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STATE OF THE ART REVIEW
Acute cardiovascular care

Acute myocardial infarction and ischaemic stroke: differences and similarities in reperfusion therapies—a review

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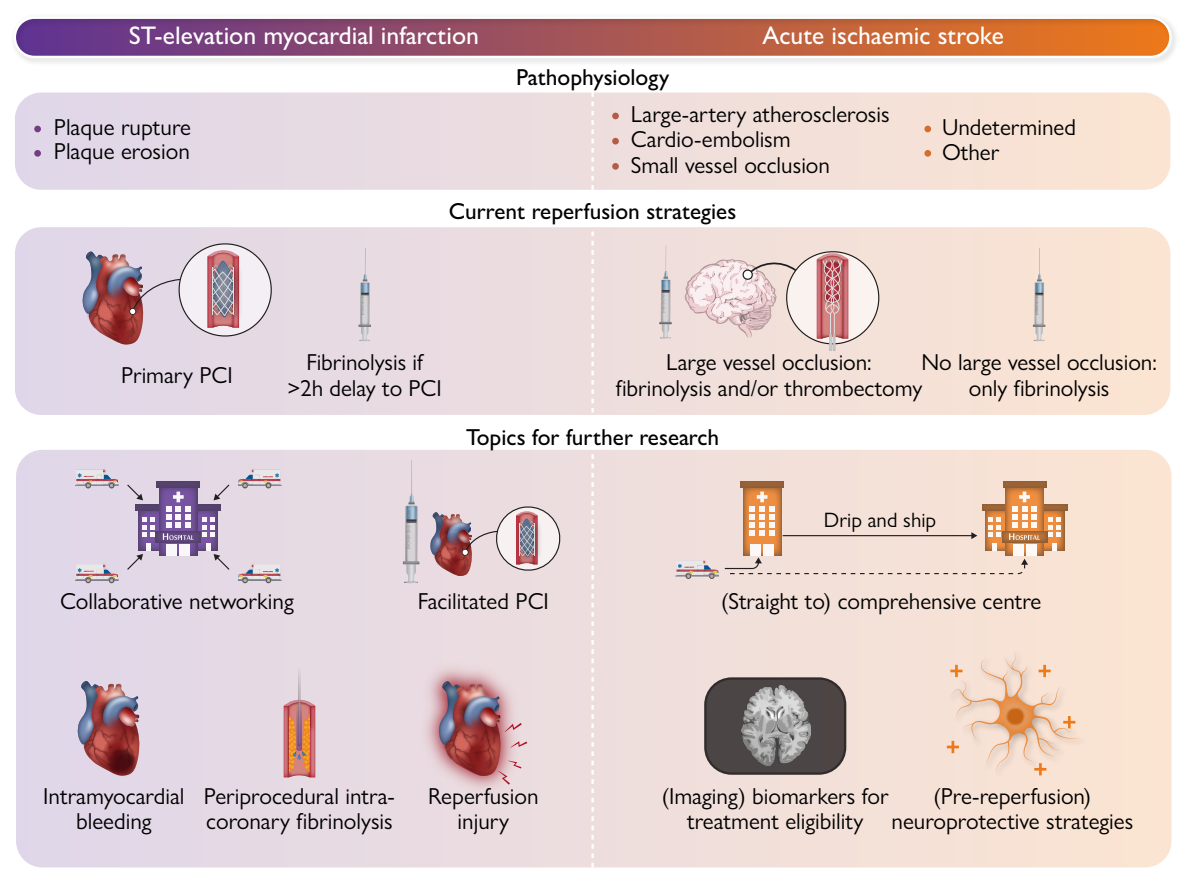
Graphical Abstract



In contrast to ST-elevation myocardial infarction (STEMI), the aetiology of acute ischaemic stroke (AIS) is more heterogeneous. Undetermined aetiology refers to the group of patients in whom no single cause is identified. More rare causes of AIS are categorized as AIS of other determined

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aetiologies (e.g. dissection, hypercoagulable state). Although both intravenous fibrinolysis and mechanical reperfusion strategies [primary percutaneous coronary intervention (PCI) for STEMI and thrombectomy for AIS] are available for treatment of both STEMI and AIS, differences in pathophysiology (in part) explain disease-specific management with a predominant role of primary PCI in STEMI, in contrast to the persisting relevance of fibrinolysis in the majority of AIS patients who are not eligible for mechanical thrombectomy. Topics for future research should focus on ways to increase the number of treatment-eligible patients, increase the success of reperfusion treatment, and reduce complications after reperfusion treatment.

Abstract

Acute ST-elevation myocardial infarction (STEMI) and acute ischaemic stroke (AIS) share a number of similarities. However, important differences in pathophysiology demand a disease-tailored approach. In both conditions, fast treatment plays a crucial role as ischaemia and eventually infarction develop rapidly. Furthermore, in both fields, the introduction of fibrinolytic treatments historically preceded the implementation of endovascular techniques. However, in contrast to STEMI, only a minority of AIS patients will eventually be considered eligible for reperfusion treatment. Non-invasive cerebral imaging always precedes cerebral angiography and thrombectomy, whereas coronary angiography is not routinely preceded by non-invasive cardiac imaging in patients with STEMI. In the late or unknown time window, the presence of specific patterns on brain imaging may help identify AIS patients who benefit most from reperfusion treatment. For STEMI, a uniform time window for reperfusion up to 12 h after symptom onset, based on old placebo-controlled trials, is still recommended in guidelines and generally applied. Bridging fibrinolysis preceding endovascular treatment still remains the mainstay of reperfusion treatment in AIS, while primary percutaneous coronary intervention is the strategy of choice in STEMI. Shortening ischaemic times by fine-tuning collaboration networks between ambulances, community hospitals, and tertiary care hospitals, optimizing bridging fibrinolysis, and reducing ischaemia–reperfusion injury are important topics for further research. The aim of this review is to provide insights into the common as well as diverging pathophysiology behind current reperfusion strategies and to explore new ways to enhance their clinical benefit.

Keywords STEMI • Ischaemic stroke • Primary PCI • Fibrinolysis • Thrombectomy • Reperfusion

Introduction

Acute ST-elevation myocardial infarction (STEMI) and acute ischaemic stroke (AIS) are vascular diseases in which the blood supply to a vital organ, respectively, the heart and brain, becomes abruptly impaired. Since normal myocyte and neuronal cellular function depend on an adequate supply of oxygen, cellular dysfunction with progression to infarction will rapidly develop when restoration of blood flow is not established. The heart and even more the brain have a high vulnerability to ischaemia with irreversible damage typically developing within minutes after disease onset,[1,2] hence the analogue treatment dogma's 'time is muscle' and 'time is brain'. These statements emphasize the importance of urgent initiation of reperfusion strategies after onset of clinical symptoms. Reperfusion treatment for STEMI was introduced in the late 1980s, many years before being evaluated and thereafter adopted by neurologists in the management of AIS. Although many similarities exist between both diseases, differences in aetiology, pathophysiology, and clinical presentation often demand an individualized and disease-tailored approach. This review aims to provide current insights into the pathophysiology and diagnostic workup of reperfusion therapy and explores ways to enhance its clinical benefit (*Graphical Abstract*).

The impact of pathophysiology on clinical presentation and treatment

STEMI caused by atherothrombotic coronary artery diseases (Type 1 myocardial infarction) is usually precipitated by abrupt rupture of an atherosclerotic plaque. Exposure of the lipid-rich plaque content to the bloodstream activates platelets and the coagulation cascade, resulting in *in situ* development of a fibrin-rich thrombus. A less well-studied but emerging cause is a superficial erosion of a proteoglycan-rich plaque that triggers the formation of a platelet-rich thrombus (*Figure 1* and *Table 1*).[3] Plaque erosions are more often seen in younger (<50 years) and female STEMI patients.[4] Other types of myocardial infarction will not be discussed as this review deals with reperfusion therapy. The presence of a coronary thrombus critically obstructing the vessel lumen will elicit an acute symptomatic event, usually involving chest pain or oppression. Thrombus formation in coronary arteries is often a dynamic process, and spontaneous, partial thrombus dissolution with recanalization of the artery and temporary disappearance of symptoms may occur. Myocytes deprived from oxygen and blood will suffer ischaemia and, without reperfusion, undergo necrosis.[1] Restoration of blood flow induces functional recovery of viable myocardium. Women with STEMI are older, present later to the hospital with a clinical picture more difficult to interpret, and have more comorbidities, and, compared with men, an alternative diagnosis (e.g. Takotsubo syndrome, coronary dissection) is more likely to be present.[5]

In contrast to STEMI, an important distinction must be made between ischaemic (87%) and haemorrhagic stroke (13%).[6] In patients with AIS, the aetiology can be divided into five categories according to the Trial of Org 10172 in Acute Stroke Treatment classification: large-artery atherosclerosis, cardio-embolism, small-vessel occlusion, stroke of other determined aetiology, and stroke of undetermined aetiology (*Table 1*).[7] Diagnostic investigations are needed to correctly identify the aetiology as this determines the optimal therapeutic management and secondary prevention strategy. In large-artery atherosclerosis, an occlusion by an embolus from a proximal atherosclerotic lesion results in reduced perfusion of a particular vascular territory in the brain, whereas the heart is the source of emboli in AIS associated with atrial fibrillation (cardio-embolism). These two aetiologies usually result in larger emboli more likely to cause a large-vessel occlusion (LVO) for which both fibrinolysis and even more so thrombectomy are efficacious treatment options. In patients with lacunar infarcts,

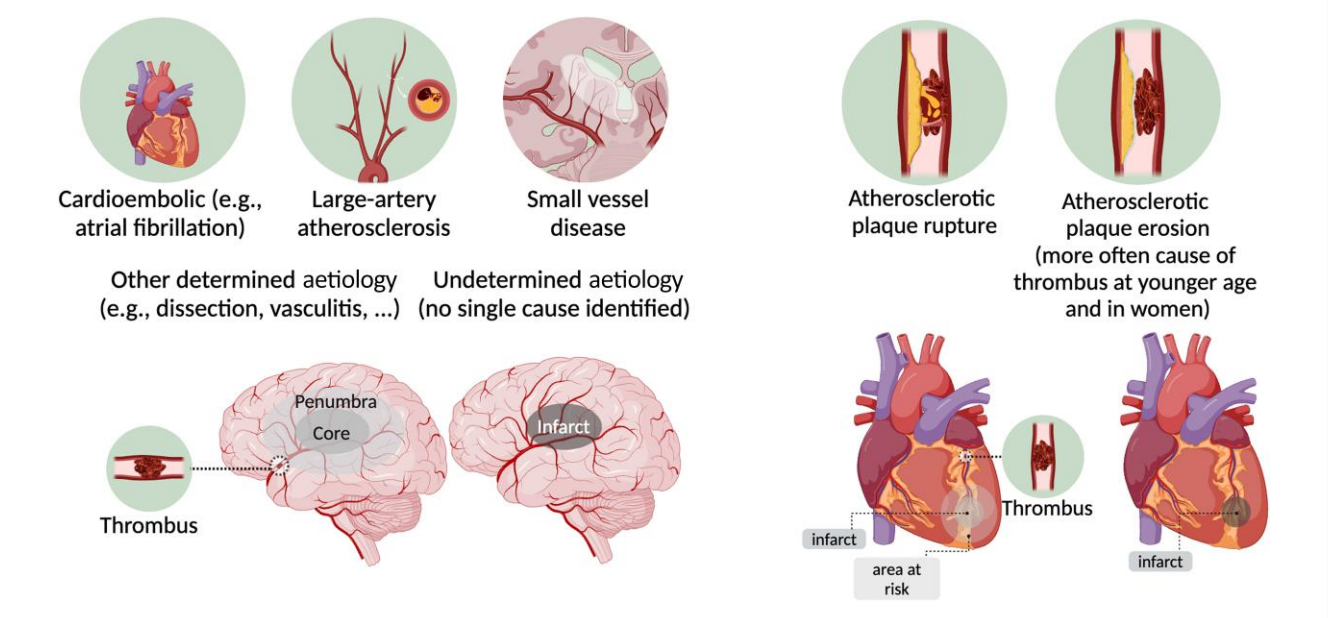

Figure 1 Pathophysiology of ST-elevation myocardial infarction and acute ischaemic stroke. Most commonly, Type 1 ST-elevation myocardial infarction is caused by *in situ* thrombus formation on a ruptured plaque or by *in situ* thrombus formation on plaque erosion. The three most common causes of acute ischaemic stroke are cardio-embolism, large-artery atherosclerosis, and small-vessel disease. While the first two often result in occlusion of a large artery, associated with a large area of hypoperfusion, the latter affects the smallest blood vessels and will give rise to small, lacunar infarcts. Typical for large-vessel occlusions, this results in a larger area of critical, hypoperfusion (penumbra) compared with the tissue that is irreversibly damaged (core). The aim of reperfusion treatment with fibrinolysis and/or thrombectomy (depending on time and imaging characteristics) is successful reperfusion and penumbral salvage

small-vessel disease is the presumed mechanism and affects small vessels <1 mm in diameter leading to subcortical infarcts, white matter hyperintensities, lacunes, perivascular spaces, microbleeds, and brain atrophy on neuroimaging and is clinically associated with AIS, but also cognitive decline (*Figure 1*).[8] As large emboli are not involved in the pathophysiology, there is no indication for thrombectomy, and treatment relies on fibrinolysis. Other rarer causes of AIS are categorized as AIS of other determined aetiology (e.g. dissection or hypercoagulable state). Acute ischaemic stroke of undetermined aetiology relates to a heterogeneous category of patients in whom no single cause is identified. These various aetiologies share a common ischaemic pathophysiological cascade, initiated by a sudden decrease in cerebral blood flow. The resulting energy depletion will lead to oedema formation due to shifts of ions and water: within minutes, fluids will shift from the extracellular to the intracellular space, resulting in cytotoxic oedema. This in turn causes an osmotic gradient resulting in extravasation of fluids over an intact blood–brain barrier, into the extracellular brain compartment (ionic oedema). After several hours, blood–brain barrier permeability changes enable leakage of larger proteins in addition to ions and water from the intravascular to extracellular space (vasogenic oedema). A more recent finding identifies the cerebrospinal fluid as a source of oedema by means of the glymphatic system.[8,9]

Clinically, patients experience an acute onset of neurological symptoms depending on the involved vascular territory. The absence of pain and presence of language and perceptual impairments contribute to delays in emergency room arrival (in comparison to STEMI), reducing treatment eligibility. Women suffer their first AIS at older age than men and have poorer functional baseline status. They experience longer delays to hospital arrival and brain imaging. Atypical and non-focal (e.g. mental state changes) stroke symptoms might be more common (although debated), and they more often suffer stroke mimics.[9,10]

Diagnosis: a simple electrocardiogram vs. imaging

The diagnosis of STEMI is based on clinical symptoms, electrocardiogram (ECG), and, at a later stage, cardiac markers of necrosis. In most patients, the decision to proceed to reperfusion therapy is based on symptoms and the presence of acute ST-segment elevations on the ECG (*Figure 2* and *Table 1*).

Based on the specific combination of stroke symptoms, the clinician might determine the affected hemisphere, localization (posterior vs. anterior circulation), and even aetiology of the AIS (lacunar syndromes vs. cortical signs). However, robustly differentiating ischaemic from haemorrhagic stroke can only be done by brain imaging and is essential to ensure a fibrinolytic can be administered safely. Potential stroke patients are usually assessed by non-contrast-enhanced computed tomography (NCCT). The primary goal is to exclude contraindications for treatment (e.g. haemorrhage) or to make an alternative diagnosis, rather than confirming a definite diagnosis of AIS, since signs of infarction are not clearly visible on NCCT in the early time window after onset.[11] Alternatively, magnetic resonance imaging (MRI) with diffusion-weighted imaging (DWI) is able to visualize cytotoxic oedema as a sign of early ischaemia almost immediately after onset.[12] Despite its superior diagnostic accuracy,[13] it is logistically more challenging in the emergency setting; hence, most hospitals rely on computed tomography (CT). Additional imaging sequences are relevant in patients who present outside the classical time window or with unknown stroke onset (*Figure 2* and *Table 1*).

Table 1 Key differences in aetiology, diagnosis, and treatment between ST-elevation myocardial infarction and acute ischaemic stroke

	STEMI (Type 1)	AIS
Pathophysiology, causes	• Ruptured atherosclerotic plaque • Superficial erosion of a proteoglycan-rich plaque	• Embolism originating from large-artery atherosclerosis • Cardio-embolic source • Small-vessel occlusion • Stroke of other determined aetiology • Stroke of undetermined aetiology
Ischaemic thresholds	Highly dependent on the presence of: • Collateral circulation • Pre-conditioning	• Neurological symptoms if CBF drops below 29 mL/100 g/min • Infarction if CBF permanently drops below <18 mL/100 g/min Highly dependent on the presence of collateral circulation, but not pre-conditioning
Tissue viability concepts in ischaemic conditions	• Infarcted myocardium: irreversibly damaged and dysfunctional tissue • Stunned myocardium: dysfunctional tissue that occurs without necrosis after interruption in coronary perfusion despite timely restoration of blood flow (reperfusion)	• Core: tissue destined to infarction with irreversible damage and permanent loss of function • Penumbra: reversibly dysfunctional tissue, immediate functional recovery with reperfusion
Diagnosis	Based on: • Clinical symptoms • Cardiac markers of necrosis (troponins) • ECG	Based on: • Clinical symptoms • Brain imaging (CT or MRI)
Mechanical reperfusion treatment	• PCI of infarct artery with drug-eluting stent • PCI of other lesions during index hospitalization	Mechanical thrombectomy
First-choice pharmacological reperfusion treatment	Tenecteplase (30 mg <60 kg, 35 mg 60–70 kg, 40 mg 70–80 kg, 45 mg 80–90 kg, and 50 mg ≥90 kg, as a bolus) Half-dose tenecteplase in patients ≥75 years (≥60 years?)	Alteplase (.9 mg/kg, of which 10% as bolus, the remaining over a 60-min infusion)
Treatment eligibility in current clinical practice (Western world)	• Primary PCI: 80% • Fibrinolysis (before PCI): 10%	• Thrombectomy: 7.1% • Fibrinolysis: 16.6%
Time windows and imaging criteria for reperfusion treatment	Pharmacological • ≤12 h after the first medical contact or ECG diagnosis and only if PCI ≤2 h impossible or unlikely Primary PCI • If performed ≤2 h after the first medical contact or ECG diagnosis by an experienced team	Pharmacological • <4.5 h after known stroke onset • 4.5–9 h after stroke onset or middle point last known well and symptom recognition if perfusion lesion–ischaemic core mismatch • <4.5 h after symptom recognition in unknown onset stroke if DWI–FLAIR mismatch Mechanical thrombectomy Based on guidelines published in 2019: • <6 h for anterior circulation LVO-related stroke • 6–24 h for anterior circulation LVO-related stroke with clinical/perfusion lesion–ischaemic core mismatch Awaiting updated guidelines for: • 0–24 h for anterior circulation LVO-related stroke with large core • 0–24 h for posterior circulation LVO-related stroke
Bridging strategies	Fibrinolysis with re-evaluation at PCI site (pharmaco-invasive strategy) recommended in patients who cannot get primary PCI within 2 h after the first medical contact or qualifying ECG	Bridging fibrinolysis recommended

CBF, cerebral blood flow; CT, computed tomography; MRI, magnetic resonance imaging; PCI, percutaneous coronary intervention; ECG, electrocardiogram; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; LVO, large-vessel occlusion.

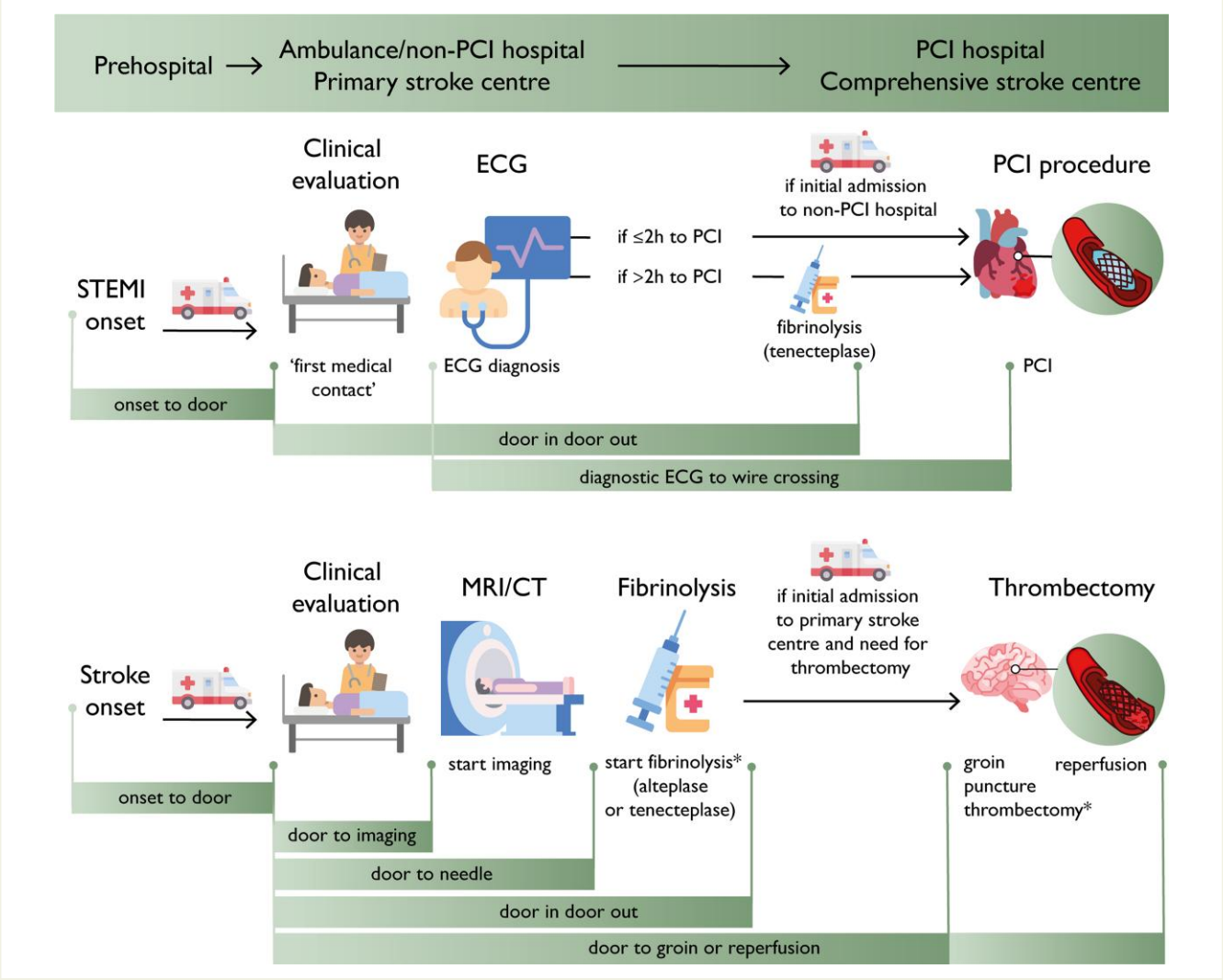

Figure 2 Diagnostic and therapeutic workflow in ST-elevation myocardial infarction and acute ischaemic stroke. Patients with ST-elevation myocardial infarction are transferred to either a hospital with or without facilities for percutaneous coronary intervention. After clinical evaluation and electrocardiogram diagnosis of ST-elevation myocardial infarction, patients will receive immediate treatment with percutaneous coronary intervention if time from electrocardiogram diagnosis to percutaneous coronary intervention initiation is 120 min or shorter. If a longer delay (>120 min) is expected (e.g. long transfer to percutaneous coronary intervention hospital), patients should receive fibrinolytic treatment and are scheduled to undergo percutaneous coronary intervention within 2–24 h after administration of fibrinolytic (pharmaco-invasive strategy) or rescue percutaneous coronary intervention if needed. Patients with acute ischaemic stroke are transferred to either a primary or comprehensive stroke centre. After a clinical assessment, patients undergo brain imaging (computed tomography or magnetic resonance), and based on time criteria and imaging findings, the decision to fibrinolytic treatment is made. If there is evidence for a large-vessel occlusion, and if other time and imaging criteria are fulfilled, the patient will undergo thrombectomy treatment (after transfer to the comprehensive stroke centre if first admitted to a primary stroke centre). *See *Table 1* for time windows and imaging criteria for reperfusion treatment. CT, computed tomography; ECG, electrocardiogram; MRI, magnetic resonance imaging; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction

Pharmacological reperfusion: differences in efficacy between ST-elevation myocardial infarction and acute ischaemic stroke

Current STEMI guidelines recommend the use of bolus fibrin–specific agents, especially tenecteplase.[14,15] A body weight–adjusted single bolus of tenecteplase (30–50 mg) was found to be equivalent to alteplase in reducing 30 days' mortality in STEMI and was associated with fewer non-cerebral bleedings (*Table 1*).[16] Current practice is to administer half-dose tenecteplase in patients ≥75 years to reduce the risk of intracranial haemorrhage (ICH). The recently published STREAM-2 trial in STEMI patients ≥60 years showed that a pharmaco-invasive treatment with half-dose tenecteplase (15–25 mg) was as effective as routine primary percutaneous coronary intervention (PCI).[17] However, the study failed to show a reduction in ICH, which was partly due to protocol violations (excess anticoagulation or uncontrolled hypertension). Still, major non-intracranial bleeding and blood transfusions were very rare. Whether half-dose tenecteplase will

become the preferred dose in all patients ≥60 years will require further study.

More than 10 years after the first successful studies of alteplase in STEMI, trials showed benefit of alteplase on functional outcome at 3 months in AIS patients treated within 3 h of stroke onset (*Table 1*).[18] Alteplase was the only approved fibrinolytic drug in AIS treatment for long, but prompted by studies in STEMI, increasing evidence supports the use of tenecteplase with higher degrees of reperfusion and clinical improvement at 24 h compared with alteplase[19] and higher rates of recanalization compared with alteplase.[20] Different meta-analyses of tenecteplase trials showed evidence of non-inferiority and superiority of tenecteplase compared with alteplase,[21,22] and non-inferiority was recently confirmed by results of the AcT trial[23] and TASTE-A trial.[24] Further studies of tenecteplase vs. alteplase in AIS are still ongoing (NCT02398656, NCT03181360), but based on the current evidence, the use of tenecteplase is already recommended for the treatment of AIS.[25]

The rise of mechanical reperfusion

In a review on this topic published in this journal in 2014, Widimsky *et al.*[26] suggested that mechanical reperfusion alone could become the preferred treatment of both STEMI and AIS. In the 10 years following this review, studies, however, have highlighted the need for a specific disease-tailored approach. First of all, differences in organ and vessel anatomy and function indeed demand a different mechanical intervention. The thick tunica media and adventitia in coronary arteries withstand the high forces and pressure delivered by balloon angioplasty or balloon-expandable stents, but a similar technique would lead to arterial injury and severe complications in the more fragile intracranial vessels.[27] Stent placement is permanent in coronary arteries, but only temporarily in intracranial arteries, since sacrificing small side branches is less well tolerated causing neurological dysfunction in the brain but has only minor effect on cardiac function.[27] Moreover, the need for pronounced antiplatelet treatment after stent placement also increases the risk of ICH, especially after fibrinolysis,[28] altogether making it a less attractive treatment option for AIS.

Primary PCI with drug-eluting stents is the therapy of choice in STEMI patients, if it can be performed by an experienced team within 2 h after the first medical contact or ECG diagnosis (*Figure 2*).[15] While systematic thrombectomy prior to stenting was the standard therapy for a while after the Thrombus Aspiration During Percutaneous Coronary Intervention in Acute Myocardial Infarction Study (TAPAS),[29] two larger trials demonstrated a lack of effect and even some harm of this strategy,[30,31] and, as a consequence, thrombectomy has been largely abandoned in primary PCI for STEMI. Bioresorbable vascular scaffolds have shown promising results in small early trials but are not available anymore due to their increased risk for scaffold thrombosis. In recent studies, complete revascularization by means of PCI of significant non-culprit lesions, performed either in the acute intervention, during or early after the index hospitalization, has shown clinical benefit.[32] A recent study suggested that a staged complete revascularization (Days 19–45) was non-inferior to immediate complete revascularization in the acute phase.[33] However, the increased risk of re-infarction or unplanned revascularization when deferring additional procedures in this study suggests that the optimal timing of the staged procedure still requires further study.

In AIS, mechanical reperfusion is performed using a stent retriever, direct aspiration method, or a combination of both. In the first technique, a self-deployable stent is expanded and retracted to remove the thrombus. The second technique applies suction directly to the thrombus.[34] Since most intracranial thrombi arise from a distant source (extracranial carotid artery atherosclerosis with artery-to-artery embolization or cardio-embolic in a setting of atrial fibrillation) in contrast to *in situ* thrombus formation in STEMI, permanent stenting of the intracranial occlusion site has no place in AIS. Even in the minority of stroke patients with *in situ* thrombosis due to intracranial atherosclerosis, studies found no benefit of elective PCI compared with aggressive antiplatelet therapy.[35–37]

Treatment eligibility for reperfusion treatment

In the Western world, around 80% of STEMI patients receive primary PCI and another 10% fibrinolysis as the initial treatment, leaving around 10% of all STEMI patients not receiving any reperfusion treatment. In the absence of contraindications, fibrinolytic treatment is still the therapy of choice for STEMI patients in remote or sparsely populated areas throughout the world.[38,39] In developing countries, streptokinase is the most frequently administered fibrinolytic for financial reasons. In these countries, primary PCI is usually reserved for private hospitals and affluent patients. In Western countries, personal and institutional economic benefits may also be a reason for an exclusive use of primary PCI.

In sharp contrast with the high treatment numbers in STEMI, only 16.6% of AIS patients received fibrinolytic therapy in 2020 according to a recent survey of a European population, but with great variation between countries (0%–62.4%).[40] The main reasons for not being treatment eligible are late presentation outside the classical time windows[41] or inability to report the exact onset time (e.g. due to aphasia, confusion, or night-time stroke onset during sleep),[42] but other reasons are the presence of non-disabling symptom or contraindications for fibrinolysis because of an increased bleeding risk. A history of STEMI in the past 3 weeks is considered a contraindication but not the simultaneous presence of a STEMI and AIS. Only 30% of AIS patients presents with an LVO potentially eligible for endovascular treatment,[43] and the number of patients receiving thrombectomy in a European population in 2020 is even lower (on average 7.1%).[40] Furthermore, most evidence for thrombectomy has been identified in patients with few comorbidities, and the treatment effect in frail patients remains largely unknown.[44] To increase these numbers, recent research has focused on expanding these time windows for reperfusion by improving symptom onset estimation, as well as organizing stroke care in collaborative networks.[45–50]

Time is muscle, time is brain, the benefit of reperfusion

Notwithstanding the popular and veracious dogma's 'time is muscle' and 'time is brain', other factors also influence the pace at which brain or heart tissue undergoes irreversible infarction. The quality of the collateral circulation influences final infarct size in both STEMI[51–53] and AIS[54] and might account for the variation in infarct progression between individuals (*Table 1*).

Nevertheless, with elapsing time, an increasing proportion of the ischaemic tissue will undergo infarction and irreversible necrosis.[1,2] The myocardium appears to be functionally less sensitive to immediate ischaemia than brain tissue, since an occlusion of 15–30 min can be tolerated without extensive myocardial dysfunction.[52,55] An equally sized lesion might have a different impact on myocardial vs. brain tissue:

necrosis of just a small part of the left ventricle might go clinically unnoticed, while a small lacunar brain infarct in the internal capsule or brainstem might result in overt hemiplegia.

The benefit of reperfusion therapy in STEMI is highly time dependent and maximal in the first hour after symptom onset (the so-called golden hour)[56,57] but remains present up till 12 h after symptom onset on average. In patients with signs of ongoing ischaemia, PCI may still be beneficial >12 h after onset.[58] Cases with evidence of ongoing ischaemia on ECG after >12 h are usually instances of a so-called stuttering infarction. These patients might report the onset of the first episode of chest pain as the onset of infarction rather than the last episode that caused persistent occlusion. In a large study of >40 000 STEMI patients treated within 6 h with lytic therapy, female sex was only borderline significantly associated with a higher 30 days' mortality in a multivariate analysis.[59] In most primary PCI surveys, higher death rates and more complications are reported in women. In one survey, the excess mortality was only seen in younger women, apparently not related to a longer reperfusion delay.[60]

In AIS, the highest chance of a good functional outcome can be reached with treatment in the first hour after onset and decreases with time, such that the risk of haemorrhagic complications typically offsets the benefits of fibrinolysis later than 4.5 h after onset.[61,62] Although the time window for endovascular treatment is longer, with current guidelines extending to 24 h for selected patients, the relationship between benefit and time remains.[63] In women, time to fibrinolysis is possibly longer, and this treatment is less often given than in men, although efficacy seems to be equal between sexes. Data on the use of thrombectomy in men vs. women are conflicting as women may present with longer onset-to-door times, but efficacy in terms of recanalization rates and 90 days' outcome seems to be similar.[10,64]

The fast and accurate identification of stroke patients by emergency medical service (EMS) personnel is critical for appropriate stroke care. Several scales have been developed and should be implemented in collaboration between EMS and stroke experts. Although clinical symptoms may vary between sexes, the diagnostic performance of the various scales to detect LVO is similar between women and men.[65] Guidelines advice that EMS leaders, in co-ordination with local, regional, and state agencies, and in consultation with medical authorities and local experts, should develop triage paradigms and protocols to ensure that patients with a known or suspected stroke are rapidly identified and assessed by use of a validated and standardized tool for stroke screening.[66]

Selecting the best treatment strategy

Primary PCI is the reperfusion treatment of choice in STEMI as it is more effective in recanalizing coronary vessels in comparison with fibrinolytic treatment and reduces the risk of ICH.[67] If primary PCI is impossible within a time window up to 2 h after the first medical contact or diagnostic ECG, immediate administration of a fibrinolytic and transfer to a PCI hospital are indicated (*Figure 2*).[14,15] In late presenters (>6 h after symptom onset), fibrinolytic therapy is no longer indicated due to lack of efficacy (more cross-linked fibrin) and risk of bleeding. Thrombus or infarct location does not necessarily influence the success of primary PCI, but outcomes after PCI are worse in patients with larger infarcts, such as after a left anterior descending coronary artery STEMI.[68]

For patients with AIS, two treatment strategies like those in STEMI are currently available: intravenous fibrinolysis and thrombectomy. In the past, a clinical need for thrombectomy was clearly established as the effect of pharmacological reperfusion was often insufficient to achieve recanalization in patients with LVO.[69] In the Western world, all primary stroke centres offer fibrinolytic treatment, but mechanical thrombectomy is often only available in larger hospitals, the so-called comprehensive stroke centres. The optimal strategy for patient triage (mothership approach with direct transfer to a comprehensive stroke centre vs. a drip-and-ship method with initial admission to a primary stroke centre for fibrinolysis followed by transfer to a comprehensive stroke centre for thrombectomy) should be a well-considered decision to minimize treatment delays, which depends on country-specific geographic and demographic characteristics (*Figure 2*).[70] Mirroring prehospital fibrinolysis in STEMI, mobile stroke units with CT equipment and an experienced stroke team on board allow rapid diagnosis, treatment initiation with fibrinolysis, and improved triage to either a primary or comprehensive stroke centres.[71]

Recent trials extended the treatment with fibrinolysis from 4.5 h after known onset or last seen well[18,72] to a known window of up to 9 h and an unknown time window based on the presence of imaging mismatch profiles.[47,48] Although more effective than fibrinolysis alone,[73] thrombectomy is only a proven beneficial therapeutic option in patients with an LVO (30% of all AIS patients).[43] Similar to fibrinolysis, initial evidence only supported thrombectomy in anterior circulation AIS up to 6 h after known stroke onset,[73] but recent trials extended this treatment window up to 24 h and to those with unknown stroke onset.[45,46] In addition to the evidence in anterior circulation AIS, there is emerging evidence for thrombectomy in patients with basilar artery occlusion and moderate to severe stroke severity up to 24 h after onset.[74,75] Although only 10% of stroke patients present with posterior circulation AIS, this is relevant given the disastrous consequences and high mortality of basilar artery occlusion.[76]

In contrast to STEMI, imaging plays a critical role in the management of AIS. Non-contrast-enhanced computed tomography is necessary to exclude haemorrhagic stroke. If clinical symptoms suggest the presence of an LVO [internal carotid artery, first (M1) or second (M2) segment of the medial cerebral artery], CT angiography (of the aortic arch, cervical and intracranial arteries) is essential to confirm the clinical suspicion. Non-contrast-enhanced computed tomography and CT angiography suffice in patients presenting in the classical time window for fibrinolysis (<4.5 h) or thrombectomy (<6 h) to guide treatment decisions, but in late presenters or unknown onset stroke, additional imaging has initially been required to discern patients who can still benefit from reperfusion treatment from those in whom treatment would be futile or even dangerous due to the risk of (haemorrhagic) complications (*Figure 3*).[61,62,77–79] The DWI–fluid-attenuated inversion recovery (FLAIR) mismatch can identify fibrinolysis-eligible patients in the unknown time window.[48,80] Another MRI-based mismatch paradigm, the perfusion-weighted imaging (PWI)–DWI mismatch, identifies penumbral tissue (*Table 1*) by differentiating the area of critical hypoperfusion (on PWI) from the ischaemic core (on DWI, tissue destined to undergo irreversible infarction). Alternatively, CT perfusion can be used to estimate both the ischaemic core and area of hypoperfusion.[81] Specific penumbral mismatch criteria were successfully defined and implemented in trials to select patients for treatment with fibrinolysis (≤9 h) or thrombectomy (≤24 h) in the late or unknown time window.[45–47,49] These principles have been adopted by international guidelines from the European Stroke Organisation[82,83] and American Stroke Association[66] but are expected to be updated in

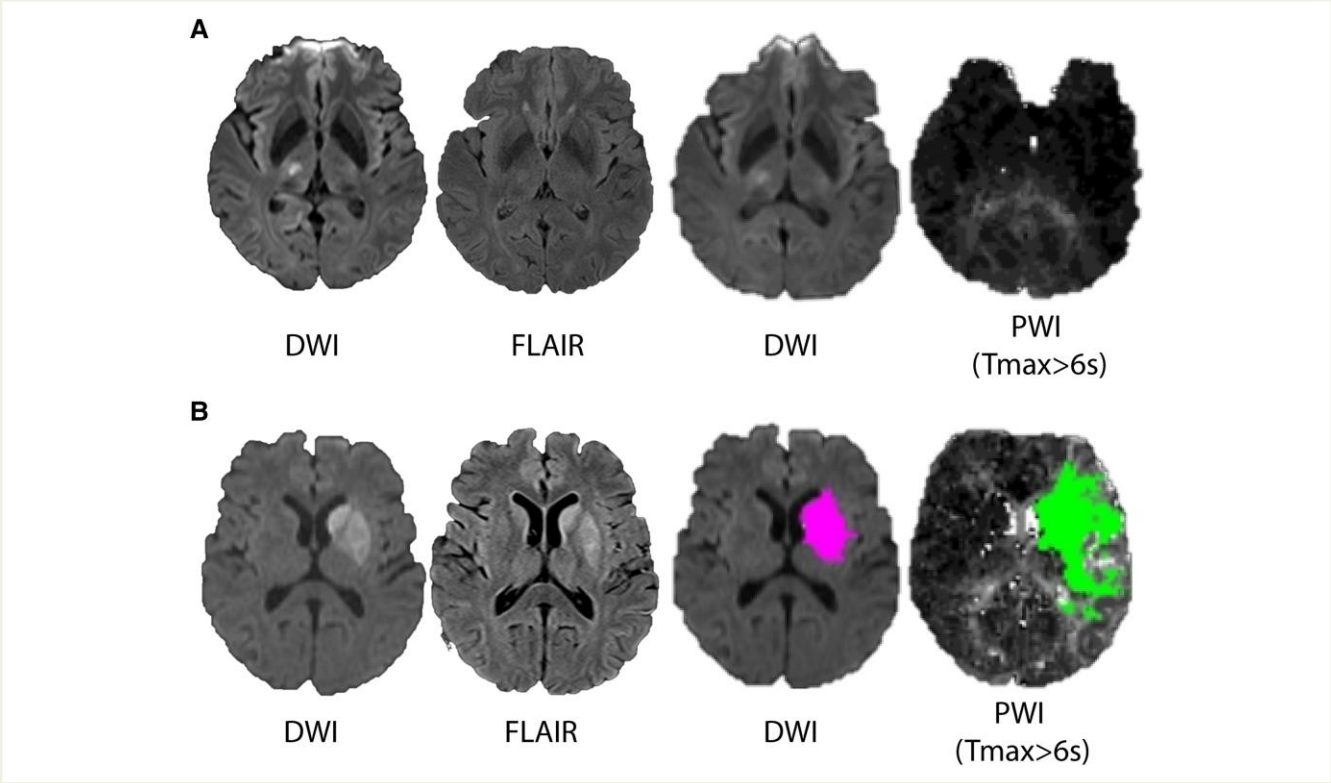

Figure 3 Imaging examples of the mismatch concepts in acute ischaemic stroke: a patient (*A*) with a diffusion-weighted imaging–fluid-attenuated inversion recovery mismatch, without perfusion lesion–ischaemic core mismatch, and a patient (*B*) without diffusion-weighted imaging–fluid-attenuated inversion recovery mismatch, with perfusion lesion–ischaemic core mismatch assessed by magnetic resonance diffusion-weighted imaging and perfusion-weighted imaging. The diffusion-weighted imaging–fluid-attenuated inversion recovery mismatch is based on visual assessment of the diffusion-weighted imaging and fluid-attenuated inversion recovery scan. The perfusion lesion–ischaemic core mismatch can be assessed on perfusion computed tomography or magnetic resonance imaging and requires post-processing of perfusion imaging to derive perfusion parameters. In the magnetic resonance imaging example above, the core lesion is calculated based on the volume with an apparent diffusion coefficient $<620 \times 10^{-6}$ mm^2/s. The perfusion lesion consists of tissue with a time to the maximum of the residue function >6 s and is visualized in green on the perfusion-weighted imaging scan. DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; Tmax, time to the maximum of the residue function. Figure adapted with permission from[112]

the future based on the results of recent trials, which have shown a benefit of thrombectomy in patients with large ischaemic cores, especially in early time windows, thereby reducing the role of advanced imaging in selecting patients with LVO eligible for thrombectomy (*Table 1*).[84]

An approach taking AIS patients directly to the angiography suite (DTAS) without prior cerebral imaging has also been the subject of clinical trials. In contrast to STEMI in which most patients have a thrombotic occlusion, only a minority of AIS patients will have an underlying LVO, resulting in a significant proportion of patients undergoing futile transport to the angio suite. However, a DTAS approach in patients with suspected LVO has been shown to decrease door to reperfusion time and improve functional outcome.[85]

To bridge or not to bridge

A pharmaco-invasive strategy in which fibrinolytic therapy is administered in the ambulance or community hospital with re-evaluation of the perfusion status on arrival in the PCI hospital has been shown to be beneficial in early presenters when it is unlikely that primary PCI can be performed within 1 h after the first medical contact.[86] When lytic therapy was unsuccessful (<50% ST-segment resolution and persistent chest pain or discomfort), rescue PCI was performed. If successful (≥50% ST-segment resolution, improvement of clinical status), no immediate but a delayed angiography (with PCI in most cases) was performed. Such a strategy is now recommended by guidelines if it is unlikely that the patient could get primary PCI within 2 h after the first medical contact or diagnostic ECG.[14,15] Fibrinolytic drugs lead to early platelet activation and a higher risk of subacute stent thrombosis, possibly interfering with the success of immediate PCI after administration of the fibrinolytic.[87] The current co-administration of $P2Y_{12}$ antagonists and enoxaparin largely neutralizes this prothrombotic effect. As a result, rescue PCI can be avoided in about two-thirds of the patients but, if needed, safely performed.[86] Because of this improved antithrombotic co-therapy, there is also renewed interest in studying facilitated PCI.[88] In a facilitated PCI strategy (not recommended by current guidelines), the effect of fibrinolysis is not evaluated on arrival at the PCI hospital before proceeding with immediate PCI. A recent trial with a bolus staphylokinase before PCI showed favourable efficacy and safety results in a population ≤75 years.[89]

Fibrinolysis in patients with LVO AIS fails to recanalize the obstructed vessel in almost 90% of the patients[69,90] and should therefore be followed immediately by endovascular treatment, not awaiting the effect of fibrinolysis (similar to the facilitated PCI approach in STEMI).[91] Via an endovascular approach, the effect of fibrinolysis can

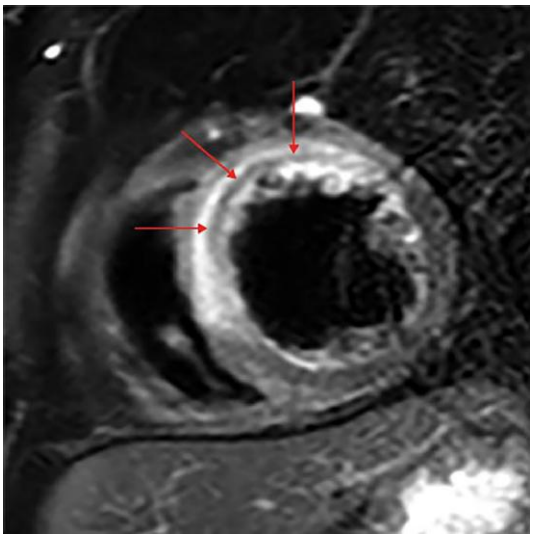

Figure 4 Example of an intramyocardial haemorrhage after primary percutaneous coronary intervention on T_2-weighted magnetic resonance imaging. The hyper-intense region represents myocardial oedema, corresponding to the area at risk of infarction. The hypo-intense sub-endocardial rim corresponds to the area with intramyocardial haemorrhage (arrows)

be assessed and, in most cases, results in documentation of persistent vessel occlusion leading to subsequent thrombectomy. Vice versa, since evidence about the treatment benefit of thrombectomy was studied in a setting with preceding fibrinolysis, guidelines recommend lytic therapy before thrombectomy in fibrinolysis-eligible patients.[82]

Bridging fibrinolysis might be advantageous since infusion of fibrinolytics can be initiated earlier after AIS onset[61] and might even obviate the need for thrombectomy by achieving recanalization before the start of the endovascular procedure,[92] although these numbers are small (<10%).[90] Fibrinolytic therapy could also facilitate mechanical extraction by softening of the thrombus, but might in adverse induce clot fragmentation and distal embolization.[93] Recanalization of small vessels that are inaccessible for thrombectomy fully relies on fibrinolytic treatment.[94]

Similar to STEMI, the question rose to assess a potential benefit of direct thrombectomy alone in comparison to a bridging fibrinolysis strategy in patients with an LVO. Two trials were able to show non-inferiority of direct thrombectomy (without preceding fibrinolytic treatment), but the results were influenced by liberally chosen non-inferiority margins as well as a long delay to fibrinolysis in the standard treatment. Furthermore, these trials were conducted in an exclusively Asian population with potentially higher rates of intracranial atherosclerosis, possibly decreasing the efficacy in the bridging lytic arm.[95,96] Other trials failed to show non-inferiority of direct thrombectomy.[97–99] A recent meta-analysis concluded that bridging fibrinolytic therapy for patients presenting within the conventional time window is beneficial compared with thrombectomy alone for achieving functional independence and successful reperfusion and is associated with lower 90 days' mortality and similar odds of symptomatic ICH, and as such, bridging fibrinolysis should be administered in eligible patients before mechanical thrombectomy.[66,83,100] However, the beneficial effect of fibrinolysis may be time dependent with only a favourable shift towards better outcomes within 2 h and 20 min after onset.[101] Beyond the conventional 4.5 h time window, the role of bridging fibrinolysis with tenecteplase was studied in patients presenting up to 24 h after presumed stroke onset with an LVO. This approach did not result in better functional outcomes in the overall population.[102]

It is of interest to note that also in STEMI patients treated with primary PCI, intramyocardial bleedings have been documented with MRI in a significant proportion of patients (around 25%; *Figure 4*).[103] These bleedings may impair recovery of left ventricular function and result in heart failure. To what extent bridging fibrinolysis increases the risk of intramyocardial bleeding is unknown.

Ongoing and future clinical research

Many patients eligible for primary PCI do not get this treatment within the recommended time window of 2 h after ECG diagnosis (or the first medical contact), and in many regions, primary PCI is just not available. In a recent large US registry performed in 648 hospitals, only 17% of STEMI patients underwent primary PCI within 2 h when inter-hospital transfer was needed,[104] and mortality was more than three times higher in those who could not undergo PCI within 2 h after arrival in the community hospital.[105] In contrast with STEMI, only a minority of patients presenting with AIS are candidates for reperfusion therapy due to contraindications or late presentation. Patients presenting with AIS should be evaluated in a timely manner and admitted to a centre capable of delivering at least acute fibrinolysis. Those eligible for thrombectomy based on vessel imaging require fast transfer to a thrombectomy-capable centre with high procedural volumes.[106] Strategies to increase treatment eligibility should therefore be the focus of future research. Artificial intelligence (AI) could be helpful in this regard as it may improve the interpretation of ECG. If this could lead to a faster and better identification of patients suitable for reperfusion is currently unknown and should be studied in the future. Artificial intelligence–based tools are already being used to guide AIS management as they allow faster identification of diagnostic and prognostic imaging features. Future applications of AI may improve the clinical assessment and prognostication of the acute event.

Despite successful mechanical reperfusion strategies in both STEMI and AIS, recanalization of the obstructed main artery does not always translate into successful reperfusion at a microvascular level. In about half of the patients with STEMI, PCI might cause distal embolization resulting in failed microvascular reperfusion, impeding full functional myocardial recovery. However, low-dose intracoronary alteplase infused early after reperfusion did not reduce microvascular obstruction[107] and might even be harmful leading to increased microvascular obstruction, myocardial haemorrhage, and reduced left ventricular ejection fraction in patients presenting with an ischaemic time >4 h.[108]

Distal embolization is just one of the multiple causes of ischaemia–reperfusion injury.[109,110] Acute inflammatory injury also plays a pivotal role and is a topic of ongoing research. In contrast to some preclinical models of AIS, evidence of reperfusion injury in human studies remains limited for AIS as imaging of this concept is challenging.[111] Several topics of ongoing and future research to improve the benefit of reperfusion are summarized in *Table 2*.[17,71,84,85,88,100,106–110,112–118]

Limitations

This review has focused on recent advances made in the diagnosis and therapeutic application of reperfusion in STEMI and AIS. Reperfusion

Table 2 Ongoing and future clinical research

STEMI	AIS
Shorten ischaemic delay times	
Collaborative networking at regional level	Collaborative networking at regional level
Facilitated PCI with reduced-dose fibrinolysis[88]	Drip and ship vs. mothership approach[106]
	Direct transfer to angio suite, mobile stroke unit[71,85]
Artificial intelligence for ECG analysis, diagnosis, and clinical assessment	Artificial intelligence to assist in imaging assessment and diagnosis as well as prediction of treatment response and outcomes
Expand eligibility for reperfusion treatment	
	Expanding criteria for thrombectomy eligibility[84]
	Imaging- rather than time-based treatment eligibility criteria[112]
Reduce reperfusion failure and prevent side effects	
Peri-procedural low-dose intracoronary fibrinolysis to prevent microvascular obstruction[107,108a]	Adjunct low-dose intra-arterial fibrinolysis after (incomplete) thrombectomy[113b]
Reduce acute inflammatory injury[109,110,114,115]	Neuroprotective strategies[116,117]
Reduced-dose tenecteplase in elderly[17]	Direct thrombectomy alone[100,118]
Prevent intramyocardial bleeding and heart failure	

[a]NCT02894138, NCT03998319, and NCT03335839.
[b]NCT05499832.

involves complex pathophysiological processes at cellular level that were not covered in this review. Research in these domains may lead to new therapies that may enhance the benefit of reperfusion in the future.

Conclusions

Although an occlusive arterial thrombus is the immediate cause of STEMI and AIS, the diagnostic and therapeutic approaches have become increasingly different. The need for imaging in AIS has made the selection and initiation of treatment more complex, but findings from recent trials suggest that a broader group of patients may benefit from thrombectomy than indicated in current guidelines. While there are several ways to improve the benefit of reperfusion treatment, facilitating collaborative networking by far remains the best way to shorten the ischaemic delay times and hence the benefit of reperfusion in both STEMI and IAS.

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Supplementary data

Supplementary data are not available at *European Heart Journal* online.

Declarations

Disclosure of Interest

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References

1. Reimer KA, Lowe JE, Rasmussen MM, Jennings RB. The wavefront phenomenon of ischemic cell death. 1. Myocardial infarct size vs duration of coronary occlusion in dogs. *Circulation* 1977;**56**:786–94. https://doi.org/10.1161/01.CIR.56.5.786
2. Saver JL. Time is brain—quantified. *Stroke* 2006;**37**:263–6. https://doi.org/10.1161/01.STR.0000196957.55928.ab
3. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, *et al.* Fourth universal definition of myocardial infarction (2018). *Eur Heart J* 2019;**40**:237–69. https://doi.org/10.1093/eurheartj/ehy462
4. Baaten CCFMJ, Nagy M, Bergmeier W, Spronk HMH, van der Meijden PEJ. Platelet biology and function: plaque erosion vs. rupture. *Eur Heart J* 2024;**45**:18–31. https://doi.org/10.1093/eurheartj/ehad720
5. Brush JE Jr, Chaudhry SI, Dreyer RP, D'Onofrio G, Greene EJ, Hajduk AM, *et al.* Sex differences in symptom complexity and door-to-balloon time in patients with ST-elevation myocardial infarction. *Am J Cardiol* 2023;**197**:101–7. https://doi.org/10.1016/j.amjcard.2023.03.009
6. Tsao CW, Aday AW, Almarzooq ZI, Alonso A, Beaton AZ, Bittencourt MS, *et al.* Heart disease and stroke statistics—2022 update: a report from the American Heart Association. *Circulation* 2022;**145**:e153–639. https://doi.org/10.1161/CIR.0000000000001052

7. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, *et al.* Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993;**24**:35–41. https://doi.org/10.1161/01.STR.24.1.35
8. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, *et al.* Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol* 2013;**12**:822–38. https://doi.org/10.1016/S1474-4422(13)70124-8
9. Ali M, van Os HJA, van der Weerd N, Schoones JW, Heymans MW, Kruyt ND, *et al.* Sex differences in presentation of stroke: a systematic review and meta-analysis. *Stroke* 2022;**53**:345–54. https://doi.org/10.1161/STROKEAHA.120.034040
10. Ospel J, Singh N, Ganesh A, Goyal M. Sex and gender differences in stroke and their practical implications in acute care. *J Stroke* 2023;**25**:16–25. https://doi.org/10.5853/jos.2022.04077
11. Wardlaw JM. Radiology of stroke. *J Neurol Neurosurg Psychiatry* 2001;**70**:I7–11. https://doi.org/10.1136/jnnp.70.suppl_1.i7
12. Lutsep HL, Albers GW, DeCrespigny A, Kamat GN, Marks MP, Moseley ME. Clinical utility of diffusion-weighted magnetic resonance imaging in the assessment of ischemic stroke. *Ann Neurol* 1997;**41**:574–80. https://doi.org/10.1002/ana.410410505
13. Lansberg MG, Albers GW, Beaulieu C, Marks MP. Comparison of diffusion-weighted MRI and CT in acute stroke. *Neurology* 2000;**54**:1557–61. https://doi.org/10.1212/WNL.54.8.1557
14. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, *et al.* 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;**61**:e78–140. https://doi.org/10.1016/j.jacc.2012.11.019
15. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, *et al.* 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J* 2023;**44**:3720–826. https://doi.org/10.1093/eurheartj/ehad191
16. Van De Werf F, Adgey J, Ardissino D, Armstrong PW, Aylward P, Barbash G, *et al.* Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. *Lancet* 1999;**354**:716–22. https://doi.org/10.1016/S0140-6736(99)07403-6
17. Van de Werf F, Ristic AD, Averkov OV, Arias-Mendoza A, Lambert Y, Kerr Saraiva JF, *et al.* STREAM-2: Half-Dose Tenecteplase or Primary Percutaneous Coronary Intervention in Older Patients With ST-Segment-Elevation Myocardial Infarction: a randomized, open-label trial. *Circulation* 2023;**148**:753–64. https://doi.org/10.1161/CIRCULATIONAHA.123.064521
18. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;**333**:1581–7. https://doi.org/10.1056/NEJM199512143332401
19. Parsons M, Spratt N, Bivard A, Campbell B, Chung K, Miteff F, *et al.* A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. *N Engl J Med* 2012;**366**:1099–107. https://doi.org/10.1056/NEJMoa1109842
20. Campbell BCV, Mitchell PJ, Churilov L, Yassi N, Kleinig TJ, Dowling RJ, *et al.* Tenecteplase versus alteplase before thrombectomy for ischemic stroke. *N Engl J Med* 2018;**378**:1573–82. https://doi.org/10.1056/NEJMoa1716405
21. Burgos AM, Saver JL. Evidence that tenecteplase is noninferior to alteplase for acute ischemic stroke: meta-analysis of 5 randomized trials. *Stroke* 2019;**50**:2156–62. https://doi.org/10.1161/STROKEAHA.119.025080
22. Katsanos AH, Safouris A, Sarraj A, Magoufis G, Leker RR, Khatri P, *et al.* Intravenous thrombolysis with tenecteplase in patients with large vessel occlusions: systematic review and meta-analysis. *Stroke* 2021;**52**:308–12. https://doi.org/10.1161/STROKEAHA.120.030220
23. Menon BK, Buck BH, Singh N, Deschaintre Y, Almekhlafi MA, Coutts SB, *et al.* Intravenous tenecteplase compared with alteplase for acute ischaemic stroke in Canada (AcT): a pragmatic, multicentre, open-label, registry-linked, randomised, controlled, non-inferiority trial. *Lancet* 2022;**400**:161–9. https://doi.org/10.1016/S0140-6736(22)01054-6
24. Bivard A, Zhao H, Churilov L, Campbell BCV, Coote S, Yassi N, *et al.* Comparison of tenecteplase with alteplase for the early treatment of ischaemic stroke in the Melbourne Mobile Stroke Unit (TASTE-A): a phase 2, randomised, open-label trial. *Lancet Neurol* 2022;**21**:520–7. https://doi.org/10.1016/S1474-4422(22)00171-5
25. Alamowitch S, Turc G, Palaiodimou L, Bivard A, Cameron A, De Marchis GM, *et al.* European Stroke Organisation (ESO) expedited recommendation on tenecteplase for acute ischaemic stroke. *Eur Stroke J* 2023;**8**:8–54. https://doi.org/10.1177/23969873221150022
26. Widimsky P, Coram R, Abou-Chebl A. Reperfusion therapy of acute ischaemic stroke and acute myocardial infarction: similarities and differences. *Eur Heart J* 2014;**35**:147–55. https://doi.org/10.1093/eurheartj/eht409
27. Carvalho de Campos Martins E, Luiz de Melo Bernardi F, Junior OT M, Micari A, Hopkins LN, Cremonesi A, *et al.* Similarities and differences between primary percutaneous coronary intervention and mechanical thrombectomy. *JACC Cardiovasc Interv* 2020;**13**:1683–96. https://doi.org/10.1016/j.jcin.2020.03.055
28. Zinkstok SM, Roos YB; ARTIS investigators. Early administration of aspirin in patients treated with alteplase for acute ischaemic stroke: a randomised controlled trial. *Lancet* 2012;**380**:731–7. https://doi.org/10.1016/S0140-6736(12)60949-0
29. Svilaas T, Vlaar PJ, van der Horst IC, Diercks GF, de Smet BJ, van den Heuvel AF, *et al.* Thrombus aspiration during primary percutaneous coronary intervention. *N Engl J Med* 2008;**358**:557–67. https://doi.org/10.1056/NEJMoa0706416
30. Frobert O, Lagerqvist B, Olivecrona GK, Omerovic E, Gudnason T, Maeng M, *et al.* Thrombus aspiration during ST-segment elevation myocardial infarction. *N Engl J Med* 2013;**369**:1587–97. https://doi.org/10.1056/NEJMoa1308789
31. Jolly SS, Cairns JA, Yusuf S, Meeks B, Pogue J, Rokoss MJ, *et al.* Randomized trial of primary PCI with or without routine manual thrombectomy. *N Engl J Med* 2015;**372**:1389–98. https://doi.org/10.1056/NEJMoa1415098
32. Mehta SR, Wood DA, Storey RF, Mehran R, Bainey KR, Nguyen H, *et al.* Complete revascularization with multivessel PCI for myocardial infarction. *N Engl J Med* 2019;**381**:1411–21. https://doi.org/10.1056/NEJMoa1907775
33. Stahli BE, Varbella F, Linke A, Schwarz B, Felix SB, Seiffert M, *et al.* Timing of complete revascularization with multivessel PCI for myocardial infarction. *N Engl J Med* 2023;**389**:1368–79. https://doi.org/10.1056/NEJMoa2307823
34. Kang D-H, Park J. Endovascular stroke therapy focused on stent retriever thrombectomy and direct clot aspiration: historical review and modern application. *J Korean Neurosurg Soc* 2017;**60**:335–47. https://doi.org/10.3340/jkns.2016.0809.005
35. Derdeyn CP, Chimowitz MI, Lynn MJ, Fiorella D, Turan TN, Janis LS, *et al.* Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): the final results of a randomised trial. *Lancet* 2014;**383**:333–41. https://doi.org/10.1016/S0140-6736(13)62038-3
36. Zaidat OO, Fitzsimmons BF, Woodward BK, Wang Z, Killer-Oberpfalzer M, Wakhloo A, *et al.* Effect of a balloon-expandable intracranial stent vs medical therapy on risk of stroke in patients with symptomatic intracranial stenosis: the VISSIT randomized clinical trial. *JAMA* 2015;**313**:1240–8. https://doi.org/10.1001/jama.2015.1693
37. Gao P, Wang T, Wang D, Liebeskind DS, Shi H, Li T, *et al.* Effect of stenting plus medical therapy vs medical therapy alone on risk of stroke and death in patients with symptomatic intracranial stenosis: the CASSISS randomized clinical trial. *JAMA* 2022;**328**:534–42. https://doi.org/10.1001/jama.2022.12000
38. Arnesen JS, Strom KH, Bonaa KH, Wiseth R. Treatment of ST-elevation myocardial infarction—an observational study. *Tidsskr Nor Laegeforen* 2019;**139**:1654–1658. https://doi.org/10.4045/tidsskr.18.0928
39. Kamona A, Cunningham S, Addison B, Rushworth GF, Call A, Bloe C, *et al.* Comparing ST-segment elevation myocardial infarction care between patients residing in central and remote locations: a retrospective case series. *Rural Remote Health* 2018;**18**:4618. https://doi.org/10.22605/RRH4618
40. Aguiar de Sousa D, Wilkie A, Norrving B, Macey C, Bassetti C, Tiu C, *et al.* Delivery of acute ischaemic stroke treatments in the European region in 2019 and 2020. *Eur Stroke J* 2023;**8**:618–28. https://doi.org/10.1177/23969873231186042
41. Kwan J, Hand P, Sandercock P. A systematic review of barriers to delivery of thrombolysis for acute stroke. *Age Ageing* 2004;**33**:116–21. https://doi.org/10.1093/ageing/afh064
42. Mackey J, Kleindorfer D, Sucharew H, Moomaw CJ, Kissela BM, Alwell K, *et al.* Population-based study of wake-up strokes. *Neurology* 2011;**76**:1662–7. https://doi.org/10.1212/WNL.0b013e318219fb30
43. Lakomkin N, Dhamoon M, Carroll K, Singh IP, Tuhrim S, Lee J, *et al.* Prevalence of large vessel occlusion in patients presenting with acute ischemic stroke: a 10-year systematic review of the literature. *J Neurointerv Surg* 2019;**11**:241–5. https://doi.org/10.1136/neurintsurg-2018-014239
44. Tiainen M, Martinez-Majander N, Virtanen P, Raty S, Strbian D. Clinical frailty and outcome after mechanical thrombectomy for stroke in patients aged ≥80 years. *J Stroke Cerebrovasc Dis* 2022;**31**:106816. https://doi.org/10.1016/j.jstrokecerebrovasdis.2022.106816
45. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, *et al.* Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med* 2018;**378**:708–18. https://doi.org/10.1056/NEJMoa1713973
46. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, *et al.* Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med* 2018;**378**:11–21. https://doi.org/10.1056/NEJMoa1706442
47. Ma H, Campbell BCV, Parsons MW, Churilov L, Levi CR, Hsu C, *et al.* Thrombolysis guided by perfusion imaging up to 9 hours after onset of stroke. *N Engl J Med* 2019;**380**:1795–803. https://doi.org/10.1056/NEJMoa1813046
48. Thomalla G, Simonsen CZ, Boutitie F, Andersen G, Berthezene Y, Cheng B, *et al.* MRI-guided thrombolysis for stroke with unknown time of onset. *N Engl J Med* 2018;**379**:611–22. https://doi.org/10.1056/NEJMoa1804355
49. Ringleb P, Bendszus M, Bluhmki E, Donnan G, Eschenfelder C, Fatar M, *et al.* Extending the time window for intravenous thrombolysis in acute ischemic stroke using magnetic resonance imaging-based patient selection. *Int J Stroke* 2019;**14**:483–90. https://doi.org/10.1177/1747493019840938
50. Koga M, Yamamoto H, Inoue M, Asakura K, Aoki J, Hamasaki T, *et al.* Thrombolysis with alteplase at 0.6 mg/kg for stroke with unknown time of onset: a randomized controlled trial. *Stroke* 2020;**51**:1530–8. https://doi.org/10.1161/STROKEAHA.119.028127

51. Flameng W, Lesaffre E, Vanhaecke J. Determinants of infarct size in non-human primates. *Basic Res Cardiol* 1990;**85**:392–403. https://doi.org/10.1007/BF01907131
52. Reimer KA, Vander Heide RS, Richard VJ. Reperfusion in acute myocardial infarction: effect of timing and modulating factors in experimental models. *Am J Cardiol* 1993;**72**: 13G–21G. https://doi.org/10.1016/0002-9149(93)90102-I
53. Christian TF, Schwartz RS, Gibbons RJ. Determinants of infarct size in reperfusion therapy for acute myocardial infarction. *Circulation* 1992;**86**:81–90. https://doi.org/10.1161/01.CIR.86.1.81
54. Jung S, Wiest R, Gralla J, McKinley R, Mattle H, Liebeskind D. Relevance of the cerebral collateral circulation in ischaemic stroke: time is brain, but collaterals set the pace. *Swiss Med Wkly* 2017;**147**:w14538. https://doi.org/10.4414/smw.2017.14538
55. Schaper W, Binz K, Sass S, Winkler B. Influence of collateral blood flow and of variations in MVO2 on tissue-ATP content in ischemic and infarcted myocardium. *J Mol Cell Cardiol* 1987;**19**:19–37. https://doi.org/10.1016/S0022-2828(87)80542-4
56. Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet* 1996;**348**:771–5. https://doi.org/10.1016/S0140-6736(96)02514-7
57. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). *Lancet* 1986;**1**:397–402. https://doi.org/10.1016/S0140-6736(86)92368-8
58. Schomig A, Mehilli J, Antoniucci D, Ndrepepa G, Markwardt C, Di Pede F, *et al.* Mechanical reperfusion in patients with acute myocardial infarction presenting more than 12 hours from symptom onset: a randomized controlled trial. *JAMA* 2005;**293**: 2865–72. https://doi.org/10.1001/jama.293.23.2865
59. Lee KL, Woodlief LH, Topol EJ, Weaver WD, Betriu A, Col J, *et al.* Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction. Results from an international trial of 41,021 patients. *Circulation* 1995;**91**:1659–68. https://doi.org/10.1161/01.CIR.91.6.1659
60. Cenko E, Yoon J, Kedev S, Stankovic G, Vasiljevic Z, Krljanac G, *et al.* Sex differences in outcomes after STEMI: effect modification by treatment strategy and age. *JAMA Intern Med* 2018;**178**:632–9. https://doi.org/10.1001/jamainternmed.2018.0514
61. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, *et al.* Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet* 2014;**384**:1929–35. https://doi.org/10.1016/S0140-6736(14)60584-5
62. Hacke W, Donnan G, Fieschi C, Kaste M, von Kummer R, Broderick JP, *et al.* Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet* 2004;**363**:768–74. https://doi.org/10.1016/S0140-6736(04)15692-4
63. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CB, Dippel DW, *et al.* Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. *JAMA* 2016;**316**:1279–88. https://doi.org/10.1001/jama.2016.13647
64. Ali M, van der Meij A, van Os HJA, Ali M, Van Zwet EW, Spaander FHM, *et al.* Sex differences in onset to hospital arrival time, prestroke disability, and clinical symptoms in patients with a large vessel occlusion: a MR CLEAN Registry substudy. *J Neurointerv Surg* 2023;**15**:e255–61. https://doi.org/10.1136/jnis-2022-019670
65. Ali M, Dekker L, Daems JD, Ali M, van Zwet EW, Steyerberg EW, *et al.* Sex differences in prehospital identification of large vessel occlusion in patients with suspected stroke. *Stroke* 2024;**55**:548–54. https://doi.org/10.1161/STROKEAHA.123.044898
66. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, *et al.* Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2019;**50**:e344–418. https://doi.org/10.1161/STR.0000000000000211
67. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003;**361**:13–20. https://doi.org/10.1016/S0140-6736(03)12113-7
68. Reindl M, Holzknecht M, Tiller C, Lechner I, Schiestl M, Simma F, *et al.* Impact of infarct location and size on clinical outcome after ST-elevation myocardial infarction treated by primary percutaneous coronary intervention. *Int J Cardiol* 2020;**301**:14–20. https://doi.org/10.1016/j.ijcard.2019.11.123
69. Riedel CH, Zimmermann P, Jensen-Kondering U, Stingele R, Deuschl G, Jansen O. The importance of size: successful recanalization by intravenous thrombolysis in acute anterior stroke depends on thrombus length. *Stroke* 2011;**42**:1775–7. https://doi.org/10.1161/STROKEAHA.110.609693
70. Ramos A, Guerrero WR, Perez de la Ossa N. Prehospital stroke triage. *Neurology* 2021;**97**:S25–33. https://doi.org/10.1212/WNL.0000000000012792
71. Walter S, Audebert HJ, Katsanos AH, Larsen K, Sacco S, Steiner T, *et al.* European Stroke Organisation (ESO) guidelines on mobile stroke units for prehospital stroke management. *Eur Stroke J* 2022;**7**:XXVII–LIX. https://doi.org/10.1177/23969873221079413
72. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, *et al.* Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008;**359**: 1317–29. https://doi.org/10.1056/NEJMoa0804656
73. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, *et al.* Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet* 2016;**387**:1723–31. https://doi.org/10.1016/S0140-6736(16)00163-X
74. Jovin TG, Li C, Wu L, Wu C, Chen J, Jiang C, *et al.* Trial of thrombectomy 6 to 24 hours after stroke due to basilar-artery occlusion. *N Engl J Med* 2022;**387**:1373–84. https://doi.org/10.1056/NEJMoa2207576
75. Tao C, Nogueira RG, Zhu Y, Sun J, Han H, Yuan G, *et al.* Trial of endovascular treatment of acute basilar-artery occlusion. *N Engl J Med* 2022;**387**:1361–72. https://doi.org/10.1056/NEJMoa2206317
76. Mattle HP, Arnold M, Lindsberg PJ, Schonewille WJ, Schroth G. Basilar artery occlusion. *Lancet Neurol* 2011;**10**:1002–14. https://doi.org/10.1016/S1474-4422(11)70229-0
77. Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D, Grotta JC, *et al.* Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet* 2010;**375**:1695–703. https://doi.org/10.1016/S0140-6736(10)60491-6
78. Mlynash M, Lansberg MG, De Silva DA, Lee J, Christensen S, Straka M, *et al.* Refining the definition of the malignant profile: insights from the DEFUSE-EPITHET pooled data set. *Stroke* 2011;**42**:1270–5. https://doi.org/10.1161/STROKEAHA.110.601609
79. Lansberg MG, Lee J, Christensen S, Straka M, De Silva DA, Mlynash M, *et al.* RAPID automated patient selection for reperfusion therapy: a pooled analysis of the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) and the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) study. *Stroke* 2011;**42**:1608–14. https://doi.org/10.1161/STROKEAHA.110.609008
80. Thomalla G, Cheng B, Ebinger M, Hao Q, Tourdias T, Wu O, *et al.* DWI-FLAIR mismatch for the identification of patients with acute ischaemic stroke within 4.5 h of symptom onset (PRE-FLAIR): a multicentre observational study. *Lancet Neurol* 2011; **10**:978–86. https://doi.org/10.1016/S1474-4422(11)70192-2
81. Lin L, Bivard A, Krishnamurthy V, Levi CR, Parsons MW. Whole-brain CT perfusion to quantify acute ischemic penumbra and core. *Radiology* 2016;**279**:876–87. https://doi.org/10.1148/radiol.2015150319
82. Turc G, Bhogal P, Fischer U, Khatri P, Lobotesis K, Mazighi M, *et al.* European Stroke Organisation (ESO)—European Society for Minimally Invasive Neurological Therapy (ESMINT) guidelines on mechanical thrombectomy in acute ischemic stroke. *J Neurointerv Surg* 2019;**11**:535–8. https://doi.org/10.1136/neurintsurg-2018-014568
83. Berge E, Whiteley W, Audebert H, De Marchis GM, Fonseca AC, Padiglioni C, *et al.* European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. *Eur Stroke J* 2021;**6**:I–LXII. https://doi.org/10.1177/2396987321989865
84. Palaiodimou L, Sarraj A, Safouris A, Magoufis G, Lemmens R, Sandset EC, *et al.* Endovascular treatment for large-core ischaemic stroke: a meta-analysis of randomised controlled clinical trials. *J Neurol Neurosurg Psychiatry* 2023;**94**:781–5. https://doi.org/10.1136/jnnp-2023-331513
85. Requena M, Ren Z, Ribo M. Direct transfer to angiosuite in acute stroke: why, when, and how? *Neurology* 2021;**97**:S34–41. https://doi.org/10.1212/WNL.0000000000012799
86. Armstrong PW, Gershlick AH, Goldstein P, Wilcox R, Danays T, Lambert Y, *et al.* Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med* 2013;**368**:1379–87. https://doi.org/10.1056/NEJMoa1301092
87. Moser M, Nordt T, Peter K, Ruef J, Kohler B, Schmittner M, *et al.* Platelet function during and after thrombolytic therapy for acute myocardial infarction with reteplase, alteplase, or streptokinase. *Circulation* 1999;**100**:1858–64. https://doi.org/10.1161/01.CIR.100.18.1858
88. Chen Z, Wang D, Ma M, Li C, Wan Z, Zhang L, *et al.* Rationale and design of the OPTIMAL-REPERFUSION trial: a prospective randomized multi-center clinical trial comparing different fibrinolysis-transfer percutaneous coronary intervention strategies in acute ST-segment elevation myocardial infarction. *Clin Cardiol* 2021;**44**: 455–62. https://doi.org/10.1002/clc.23582
89. Chen P, Eikelboom JW, Tan C, Zhang W, Xu Y, Bai J, *et al.* Single bolus r-SAK before primary PCI for ST-segment-elevation myocardial infarction. *Circ Cardiovasc Interv* 2024;**17**:e013455. https://doi.org/10.1161/CIRCINTERVENTIONS.123.013455
90. Mueller L, Pult F, Meisterernst J, Heldner MR, Mono ML, Kurmann R, *et al.* Impact of intravenous thrombolysis on recanalization rates in patients with stroke treated with bridging therapy. *Eur J Neurol* 2017;**24**:1016–21. https://doi.org/10.1111/ene.13330
91. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, *et al.* 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2018;**49**:e46–110. https://doi.org/10.1161/STR.0000000000000158
92. Seners P, Turc G, Maier B, Mas JL, Oppenheim C, Baron JC. Incidence and predictors of early recanalization after intravenous thrombolysis: a systematic review and meta-analysis. *Stroke* 2016;**47**:2409–12. https://doi.org/10.1161/STROKEAHA.116.014181

93. Kaesmacher J, Kleine JF. Bridging therapy with i. v. rtPA in MCA occlusion prior to endovascular thrombectomy: a double-edged sword? *Clin Neuroradiol* 2018;**28**:81–9. https://doi.org/10.1007/s00062-016-0533-0
94. Desilles JP, Loyau S, Syvannarath V, Gonzalez-Valcarcel J, Cantier M, Louedec L, *et al.* Alteplase reduces downstream microvascular thrombosis and improves the benefit of large artery recanalization in stroke. *Stroke* 2015;**46**:3241–8. https://doi.org/10.1161/STROKEAHA.115.010721
95. Zi W, Qiu Z, Li F, Sang H, Wu D, Luo W, *et al.* Effect of endovascular treatment alone vs intravenous alteplase plus endovascular treatment on functional independence in patients with acute ischemic stroke: the DEVT randomized clinical trial. *JAMA* 2021;**325**:234–43. https://doi.org/10.1001/jama.2020.23523
96. Yang P, Zhang Y, Zhang L, Zhang Y, Treurniet KM, Chen W, *et al.* Endovascular thrombectomy with or without intravenous alteplase in acute stroke. *N Engl J Med* 2020;**382**:1981–93. https://doi.org/10.1056/NEJMoa2001123
97. LeCouffe NE, Kappelhof M, Treurniet KM, Rinkel LA, Bruggeman AE, Berkhemer OA, *et al.* A randomized trial of intravenous alteplase before endovascular treatment for stroke. *N Engl J Med* 2021;**385**:1833–44. https://doi.org/10.1056/NEJMoa2107727
98. Suzuki K, Matsumaru Y, Takeuchi M, Morimoto M, Kanazawa R, Takayama Y, *et al.* Effect of mechanical thrombectomy without vs with intravenous thrombolysis on functional outcome among patients with acute ischemic stroke: the SKIP randomized clinical trial. *JAMA* 2021;**325**:244–53. https://doi.org/10.1001/jama.2020.23522
99. Fischer U, Kaesmacher J, Plattner PS, Butikofer L, Mordasini P, Deppeler S, *et al.* SWIFT DIRECT: Solitaire With the Intention For Thrombectomy Plus Intravenous t-PA Versus DIRECT Solitaire Stent-retriever Thrombectomy in Acute Anterior Circulation Stroke: methodology of a randomized, controlled, multicentre study. *Int J Stroke* 2022;**17**:698–705. https://doi.org/10.1177/17474930211048768
100. Turc G, Tsivgoulis G, Audebert HJ, Boogaarts H, Bhogal P, De Marchis GM, *et al.* European Stroke Organisation (ESO)—European Society for Minimally Invasive Neurological Therapy (ESMINT) expedited recommendation on indication for intravenous thrombolysis before mechanical thrombectomy in patients with acute ischemic stroke and anterior circulation large vessel occlusion. *J Neurointerv Surg* 2022;**14**:209. https://doi.org/10.1136/neurintsurg-2021-018589
101. Kaesmacher J, Cavalcante F, Kappelhof M, Treurniet KM, Rinkel L, Liu J, *et al.* Time to treatment with intravenous thrombolysis before thrombectomy and functional outcomes in acute ischemic stroke: a meta-analysis. *JAMA* 2024;**331**:764–77. https://doi.org/10.1001/jama.2024.0589
102. Albers GW, Jumaa M, Purdon B, Zaidi SF, Streib C, Shuaib A, *et al.* Tenecteplase for stroke at 4.5 to 24 hours with perfusion-imaging selection. *N Engl J Med* 2024;**390**:701–11. https://doi.org/10.1056/NEJMoa2310392
103. Ganame J, Messalli G, Dymarkowski S, Rademakers FE, Desmet W, Van de Werf F, *et al.* Impact of myocardial haemorrhage on left ventricular function and remodelling in patients with reperfused acute myocardial infarction. *Eur Heart J* 2009;**30**:1440–9. https://doi.org/10.1093/eurheartj/ehp093
104. Jollis JG, Granger CB, Zegre-Hemsey JK, Henry TD, Goyal A, Tamis-Holland JE, *et al.* Treatment time and in-hospital mortality among patients with ST-segment elevation myocardial infarction, 2018–2021. *JAMA* 2022;**328**:2033–40. https://doi.org/10.1001/jama.2022.20149
105. Danchin N, Popovic B, Puymirat E, Goldstein P, Belle L, Cayla G, *et al.* Five-year outcomes following timely primary percutaneous intervention, late primary percutaneous intervention, or a pharmaco-invasive strategy in ST-segment elevation myocardial infarction: the FAST-MI programme. *Eur Heart J* 2020;**41**:858–66. https://doi.org/10.1093/eurheartj/ehz665
106. Nogueira RG, Haussen DC, Smith EE, Sun JL, Xian Y, Alhanti B, *et al.* Higher procedural volumes are associated with faster treatment times, better functional outcomes, and lower mortality in patients undergoing endovascular treatment for acute ischemic stroke. *Ann Neurol* 2023. https://doi.org/10.1002/ana.26803
107. McCartney PJ, Eteiba H, Maznyczka AM, McEntegart M, Greenwood JP, Muir DF, *et al.* Effect of low-dose intracoronary alteplase during primary percutaneous coronary intervention on microvascular obstruction in patients with acute myocardial infarction: a randomized clinical trial. *JAMA* 2019;**321**:56–68. https://doi.org/10.1001/jama.2018.19802
108. McCartney PJ, Maznyczka AM, Eteiba H, McEntegart M, Oldroyd KG, Greenwood JP, *et al.* Low-dose alteplase during primary percutaneous coronary intervention according to ischemic time. *J Am Coll Cardiol* 2020;**75**:1406–21. https://doi.org/10.1016/j.jacc.2020.01.041
109. Heusch G. Myocardial ischaemia-reperfusion injury and cardioprotection in perspective. *Nat Rev Cardiol* 2020;**17**:773–89. https://doi.org/10.1038/s41569-020-0403-y
110. Ibanez B, Heusch G, Ovize M, Van de Werf F. Evolving therapies for myocardial ischemia/reperfusion injury. *J Am Coll Cardiol* 2015;**65**:1454–71. https://doi.org/10.1016/j.jacc.2015.02.032
111. Nour M, Scalzo F, Liebeskind DS. Ischemia-reperfusion injury in stroke. *Interv Neurol* 2013;**1**:185–99. https://doi.org/10.1159/000353125
112. Scheldeman L, Wouters A, Lemmens R. Imaging selection for reperfusion therapy in acute ischemic stroke beyond the conventional time window. *J Neurol* 2022;**269**:1715–23. https://doi.org/10.1007/s00415-021-10872-4
113. Renu A, Millan M, San Roman L, Blasco J, Marti-Fabregas J, Terceno M, *et al.* Effect of intra-arterial alteplase vs placebo following successful thrombectomy on functional outcomes in patients with large vessel occlusion acute ischemic stroke: the CHOICE randomized clinical trial. *JAMA* 2022;**327**:826–35. https://doi.org/10.1001/jama.2022.1645
114. Broch K, Anstensrud AK, Woxholt S, Sharma K, Tollefsen IM, Bendz B, *et al.* Randomized trial of interleukin-6 receptor inhibition in patients with acute ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2021;**77**:1845–55. https://doi.org/10.1016/j.jacc.2021.02.049
115. Del Buono MG, Damonte JI, Moroni F, Chiabrando JG, Markley R, Turlington J, *et al.* Clinical and pharmacological implications of time to treatment with interleukin-1 blockade in ST-segment elevation myocardial infarction. *J Pharmacol Exp Ther* 2023;**386**:156–63. https://doi.org/10.1124/jpet.123.001601
116. Hernandez-Jimenez M, Abad-Santos F, Cotgreave I, Gallego J, Jilma B, Flores A, *et al.* Safety and efficacy of ApTOLL in patients with ischemic stroke undergoing endovascular treatment: a phase 1/2 randomized clinical trial. *JAMA Neurol* 2023;**80**:779–88. https://doi.org/10.1001/jamaneurol.2023.1660
117. Hill MD, Goyal M, Menon BK, Nogueira RG, McTaggart RA, Demchuk AM, *et al.* Efficacy and safety of nerinetide for the treatment of acute ischaemic stroke (ESCAPE-NA1): a multicentre, double-blind, randomised controlled trial. *Lancet* 2020;**395**:878–87. https://doi.org/10.1016/S0140-6736(20)30258-0
118. Trifan G, Biller J, Testai FD. Mechanical thrombectomy vs bridging therapy for anterior circulation large vessel occlusion stroke: systematic review and meta-analysis. *Neurology* 2022;**98**:e1361–73. https://doi.org/10.1212/WNL.0000000000200029