Changing Paradigm in Acute Stroke Management

Introduction

Stroke remains a leading cause of death and long-term disability, requiring prolonged rehabilitation and nursing care, thus a major healthcare and economic burden. Although intravenous (IV) thrombolysis using recombinant tissue plasminogen activator (rt-PA or t-PA) has been used as a working horse in most stroke treatment units, this mode of treatment has been plagued by many innate shortcomings like a narrow therapeutic time window (<4.5 hours), strict exclusion criteria, poor early recanalization rates (21%), frequent re-occlusions. The apprehension of intra cerebral haemorrhage (ICH), reported around 6.3% in National Institute of Neurological Disease and Stroke (NINDS) trial [1], unsuitability in T-occlusions, M1 occlusions and large clot burden [2] further make IV t-PA inept in many clinical settings. Studies on Intra-arterial (IA) thrombolysis, found statistically significant improvement in neurological outcome when compared to IV t-PA and the higher cost of IA-therapy is often compensated by reduction in long term care and rehabilitation. The Prolyse in Acute Cerebral Thrombolysis (PROACT) followed by the PROACT II [3] have laid the foundation for IA-thrombolysis. Recanalization in the range of 66%, complete Recanalization (Thrombolysis in Myocardial Infarction (TIMI) grade 3) in 19% and improved outcome with IA-thrombolysis made it a definite advantage over IV rt-PA. Despite higher recanalization rates, the relative unpredictability of this form of treatment led to search for better tools to treat acute stroke. Combined clot disruption and IA-thrombolysis was initiated in the clinical setting by Barnwell et al. [4]. This early experience underscored the need for safe and reliable clot retrieval systems.

Endovascular intervention was in its early stages during publication of NINDS trial. A short spell of mechanical retrieval of clot using MERCI device did not succeed in making a mark in terms of clinical benefit, owing to the inherent deficiency in initial device design. But over the last two decades there have been an exponential rise in the number of endovascular tools. The protean nature of these tools has been complemented by a paradigm shift in acute stroke management in favor of Mechanical Thrombectomy (MET). The validation of incorporating these devices, improving expeditious treatment and image guided patient selection are encompassed in seven positive trials, MR CLEAN [5], EXTEND IA [6], ESCAPE [7], SWIFT PRIME [8], REVASCAT [9], THRACE [10] and THERAPY [11].

Intravenous Thrombolysis: Defining the Current Indications

Intravenous recombinant tissue plasminogen activator (rt-PA) is the approved treatment for acute ischemic stroke within 4.5 hours of symptom onset as evidenced by two placebo controlled trials [1,12]. A narrow therapeutic time window (<4.5 hours), strict exclusion criteria, poor early recanalization rates (21%), frequent re-occlusions for IV rt-PA still debase this mode of treatment. EPITHED and DEFUSE have tried to suggest through multimodal neuroimaging with attenuation of infarct growth and target mismatch that IV rt-PA therapy can include patients up to 6 hours [13,14], DEFUSE further defines “target profile” and “malignant profile” using DWI and PWI to further delineate suitability for patients in terms of clinical response rates and avoid reperfusion related brain hemorrhage.

Tenecteplase, a third generation t-PA, has better fibrin binding affinity and greater resistance to inactivation compared to Alteplase. Similarly Desmoteplase, a drug derived from saliva of vampire bats, is more selective for fibrin without any deleterious effect on blood brain barrier (BBB), was thought to hold the future of IV therapy as evidenced by DIAS and DEDAS, two promising phase –II studies [15,16]. But the DIAS-2, DIAS-3 suggested no improvement in functional outcome when given to patients who had ischemic stroke and major cerebral artery occlusion beyond 3 hours [17,18] this led to stop recruitment for DIAS-4 as the study was unlikely to reach its primary endpoint with the current protocol [19].

Further attempt to use adjunctive strategies like sonothrombolysis by the CLOTBUST-HF study [20], which is at best a small case series, needs validation in larger models before acceptability comes to routine practice.

Intra-Arterial Thrombolysis: Lack of Level 1 Evidence

The shortcomings of the Prolyse in acute Cerebral Thromboembolism (PROACT) trial, to reflect improvement in neurological outcomes [3] in the IA Pro-Urokinase arm has been overcome by its successor PROACT II by using a control group (no IA infusion) and recruiting higher patient numbers. This attempt to expiate the clinical outcomes of its predecessor (90-day mRS 0-1: 26% vs. 17%, P=0.16), primary efficacy analysis with the revised outcome showed improvement in patient morbidity in the IA pro-Urokinase arm (mRS 0-2: 40% vs 25%, P=0.04) [21]. Thrombolysis by intravenous rt-PA brings substantial benefit in
acute stroke, however, a large number of patients do not respond to this treatment. Intra-arterial thrombolysis may improve overall outcome in patients with basilar artery occlusion but predicting benefit of therapy is still difficult in individual patient [22]. The Middle Cerebral Artery Embolism Local Fibrinolytic Interventional Trial (MELT) though prematurely aborted owing to intra-trial approval of IV rt-PA in Japan still reflects 52.7% recanalization rates and secondary benefit in functional outcome (mRS 0-1; 42.1% vs. 22.8%, P=0.017). The primary outcome in MELT had no statistical difference. Lower baseline NIHSS scores, possibly contributed to improved outcomes in the control group [23]. Combined IV and IA t-PA in acute stroke management have been evaluated by the Emergency Management Of Stroke (EMS) [24], Interventional Management Of Stroke (IMS-II) [25] and RECANALISE study [26] albeit their low enrolment numbers and possibility of selection bias failed to demonstrate improvement in clinical outcome in the combined IV-IA rt-PA arm despite superior recanalization rates (47-80% TIMI 2-3) [3,22,21,23-27]. There is a lack of level 1 evidence demonstrating superiority of IA-thrombolysis over IV therapy despite multitude of trials in this direction. The multitude of IA thrombolytic agents offer promise in selected patients with acute ischemic stroke without a significant risk of Intra-cerebral haemorrhage.

Mechanical Thrombectomy: The Paradox Of Choice

There has been a steady proliferation of devices aimed at mechanical thrombectomy (MET), ranging in shapes like screws, baskets to retrievable stents; and function like retrievers and aspirators. This treatment modality has undergone sufficient audit in terms of equivocal (rather pessimistic) trials to the most recent evidences which have made the paradigm shift towards use of MET as first line treatment in select setting.

Devices

MET devices can be categorized into two types based on their mechanism of action: retrievers-approach distal to thrombus, aspiration device-approach proximal to thrombus. The genre of retrievers started with the Mechanical Embolus Removal in Cerebral Ischemia (MERCI, Concentric medical, California, USA). MERCI is a flexible corkscrew-shaped device constructed of nitinol memory wire, designed to remove blood clots from the brain with ischemic stroke. The Multi MERCI trial, an international, multicenter prospective study evaluated combined safety and efficacy of IV t-PA with MERCI device when used within 8 hours of stroke. Successful recanalization (TIMI 2-3) was achieved in 57.3% of patients and 68.5% after adjunctive therapy; 36% of these patients had a favourable neurological outcome [27]. MERCI was approved by FDA in 2004, based on uncontrolled trial as the regulatory requirements for devices was different from that of drugs [28]. This mercy of FDA toward MERCI led to a series of heterogeneous non-inferior trials which revealed only equivocal results towards MET. Following MERCI there ushered a series of devices specifically directed towards thrombectomy.

The CATCH device (Balt Extrusion, Montmorency, France) is a self expanding nitinol basket used to retrieve thrombi using a distal approach [29]. The Solitaire FR (Ev3, California, USA), FDA approved in 2012, comprises of a retrievable stent (stentriever) that promotes restoration of blood flow by providing radial force to open and restore occluded vessels simultaneously allow administration of adjunctive medical therapy and retrieve clots via an open ended basket [30,31]. The Solitaire With Intention for Thrombectomy (SWIFT) randomized clinical trial observed a significantly higher recanalization rate (TIMI score 2-3) obtained with Solitaire device compare to MERCI (61% VS. 24%; p<0.0001) and a more favourable 3 month neurological outcome (58%vs. 33%, P=0.0001).

Recent inclusion into this select group include the TREVO device (Concentric Medical, California, USA) [32,33] and the REVIVE system (Codman & Shurtleff Inc, Massachusetts, USA) [34]. Both TREVO and REVIVE feature close ended distal end to prevent clot embolization. However, the TREVO device employs radiopaque stent wires allowing better visibility during deployment and angiography. TREVO 2 trial demonstrated significantly higher recanalization rates with TREVO as compared to MERCI. However, it was noted that perforations were 10 times more common using the MERCI device (1% vs. 10%, P=0.02). Aspiration devices use a proximal approach using several aspiration techniques. The Penumbra system (Penumbra Inc, California, USA) [35] is composed of a reperfusion catheter, separator and a thrombus removal ring. It removes thrombus using aspiration and extraction. The Penumbra Pivotal Stroke Trial, The Penumbra POST study, and recently the SPEED study revealed 81% to 91% successful recanalization with 25 to 41% improvement in clinical outcome. Symptomatic intracranial hemorrhage was 14% in Pivotal trial, 6% in POST study and 14% in SPEED study [36-38].

Similar devices using monorail catheters, which aspirate clot using negative pressure include QuickCat (DSM Inc, Philadelphia, USA) and PRONTO (Vascular Solutions Ins, Minnesota, USA) [39] have come into use for MET. However, there is insufficient data for their use in acute stroke. The abundance of device numbers and the aclarity of the industry to introduce even newer tools must be made coherent; by formulating randomized controlled trials (RCT) which can juxtapose all such devices and make the scientific community acquaintance to a particular or a select few device as the current gold standard to impart MET.

The Final Nail in the Coffin for Met: Poor Trial Design [28]

Initial attempts at interventional stroke treatment brewed futile and initial trials published before December 2014 aimed at sealing the fate of this novel treatment. Contrary to SWIFT and Diffusion and Perfusion Imaging Evaluation for Understanding of Stroke evolution 2(DEFUSE 2) the three trials that tried to initiate clinical nihilism toward MET were Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS Expansion) [40], Interventional management of Stroke (IMS-III) [41] AND Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) [42].

SYNTHESIS Expansion trial did not confirm large vessel occlusion, resulting in patients without large vessel occlusion being randomly assigned to endovascular group. The selective

Citation: Husain S, Somnath J (2017) Changing Paradigm in Acute Stroke Management. J Neurol Stroke 6(4): 00206.
DOI: 10.15406/jnsk.2017.06.00206
nature of this mode of treatment offered on a random basis, due to the generalizability of the study, resulted in a neutral clinical outcome. IMS-III was plagued by similar randomization issues, apart from use of outdated approaches like MERCI and IA thrombolysis. The MR RESCUE results were skewed owing to non-use of stentriever in the endovascular arm and including patients with infarct volumes up to 90 ml, which are considered very large and refractory to any revascularization [40-42].

At the time of their publication, these studies were felt to be the final blow to endovascular treatment for stroke, however; close review of these skewed studies demonstrated that improper patient selection and outdated endovascular therapy resulted in inadequate recanalization and hence poor clinical outcome. Their conclusions should be viewed with caution and judicious consideration of the fore mentioned limitations. The outcomes of these trials are more related to the nature of the design of these trials, than a true reflection of what these trials had aimed at their initiation. It also reflects on the domino effect of regulatory regimes that short-cut scientific scrutiny by approving devices on 'surrogate' markers than by rigorous clinical end-points that are usually insisted for newly introduced drugs. Stroke trials, given the mechanistically simple nature of the disease, help us to decipher this phenomenon in reasonable detail. We could only guess the magnitude of effects of the 'yet unknown' subgroups in clinical trials on diseases where pathogenic pathways are extremely complex, and where simple mechanistic reasoning is unrewarding [28].

Unnailing Vespers: Recent Trials and Met

The aftermath of the fore mentioned trials was followed by seven positive trials towards MET. The incorporation of newer devices, improving image based selection and more expedient treatment times have resulted in these positive findings in MR CLEAN [5], EXTEND IA [6], ESCAPE [7], SWIFT PRIME [8], REVASCAT [9], THRACE [10] and THERAPY [11].

The first trial in the series was MR CLEAN (Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in Netherlands) was unique in the sense that it was the first randomized controlled trial to demonstrate the superiority of intra-arterial treatment [5]. This trial enrolled patients with clinical and radiological evidence of proximal anterior circulation ischemic stroke who presented within 6 hours of onset and were randomized to receive intra-arterial thrombolysis (mechanical or pharmacological) at the discretion of the interventionist. The primary outcome i.e. 90 day NIHSS showed significant improvement (adjusted OR 1.67, 95% CI 1.21-2.30). The incidence of functional independence, defined as mRS 0-2 was also higher in intervention arm (32.6% vs. 19.1%). The advantages in this trial included increased availability of CTA to confirm presence of proximal anterior circulation occlusion, use of newer generation stentriever in 82% of all patients. The evidence of this trial was so profound that it led to premature termination of numerous similar subsequent trials.

The EXTEND-IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra-Arterial) enrolled patients with ICA or MCA occlusions within 4.5 hours of onset, with CT evidence of perfusion mismatch and core infarct volume of less than 70 ml and randomized them to receive MET with the Solitaire device following IV t-PA vs. IV t-PA alone. The significant superior neurological outcome in Endovascular arm i.e. at 3 day (absolute increase 43%) and at 90 days (mRS 0-2 absolute increase 31%) and immaculate safety profile led to premature termination after randomization of 70 patients [6].

The ESCAPE (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times) included patients of proximal anterior circulation ischemic stroke within 12 hours of stroke onset with good collaterals and small infarct core based on ASPECTS score>6, NIHSS>5, multiphase CTA to identify collaterals. Those enrolled were randomized to receive medical management vs. rapid endovascular treatment predominantly using stentriever, within 60 minutes. The absolute increase in functional independence was 23.7% and absolute reduction in mortality was 8.6% [7].

SWIFT-PRIME (“Solitaire” FR as Primary Treatment for Acute Ischemic Stroke) enrolled T-PA eligible patients within 4.5 hours of stroke onset with NIHSS>8 and ASPECTS score >6 were randomized to receive IV t-PA and endovascular therapy with Solitaire device vs. IV t-PA alone. Again the endovascular and t-PA arm demonstrated favourable results i.e.90 days functional independence (mRS 0-2) was 25% higher than control arm. More notably there was 88% successful reperfusion (TICI 2b-3) [8].

The REVASCAT (Endovascular Revascularization With Solitaire Device vs Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours) included patients with Intracranial ICA or proximal MCA strokes within 8 hours who were ineligible for IV t-PA or had no recanalization within 30 minutes of IV t-PA with ASPECTS score>6 were included. The absolute functional independence was 15.5% more than control arm, though this low value could be attributed to use of less accurate ASPECTS scoring criteria to estimate infarct core [9].

THRACE enrolled strokes of either anterior circulation or posterior large vessel occlusion presenting within 5 hours, to receive mechanical thrombectomy after IV t-PA or IV t-PA alone. Preliminary results suggested significant benefit in endovascular arm [10].

THERAPY (The Randomized Concurrent Controlled Trial to Assess The Penumbra System’s Safety and Effectiveness in The Treatment Of Acute Stroke), albeit prematurely halted due to positive results from the prior studies, was unique in itself as it included patients with large clot burden (length >8mm) and use of Penumbra device as the sole endovascular tool. Preliminary results indicated that differences in 90 days mRS 0-2 was not statistically significant [11]. In spite of the positive results of MET, the occasional instances of reperfusion injury make us question the criteria for instituting this therapy. There are still undefined criteria like status of collateral circulation, which needs elaborative research in this regard. Radiological indicators like large penumbra with a small core could be merely a MR surrogate to the actual collateral circulation to an affected area, rather definite CT or MR perfusion studies and collateral flow grading
Changing Paradigm in Acute Stroke Management

Heterogeneity of Collateral Vessels: Outcome in Stroke Recanalization [43]

In their study Bang et al. [43] have brought into light a very important association of collateral circulation and outcome following revascularization therapy. They have analyzed pre-treatment collateral circulation and its relationship with recanalization and clinical outcome. Pre-treatment angiographic collateral grades were evaluated using ASITN/SIR collateral flow grading system and pre-treatment MRI. The results revealed higher recanalization rate in patients with better pre-treatment collaterals (p<0.001). Similarly 7-day volume of infarct volume of infarct growth on MRI was highest with poor pre-treatment collaterals and thus poor recanalization. Collaterals provide the ischemic preconditioning which limit the infarct volume and improve clinical outcomes in well-collateralized patients. The study limitation was that this study was not an RCT and the revascularization therapy was not standardized (ranging from IV t-PA to MET).

The Paradigm Shift

The management of acute stroke moved from no treatment towards IV thrombolysis, with present day learning suggesting it to be a first line treatment within the window period. IV therapy is only effective in 40% of patients. New evidence suggest IV treatment inefficient in Lacunar stroke and grossly ineffective in T-occlusion and stroke with large clot burden (>4mm) and these may be considered as relative contraindications for IV therapy, where this form of treatment must not be considered at all. The era of intra-arterial thrombolysis died its own death (reasons for this outcome is unclear), in spite of a well conducted PROACT II trial.

The vicissitude for endovascular treatment for acute stroke has been paved by device innovation, misplaced regulatory policies, ill defined randomized controlled trials and the final respite coming from the latest trials validating this form of treatment. Proper patient selection through sophisticated imaging techniques, ability to deliver endovascular therapy in a race against time and state of the art tools make endovascular therapy the cornerstone of management of acute ischemic stroke today.

Enthusiasm towards use of Mechanical devices tested by ill structured trials like SYNTHESIS expansion, IMS III and MR RESCUE resulted in failed studies and poor results. This was soon followed be execution of properly designed and executed trials like MR CLEAN, EXTEND IA, ESCAPE, SWIFT PRIME, REVASCAT etc. which proved time and again the superiority of MET and led to cessation of most of these trials prematurely, owing to proven superiority of the MET arm. This success story has opened a new dimension in acute stroke management.

However current indications of MET are not well defined. In our view the following criteria could be considered ideal for considering Mechanical thrombectomy. All inclusion criteria similar to NINDS criteria for IV thrombolysis along with-

1. Acute stroke due to large vessel occlusion with large clot burden which can be easily picked up by 'dense vessel sign'.
2. Presence of good collateral circulation, demonstrated by CT perfusion study or assessment on DSA.
3. Completion of revascularization – temporary or permanent within 260 minutes.

Reference

1. National Institute of Neurological disorders and stroke rt-PA Stroke Study Group (1995) Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 333(24): 1581-1587.
2. Barreto AD, Albright KC, MPH, Hallevi H, Grotta JC, et al. (2008) Thrombus Burden Is Associated With Clinical Outcome After Intra-Arterial Therapy for Acute Ischemic Stroke. Stroke 39(12): 3231-3235.
3. Del Zoppo GJ, Higashida RT, Furlan AG, Pessin MS, Rovly HA, et al. (1998) PROACT: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. PROACT investigators. Prolyse in acute cerebral thromboembolism. Stroke 29(1): 4-11.
4. Barnwell SL, Clark WM, Nguyen TT, O’Neill OR, Wynn ML, et al. (1994) Safety and efficacy of delayed intrarterial urokinase therapy with mechanical clot disruption for thromboembolic stroke. AJNR Am J Neuroradiol 15(10): 1817-1822.
5. Berkhemer OA, Fransen PS, Beumer D, Van den Berg LA, Lingsma HE, et al. (2015) A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 372(1): 1009-1018.
6. Campbell BC, Mitchell PJ, Kleijng Tj, Dewey HM, Churilov L, et al. (2015) Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 372(11): 1009-1018.
7. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, et al. (2015) Randomized assessment of rapid endovascular treatment of Ischemic stroke. N Engl J Med 372(11): 1019-1030.
8. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, et al. (2015) Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med 372(24): 2285-2295.
9. Jovin TG, Chamorro a, Gobo E, de Miquel MA, Molina CA, et al. (2015) Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med 372(24): 2296-2306.
10. Braicard S, Ducrocq X, Mus JL, Soudant M, Oppenheim C, et al. (2015) THRACE: Trial and cost effectiveness evaluation of intraarterial thrombectomy in acute ischemic stroke. Clinical trials.gov NCT01062698.
11. Mocco J, Khatri P, Zaidat O (2015) The randomized concurrent controlled trial to assess the penumbra system’s safety and effectiveness in the treatment of acute stroke. In: European stroke organization (ESO) conference.
12. Hacke W, Kaste M, Bluhmki E, Brozman M, Davales A, et al. (2008) Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 359(13): 1317-1329.
13. Davis SM, Donnan GA, Parsons MW, Levi C, Butcher KS, et al. (2008) Effects of alteplase beyond 3 h after stroke in the e choplanar imaging thrombolytic evaluation (EPITHET) a placebo controlled randomised trial. Lancet Neurol 7(4): 299-309.
14. Albers GW, Thijs VN, Wechler L, Kemp S, Schlaug G, et al. (2009) Magnetic resonance imaging profiles predict clinical response to early reperfusion: the diffusion and perfusion imaging evaluation for understanding stroke evolution (DEPUSE) study. Ann Neurol 60(5): 508-517.

15. Hacke W, Albers G, Al-Rawi Y, Bogousslavsky J, Davalos A, et al. (2005) The desmopressin in Acute ischemic stroke trial (DIAS): a phase II MRI based 9-hour window acute stroke thrombolysis trial with intravenous desmopressin. Stroke 36(1): 66-73.

16. Furlan AG, Eyding D, Albers GW, Al-Rawi Y, Lees KR, et al. (2006) Dose escalation of desmopressin for acute ischemic stroke (DEPAS): Evidence of safety and efficacy 3-9 hours after stroke onset. Stroke 37(5): 1227-1231.

17. Hacke W, Furlan AJ, Al-Rawi, Piebach JB, Gruber F, et al. (2009) Intravenous desmopressin in patients with acute ischemic stroke selected by MRI perfusion-diffusion weighted imaging or Perfusion-CT (DIAS-2): a prospective, randomised, double blind, placebo-controlled study. Lancet Neurol 8(12): 141-150.

18. Albers GW, von Kummer R, Trueken T, Jensen JK, Ravn GM (2015) Safety and efficacy of desmopressin given 3-9 h after ischemic stroke in patients occlusion or high grade stenosis in major cerebral arteries (DIAS-3): a double blind, randomized, placebo-controlled phase 3 trial. Lancet Neurol 14(6): 575-584.

19. Lundbeck (2017) Efficacy and Safety Study of Desmopressin to Treat Acute Ischemic Stroke (DIAS-4). Clinicaltrials.gov NCT00856661.

20. Barreto AD, Alexandrow AV, Shen L, Sisson A, Bursaw AW, et al. (2013) CLOTBUST-handfree; Pilot Safety study of a novel operator-independent ultrasound device in patients with acute ischemic Stroke. 44(12): 3376-3381.

21. Furlan A, Hijashida R, Wechsler L, Gent M, Rowley H, et al. (1999) Intra-arterial prourokinase for acute ischemic stroke. JAMA 282(21): 2003-2011.

22. Husain S (2004) Clinical and radiological predictors of recanalisation time to define a rapid scoring system. J Neurol Neurosurg Psychiatry 75(6): 811-812.

23. Ogawa A, Mori E, Minematsu K, Taki W, Takahashi A, et al. (2007) Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke: the middle cerebral artery embolism and revascularization of large vessel occlusion in acute ischemic stroke. Japan. Stroke 38(10): 2633-2639.

24. Lewandowski GA, Frankel M, Tomsick TA, Broderick J, Frey J, et al. (1999) Combined intravenous and intra-arterial rt-PA vs intraarterial therapy of acute ischemic stroke: Emergency management of Stroke (EMS) Bridging trial. Stroke 30(12): 2598-2605.

25. The IMS II trial investigators (2007) The interventional management of stroke [IMS] II study. Stroke 38(7): 2127-2135.

26. Mazighi M, Serfaty JM, Labreuche J, Laissy JP, Meseguer E, et al. (2009) Comparison of intravenous alteplase with a combined intravenous-endothrombolytic approach in patients with stroke and confirmed arterial occlusion (RECANALISE study). Lancet Neurol 8(9): 802-809.

27. Smith WS, Sung G, Saver J, Budzik R, Duckwiler G, et al. (2008) Mechanical thrombectomy for acute ischemic stroke: final results of the multi MERCI trial. Stroke 39(4): 1205-1212.

28. Srijithesh RS, Husain S (2014) Influence of trial design, heterogeneity and regulatory environment on the results of clinical trials: An appraisal in the context of recent trials on acute stroke intervention. Ann Indian Acad Neurol 17(4): 365-370.

29. Mourad I, Brunel H, Costalat V, Riquelme C, Lobotesis K, et al. (2011) Mechanical Thrombectomy in acute ischemic stroke: catch device. AJNR Am J Neuroradiol 32(8): 1381-1385.

30. PapaPanagiotou P, Roth C, Walter S, Behnke S, Politi M, et al. (2010) Treatment of acute cerebral artery occlusion with a fully recoverable intracranial stent. Circulation 121(23): 2659-2666.

31. Natarajan SK, Siddiqui AH, Hopkins LN, Levy EI (2010) Retrieval detachable stent-platform-based thrombectomy device (Solitaire®FR) for acute stroke revascularization: first demonstration of feasibility in a canine stroke model. Vasc Dis Manag 7: 120-125.

32. Nougiera RG, Latsep H, Gupta R, Jovin T, Albers GW, et al. (2012) Trevo versus Merci retriever for thrombectomy revascularization of large vessel occlusions in acute ischemic stroke: (TREVO 2) a randomized trial. Lancet 380(9849): 1231-1240.

33. San Roman L, Obach V, Basco J, Macho J, Lopez A, et al. (2012) Single-center experience of cerebral artery thrombectomy using the TREVO device in 60 patients with acute ischemic stroke. Stroke 43(6): 1657-1669.

34. Rhode S, Haehnel S, Herweh C, Pham M, Stampa S, et al. (2011) Mechanical Thrombectomy in acute embolic stroke: preliminary results with revive device. Stroke 42(10): 2954-2956.

35. Bose A, Henkes H, Alffe K, Reith W, Mayer TE, et al. (2008) The penumbra system: a mechanical device for the treatment of acute treatment of acute stroke due to thrombembolism. AJNR Am J Neuroradiol 29(7): 1409-1413.

36. Frei D, Gerber J, Turk A, McPherson M, Heck D, et al. (2013) The SPEED study: initial clinical evaluation of the Penumbra novel 054 Reperfusion Catheter. J Neurointerv Surg Suppl 1: 174-176.

37. Penumbra Pivotal Stroke Trial Investigators (2009) 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 40(8): 2761-2768.

38. Tarr R, Hsu D, Kulcsar Z, Bonvin C, Rufenacht D, et al. (2010) The POST trial: initial post-market experience of the Penumbra system: revascularization of large vessel occlusion in acute ischemic stroke in the United States and Europe. J NeurolInterv Surg 2(4): 341-344.

39. Hernandez E, Goel N, Dougherty KG, Strickman NE, Krajcer Z (2009) Benefits of catheter thrombectomy during carotid stenting: a preliminary study. Tex Heart Inst J 36(5): 404-408.

40. Ciccone A, Valvassori L, Michelatti M, Sgolo F, Ponzo M, et al. (2013) SYNTHESIS expansion Investigators. Endovascular Treatment of acute ischemic stroke. N Engl J Med 369(10): 904-913.

41. Broedrick JP, Palesh YY, Demchuk AM, Yeatts SD, et al. (2013) Interventional Management of Stroke[IMS] III Investigators. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. N Engl J Med 368(10): 893-903.

42. Kidwell CS, Jahan R, Gornbein J, Alger JR, Nenov V, et al. (2013) A Trial of imaging selection and endovascular treatment for ischemic stroke. N Engl J Med 368(10): 893-903.

43. Bang Y, Saver JL, Kim SJ, Kim GM, Chung CS, et al. (2011) Collateral Flow predicts response to endovascular therapy for acute ischemic stroke. Stroke 42(3): 603-609.