombolysis and mechanical intervention, lower number of suitable patients, and thus longer learning curves of the staff. Thus, starting acute stroke interventional programme requires a lot of learning, discipline, and humility.

Reperfusion strategies combining thrombolysis with immediate intervention (i.a. thrombolysis or i.v. thrombolysis followed by mechanical intervention) in general failed in both acute disorders (STEMI and stroke) mainly due to the following reasons: (i) the fibrinolytic effect is always systemic and not directly dependent on the dose or site of administration, (ii) the catheter manipulation in a 'fibrinolytic state' causes more bleeding complications than simple i.v. thrombolysis, (iii) when thrombolysis is preceding mechanical intervention, the start of invasive procedure is always somewhat delayed (this delay may be critical if the intervention is indicated for clinical thrombolysis failure). Randomized trials comparing different reperfusion strategies provided similar results in acute ischaemic stroke as in STEMI. Thus, it might be expected that also a randomized trial comparing direct (primary) CBT vs. i.v. thrombolysis could show superiority of CBT if the mechanical intervention would be initiated without delay. Such randomized trials are needed to define the role of CBT in acute stroke treatment.

Table 2 Summary of the outcomes of various reperfusion strategies in randomized trials

	STEMI death/ re-MI/ stroke	Acute stroke death/severe disability (mRs > 2)
Conservative (no reperfusion)	15–30%	55–75%
I.V. thrombolysis	11–16%	48–63%
Local (i.a.) thrombolysis	10–15%	51–60%
Facilitated intervention (thrombolysis + intervention)	9–14%	59–79%
Primary catheter-based intervention (no thrombolysis)	5–9%	No randomized trials published

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References

1. Chazov EI, Matveeva LS, Mazaev AV, Sargin KE, Sadovskaia GV, Ruda MI. Intracoronary administration of fibrinolysin in acute myocardial infarct. *Ter Arkh* 1976;**48**:8–19.
2. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986;**1**:397–402.
3. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988;**2**:349–360.
4. Meyer J, Merx W, Schweizer P, Dörr R, Lambertz H, Bethge C, Erbel R, Effert S. Selective intracoronary lysis and transluminal coronary dilation as an immediate measure in acute myocardial infarct. *Verh Dtsch Ges Herz Kreislaufforsch* 1982;**48**:157–165.
5. Hartzler GO, Rutherford BD, McConahay DR, Johnson WL Jr, McCallister BD, Gura GM Jr, Conn RC, Crockett JE. Percutaneous transluminal coronary angioplasty with and without thrombolytic therapy for treatment of acute myocardial infarction. *Am Heart J* 1983;**106**(5 Pt 1):965–973.
6. Zijlstra F, de Boer MJ, Hoorntje JC, Reiffers S, Reiber JH, Suryapranata H. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. *N Engl J Med* 1993;**328**:680–684.
7. Grines CL, Browne KF, Marco J, Rothbaum D, Stone GW, O'Keefe J, Overlie P, Donohue B, Chelliah N, Timmis GC. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. The Primary Angioplasty in Myocardial Infarction Study Group. *N Engl J Med* 1993;**328**:673–679.

8. Gibbons RJ, Holmes DR, Reeder GS, Bailey KR, Hopfenspirger MR, Gersh BJ. Immediate angioplasty compared with the administration of a thrombolytic agent followed by conservative treatment for myocardial infarction. The Mayo Coronary Care Unit and Catheterization Laboratory Groups. *N Engl J Med.* 1993;**328**: 685–691.
9. Widimsky P, Janoušek S, Vojáček J. Czech Society of Cardiology guidelines for the diagnosis and treatment of acute myocardial infarction (Q-wave/ST elevations/ bundle branch block). *Cor Vasa* 2002;**44**:K123–K143.
10. Fletcher AP, Alkjaersig N, Lewis M, Tulevski V, Davies A, Brooks JE, Hardin WB, Landau WM, Raichle ME. A pilot study of urokinase therapy in cerebral infarction. *Stroke* 1976;**7**:135–142.
11. Mori E, Yoneda Y, Tabuchi M, Yoshida T, Ohkawa S, Ohsumi Y, Kitano K, Tsutsumi A, Yamadori A. Intravenous recombinant tissue plasminogen activator in acute carotid artery territory stroke. *Neurology* 1992;**42**:976–982.
12. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995; **333**:1581–1587.
13. Adams HP Jr, Adams RJ, Brott T, del Zoppo GJ, Furlan A, Goldstein LB, Grubb RL, Higashida R, Kidwell C, Kwiatkowski TG, Marler JR, Hademenos GJ, Stroke Council of the American Stroke Association. Guidelines for the early management of patients with ischemic stroke: a scientific statement from the Stroke Council of the American Stroke Association. *Stroke* 2003;**34**:1056–1083.
14. Bellon RJ, Putman CM, Budzik RF, Pergolizzi RS, Reinking GF, Norbash AM. Rheolytic thrombectomy of the occluded internal carotid artery in the setting of acute ischemic stroke. *Am J Neuroradiol* 2001;**22**:526–530.
15. Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, Khatri P, McMullan PW Jr, Qureshi AI, Rosenfield K, Scott PA, Summers DR, Wang DZ, Wintermark M, Yonas H, American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Peripheral Vascular Disease, and Council on Clinical Cardiology. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013;**44**:870–947.
16. Adeoye O, Hornung R, Khatri P, Kleindorfer D. Recombinant tissue-type plasminogen activator use for ischemic stroke in the United States: a doubling of treatment rates over the course of 5years. *Stroke* 2011;**42**:1952–1955.
17. Widimsky P, Wijns W, Fajadet J, de Belder M, Knot J, Aaberge L, Andrikopoulos G, Baz JA, Betriu A, Claeys M, Danchin N, Djambazov S, Erne P, Hartikainen J, Huber K, Kala P, Klinceva M, Kristensen SD, Ludman P, Ferre JM, Merkely B, Milicic D, Morais J, Noc M, Opolski G, Ostojic M, Radovanovic D, De Servi S, Stenestrand U, Studencan M, Tubaro M, Vasiljevic Z, Weidinger F, Witkowski A, Zeymer U, European Association for Percutaneous Cardiovascular Interventions. Reperfusion therapy for ST elevation acute myocardial infarction in Europe: description of the current situation in 30 countries. *Eur Heart J* 2010;**31**:943–957.
18. Kristensen SD, Fajadet J, Di Mario C, Kaifoszova Z, Laut KG, Deleanu D, Gilard M, Guagliumi G, Goktekin O, Jorgova J, Kanakakis J, Ostojic M, Pereira H, Sabate M, Sobhy M, Vrints C, Wijns W, Widimsky P. Implementation of primary angioplasty in Europe: stent for life initiative progress report. *EuroIntervention* 2012;**8**:35–42.
19. Ahmed S, Antman EM, Murphy SA, Giugliano RP, Cannon CP, White H, Morrow DA, Braunwald E. Poor outcomes after fibrinolytic therapy for ST-segment elevation myocardial infarction: impact of age (a meta-analysis of a decade of trials). *J Thromb Thrombolysis* 2006;**21**:119–129.
20. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, Larrue V, Lees KR, Medeghri Z, Machnig T, Schneider D, von Kummer R, Wahlgren N, Toni D; ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008;**359**:1317–1329.
21. IST-3 Collaborative Group, Sandercock P, Wardlaw JM, Lindley RI, Dennis M, Cohen G, Murray G, Innes K, Venables G, Czlonkowska A, Kobayashi A, Ricci S, Murray V, Berge E, Slot KB, Hankey GJ, Correia M, Peeters A, Matz K, Lyrer P, Gubitz G, Phillips SJ, Arauz A. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. *Lancet* 2012;**379**:2352–2363.
22. Wardlaw JM, Murray V, Berge E, Del Zoppo GJ. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev* 2009:CD000213. doi: 10.1002/ 14651858.CD000213.pub2.
23. Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D, Grotta JC, Albers GW, Kaste M, Marler JR, Hamilton SA, Tilley BC, Davis SM, Donnan GA, Hacke W; ECASS ATLANTIS, NINDS and EPITHET rt-PA Study Group, Allen K, Mau J, Meier D, del Zoppo G, De Silva DA, Butcher KS, Parsons MW, Barber PA, Levi C, Bladin C, Byrnes G. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet* 2010;**375**:1695–1703.
24. Kennedy JW, Ritchie JL, Davis KB, Fritz JK. Western Washington randomized trial of intracoronary streptokinase in acute myocardial infarction. *N Engl J Med* 1983;**309**: 1477–1482.
25. Rentrop KP, Feit F, Blanke H, Stecy P, Schneider R, Rey M, Horowitz S, Goldman M, Karsch K, Meilman H. Effects of intracoronary streptokinase and intracoronary nitroglycerin infusion on coronary angiographic patterns and mortality in patients with acute myocardial infarction. *N Engl J Med* 1984;**311**:1457–1463.
26. Simoons ML, Serruys PW, vd Brand M, Bär F, de Zwaan C, Res J, Verheugt FW, Krauss XH, Remme WJ, Vermeer F. Improved survival after early thrombolysis in acute myocardial infarction. A randomised trial by the Interuniversity Cardiology Institute in The Netherlands. *Lancet* 1985;**2**:578–582.
27. Patel B, Kloner RA. Analysis of reported randomized trials of streptokinase therapy for acute myocardial infarction in the 1980s. *Am J Cardiol* 1987;**59**:501–504.
28. Widimský P, Groch L, Zelízko M, Aschermann M, Bednár F, Suryapranata H. Multicentre randomized trial comparing transport to primary angioplasty vs immediate thrombolysis vs combined strategy for patients with acute myocardial infarction presenting to a community hospital without a catheterization laboratory. The PRAGUE study. *Eur Heart J* 2000;**21**:823–831.
29. Mazighi M, Meseguer E, Labreuche J, Amarenco P. Bridging therapy in acute ischemic stroke. A systematic review and meta-analysis. *Stroke* 2012;**43**:1302–1308.
30. Furlan A, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, Pessin M, Ahuja A, Callahan F, Clark WM, Silver F, Rivera F. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in acute cerebral thromboembolism. *JAMA* 1999;**282**:2003–2011.
31. Ogawa A, Mori E, Minematsu K, Taki W, Takahashi A, Nemoto S, Miyamoto S, Sasaki M, Inoue T, MELT Japan Study Group. Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke: the middle cerebral artery embolism local fibrinolytic intervention trial (MELT) Japan. *Stroke* 2007;**38**: 2633–2639.
32. Kharitonova T, Ahmed N, Thoren M, Wardlaw JM, von Kummer R, Glahn J, Wahlgren N. Hyperdense middle cerebral artery sign on admission CT scan—prognostic significance for ischaemic stroke patients treated with intravenous thrombolysis in the safe implementation of thrombolysis in Stroke International Stroke Thrombolysis Register. *Cerebrovasc Dis* 2009;**27**:51–59.
33. De Silva DA, Brekenfeld C, Ebinger M, Christensen S, Barber PA, Butcher KS, Levi CR, Parsons MW, Bladin CF, Donnan GA, Davis SM. The benefits of intravenous thrombolysis relate to the site of baseline arterial occlusion in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET). *Stroke* 2010;**41**:295–299.
34. Riedel CH, Zimmermann P, Jensen-Kondering U, Stingele R, Deuschl G, Jansen O. The importance of size: successful recanalization by intravenous thrombolysis in acute anterior stroke depends on thrombus length. *Stroke* 2011;**42**:1775–1777.
35. Saver JL, Yafeh B. Confirmation of tPA treatment effect by baseline severity-adjusted end point reanalysis of the NINDS-tPA stroke trials. *Stroke* 2007;**38**:414–416.
36. Vermeer F, Oude Ophuis AJ, vd Berg EJ, Brunninkhuis LG, Werter CJ, Boehmer AG, Lousberg AH, Dassen WR, Bär FW. Prospective randomised comparison between thrombolysis, rescue PTCA, and primary PTCA in patients with extensive myocardial infarction admitted to a hospital without PTCA facilities: a safety and feasibility study. *Heart* 1999;**82**:426–431.
37. Califf RM, Topol EJ, Stack RS, Ellis SG, George BS, Kereiakes DJ, Samaha JK, Worley SJ, Anderson JL, Harrelson-Woodlief L. Evaluation of combination thrombolytic therapy and timing of cardiac catheterization in acute myocardial infarction. Results of thrombolysis and angioplasty in myocardial infarction—phase 5 randomized trial. TAMI Study Group. *Circulation* 1991;**83**:1543–1556.
38. ASS, ENT-4 Investigators. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. *Lancet* 2006;**367**:569–578.
39. Armstrong PW, Gershlick AH, Goldstein P, Wilcox R, Danays T, Lambert Y, Sulimov V, Rosell Ortiz F, Ostojic M, Welsh RC, Carvalho AC, Nanas J, Arntz HR, Halvorsen S, Huber K, Grajek S, Fresco C, Bluhmki E, Regelin A, Vandenberghe K, Bogaerts K, Van de Werf F; STREAM Investigative Team. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med* 2013;**368**: 1379–1387.
40. Broderick JP, Palesch YY, Demchuk AM, Yeatts SD, Khatri P, Hill MD, Jauch EC, Jovin TG, Yan B, Silver FL, von Kummer R, Molina CA, Demaerschalk BM, Budzik R, Clark WM, Zaidat OO, Malisch TW, Goyal M, Schonewille WJ, Mazighi M, Engelter ST, Anderson C, Spilker J, Carrozzella J, Ryckborst KJ, Janis LS, Martin RH, Foster LD, Tomsick TA; Interventional Management of Stroke (IMS) III Investigators. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. *N Engl J Med.* 2013;**368**:893–903.
41. Widimský P, Budesínský T, Vorác D, Groch L, Zelízko M, Aschermann M, Branny M, St'ásek J, Formánek P; 'PRAGUE' Study Group Investigators. Long distance transport for primary angioplasty vs immediate thrombolysis in acute myocardial infarction. Final results of the randomized national multicentre trial—PRAGUE-2. *Eur Heart J* 2003;**24**:94–104.

42. Andersen HR, Nielsen TT, Rasmussen K, Thuesen L, Kelbaek H, Thayssen P, Abildgaard U, Pedersen F, Madsen JK, Grande P, Villadsen AB, Krusell LR, Haghfelt T, Lomholt P, Husted SE, Vigholt E, Kjaergard HK, Mortensen LS, DANAMI-2 Investigators. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. *N Engl J Med* 2003;**349**:733–742.
43. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003;**361**:13–20.
44. White CJ, Abou-Chebl A, Cates CU, Levy EI, McMullan PW, Rocha-Singh K, Weinberger JM, Wholey MH. Stroke intervention: catheter-based therapy for acute ischemic stroke. *J Am Coll Cardiol* 2011;**58**:101–116.
45. The Penumbra Pivotal Stroke Trial Investigators. The Penumbra Pivotal Stroke Trial: safety and effectiveness of a new generation of mechanical devices for clot removal in intracranial large vessel occlusive disease. *Stroke* 2009;**40**:2761–2768.
46. Saver JL, Jahan R, Levy EI, Jovin TG, Baxter B, Nogueira RG, Clark W, Budzik R, Zaidat OO, SWIFT Trialists. Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. *Lancet* 2012;**380**:1241–1249.
47. Nogueira RG, Lutsep HL, Gupta R, Jovin TG, Albers GW, Walker GA, Liebeskind DS, Smith WS; TREVO 2 Trialists. Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial. *Lancet* 2012;**380**:1231–1240.
48. Dorn F, Stehle S, Lockau H, Zimmer C, Liebig T. Endovascular treatment of acute intracerebral artery occlusions with the Solitaire stent: single-centre experience with 108 recanalization procedures. *Cerebrovasc Dis* 2012;**34**:70–77.
49. Jovin TG, Liebeskind DS, Gupta R, Rymer M, Rai A, Zaidat OO, Abou-Chebl A, Baxter B, Levy EI, Barreto A, Nogueira RG. Imaging-based endovascular therapy for acute ischemic stroke due to proximal intracranial anterior circulation occlusion treated beyond 8 hours from time last seen well: retrospective multicenter analysis of 237 consecutive patients. *Stroke* 2011;**42**:2206–2211.
50. Almekhlafi MA, Menon BK, Freiheit EA, Demchuk AM, Goyal M. A meta-analysis of observational intra-arterial stroke therapy studies using the Merci device, Penumbra system, and retrievable stents. *AJNR Am J Neuroradiol* 2012. Published online ahead of print 26 July.
51. Abou-Chebl A, Lin R, Hussain MS, Jovin TG, Levy EI, Liebeskind DS, Yoo AJ, Hsu DP, Rymer MM, Tayal AH, Zaidat OO, Natarajan SK, Nogueira RG, Nanda A, Tian M, Hao Q, Kalia JS, Nguyen TN, Chen M, Gupta R. Conscious sedation versus general anesthesia during endovascular therapy for acute anterior circulation stroke: preliminary results from a retrospective, multicenter study. *Stroke* 2010; **41**:1175–1179.
52. Papanagiotou P, Roth C, Walter S, Behnke S, Grunwald IQ, Viera J, Politi M, Körner H, Kostopoulos P, Haass A, Fassbender K, Reith W. Carotid artery stenting in acute stroke. *J Am Coll Cardiol* 2011;**58**:2363–2369.