SYSTEMATIC REVIEW

Systematic Review: Newer Perspective in the Medical Management of Acute Ischaemic Stroke

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Abstract

Introduction: Acute ischaemic stroke (AIS) remains a leading cause of mortality worldwide, where timely management is crucial in minimising neurological damage. This study reviews the latest evidence concerning the medical management AIS.

Methods: A systematic literature review was conducted using the EMBASE database to explore medical management strategies for AIS. Systematic reviews and meta-analyses from the past five years underwent abstract screening by two reviewers. Eligible abstracts were then evaluated through full-text reading based on the eligibility criteria. Out of 174 identified citations, 21 studies were included in the narrative analysis.

Results: Current evidence supports alteplase as the first-line treatment for AIS. However, tenecteplase is emerging as a promising alternative with similar efficacy and lower risks. Recent clinical trials suggested the use of aspirin within 24 hours of onset, and the consideration of dual antiplatelet therapy for prevention. Routine use of anticoagulants is discouraged, but low molecular weight heparin may have a role in certain stroke types. Emerging neuroprotective agents like edaravone, minocycline, vinpocetine, and salvianolic acids show promise but require more research for inclusion in treatment guidelines.

Conclusion: Medical management of AIS primarily relies on alteplase as the gold-standard treatment. Our analysis highlights tenectaplase as a possible alternative as well as the potential benefits of antithrombotic agents and neuroprotectants for post-stroke recovery and prevention. With variations in clinical efficacy outcomes due to limited subgroup analyses, it is important to conduct large multicentre trials to further evaluate the various management strategies in order to establish optimal care which is personalised.

Keywords: *Acute ischaemic stroke, Medical management, Alteplase, Antithrombotic agents, Neuroprotectants*

Introduction

Acute ischaemic stroke (AIS) is characterised by an interruption of blood circulation in the brain, limiting blood and oxygen delivery[1]. Stroke is the second leading cause of mortality worldwide, with approximately 12 million individuals suffering from an ischaemic stroke annually[2]. Stroke incidents can be classified as either ischaemic, which accounting for about 87% of all cases, or haemorrhagic, caused by a rupture of a blood vessel in the brain[3]. The underlying pathophysiology of ischemic stroke is most commonly due to thrombosis, typically of cardio-embolic origin secondary to atrial fibrillation or other arrhythmias[3]. Other less common causes include large-vessel stenosis, small-vessel disease, and infective vegetations[3].

Stroke is a medical emergency with severe consequences to the patient's quality of life. Despite current medical management, 60-80% of patients face either mortality or a lack of full recovery within 90 days following infarction[4]. The management of anterior circulation stroke has been shown to require a multidisciplinary approach and is in constant evolution[5]. 75-80% of strokes occur in the anterior circulation, with the rest occurring in the posterior circulation[6]. Currently, the gold standard treatment for AIS is the thrombolytic agent alteplase, which dissolves the clots in order to restore brain perfusion. Additionally, mechanical thrombectomy, an interventional approach that removes the clots using a catheter, is often considered[7]. Although effective, thrombectomy carries a 15% risk of complications, including arterial perforation and post-operative haemorrhage, which can be life-threatening[8]. Due to the high-risk nature of invasive procedures, it is crucial to optimise medical management and continue efforts to discover new pharmacological agents for AIS treatment.

An evidence-based approach is required for a high standard of medical care, especially when considering the introduction of novel therapeutics. Therefore, the

aim of this review is to evaluate the current evidence-based medical management of acute ischaemic strokes.

Method

Database search

A systematic review database search was conducted on October 25th, 2022 via the EMBASE database. The search was limited to the last 5 years to focus on the evidence and justification of the current management strategies for acute ischaemic stroke. The aim for this review was to evaluate the current medical management strategies for acute ischaemic stroke, therefore, the keywords used were 'medical management' or 'management' and 'acute ischaemic stroke' or 'anterior circulation stroke'. As the focus was solely on medical management, surgical management keywords such as 'thrombectomy' and 'endovascular' were removed by using the NOT function. Finally, to find literature which has high level of evidence **(Table 1)**, an exclusive search was conducted looking for 'meta analysis' or 'systematic review'. The full search strategy is as below:

('medical management'/exp OR 'medical management' OR 'management' OR (medical AND ('management'/exp OR management))) NOT 'thrombectomy' NOT 'endovascular' AND ('acute ischemic stroke'/exp OR 'acute ischemic stroke' OR 'acute ischaemic stroke'/exp OR 'acute ischaemic stroke' OR 'anterior circulation stroke'/exp OR 'anterior circulation stroke') AND ('meta analysis'/de OR 'systematic review'/de) AND ('article'/it OR 'review'/it) AND (2018:py OR 2019:py OR 2020:py OR 2021:py OR 2022)

Study selection

Screening of title and abstracts: Two reviewers screened each article by title and abstract of the retrieved search results in EMBASE based on the eligibility criteria **(Table 2)**. Any conflicts in inclusion or exclusion were discussed until a consensus was reached.

Table 1. **Levels of Evidence Grading System**[9]

Level	Type of Evidence
1a	Systematic Review (with homogeneity) of Randomised Clinical Trials (RCT)
1b	Individual RCT (with narrow confidence intervals)
1c	All or none study
2a	Systematic Review (with homogeneity) of cohort studies
2b	Individual cohort study (including low quality RCT, e.g. <80% follow-up)
2c	"Outcomes" research (i.e. audits)
3a	Systematic Review (with homogeneity) of case-control studies
3b	Individual case-control study
4	Case series (and poor-quality cohort and case-control studies)
5	Expert opinion without critical appraisal

Full-text review: The included abstracts were downloaded and assessed based on their full text. Two reviewers independently screened each paper for inclusion or exclusion based on the eligibility criteria **(Table 2)**.

Results of Database Search

Database search

The EMBASE database identified 174 citations based on the eligibility criteria for this review **(Table 2)**. Seven duplicates were found, and 167 citations were moved to title and abstract screening in the systematic review management tool Covidence[10]. 100 citations were excluded based on title and abstract. Upon full-text review of 67 citations, 46 were further excluded, leaving 21 citations for inclusion in the narrative analysis. The 2020 PRISMA guidelines[11] were used for this literature review to ensure a systematic approach to searching the literature. A flow diagram of the database search methods is shown in **Figure 1.**

For each study included in this review, seven important components were extracted and presented in a table as seen in **Table 2**. The seven aspects include:

1. Name of journal and year of publication
2. Number of studies included in the systematic review/meta-analysis
3. Number of participants and their mean age
4. Grading scale of evidence
5. Type of medical management
6. Type of group comparison
7. Outcome of study

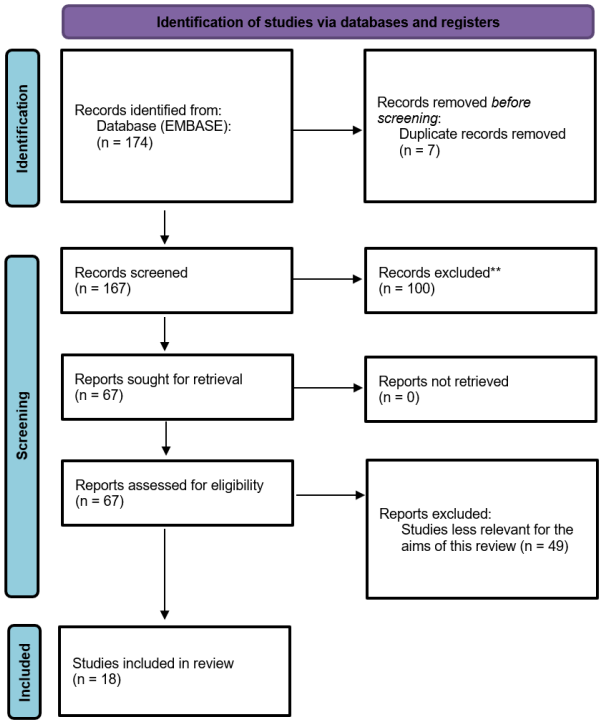

Figure 1. **PRISMA flowchart**

Table 2. **Eligibility Criteria**

	Inclusion Criteria	Exclusion Criteria
Publication year	Last 5 years (Oct 2018 – Oct 2022)	
Language	Restricted to English language	
Types of articles	Scientific articles published in peer-reviewed journals with available full texts that analyse at least one RCT	• Popular articles, grey literature • Editorials, commentaries etc. • Abstracts only • Conference abstracts • Trial registries
Study design	Systematic reviews and/or meta-analysis	• Study protocols • Clinical trials • RCTs • Case series • Case reports • Observational studies
Population	• Patients with anterior circulation stroke • Patients with acute ischaemic stroke	• Posterior circulation stroke • Haemorrhagic stroke • Comorbidities with specific medications (statins, heparin prior to intervention) • Large vessel occlusion • Specific patient populations (aspirin allergy, dyspepsia)
Interventions	Any patient targeted pharmacological approach to treating anterior circulation stroke	• Thrombectomy • Any other surgical interventions • Herbal medicine
Outcomes	• Neurological improvement • Risk of intracranial haemorrhage (ICH) • Mortality • Recurrent ischaemic stroke (RIS) post intervention	Failure of intervention

Main findings

Thrombolysis

The current guidelines for the pharmacological treatment of acute ischemic stroke (AIS) recommend the use of alteplase within 4.5 hours of onset of stroke symptoms[30]. Alteplase, a fibrinolytic agent often referred to as tissue plasminogen activator (tPA), converts plasminogen to plasmin, an enzyme that breaks down fibrin into fibrin degradation products, thereby dissolving the blood clot[31]. However, as a fibrinolytic agent, it also increases the risk of symptomatic intracerebral haemorrhage (sICH). Jia and colleagues investigated the safety and efficacy of alteplase treatment in ischaemic stroke and found that, although it resulted in better functional outcomes compared to other non-thrombolytic treatments, the risk of sICH was 4.46 times higher with alteplase use[12]. Therefore, it is crucial that these agents are administered with extra care and continued monitoring. A recent meta-analysis indicated that low-dose alteplase (<0.75mg/kg) could achieve a prognosis similar to the standard dose (0.9 mg/kg) with a reduced incidence of sICH[13]. Regarding the timing of administration, two meta-analyses concluded that the risk of sICH significantly increases beyond 4.5hrs after symptom onset, making timely administration of alteplase crucial[14, 15].

Although alteplase is the current recommended fibrinolytic agent for thrombolysis, tenecteplase is another agent that has shown promising results. Two recent meta-analyses compared the safety and efficacy of alteplase and tenecteplase[16, 17]; both studies concluded that tenecteplase demonstrated higher recanalisation rate and early neurological improvement with doses of 0.20-0.25 mg/kg. Safety considerations showed that sICH and mortality rates were comparable between both drugs. Tenecteplase also has a longer half-life and is suitable for a single bolus administration, making it preferable for patients requiring transfer for endovascular therapy. Additionally, tenecteplase has been shown to be more cost-effective, with an approximate cost of $3000 for 25mg of tenecteplase compared to $8000 for 90mg of alteplase which are appropriate dosages for a 100kg person[32]. A change to tenecteplase as the primary medication could potentially save hospitals and patients a substantial amount of money. These results strongly suggest that tenecteplase is a compelling alternative to alteplase, warranting a reassessment of The National Institute for Health and Care Excellence (NICE) guidelines to consider tenecteplase as the first-line medication for intravenous thrombolysis (IVT).

Anti-thrombotics

In addition to their prominent role in long-term secondary cardiovascular prevention, anti-platelets are also important for treating AIS. Primary antiplatelet agents in the treatment of AIS are Aspirin and Clopidogrel. Aspirin irreversibly inhibits cyclooxygenase (COX), leading to reduced thromboxane A2 (TXA2) production

and thus permanently inhibiting platelet aggregation[33]. Clopidogrel inhibits platelet aggregation through the P2Y12-receptor pathway, working synergistically with aspirin in platelet-aggregation assays[34]. NICE guidelines recommend the use of aspirin within 24 hours of AIS onset[30]. Minhas and colleagues confirmed the safety and efficacy of early antiplatelet therapy, especially within 48 hours of onset[18].

The increased risk of bleeding is offset by reductions in mortality or dependency and incidence of recurrent ischaemic stroke. Dual antiplatelet therapy (DAPT) with aspirin and clopidogrel, as opposed to aspirin alone, has been linked with a reduced risk of recurrent ischaemic stroke but increases bleeding risk, which can be minimised by limiting the duration of DAPT[19]. Physicians must balance efficacy and safety when prescribing antiplatelets, and should consider risk factors such as a history of stroke or intracranial haemorrhage[35].

According to the NICE guidelines, anticoagulants are not recommended for routine use in AIS[30]. Wang and colleagues found no benefit from early anticoagulation, with reductions in recurrent ischaemic stroke and pulmonary emboli being offset by an increased risk of sICH and extracranial haemorrhage[20]. Xia and colleagues found low molecular weight heparin (LMWH) offered no additional benefits over aspirin in an unselected patient population while increasing the risk of extracranial haemorrhage[21]; however, in patients with non-cardioembolic ischaemic stroke, LMWH reduced incidence of early neurological degeneration and recurrent ischaemic stroke while improving independence. Thus, the use of anticoagulants such as LMWH may depend on the type of ischaemic stroke and must be used with caution.

Neuroprotectants

An alternative intervention involves the use of neuroprotectants which help to reduce neurological damage following reperfusion to the ischaemic region. These novel interventions are currently not part of the NICE guidelines; however, recent promising have shown efficacy in reducing irreversible neuronal damage.

For the free-radical scavenger edavarone, Chen and colleagues found increased neurological improvement and decreased mortality rates at three months post-stroke[22]. It is thought that edavarone removes free radicals produced due to brain tissue ischaemia, leading to a reduction in oxidative stress. They concluded that edaravone has clear benefits in treating AIS and has been used within the Asian health system[22]. Hu and colleagues found similar results in their systematic review of the use of edaravone combined with alteplase, in which there was a reduction in National Institutes of Health Stroke Scale (NIHSS) scores as well as a reduced risk of ICH[23]. NIHSS is a standardised scale estimating stroke severity, ranging from 0 to 42, with higher scores indicating greater severity[36]. Moreover, Yang and colleagues found that adding a kallikrein glycoprotein neovascularisation agent (human urinary kallidinogenase) to edaravone significantly improved NIHSS scores better than edaravone alone[24]. Human urinary kallidinogenase (HUK) activates the kallikrein/kinin system (KKS) inducing angiogenesis and neovascularisation, potentially restoring blood supply in the ischaemic regions[24].

Other neuroprotectants include minocycline, a tetracycline with neuroprotective properties, which was found to reduce NIHSS scores in AIS patients after three months[25]. Vinpocetine and salvianolic acids, which are both plant derivates, similarly showed reductions in three-month NIHSS scores[26, 27]. In addition to pharmacological neuroprotectants, alternatives like remote ischaemic conditioning and normobaric oxygen therapy, when administered for three to six hours, have both been found to reduce NIHSS scores, although these studies have limited clinical use and evidence of benefit[28, 29]. These novel therapeutic approaches may continue to develop and may have potential to be added in the NICE guideline regimen for treating AIS in the future.

Discussion

The findings from recent research on the medical management of acute ischaemic stroke suggest that alteplase remains to be the gold standard and most effective treatment option; however, it should be administered with careful consideration due to the associated risk of sICH. Meanwhile, tenecteplase shows promise as a viable alternative to alteplase, as it offers similar efficacy with a potentially lower risk profile. Perhaps, a more large-scale multi-centred clinical trial is necessary to confirm whether tenecteplase should be the first line treatment instead of alteplase. The guidelines recommend antiplatelet therapy with aspirin, especially within the first 24 hours of acute ischaemic stroke onset, and dual antiplatelet therapy may be considered for recurrent ischaemic stroke prevention, although this approach should carefully balance its benefits against the risk of bleeding.

Anticoagulants are generally discouraged for routine use in AIS due to the increased risk of sICH. However, low molecular weight heparin (LMWH) might have a role in specific stroke types such as strokes of non-cardioembolic origin. Additionally, emerging neuroprotective agents like edaravone, minocycline, vinpocetine, and salvianolic acids demonstrate the potential to reduce neurological damage, but further research is needed to solidify their inclusion in treatment guidelines and understand their long-term effects. These findings emphasise the importance of tailoring AIS treatments to the individual needs of the patient while exploring possible alternatives to the standard approach.

Regarding long-term outcomes in patients treated with IVT, DAPT and neuroprotectant agents, a cohort study by Muruet et al with a ten-year follow up found that thrombolysis with intravenous alteplase is linked to better long-term survival and functional outcomes, with treated patients living on average one year longer than controls[37]. Additionally, a recent systematic review found that both short-term and long-term use of DAPT reduces risk of stroke; however, the risk of intracranial bleeding increases with DAPT use beyond three months[38]. Edaravone, a promising neuroprotective agent, has been

Table 3. **Data extraction from included papers**

Author and Year	Number of studies included	Number of participants	Mean age (years)	Grading Scale of Evidence	Medical Management	Comparison	Outcome	Reference
Sun et al., 2022	16	5,846	N/A	1a, 2a	Alteplase for mild ischaemic stroke (MIS) ("MIS patients generally do not undergo thrombolytic therapy, as clinicians generally assume these patients to have a better prognosis…)	rt-PA thrombolytic therapy vs. other non-thrombolytic treatments	• Good functional prognosis (mRS 0-1): Patients who underwent thrombolytic therapy had better outcomes at 3 months post-treatment relating to patients that underwent non-thrombolytic treatment. • Risk of sICH was 4.46 times higher in patients that underwent rt-PA treatment relating to patients that underwent non-thrombolytic treatment. • Mortality: rt-PA and non-thrombolytic treatments were not correlated with differences in mortality. • MIS cases exhibited improved 90-day favourable functional outcomes following alteplase treatment relative to controls. However, such treatment was also correlated with an enhanced chance of sICH	12
Cheng et al., 2018	12	7,686 low-dose: (n = 2888) standard-dose: (n = 4798)	N/A	1a	Low-dose tPA and normal dose tPA	Low dose tPA vs normal dose tPA	• Improved mRS scores with low-dose tPA, lowered incidence of sICH, similar effect of mortality and neurological function. • Low-dose tPA is highly recommended in AIS patients.	13
Jia et al., 2021	4	848	N/A	1a	Use of IVT (IVT group) among AIS patients with unclear symptom onset or extended time window (i.e., >4.5 hrs) Mean time window in the IVT group was 7.2 to 10.3 hrs and 7.3 to 10.4 hrs in the CG	IVT vs control group (CG)	• The functional independence at 90 days: There was a significant difference between the IVT group and the CG with the IVT group having better functional independence. • Meta-analysis of sICH found that the IVT group had higher rates than the CG and there was no significant difference between the IVT group and the CG in incidence of death. • The results of this meta-analysis confirmed that IVT was beneficial for patients with stroke lasting >4.5 h, and this treatment method can effectively improve the clinical functional outcome of patients compared with placebo	14
Chen et al., 2020	12	3,402	70	1a	Alteplase <3 hrs, Alteplase 3–4.5 hrs, Alteplase >4.5 hrs post-AIS	Alteplase vs control	• IV alteplase regardless of the time delay significantly improved the proportion of patients with modified Rankin Scale (mRS) scores 0–1 at 90 days after acute ischaemic stroke whereas IV alteplase used within 3 hours was more effective than that exceeding 3 hours. • V alteplase beyond 3 hours significantly increased the rate of symptomatic intracerebral haemorrhage within 36 hours compared with placebo but that within 3 hours was comparable with placebo.	15
Oliveira et al., 2021	8	2,031	69	1a	Various time windows ranging from <3hrs to <6 hrs Tenecteplase dosage: 0.1, 0.2, 0.25, 0.4 mg/kg	Tenecteplase vs alteplase	• Tenecteplase demonstrated an increase in recanalization rate and early neurological improvement. • No differences shown in terms of sICH, or mortality. • 0.20–0.25 mg/Kg tenecteplase dose might be preferable to other dosages as it was associated with higher early neurological improvement rates and a tendency for better functional outcome at 3 months. • The results of this study strongly suggest that tenecteplase is a valid alternative to alteplase for thrombolysis in ischemic stroke patients.	16

Table 3. **Data extraction from included papers (Cont.)**

Author and Year	Number of studies included	Number of participants	Mean age (years)	Grading Scale of Evidence	Medical Management	Comparison	Outcome	Reference
Kheiri et al., 2018	5	1,585 Tenecteplase: (n = 828) Alteplase: (n = 757)	70.8	1a	Tenecteplase dosage: 0.25mg/kg, 0.1mg/kg, or 0.4mg/kg Alteplase dosage: 0.9mg/kg	Tenecteplase vs alteplase	• Tenecteplase-treated patients were more likely to achieve complete recanalization of the occluded vascular territory and early neurological improvement. • No differences with regards to excellent recovery (mRS 0–1), functional independence (mRS 0–2), or poor recovery (mRS 4–6). • Tenecteplase-treated patients had no increased risk of symptomatic or any intracerebral haemorrhage or mortality compared with alteplase-treated patients. • Tenecteplase with a dose of 0.25 mg/kg was most effective in achieving early neurological improvement, complete and partial recanalization, and excellent mRS outcomes, without increased risks of intracerebral haemorrhage or mortality. • Study demonstrated tenecteplase's efficacy and safety profile were similar to, and sometimes even better than, alteplase in AIS patients	17
Minhas et al., 2022	11	42,262	N/A	1a	Oral antiplatelet therapy started within 14 days of stroke - aspirin (160 mg to 300 mg daily started within 48hrs of stroke symptom onset) other drugs: thienopyridine derivatives inhibiting adenosine diphosphate receptors (dipyridamole, cilostazol) and thromboxane A2 antagonists (ozagrel)	Oral antiplatelet therapy vs controls	• Death and dependency = Oral antiplatelet therapy led to a significant reduction at end of follow up, significant reduction at end of treatment period, reduction at final followup of greater than 1 month. • Oral antiplatelet therapy led to a reduction in recurrent ischaemic/unknown stroke. • Symptomatic ICH = increased odds for oral antiplatelet therapy but not statistically significant. • Any recurrent stroke/ICH = Oral antiplatelet therapy reduced odds of ischaemic stroke but also increased odds of symptomatic ICH. • Significant increase in risk of extracranial haemorrhage for oral antiplatelet therapy.	18
Yang et al., 2021	7	133,502	N/A	1a	Doses of clopidogrel and aspirin: 75mg and 325 mg once daily, respectively.	Clopidogrel and aspirin (DAPT) vs aspirin monotherapy	• Clopidogrel plus aspirin significantly lowered the risk for recurrent stroke compared with aspirin monotherapy. • All included reviews concluded that dual antiplatelet therapy (DAPT) appeared to be more effective and safer than monotherapy, and that using DAPT for as short as possible maximises benefit without increasing the risk for bleeding.	19
Wang et al., 2021	28	24,025	N/A	1a	Subcutaneous and intravenous standard unfractionated heparin, low-molecular-weight heparins, subcutaneous and intravenous heparinoids, oral vitamin K antagonists, factor Xa inhibitors, and specific thrombin inhibitors.	Anticoagulant therapy (started within two weeks of stroke onset) vs control	• Anticoagulation was associated with a statistically significant reduction in recurrent ischaemic stroke (OR 0.75, 95% CI 0.65 to 0.88; P =0.0003; 12 RCTs, 21,605 participants. • Early anticoagulation significantly increased symptomatic intracranial haemorrhage more than twofold. • Anticoagulation was associated with a significant reduction in pulmonary embolism. • Anticoagulation was associated with a significant increase in major extracranial haemorrhage. • Anticoagulation was associated with a significant reduction of deep vein thrombosis, although a majority of deep vein thromboses detected were subclinical and asymptomatic.	20

Table 3. **Data extraction from included papers (Cont.)**

Author and Year	Number of studies included	Number of participants	Mean age (years)	Grading Scale of Evidence	Medical Management	Comparison	Outcome	Reference
Xia et al., 2022	5	4,625	N/A	1a	Low molecular weight heparin (LMWH) vs. aspirin for early management (within 14 days of onset)	LMWH vs Aspirin	• Recurrent ischaemic stroke (RIS): No significant difference between LMWH and aspirin (RR: 1.02, 95% CI: 0.74–1.39). • Independence (mRS of 0-2): All five RCTs reported an mRS score of 0–2 at the end of follow-up (3 months for one study and 6 months for remainder); no difference between LMWH and aspirin (RR: 1.00, 95% CI: 0.95–1.06). • Death from any cause during treatment period and at the end of follow-up: No significant difference between LMWH and aspirin both in the treatment period (RR: 1.14, 95% CI: 0.97–1.27) and at the end of follow-up (RR: 1.01, 95% CI: 0.92–1.10). • Symptomatic intracranial haemorrhage during treatment period: No difference between LMWH and aspirin (RR: 1.19, 95% CI: 0.95–1.49). • LMWH was significantly associated with extracranial haemorrhage (RR: 1.16, 95% CI: 1.04–1.29; I2 = 37.9%, P=0.168).	21
Chen et al., 2021	7	2,069	70.1	1a	Three RCTs investigated patients with a treatment time window within 24 h, and three RCTs investigated patients with stable vital signs who were admitted to hospitals during 24-72 hours after the onset of stroke. Five RCTs investigated patients treated with edaravone for two weeks and the other two RCTs included patients treated with edaravone for one week. Four RCTs evaluated outcome at the long-term follow-up, namely three months or later. The other three RCTs made an assessment at two weeks follow-up.	Comparison of edaravone plus conventional therapy vs routine treatment alone Edaravone vs placebo or no intervention	• Three RCTs including 1720 patients reported the mortality at three months follow-up → a significant reduction of mortality was observed in the edaravone group than in the control group (RR = 0.55, 95% CI, 0.43- 0.70, I 2 = 0%; p < 0.01). • Four RCTs including 1778 patients evaluated the improvement of neurological impairment according to the authors' judgements at three-month follow-up → a significant improvement of neurological impairment was observed in the edaravone group than in the control group (RR = 1.54, 95% CI, 1.27-1.87, I 2 = 0%; P < 0.01). • Four RCTs including 466 patients reported the incidence of adverse events during the treatment → there was no significant difference in the incidence of adverse reactions between two groups (RR = 0.83, 95% CI: 0.51-1.34, P = 0.43) including nausea, skin rash, and abnormal liver function.	22
Hu et al., 2021	17	1,877 Edaravone: (n = 939) No Edaravone: (n = 938)	N/A	1a	Edaravone dosage: 60 mg/day	rt-PA combined with edaravone vs control	• 15 studies showed that rt-PA combined with edaravone treatment was associated with a reduced NIHSS score. • Eight studies with 946 patients reported ICH. Five studies indicated that edaravone treatment could not reduce the rate of intracranial haemorrhage, while another three studies reported a significant reduction of ICH in the edaravone group. • Pooled analysis found that edaravone treatment was associated with a lower risk of ICH • Four studies involving 442 patients: Pooled analysis demonstrated that no significant relationship between edaravone treatment and mortality could be shown.	23

Table 3. **Data extraction from included papers (Cont.)**

Author and Year	Number of studies included	Number of participants	Mean age (years)	Grading Scale of Evidence	Medical Management	Comparison	Outcome	Reference
Yang et al., 2021	13	1,242	50+	2b	Human urinary kallidinogenase (HUK) dosage: 0.15 PNA/day Edaravone dosage: 30 mg/day The mean values for clinical outcomes were assessed at 14 days.	HUK and edaravone vs edaravone alone	• The random-effect model revealed that the NIHSS score of patients treated with HUK combined with edaravone was lower than that of patients treated with edaravone alone, and the difference was statistically significant (WMD = −3.92, 95% CI (−4.82, −3.02), p < .0001), with high evidence of the heterogeneity(I2 = 98.0%, p < .001). • The result of pooled effect by fixed-effect model showed that compared with edavarone alone group, the ADL score of the HUK combined with edavarone group was significantly higher (WMD = 14.13, 95% CI (10.67, 17.60), p < .0001), with considerable heterogeneity among studies (I2 = 93.8%, p < .0001).	24
Malhotra et al., 2018	7	426	N/A	1a	Minocycline alongside standard treatment (tPA)	Minocycline + standard treatment vs standard treatment	Minocycline is a safe and efficacious agent in the treatment of acute ischemic strokes	25
Panda et al., 2022	4	837	62.4	1a	Vinpocetine started within 14 days of AIS Median dose: 30mg/day	Vinpocetine + standard treatment vs standard treatment alone)	• Vinpocetine has some promising efficacy in patients with ischemic stroke when used in the acute stage in reducing the disability, but presently there is not enough evidence to suggest it also reduces case fatality. • More double-blind, placebo-controlled RCTs of adequate sample size are needed before making recommendations for the routine administration of vinpocetine for all patients with acute ischemic stroke.	26
Xin et al., 2020	58	5,309	N/A	1a	Salvianolic acid (SA) treatment alongside standard western medical treatment (tPA, antiplatelet therapy, cerebral protectants)	SA + standard treatment vs standard treatment	• SA can significantly improve the total clinical effectiveness rate of ACI patients. • The use of SA remarkably increased the neurological functions, short-term daily living ability recovery, and cognitive functions of ACI patients	27
Zhao et al., 2018	7	735	N/A	1a	Remote ischaemic conditioning (RIC) (for prevention and treatment of ischaemic stroke)	RIC vs. non-RIC or standard medical management alone	• RIC did not significantly reduce the final infarct volume in people with acute ischaemic stroke who received intravenous thrombolysis, but it might increase the death or dependency of these people. • Neurological impairment and psychological impairment were not significantly improved by RIC in this patient population.	28
Bo et al., 2019	6	292	N/A	1a	Normobaric Oxygen (NBO) Oxygen therapy time window (<20 min, 20-120 mins, >120 mins); Oxygen concentration (29%, 45%, 61%); Air circulation (none, 3hrs NBO + 2hrs air, 6hrs NBO + 2 hrs air); Duration (24hrs, 48hrs, 72hrs)	NBO vs control groups	• NBO induced greater improvement in neurological recovery after stroke. • Improved ADL and disability of patients. • No effect on recurrence rate and mortality of AIS	29

Abbreviations: mRS = modified rankin scale, sICH = symptomatic intracranial haemorrhage, rt-PA = recombinant tissue plasminogen activator, IVT = intravenous thrombolysis, AIS = acute ischaemic stroke, CG = control group, DAPT = dual antiplatelet therapy, ADL = activities of daily living, NBO = Normobaric Oxygen, RIC = remote ischaemic conditioning, SA = salvianolic acid, ACI = acute cerebral infarction

shown to improve daily activities, reduce neurological deficits, and increase recanalisation rates in the short term[39]. However, further research and validation through larger clinical trials are necessary to ascertain its long-term effects.

The majority of our findings were derived from systematic reviews of randomised control trials (RCTs) which are considered to be the gold standard in evaluating the efficacy of health interventions. Furthermore, the method and search strategy in this paper allowed for investigation into a variety of medical management strategies of acute ischaemic stroke, including the most efficacious pharmacological agent to use for AIS in the general population[14-17, 30] and the role of newer agents like neuroprotectants[22-29]. Furthermore, we integrated two network meta-analyses, which, in contrast to conventional pair-wise meta-analysis, allows for the generation of multiple pooled effect estimates. This enables the ranking of interventions based on efficacy for example the different time points in which alteplase can be administered[15,17]. This review also included studies published in non-English languages, which included studies from all over the world which reduces the impact of language and culture bias on the total estimate of treatment effectiveness.

However, there are several limitations of the studies included in our analysis. There are high levels of heterogeneity in several clinical outcomes observed in the papers discussing the efficacy of different pharmacological agents in AIS. Most of the included studies' analyses failed to separate the percentage of people with certain stroke subtypes and stroke aetiologies, which may have had an impact on how well participants respond to thrombolytic agents. Data collection on neuroprotective agents was challenging due to limitations in the studies such as small homogenous populations (entirely Chinese cohorts), which may limit generalisability. Furthermore, in several instances, the methodological design of the studies was described as improper or incomplete, oftentimes not including long-term outcomes at six months or a year. Therefore, it was difficult to state whether the medical management had a long-term significant effects on the cohort.

Another notable limitation of the studies included in our analysis is the absence of subgroup analysis examining the potential impact of sex and ethnicity on the efficacy of thrombolytic agents, antiplatelet agents and neuroprotectants. A recent systematic review and meta-analysis by Liu et al. found that female stroke patients treated with IVT were more likely to exhibit worse functional outcomes compared to males, although the safety profile regarding haemorrhagic complications from was similar between sexes[40]. Additionally, a study by Mehta et al. identified potential differences in the side-effect profile of thrombolysis linked to the patient's ethnicity[41]. The incidence of sICH was slightly higher in patients of African or Afro-Carribean and Asian ethnicity in comparison to Caucasian patients[41]. Further research is required to explore sex- and ethnicity-linked differences in outcomes of thrombolysis and stroke management in order to develop personalised treatment strategies.

Conclusion

Medical management of AIS remains a first-line treatment, with alteplase recommended as the gold-standard treatment. Our analysis also indicates that antithrombotic agents and neuroprotectants have potential advantages in promoting functional recovery post-stroke as well as secondary prevention. However, only a small percentage of the reviews we evaluated included a subgroup analysis which can lead to varying clinical efficacy outcomes. Therefore, this paper highlights the need for more multicentral, large sample-size trials with subgroup analysis to determine the best practices for personalised AIS management. ◄

Declarations

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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