Emerging Strategies For Prevention And Management Of Revolutionizing Stroke Care-A Review Study

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ABSTRACT

Stroke can be defined as a neurological deficit associated with an acute focal injury to the central nervous system. The burden of stroke has increased by 70 percent in the last three decades. The continuing disability attributed to stroke results in a compromised quality of life in most patients. This compels further research to provide better outcomes. The DORIC trial concluded the addition of adjunctive cilostazol in

type II diabetes mellitus patients with intermittent claudication symptoms, to be an effective preventive strategy. The beneficial effects of rivaroxaban and aspirin for stroke prevention in patients with coronary and peripheral artery disease have been demonstrated in the COMPASS study. Another such research, the ENCHANTED trial, proposed a modest reduction in symptomatic intracranial haemorrhage (sICH) with low-dose alteplase in ischemic stroke patients. Also, intensive systolic blood pressure (SBP) lowering has been illustrated to result in negative effects in ischemic stroke. In thrombolysis patients, decompressive hemicraniectomy (DCH) indicated favourable outcomes by reducing the intracranial pressure (ICP) and preventing brain herniation. Two left atrial appendage occlusion (LAAO) devices have been investigated in the Amulet IDE trial, which signified a similar efficacy and safety with the Amulet occlude and the Watchman device. One of the recent trials has also demonstrated positive therapeutic outcomes with an NMDA receptor antagonist, memantine, in improving brain functioning, recovering neuronal injury, and reducing cerebral ischemia. This review aims to summarize several research observations to advance the prevention and management of ischemic stroke.

KEYWORDS: Ischemic Stroke, Neurological Deficit, Neuroprotection, Thrombosis, Prevention, Management.

INTRODUCTION

Stroke is the second leading cause of mortality and long-term disability worldwide. The global prevalence of stroke is 101.5 million, with 14 million new cases each year. Ischemic stroke accounts for 87% of all types of strokes, where blood flow to the brain is obstructed predominantly due to thrombosis or embolism.[1] Ischemic stroke is characterized by the classic stroke symptoms of facial drooping, one-sided weakness of the limbs, and speech difficulties.[2] The multi-factorial etiologies include both, modifiable and non-modifiable risk factors. Timely restoration of blood flow is of immense importance to preserve neurological function.[3] Currently, only rtPA (recombinant tissue plasminogen activator) is the only approved therapy, but it has its limitations such as a narrow benefit window and possible hemorrhagic side effects. Thus, novel treatment options are indispensable given that stroke

poses a medical threat to human health and quality of life.[4] During the last decade, several research studies have been conducted, to develop better management alternatives for stroke.[5] In this review, we have focused our discussion on the recently studied preventive and treatment plans in patients at-risk and those who suffered a stroke, respectively; based on a comprehensive understanding of experimental literature. A discussion featuring various trials and research has been taken note of, which includes evaluation of adjunctive cilostazol in the DORIC trial, discontinuation of rivaroxaban and aspirin combination in the COMPASS trial, and decompressive hemicraniectomy (DCH). Further, the Amulet IDE trial has been discussed, which compared two left atrial appendage occlusion (LAAO) devices. The role of the NMDA receptor was assessed and the effects of memantine were explained. Many such studies, including pharmacologic and non-pharmacologic surgical interventions, have also been discussed. Figure 1 outlines the pathophysiological events involved in the development of ischemic stroke.

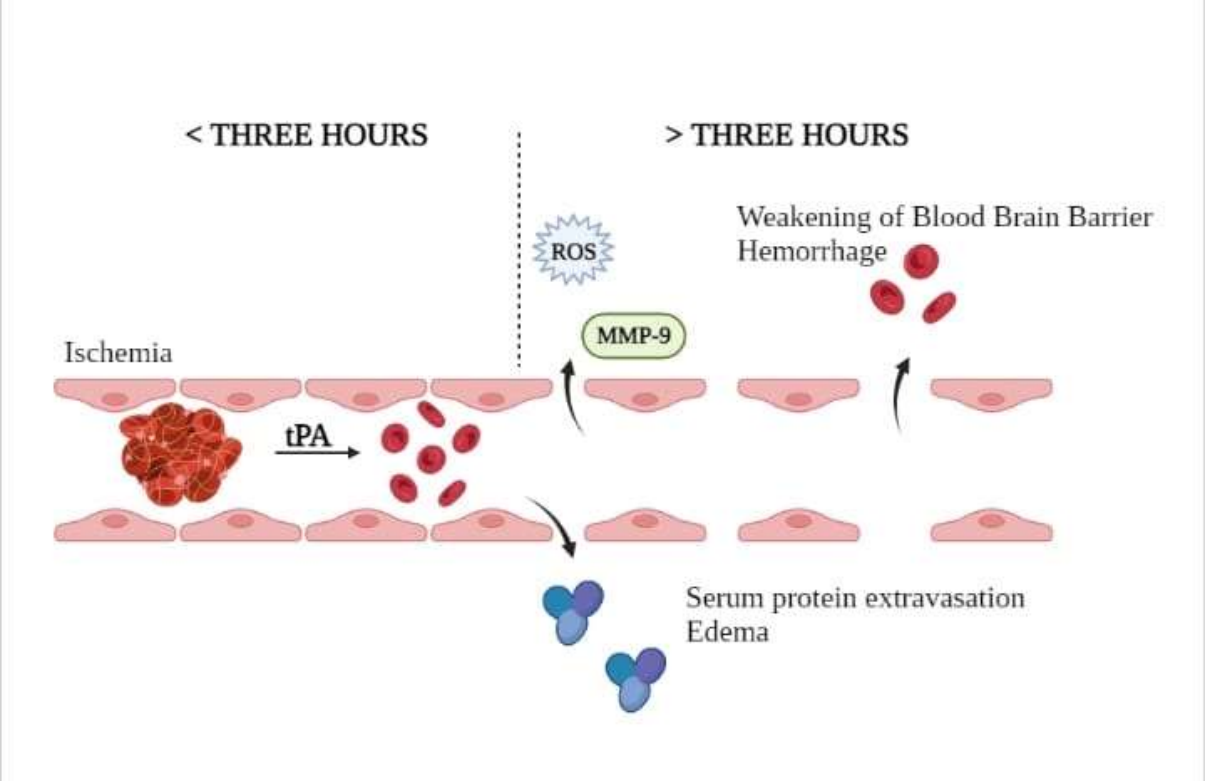

Figure 1. The pathogenesis of ischemic stroke has been depicted in this diagram.

DORIC is a phase IV trial, which evaluated the efficacy and safety of adjunctive cilostazol added to clopidogrel in type II

diabetes mellitus sufferers with intermittent claudication signs and symptoms, in the prevention of ischemic vascular events like stroke and myocardial infarction. Cilostazol is a phosphodiesterase-III (PD-III) inhibitor, having anti-platelet, anti-thrombotic, anti-inflammatory, and vasodilatory action added to its anti-mitogenic property. T2DM patients are at an increased danger of developing lower extremity arterial disease (LEAD), which is likewise associated with other vascular events and in even worse situations, lower limb amputation. As a consequence, the prevention of acute vascular events in this populace of patients is of more significance. This research concluded cilostazol is effective and safe in terms of bleeding risk, as an accessory to clopidogrel in decreasing the occurrence of acute vascular events like stroke and MI.[6] Figure 2 demonstrates the novel approaches studied for ischemic stroke management.

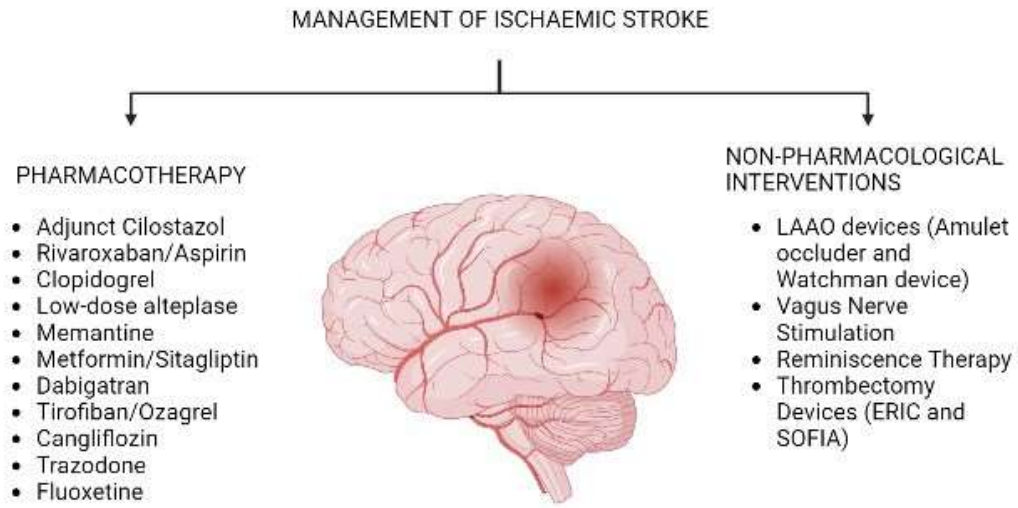

Figure 2. A figure showcasing the various novel approaches in ischemic stroke management.

The COMPASS study examined the outcome of discontinuation of the anti-thrombotic, rivaroxaban and aspirin combination in patients with chronic coronary and peripheral artery disease. Rivaroxaban, an inhibitor of the coagulation factor Xa and aspirin, a cyclooxygenase-1 inhibitor, when given in a combination regimen, demonstrated a pronounced reduction in the incidence of stroke and other thromboembolic events.

Discontinuation of the combination was suggestive of a striking increase in the rate of occurrence of stroke within the next 2 to 6 months. The trial was stopped after a follow-up period of 23 months, owing to the clear beneficial effects of the combination shown.[7]

A study investigated the association between PAR-1 gene F2R polymorphism and the response to clopidogrel treatment. The patients with stroke/TIA were randomized to receive either clopidogrel, a P2Y12 inhibitor, plus aspirin, or aspirin alone. SNP genome sequencing demonstrated that the T allele of F2R was linked to a better clinical response from the combination of clopidogrel plus aspirin, than aspirin alone. The probable mechanism behind this could be the platelet activation mediated by PAR-1 before the actions of P2Y12. In F2RIVSn-14T allele carriers, there is a reduced expression of PAR-1 on the platelet surface and consequently, a decrease in its procoagulant activity. This, in turn, is synergized by P2Y12 receptor inhibition by clopidogrel. Also, a significant clinical benefit was shown in F2RIVSn-14T allele carriers with CYP2C19 loss of function alleles, which could be attributed to the residual active metabolite of clopidogrel.[8]

A recent trial was conducted with the preliminary purpose of assessing the outcomes of decompressive hemicraniectomy (DCH) in thrombolysis patients with acute ischemic stroke (AIS), most of whom had a large vessel occlusion and severe neurological decline. Patients who presented late and had improbable access to perform mechanical thrombectomy. In previous studies, DHC was known to provide improved outcomes by reducing the ICP and preventing brain herniation. But these studies mainly included non-thrombolyzed young-middle-aged participants. When thrombolysis has restricted utility, as in large vessel occlusion when the risk of ICH is high and when endovascular clot retrieval (EVT) is unavailable, DCH was thought to be beneficial. The AHA/ASA guidelines also recommend DCH in cases of severe neurological deficits, as with malignant brain edema from middle cerebral artery occlusion within 48 hours, despite medical interventions. But the ENCHANTED trial exhibited the pitfalls of DCH in a wide range of patients with ICH, mass effect, and large vessel occlusion. A worse recovery was evident in the patients who received DCH, as compared to those who did not. [9]

A recent research study, BP-TARGET, evaluated the efficacy of intensive BP lowering in patients with acute ischemic stroke

(AIS) after successful management with endovascular therapy. It has been postulated that an elevation in the systolic blood pressure (SBP), post-endovascular therapy, may result in an increased risk of intraparenchymal hemorrhage. Hence, SBP lowering may be thought of as a strategy to prevent ischemia-reperfusion lesions, but with a risk of infarct growth. Also, SBP levels if below 120 mm Hg, have an uncertain safety. Current guidelines suggest SBP<185 mm Hg prior to endovascular therapy and 180 mm Hg, 24 hours post-endovascular therapy to be optimal. The BP-TARGET trial has implied the inadequacy of intensive SBP lowering in preventing any significant risk of reperfusion injury, as marked by radiographic evidence of an intraparenchymal hemorrhage on brain CT scans. The reason behind the same, may in part be explained by the progression of focal hypoperfusion lesions into infarction with an intensive SBP lowering, especially in cases of large acute ischemic stroke volumes. The negative effect of an intensive SBP control may also be substantiated by the observation of a persistent venous post-capillary thrombosis, even after successful reperfusion (TICI grade 3). Lastly, an increased mortality rate in the patients under the intensive SBP lowering group sums up the offset. [10]

The Amulet IDE trial compared the safety and efficacy of two left atrial appendage occlusion (LAAO) devices, the Amulet occluder, and the Watchman device in those who had nonvalvular atrial fibrillation, with a significant risk of stroke. In nonvalvular atrial fibrillation, there is a known stagnation of blood flow in the left atrial appendage, resulting in the formation of a local thrombus. Since oral anticoagulation is associated with high bleeding risk and the drawback of long-term therapy, percutaneous LAAO devices have been developed to prevent thrombus embolization. While the Watchman device operates via a single-seal mechanism, the Amulet has been advanced to work through a dual-seal mechanism, which was thought to reduce the risk of a leak. Patients treated with the Amulet occluder were discharged either with aspirin plus clopidogrel, or aspirin plus an oral anticoagulant, and with warfarin, in case of the Watchman device. An increased risk of late pericardial effusion was observed with oral anticoagulation, as compared to antiplatelet therapy. This implies the utilization of less intensive antithrombotic therapy with antiplatelet agents to be more beneficial. The study concluded the Amulet occluder to be non-inferior as compared to the Watchman device when considering safety and efficacy. However, it was shown to be

superior to the Watchman device concerning its potential to provide a competent LAA occlusion.[11]

The ENCHANTED trial was conducted to determine if low-dose alteplase provided any significant benefit over standard dose in patients with lacunar and non-lacunar acute ischemic stroke (AIS). It has been known that the lacunar subtype has a more benign course, relative to the other subtypes, and most commonly, IV thrombolysis is started with. Thrombolysis-associated intracerebral hemorrhage (ICH) mandated research to figure out if dose adjustment can provide any benefit. One of the findings of the trial implicated the more favorable functional outcomes with lacunar stroke, as compared to its non-lacunar counterparts. However, no consequential advantage was seen with low-dose alteplase, except a modest reduction in the risk of symptomatic intracerebral hemorrhage (sICH).[12]

The effects of memantine on neuronal recovery after an ischemic stroke were studied in patients who had a mild-to-moderate ischemic stroke. Matrix metalloproteinases (MMP) are involved in tissue destruction and hence, the levels of neuronal injury biomarkers, MMP-2 and MMP-9 were tested, along with NIHSS and BI scores for neurologic functioning and activities of daily living, respectively. The neuroinflammation caused during a stroke event is associated with significant tissue destruction, due to a cascade of events causing excessive glutamate stimulation and NMDA-receptor hyperfunction. A widespread brain injury and blood-brain barrier breakdown are common in ischemic stroke. As a consequence, memantine, an uncompetitive NMDA-receptor antagonist, was studied for its anti-inflammatory and neuroprotective action in ischemic stroke. The results of this trial indicated a significant reduction in MMP-9 levels. The reduction in MMP-2 levels in the intervention group was probably not observed due to the delayed changes in MMP-2 levels in stroke. Therefore, memantine can be considered a promising agent in improving brain functioning, recovering neuronal injury, and reducing cerebral ischemia which are very commonly associated with ischemic stroke.[13] Figure 3 depicts the mechanism of action of memantine in ischemic stroke.

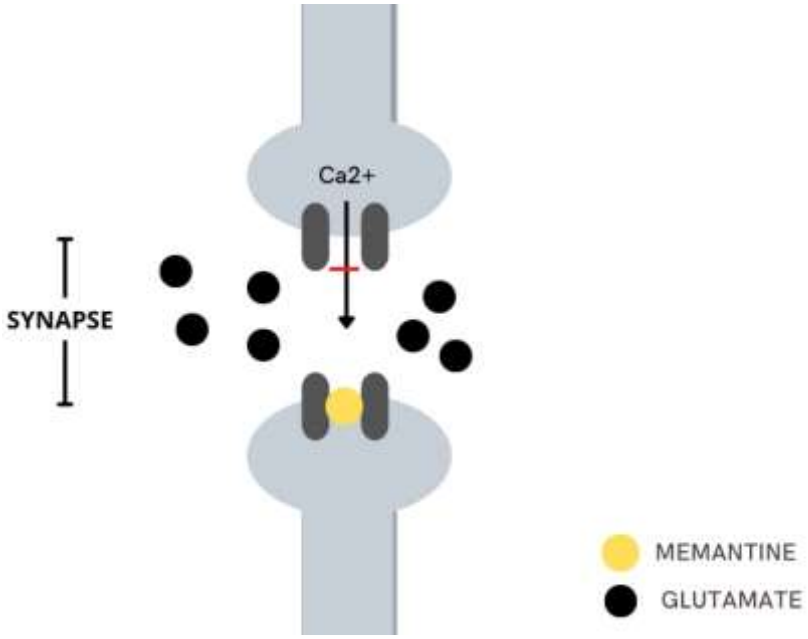

Figure 3. A diagrammatic representation of the functioning of memantine in ischemic stroke.

A high prevalence of impaired glucose tolerance (IGT) after a transient ischemic attack (TIA) or a minor ischemic stroke has been reported and is associated with unfavorable cardiovascular outcomes and recurrent stroke attacks. As a consequence, a rigid glycaemic control could decrease the risk of stroke in patients with diabetes or an IGT. The MAAS (metformin and sitagliptin in patients with impaired glucose tolerance and a recent TIA or minor ischaemic Stroke) trial assessed the efficacy and safety of two antidiabetic medications, metformin, and sitagliptin, in patients who had a TIA or a minor ischemic stroke and an IGT. Metformin is a biguanide, which is the most commonly used agent in diabetic patients and sitagliptin is a DPP-4 inhibitor, having a better safety profile and an enhanced action on B-cell functioning. Patients in the study were randomized to receive either metformin, sitagliptin, or 'no intervention' and the 2-hour post-load glucose, fasting glucose, and HbA1c levels. The effect of these antidiabetic medications on endothelial function, blood coagulation, inflammation, and the fibrinolytic system, is presumed to be involved in the prevention of cardiovascular events in IGT patients. The results of this study reported no significant effect of metformin or sitagliptin on the 2-hour post-load glucose levels, but a reduction in the fasting plasma glucose and HbA1c levels was noted. Hence, it could be concluded that these medications may be involved in increasing the regression to normal glucose metabolism, which

further causes a reduction in cardiovascular system-related morbidity and mortality. Some other studies have demonstrated better effects of newer agents like pioglitazone, on cardiovascular risk and stroke recurrence.[14]

Large artery occlusion (LAO) stroke requires reopening of the occluded artery without delay. Reperfusion is commonly achieved via intravenous thrombolysis (IVT). But in cases where IVT is not tolerated or is contraindicated, intra-arterial clot extraction i.e. mechanical thrombectomy (MT) is performed, to restore the perfusion. Mechanical thrombectomy also provides better clinical and functional outcomes, as compared to IVT. This is most commonly done using devices called stent-retrievers. But the conventional stent retrievers have certain drawbacks like the distal, tortuous vessels and those occluded by a long thrombus, not being accessible. A phase II trial evaluated the effectiveness of two novel devices for mechanical thrombectomy (MT), ERIC stent retriever, and SOFIA, a distal access catheter (DAC). The MicroVention ERIC (Embolus Retriever with Interlinked Cage) retriever device makes access to the distal, tortuous vessels possible and also facilitates the retraction of large thrombi. These advantages are attributed to its longer length and multiple connecting clot retrieval cages. The ERIC also benefits in saving time as it does not need to stay open for long periods to engage the clot. The second device is the MicroVention SOFIA (Soft torqueable catheter Optimized For Intracranial Access) distal access catheter, used for aspiration of the clot. If clot aspiration is unsuccessful, then the same DAC is utilized to deploy a stent retriever. This device also provides easier access to the vessels, which are usually not accessed using conventional thrombectomy devices. Despite the novel mechanistic concept and advantages of these novel devices, no statistically significant difference was found between ERIC and SOFIA, from the devices utilized in the control arm.[15]

In individuals who have suffered a stroke, a wide range of complications occur, ranging from motor disturbances to speech impairment. Amongst these, a very common and serious disabling effect is on cognition. While the physical effects tend to improve during the recovery phase, cognitive impairment generally worsens with time, regardless of the stroke severity. Vascular cognitive impairment (VCI) ranges from mild cognitive impairment (MCI) to dementia and these usually lead to damage to executive function, including working memory. This significantly afflicts the affected

individual and this compels researchers to study the effects of certain products on cognitive improvement. One such study assessed the effect and safety of a dietary supplement, N-Pep-12, on neuro-recovery after ischemic stroke. N-Pep-12 is a peptide compound that has been known to exhibit neuroprotective and pro-cognitive activity. This trial concluded N-Pep-12 to be beneficial in accelerating neuroprotection and recovery in individuals after supratentorial ischemic stroke. Evaluation of this peptide supplement was conducted mostly during the subacute phase and the chronic phase in certain participants; hence the study implies a better effect of the supplement from the extension of the treatment period within the chronic phase.[16]

VNS-REHAB, a pivoted, randomized, triple-blinded, sham-controlled study, demonstrates an improvement in upper limb motor function in patients receiving vagus nerve stimulation when combined with rehabilitation. The primary outcome was measured via assessment of change in FMA-UE from baseline, compared to after the completion of therapy, while secondary outcomes included clinically meaningful response on FMA-UE score at day 90; change in WMFT-functional score (day 90 compared to baseline). The intervention requires surgical device implantations. Other than a low rate of vocal cord palsy, which has been documented earlier, no serious adverse events associated with the device were reported. The study concludes that VNS could be a potential target, and should be extensively studied for the improvement of limb impairment in stroke survivors.[17]

A study was conducted to assess the benefits of RTBC (Reminiscence Therapy Based Care) in post-stroke patients where mental restoration is a big challenge. Along with the conventional care and therapy, the RTBC group patients were given a twice a month reminiscence therapy. At the end of 12 months, patients in the intervention group showed greater improvement than the control group, in all terms, including a reduction in cognitive impairment, alleviation of anxiety and depression. Furthermore, the satisfaction scores of the RTBC group were also higher, suggesting RTBC could be proved as an acceptable addition to the traditional therapy.[18]

A study evaluated the safety and efficacy of prior antiplatelet therapy in patients undergoing EVT after AIS. Antiplatelet therapy presents itself with a dilemma, particularly in stroke patients, with benefits of prevention of ischaemic stroke and

risks of developing a hemorrhage. The study focuses on the occurrence of sICH as a primary outcome, while functional assessment through modified Rankin scale is the secondary.[19]

A study under the VOYAGER PAD trialanalyzed the occurrence of vascular events including limb and cardiovascular events in patients with symptomatic PAD (Peripheral artery disease). Two groups, rivaroxaban plus aspirin, and aspirin alone, were assessed to determine the safety and efficacy of rivaroxaban in such patients. Follow-up was taken at 1, 3, 6 months after the beginning of the study, and every six months thereafter. It was seen that the combination of rivaroxaban and aspirin was far more beneficial than aspirin alone, concerning the total events. It was also noticed that patients undergoing LER are at a greater risk of limb and cardiovascular events, with recurrent peripheral revascularization being a frequent event.[20]

The CREDENCEtrial investigated the effects of canagliflozin on stroke in patients with type 2 diabetes mellitus and chronic kidney disease. Face to face and telephone-based follow-ups were scheduled, for assessment of primary and secondary outcomes. Although there was no significant effect seen in the treatment of stroke through SGLT2 inhibitors, certain stroke risk factors were improved. In severely impaired kidney function, Canagliflozin improved the eGFR, which could be discerned as a favorable effect in the prevention of stroke.[21]

A study, secondary to the AFFINITY trial, was conducted, when the latter did not show any functional benefits of fluoxetine 20 mg once daily for six months in post-stroke patients. The study aims to determine any sustained effects 12 months later. It is observed that there is no significant difference between the fluoxetine and placebo groups, while fluoxetine increased the risk of adverse effects like falls, bone fractures, and seizures. There is a slight reduction in the occurrence of ischemic stroke in the intervention group, but it was concluded that it was a chance finding.[22]

Another study was conducted to evaluate the efficacy and safety of tirofiban combined with heparin compared to aspirin plus clopidogrel within 48 hours of mild to moderate AIS. Tirofiban is a highly selective, fast-acting nonpeptide GPIIb/IIIa antagonist which is used to treat acute coronary syndrome up to 48 h after onset. It is administered intravenously, and the final common pathway of platelet aggregation is significantly stronger than the common antiplatelet drugs, as well as preventing thrombosis. Micro-emboli are also potentially

cleared up by Tirofiban. The treatment group was intravenously infused with 100 mL Tirofiban + 12500 U Heparin for 48 hours, followed by 100 mg Aspirin QD+75 mg Clopidogrel as maintenance for 14 days and then Aspirin or clopidogrel for secondary prevention. The treatment group showed a decrease in NIHSS and an increase in BI as compared to the control group and the difference was statistically significant. The study concluded that tirofiban combined with heparin in the first 48 hours of mild to moderate AIS can significantly reduce the risk of progressive stroke and can also improve neurological function. Long-term prognosis is also improved in acute mild to moderate AIS when tirofiban is used in combination with heparin.[23]

A randomized, double-blind, placebo-controlled, crossover pilot study was performed to evaluate the efficacy of trazodone on OSA after ischemic stroke. Patients received 100 mg trazodone or placebo just before polysomnography with an approximately 1-week washout period. Trazodone is a non-myorelaxant, sedative antidepressant that acts on the medullary serotonergic neurons which are responsible for central respiratory chemoreception and carbon-dioxide induced arousal. Therefore, trazodone decreases OSA severity. Since the respiratory arousal threshold is lower in REM sleep compared to NREM sleep the effect of trazodone on respiratory arousal might be more pronounced in REM sleep. The study concluded that trazodone significantly increased the percentage time of slow-wave sleep and improved almost all the parameters of OSA severity (without increasing nocturnal hypoxia) including AHI and minimum oxygen saturation, respiratory arousal index. Hence, OSA with comorbid ischemic stroke responds quite well to trazodone antidepressant.[24] Figure 4 shows the mechanism of action of trazodone in ischemic stroke and obstructive sleep apnoea management.

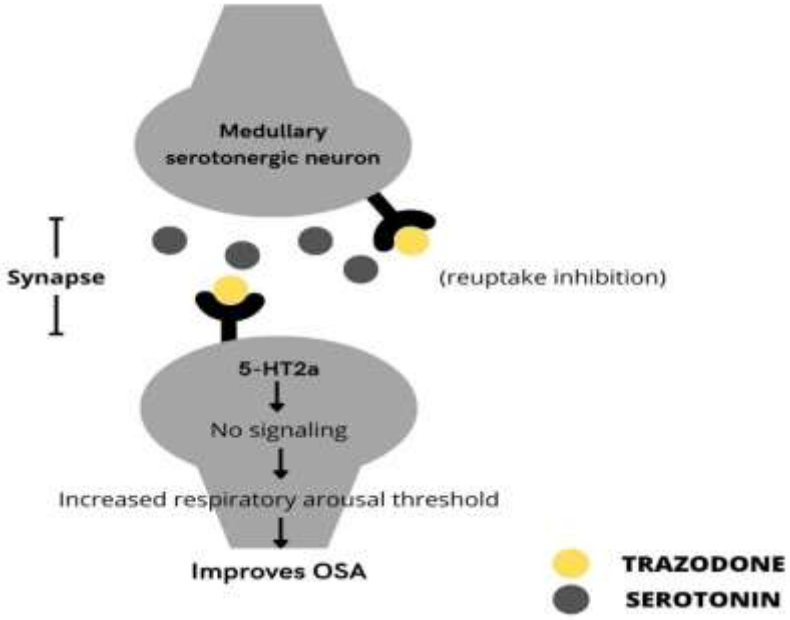

Figure 4. A brief overview of the mechanism of action of trazodone in ischemic stroke and obstructive sleep apnoea management.

RE-SPECT ESUS is a randomized, double-blind trial that assessed the safety and efficacy of dabigatran vs. aspirin for preventing secondary stroke in embolic stroke patients of undetermined source in a prespecified subgroup of East Asian patients. The primary efficacy outcome was a recurrent stroke and the primary safety outcome was major bleeding. Dabigatran is an oral thrombin inhibitor while aspirin is acetylsalicylic acid. The trial concluded that dabigatran did not show any superiority compared to aspirin in preventing recurrent stroke in patients with ESUS. There was no statistically significant difference in recurrent stroke or major bleeding in East Asian patients receiving dabigatran versus aspirin. However, death from any cause occurred more in the dabigatran group.[25]

A prospective, double-blind, randomized-controlled study was conducted to investigate the safety and efficacy of combined tirofiban and ozagrel therapy in the treatment of progressive stroke patients who fall outside the time window of thrombolytic therapy. Patients received either monotherapy with tirofiban or ozagrel or a combination of tirofiban and ozagrel. Tirofiban is a highly selective, fast-acting, reversible non-peptide platelet surface glycoprotein (GP) IIB/III receptor antagonist which is widely used in the treatment of various cardiovascular diseases, and the prevention of coronary heart

disease. Ozagrel is a Thromboxane synthetase inhibitor used in the treatment of ischemic stroke. There was no significant difference in NIHSS score in all the groups at 4 weeks. The study concluded that monotherapy with tirofiban or ozagrel improves neural function and reduces platelet aggregation and fibrinogen formation at 4 weeks without increasing the risk of hemorrhage in stroke patients. However, the combination of tirofiban and ozagrel may facilitate this process.[26]

The open-label, multicentre and randomized trial was conducted to demonstrate the value of administering intravenous alteplase before EVT in ischemic stroke patients. Alteplase is a tissue plasminogen activator that converts plasminogen to plasmin, which causes lysis of fibrin as well as fibrinogen. The study concluded that EVT alone is neither superior nor inferior to the intravenous Alteplase administration followed by EVT concerning 90 days disability outcome after stroke.[27]

THALES trial was conducted to examine the effect of a combination of ticagrelor plus aspirin versus aspirin alone in patients who had a mild to moderate acute non-cardioembolic ischemic stroke with an NIHSS score of 5 or less or TIA and who were not undergoing thrombolysis or thrombectomy. Ticagrelor is a directly acting antiplatelet agent which reversibly binds and inhibits the P2Y12 receptor on platelets and it does not require metabolic activation, unlike clopidogrel. After an acute ischemic stroke or TIA, the risk of subsequent stroke mainly occurs in the first month. So, a 30 days treatment trial was considered appropriate in reducing the risk of subsequent stroke or death. Results were more favorable towards the ticagrelor-aspirin combination compared to Aspirin alone in terms of reducing the risk of the composite stroke or death within 30 days but the incidence of disability was similar in both the groups. However, severe bleeding was more frequent in the combination group.[28-29] All the studies described herewith are enlisted with brief details about their patient population, objectives, endpoints and results in Table 1.

Table 1. A summarised representation of all the recent research data on the prevention and management of ischemic stroke, including the study objectives, endpoints and results.

TRIAL	PARTICIPANTS	OBJECTIVE	ENDPOINTS	RESULT
DORIC [6]	Type 2 Diabetes Mellitus patients with LEAD, having intermittent claudication symptoms (stage IIa, IIb according to the Fontaine classification) who have been receiving Clopidogrel (75 mg/day).	To assess if the addition of cilostazol (100 mg, twice a day) to clopidogrel-treated patients is efficacious in the prevention of acute vascular events.	Primary efficacy end-point-composite of acute ischemic stroke/transient ischemic events/acute myocardial infarction and death from vascular diseases.	Improved pain-free walking distance and ABI values and a significant reduction in acute ischemic stroke/TIA events.
COMPASS [7]	Chronic coronary or peripheral artery disease patients.	To assess the consequences of discontinuing rivaroxaban (2.5 mg, twice daily) plus aspirin (100 mg/day) and switching to non-study aspirin monotherapy.	Primary end-point- a composite of MI, stroke, or CV death.	The combination of rivaroxaban plus aspirin was clearly shown to be beneficial, with mainly an increased incidence of stroke and a greater risk of thromboembolic events, over the discontinuation of the combination regimen.
F2R polymorphisms and clopidogrel efficacy and safety in patients with minor stroke or TIA[8]	Patients with minor stroke or TIA.	To test the association of PAR-1 gene F2R polymorphisms and clopidogrel efficacy in minor stroke/TIA patients.	Primary efficacy end-point-recurrent stroke.	F2RIVSn-14T allele carriers were shown to have a reduced rate of stroke recurrence as compared to non-carriers, i.e. CYP2C19 genotyping was associated with variability in clopidogrel response.
Early decompressive hemicraniectomy in thrombolyzed acute ischemic stroke patients from the international ENCHANTED trial[9]	Patients with a malignant hemispheric AIS, who presented late, and those in whom access to mechanical thrombectomy was not available. The patients were randomized to receive either low-dose (0.6 mg/kg) alteplase or standard dose (0.9 mg/kg) and were on intensive or standard BP control, or both.	To determine the outcomes of DHC in thrombolyzed patients having an AIS.	Primary outcome-death or disability, scores 2-6 on the mRS.	Patients who underwent DCH were found to have a poor prognosis as compared to those who did not undergo DCH. Also, DCH was associated with a significant risk of ICH. In cases of severe neurological deterioration, DCH had very poor outcomes.
BP-TARGET[10]	Patients with AIS due to a large vessel occlusion of anterior circulation (TICI stage 2b or 3), were successfully treated with endovascular therapy. The patients were randomized into an intensive SBP lowering group (target-100-129 mm Hg) or a standard care SBP (target-130-185 mm Hg).	To assess if intensive BP lowering in AIS patients' post-endovascular therapy is beneficial in reducing the rates of intraparenchymal hemorrhage.	Primary outcome-the rate of radiographic intraparenchymal hemorrhage on brain CT, 24-36 hours after reperfusion.	The study manifested no efficacy of intensive BP lowering in reducing the risk of intraparenchymal hemorrhage.
The Amulet IDE trial[11]	Patients with nonvalvular atrial fibrillation who were at an increased risk of stroke were randomized into two groups: to undergo percutaneous implantation of the Amulet occluder or the Watchman device, as a means of providing LAAO.	To assess which device provided a better outcome, in terms of stroke prevention at 18 months, the Amulet occluder or the watchman device.	Primary efficacy endpoint-composite of ischemic stroke or systemic embolism at 18 months.	The Amulet occluder was found to be non-inferior to the Watchman device in terms of both safety and effectiveness for stroke prevention. Also, the Amulet occluder was manifested as superior with regard to LAA occlusion.

The ENCHANTED [12]	Patients with lacunar and non-lacunar AIS.	To determine the differential efficacy and safety of low-dose (0.6 mg/kg) versus standard-dose (0.9 mg/kg) alteplase for lacunar and non-lacunar stroke.	Primary outcome-disability or death (mRS-2-6) over 90 days post-randomization.	The trial showed that lacunar AIS is associated with more favorable outcomes as compared to non-lacunar stroke, regardless of the dose administered. Low-dose alteplase was shown to reduce the risk of sICHbut no significant advantage of low-dose alteplase over standard-dose alteplase was found, in terms of efficacy.
The effects of memantine on the serum concentrations of matrix metalloproteinases and neurologic function of patients with ischemic stroke[13]	Patients with mild-to-moderate ischemic stroke were randomized to the intervention group (20 mg memantine) or the control group.	To analyze the neuroprotective effect of memantine in improving the neuronal function post-ischemic stroke.	Primary outcome-reduction in biomarkers of neuronal inflammation-gelatinase A/MMP-2 and gelatinase B/MMP-9, and assessment of neuronal function in terms of NIHSS and BI scores.	During the first 5 days of treatment with memantine, a significant difference in the reduction of levels of MMP-9 in both groups was observed, emphasizing the activity of memantine in post-stroke neuronal recovery.
MAAS trial.[14]	Patients with a clinical diagnosis of TIA, amaurosis fugax, or a minor ischemic stroke, within the previous 6 months and who had an impaired glucose tolerance. Patients were randomized to receive metformin (500 mg BD, eventually increasing the dose up to 1000 mg BD), sitagliptin (100 mg every day), or no antidiabetic medication.	To evaluate the efficacy and safety of metformin and sitagliptin in preventing recurrence of stroke and other cardiovascular events, and resolving impaired glucose tolerance in patients who had a TIA or a minor ischemic stroke and an impaired glucose tolerance.	Primary outcome-2-hour post-load glucose levels.	Metformin and sitagliptin did not show any effect on the 2-hour post-load glucose, but a moderate reduction in the fasting glucose and HBA1c levels was shown.
Evaluation of novel thrombectomy devices: ERIC, a retriever device and SOFIA, a distal access catheter.[15]	Patients with proximal LAO stroke, with NIHSS ≥6 and a limited ischemic change on CT imagery.	To evaluate the effectiveness of two novel thrombectomy devices, ERIC retriever and SOFIA, a distal access catheter in LAO stroke patients.	Primary outcome-modified TICI score.	The effect of the novel ERIC and SOFIA devices wasstatistically found to be no different from the existing CE-marked MT devices.
The N-Pep-12 clinical trial.[16]	Individuals who suffered an ischemic stroke with no significant pre-stroke disability (pre-stroke mRS of 0 or 1). They were randomized to either receive 90 mg of N-Pep-12 per day for 30 days, or a control group.	To assess the effect of an N-Pep-12, a dietary supplement, on neuro-recovery and protection post-stroke.	The primary outcome was assessed via five neuropsychological scales- MoCA, Processing Speed Index, Digit Span, Hospital Anxiety and Depression Scale, and Color Trails Test.	N-Pep-12 was found to benefit in enhancing neuro-recovery post-ischemic stroke.

VNS-REHAB[17]	Patients having a history of unilateral supratentorial ischaemic stroke that occurred between 9 months and 10 years before participation. FMA-UE score of 20-50 was required for eligibility. Randomly, patients were assigned to rehabilitation paired with vagus nerve stimulation (VNS group), or rehabilitation, along with sham stimulation (control group) in a 1:1 ratio.	To determine the safety and efficacy of vagus nerve stimulation, paired with rehabilitation.	Primary outcome: measured via assessment of change in FMA-UE from baseline, compared to after the completion of therapy.	The FMA-UE scores were much improved in patients receiving vagus nerve stimulation, compared to the controlled group, ameliorating the upper limb motor function.
RTBC program for relieving post-stroke cognitive impairment, anxiety, and depression.[18]	130 patients, suffering from AIS, with the ability to complete the questionnaire assessment. Block randomization was used with a block size of four, and patients were assigned to either control or RTBC group.	To evaluate the efficacy of RTBC in post-stroke patients; to determine whether reminiscence therapy helps reinstate cognitive impairment and alleviates depression and anxiety in AIS patients.	Patients were assessed every three months for a year (M0, M3, M6, M9, and M12) using two scales each for cognitive impairment (MMSE and MoCA), anxiety (HADS-A and SAS), and depression (HADS-D and SDS).	RTBC group showed much improvement when compared to the control group, in terms of cognitive function, depression as well as anxiety.
Prior antiplatelet therapy in patients undergoing endovascular treatment for acute ischemic stroke.[19]	Propensity-score matched cohort analysis was performed where 437 patients without prior antiplatelet therapy were matched with 937 patients who were on prior antiplatelet therapy.	To compare the safety and efficacy outcomes of EVT, after AIS, with or without prior antiplatelet therapy.	The primary endpoint was the occurrence of sICH, within 90 days.	There was no significant increase in the risk of sICH in patients on prior antiplatelet therapy.
Total Event Reduction in VOYAGER PAD trial.[20]	Patients with symptomatic PAD and an uneventful revascularization procedure within 10 days to treat infrainguinal PAD. Aspirin 100 mg was administered to all patients as background therapy, along with either rivaroxaban 2.5 mg or a matching placebo, randomly assigned in a 1:1 ratio.	To determine the composition of events, including cardiovascular and limb events, along with evaluation of safety and efficacy outcomes of rivaroxaban in first and total events.	Primary efficacy outcomes included the first occurrence of acute limb ischemia, major amputation for vascular causes, non-fatal myocardial infarction, non-fatal ischemic stroke, or cardiovascular death, including the death of unknown etiology.	32% of the total patients experienced at least one non-fatal vascular event. Given the total vascular events, rivaroxaban in combination with aspirin provides much more significant benefits than aspirin alone.

CREDENCE TRIAL[21]	Patients with T2DM and CKD, taking ACE or ARB for at least a month before enrolment.	To explore the effects of canagliflozin on stroke and stroke risk markers, in patients with T2DM and CKD. .	Primary outcomes included the occurrence of fatal and nonfatal strokes.	The effects of canagliflozin were non-significant on the treatment of stroke; however, it did have some preventive effects, improving systolicblood pressure, diastolic blood pressure, body weight, HbA1c, high-density lipoprotein cholesterol (HDL-C), UACR, and eGFR.
Twelve months outcome of AFFINITY trial.[22]	Patients recently (2-15 days prior to enrolment) diagnosed with a stroke, ischemic or hemorrhagic.	Since no effects were seen after the 6-month administration of fluoxetine, its long-term effects were explored in this study.	The primary outcome included function, which was measured by modified Rankin scale.	There was no significant benefit of 6-month fluoxetine treatment in post-stroke patients, even after 12 months.
Tirofiban combined with heparin.[23]	Patients with mild to moderate ischemic stroke.	To evaluate the efficacy and safety of Tirofiban combined with heparin in the treatment of mild to moderate AIS.	NIHSS, BI, ESRS, platelet, plasma PT, FB, APTT before treatment, 48-hour after treatment, and 14days after treatment. MRS of 90 days.	Platelets were decreased significantly following 48-hour treatment.PT and APTT significantly increased following treatment. No significant difference in FB before and after treatment. The long-term prognosis in the treatment group was increased as compared to the control. Tirofiban combined with heparin can reduce the risk of progressive stroke in the 48 hours and it can improve neurological function from acute mild to moderate AIS.
Trazodone for obstructive sleep apnoea after ischemic stroke.[24]	Patients with post-acute ischemic stroke who were admitted to the rehabilitation ward.	To evaluate the beneficial effect of Trazodone in Acute ischemic stroke patients with OSA and low arousal threshold.	ECG, Polysomnography, BI, Epworth sleepiness scale, Patient Health Questionnaire-9, 24-hour ambulatory BP monitoring, heartrate.	All parameters of OSA severity weresignificantly improved except mean SP02. AHI was significantly improved in the trazodone group except for 1 patient. Mean BP and diastolic BP were lower in responders. Respiratory arousal index was decreased and %time of SWS, level of minimum SPO2 was significantly increased.
RE-SPECT ESUS trial.[25]	Patients with a recent embolic stroke of undetermined source.	To assess the outcome of dabigatran vs. aspirininpatientswith an embolic stroke of an undetermined source.	The primary efficacy outcome was time to first recurrent stroke of ischemic, hemorrhagic, or unspecified type and the primary safety outcome was time to first major bleeding, modified Rankin Scale.	There was no statistically significant difference in recurrent stroke or major bleeding.
Tirofiban combined with ozagrel in treatment of progressive cerebral infarction.[26]	Patients with acute ischemic stroke who fall out of the therapeutic window of thrombolytic therapy.	To investigate the efficacy and safety of combined tirofiban-ozagrel therapy for treating progressive stroke patients.	PAG, TT, PT, APTT, FIB, NIHSS scores, BI, mRS to evaluate disability following 3 months.	There was no significant difference in NIHSS scores in 3 groups. Levels of PAG and FIB in the tirofiban/ozagrel group were significantly lower than those in the tirofiban and ozagrel group. No significant difference was found in BI and mRS scores of patients with different groups.

Intravascular Alteplase before EVT for stroke.[27]	Patients with stroke who presented directly to the hospital and were capable of giving EVT as well as intravenous alteplase.	To evaluate the effect of giving intravenous Alteplase before EVT in stroke patients.	The primary endpoint is the functional outcome on the modified Rankin Scale and the safety endpoint-death from any cause and symptomatic intracerebralhemorrhage.	EVT alone showed neither superiority nor inferiority compared to Alteplase followed by EVT with regard to disability outcome at 90 days after stroke. Both groups showed a similar incidence of symptomaticintracerebralhemorrhage.
THALEStrial [28]	Patients who had a mild to moderate non-cardioembolic ischemic stroke with an NIHSS score of 5 or less or TIA who were not undergoing thrombolysis or thrombectomy.	To assess the effect of Ticagrelor-aspirin combination versus placebo plus aspirin in patients with mild to moderate AIS or TIA.	The primary outcome is a composite of stroke or death (including all causes of death) within 30 days. The secondary outcome is a first subsequent ischemic stroke and incidence of disability measured as an mRS score within 30 days. The primary safety outcome is severe bleeding classified according to the GUSTOtrial. Stroke events- as both progression of the index stroke and new stroke events.	A combination of Ticagrelor and Aspirin showed a lower risk of stroke or death compared to Aspirin alone. There was no significant difference in the incidence of overall disability among the two groups. The risk of severe hemorrhage was higher with the combination than aspirin alone.
The smoking paradox in ischemic stroke patients treated with intra-arterial thrombolysis in a combination of mechanical thrombectomy-VISTA-Endovascular.[29]	Patients with Acute ischemic stroke with proven large vessel occlusion, enrolled in endovascular RCTs.	To evaluate the effect of smoking on outcome following EVT with mechanical thrombectomy alone vs. in a combination of intra-arterial thromboly sis.	Primary endpoint-3 modified Rankin Scale assessed 90 days post-stroke (mRS</>2).	A consistent shift in RR of smokers indicated possible better functional outcomes and mortality rates in smokers but it may be due to index-event bias of smokers alone (younger age and fewer comorbidities in the smoking group.) However, in patients treated with mechanical thrombectomy alone, smoking had no effect on clinical outcomes.

ABI-ankle-brachial index, ACEi-angiotensin converting enzyme inhibitor, AFFINITY- Assessment of Fluoxetine in Stroke Recovery, AHI- Apnea-hypopnea index, AIS- acute ischemic stroke, APTT-activated partial thromboplastin time, ARB-angiotensin receptor blocker, BI- Barthel index, BP- blood pressure, CKD-chronic kidney disease, COMPASS-Cardiovascular Outcomes for People Using Anticoagulation strategies, CREDENCE-Canagliflozin and Renal Events in

Diabetes with Established Nephropathy Clinical Evaluation, CT-computed tomography, CV- cardiovascular, DHC-decompressive hemicraniectomy, DORIC-Diabetic Artery Obstruction: Is It Possible to Reduce Ischemic Events With Cilostazol?, ECG- electrocardiogram, eGFR-estimated glomerular filtration rate, ENCHANTED- Enhanced Control of Hypertension and Thrombolysis Stroke Study, ERIC-Embolus Retriever with Interlinked Cage,ESRS-Essen Stroke Risk Score, ESUS- Embolic Stroke of Undetermined source, EVT-endovascular treatment, FB-plasma fibrinogen, FMA-UE- Fugl-Meyer Assessment-Upper Extremity, GUSTO-Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries, HADS-hospital anxiety and depression scale, HbA1c- glycosylated haemoglobin 1c, HDL-C-High-Density Lipid Cholesterol, ICH- intracranial hemorrhage, LAAO- left atrial appendage occlusion, LAO- large artery occlusion, LEAD-lower extremity arterial disease, MAAS trial-metformin and sitagliptin in patients with impaired glucose tolerance and a recent TIA or minor ischaemic Stroke trial, MI-myocardial infarction, MMP-matrix metalloproteinases, MMSE-mini-mental state exam, MoCA- Montreal cognitive assessment, mRS- modified Rankin scale, MT- mechanical thrombectomy, NIHSS- National Institute of Health Stroke Scale, OSA-obstructive sleep apnea, PAD-peripheral artery disease, PAG- platelet aggregation, PAR-1- protease-activated receptor-1, PT- prothrombin time, RR- relative risk, RTBC-reminiscene therapy based care, SAS-sedation agitation scale, SBP- systolic blood pressure, SDS-sheehan disability scale, sICH-symptomatic intracerebral haemorrhage, SOFIA-Soft torqueable catheter Optimized For Intracranial Access, SWS-slow wave sleep, T2DM- Type II Diabetes Mellitus, THALES-Transient IscHemic Attack Treated with TicAgreLor and Aspirin for PrEvention of Stroke and Death, TIA-transient ischemic attack, TICI- thrombolysis in cerebral infarction, UACR- Urine albumin to creatinine ratio, UACR-Urine albumin to creatinine ratio , VISTA-Virtual International Stroke Trials Archive, VNS-REHAB- Vagus Nerve Stimulation paired with Rehabilitation, VOYAGER PAD- Vascular Outcomes Study of ASA (acetylsalicylic acid) Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for peripheral artery disease.

CONCLUSION

The trial studied the smoking paradox in ischemic stroke patients treated with mechanical thrombectomy alone or in the combination of intra-arterial thrombolysis. The mechanism

behind the suspected increased treatment efficacy in smokers might be due to the reduction of endogenous tPA release from endothelial cells in smokers which causes hypercoagulability and increased risk of intravascular thrombus formation these thrombi are more fibrin-rich and thus more susceptible to exogenous tPA. Thus, smoking may increase the efficacy of thrombolysis by modifying clot dynamics. Tobacco smoking alone had no clear clinical benefits on functional recovery post-stroke in patients with proven vessel occlusion. A consistent shift in RR of smokers indicated possible better functional outcomes and mortality rates in smokers but it may be due to index-event bias of smokers alone (younger age and fewer comorbidities in the smoking group.) However, in patients treated with mechanical thrombectomy alone, smoking did not affect clinical outcome. Newer therapeutic strategies with a tolerable adverse event profile and a low hemorrhagic incidence are particularly required, to overcome the limitations posed by rt-PA. Hence, the continuing development of drugs, devices, and other non-pharmacologic measures is the only approach to obtaining the desired therapeutic benefits at present.

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