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Treatments in Ischemic Stroke: Current and Future

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Acute ischemic stroke therapy · Ischemic stroke secondary prevention · Neuroprotection · Telestroke · COVID-19

Abstract
Background and Aim: Despite progress made over the last 30 years, stroke is still a leading cause of disability and mortality; likewise, its burden is expected to increase over the next decades, due to population growth and aging. The development of drugs with better safety-efficacy profiles as well as strategies able to improve ischemic stroke management from the pre-hospital setting is needed. ***Summary:*** The pathophysiology of ischemic stroke involves multiple pathways resulting in cerebral artery obstruction and brain tissue ischemia. To date, the only approved drug for acute ischemic stroke is intravenous thrombolytic alteplase. Intravenous thrombolysis (IVT) can be administered alone or in combination with endovascular treatment (EVT) with mechanical thrombectomy, in case of large vessel occlusion and generally within 6 h from symptoms onset. The risk of potential bleeding complications, especially symptomatic intracerebral hemorrhage, is one of the reasons for the reluctance to administer IVT. Tenecteplase is a promising alternative fibrinolytic agent, having a better safety profile than alteplase. Moreover, recent evidences have allowed an extension of the IVT ± EVT time window for patients with unknown onset time and for those with a known onset time thanks to the new "tissue-window" approach guided by advanced neuroimaging techniques, which also helps in collateral circulation estimation. Regarding primary-secondary prevention, researchers are focused on improving the efficacy of antithrombotic drugs with a "hemostasis-sparing" approach. Neuroprotective agents are also under development, particularly stem cells. The COVID-19 pandemic has critically stressed global healthcare systems, with collateral damage resulting in access delivery of only emergency care, such as ischemic stroke. Regarding telemedicine, it has had a minor role in acute stroke management, and with the onset of COVID-19, this role will most likely be adopted to increase access and delivery in stroke assessment, but also in the follow-up.

Introduction

Stroke is a leading cause of disability in adults worldwide and the second for cardiovascular diseases-related mortality [1–3]. Due to population growth and aging, a significant increase in the burden of stroke is expected for at least the next few decades [2, 4]. Despite progress in the

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understanding of the pathophysiological mechanisms underlying stroke over the past 3 decades, concerning early diagnosis and the development of protocols that have reduced the door-to-needle time for acute ischemic stroke (AIS) treatment, several clinical gaps remain unsolved. Different imaging techniques are routinely used in the diagnosis and management of AIS, including computed tomography (CT) and magnetic resonance imaging (MRI). The evaluation of MRI mismatch between diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR), as well as CT perfusion (CTP) imaging can distinguish between core and penumbra [5]. These two advanced neuroimaging modalities have been used in an extended time window to select patients who are likely to benefit from both intravenous thrombolysis (IVT) and endovascular treatment (EVT) reperfusion strategies, also those presenting beyond the 4.5–6 h time window or with unknown/wake-up onset time.

Moreover, COVID-19 pandemic has stressed global healthcare systems, which has affected the carrying out of necessary follow-up and screening, therein opening the field for a greater implementation of telestroke. This narrative review highlights the current ischemic stroke care strategies in use and suggests feasible strategies that could remedy any unmet clinical needs.

Primary Prevention in Ischemic Stroke

Overall, ninety percent of all strokes worldwide could be prevented with stricter primary prevention of recognized modifiable risk factors: hypertension, smoking, obesity, diet, physical inactivity, diabetes, alcohol intake, psychosocial factors, cardiac disease, and apolipoprotein ratios [6–9], whereas age is an important nonmodifiable risk factor. As for animal model studies, most have used young animals free of human-shared comorbidities, resulting in poor data translatability. Additionally, stroke patients are often elderly with multiple comorbidities associated with worse stroke outcomes [10].

Among cardiovascular diseases, atrial fibrillation (AF) is the most common cardiac arrhythmia, estimated to affect 33 million subjects worldwide, and associated with a reported 5-fold increased risk in the number of ischemic strokes [11]. While vitamin-K antagonists (VKAs) had been the cornerstone of anticoagulation in AF patients, anticoagulant use has increased over the last few years with the introduction of the direct oral anticoagulants (DOACs), which are noninferior to VKAs in terms of efficacy, but are reported to have a better safety profile, due to a reduction in major bleeding rates: 50% decrease in the rates of symptomatic intracerebral hemorrhage (sICH) [12–15]. Despite the reported benefit-risk profile for DOACs, there is still a residual risk for developing either an ischemic stroke and/or a systemic embolism as well as major and clinically relevant nonmajor bleeding. The development of safer molecules is a primary objective of current clinical research. A selective inhibition of single factors active in the intrinsic pathway of the coagulation preserves the extrinsic and common pathways of thrombin generation intact for hemostasis, leading to an antithrombotic effect but a reduced bleeding risk. Data on coagulation factor deficiency, both in animal models and in humans, suggest that factor XI (FXI) deficiency is associated with a nonsignificant incidence of bleeding and a lower risk of ischemic events [16, 17]. In fact, FXI plays a major role in the clotting pathway, but carriers of FXI deficiency generally show relatively mild bleeding phenotypes, thus making this factor a potential selective target for new anticoagulant molecules, thanks to a potentially reduced bleeding risk, compared to most current standards of care. Thereby, clinical research is presently focusing on the better understanding of the antithrombotic benefits. Moreover, focus is on trying to reduce bleeding risk via the selective inhibition of coagulation factors in the intrinsic cascade.

Acute Ischemic Stroke Treatment

The only approved pharmacological systemic therapy for AIS is IVT with alteplase, an recombinant tissue plasminogen activator (rtPA) [18–21] that is usually recommended to be administered within 4.5 h of symptom onset. IVT can be administered alone or in combination with EVT with mechanical thrombectomy (MT), in case of large vessel occlusion (LVO). MT is recommended within 6 h from symptoms onset in patients with LVO in combination with IVT within 4.5 h of symptom onset and alone between 4.5 h and 6 h of symptom onset [22–26].

Different imaging techniques are routinely used in the diagnosis and management of AIS, including CT and MRI. As well as proving the diagnosis of AIS, these modalities allow to assess the brain tissue perfusion status. In particular, they distinguish the irreversibly damaged ischemic core from the potentially salvageable penumbra tissue. MRI in patients with AIS with a known time of symptom onset has identified the presence of a visible ischemic lesion on DWI, combined with the absence of a clearly visible hyperintense signal in the same region on

FLAIR, as predictive of symptom onset within 4.5 h before imaging [27]. Additionally, also CTP imaging can distinguish between core and penumbra [5]. These two modalities have been used in an extended time window to select patients who are likely to benefit from both IVT and EVT reperfusion strategies, when the time of AIS onset is unknown or beyond the 4.5–6 h time window. In addition, CT angiography (CTA) and MR angiography allow the identification of LVO and can clarify the AIS etiology [28].

The supplementary branches, which vicar cerebral blood flow when main vessels are occluded, represent the cerebral collateral circulation. Each AIS patient has a different collateral status which affects revascularization success and functional prognosis [29]. Several imaging techniques can evaluate the collateral status during AIS, but there is no uniform recommendation on the use of a modality over another. CTA or MRI angiography can evaluate the cerebral collateral circulation in the circle of Willis with moderate-to-good diagnostic efficiency, but has limited power in evaluating the leptomeningeal collaterals [29]. CTP may provide information of collaterals, and it can be performed rapidity and is largely accessible in emergency room; moreover, the information acquired by this exam can be combined with nonenhanced CT and CT angiographic data, especially in patients with anterior circulation stroke [30, 31]. Different MRI perfusion parameters have been used to measure collateral status, but optimal parameter to predict collateral grade has seldom been reported. Nonetheless, these techniques allow to evaluate collateral status by the direct comparison with MRI diffusion and perfusion images, without the need for additional acquisition of conventional angiography or MRI dedicated for collateral assessment [32]. Arterial spin labeling MRI is a promising noncontrast perfusion imaging method to assess the cerebral collateral status: it can provide anatomic and dynamic blood flow information in the circle of Willis, similar to that obtained with conventional angiography, without the use of contrast medium [33].

Recent evidences have allowed an extension of the IVT time window for patients with unknown onset time and for those with a known onset time up to 9 h, thanks to the new "tissue-window" approach guided by advanced neuroimaging techniques [34, 35]. These include "wake-up strokes," which is a non-negligible sub-group of AIS where patients had no abnormality before sleep while waking up with neurological deficits, accounting for up to 25% of all AISs [36]. 2021 ESO guidelines on IVT recommend IVT with alteplase for patients with AIS of 4.5–9 h duration (known onset time) and with CT or MRI core/perfusion mismatch, and for whom MT is either not indicated or not planned [20, 37]. Moreover, they recommend IVT for patients with wake-up stroke, who were last seen well more than 4.5 h earlier, who have MRI DWI-FLAIR mismatch, and for whom MT is either not indicated or not planned. Finally, for patients with wake-up stroke and a CT or MRI core/perfusion mismatch within 9 h from the midpoint of sleep, and for whom MT is either not indicated or not planned, they recommend IVT with alteplase [20, 37].

sICH is an uncommon (2–7% rate) but severe IVT complication [38]. Due to this bleeding risk, the narrow therapeutic window and the limited/delayed access to stroke centers, only 10–20% of patients receive fibrinolytic treatment [39, 40], with an undefinable undertreatment of probably eligible patients. The approval of safer and more effective thrombolytic agents would greatly increase the treatment access and improve upon outcome [41–43].

Tenecteplase is a next-generation genetically modified rtPA and is currently the most promising alternative agent: in fact, it is the first-line IV thrombolytic drug for myocardial infarction [44] having similar efficacy, but a better safety profile than alteplase, due to its lower risk of hemorrhagic transformation, greater fibrin specificity, faster onset of action, and longer half-life [45, 46]. Additionally, it is administrated via a single IV bolus, as opposed to the 1-h infusion for alteplase.

Current 2021 ESO guidelines [20] for patients with AIS of <4.5 h duration and not eligible for MT suggest IVT with alteplase over tenecteplase. EVT with MT within 6 h from symptom onset is known to be safe and effective in reducing neurological disability when administered in AIS patients affected by a large cerebral artery occlusion [22–26]. However, only 10–20% of stroke patients are eligible for EVT; besides, access to thrombectomy centers in less than 6 h after symptom onset is not feasible in many parts of the world [47–49]. Moreover, even in case of a successful recanalization of the occluded vessel, the clinical outcome may still be poor, a phenomenon called "futile recanalization," and this is still notable defy of EVT [50]. Futile recanalization is probably relatively common, seen that the rates of associated good clinical outcomes are reported to be reached in less than a half of patients, although the favorable recanalization is obtained in more than 75% of cases [50, 51]. Neuroinflammatory responses and microcirculation damage probably are the key points in the pathophysiology of AIS, and they have been described as part of the process deter-

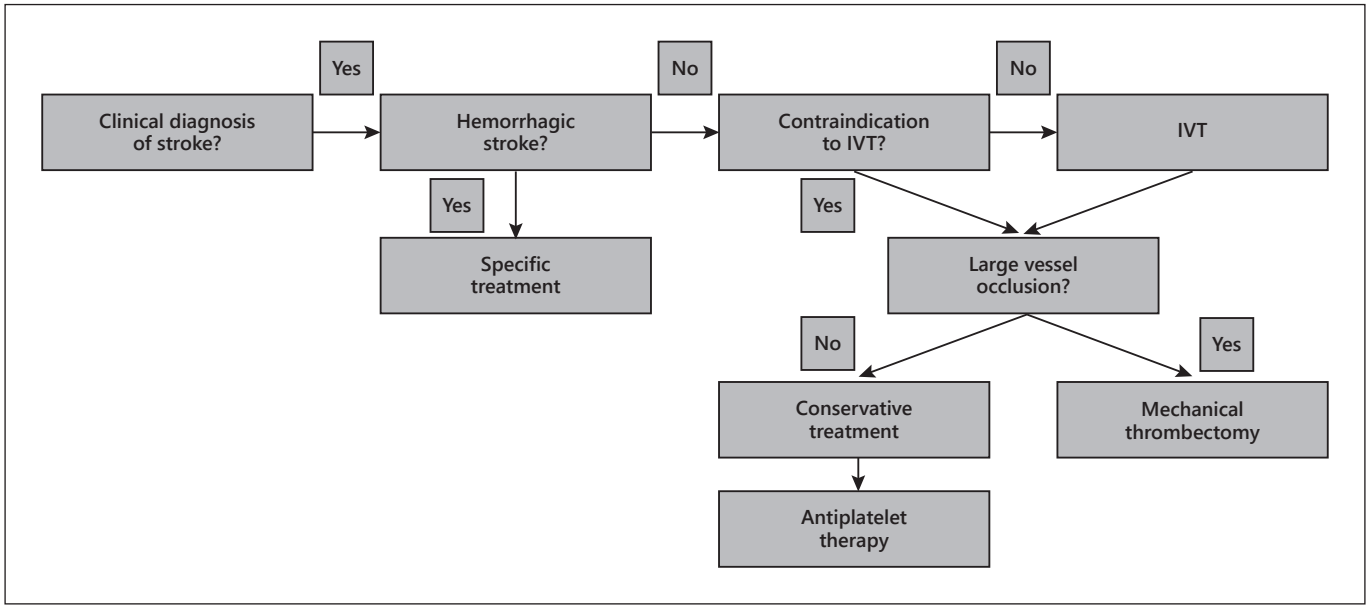

Fig. 1. Acute ischemic stroke treatment. IVT, intravenous thrombolysis.

mining the secondary progression of ischemic lesions, remodeling, and tissue repair [52]. However, there is still no definite evidence on the association between inflammatory biomarker levels and functional outcome in patients with AIS who achieved successful recanalization [51, 53], nor effective therapeutic options are available.

Recently, the time window for IVT ± EVT has been extended for selected patients with AIS with unknown onset time or wake-up stroke, when performed with a neuroimaging-guided approach [20, 21, 34, 35, 47, 54–56]. Recent 2019 ESO-ESMINT guidelines on MT for AIS patients, in adults with anterior circulation LVO-related AIS presenting between 6 and 24 h from time last known well and fulfilling the selection criteria of DEFUSE-3 or DAWN, recommend MT plus best medical management (including IVT whenever indicated) over best medical management alone to improve functional outcome, without upper age nor NIHSS score limits [54–56].

For patients directly admitted to a thrombectomy-capable center ("Mothership" paradigm) for an AIS ≤4.5 h of symptom onset with anterior circulation LVO and eligible for both IVT and MT, 2022-ESO guidelines [57] recommend IVT plus MT over MT alone. Moreover, for patients directly admitted to a thrombectomy-capable center ≤4.5 h of symptom recognition after wake-up AIS caused by anterior circulation LVO, they recommend IVT plus MT over MT alone in patients with eligibility imaging criteria (DWI-FLAIR mismatch or CTP core/penumbra mismatch). On the other hand, for patients admitted to a nonthrombectomy-capable center ("drip-and-ship" paradigm) for an AIS (≤4.5 h of symptom onset) with anterior circulation LVO and who are eligible for both treatments, 2022-ESO guidelines recommend IVT followed by rapid transfer to a center with thrombectomy facilities over omitting IVT and transfer to a center with thrombectomy facilities; however, IVT should not delay the transfer to a center with thrombectomy facilities (Fig. 1, 2).

This advance in stroke treatment allows to treating a greater number of eligible patients. Likewise, the approval of a safer, faster, and more manageable thrombolytic agent might result in increased rates of patients being treated with EVT, with reduced door-to-needle and door-to-groin times and positive impact on the functional outcome of treated patients [58, 59]. Already, 2019-ESO guidelines for patients with AIS of <4.5 h duration and with LVO who are candidates for MT and for whom IVT is considered before thrombectomy recommend IVT with tenecteplase 0.25 mg/kg over alteplase 0.9 mg/kg, but reporting a low quality of the evidences.

There are other fibrinolytic agents being evaluated in clinical trials for the treatment of AIS. These include desmoteplase [60–66], recombinant staphylokinase [67],

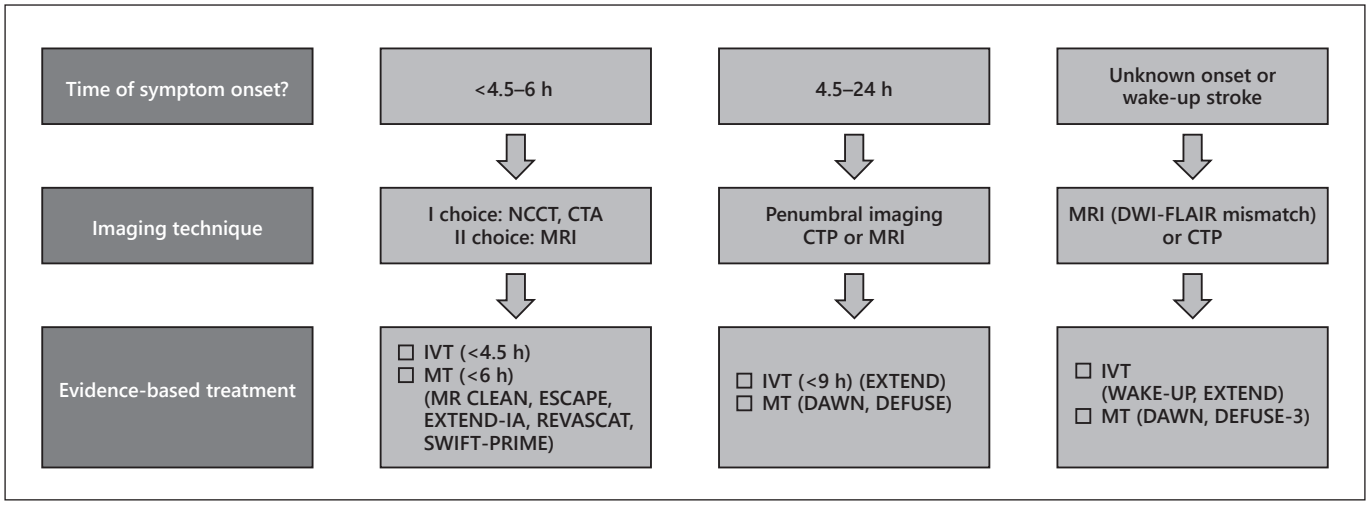

Fig. 2. Neuroimaging-guided acute ischemic stroke treatment. NCCT, noncontrast cerebral tomography; MRI, magnetic resonance imaging; CTP, cerebral tomography perfusion; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; IVT, intravenous thrombolysis; MT, mechanical thrombectomy.

and modified urokinase [68]; but with their preliminary nonrobust data, their efficacy-safety profiles appeared to be weak.

Early Secondary Prevention of Ischemic Stroke

Patients treated with alteplase are known to suffer from re-occlusion of cerebral arteries 14%–34% of cases, which is often associated with clinical worsening and poorer outcome [69, 70]. The mainstay of early secondary prevention is 160–300 mg per day acetylsalicylic acid (ASA), administered within 48 h from stroke onset [21, 71, 72].

In cases of acute noncardioembolic minor ischemic stroke (defined as NIHSS score ≤3) and noncardioembolic high-risk TIA (defined as ABCD2 score ≥4), dual antiplatelet therapy (DAPT) (aspirin and clopidogrel, or aspirin and ticagrelor), administered within 12–24 h from onset of symptoms, is a recommended strategy [71–73]. Current guidelines recommend 21 days of DAPT with aspirin and clopidogrel, followed by antiplatelet monotherapy, in both those patients with a noncardioembolic minor ischemic stroke and those with patients with high-risk TIA occurring over the last 24 h [72–89]. Moreover, in the case of mild to moderate ischemic strokes with NIHSS ≤5, high-risk TIA with ABCD2 score ≥6 or other high-risk factors, including intracranial atherosclerotic disease or internal carotid artery stenosis of at least 50% that could account for the clinical presentation, guidelines recommend 30 days of DAPT with aspirin and ticagrelor followed by antiplatelet monotherapy [72–89].

Data suggest that the administration of antithrombotic agents, including aspirin, glycoprotein IIb/IIIa inhibitors, or thrombin inhibitors, during or immediately after alteplase infusion might reduce the risks of re-occlusion and therefore improve functional outcome [90, 91]. However, their administration in combination and/or immediately after revascularization therapies has not been approved due to the lack of evidence regarding safety. There are several drugs under investigation for their suitability to act as an adjunct to thrombolytic therapy. One of this promising novel antiplatelet agents is called ACT017-glenzocimab with a specific aim to improve the efficacy of reperfusion therapies without sacrificing an acceptable safety profile (92). Glenzocimab is a humanized monoclonal antigen-binding fragment (Fab) targeting human platelet glycoprotein VI, which could be utilized as an antiplatelet. Specifically, recent data from an interim analysis on safety from glenzocimab phase I trial data have suggested a favorable safety profile for sICH equal to 1.7%; the highest dose of 1,000 mg has been selected for phase IIa study [92]. Also, anticoagulants are being investigated for the benefits of their early administration, which might reduce the rates of re-occlusion, without sacrificing an acceptable safety profile. To this regard, argatroban is a reversible and direct thrombin inhibitor with a rapid onset of action, a strong inhibitor of both fibrin formation

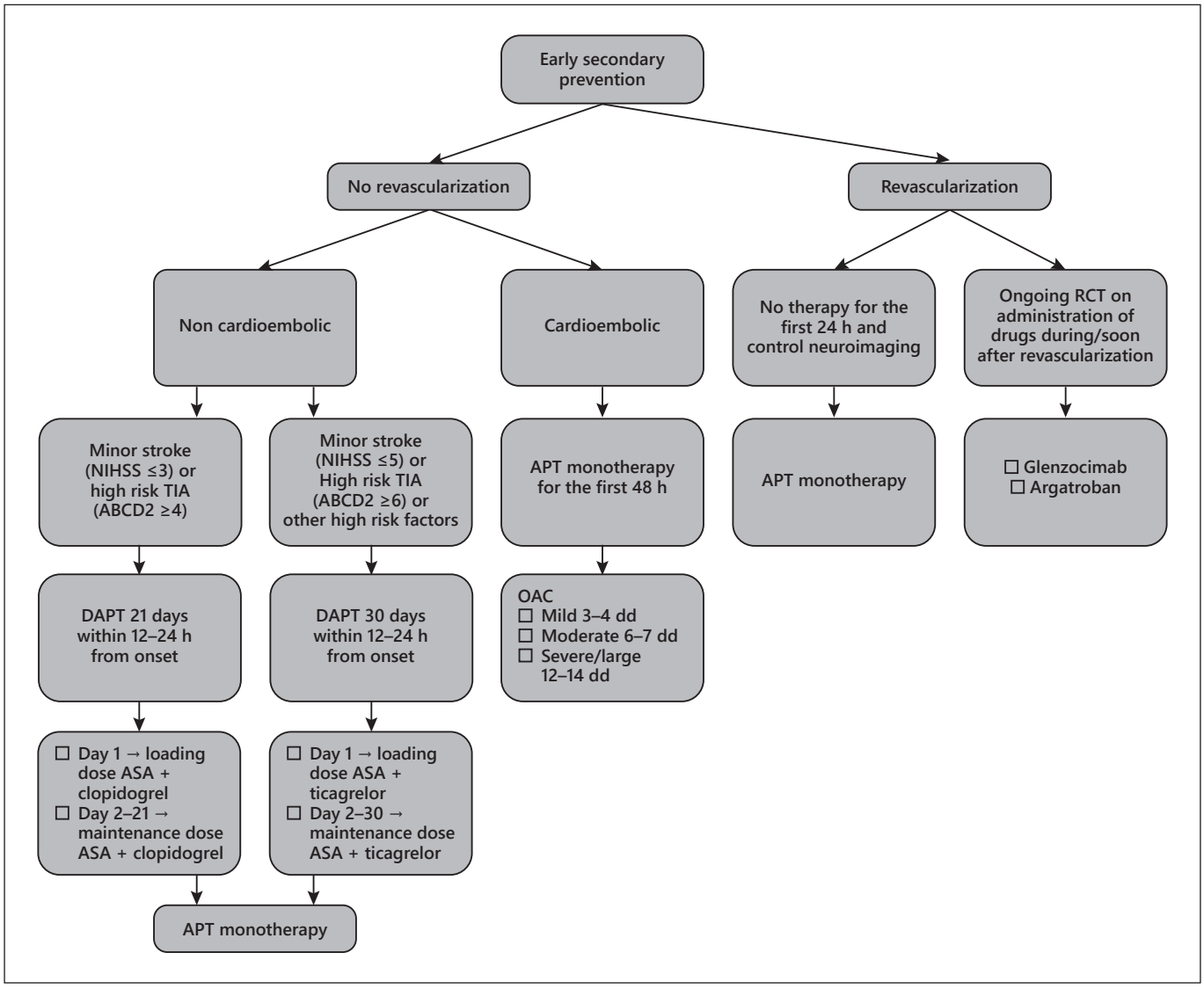

Fig. 3. Early secondary prevention in acute ischemic stroke. TIA, transient ischemic attack; DAPT, dual antiplatelet therapy; ASA, acetylsalicylic acid; APT, antiplatelet therapy; OAC, oral anticoagulation; RCT, randomized controlled trials.

and platelet aggregation but does not inhibit other serine proteases. A recent meta-analysis has suggested that argatroban infusion is an effective and safe therapeutic option for improving functional outcomes [93]. Finally, there are several ongoing studies evaluating the safety and efficacy profiles of argatroban when used as an adjunct to IVT.

Regarding the optimal timing for anticoagulation for post-acute cardioembolic ischemic stroke treatment, current international guidelines do not provide recommendations. For this, several ongoing randomized controlled trials (RCTs) have been investigating this topic. Due to a paucity of data from RCTs, with the exception of Triple AXEL trial [94], the 2019-European Stroke Society guidelines for secondary prevention of stroke [95] do not currently offer recommendations on optimal timing for initiating anticoagulation treatment. However, some observational evidence has suggested an optimal time of 4-14 days for anticoagulation post-AIS [96]. As an expert opinion, ESO guidelines suggest administering antiplatelet therapy in the first 48 h after ischemic stroke in those patients with AF; subsequently, it is considered reason-

able to start therapy at day 3 or 4 from the index stroke in patients with mild stroke and small infarcts (<1.5 cm) and at day 7 for moderate infarcts. For large infarcts, anticoagulation treatment might be best delayed for 14 days after the index stroke (Fig. 3).

A recent pooled data analysis of prospective registries reported that in Japanese and European populations, DOAC initiation within 1-2-3 or 4 days, according to stroke severity, suggested a decrease in the risk of recurrent stroke or systemic embolism without an increase in major bleeding. These findings support the several ongoing randomized trials that seek to establish the optimal timing of DOAC initiation [97].

Secondary Prevention of Ischemic Stroke

Regarding secondary prevention, in AF patients current guidelines recommend, instead of VKAs, one of the four DOACs, apixaban, dabigatran, edoxaban, and rivaroxaban, for their noninferior effectiveness, when compared to VKAs, but safer profiles [12–15]. VKAs remain the first choice for AF patients with rheumatic mitral valve disease and/or a mechanical heart valve prosthesis [41, 98, 99].

As aforementioned, DOACs have a residual bleeding risk and the development of specifically designed reversal agents of their anticoagulant activity has been one of the most significant achievements to increase their use in clinical practice. Idarucizumab is a monoclonal antibody fragment, developed to reverse the anticoagulant effect of dabigatran which allows in emergency situations, to rapidly, durably, and safely reverse the anticoagulant effect of dabigatran [100]. Regarding anti-activated factor X (FXa) DOAC, andexanet alfa is a modified recombinant inactive form of human FXa developed for reversal of FXa inhibitors. In the ANNEXA-4 study, in patients with acute major bleeding associated with the use of a FXa inhibitor (including enoxaparin), treatment with andexanet alfa markedly reduced anti-FXa activity, and 82% of patients had excellent or good hemostatic efficacy at 12 h [101]. The ANNEXA-4 sub-study results, evaluating the hemostatic efficacy of andexanet alfa in ICH secondary to anti-FXa, reported a reduced anti-FXa activity in FXa inhibitor-treated patients with ICH, with a high rate of hemostatic efficacy [102]. Andexanet alfa has been recently approved by the US Food and Drug Administration, but some issues slow down its widespread use, such as its brief half-life, poor correlation between in vitro activity and clinical efficacy, and finally, regarding its safety profile, given the in vitro effects and clinical thrombosis rates of up to 18% in early studies [103]. Other promising reversal agents, with an extended indication on anticoagulants, are aripazine and ciraparantag. Aripazine is a small molecule which in vitro bind noncovalently low-molecular-weight heparin, fondaparinux, FXa inhibitors, and dabigatran. In phase 2 clinical trials, it is reported to effectively normalize the whole blood clotting time within 10 min, compared to 12–15 h with placebo [104, 105]. Ciraparantag is a small molecule which binds noncovalently to unfractionated heparin and low-molecular-weight heparin. It appears to substantially reduce blood loss in animal models and is potentially effective as DOAC reversal agent. Ciraparantag is currently investigated in phase 2 clinical trials (NCT04593784) [106].

On the other hand, the development of safer anticoagulant drugs would improve the management of these patients. The inhibitors of FXIa are expected to have better safety profiles; in fact, data on animal and human carriers of FXI deficiency have suggested that they have a nonsignificant incidence of bleeding but a lower risk of ischemic events, when compared to hemophilia A and B factors VIII-IX deficiencies. Several ongoing trials are evaluating the safety and efficacy of anti-FXIa in secondary prevention of ischemic stroke. Underlying the favorable net clinical benefit of anti-FXIa is thought to be its selective inhibition within the intrinsic cascade coagulation factors, guaranteeing that both the extrinsic and common pathways remain free for thrombin generation and intact for hemostasis, making the hemostasis-sparing anticoagulation approach possible.

For secondary prevention in the absence of AF, aspirin is the most widely used agent, with a relative risk reduction of 15% for any type of stroke [107]. In other words, thrombotic events can occur despite being on antiplatelet therapy. Uniform definitions of the mechanism underlying ischemic recurrences when already on antiplatelet treatment are lacking. Rigorously, "antiplatelet resistance" defines the laboratory evidence of insufficient inhibition of platelet aggregation by antiplatelet agents in vitro, while "clinical resistance" and "treatment failure" refer to the inability of antiplatelets to prevent atherothrombotic events [108, 109]. Platelets are known to have multiple pathways for activation and aggregation, and a single antiplatelet may not inhibit all of these [108, 109]. Ischemic stroke is a heterogeneous disorder, deriving from typically several concomitant mechanisms, and multiple factors need to be considered and managed when evaluating a stroke recurrence while not all recurrent strokes have laboratory evidence of antiplatelet resis-

tance. In fact, patient nonadherence to prescribed therapy is also another factor responsible of recurrent ischemic events. So, identifying the etiology of a recurrence and any related modifiable risk factor is necessary [109, 110]. Some ongoing trials are evaluating the characteristics and the role of antiplatelet resistance in ischemic stroke recurrences (ASTRO study-FADOI [111]; NCT03823274; NCT05004233; NCT05151263). As well, there are several ongoing trials concerned with developing a tailored approach more effective ischemic stroke secondary prevention. Clopidogrel is another antiplatelet agent. A meta-analysis showed lower risks of recurrent stroke and bleeding events for clopidogrel compared to aspirin [112].

Brain Swelling, Neuroprotection, and Stem Cells in Ischemic Stroke

Despite advances in the understanding in stroke pathophysiology, recognition of symptoms, and progress in acute stroke care, several clinical needs remain unmet. Of these, acute revascularization therapies have become highly effective but remain strictly time dependent, requiring specialized centers, thus resulting feasible only for a minority of patients. Consequently, only one half of ischemic stroke survivors achieve functionally independence [113, 114]. Moreover, both IVT and MT stop ischemic injury, but are unable to reduce any additional damage that might be associated with post-reperfusion inflammatory response. Additionally, these treatments are not able to promote neuro-regeneration. Additionally, effective secondary prevention is hindered by a limited number of available drugs and a low patient adherence to the prescribed therapies. In an attempt to overcome these limits, many "rtPA helpers" are being researched and several of these agents appear promising, having suggested reductions in hemorrhagic transformation and infarct volume along with induced stabilization of the blood-brain barrier in animal stroke models; notwithstanding, only a minority of these "rtPA helpers" have entered clinical trials, and at the moment, results have been disappointing.

Many drugs have been tested for their neuroprotective effect on ischemic stroke; however, none have shown any clinically beneficial results. The failure to develop effective neuroprotective drugs against ischemic stroke could be in part explained by a lack of adequate animal models having been tested. In fact, several preclinical studies have reported favorable effects in terms of safety and efficacy, but experimental studies evaluating new stroke therapies have been mostly performed in young, otherwise healthy rodents, which have a shorter life expectancy. These models cannot replicate human vascular risk factors, nor time exposure and comorbidities of real-world stroke patients. These risk factors are known to worsen post-ischemic neurological outcome and brain plasticity and tend to reduce the brain response to recovery-inducing/plasticity-promoting treatment [115].

As part of the secondary damage of the ischemic brain tissue, in particular when ischemia involves a large part of a hemisphere, space-occupying cerebral edema and intracranial hypertension can occur. These are potentially life-threatening complications in the first few days after large hemispheric or cerebellar infarction, which can lead to neurological deterioration, increase in mortality, and poor functional outcome [116, 117]. Regarding pharmacological treatment of patients with space-occupying hemispheric ischemic stroke, no RCT has been conducted to compare osmotic therapy with nonosmotic therapy; moreover, with conservative treatment alone, mortality rates have been reported to be up to 80% [118]. In a meta-analysis of these trials, decompressive surgery undertaken within 48 h of stroke onset has been reported to reduce mortality and increase the favorable functional outcome [119]. The European and American Guidelines state that, in patients with space-occupying hemispheric infarction, it is reasonable to use short-term osmotic agents, like mannitol or hypertonic saline. However, the benefit-risk ratio of osmotic therapy and its benefit in reducing the mortality rate or a poor outcome are still unclear [21, 120]. Regarding corticosteroids, there is even more lack of evidence of their efficacy on brain swelling secondary to AIS; moreover, corticosteroids, in standard or high doses, potentially increase the risks of infectious complications. For these reasons, major guidelines recommend against their administration for indication. Currently, the only recommended treatment with a reported benefit from RCTs results on mortality and disability is decompressive surgical therapy [21, 120].

As part of the heterogeneous category of neuroprotectors, several trials have been investigating agents for their possible use in the treatment of brain swelling; in fact, they are not exclusively designed for the acute phase. Deferoxamine, an iron chelator, has been investigated in TANDEM-1 trial (NCT00777140): by treating iron overload, the agent might reduce brain edema, which has been associated with greater brain injury, both after ischemia and reperfusion. Another investigation has been conducted on the antidiabetic sulphonylurea glyburide, which has been reported to prevent cerebral edema in an-

terior circulation malignant strokes [121] (NCT01794182, NCT01268683). However, current ESO guidelines [120] suggest against the use of glyburide in routine clinical practice as a means to reduce the risk of mortality or poor outcome in patients with space-occupying hemispheric infarction.

Regarding collateral circulation, nonmodifiable factors, such as aging and genetics, in adjunct to several modifiable ones, such as systemic diseases (cardio-cerebro-vascular or pulmonary disorders, dehydration) or medications (antihypertensives) [122], might negatively influence its status [123]. The management of these conditions could help to reduce the risk of collateral failure during AIS. Collateral enhancing intervention is a potential strategy to sustain blood flow within ischemic regions, in particular in patients who are ineligible for revascularization therapy (i.e., beyond the therapeutic time window), or those with poor collaterals in whom unfavorable revascularization effect is expected. Collateral enhancing strategies include induced hypertension, lying flat head position, volume expansion, and sphenopalatine ganglion stimulation [122, 124]. Regarding pharmacological treatments, nitric oxide, albumin, tumor necrosis factor-α inhibitors, sildenafil, erythropoietin, and statins have shown to increase arteriogenesis in animal models and in preclinical/clinical studies; however, the few large RCTs in AIS patients reported negative results [29]. Potential reasons for these failures mainly include the lack of assessment of the effects of such therapies on collateral flow. Further studies are needed with a better patient selection and the use of advanced neuroimaging techniques to assess the collateral status. Currently, some clinical trials are ongoing employing various strategies (COLISEUM, NCT04882657; "Protective Effects of Edaravone Dexborneol," NCT05024526; COMET-AIS, NCT05051397) [29]. As part of neuroprotective strategy, several studies are investigating for beneficial effect from stem cell transplantation in ischemic stroke. Results from animal experiments and a few clinical trials [125, 126] have been the impetus. Mesenchymal stem cells (MSCs) have been the most studied subtype of stem cells, as they have shown to be promising therapeutic option for ischemic stroke patients [127]. In fact, MSCs have properties of self-renewal and are multipotential for differentiation; likewise, their sampling does not raise ethical concerns being that they can be isolated from various tissues as bone marrow, umbilical cord, adipose tissue, placenta, and tissues originated from the neural crest (e.g., dental pulp) [128]. Another type of stem cells with a potential role in ischemic stroke treatment is neural stem cells, less studied than MSCs, due to ethical issues as they are typically fetuses-derived. MSCs promote neurotrophic and regeneration by multiple mechanisms: regulation of the immune and inflammatory response, production of biologically active cytokines and growth factors, induction of angiogenesis through paracrine or autocrine production of appropriate cytokines. Preclinical studies have shown that MSC therapy has a promising safety and efficacy profiles, but some investigators have raised concern regarding potential serious adverse effects as tumor growth, immunodepression, and pulmonary embolism [129], even if they appear to be less frequent than in induced pluripotent stem cell transplantation [113]. Many clinical trials have produced conflicting results to date, achieving safe transplantation, but without confirmation of functional improvement [130–133]. Large phase 3 trials are needed to clarify these queries and to define the role of stem cells in ischemic stroke treatment. Two phase 3 clinical trials on MSCs are ongoing (MASTERS-2, NCT03545607; TREASURE, NCT02961504).

Telemedicine and Mobile Stroke Units

The 2019 AHA/ASA guidelines [21] recommended teleradiology systems approved by the US Food and Drug Administration (FDA) for sites without in-house imaging interpretation expertise, for timely review of brain imaging in patients with suspected acute stroke (evidence IA). Moreover, when implemented within a telestroke network, teleradiology systems approved by the FDA deemed to be effective in supporting rapid imaging interpretation in time for IV alteplase administration decision-making (evidence IA). The use of telemedicine/telestroke resources and systems should be backed by healthcare institutions, governments, payers, and vendors as one method to promote adequate 24/7 coverage and care of acute stroke patients in a variety of settings [21]. Moreover, telestroke/teleradiology evaluations of AIS patients can be effective for reliable screening for IV alteplase eligibility. Results from the Stroke Team Remote Evaluation Using a Digital Observation Camera (STRokEDOC) pooled analysis supported the hypothesis that telemedicine consultations, which included teleradiology, compared with telephone-only, resulted in statistically significantly more accurate IV alteplase eligibility screening for patients exhibiting symptoms and signs of an acute stroke syndrome in Emergency Departments [134]. Therein, the delivery of IV alteplase guided by telestroke consultation can be beneficial (evidence IIA).

Concerning specifically this, a systematic review and meta-analysis reported that sICH rates were similar between patients treated with telemedicine-guided IV alteplase and those receiving IV alteplase at stroke units, with no observed differences in mortality or functional independence at 3 months [135]. Telestroke networks may be reasonable for triaging patients with AIS who may be eligible for interfacility transfer, in order to be considered for emergency MT (evidence IIB). An observational study compared clinical outcomes of EVT between patients with anterior circulation stroke transferred after teleconsultation and those directly admitted to a tertiary stroke unit. From this study, similar rates of reperfusion (56.2% vs. 61.2%; $p = 0.567$) and favorable functional outcomes (18.8% vs. 13.7%; $p = 0.470$) were observed between the groups. In light of this, telestroke networks enable the triage and the delivery of EVT to selected ischemic stroke patients transferred from remote hospitals [136]. Providing alteplase decision-making support via telephone consultation to community physicians is feasible and safe and may be considered when a hospital does not have access to either an in-person stroke team or a telestroke system (evidence IIB). Fong et al. [137] investigated the efficacy and safety of IVT stroke service by telestroke when a stroke neurologist was not available on-site: patients treated without a neurologist on-site achieved similar outcomes. Telephone consultation and teleradiology-guided IV stroke thrombolysis, with the support of on-site internist, were reported to be safe and efficacious [137].

The Mobile Stroke Unit (MSU) was launched in 2003 [138], comprised of standard ambulance equipment, a CT scanner, point-of-care laboratory equipment, telemedicine capabilities, and the ability to administer rtPA. The rationale of a mobile ED is to treat, as soon as possible, AIS patients, given that achieving reperfusion in the first "golden hour" has the potential to reduce stroke volume and subsequent disability to a minimum [139]. MSU safety and efficacy have been reported in several studies [140–142]. Moreover, MSU seems to expedite IVT to facilitate EVT for patients with LVO [143]. However, the true impact of MSU on clinical outcomes is unclear, since most MSU studies have not reported clinical outcomes [143]. Two recent studies, a non-RCT and an RCT, reported that in patients with acute stroke who were eligible for rtPA, global disability at 3 months was lower with MSU compared to in-person professional stroke care [144, 145]. As well, a recent review reported that MSU resulted in shorter onset-to-treatment times in mostly urban settings [146].

The European Academy of Neurology (EAN) and the European Stroke Organization have jointly drawn up a series of recommendations in a consensus statement and practical guidance for pre-hospital management of stroke [147]. Regarding telemedicine and MSUs, due to a lack of evidence (2017), no recommendation on the value of pre-hospital telemedicine was reported. Regarding MSU, the authors did not recommend the routine use of MSUs as there was insufficient evidence of functional outcome benefit; however, the authors did suggest that MSU can reduce onset-to-needle times for IVT in patients with ischemic stroke and can be an option for certain regions where ambulance transport is unreliable. MSUs allowing CTA could be useful for the early identification of patients with large artery occlusion. These results need to be supported by RCTs.

Stroke during COVID-19 Pandemic

COVID-19 has critically stressed the global healthcare systems, which not only has affected virally infected patients, but has also generated collateral damage on acute time-dependent conditions, particularly cerebrovascular and cardiovascular diseases. There has been a significant reduction in the number of stroke admissions [148–151], due to a shrinking of the primary prevention system, cancellations of follow-up visits for secondary prevention, and also the need for a reorganization of the emergency system. Some European countries have reorganized their centralization of acute stroke treatment to a limited number of hospitals, and stroke unit beds have been, in part, readapted into intermediate or intensive care beds for COVID-19 patients, with multidisciplinary management being limited [152]. Access to the ED for minor strokes and TIAs has been dramatically reduced. Moreover, with COVID-19 lockdown many strokes occurred during isolation, and many of these patients arrived late, or never, to hospital for care [148]. In addition, access to time-dependent stroke therapies has been severely limited or delayed by a lack of transportation, emergency service overloads, disrespect for previous stroke paths, and a lack of CT availability [153–157].

During the early phases of COVID-19, there was a relatively high prevalence of thrombotic events, mainly among patients with severe COVID-19 but also among mildly symptomatic or asymptomatic patients [148, 158]. SARS-CoV-2 infection is a risk factor for cardiovascular complications and thrombotic events, including myocardial injury, fulminant myocarditis, cardiac arrhythmia,

ischemic stroke, and venous thromboembolism [158]. Moreover, the virus has been associated with the onset of neurological symptoms, but the exact mechanisms of its neurotropic characteristics are not fully understood, which might include direct infection pathways, immune mediated injury, and brain damage due to systemic hypoxia [159]. In order to provide precise data on the outcomes of these neurological manifestations, an international registry (ENERGY) was created by the EAN in collaboration with European national neurological societies and the Neurocritical Care Society and Research Network (NCRN) [160]. Despite the increasing number of published studies which have correlated ischemic stroke with COVID-19, a causal relationship with SARS-CoV-2 infection remains unclear. More reliable data on stroke prevalence should be provided by ongoing international prospective multicenter studies [161]. In recent systematic reviews, an increased incidence rate of AIS in COVID-19 patients was reported [148, 150, 162] with an average of 1.5% (from 0.1% to 6.9%) among hospitalized patients. Moreover, in a recent meta-analysis, patients with severe COVID-19 had a five-fold increase in the risk of stroke (OR = 5.1, 95% CI: 2.72–9.54) [163], and these data could even be underestimated, in particular in sedated and mechanically ventilated patients [154, 164]. Compared to non-COVID-19 patients, patients with COVID-19 suffering a stroke presented in the emergency room in delay were younger, more likely male, with a more severe clinical presentation compared to controls, higher NIHSS on admission and frequently with LVO [165], significantly less likely to receive acute revascularization treatments [166], with longer hospitalization duration, poorer clinical and neuroradiologic outcomes, higher rates of early re-occlusion, and an increased mortality [148, 167–170]. The etiology of AIS in COVID-19 patients has been more often cardioembolic or cryptogenic [163, 169]; this last could be attributed to an incomplete diagnostic path due to the limited availability of resources in the under-pressure healthcare system.

IVT remains the standard of care also for these patients; however in a small series of patients, IVT has been reported to be associated with catastrophic hemorrhage [171]. In fact, thrombocytopenia and coagulopathy are frequently present in COVID-19 patients, so the indication for revascularization therapies should be weighed on a case per case basis [148]. The high re-occlusion rate of LVO strokes and the decreased efficacy of intravenous rtPA seen in patients with COVID-19 may be partially attributed to a "hyperinflammation syndrome" [172]. In fact, a recent study on tocilizumab, an interleukin-6 antagonist, in hospitalized patients with COVID-19, did not show any relevant difference in patients treated with tocilizumab, either in clinical deterioration or in thrombotic events, although one of the limits of the study was a small number of included patients which underpowered the possibility to draw any reliable conclusions on its efficacy in preventing thrombotic events [173]. Several drugs, including stem cells, are currently under investigation for their immunomodulatory impact on hyperinflammation syndrome which is known to be associated with thromboembolic events (Clinical Trial of the Use of Anakinra in Cytokine Storm Syndrome Secondary to COVID-19 [ANA-COVID-GEAS. NCT04443881]).

Telemedicine has already played a beneficial role in AIS management [174], and its further use during the COVID-19 pandemic could lead to improvements in stroke screening and follow-up, not to mention favoring the enrollment process of stroke patients into research trials [175]. However, in some registries a reduction in the number of telestroke evaluations was registered during COVID-19. Those patients were on average younger and had a higher NIHSS, probably reflecting thrombotic complications in atypical stroke populations [176–178]. The reasons for the decrease in telestroke requests and urgent stroke treatment recommendations have been probably multifactorial, and this highlights the importance of continued public health measures to encourage patients and their families to seek emergency medical care at symptom onset, despite pandemic setting.

Telemedicine has yet been utilized during infectious outbreaks for many years. In a recent review, telemedicine was confirmed to be a safe expert support system for hospitals during infectious outbreaks. Among its merits, it makes high-quality medical procedures possible, limits potentially contagious interhospital transfers, saves critical resources such as protective gear and rescue/emergency transport services, and offers safe home office work for medical specialists [179].

Conclusion

Despite recent advances in thrombolytic and endovascular therapies, many IS patients die or remain with severe disability; moreover, effective secondary prevention is hampered by a restricted choice of medications and a low level of patient adherence to prescribed treatments. The recent extension of the time window for IVT ± EVT guided by mismatch advanced neuroimaging techniques has opened up the possibility of including more patients

as revascularization therapy candidates, also those presenting beyond the 4.5–6 h time window or with unknown/wake-up onset time. Additionally, the development of safer and more manageable thrombolytic agents would result in increased rates of treated patients, of which tenecteplase is by far most promising alternative agent. With endovascular therapy advances, multiple studies are investigating whether thrombolytic therapy can be bypassed in patients with LVO, where initial presentation is at thrombectomy or comprehensive stroke centers, in order to be treated with primary MT, as the case of acute myocardial infarction. To date, these studies have failed to provide any shared results and not one of these studies has reported an overall noninferiority when compared to combined treatment [180]. Moreover, the use of advanced neuroimaging techniques could allow the evaluation of collateral circulation status before and after revascularization strategies, to more consciously guide the management of AIS patients and reduce the rate of "futile recanalization," as well as the design of clinical trials on interventions having collateral circulation as target to obtain a better clinical outcome.

Another limit of currently available revascularization strategies is that they are unable to limit the secondary damage associated with inflammation and oxidative damage during reperfusion, nor can they promote neuronal regeneration. Besides, a non-negligible percentage of treated patients suffers from re-occlusion and neurological deterioration, with generally worse clinical outcome, in particular, in large hemispheric AIS where efficacious drugs to treat brain swelling are lacking, leaving decompressive surgery the only strategy to reduce mortality and disability rates. The development of efficacious "rtPA helpers," administered during or soon after revascularization, and post-acute drugs with neuroprotective and neurotrophic activities, is under investigation in several trials. The failure of clinical trials after translation from positive preclinical animal studies could be in part explained by a lack of an adequate animal model for human ischemic stroke. Future animal studies will need to model long-term risk factor exposure as well as exposure to combinations of risk factors. Finally, treatment studies need to involve middle-aged or aged animals, which are more realistic models and therein would reduce the risk of translational clinical research failure.

With regard to secondary prevention, a principal fear of antithrombotic therapy is the risk of hemorrhagic complications; in fact, the longer the treatment period with antiplatelets or anticoagulants, the greater the risk of bleeding. This subtle risk-benefit balance could turn out to be underlying patient's nonadherence and discontinuation of therapy. Doubtless, the development of reversal drugs, which can stop the anticoagulant effect of DOACs in emergency situations, has reassured clinicians and helped the widespread of these novel agents in clinical practice. However, the use of reversal agents should be an exception, and to overcome these limitations, the trend in the current clinical research for experimental drugs is moving toward a "hemostasis-sparing" mechanism of action. In particular, regarding anticoagulation, the contact activation inhibitors and particularly those of FXI seem to be promising agents for the prevention of thromboembolic events, leaving the physiologic hemostatic pattern free to intervene in case of need. The results from the ongoing RCTs should clarify if this is a winning approach.

Aspirin is the most widely used agent for secondary prevention, but thrombotic events can occur despite being on antiplatelet therapy. However, stroke has a complex pathophysiology and identifying the correct mechanism of the recurrence and any modifiable risk factor seems to be the best approach before accusing antiplatelet treatment of any failure [109, 110]. Some ongoing trials share the aim of evaluating the characteristics and the role of antiplatelet resistance in ischemic stroke recurrences. Research into precision medicine will lead to individualized treatment strategy, thereby reducing the recurrence rates of ischemic stroke.

Future clinical randomized trials are needed to further evaluate the safety and efficacy of several promising antiplatelet and anticoagulant therapies, as well as their combinations, for the treatment of acute and post-AIS. Moreover, investigations are required into experimental drugs which might be effective in reducing inflammatory and reperfusion damage which are associated with worse functional outcome in ischemic stroke patients.

Regarding the COVID-19 pandemic, there is a reasonable probability that we should cohabit with the virus, also in a more favorable endemic phase, but for a period of an actually unforeseeable duration; doubtless, the pre-COVID-19 dedicated paths need to be reinstated to guarantee guideline recommended stroke management [153, 181, 182]. Further studies are required for COVID-19 patients with AIS, both for the acute phase treatments and for their primary and secondary prevention.

Key Messages

- Ninety per cent of all strokes worldwide could be prevented with stricter primary prevention.

- Despite the demonstrated benefit-risk profiles associated with DOACs, the development of drugs with better safety-efficacy profiles for primary and secondary prevention for nonvalvular AF is a major clinical need.
- Tenecteplase is a new-generation thrombolytic drug, with similar efficacy, but a better safety profile compared to alteplase, and it will most likely become the first treatment choice for AIS if the preliminary data of ongoing RCTs are confirmed.
- Many drugs have been tested for their neuroprotective effect on ischemic stroke. Several ongoing studies on heterogeneous drugs, especially stem cells, are investigating rtPA helper roles, with potential neuroprotective and neuronal regeneration effects.
- Telestroke and mobile stroke units should be implemented to speed up pre-hospital management and to implement stroke medicine in deficient or rural areas.
- A greater use of telestroke should be encouraged in order to improve in stroke assessment, from the outpatient to the inpatient level, but also in the follow-up.
- COVID-19-friendly stroke paths need to be implemented to guarantee the access and delivery of standard of care.

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Conflict of Interest Statement

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