View Point

Innovations in Acute Stroke Reperfusion Strategies

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Abstract

Vascular neurology is witnessing unprecedented innovations in the management of acute ischemic stroke, especially in reperfusion strategies. The emergence of mechanical thrombectomy with new generation devices has revolutionized the treatment of acute ischemic stroke with large vessel occlusion. The reperfusion strategies are evolving with the extension of the window period for thrombolysis and endovascular therapy through the concept of "tissue clock" in addition to the established "time clock." The newer generation of thrombolytic drugs like tenecteplase are promising exciting times ahead in acute stroke care. In this "viewpoint,'" the evolution of reperfusion therapy in acute ischemic stroke will be discussed followed by recent innovations in reperfusion strategies.

Keywords: Acute stroke therapy, ischemic stroke, magnetic resonance imaging, recombinant tissue plasminogen activator, reperfusion therapy, tenecteplase, thrombectomy, thrombolytic therapy

Introduction

During the past three decades, acute stroke reperfusion strategies have evolved from nihilism to thrombolytic therapy followed by endovascular therapy and recently to next generation endovascular devices and thrombolytic agents. The eligibility criteria and the drugs/devices for these two approved therapies have further evolved over the past two decades. Figure 1 depicts the time line of evolution of thrombolytic and endovascular therapy in stroke. We will discuss below the innovations in reperfusion strategies under the concepts of "Time clock" and "Tissue clock."

Thrombolysis in Acute Ischemic Stroke – "Time Clock"

During the initial evolution, the main concept of stroke thrombolysis was "time is brain" and the thrombolytic drug had to be administered as early as possible. The efficacy of these agents depends on the age of clot, size, and location since the higher density of cross-linking of fibrin makes clot harder, more compact and difficult to dissolve.[1] Unlike the initial thrombolytic agents such as streptokinase and urokinase, the only Food and Drug Administration (FDA) approved tissue plasminogen activator (tPA) in stroke, alteplase (recombinant rtPA) is a fibrin selective analog with a short half-life. The dose of intravenous alteplase is 0.9 mg/kg up to 90 mg; 10% as a bolus followed by 1 h infusion. Several trials such as the National Institute of Neurological Disorders and Stroke (NINDS) and the European Collaborative Acute Stroke Study (ECASS) had proven the benefit for rtPA in acute ischemic stroke within 3 h.[2,3] Several prospective observational registries like Canadian alteplase for stroke effectiveness study registry,[4] and safe implementation of thrombolysis in stroke-international stroke thrombolysis register showed similar rates of mortality, symptomatic intracranial hemorrhage (ICH) within 24 h and functional independence.[5] An individual patient data (IPD) meta-analysis of the randomized controlled trials (RCTs) showed that thrombolysis using alteplase within 3 h of stroke onset led to a good outcome (33% vs. 23%, odds ratio [OR] 1.75 [confidence interval [CI] 1.35–2.27]).[6]

The ECASS III trial showed the benefit of thrombolysis with alteplase in patients with clearly defined symptom onset between 3 and 4.5 h of stroke onset (modified Rankin scale [mRS] 0–1 at 3 months, 52.4% vs. 45.2%, OR 1.34, CI 1.02–1.76). IST-3 trial had 1177 patients in the 3–4.5 h window period and the primary outcome was mRS 0–2 at 6 months (adjusted OR 0.73, 99% CI 0.5–1.07). In the IPD meta-analysis, thrombolysis with alteplase showed benefit for patients with stroke onset within 3–4.5 h. (mRS 0–1, 35.3% vs. 30.1%, adjusted OR 1.26, 95% CI 1.05–1.51).[6] Thrombolysis with alteplase is approved from 3 to 4.5 h in Europe, Australia, and many countries including all the leading guidelines. However, US FDA has approved alteplase for thrombolysis only up to 3 h. This may be due to the controversy in the evidence for thrombolysis using alteplase in 3–4.5 h. In the ECAS III trial, there were baseline differences in the form of lower proportion of patients with the previous stroke in alteplase group (7.7% vs. 14.1%, $P = 0.003$). When these patients were excluded and analyzed there was no significant difference in the primary outcome between alteplase

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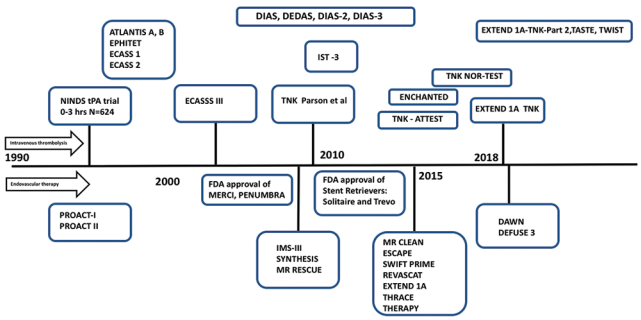

Figure 1: Timeline of major stroke trials

and placebo (OR 1.19, 95% CI 0.89–1.59).[7] In the IST-3 trial, even though the statistical analysis plan mentioned subgroup analysis using 95% CIs, in the final analysis, the authors used 99% CIs. Alper *et al.* had done an unadjusted analysis of this data using 95% CI and uncovered a significant reduction in functional outcome (OR 0.76, 95% CI 0.60–0.97, NNH = 16).[8] Thrombolytic therapy beyond 4.5 h was not found beneficial in three trials which used the then existing conventional inclusion criteria (ATLANTIS-A, ATLANTIS-B, and IST-3).[9-11]

Innovations in Stroke Thrombolysis

Risk of major ICH, low recanalization rates for large vessel occlusion, the requirement for continuous infusion, and narrow window period are the major limitations of the currently approved thrombolytic agent, alteplase. Stroke research in the last decade has tried to surpass these limitations.

Low dose Versus Standard dose Alteplase

The popular belief that there is higher risk of bleeding in Asians had led to approval of lower dose alteplase (0.6 mg/kg) in Japan based on a single group, open-label study with 103 patients.[12,13] The ENCHANTED (enhanced control of hypertension and thrombolysis stroke study) trial assessed whether low dose alteplase was as effective as the usual dose in efficacy and risk for hemorrhage in a noninferiority hypothesis. It did not show noninferiority of low dose alteplase in decreasing death or disability after AIS (mRS 2–6, 53.2% vs. 51.1%, OR 1.09, 95% CI 0.95–1.25, P = 0.51 for noninferiority). However, the rate of symptomatic ICH was significantly lower in low dose alteplase (1.0% vs. 2.1%; OR 0.48; 95% CI, 0.27–0.86; P = 0.01). The secondary analysis of ENCHANTED trial found no clear differential benefit of low dose alteplase in older, Asian, or severely affected patients with AIS compared to standard dose alteplase.[14] Hence, the clinical equipoise remains regarding low dose alteplase even though it is now known that risk of sICH is lesser.

Thrombolysis in Minor Nondisabling Stroke

The role of thrombolysis with alteplase in minor non-disabling stroke is ambiguous. The AHA 2018 guidelines states that "within 3 h from symptom onset, treatment of patients with mild ischemic stroke symptoms that are judged as non-disabling may be considered. Treatment risks should be weighed against possible benefits; however, more study is needed to further define the risk-to-benefit ratio (Class IIb; LOE C)." The first RCT on thrombolysis in acute mild ischemic stroke with no disabling deficit (PRISMS - A Study of the Efficacy and Safety of Alteplase in Participants With Mild Stroke-NCT02072226) recently was stopped early due to slow recruitment.[15] The trial had enrolled 313 patients (out of intended 948 patients) and hence was underpowered. An ITT analysis was done for 156 patients in the alteplase group and 157 in the aspirin-only group. Treatment with alteplase (vs. Aspirin) did not increase the likelihood of favorable functional outcome at 90 days (adjusted absolute risk difference, −1.1%; 95% CI, −9.4%–7.3%). The rate of symptomatic ICH (3.2% vs. 0%) and any ICH (7.1% vs. 3.3%) was more in the alteplase group. Hence among patients with low NIHSS scores and with no disabling deficits, alteplase did not benefit and increases the risk of ICH.[16] However, since the study was terminated early, definite conlucions cannot be made. The idea of "nondisabling" minor stroke has a subjective element into it which further adds question over its generalizability. In our clinical practice, we thrombolyze minor stroke after explaining the risk benefit ratio.

Thrombolysis in wake-up stroke

Role of thrombolytic agents in wake-up stroke was controversial since the time of onset of stroke is unknown. Wake-up trial (magnetic resonance imaging [MRI]-guided thrombolysis for stroke with unknown time of onset) was designed to answer this highly clinically relevant research question.[17] It was a multicenter, randomized double-blind placebo controlled trial which recruited stroke patients with unknown onset and co-existing diffusion- fluid attenuated inversion recovery (FLAIR) mismatch in MRI. This mismatch (ischemic lesion visible in diffusion images but no lesion in FLAIR images) indicates that stroke might have occurred within 4.5 h. They had excluded patients planned for thrombectomy. The trial was stopped early due to lack of funding after enrolling 503 patients of the estimated 800 patients. The primary outcome of mRS 0–1 was achieved significantly higher by alteplase group compared to the placebo group (53.3% vs. 41.8%, adjusted OR 1.61, 95% CI 1.09–2.36, P = 0.02) with number needed to treat (NNT) of 8.7. There was no difference in rate of symptomatic hemorrhage (2% vs. 0.4%, OR 4.95, 95% CI 0.57 to 42.87, P = 0.15). This gives hope to wake up stroke patients without large vessel occlusion and still have a salvageable ischemic penumbra.

Extending Window Period for Thrombolysis

European Cooperative Acute Stroke Study-4: Extending the time for thrombolysis (ECASS-4: ExTEND) in emergency neurological deficits trial was a randomized double-blind placebo-controlled study which tested the hypothesis that acute ischemic stroke patients with significant penumbral mismatch at 4.5–9 h after onset of stroke or wake upstroke, will have

better clinical outcome compared to placebo.[18] The primary outcome was day 90 categorical shift in mRS. The planned sample size was 264. The trial was stopped early after recruiting 120 patients due to slow recruitment and many patients were eligible for mechanical thrombectomy. The results of this study were presented in ESO conference, 2018 (not published). The trial failed to demonstrate efficacy and the primary endpoint was mRS shift OR 1.23 (95% CI 0.66–2.32).[19] The secondary outcome of mRS 0–1 was 35% vs. 28.6%, OR 1.38 (95% CI 0.63–3.01). The trial was underpowered and hence strong conclusions cannot be made out of these results.

Next Generation Thrombolytic Agent- Tenecteplase

An ideal thrombolytic agent should be efficacious, fast and long-acting, with higher fibrin specificity, without procoagulant effect, lesser intracranial/systemic hemorrhages, active in platelet-rich thrombi and finally also be cost-effective. Many "next generation" thrombolytic agents evolved over the last decade and the most promising one is tenecteplase (TNK) which is a genetically modified tPA with pharmacologic advantage over alteplase. TNK amino acid sequence differs from alteplase at three sites. TNK has a similar mechanism of action but has 14-fold greater fibrin specificity, 80-fold greater resistance to inactivation by plasminogen activator inhibitor-1, no procoagulant action, longer half-life (18 min), and slower plasma clearance compared to alteplase.[20,21] [Table 1] Hence, the availability of a thrombolytic agent which can be given as a single intravenous bolus in acute ischemic stroke was exciting.

Table 1: Comparison of pharmacokinetic and pharmacodynamic properties of alteplase and tenecteplase

Properties	TPA	TNK
Fibrin specificity	++	+++
Thrombolytic potency	+	+++
PAI-1 resistance	−	++
Fibrinogen depletion	++	+
PRT activity	++	+++
Clearance (ml/kg/min)	16.1	1.9

TPA=Tissue plasminogen activator, TNK=Tenecteplase, PRT=Platelet-rich thrombus, PAI-1=Plasminogen activator inhibitor-1, - No action, + Activity present, ++ and +++ Indicates higher grades of activity

Evidence for Tenecteplase in Acute Ischemic Stroke

Haley *et al*. showed the safety of TNK in acute ischemic stroke in an open labeled dose escalation study involving 88 patients using 4 doses of TNK (0.1, 0.2, 0.4, and 0.5 mg/kg). Symptomatic ICH occurred only in 0.5 mg/kg (2/13, 13% of patients).[22] This was followed by four phase 2 trials which gave reasonable assurance regarding the safety and efficacy of TNK. Parson *et al*. (2009) showed in a prospective non-randomized trial, greater efficacy of intravenous TNK (0.1 mg/kg) in acute ischemic stroke patients with a defined ischemic-perfusion mismatch from a proximal vessel occlusion. IV TNK arm had greater reperfusion, lesser infarct growth, and better early clinical improvement than patients who received IV TPA (0.9 mg/kg) in the 3-h window. However, the first randomized controlled trial comparing three doses of TNK with alteplase within the 3 h window period was stopped early due to slow enrolment. However, the 0.4 mg/kg TNK arm had an increased risk of hemorrhage. No definite conclusion on superiority or noninferiority could be drawn from it. Parson *et al*. (2012) came up with their first Phase II RCT on 75 AIS patients (perfusion mismatch with large vessel occlusion, 0–6 h) with three arms (0.1 mg/kg TNK, 0.25 mg/kg TNK and 0.9 mg/kg TPA). Both the TNK arms had better reperfusion and clinical improvement at 24 h compared to alteplase. The study had a selection bias for small cerebral infarctions affecting its generalizability.[23] Another phase 2 trial (ATTEST- Alteplase versus TNK for thrombolysis after ischemic stroke) failed to show any significant difference between alteplase and TNK in AIS patients within 4.5 h.[24] They used conventional eligibility criteria for inclusion in trial and then used computed tomography (CT) perfusion and CT angiography to find out the percentage of "initial territory-at-risk" on CT perfusion that did not ultimately develop into infarct on the follow-up noncontrast CT scan (primary outcome). Around 35% of patients were excluded from the primary analysis since they did not have adequate imaging and also there were significant baseline differences which might have affected the results ultimately.

The first phase III clinical trial with 1100 patients was published in 2017 (Nortest- Norwegian TNK stroke trial) which had a clinical primary outcome.[25] There was no difference in the primary outcome of mRS 0–1 at 3 months (64% vs. 63%, OR 1.08, CI 0.84–1.38, $P = 0.52$). In both the groups, the frequency of symptomatic ICH was similar. The major limitation of the trial was that >80% of patients had minor stroke or stroke mimic and were anyway more likely to have a good prognosis.[26] EXTEND-TNK (TNK versus Alteplase before Endovascular Therapy for Ischemic Stroke) trial (2018) showed that in AIS patients (<4.5 h) with large vessel occlusion eligible for thrombectomy, TNK caused better reperfusion (22% vs. 10%, OR 2.6, CI 1.1–5.9) compared to alteplase. There was no difference in proportion of patients who had functionally independent outcome (mRS 0–2) or excellent outcome (mRS 0–1).

A meta-analysis of three phase 2 RCTs[24,27,28] and one Phase 3 RCT[25] involving 1334 patients did not show any significant difference in mRS at 90 days, mortality at 90 days or any ICH/symptomatic ICH.[29] The authors claimed that "TNK group compared to the alteplase group had significantly better early major neurological improvement (RR = 1.56, 95% CI 1.00, 2.43, $P = 0.05$)." The authors have mentioned its grade evidence profile as critical outcome with moderate certainty. We searched Medline and Cochrane library for research papers published in English before May 2018. We

could find only EXTEND-TNK trial which was not included in the meta-analysis discussed above. We have updated this meta-analysis adding EXTEND-TNK trial [Figure 2].[30] There was significant difference in early neurological improvement favoring TNK (RR = 1.28, 95% CI 1.01, 1.63, $P = 0.05$). Early neurological improvement was defined as improvement in NIHSS ≥8 points or a score of 0–1 at 24–72 h. There was no difference in other outcomes like good functional outcome at 3 months, any ICH, symptomatic ICH or mortality.

There is a compelling cost-effective argument favoring TNK over alteplase, but we need cost effective/benefit analysis studies to prove the advantage. The results of the previous meta-analysis and our updated meta-analysis show that TNK is likely to come up as a cheaper and more effective alternative to alteplase. But have we reached there yet to recommend it universally- technically not yet! The results of the on-going clinical trials (TASTE, ATTEST-2, TEMPO-2, TWIST, EXTEND-IA TNK Part 2) should be awaited to deliver the final verdict on clinical superiority of TNK over alteplase. But since the drug is approved by DGCI in India, the treating neurologist can decide on using TNK or alteplase with in window period of 3 h after taking informed consent. There is still controversy over the dose of TNK approved by DGCI, which was 0.2 mg/kg. This was based on the results of two open label studies which compared the 0.2 mg/kg dose with historical comparison with NINDS trial data.[31] However, the dose in current clinical practice is 0.25 mg/kg and whether 0.4 mg/kg is better for large vessel occlusion is investigated in EXTEND-IA-TNK Part 2 trial. Since TNK can reperfuse 22% of large vessel occlusion, as shown in EXTEND-TNK trial, it may be useful in settings where endovascular therapy is not available. In our clinical practice, we use teneteplase in acute ischemic stroke within 3 h and with large vessel occlusion where EVT is not feasible (due to technical, anatomical, or financial issues).

Endovascular Therapy – "Tissue Clock"

Early window endovascular trials

Ever since the results of Multicentre Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial and the following domino effect of multiple trials being stopped prematurely [Table 2], the standard of care for acute ischemic stroke (<6 h) with an anterior circulation large vessel occlusion has been mechanical thrombectomy with stent retrievers.[32] The result of these 6 endovascular RCTs (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, EXTEND-1A, THRACE) contradicted the results of the three previous RCTs (IMS-3, SYNTHESIS, and MR RESCUE). The reasons for the success of these trials are many including newer (better) technology, better workflow, and patient selection (smaller baseline infarct volume with confirmed large vessel occlusion). The IPD meta-analysis of 5 trials (HERMES collaboration) with 1287 patients showed precise superiority of mechanical thrombectomy (mRS 0–1 at 90 days, 26.9% vs. 12.9%, OR 2.49, 95% CI 1.·84–3.35; $P < 0·0001$; mRS 0–2 at 90 days, 46% vs. 26.5%, OR 2.35, CI 1.85–2.98, $P < 0.0001$).[33] NNT to reduce one point in mRS was 2.6.

Late window endovascular trials

The year 2018 witnessed two landmark trials (DAWN and DEFUSE 3) which brought high-quality evidence to extend

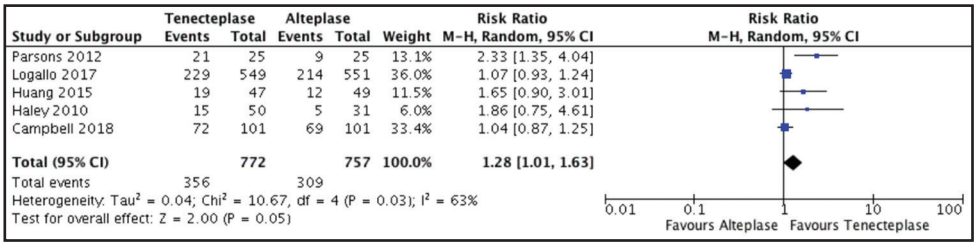

Figure 2: Forest plot of updated meta-analysis of comparison: Tenecteplase versus Alteplase for early major neurological improvement

Table 2: Comparison of endovascular trials with second generation devices[1]

RCT	MR CLEAN	ESCAPE	EXTEND-IA	SWIFT PRIME	REVASCAT	Therapy	Thrace
Number of patients	500 (267/233)	315 (150/165)	70 (35/35)	196 (98/98)	206 (103/103)	108 (54/54)	412 (208/204)
Baseline NIHSS (median)	18 (14–22) versus 17 (14–21)	17 (12–20) versus 16 (13–20)	13 (9–19) versus 17 (13–20)	17 (13–19) versus 17 (13–20)	17 (12–19) versus 17 (14–20)	NR	17 (13–20) versus 18 (15–21)
Median stroke onset to groin puncture (min)	260	241	210	224	269	226	255
mRS (0–2) at 90 days %	19.1 versus 32.6	29.3 versus 53	40 versus 70	35.5 versus 60.2	28.2 versus 43.7	30.4 versus 38	42.1 versus 54.2
NNT	7.1	4.2	3.2	4.0	6.3	13.2	8.3

RCT=Randomized controlled trial, NIHSS=National Institutes of Health Stroke Scale, NNT=Number needed to treat, mRS=Modified Rankin scale, IA=Intra-arterial

the window period for endovascular intervention up to 24 h by careful selection of patients.[34,35] DAWN (DWI or CTP Assessment with clinical mismatch in the triage of wake-up and late presenting strokes undergoing neuro intervention with trevo) trial was the first RCT to compare endovascular therapy with standard of care in acute ischemic stroke patients who were last known to be well 6–24 h earlier.[34] Similar to RCTs with the second generation devices, DAWN trial carefully selected patients with small established infarct and a large vessel occlusion in the anterior circulation. The trial used the concept of "clinical-core mismatch" which was a significant clinical deficit disproportionately severe compared to the already established infarct. The infarct volume was measured by automated software on CT perfusion or MRI DWI imaging. The eligibility criteria were one of the following: "Group A: Age ≥80 years, NIHSS ≥10, core infarct <21 mL; Group B: Age <80 years, NIHSS ≥10, infarct <31 mL; Group C: age <80 years, NIHSS ≥20, infarct 31–<51 mL." DAWN trial enrolled 206 patients (EVT 107 vs. Medical 99). The enrolment was stopped early after prespecified interim analysis which showed a high probability of success. Around 60% of patients had wake up stroke (unknown stroke onset). Compared to medical arm, thrombectomy arm had significant benefit on the 90-day utility-weighted mRS (5.5 vs. 3.4) and rate of functional independence (mRS 0–2, 49% vs. 13%). This benefit was consistent across stroke severity, age, site of vessel involvement, and stroke presentation (witnessed vs. unwitnessed vs. wake-up). The patients selected by "tissue window" in DAWN trial had similar rate of functional independence (mRS 0–2) when compared to "time window" in HERMES meta-analysis (DAWN, mRS 0–2 49% vs. HERMES mRS 0–2 46%).

DEFUSE 3 (endovascular therapy following imaging evaluation for ischemic stroke) trial reinforced the shift in paradigm created by DAWN trial. It enrolled 182 AIS patients (6–16 h after the time last known well) and also was stopped early for efficacy.[35] The inclusion criteria were the presence of proximal large vessel occlusion, initial infarct volume <70 ml and ratio of volume of ischemic tissue on perfusion imaging to infarct volume of 1.8 or more and an absolute volume of penumbra 15 ml or more assessed by CT perfusion or MR diffusion. Thrombectomy arm had a favorable shift in mRS at 90 days (OR, 2.77; $P < 0.001$) and a higher percentage of patients who were functionally independent (mRS 0–2, 45% vs. 17%, $P < 0.001$). There was lesser 90-day mortality in the endovascular arm and there was no difference in symptomatic ICH or serious adverse events. Thus, both DAWN and DEFUSE 3 have brought Class I evidence for mechanical thrombectomy for selected patients satisfying their inclusion criteria.

Both these trials were stopped early which could have led to overestimation of effect of mechanical thrombectomy.[36,37] Majority of patients in both the trials were wake up strokes, which tend to occur close to awakening. Hence, many of these patients might be biologically within the established window period of 6 h and the control group in these trials might have been a disadvantage. Even then these trials have shown that in wake-up strokes with small core and large penumbra with large vessel occlusion, mechanical thrombectomy can significantly change the outcome. A summary of absolute risk reduction and NNT of alteplase and endovascular thrombectomy is depicted in Table 3.[6]

Late window paradox

DAWN and DEFUSE trials have shown us the concept of "late window paradox."[38,39] Since "time is brain," interventions done >6 h of stroke onset should be less beneficial than those done within 6 h. However, results of DEFUSE and DAWN were better than those endovascular trials done within 6 h. In fact, DAWN had the largest absolute increase (35.5%) in functional independence across any stroke therapy trial even after median time from stroke onset being 12.5 h. DEFUSE 3 had 28% increase in functional independence and had the largest reduction in mortality/severe morbidity (20%) ever achieved. Even HERMES (pooled analysis of five early window endovascular RCTs) had only 19.5% absolute increase in functional independence and 11% decrease in mortality. All these trials had similar patients, stroke severity, thrombectomy devices, and reperfusion achievement. This better results in late window endovascular trials are called "late window paradox." Various factors affect this phenomenon. A significant number of stroke patients with LVO have very protracted growth of the ischemic core for 12 h or even longer. It is the good collateral circulation which keeps the ischemic core size small for this long period and eventually fails to increase the size of infarct. Hence, DAWN and DEFUSE had enrolled patients with very small ischemic core, very slow growth rate of infarct, and large penumbra. The medical arm of these trials would have poor outcomes as most of them would not receive IV TPA as they are

Table 3: Absolute risk reduction and number needed to treat in intravenous thrombolysis (alteplase) and endovascular thrombectomy

	ARR (%)	NNT
Intravenous thrombolysis (alteplase) mRS 0–1 at 90 days		
Based on IPD meta-analysis (Emberson *et al.* Lancet 2014)		
≤3 h (*n*=1549)	9.8	10
>3≤4.5 h (*n*=2768)	5.2	19
ECASS 3 (3–4.5 h) (*n*=821)	7.2	13.8
Endovascular therapy (mRS 0–2 at 90 days)		
MR CLEAN (*n*=500, WP=6 h)	14	7.1
ESCAPE (*n*=315, WP=12 h)	24	4.2
REVASCAT (*n*=206, WP=8 h)	16	6.3
SWIFT PRIME (*n*=196, WP=6 h)	25	4.0
EXTEND -1A (*n*=70, WP=6 h)	33	3.2
HERMES (IPD meta-analysis of 5 trial, *n*=1287)	19.5	2.6
DAWN (*n*=206, WP=6–24 h)	35.5	2.8
DEFUSE (*n*=182, WP=6–16 h)	28	3.6

ECASS=European Collaborative Acute Stroke Study, IPD=Individual patient data, NNT=Number needed to treat, mRS=modified Rankin scale, ARR=Absolute risk reduction, WP=Window period

out of window period of 4.5 h and their collateral circulation will eventually fail causing large infarct.

Conclusion

The recent advances in the reperfusion strategies have added "tissue window" to the existing "time window" and many patients with small ischemic core, large penumbra, good collaterals may benefit from mechanical thrombectomy if they have a proximal LVO even if they arrive within 6–24 h of stroke onset. Wake up stroke patients with unknown stroke onset may also benefit from thrombolysis with alteplase if they have diffusion-FLAIR mismatch. The next generation thrombolytic agent, TNK has shown huge promise and the results of the on-going trials are eagerly awaited to provide definite evidence for its clinical superiority over alteplase.

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Conflicts of interest

There are no conflicts of interest.

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