Acute ischemic stroke management

Concepts and Controversies. A narrative review

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Acute ischaemic stroke management: Concepts and Controversies. A narrative review

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Abstract

Introduction: Amongst the 25.7 million survivors and 6.5 million deaths from stroke between 1990 and 2013, ischemic strokes accounted for approximately 70% and 50% of the cases, respectively. With patients still suffering from

complications and stroke recurrence, more questions have been raised as to how we can better improve patient management.

Areas covered: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and Newcastle-Ottawa Scale (NOS) were adopted to ensure a comprehensive inclusion of quality literature from various sources. PubMed and Embase were searched for evidence on thrombolysis, mechanical thrombectomy, artificial intelligence (AI), antiplatelet therapy, anticoagulation and hypertension management.

Expert opinion: The directions of future research in these areas are dependent on the current level of validation. Endovascular therapy and applications of AI are relatively new compared to the other areas discussed in this review. As such, it is important for future studies to focus on validating their efficacy. As for thrombolysis, antiplatelet and anticoagulation therapy, their efficacy has been well-established and future research efforts should be directed towards adjusting its use according to patient specific factors, starting with factors with the most clinical relevance and prevalence.

Keywords: Stroke, thrombolysis, thrombectomy, anticoagulation, antiplatelet, artificial intelligence.

Article highlights

- Patient with confirmed small ischemic penumbra secondary to proximal occlusion are likely to benefit from mechanical thrombectomy (MT) and intravenous thrombolysis. Further validation studies into (1) the applications of MT in treating basilar occlusions, (2) the benefits of

concurrent internal carotid artery stenting or dilation and (3) artificial intelligence software are required.

- Dual antiplatelet therapy post-ischemic stroke is superior to mono- and triple- therapy. There are currently ongoing trials looking into dual antiplatelet therapies involving ticagrelor and its optimal treatment duration.
- Direct oral anticoagulants (DOACs) are superior to warfarin for secondary prevention of stroke with lower bleeding risks. Research into DOAC dose adjustment in advanced chronic kidney disease and the optimum time to initiate DOAC post-stroke is currently underway.
- Maintaining tight blood pressure control is recommended throughout the different phases of stroke management. Further randomized trials are required to determine the ideal blood pressure range at each phase.

1. Introduction

According to the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) in 2015, stroke is a leading cause of mortality and disability [1]. It is expected the burden of stroke will continue to increase until effective treatment and prevention strategies are more widely implemented [2].

According to an old definition of stroke in the 1970s, the 24-hour mark separates a ‘stroke’ from a ‘transient ischemic attack’ (TIA) [3]. However, the American Heart Association (AHA) and American Stroke Association (ASA) re-defined TIA in 2009 as ‘a brief episode of neurological dysfunction caused

by focal brain or retinal ischaemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction' [4]. Strokes have been divided into ischemic or primary hemorrhagic strokes [5], with ischemic strokes being secondary to thrombosis, embolism, hypoperfusion and cerebral venous sinus thrombosis [3 6-8].

This review will specifically address the management of an acute ischemic stroke, notably the areas of thrombolysis, mechanical thrombectomy, utility of artificial intelligence and medications commonly used to lower the risk of a further ischemic stroke. In each section, a timeline of how key conflicts in these areas emerged and were addressed over the years will be discussed, along with the current challenges.

2. Methods

This narrative review adopted the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement and the Newcastle-Ottawa Quality Assessment Scale (NOS) to ensure a comprehensive inclusion of quality literature from various sources. The following search string was used: (((stroke) AND ((atrial fibrillation) OR (prophylaxis) OR (imaging) OR (Anticoagulation) OR (antithrombotic) OR (vitamin K Antagonist) OR (management) OR (endovascular) OR (thrombectomy))). PubMed and Embase along with abstracts from national and international cardiovascular meetings were searched accordingly from conception of the database to April 2014, yielding more than 100,000 results given the breath of topics discussed. Articles were selected mainly by CL, AJ and RD with disputes settled by the senior supervising author GL. Articles used include but are not limited to major trials, cohort studies and meta-

analyses. Bibliographies of the included articles were also scanned for other relevant papers. Finally, the supplements of major journals were searched manually to identify relevant abstracts that were yet to be published as peer-reviewed papers.

3. Thrombolysis

The evidence for thrombolysis in patients with stroke first emerged in 1995 through the National Institute of Neurological Disorders and Stroke (NINDS) trial [9]. In 2001, a conditional license for the use of thrombolysis was given by the European Union, which was made permanent following two iconic studies, namely the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) and the European Cooperative Acute Stroke Study (ECASS) III [10] [11]. Both studies assessed the safety and efficacy of intravenous alteplase as the mainstay for thrombolytic therapy. SITS-MOST confirmed that in an ischemic stroke, the use of alteplase is effective in routine clinical use when used within 3 hours. This 3-hour threshold was subsequently extended to 4.5 hours after the ECASS trial. Once the onset of ischemic stroke has been established to be less than 4.5 hours, alteplase can be administered at 900 micrograms/kg accordingly. This is a widely accepted approach with alterations according to local hospital guidelines. More recently, the Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) compared a lower dose (600 microgram/kg) alteplase against the standard dose, which showed a lower risk of intracranial hemorrhage, but did not adequately assess if a lower dose regime was of similar efficacy [12].

In 2012, the third International Stroke Trial (IST-3) established that thrombolysis with alteplase maintains an overall benefit with improved functional outcome even when used within 6 hours. This benefit did not seem to diminish in the subset of patients over the age of 80 [13]. A meta-analysis of nine randomised controlled trials (NINDS A-B, ECASS I-III, ATLANTIS A-B, EPITHET and IST-3) conducted by the Stroke Thrombolysis Trialists' Collaborative Group, confirmed that irrespective of age and stroke severity, the outcomes were in favor of the use of alteplase in the early treatment phase; however, the odds of beneficial stroke outcomes were not statistically significant in a sub-analysis of alteplase use after 4.5 hours [14]. In 2019, a further meta-analysis of three trials (EXTEND, ECASS4-EXTEND and EPITHET) studied if additional perfusion imaging could better direct thrombolysis treatment in patients with stroke symptoms after 4.5 hours or with symptoms on waking. It concluded that patients with salvageable brain tissue on perfusion-diffusion MRI or CT perfusion were more likely to have better functional outcomes when thrombolysis was given instead of placebo [15].

The fundamental principle of alteplase prescription in ischemic strokes, though constantly evolving, remains a relatively straightforward concept. However, confounding patient variables such as ongoing medical and drug histories introduces complexity to this algorithm. For example, the officially approved dosage of intravenous alteplase is 600 microgram/kg in Japan versus the usual 900 micrograms/kg in other countries [16]. A meta-analysis conducted by Whiteley *et al*. also found atrial fibrillation (AF), congestive cardiac failure, renal impairment, prior antiplatelet therapy, leukoaraiosis and

visible cerebral infarction on pre-treatment brain imaging placed patients at greater risk of intracerebral hemorrhage but the extent of these factors was not quantified [17]. Other studies have suggested that the safety and efficacy of intravenous thrombolysis remained unaffected in patients with prior anti-platelet therapy [18] and heart failure [19]. Patients with concurrent atrial fibrillation, however, had worse outcomes if thrombolysed when compared against non-AF stroke patients [20].

Intravenous thrombolysis (IVT) can be used in patients receiving the direct thrombin inhibitor, dabigatran, after administration of idarucizumab, a human monoclonal antibody for reversal of anticoagulation effects [21]. However, a recent meta-analysis found no significant increase in the risk of haemorrhage or early mortality in patients who received pre-thrombolysis idarucizumab compared to those who did not. Shahjouei *et al*. also went on to conclude that despite the intake of direct oral anticoagulation (DOAC) within 48 hours prior to administration of IVT was not associated with a significant increase risk of bleeding [22].

In more recent studies and consensus statements, IVT after reversal of the anticoagulation effect of dabigatran is considered safe and efficacious, especially when thrombectomy cannot be performed in a timely manner [23 24]. As for ischemic stroke patients on vitamin K antagonists (VKAs), thrombolysis can be given if the international normalized ratio (INR) is <1.7. There is some evidence that thrombolysis can also be given if INR is >1.7 as long as intravenous infusion of prothrombin complex concentrate and vitamin K are given prior to this [25]. However, there are no large prospective randomized controlled trials to confirm these approaches.

In 2018, the American Heart/Stroke Association advanced a new recommendation that Tenecteplase (TNK) can be considered as an alternative to alteplase in patients with an acute ischemic stroke [26]. The efficacy of TNK has been confirmed in a meta-analysis of five randomized controlled trials (TNK-S2B, Australian TNK, ATTEST, Nor-Test and EXTEND-IA TNK) [27-31], showing non-inferiority to alteplase in both the primary efficacy (freedom from disability mRS 0-1 at 3 months) and secondary safety outcomes [32]. It is worth noting that the greatest weight of evidence is from a trial that recruited patients with mild neurological deficits, which allows for a better chance in achieving the primary efficacy outcome with TNK [30]. However, in contrast to the EXTEND-IA TNK trial, similar non-inferior primary and secondary outcomes were also observed when patients with mainly large vessel occlusions and major neurological deficits were included [31]. If other factors such as ease of administration and cost were also taken into account [33], it makes for a strong case that TNK should be used over alteplase for thrombolysis in ischemic strokes. Perhaps the reluctance to initiate TNK stems from the uncertainty revolving the optimal dose and timing of administration of TNK, which saw a significant degree of heterogeneity in a published meta-analysis conducted [32]. As such, the EXTEND-IA part 2 trial is currently underway to better inform TNK dosage administration [34]. A summary of the key trials can be seen in **Supplementary Table 1.**

4. Mechanical thrombectomy (MT)

Up until 2015, IVT remained the mainstay of treatment for ischemic strokes occurring within 4.5 hours [11]. This was likely because of the volume of evidence supporting the use of IVT and the negative trials (IMS-3,

SYNTHESIS and MR-RESCUE) published in 2013 concerning endovascular methods [35-37]. However, the use of IVT is not without its limitations, being ineffective in patients with proximal vessel occlusions, with only 30% and 10% achieving adequate recanalization in middle cerebral artery (MCA) and carotid artery occlusions respectively [38]. Furthermore, there were significant shortcomings in these trials to adequately assess the efficacy of MT. In the IMS-3 and SYNTHESIS trials, the use of imaging modalities was suboptimal and thus not applied to the patient population. Also, when computed tomography angiography (CTA) was used, the extent of salvageable penumbra was not evaluated [35 36]. In the MR-RESCUE trial, even though magnetic resonance imaging (MRI) profiles were available, the trial was based on patients with a significant delay in MT (mean delay of 6.35 hours), again suboptimal for its use [37].

It was only in 2015 when a number of trials with more stringent patient selection processes were published to assess the benefits of MT, which were the MR-CLEAN, EXTEND-IA, ESCAPE, SWIFT-PRIME and REVASCAT trials [39-43]. These trials confirmed that patients with a proximal occlusion with small ischemic core volume who received early endovascular intervention demonstrated a clear benefit when used in conjunction with IVT. A meta-analysis of these eight trials confirmed the overall benefit of MT [44], leading to guidelines recommending MT in combination with IVT in patients with proximal artery occlusion strokes within the first 6 hours of symptom onset. In 2016, another meta-analysis also confirmed that patients over the age of 80 were not exempt from receiving MT and IVT treatment, as there was no significant difference in mortality and complications [45].

Some guidelines have also extended this principle further, suggesting MT should remain as the first-line treatment in patients with large vessel occlusions if IVT is contraindicated, citing evidence from the ESCAPE and REVASCAT trials [41 43]. A small prospective observational study compared MT to MT with IVT [46], and despite similar recanalization and complication rates in both groups, functional independence was significantly more prevalent in the MT with IVT group. However, results observed in a recent Chinese trial comparing endovascular thrombectomy alone against endovascular thrombectomy with intravenous alteplase (<4.5 hours) in patients with large vessel occlusions concluded otherwise [47]. Yang *et al*. found endovascular thrombectomy alone to be non-inferior to the combination group when both the primary efficacy and secondary safety outcomes were concerned [47]. Ongoing trials evaluating similar comparisons along with trials looking into endovascular treatment for strokes with low National Institute of Health Stroke Scale (NIHSS) score are currently awaited [48-50]. To date, there have been no randomized trials comparing primary MT against standard medical treatment in patients where IVT is contraindicated.

Despite multiple trials with MT, there are still unanswered questions. The 2015 trials have gathered some insight into how the use of perfusion imaging can better select patients who will likely benefit from MT. There is a correlation between the benefits of MT and extent of the ischemic penumbra [51]. Both MRI and CT can quantify salvageable tissue and the quality of collateral circulation [52-55]; however, only a small proportion of patients in recent trials were selected with appropriate imaging modalities. The recent MT trials additionally provide little insight into patients with distal MCA and

basilar occlusions, likely attributed to MT techniques being restricted to the proximal segment of the anterior cerebral artery and to divisions of the MCA.

Given the severe prognosis of basilar occlusions [56], data on this subset of patients will be vital in optimizing therapeutic decision-making. The BASICS study did provide some supplementary data on this front but an adequately powered randomized controlled trial investigating this is needed [57]. Several systematic meta-analyses of case series and registry data suggest that MT provides a better outcome in patients with basilar artery occlusion (BAO) [58-60]. This notion is especially promising when considered in conjunction with the recent non-randomized Acute Basilar Artery Occlusion Study (BASILAR) [61], which reported better functional and safety outcomes in patients receiving standard medical treatment plus endovascular therapy compared to those receiving standard medical treatment.

There are other peripheral, yet relevant, factors to consider around MT such as the use of general anesthesia versus conscious sedation and the use of endovascular internal carotid artery (ICA) stenting. The choice of anesthesia in the EXTEND-IA trial was solely a medical decision made between the interventionist and anesthetist, with general anesthesia being used in only 30% of patients [40]. However, post-hoc analysis of the MR-CLEAN trial and IMS III study were in favor of performing MT under local anesthesia, given an association with lower mortality rates [39 62]. A meta-analysis (9 studies and 1379 patients) on MT for anterior circulation ischemic strokes [63] found no significant difference between conscious sedation and general anesthesia in relation to functional independence at 3 months. In an observational study, Wu et al., observed no significant difference in functional

outcomes and complication rates [64]. Contrary results were observed from the DEFUSE-3 analysis in 2019, which suggested that conscious sedation resulted in better rates of functional independence at 3 months [65]. As such, the question of anesthesia for MT remains a controversial issue and team-based decisions are needed, which is in line with the policy statement from the American Heart and Stroke Association [66].

Another area that has been scarcely explored in previous MT trials was the use of acute stenting of the extra-cranial ICA alongside antithrombotic therapy in combination with intracranial MT in patients with tandem lesions. The pathophysiological consideration for this lies between the facilitation of intracranial clot lysis with improved proximal flow and increased risk of symptomatic intracranial hemorrhage, since the patient will require additional antiplatelet therapy on top of IVT [67].

There is variation in practices between interventionists with either acute stenting or dilation of the ICA, and some practitioners choose to avoid treating the extra-cranial ICA altogether [68]. In 2018, Papanagiotou et al. reported an international, multicenter registry, demonstrating that acute stenting of the ICA with antithrombotic therapy is associated with higher recanalization rates in patients with tandem lesions [69]. Regardless, evidence for the optimal approach towards tandem lesions remain scarce and would benefit from further robust randomized controlled trials. The summary findings for both thrombolysis and thrombectomy can be seen on **Table 1 and Supplementary Table 2**.

5. Artificial intelligence and deep learning models

Having established the core treatment measures for acute ischemic strokes, of IVT or MT, effective imaging and interpretation consistently remains pivotal in governing optimal timely interventional decisions [70] [71]. Artificial Intelligence (AI) has been proposed to deal with the inconsistencies in interpretation of perfusion, angiographic and ASPECTS (Alberta Stroke Programme Early CT score) data [72]. Several commercial software platforms have been made available to address the following: (i) stroke core and penumbra size and mismatch quantification; (ii) detection of vascular thrombus or occlusion; and (iii) predication of acute complications: Brainomix (Oxford, UK), iSchemaView (Menlo Park, California, USA), and Viz.ai.

To date, there have been multiple studies comparing the AI e-ASPECTS algorithm offered by Brainomix against individual radiologists and consensus radiologists [73-78], which largely concluded that the e-ASPECTS algorithm performed on par with or outperformed neuroradiologists. In 2018, Guberina *et al*. found the Brainomix algorithm to be more sensitive but less specific [76]. The e-ASPECTS algorithm was released in 2015, primarily to interpret non-contrast CT scans to provide a numerical ASPECTS and comparison between acute and non-acute hypodense regions [72]. In 2018, Brainomix introduced e-CTA, which uses convolutional neural networks (CNN) instead of ML to determine the presence of LVOs from CTA scans, similar to the iSchemaView RAPID system. However, no validation data have been made available to accurately assess this software. As opposed to Brainomix, in 2012 iSchemaView validated the use of AI perfusion imaging for stroke in the DEFUSE 2 study using its RAPID software [51]. It has been

applied in multiple LVO MT trials, such as the EXTEND IA, SWIFT PRIME, CRISP, DEFUSE 2 and 3, and DAWN trials [40 42 51 79-81].

The RAPID software operates by analyzing CT and MRI perfusion studies to generate a colorimetric perfusion map detailing the infarct core and ischemic penumbra regions dichotomously. RAPID is able to predict with 83% accuracy the post-thrombectomy infarct core volume and the MRI core to penumbra mismatch with outstanding sensitivity and specificity [42 79 82 83]. It was only recently that an ASPECTS component, a CTA vessel density detection application and binary output thrombectomy selection guide were introduced, but validation data remains unavailable.

The newest AI LVO stroke and perfusion analytics software is from Viz.ai, receiving FDA clearance in 2018. The functionalities and output from the Viz LVO and Viz CTP platforms are similar to ones provided by Brainomix and iSchemaView. However, Viz provides additional interface features to expedite stroke care, including automatic LVO detection and delivery of dynamic CTP or CTA images to relevant healthcare professionals' mobile devices. Despite demonstrating increased efficiency in notification and earlier LVO treatment [84], there remains a lack of evidence surrounding the accuracy of LVO stroke detection and perfusion analysis to justify routine clinical use.

In summary, further validation studies and clinical trials are warranted to enable a more robust comparison and application into routine clinical use. In contrast to the AI in imaging perfusion and ASPECTS, literature regarding the use of AI in LVO detection be it directly or indirectly, remains confined to mainly conference abstracts and thus will benefit enormously from peer-

reviewed validation studies. The diagnostic validation, management and future directions of these software applications are summarized in **Table 2**.

6. Antiplatelets

Despite the early efforts of IVT and MT, many patients still suffer from residual functional deficits as well as neurological and medical complications, which are major causes of morbidity and mortality if not managed appropriately [85] [86].

Multiple trials and meta-analyses have confirmed the benefits of antiplatelet therapy in patients with ischemic strokes and transient ischemic attacks (TIAs) [87]. The anchor antiplatelet therapy has always been aspirin [88], followed by newer options such as ticagrelor [89] and clopidogrel [90]. The CAPRIE trial was the only randomized, blinded trial that did a head to head comparison between clopidogrel and aspirin in patients with ischemic stroke. Despite the relative risk reduction of 7.3% favoring clopidogrel, it was not found to statistically significant. There was no significant difference in complication rate between the two treatment arms [91]. Conversely with ticagrelor, even though no significant difference in the composite outcome (stroke, myocardial infarction and death) was seen, a significant reduction in ischemic stroke occurrence was seen when compared to aspirin monotherapy [89].

Further trials have investigated the optimal antiplatelet monotherapy, dual therapy and triple therapy regimes for preventing stroke recurrences [92] [93]. In a 2018 meta-analysis, Hao *et al*. reported three trials consisting of more than 10,000 patients, to compare aspirin monotherapy against aspirin and

clopidogrel dual therapy [93]. Dual antiplatelet therapy showed a 2% absolute reduction in subsequent strokes with only a 0.2% absolute increase in risk of moderate to severe bleeding. Based on the trials involved, it has been recommended that dual antiplatelet therapy can be stopped after 10 to 21 days [93]. Another meta-analysis regarding non-cardioembolic ischemic strokes also supported the utility of dual antiplatelet therapy over monotherapy, but found a significant increase in risk of major bleeding [94].

Previous trials have documented the effectiveness of Cilostazol, a phosphodiesterase 3 inhibitor, to be effective in stroke prevention [95 96]. A recent randomized controlled trial comparing monotherapy (aspirin or clopidogrel) to dual therapy (cilostazol with either aspirin and clopidogrel) suggested effective reduction in ischaemic stroke recurrence with similar risk of bleeding with cilostazol dual therapy [97]. In a recent phase 3 randomised trial, the effectiveness of triple antiplatelet therapy with aspirin, clopidogrel and dipyridamole was assessed, which concluded that the benefits of preventing stroke recurrence plateaus with two antiplatelet medications and adding an additional antiplatelet confers not only a significant increase in bleeding risk but no reduction in the incidence and severity of recurrent strokes or TIAs [92].

7. Anticoagulation

The introduction of anticoagulants is indicated usually for preventing recurrent ischemic strokes of cardiac origin, specifically in patients with atrial fibrillation (AF). Clinical practice with warfarin tends to aim for an INR between 2.0 and 3.0 in patients with AF with good quality anticoagulation control (Time

in Therapeutic Range, TTR >70%), which has been reported to decrease the odds of recurrent strokes by two-thirds [98]. Chao *et al*. have also discussed the use of lower INR ranges, especially in an Asian population [99]. This notion stemmed from a sub-analysis of the ENGAGE AF-TIMI 48 trial, which found Asian patients to be more susceptible to intracranial hemorrhage despite a lower INR range [100]. The adoption of a lower INR range can be seen in guidelines provided by several Asian societies, especially in elderly patients [101 102]. In a recent meta-analysis of 79 randomized controlled trials, it was suggested a target INR range between 2.0 and 3.0 should remain across all ethnic groups. Despite a lower risk of intracranial bleeding and similar risk of mortality, a lower INR range in the East Asian population was associated with an increased risk of thromboembolism [103]. However, Pandey *et al*. only compared between patients with a target INR range of 1.5 to 2.0 and 2.0 to 3.0, giving rise to a proposed prophylactic range of 2.0 to 2.5. This was subsequently addressed by McDowell *et al*., who found the combined rates of intracranial hemorrhage and ischemic stroke to be lowest when INR was observed between 2.0 to 2.5 [104]. Regardless, this finding is based on a combination of several observational studies and would greatly benefit from higher quality, prospective and randomized ones.

Several scoring tools such as the CHA_2DS_2-VASc and HAS-BLED score have been routinely used to guide clinicians in prescribing anticoagulation [105 106]. Multiple Phase III clinical trials of DOACs compared to warfarin have been conducted, showing that they are non-inferior to Warfarin, with lower rates of major bleeding [107-111]. Ruff et al [112] performed a meta-analysis of the 4 major trials (RE-LY, ROCKET AF, ARISTOTLE and

ENGAGE AF TIMI 48), showing that DOACs were associated with lower stroke/systemic embolism and major bleeding compared to warfarin, as well as significantly fewer hemorrhagic strokes, intracranial bleeding and all-cause mortality. Wang et al reported a meta-analysis of the same 4 trials, which compared standard and low dose DOACs to warfarin in Asian versus non-Asian populations [113]. There is no significant difference in outcome measures between the two populations with low-dose DOACs but standard-dose DOACs was found to be superior for both stroke prevention and safety profile in the Asian population.

These findings were further complemented by large real world observational data, for example, the ARISTOPHANES (Anticoagulants for Reduction in Stroke: Observational Pooled Analysis on Health Outcomes and Experience of Patients) and NAXOS (Evaluation of Apixaban in Stroke and Systemic Embolism Prevention in Patients with Nonvalvular Atrial Fibrillation) studies [114 115]. The ARISTOPHANES study reinforced the non-inferiority of DOACs to warfarin in stroke prevention but only Apixaban and Dabigatran were associated with a lower risk of major bleeding. Comparisons between different DOACs were also done to demonstrate apixaban as the preferred DOAC of choice when rates of stroke and major bleeding are considered [114]. The NAXOS study similarly found DOACs to be associated with superior safety, effectiveness and lower mortality than warfarin; however, apixaban was not more effective than other DOACs (rivaroxaban and dabigatran) but had a superior safety profile was only seen when compared against rivaroxaban [115].

Over the years, other areas of uncertainty regarding DOACs have also emerged such as (i) the dosing regimens in patients with concurrent chronic kidney disease (ii) restarting anticoagulation in patients with post-intracranial hemorrhage (iii) the optimal time to start anticoagulation post-cardioemobolic stroke and (iv) adherence and compliance.

AF and chronic kidney disease (CKD) are becoming increasingly prevalent given the many risk factors in common [116]. However, the landmark clinical trials have excluded patients with severe or end-stage CKD [116]. In patients with early-stage CKD, despite evidence suggesting a superior benefit-risk profile of DOACs compared to VKAs, data was insufficient for late or end-stage CKD and were mainly derived from sub-analysis of trials [117]. Even though there have been attempts in proposing management guidelines [118], the need for more robust clinical trials to decipher anticoagulation use in this subset of patient's remains.

Similarly, with restarting anticoagulation in patients post intra-cerebral bleeds, there is currently still a lack of high-quality evidence to guide clinical decision-making. This is especially pertinent to patients with mechanical heart valves, high risk of pulmonary embolism or AF with high CHA_2DS_2-VASc scores [119] as prolonged cessation of anticoagulation predisposes these patients to a significantly higher risk of thromboembolism [120]. As such, Li et al. [121] proposed that clinical decisions as well as future research efforts should focus mainly on the risk evaluation of thromboembolism and hemorrhage, choice of anticoagulation and the appropriate time to reinitiate anticoagulation.

The optimal time to start anticoagulation post- cardioembolic stroke remains the subject of investigation in several ongoing trials [85]. The RAF

study was the first observational study to shed some insight into this, proposing that anticoagulation treatment for secondary prevention should be initiated between 4 and 14 days from stroke onset [122], but also pointed to the CHA_2DS_2-VASc score, National Institutes of Health Stroke Scale (NIHSS), size of ischemic lesions and type of anticoagulation as independent predictors of stroke recurrence and bleeding. In 2016, the RAF study proposed a model for anticoagulation initiation based solely on the size of the lesion from CT or MRI findings: for small, medium and large lesions, anticoagulation can be started after 3 to 4 days, 7 days and 14 days respectively while concurrently stopping antiplatelet therapy [123]. Recently, several protocols for ongoing trials have been published and are currently underway to better determine the optimal time delay for anticoagulation, namely the START, TIMING, OPTIMAS and ELAN trials [124-127]. The summary flow of anticoagulation and antiplatelet administration based on the current evidence can be seen in **Figure 1**.

Despite the well-documented benefits of anticoagulation in secondary stroke prevention, it is highly dependent on patient adherence and compliance to taking prescribed anticoagulants to reflect the outcomes outlined in studies. A meta-analysis by Shehab et al. reported that suboptimal adherence to anticoagulants, especially amongst AF patients, is associated with more adverse outcomes [128]. In a recent review by Raparelli *et al*., adherence and persistence to warfarin and the various types of DOACs were discussed [129]. In a recent study based off a small Korean cohort (n=719), an overall compliance (prescribed doses taken >80%) of 92.2% was achieved in once and twice daily DOAC groups [130]. When compared to a countrywide

observational study conducted in the United Kingdom, the overall compliance was only 55.2%. This study also supported the previous finding that adherence rates have generally declined over time [131]. The reasons for non-compliance spans over a wide range of bio-psycho-social factors, which suggest that the strategy required to address non-adherence has to be personalized to individual patients [129]. The use of several scoring systems such as MMAS-8 and SAMe-TT_2R_2 for vitamin-K antagonist treatment in AF has also been proposed for a more targeted approach [132]. By identifying specific patients or patient groups who are more susceptible, greater attention and patient specific strategies can be developed to improve adherence.

8. Hypertension management

The hemodynamic management post stroke remains controversial, especially with regard to blood pressure [133 134]. In one study with more than 250,000 patients, approximately 75% of patients with ischemic stroke had a systolic blood pressure greater than 140mmHg [133]. Observational studies have shown that elevated blood pressure in patients with ischemic stroke confers worse clinical outcomes [135-137], similarly for patients with low blood pressure [138] and abrupt systolic blood pressure decline (>20 mmHg) [139 140].

The International Stroke Trial advised to maintain a systolic blood pressure between 140 and 179 mmHg [138]. However, the optimal blood pressure range has varied significantly between different studies [139 141]. In the 2018 American Heart Association (AHA) guidelines, it was recommended that blood pressure up to 220/120 mmHg can be permitted only if patients have no contraindications to elevated blood pressure and are not for IVT or intra-

arterial therapy (IAT) [26]. Further blood pressure targets depending on the clinical status of the patient have also been recommended [26].

Following initial assessment, the Society of Neuroscience in Anesthesiology and Critical Care maintain a systolic blood pressure between 140 and 180 without an aggressive drop in blood pressure during the revascularization process [142]. This was based on observational studies suggesting aggressive blood pressure drops and higher average maximal systolic blood pressure to be associated with unfavorable outcomes [143 144]. It is also commonly seen in patients who underwent IAT whilst on general anesthesia to have more significant blood pressure fluctuations, especially during the induction phase [145-147]. This risk of hypotension is not restricted to general anesthesia and can be seen with conscious sedation as well [148]. Further validation that general anesthesia is associated with more frequent mean arterial pressure drops can also be seen in randomized controlled trials [149-151]. Despite blood pressure variations with general anesthesia and conscious sedation, several randomized controlled trials (GOLIATH, SIESTA and ANSTROKE) have found no significant difference in safety, short-term (24 hours post procedure) and long-term (3 months) efficacy outcomes between the two sedation methods [150-152]. Based on these trials and observational studies, the use of either general anesthesia or conscious sedation is reasonable and also emphasizes the need for tight blood pressure control during revascularization.

There is usually a physiological decline in blood pressure over the 24 hours following recanalization therapy [153]. Similar to non-recanalized patients, recanalized patients with persistently raised blood pressure are at an

increased risk of intracranial hemorrhage [154] [155]. As such, the 2018 AHA guidelines suggested maintaining a blood pressure less than 180/105 mmHg to mitigate the risk of intracranial hemorrhage and reperfusion injury [26] [156]. However, since the rates of early revascularization are significantly lower with IVT when compared to IAT, maintaining a blood pressure closer to 180/105 to ensure adequate perfusion should be prioritized with IVT treatment [157]. Conversely, with IAT where recanalization is achieved in the majority of patients [158], having a blood pressure closer to 180/105 might increase the risk of reperfusion injury.

Currently, there are no randomized trials that specifically examine blood pressure control following IAT. The only available evidence comes from a single center observational study by Goyal *et al*., which focused on IAT patients with good recanalization status. This study showed that despite requiring antihypertensive medications, patients within the lower blood pressure brackets (<160/90mmHg) have lower rates of mortality at 3 months [159]. This leaves the question of blood pressure management in patients with incomplete or poor perfusion post-IAT. Even though the data available for this group of patients are scarce, lessons can be drawn from the approach with IVT, aiming for a target systolic blood pressure close to 180 to ensure adequate perfusion. **Table 3** summarizes the current evidence pertaining to blood pressure management at different time points in relation to the patient's operative status.

9. Conclusion

It is evident that the management of an acute ischemic stroke is still evolving, with research efforts spanning from timely diagnosis with appropriate imaging and AI, use of thrombolytic agents and IAT to secondary prevention strategies and improving patient adherence and compliance to prescribed medication. This narrative review focused on the progress of three core components following an ischemic stroke: (i) investigations and interpretation (ii) acute management and (iii) secondary prevention. Within each component, a summary of known and validated concepts, new areas of concern and future direction(s) has been explained. It is clear however, that ischemic stroke diagnosis and treatment is advancing and as much as new management options such as the use of artificial intelligence are being introduced, there is research potential for guiding patient-specific clinical decisions.

10. Expert opinion

The management of an ischemic stroke, from investigations to secondary prevention, has been evolving and adapting to the constant influx of new evidence. With the introduction of new medical or surgical interventions, initial research efforts will mainly focus on validating its effectiveness and complications before progressing to cater for patient specific factors. The efficacy of thrombolysis has been validated before the advent of Mechanical Thrombectomy (MT), allowing for current research questions in thrombolysis to revolve around patient specific differences such as ethnicity and anticoagulation status [12 16 17 22]. Conversely, the efficacy in MT faced an initial backlash due to the lack of patients with adequate imaging

evidence [35-37] before trials with more stringent patient selection criteria were done to validate its use in 2015 [39 40]. Even then, the patient population who met this criterion was limited. Given the relative longevity of thrombolysis, anticoagulation and antiplatelets, future research goals will likely pertain to optimizing their use in patients with confounding factors while newer interventional and investigative modalities such as MT and AI will require further validation studies to confirm its efficacy. We believe that there is potential for a validated and optimized AI software to identify patients who are most likely to benefit from novel interventions, such as MT. Future research to compare the short and long term outcomes of MT between patient populations selected by healthcare professionals and the optimized AI software is needed. In terms of novel agents, ongoing trials into new neuro-protective agents are also currently underway, which we believe will synergize with current measures to achieve early recanalization [160 161].

Based on the current evidence, the additive benefits of antiplatelet therapy plateaus at two antiplatelet drugs with additional agents conferring increased bleeding risk. However, Ticagrelor was introduced as the new antiplatelet therapy in 2011 [162]. Ticagrelor-aspirin has been compared to Clopidogrel-aspirin dual therapy in a recent trial [163] to show similar efficacy but significantly increased risk of non-severe bleeding in patients with acute minor or transient ischemic stroke. Even though there are currently ongoing trials evaluating the effectiveness of Ticagrelor dual antiplatelet therapy, the trials thus far were based predominantly on a Caucasian population. As such, the applications of Ticagrelor in the non-Caucasian population should also be further explored. Given that benefits of dual antiplatelet therapies are found to

be most pronounced within 7 days [164], concurrent studies into the optimal duration for dual antiplatelet therapy are also needed.

Similar to anticoagulation timing, the optimal time to initiate anticoagulation therapy post-stroke has not been explored in great detail and is currently the subject of multiple ongoing trials (**Supplementary Table 3**). The issue is to strike a balance between adequate secondary prevention of a recurrent ischemic stroke while also limiting the bleeding risks from prematurely starting anticoagulation. Another area that has received a large amount of attention is the use of anticoagulation in patients with renal dysfunction. This is understandable because as research aims at tailoring existing therapies to specific patient factors, and in this case, CKD has a high global prevalence of approximately 12% with majority at stage 3 [165]. Multiple trials have confirmed DOACs to be safe in CKD stages 1 to 3 but the choice of DOACs versus warfarin still remains as a point of contention in patients with advanced end stage or stage 4 CKD [166]. Given the risk of AF and secondary stroke is greater as renal function worsens, it is becoming increasingly important for research into this specific area to be prioritized [167].

It is worth noting that the management of ischemic strokes is not limited to the measures discussed in this narrative review. Other areas such as lipid-lowering medications and lifestyle factor optimization also play a pivotal role in the management and secondary prevention of ischemic stroke [168] [169], ranging from statin selection to the potential application of the new proprotein convertase substilisin/kexin type 9 (PCSK9) inhibitors [170] [171]. Under more specific circumstances, evidence is also vastly available for managing patients with ischemic stroke secondary to carotid stenosis, dissections and

patent foramen ovale [172-174]. This is to illustrate the breath of literature available that dwells into the management of ischemic strokes, but also to highlight that it is beyond the remit of this narrative review and expertise to cover all possible established and speculative management strategies in sufficient detail. Further narrative and systematic reviews into various aspects of ischemic stroke management are periodically warranted to provide comprehensive yet succinct updates.

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Thrombolysis	Key Findings
Clinical Benefits	Thrombolysis leads to better stroke outcomes (no significant disability at 3–6 months, modified Rankin Score of 0 or 1) [14,15] Immediate efficacy determines long-term benefits [9]
Timing of administration	Earlier administration associated with bigger proportional benefit [1] Best outcomes if treated within 3 hours [14] Good outcomes up to 4.5 hours after stroke onset [14,11]
Correlates to worse outcomes following thrombolysis	Atrial fibrillation [20] Heart failure [19] Renal impairment [17] Leukoaraiosis [17] Visible acute cerebral ischemic lesion on pretreatment brain imaging [17] Stroke severity [14]
Important complications	Intracranial haemorrhage [14,15,9,11,17,13] Intracranial haemorrhage less common in low-dose alteplase [12] Overall 6-month mortality rate similar between thrombolysed patients vs. controls [11,13]
Thrombectomy	**Key Findings**
Clinical Benefits	Thrombectomy alone or as thrombolysis adjunct leads to better rates of functional independence up to 3 months post-stroke.[40,41,42,43,44] Good outcomes irrespective of patient characteristics or geographical location.[45]
Factors supporting use of thrombectomy	Aged 80 years or older.[45] >300 minutes after symptom onset.[45] If not eligible for intravenous thrombolysis.[45,46]
Timing of administration	Earlier reperfusion leads to better clinical outcomes.[51] Treatment within 6-8 hours appears effective and safe.[40,43]
Important complications	No significant difference in mortality nor intracerebral haemorrhage rates.[40,41,42,43,44] Potentially leads to reduced mortality rates.[41]

Table 1. Key findings for thrombolysis and thrombectomy

	Brainomix	iSchemaView	
Diagnosis	- e-ASPECTS (2015) – well validated for contrast CT interpretation and ASPECTS - e-CTA (2018) introduced to detect LVOs in CTA scans – insufficient validation	-ASPECTS and CTA vessel density software (2018) – insufficient validation -RAPID (2013) – well validated for analysis of CT and MRI perfusion studies	
Management	-Aids decision making -Predicts post-thrombectomy infarct volume and function independence	-Further aids decision making about endovascular stroke treatment	
Future directions	-Further validation of e-CTA -Possible implementation of an automated communication interface	-Further Validation studies for ASPECTS and CTA vessel density software -Possible implementation of an automated communication interface	

Table 2. Summary table of commercial Artificial Intelligence (AI) software for stroke imagi communication. **ASPECTS** = Alberta stroke program early CT scoring. **CT** = Computed Tomography. **C LVO** = Large Vessel Occlusion. **MRI** = Magnetic Resonance Imaging.

Blood Pressure and Outcomes in Acute Ischaemic Stroke

	First Author (Year) (Ref. #)	Study Type	Sample Size	Findings
Acute Ischaemic Stroke	Ishitsuka et al. (2014) (135)	Prospective	n = 4345 ischaemic stroke n = 1874 with inpatient outcome	Systolic BP (% good neurol recovery): - 133-143: 61% - 144-153: 57% - 154-165: 51% - > 166: 47%
	Vemmos et al. (2003) (136)	Prospective	n = 240 hyperacute stroke	24-Hour Systolic BP signifi associated with brain oedem Odds Ratio 1.25 between ea mmHg increase and brain o
	Yong et al. (2008) (137)	Retrospective	n = 793 acute ischaemic stroke	Placebo-treated patients: favourable outcome at day 9 inversely associated with hi maximum 24-hour BP (Odd Ratio 0.76).
	Leonardi-Bee et al. (2002) (138)	Retrospective	n = 17398 acute ischaemic stroke	Early death increased by 17 per 10 mmHg below 150 m SBP, and by 3.8% per 10 m above 150 mmHg SBP. Recurrent ischaemic stroke 14-days increased by 4.2% mmHg increase in SBP.
	Castillo et al. (2004) (139)	Prospective	n = 304 acute ischaemic stroke	SBP drop > 20 mmHg withi first day most important prognostic factor of poor ou
	Gonzalez et al. (2006) (141)	Prospective	n = 357 acute ischaemic stroke	Emergency Department: BP 155/70 mmHg more likely t at 90 days.
Intra-Operative	Lowhagen et al. (2015) (143)	Retrospective	n = 180 acute ischaemic stroke	In patients undergoing endovascular therapy receiv general anaesthesia, fall in m arterial BP of > 40% predict poor neurological outcome.
	John et al. (2016) (144)	Retrospective	n = 147 anterior circulation acute ischaemic stroke receiving IAT	Lower maximum intraproce SBP (proposed target < 160 mmHg) was an independent predictor of good outcome (0.93)
	Treurniet et al. (2018)	Subgroup	n = 60 thrombectomy	Decrease of 10 mmHg mean

	(147)		patients who underwent GA (MR-CLEAN)	arterial pressure during gene anaesthesia (versus baseline to 1.67 lower odds of a good neurological outcome.
	Whalin et al. (2017) (148)	Retrospective	n = 256 anterior circulation acute ischaemic stroke	During monitored anaesthet (conscious sedation), >10% arterial pressure below base associated with poor outcon 4.38).
Post-Operative	Delgado et al. (2008) (153)	Prospective	n = 80 with stroke with known middle cerebral artery occlusion treated with IV tPa	Blood pressure variability is associated with greater diffu weighted imaging lesion gro and worse patient prognosis
	Maier et al. (2018) (154)	Prospective	n = 168 acute ischaemic stroke with successful endovascular therapy	In the first 24-hours post- E higher mean (cut-off 141 m and maximum (cut-off 159 mmHg) SBP were associate poorer recovery.
	Ahmed et al. (2009) (156)	Retrospective	n = 11080 acute ischaemic strokes with BP recorded post-thrombolysis	Maintained systolic BP of 1 mmHg from 2 to 24 hours p thrombolysis associated wit favourable outcomes (p < 0.
	Goyal et al. (2017) (159)	Prospective	n = 217 acute ischaemic strokes treated with thrombectomy	Increase of 10 mmHg in maximum SBP in the 24-ho post-mechanical thrombecto associated with poorer funct independence (OR 0.70) and higher mortality (OR 1.49) a months. BP <160/90 mmHg hours post-MT is associated lower 3-month mortality (O 0.08).

Table **3** – Table highlighting the outcomes associated with blood pressure and its variations in acute ischaemic during endovascular therapy, post-thrombolysis and thrombectomy. An important recurring theme across al subsections describes the U-shaped trend (too low or high of a systolic blood pressure associated with poor neuro outcomes). **BP =** blood pressure, **SBP** = systolic blood pressure, **OR** = Odds Ratio, **IAT** = intra-arterial thrombolysi general anaesthesia. **EVT =** endovascular therapy. **MT =** mechanical thrombectomy. **tPa** = tissue plasminogen activa

	Trial (ref #)	First Author	Study Type	Sample Size	Main findings
Thrombolysis	NINDS (Part 1) (14)	NINDS (1995)	RCT double-blinded	• n = 144 tPA, • n =147 placebo	• Investigated the efficacy of tPA for ischaemic str • No significant differences in clinical activity (def tPA and placebo at 24 hour.
	NINDS (Part 2) (9)	NINDS (1995)	RCT double-blinded	• n = 168 tPA • n = 165 placebo	• Investigated the long-term efficacy of tPA for isc • At 3 months: significantly more favourable outco (Wald Test: OR 1.7, 95% CI 1.0 -1.7, p = 0.026). • In terms of safety, symptomatic ICH within 36 h mortality at 3 months.
	SITS-MOST (10)	Wahlgren et al. (2007)	Prospective, Observational	• n = 6483 (50% from centres with little experience)	• Confirmed the safety and efficacy of IV Alteplas pooled RCT results. • At 24 hours, symptomatic ICH noted in 1.7% (n = pooled RCT 8.6% (n = 40/465, 95% CI 6.3-11.6) • Mortality was 11.3% (n = 701/6218, 95% CI 10.5
	ECASS I (14)	Hacke et al. (1995)	RCT double-blinded	• n = 620	• Investigated the efficacy and safety of higher-dos • At 90 days, excellent mRS (p = 0.035) and comb placebo. • No difference in mortality or ICH at 30 days note were noted in patients receiving tPA.
	ECASS II (14)	Hacke et al. (1998)	RCT double-blinded	• n = 391 placebo • n = 409 tPA	• Investigated the efficacy of tPA when administer • Initial analysis revealed the tPA group had favou significant. • Post-hoc analysis revealed the tPA group (n = 22 placebo (n = 180/391, 46.0%, p = 0.024). Differe • Symptomatic ICH seen in 8.8% of tPA and 3.4%
	ECASS III (11)	Hacke et al. (2008)	RCT double-blinded	• n = 418 tPa • n = 403 placebo	• Investigated the efficacy and safety of tPA when • At 90 days, significantly more tPA patients attain analysing 90-day NIHSS, GOS, mRS, Barthel's t • Symptomatic ICH was more frequent with tPA (2
	IST-3 (13)	IST-3 (2012)	RCT open-label	• n = 1515 tPA • n = 1520 control	• Investigated the efficacy of tPA when administer • No significant differences in favourable Oxford H • 7-day mortality in the tPA group was higher (11% mortality in the tPA group from 7 days to 6 mont group (common OR 1.27, 95% CI 1.10-1.47, p =
	ATLANTIS (A) (14)	Clark et al. (1999)	RCT double-blinded	• n = 272 tPA • n = 275 placebo	• Investigated the efficacy of tPA when administer • At 30 and 90 days, no differences between tPA a • The tPA group experienced an increased rate of s versus placebo, but there was no significant diffe
	ATLANTIS (B) (14)	Albers et al. (2002)	RCT double-blinded	• n = 38 tPA • n = 23 placebo	• Investigated the efficacy of tPA when administer • At 90 days, a favourable NIHSS outcome was se • Symptomatic and fatal ICH were more frequent i in mortality at 90 days.
	EPITHET (14,15)	Davis et al. (2008)	RCT double-blinded	• n = 52 tPA • n= 49 placebo	• Investigated the impact of tPA (when administere with penumbral mismatch (n = 85/101). • There were no significant differences in infarct g versus placebo. However, reperfusion was signif (p < 0.001) and better functional outcomes (p = 0
	EXTEND (15)	Ma et al. (2019)	RCT open-label	• n = 113 tPA • n = 112 placebo	• Terminated early due to positive results from pre 9 hours of ischaemic stroke to patients with radio • At 90 days, excellent mRS outcomes (0-1) were s 29.5%, RR 1.44, 95% CI 1.01-2.06, p = 0.04). • Symptomatic ICH was increased with tPA (n = 7 there was no difference in 90-day mortality.
	ECASS4-EXTEND (15)	Amiri et al. (2016)	RCT double-blinded	• In progress	• Ongoing trial investigating the efficacy of tPA w penumbral mismatch on MRI.
	TNK-S2B (27)	Haley et al. (2010)	RCT double-blinded	• n = 112	• Trial was prematurely terminated for slow enroll • Demonstrated potential efficiency of a novel desi • No significant difference between in 3-month eff • Symptomatic intracranial haemorrhage highest in
	Australian TNK (28)	Parson et al. (2012)	RCT open-label	• n = 25 tPA • n = 50 TNK	• TNK associated with significantly better reperfus • 0.1mg/kg TNK had greater clinical improvement • 0.25mg/kg TNK associated with improvement or

	ATTEST (29)	Huang et al. (2015)	RCT open-label	• n = 49 tPA • n = 47 TNK	• Neither radiological or clinical outcomes differed • Safety outcomes also did not differ between the t
	NOR-TEST (30)	Logallo et al. (2017)	RCT open-label	• n = 551 tPA • n = 549 TNK	• Primary outcome (excellent functional outcome a • Safety outcome (serious adverse events), TNK vs • TNK was not superior to tPA and showed a simil
	EXTEND-IA TNK (31)	Campbell et al. (2018)	RCT open-label	• n = 101 tPA • n = 101 TNK	• The primary outcome was reperfusion of greater time of the initial angiographic assessment. • The primary outcome occurred in 22% of the pat difference, 12 percentage points; 95% confidence noninferiority; P=0.03 for superiority) • Tenecteplase resulted in a better 90-day functiona ratio, 1.7; 95% CI, 1.0 to 2.8; P=0.04). • No significant difference in symptomatic intracer
	EXTEND-IA TNK Part II (34)	Campbell et al. (2020)	RCT open-label	• In progress	• Ongoing trial comparing the efficacy of 0.4mg/k within 4.5 hours.

Supplementary table 1: Key thrombolysis trials used in the manuscript and its key findings

	Trial (ref #)	First Author	Study Type	Sample Size	Main findings
Endovascular	IMS-3 (35)	Broderick et al. (2013)	RCT open-label, blinded end-point	• n = 434 tPA + endovascular • n = 222 tPA	• Investigated the efficacy of tPA (administered within 3 interventions (mechanical thrombectomy or IA-tPA). • At 90 days, there were no significant differences in func in rate of symptomatic ICH within 30 hours of interven
	SYNTHESIS (36)	Ciccone et al. (2013)	RCT open-label, blinded end-point	• n = 181 endovascular • n = 181 tPA	• Investigated the efficacy of tPA versus endovascular int 4.5 hours of ischaemic stroke. • Median onset-to-treatment time was significantly lower (3.75 hours). At 90 days, there were no differences in fa versus 30.4% endovascular (n = 55/181, OR 0.71, 95% • There was no significant difference in rate of fatal ICH.
	MR-RESCUE (37)	Kidwell et al. (2013)	RCT open-label, blinded end-point	• n = 64 endovascular • n = 54 usual care	• Investigated the efficacy of endovascular interventions delivered within 8 hours of large vessel, anterior circula according to penumbral pattern. • At 90 days, there were no differences mortality, sympto according to favourable and non-penumbral patterns.
	MR-CLEAN (39)	Berkhemer et al. (2015)	RCT open-label, blinded end-point	• n = 233 endovascular • n = 267 usual care	• Investigated the efficacy of endovascular interventions when delivered within 6 hours of ischaemic stroke to pa • At 90-days, 32.6% of the endovascular group (n = 76/23 usual care alone (n = 51/267, OR 2.16, 95% CI 1.39-3.3 intervention (OR 1.67, 95% CI 1.21-2.30). • There were no differences in rate of symptomatic ICH c
	EXTEND-IA (40)	Campbell et al. (2015)	RCT open-label, blinded end-point	• n = 35 thrombectomy + tPA • n = 35 tPA.	• Terminated early due to results of interim analysis. Inve versus tPA alone when administered within 4.5 hours o favourable penumbral pattern. • At 24 hours, 100% of ischaemic territory was reperfuse The 3-day NIHSS improvement (80% vs 37%, p = 0.00 0.01) were increased with thrombectomy. • There were no differences in rate of mortality or sympto
	ESCAPE (41)	Goyal et al. (2015)	RCT open-label, blinded end-point	• n = 165 endovascular • n = 150 control	• Terminated early due to results of interim analysis. Inve usual care alone when delivered within 12 hours of isch intracranial occlusion. • At 90 days, endovascular intervention was significantly and reduced mortality (10.5% vs 19.0%, p = 0.04) versu 2.6, 95% CI 1.7-3.8, p < 0.001. • There was no difference in rate of symptomatic ICH.
	SWIFT-PRIME (42)	Saver et al. (2015)	RCT open-label	• n = 98 tPA • n = 98 tPA + thrombectomy	• Terminated early due to results of interim analysis. Inve with tPA versus tPA alone when delivered within 6 hou circulation occlusions and small infarct core. • At 90 days, shift analysis revealed tPA with thrombecto functional independence (mRS 0-2) was significantly hi • There were no significant differences in 90-day mortalit
	REVASCAT (43)	Jovin et al. (2015)	RCT open-label, blinded end-point	• n = 103 thrombectomy + usual care • n = 103 usual care	• Terminated early due to positive results from earlier tria retriever) versus usual care alone, when delivered withi occlusion and absence of large infarct on neuroimaging • At 90 days, higher rates of favourable mRS (0-2) seen w Shift analysis yielded significant association with throm 1.7, 95% CI 1.05-2.8). • No difference in mortality or symptomatic ICH
	CRISP (51)	Lansberg et al. (2017)	Prospective Cohort	• n = 190	• Investigated the utility of CT perfusion imaging for sele (small ischaemic core and large penumbra) up to 18 hou • Reperfusion was significantly more associated with fav versus those without mismatch (44%, p = 0.002). This t 6 hours or > 6 hours within ischaemic stroke.
	DEFUSE 2 (78)	Lansberg et al. (2012)	Prospective Cohort	• n = 99	• Investigated the utility of MRI for selecting endovascul ischaemic stroke. • Reperfusion was significantly more associated with fav = 46/78, 59%, OR 8.8, 95% CI 2.7-29.0), versus those v 0.003).
	DEFUSE 3 (78)	Albers et al. (2018)	RCT open-label, blinded end-point	• n = 92 endovascular • n = 90 usual care	• Terminated early due to results of interim analysis. Inve care alone, when delivered within 6 - 16 hours of ischae favourable penumbra. • At 90-days, shift analysis revealed thrombectomy was s and the thrombectomy group (45%) was significantly m p < 0.001). • No significant differences in 90-day mortality or sympto

	DAWN (80)	Noguiera et al. (2018)	RCT open-label, blinded end-point	• n = 107 thrombectomy • n = 99 control	• Terminated early due to results of interim analysis. Inve care alone, when delivered within 6 - 24 hours of ischae clinical deficit-infarct volume mismatch. • At 90 days, mean utility-weighted mRS favoured throm outcome). Rate of favourable 90-day mRS (0-2) was sig 21-44; PPoS >0.999). • No difference in symptomatic ICH or 90-day mortality.
	SWIFT-DIRECT (48)	Fischer et al.	RCT open-label, blinded end-point	• In progress	• Specific to patients with AIS secondary to large vessel c • Comparison between direct mechanical thrombectomy a • Primary outcome: 90-day functional outcome; Secondar in AIS patients
	TESLA (49)	Yoo et al.	RCT open-label, blinded end-point	• In progress	• Specific to patients with moderate-large infarcts • Comparison of best medical management alone against • Outcome measures yet to be clearly stated
	ENDOLOW (50)	Nogueira et al.	RCT open-label, blinded end-point	• In progress	• Specific to patients presenting within 8 hours of ischem scores (0-5) • Group comparisons: immediate mechanical thrombecto • 90-day clinical outcomes (mRS distribution)

Supplementary table 2: Key endovascular trials used in the manuscript and its key findings

	Trial (ref #)	First Author	Study Type	Sample Size	Main findings
Anti-Hypertensive	ENCHANTED (12)	Anderson et al. (2019)	Open-label RCT, blinded end-point	• n = 1081 intensive BP • n = 1115 routine BP	• In tPA-eligible patients, investigated the outcomes of BP (sBP < 180 mmHg) control over 72-hours, startin • At 90-days, no significant differences in mRS or occu
Anti-Platelets	CAPRIE (91)	CAPRIE (1996)	RCT, blinded	• n = 19,185	• Investigated the efficacy of Clopidogrel 75 mg OD ve MI, or symptomatic PVD. Patients were followed-up • Clopidogrel therapy had a 5.32% annual risk of ischa versus aspirin (5.83% annual risk) with a relative risk
Anti-Coagulation	ENGAGE AF-TIMI 48 (112)	Giugliano et al. (2013)	RCT, double-blinded, double-dummy	• n = 7036 Warfarin • n = 7035 high-dose Edoxaban • n = 7034 low-dose Edoxaban	• Investigated the efficacy and safety of Edoxaban BD patients with moderate-high risk AF. • Annual rate of stroke/systemic embolism was signific Edoxaban (HR 0.79, 97.5% CI 0.63 - 0.99, p < 0.001 1.31, p = 0.005). • Annual rate of major bleed was higher for Warfarin a 0.91, p <0.001). There was no difference in annual ris
	RE-LY (112)	Connolly et al. (2009)	RCT, Dabigatran participant blinded, Warfarin open-label, blinded end-point	• n = 6015 Dabigatran 110 mg BD • n = 6076 Dabigatran 150 mg BD • n = 6022 Warfarin	• Investigated the efficacy and safety of Dabigatran BD patients with AF. • Annual rate of stroke /systemic embolism was signifi 110 mg (RR 0.91, 95% CI 0.74 - 1.11, p < 0.001) and 0.001). • Annual rate of bleed was higher only for 3.36% Warf haemorrhagic stroke at 0.38% for Warfarin, 0.12% D 0.001).
	ROCKET AF (112)	Patel et al. (2011)	RCT double-blinded	• n = 7131 Rivaroxaban • n = 7133 Warfarin	• Investigated the efficacy of Rivaroxaban 20 mg OD v patients with non-valvular AF. • Annual rate stroke/systemic embolism was significan 0.79, 95% CI 0.66-0.96, p <0.001), this was preserve • There was no difference in clinically-relevant bleedin (0.5% versus 0.7% Warfarin, p = 0.02) and fatal bleed
	ARISTOTLE (112)	Granger et al. (2011)	RCT double-blinded	• n = 9120 Apixaban • n = 9081 Warfarin	• Investigated the efficacy of Apixaban 5 mg BD versu with AF + min. 1 risk factor for stroke. • Apixaban when compared to Warfarin significantly re 1.60%, HR 0.79, 95% CI 0.66-0.95, p < 0.001 non-in 3.09%, HR 0.69 95% CI 0.6-0.8, p <0.001) and annua 95% CI 0.35-0.75, p <0.001).
	ARISTOPHANES (114)	Lip et al. (2018)	Retrospective Observational	• n = 434, 046 (6 matched cohorts)	• Investigated the efficacy and safety of NOAC and Wa • Lower rates of stroke/systemic embolism were observ 0.82, 95% CI 0.71-0.95) and Rivaroxaban (HR 0.79, 9 • Apixaban (HR 0.60, 95% CI 0.56 - 0.63) and Dabigat rates of major bleed versus Warfarin. Rivaroxaban (H Warfarin.
	NAXOS (115)	Van Ganse et al. (2020)	Observational	• n = 321, 501 patients between 2014-2016.	• Investigated the efficacy and safety of NOAC and Wa 35% VKA, 27.2% Apixaban, 31.1% Rivaroxaban, 6.9 • Apixaban displayed a lower propensity-score matche 0.46) and Rivaroxaban (HR 0.67, 95% CI 0.63-.0.72) • Apixaban had a reduced risk of stroke/systemic embo Rivaroxaban (HR 1.05, 95% CI 0.97-1.15) or Dabigat
	RAF (122)	Paciaroni et al. (2015)	Prospective cohort	• n = 1029	• Investigated the efficacy and safety associated with a ischaemic stroke. • Commencement of anticoagulation 4-14 days after str embolism/major ICH (HR 0.53, 95% CI 0.30-0.93, p days. • Only 7% of patients receiving oral anticoagulation ex reduction (p = 0.003) versus LMWH alone (16.8%) o
	START (124)	King et al. (2019)	RCT open-label, blinded end-point	• In progress	• Ongoing trial investigating the optimal time for initia risk of AF-related stroke versus haemorrhagic transfo • Mild-moderate strokes are randomised to Day 3/6/10/ randomised to Day 6/10/14/21.
	TIMING (125)	Asberg et al. (2017)	RCT open-label	• In progress	• Ongoing trial investigating the optimal time for initia risk of AF-related stroke versus haemorrhagic transfo • Patients are randomised to early (< 4 days) or delayed safety of both arms.
	OPTIMAS (126)	Chief investigator: Professor David Werring	RCT, partial-blinded	• In progress	• Ongoing trial investigating the optimal time for initia risk of AF-related stroke versus haemorrhagic transfo • Patients are randomised to early (< 4 days) or standar

	ELAN (127)	Chief investigator: Professor Urs Fischer	RCT, assessor-blinded	• In progress	• Ongoing trial investigating the optimal time for initia risk of AF-related stroke versus haemorrhagic transfo • Patients are randomised to early (<48 hours for mild/ minor, day 6 for moderate, day 12 for major infarcts)

Supplementary table 3: Key anti-hypertensive, anti-platelet and anticoagulation trials used in the manuscript and its key findings. BP = blood pressure, tPA = tissue plasminogen activator. mRS = modified rankin scale, MI = myocardial infarction, PVD = peripheral vascular disease, AF = atrial fibrillation, VKA = vitamin k antagonists, RR = risk ratio, HR = Hazard Ratio, ITT = intention to treat, NOAC = new oral anti-coagulant, LMWH = low molecular weight heparin

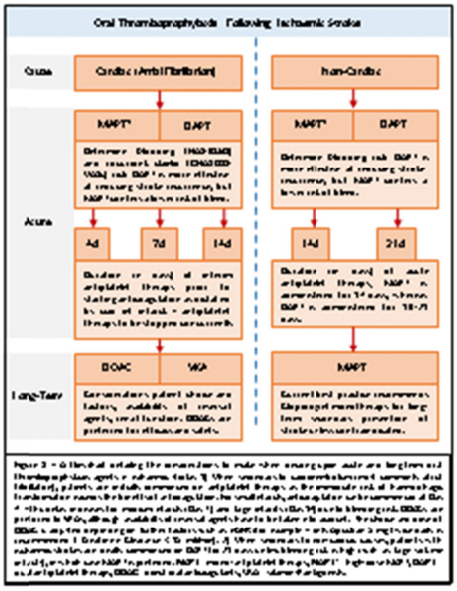

Figure 1