nature reviews cardiology

https://doi.org/10.1038/s41569-024-01076-0

Consensus statement

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Clinical and subclinical acute brain injury caused by invasive cardiovascular procedures

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Abstract

Over the past 50 years, the number and invasiveness of percutaneous cardiovascular procedures globally have increased substantially. However, cardiovascular interventions are inherently associated with a risk of acute brain injury, both periprocedurally and postprocedurally, which impairs medical outcomes and increases health-care costs. Current international clinical guidelines generally do not cover the area of acute brain injury related to cardiovascular invasive procedures. In this international Consensus Statement, we compile the available knowledge (including data on prevalence, pathophysiology, risk factors, clinical presentation and management) to formulate consensus recommendations on the prevention, diagnosis and treatment of acute brain injury caused by cardiovascular interventions. We also identify knowledge gaps and possible future directions in clinical research into acute brain injury related to cardiovascular interventions.

Sections

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Introduction

Cardiovascular interventions are inherently linked to a risk of non-traumatic acute brain injury (ABI)[1]. Haemorrhage and ischaemic stroke are the most devastating examples of ABI, but even covert ABI can herald the risk of future adverse consequences (such as memory loss, cognitive decline, early dementia or stroke)[2]. With the increasing number[3,4] and invasiveness[5] of percutaneous cardiovascular interventions, and with progressively ageing patient populations (who are particularly vulnerable to ABI[6,7]) burdened by a growing number of comorbidities, periprocedural and/or postprocedural ABI is becoming an increasing problem, from both medical and health economic perspectives[8,9].

European and North American guidelines on the management of ischaemic stroke and intracranial haemorrhage (ICH)[10–14] do not cover the topic of stroke specifically caused by invasive procedures. No position documents or guidelines focus on periprocedural and postprocedural ABI. Therefore, in this international Consensus Statement, we compile the available knowledge (including data on prevalence, pathophysiology, risk factors, clinical presentation and management) to formulate consensus recommendations on the prevention, diagnosis and treatment of ABI caused by cardiovascular interventions. Additionally, we define current knowledge gaps and possible future directions in clinical research. Key terms used in this article are defined in Box 1.

Methods

An international panel of experts in the field of cardiology (including invasive cardiac procedures), cardiac surgery and neurology (including neurointerventions and neuroimaging) performed a rigorous search for the relevant literature, identifying studies that address the prevalence, pathophysiology, risk factors, management and methods of prevention of cardiovascular procedure-related ABI. This comprehensive review extended across multiple databases, including PubMed, Embase and the Cochrane Library, incorporating studies up to March 2024, without language limitations. Additionally, reference lists of relevant papers were meticulously examined to include applicable studies. The writing and reviewing process was collaborative and iterative. Groups of authors were assigned specific sections of the Consensus Statement to focus on, and the entire group scrutinized each part through a series of iterative rounds. When evaluating the strength of the evidence, we considered anticipated patient outcomes and potential biases or modifying factors, such as patient demographics, follow-up duration, and patient or clinician preferences. In areas where evidence was limited or contentious, the expert group achieved consensus through collective agreement. Recommendations were subject to a systematic voting process, including anonymous voting on the final version, with at least 80% of voters required to agree for inclusion. The results of the anonymous voting are included in the Supplementary information.

This Consensus Statement summarizes the final conclusions and recommendations agreed on by the expert panel, on the basis of the best available evidence and expert opinion, and the recommendations are graded according to the Oxford Centre for Evidence-Based Medicine level of evidence, with grading from level 1 (the highest level of evidence) to level 5 (the lowest level of evidence)[15].

Scope of the problem

Over the past 50 years, the number and invasiveness of percutaneous cardiovascular procedures performed worldwide have expanded substantially. The European Registry of Percutaneous Coronary Interventions (PCIs) has shown that the overall number of coronary angiography procedures increased between 1992 and 2003 from 1,250 to 3,500 per million inhabitants, and the number of PCI and coronary stenting procedures increased from 335 to 1,300 and from 5 to 1,100 per million inhabitants, respectively[16]. Furthermore, in 2016, according to a 16-country survey conducted by the European Association of Percutaneous Cardiovascular Interventions, the median annual number of diagnostic cardiac catheterizations and percutaneous coronary angioplasties per million inhabitants in Europe was even higher, reaching 5,131 and 2,478, respectively[17]. Similar trends were observed in the use of cardiac electronic implantable devices. The number of cardiac pacemaker implantations per million inhabitants in European Society of Cardiology countries increased from 614 in 2010 to 641 in 2014; similarly, the number of catheter ablations, transcatheter aortic valve implantations (TAVIs) and transcatheter interventions for congenital shunts all increased[18–20].

In addition, procedure complexity and invasiveness are increasing. Data from the European Registry of Chronic Total Occlusion (CTO) demonstrate that, between 2008 and 2015, the number of patients enrolled in the registry rose from 3,027 to 17,626, involving increasingly more challenging lesions with a higher proportion of in-stent CTOs, longer occlusion duration and longer CTO length[5]. In parallel, more sophisticated (and often aggressive) tools and techniques were used (such as more guidewires and balloons and more frequent use of endovascular ultrasonography and a retrograde approach)[5].

Furthermore, interventions are constantly shifting to be performed in older populations with more comorbidities. In a report from the National Heart, Lung, and Blood Institute-sponsored registries, patients undergoing PCI in the first decade of the twenty-first century were older and more often reported comorbidities than patients undergoing PCI 20 years earlier[21].

The annual number of patients in the USA experiencing in-hospital stroke after cardiovascular interventions is estimated to exceed 7,700, including 2,265 after coronary artery bypass graft (CABG) surgery, 1,920 after PCI, 1,168 after TAVI, 1,016 after cardiac catheterization and 68 after atrial fibrillation (AF) ablation[22]. Considering the increasingly ageing patient population with multimorbidity, the incidence of procedure-related complications, including those related to the central nervous system, is likely to rise.

Clinical presentation and consequences

The Neurologic Academic Research Consortium has established a classification system for stroke occurring after surgical and catheter-based cardiovascular procedures[23]: type 1 or overt central nervous system injury, type 2 or covert central nervous system injury, and type 3 – neurological dysfunction without central nervous system injury (including transient ischaemic attack (TIA) or delirium). Within these categories, further subclassification describes the underlying stroke mechanisms, including ischaemia with or without secondary haemorrhagic conversion, ICH and global hypoxia. Similarly, the Valve Academic Research Consortium 3 has proposed standardized definitions for cerebrovascular events after TAVI[24]. In this section, we describe the presentation and consequences of overt and covert procedure-related ABI. Type 3 neurological dysfunction is beyond the scope of this Consensus Statement.

Subclinical or covert lesions

Procedure-related ABI can remain clinically asymptomatic. This form of subclinical or covert ABI comprises brain lesions on neuroimaging that are either not accompanied by congruent signs of focal neurological dysfunction in a clinical examination by an experienced neurologist or

Box 1 | Definitions

Acute acquired non-traumatic brain injury
Post-birth, non-traumatic damage to the brain caused by intrinsic factors such as lack of oxygen, with signs, symptoms or imaging evidence that occur shortly (seconds to minutes) after the insult[399].

Infarction of the central nervous system
Brain, spinal cord or retinal cell death attributable to ischaemia, on the basis of pathological, imaging or other objective evidence of focal ischaemic injury in a defined vascular distribution, or with clinical evidence based on symptoms persisting ≥24 h or until death, if other aetiologies have been excluded[400].

Stroke
A neurological deficit attributed to an acute focal injury of the central nervous system by a vascular cause, with symptoms persisting ≥24 h or until death[400].

Transient ischaemic attack
Brief episode of neurological dysfunction resulting from focal brain, spinal cord or retinal ischaemia, not associated with permanent cerebral infarction[401].

Intracranial haemorrhage
Any bleeding within the intracranial vault, including the brain parenchyma and surrounding meningeal spaces (epidural, subdural or subarachnoid space)[402].

Intracerebral haemorrhage
A focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma[400].

Haemorrhagic stroke
Rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood in the brain parenchyma or ventricular system that is not caused by trauma[400].

Ischaemic stroke
An episode of neurological dysfunction caused by focal cerebral, spinal or retinal infarction[400].

Covert brain injury
Imaging or neuropathological evidence of central nervous system infarction, without a history of acute neurological dysfunction attributable to the lesion[400].

Dementia
A clinical syndrome characterized by progressive acquired global impairments of cognitive skills and ability to function independently[403].

Delirium
A clinical state characterized by a combination of disturbance in attention and awareness, with additional disturbance in cognition (such as memory deficit or disorientation), that develops over a short period of time (hours to a few days) and tends to fluctuate in severity during the course of the day, not explained by another pre-existing, established or evolving neurocognitive disorder, with evidence that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal, or exposure to a toxin[404].

Myocardial infarction
Presence of acute myocardial injury detected by abnormal cardiac biomarkers in the setting of evidence of acute myocardial ischaemia[405].

Atrial fibrillation
A supraventricular tachyarrhythmia with uncoordinated atrial electrical activation and consequently ineffective atrial contraction, manifesting electrocardiographically as irregularly irregular R–R intervals (when atrioventricular conduction is not impaired), absence of distinct repeating P waves and irregular atrial activations[295].

Ventricular tachycardia
Three or more consecutive beats with a rate >100 bpm originating from the ventricles, independently of atrial and atrioventricular nodal conduction[406].

Heart failure
A clinical syndrome consisting of cardinal symptoms (breathlessness, ankle swelling and fatigue) that can be accompanied by signs (such as elevated jugular venous pressure, pulmonary crackles and peripheral oedema), caused by a structural and/or functional abnormality of the heart that results in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise[407].

not neuroanatomically related to the clinical complaints of the patient. In this context, the term 'silent' lesion is sometimes used in the literature. Given the limitations of clinical neurological examination and the link between asymptomatic lesions and long-term clinical and cognitive deficits, we prefer to use the term 'covert' lesions[25].

Covert brain lesions can be ischaemic or haemorrhagic and are often detectable only on brain MRI using diffusion-weighted imaging for ischaemic lesions or T2* or susceptibility-weighted imaging sequences for haemorrhagic lesions such as cerebral microbleeds, parenchymal haemorrhage or focal subarachnoid haemorrhage. To distinguish acute lesions from lesions that already existed before the cardiac procedure, brain MRI and clinical neurological assessments before and after the procedure are needed. Although ischaemic lesions detected with diffusion-weighted imaging are likely to have developed recently, preprocedural and postprocedural studies are needed to determine the age of haemorrhagic lesions.

The incidence of covert brain lesions markedly exceeds the incidence of clinically symptomatic stroke by more than tenfold,

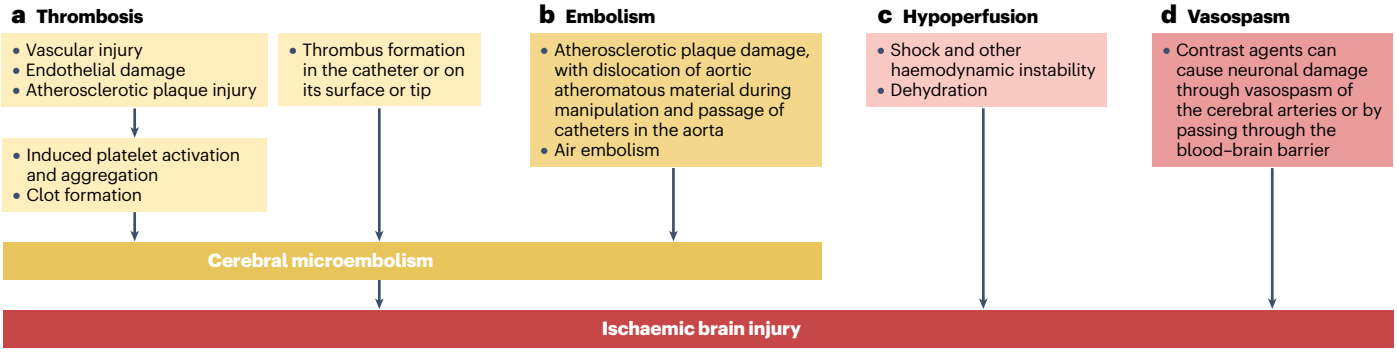

Fig. 1 | Mechanisms of ischaemic brain injury caused by percutaneous coronary procedures. a, Mechanical injury caused by catheters, guidewires and other devices during percutaneous procedures can lead to vascular injury, including endothelial damage and/or atherosclerotic plaque rupture with platelet activation and aggregation leading to thrombus formation. Thrombi can also form on the surface (or tip) of catheters, guidewires or other intravascular devices owing to lack of or inappropriate flushing, wiping and/or antithrombotic therapy, leading to cerebral embolism. **b**, In addition, plaque damage with dislocation of its atheromatous content during manipulation and passage of guidewires, catheters and other intravascular devices can lead to cerebral embolism. Lack of or inadequate aspiration and/or irrigation can lead to air embolism. **c**, Another mechanism of ischaemic brain injury during cardiac catheterization or percutaneous coronary intervention is hypoperfusion, especially prolonged hypoperfusion, as a result of shock or other haemodynamic instability and/or dehydration. **d**, Contrast media can cause neuronal damage owing to vasospasm of cerebral arteries and neurotoxicity of intravascular contrast media (mainly administered intra-arterially) or by crossing the blood–brain barrier.

depending on the procedure. Population-based studies conducted in the older general population, such as the Rotterdam Scan Study[26], demonstrated an association between covert brain lesions and incident symptomatic stroke (HR ~4) and dementia (HR ~2) during long-term follow-up. Importantly, whether procedure-related brain lesions confer the same risk as brain lesions that developed spontaneously remains to be established. Several studies have not documented an effect of procedure-related covert brain lesions on cognitive scores, at least with short-term follow-up and crude screening instruments[1,27]. The clinical consequences of covert brain lesions seem to depend on alterations in the surrounding brain tissue and the number and volume of lesions, suggesting a cumulative effect[28,29].

Symptomatic brain injury

A stroke is defined as an acute or sudden onset of focal neurological deficits. The most common signs and symptoms include focal weakness and/or numbness, aphasia defined as impaired language production or comprehension, visual field disturbance such as homonymous hemianopia or quadrantanopia, diplopia, hemispatial neglect, dysarthria, vertigo or ataxia[23]. These signs can be masked in the periprocedural phase.

The categorization of procedure-related stroke is based on the timing of onset and detection, leading to two primary categories: intraprocedural and postprocedural. Intraprocedural stroke that occurs during the respective intervention while undergoing general anaesthesia or deep sedation is typically diagnosed when the patient emerges from anaesthesia. The most common mechanisms for intraoperative ischaemic stroke are thromboembolism and hypoperfusion. Thromboembolism accounts for approximately 70–80% of cases of intraoperative stroke and is often associated with manipulation of the aorta. Conversely, hypoperfusion can result in border zone or watershed strokes, which are less common, comprising 20–30% of cases of intraprocedural stroke[30–32].

Postprocedural stroke occurs in the early or late postprocedural phases. Early postoperative stroke, within the first 7 days after the procedure, is primarily attributable to postoperative arrhythmias, particularly AF, and haemodynamic factors. By contrast, late postoperative stroke, occurring between 7 days and 1 month after the intervention, is commonly associated with the overall atherothromboembolic risk factors of the patient. Postprocedural stroke often presents with focal lesions, although watershed strokes can also be observed[33,34].

Both intraprocedural stroke and postprocedural stroke are linked to reduced short-term and long-term survival. Data from the US National Inpatient Sample demonstrated a 2.4-fold higher in-hospital mortality, a more than twofold longer length of hospital stay, a threefold higher non-home discharge from hospital and >60% higher costs in patients with ischaemic stroke after PCI than in those without[35]. Outcomes are even worse in patients with haemorrhagic stroke after PCI[36].

Pathophysiology, prevalence and risk factors

Percutaneous coronary intervention

Pathophysiology. Ischaemic and haemorrhagic ABIs associated with PCI have various mechanisms and risk factors. Ischaemic ABI could be related to thrombosis, (air) embolism, hypoperfusion and vasospasm (Fig. 1), with most periprocedural ischaemic brain events caused by cerebral embolism[22,35–38]. ICH is mainly the consequence of periprocedural antithrombotic therapy, especially fibrinolytic agents, anticoagulation or dual antithrombotic therapy[39,40]. Patient-related and procedure-related risk factors for ischaemic and haemorrhagic ABI are listed in Boxes 2 and 3.

PCI in patients with acute myocardial infarction transiently heightens the risk of ICH in the periprocedural phase, and first exposure to antiplatelet therapy and the use of periprocedural anticoagulation also increases the risk[40]. Other reasons for neurological symptom onset include contrast-induced encephalopathy, local anaesthetic systemic toxicity and delirium.

Prevalence. An estimated 1.5 million patients undergo PCI and coronary angiography procedures annually in the USA[22,41,42]. In Europe,

the annual number of cardiac and coronary catheterizations and PCI is as high as 5,100 and 2,400 per million inhabitants, respectively[17]. The risk of symptomatic brain injury is approximately 0.1–0.4% for cardiac catheterization and 0.4% for PCI[22,36,37,41,43] and is determined by procedure complexity (Table 1).

In the context of acute myocardial infarction, PCI increases the risk of intracranial bleeding in the early periprocedural phase but has an overall lower risk than fibrinolytic therapy[44–46]. One large, retrospective registry, comprising 219,274 patients who underwent a first PCI, reported an incidence of ICH of 21.66 cases per 1,000 person-years in the first 30 days and <1 case per 1,000 patient-years after that[40].

The PCI-associated risk of ABI shows little geographical variation, but ethnicity and demographic variables might be associated with the incidence of neurological complications. In a large, single-centre US registry of 25,626 patients undergoing PCI mainly for acute coronary syndrome, African American ethnicity was strongly and independently associated with the occurrence of neurological events (OR 2.4, 95% CI 1.5–3.9, $P < 0.001$)[47]. A single-centre, prospective registry in 1,022 Vietnamese patients undergoing PCI, mainly for acute coronary syndrome, reported an in-hospital stroke rate of 0.5%[48], and a Japanese registry of 17,966 patients undergoing PCI identified periprocedural stroke in 0.3% of patients[49]. In a multicentre Australian PCI registry of 29,012 consecutive patients undergoing PCI, the in-hospital rate of cerebrovascular event or stroke was 0.2% and 1.0%, respectively, and the 30-day rate of stroke in patients aged <80 years or ≥80 years was 0.4% and 1.3%, respectively[50].

Catheter ablation

Pathophysiology. Left-sided heart catheter ablation procedures, like other left-sided heart diagnostic and interventional procedures, are associated with a low but consistent risk of clinical and subclinical ABI[37]. These lesions are nearly always the result of embolism, whereas haemorrhagic ABI, in the context of therapeutic or supratherapeutic anticoagulation, is much less common (Fig. 2).

Both solid and gaseous emboli are known to occur during catheter ablation[51]. Activation of the coagulation cascade by foreign bodies in the form of catheters, guidewires, electrodes and balloon materials leads to thrombus formation with an embolic risk, similar to other cardiac catheterization procedures[37]. Radiofrequency catheter ablation leads to heat-induced coagulation of circulating blood proteins, entrapping blood cells and producing so-called 'coagulum' and generating 'char' (blood and tissue accumulation on the catheter tip) at high temperatures[52]. Thrombus can develop on the lesion surface, especially in the presence of endothelial or tissue disruption such as with a 'pop' (an intramyocardial steam explosion). Laboratory studies of cryoablation have demonstrated a lower degree of blood damage, platelet activation and thrombogenesis, and animal studies have revealed less endothelial disruption[53]. Thrombi forming within sheaths, as well as atheroma components, including lipid and calcium debris, are other sources of embolic material. Finally, gaseous emboli from microbubbles generated during tissue heating or air bubbles sucked into introducers or trapped in catheters also have a role[54]. The newly commercialized technique of high-voltage pulsed-field ablation has a

Box 2 | Risk factors for ischaemic ABI

Risk factors for ischaemic acute brain injury (ABI) during coronary procedures or cardiac catheterization[35–38,43,297–299,301,302,304–306].

Patient-related factors

- Advanced age
- Female sex
- Smoking
- Severe and/or diffuse atherosclerosis, especially atherosclerotic disease of the aortic arch and cerebral arteries or multivessel coronary artery disease
- Previous myocardial infarction
- Previous stroke
- Arterial hypertension, particularly without proper blood pressure control
- Diabetes mellitus
- Kidney failure
- Acute coronary syndrome: increased rate of periprocedural stroke if percutaneous coronary intervention (PCI) was performed urgently or during an emergency situation (0.6% versus 0.3% for an elective procedure)
- History of valvular heart disease
- Heart failure, especially congestive heart failure
- Cardiogenic shock and other haemodynamic instability

Procedure-related factors

- Extensive catheter manipulation: the incidence of microembolization is strongly associated with catheter exchange manoeuvres and manipulation
- Number of catheters used: procedures with more than two catheters had double the incidence of microemboli
- Extended procedural time
- Amount of contrast agent used
- Scraping of aortic atherosclerotic plaques (more common with large catheters)
- Infrequent catheter flushing with heparinized saline
- Transradial approach: twofold increase in the incidence of covert brain injury with a transradial approach versus a transfemoral approach when biomarkers were used to detect covert ABI[297], but no significant difference reported in an imaging study[299]; modern studies and meta-analyses for various patient populations reported no significant differences in the risk of symptomatic brain injury with a transradial versus a transfemoral approach[408] or the incidence of stroke or transient ischaemic attack between the two radial approaches (0.2% with the right radial approach versus 0.1% with the left radial approach[409])
- Internal mammary artery angiography
- PCI for chronic total occlusion
- Complex PCI
- Lesion complexity and thrombus burden
- Procedure with crossing of the aortic valve
- PCI of a bypass graft
- Atherectomy
- Intra-aortic balloon counterpulsation and use of mechanical circulatory support devices
- Use of an aspiration catheter
- Urgent procedure

predominantly non-thermal effect but can generate microbubbles from an electrochemical reaction[55], which might be facilitated by higher energies and associated with unexpected thermal effects.

Hypotension and/or severely reduced cardiac output can occur during catheter ablation of ventricular tachycardia (because of spontaneous or induced sustained ventricular tachycardia) and contribute to ischaemic brain lesions. The mechanisms that occur during catheter ablation of AF or left atrial flutter are also applicable to ablation procedures for ventricular tachycardia.

The underlying mechanism of covert or subclinical ABI is thought to be similar to that for the clinically symptomatic syndrome, with thrombi, heat-induced coagulum and gaseous emboli all contributing. Intraprocedural transcranial Doppler monitoring has shown that most embolizing signals represent gaseous material and are associated with the trans-septal puncture and tissue ablation[51,56]. Spontaneous echo contrast, longer left atrial dwelling and procedure times, and intraprocedural electrical cardioversion all favour the occurrence of these covert lesions[57]. The specific pathophysiological pathways for catheter ablation-induced ABI are summarized in Fig. 2.

Prevalence of subclinical lesions. Covert cerebral lesions have been described after left-sided catheter ablation procedures[58]. After catheter ablation of AF, the prevalence of subclinical brain lesions ranges from 1% to 38%[57], although one prospective study found a prevalence of about 86%, as detected by brain MRI[59].

The use of multi-electrode radiofrequency ablation catheters (such as the Pulmonary Vein Ablation Catheter from Medtronic and the nMARQ Pulmonary Vein Isolation System from Biosense Webster) is associated with particularly high rates of covert brain lesions, and deactivation of specific overlapping electrodes has reduced lesion rates[60] (Table 1). Even pulmonary vein isolation using pulsed-field ablation produces covert brain lesions in 18.7% of patients who underwent MRI in the PULSE-EU study[61]. One prospective study of three modalities of catheter ablation of AF (phased or irrigated radiofrequency ablation or cryoablation) found a 49% incidence of new covert lesions but did not find a correlation between microembolic signals on intraprocedural transcranial Doppler ultrasonography and covert cerebral embolism burden on MRI[62].

Prevalence of symptomatic brain injury. The occurrence of catheter ablation-induced ABI has changed over time. Initially, left-sided accessory pathway catheter ablation used retrograde transaortic valve access with non-irrigated temperature-agnostic radiofrequency ablation, which could cause embolic material from an overheated tissue–electrode interface and retrograde transaortic catheter passage. A single-centre series of 153 left-sided accessory pathway ablations reported embolic events with an incidence of 2%[63].

The advent of pulmonary vein ablation and related procedures, such as ablations for left atrial flutter and left ventricular tachycardia, have increased exposure of the left side of the heart to the embolic potential of catheter ablation. With the use of contemporary techniques (open-tip irrigated radiofrequency catheters, continuous irrigation of long left-sided sheath introducers and multi-electrode diagnostic catheters with a heparinized saline solution), the residual thromboembolic rate after catheter ablation of AF was reported in a meta-analysis of 29 studies to be 0.7%[64] (Table 1). A prospective, multicentre study of ablation of ventricular arrhythmias found a 4.9% incidence of TIA and no occurrence of stroke[65].

Box 3 | Risk factors for ICH

Risk factors for intracranial haemorrhage (ICH) during coronary procedures or cardiac catheterization.

Patient-related factors

- Older age[39,40], especially age ≥75 years[40]
- Number of antithrombotic drugs[39]: twofold increase in risk with each additional drug
- Previous stroke or transient ischaemic attack[39,40]: up to twofold increase in risk
- Intracranial aneurysm and other vascular malformations (predisposition to leaks or ruptures)
- High systolic blood pressure[39,40]
- Diabetes mellitus[40]
- Atrial fibrillation[40]
- Chronic pulmonary disease[40]
- End-stage renal disease[40]: one of the strongest predictors of ICH, with a 3.5-fold increase in risk
- Dementia[40]: cerebral amyloid angiopathy is associated with ICH, cognitive impairment and dementia in older patients, which might suggest a shared pathogenesis[410,411]
- Cerebral amyloid angiopathy[40,410]
- Use of vitamin K antagonist (VKA)[40]: associated with a twofold increase in the risk of ICH, in contrast to the use of direct oral anticoagulants
- Use of combined antiplatelet and anticoagulant drugs[40]: substantial increase in the number of patients with ICH when a VKA was combined with antiplatelet therapy compared with a VKA alone (321 patients versus 30 patients)[40]
- ST-segment elevation myocardial infarction presentation[412]
- Female sex[412]
- Cardiac arrest[412]: nearly twofold increase in the risk of ICH in patients with acute myocardial infarction
- Concomitance of many risk factors[413]: an analysis of the most common risk factors for ICH (age ≥75 years, previous stroke or transient ischaemic attack, and arterial hypertension) showed that the annual rate of ICH increased from 0.1% in patients with none of these risk factors to 0.2% in patients with one factor, 0.6% in patients with two factors and 1.3% in patients with three factors[413]
- Multi-organ failure[412]: 2.5-fold increase in risk

Procedure-related factors

- Mechanical circulatory support[412]: 1.6-fold increase in risk
- Invasive mechanical ventilation[412]
- Fibrinolytic therapy[412]: strongest risk factor for ICH (fourfold increase in risk)

Table 1 | Prevalence of ABI after cardiovascular interventions

Target	Cardiovascular intervention	Prevalence of ischaemic/haemorrhagic ABI (%)			
		Covert ABI	Refs.	Symptomatic ABI	Refs.
Percutaneous interventions					
Coronary arteries	Coronary angiography or cardiac catheterization	5.2–20/NA	38,297–299	0.1–0.4/0.003 (0.009 at 90 days)	22,38,43,300
	All PCI	13–38/NA	22,297	0.1–0.5 (1.0 in hospital; 1.3 at 30 days in patients aged ≥80 years)/0.015–0.12	22,36,37,40, 48–50,301–303
	Complex PCI, PCI of chronic total occlusions or other high-risk PCI (such as for acute coronary syndrome)	60/NA	304	0.6–0.96/0.08–0.15[a]	35,305,306
Left atrial appendage	Percutaneous closure	4.8–48/0–28	307–310	0–4.0 (0–0.03 at 6–12 months)/ 0–0.4 (0–0.2 at 6–12 months)	307,308,311–320
Atrial fibrillation	Open-irrigated, single-point radiofrequency catheter ablation	1–86/NA	57,59	0.1–1.0 (TIA: 0.1–0.7; 1.4 stroke or TIA in patients aged ≥85 years)/0.01–0.1	64,66,67,321–326
	Multipolar radiofrequency catheter ablation	33–37/NA	327,328	0.12–2.12 (TIA: 0.37)/NA	329–332
	Pulsed-field catheter ablation	3–19/NA	61,333	0.39 (TIA: 0.11–0.8)/NA	334,335
	High-power, short-duration catheter ablation[b]	44/NA	336	0–0.32 (TIA: 0.16)/NA	337–340
	Very high-power, short-duration catheter ablation[c]	8.2–26/NA	341–343	0–0.17 (TIA: 0.17)/NA	343–345
	Cryoablation	4.3–27/NA	328,346,347	0.17–0.4 (1.4 at 36 months)/NA	66,321,322,348
Mitral valve	Transcatheter edge-to-edge repair	69–88/45	310,349–351	0.2–2.6/NA	93,352–356
	Transcatheter mitral valve implantation	–	–	4–6.9 (2.4 at 173 days)/NA	94,357
	Transcatheter mitral valve in bioprosthetic valve implantation	–	–	0–7.1 (0–7.1 at 60 months)/3.3 (7.1 at 60 months)	358–363
	Transcatheter mitral valve in annuloplasty ring implantation	–	–	0–5.4 (0–12.5 at 6 months)/3.3 (3.4 at 60 months)	358,360,361,363
Aortic valve	Transcatheter aortic valve implantation	58–100/23	1,102,103,364	1.6–3.3 (5.0–5.4 at 1 year)/0.11 (0.57 at 90 days)	109,110,365–368
	Transcatheter aortic valve in bioprosthetic valve implantation	–	–	1.1–3.5 (4.3–4.6 at 1 year)/NA	369,370
Congenital heart disease	All percutaneous interventions	–	–	0.1–0.16/NA	371–373
	Percutaneous closure of patent foramen ovale or atrial septal defect	3.3/NA	374	0–2.9 (0.9 at 36 months)/NA	375–377
Pulmonary vein	Balloon angioplasty or stenting	–	–	7.6 (TIA: 2.9)/NA	378,379
Aorta	Balloon angioplasty or stenting for native aortic coarctation or recoarctation	–	–	0–0.7 (ischaemic stroke 2.2 and TIA 5.0 for recoarctation)/NA	380–383
Surgical interventions					
Coronary arteries	CABG surgery	25–61/67	1,384,385	1.1–4.5/0.01–0.3 (0.04 at 90 days; 2.6 at 6 years)	42,155,157, 300,386–390
	Beating-heart CABG surgery	0–15/NA	1,384	1.1–1.9/NA	157,388
Aortic valve	Surgical aortic valve replacement	30–44/NA	1,391	1.2–4.8 (4.6 at 1 year)/0.13 (0.2 at 90 days)	42,155,159, 300,365,388
Mitral valve	Surgical mitral valve replacement	28[d]/NA	392	1.9–8.8/NA	42,155,159,388
	Surgical mitral valve repair	–	–	0.9–1.8/NA	42,393
Multiple	CABG surgery plus mitral valve repair	–	–	2.1–4.1/NA	42,393
	CABG surgery plus aortic or mitral valve repair or replacement	38/NA	394	2.0–7.9/NA	42,159,389,393
	Multiple valves	–	–	2.1–9.7/NA	42,388

ABI, acute brain injury; CABG, coronary artery bypass graft; NA, not available; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack. [a]24.3% of all patients with acute coronary syndrome and in-hospital stroke had intracranial bleeding, which equates to 0.15% of the study population. [b]Application power of 50 W delivered over 8–15 s. [c]Application power of 60–90 W delivered over 4–10 s. [d]Minimally invasive approach.

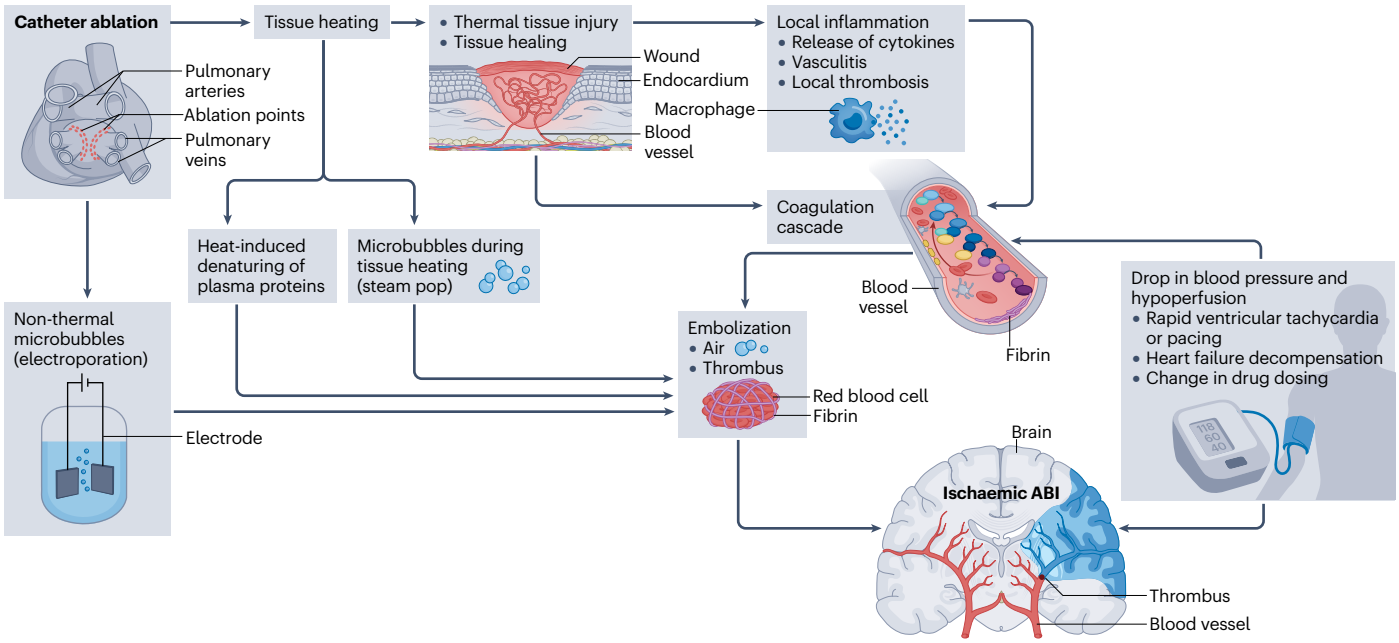

Fig. 2 | Specific pathophysiological pathways by which catheter ablation induces ABI. Catheter ablation-induced tissue heating causes thermal injury of atrial or ventricular tissue, leading to local inflammation in thermally damaged areas and activation of the coagulation cascade, which predisposes to thrombus formation and can cause embolization and acute brain injury (ABI). An excessive rise in local tissue temperature, often combined with forced pressure from the lead tip of the catheter, provokes tissue boiling and gas evaporation (called steam pop), which can cause embolization and ischaemic ABI, in addition to mechanical complications from tissue damage (resulting in cardiac tamponade). Contact of the heated electrode with blood can lead to denaturation of plasma proteins, and the clots that are formed can embolize to the cerebrovascular system. Newer ablation techniques, such as electroporation, can result in the formation of gaseous microbubbles owing to non-thermal effects (hydrolysis or displacement of nitrogen gas from the blood). The microbubbles, especially if they are large in diameter, can affect blood flow in various vascular beds, including in the brain. A drop in blood pressure associated with the ablation procedure (during rapid ventricular tachycardia or pacing) can cause cerebral hypoperfusion and ischaemic ABI.

Geographical variation in the risk of ABI caused by catheter ablation is unlikely. In the Japanese Catheter Ablation Registry of more than 55,000 procedures, cerebral or systemic thromboembolism after any catheter ablation occurred in 0.2% (0.2% in AF ablations versus 0.09% in non-AF ablations)[66], and in the nationwide Japanese JROAD-DPC study, stroke or TIA after radiofrequency or cryoballoon (14% of patients) ablation for AF occurred in 1% overall, but in 1.4% of those aged >85 years[67]. In the Australia and New Zealand registry, the 30-day rate of stroke or TIA after AF ablation was 0.24% (0.11% in hospital)[68], and in another nationwide hospitalization registry of 30,601 patients undergoing catheter ablation for AF in that region, the rate of rehospitalization for stroke at 10 years after ablation was 0.7 per 100 person-years[69]. In a Latin American registry of 15,099 catheter ablation procedures of all types (120 centres in 13 participating countries), stroke complicated 0.03% of procedures and TIA complicated 0.08% of procedures[70].

Left atrial appendage closure

Pathophysiology. As an invasive procedure involving manipulation across the septum and in the left atrium, left atrial appendage (LAA) closure (LAAC) is associated with various risks of embolic brain injury and stroke (Fig. 3). Long-term factors contributing to later ABI include residual peridevice leak (PDL) and device-related thrombus (DRT). Of note, the LAA orifice is typically oval, whereas LAAC devices are usually circular, leading to the potential for residual leakage[71,72]. The procedure-specific pathways by which LAAC is related to the occurrence of ABI are summarized in Fig. 3.

PDL >5 mm in size is regarded as incomplete LAAC and might require either continuation of anticoagulation or PDL closure[71,73,74], but a definition incorporating the LAA anatomy and the leak mechanism might be more clinically relevant[71,75]. Data on the clinical effect of PDL are limited, with conflicting conclusions. In the NCDR-LAAO registry, PROTECT AF trial, PREVAIL trial and CAP2 registry, small leaks (<5 mm) were associated with a significant increase in the risk of ischaemic stroke, TIA and systemic embolism (HR 1.15) at 1 year[71,73]. The limited number of patients with large PDLs and the use of anticoagulants might explain the absence of a significant relationship between large PDL and thromboembolic events. A meta-analysis showed that any echocardiography-reported PDL, regardless of its size, was associated with a higher risk of thromboembolism (OR 2.04), major bleeding (OR 1.12) and all-cause death (OR 1.16). The presence of CT-detected PDLs was not significantly associated with outcomes[76].

DRT is the second important, but relatively uncommon, procedural complication of LAAC and is more strictly associated with increased thromboembolic risk. Most DRTs occur early after implantation; typically, two-thirds occur within 90–180 days and up to 20% later than 6–12 months[71,77]. Diagnosis of DRT is mainly based on transoesophageal echocardiography (TEE) or cardiac CT. Intracardiac echocardiography and cardiac MRI are alternative diagnostic imaging modalities. Cardiac CT can identify subtle changes such as hypoattenuated thickening.

Categorizing hypoattenuated thickening as low grade or high grade has prognostic value and therapeutic implications. Low-grade hypoattenuated thickening typically represents device healing and poses a low embolic risk, whereas high-grade hypoattenuated thickening (definite DRT) requires intensified anticoagulation therapy[71,78,79]. In a prospective study, low-grade hypoattenuated thickening occurred in 23.8% of patients and high-grade hypoattenuated thickening occurred in 5.1% of patients at a mean of 4.2 ± 1.7 months after LAAC[79]. Only high-grade hypoattenuated thickening was significantly associated with an increased risk of stroke (HR 4.6)[79].

The established risk factors for DRT are non-paroxysmal AF (OR 1.90–2.24), renal insufficiency (OR 4.02), hypercoagulable disorders (OR 17.5), pericardial effusion (OR 13.45), deep device implantation (such as >10 mm from the pulmonary vein limbus; OR 2.41), a history of TIA or stroke (OR 2.31), vascular disease (OR 2.06), LAA diameter (OR 1.06 per 1 mm increase), left ventricular dysfunction or reduced left ventricular ejection fraction (OR 0.96 per 1% increase) and older age (HR 1.07 per 1-year increase)[71,78,80–84]. Other potential risk factors for DRT include previous thromboembolism[81], a history of LAA thrombus, spontaneous LAA echo contrast, reduced LAA peak emptying velocities, incomplete LAA sealing[85], larger LAAC device size[81] and type of device (the Amplatzer Amulet LAA Occluder (Abbott Cardiovascular) was associated with a slightly lower rate of DRT than the WATCHMAN 2.5 LAAC device (Boston Scientific) in the Amulet IDE trial, perhaps related to the closure geometry or an effect on healing)[71,82].

Other procedures focused on thromboprophylaxis are thoracoscopic LAA occlusion and surgical LAAC or LAA elimination, especially during cardiac surgery undertaken for other reasons[86]. One of the most important issues is that elimination of the appendage and suture of the stump should be preferred because of the risk of recanalization after occlusion or stapling[87].

Prevalence. During early experience with LAAC, rates of procedural complications, including embolism, were fairly high[71]. Data on the short-term incidence of periprocedural ABI and other complications with a potential effect on cerebral or systemic embolism after percutaneous LAAC are presented in Table 1.

Residual PDL is not uncommon, with variation in the incidence related mainly to the definition of PDL or the diagnostic method used (CT or TEE). In an analysis of more than 50,000 patients who underwent LAAC in the USA between 2016 and 2019, 26% had a small PDL (0–5 mm) and 0.7% had a large PDL (>5 mm) at 45 ± 14 days after the procedure[73].

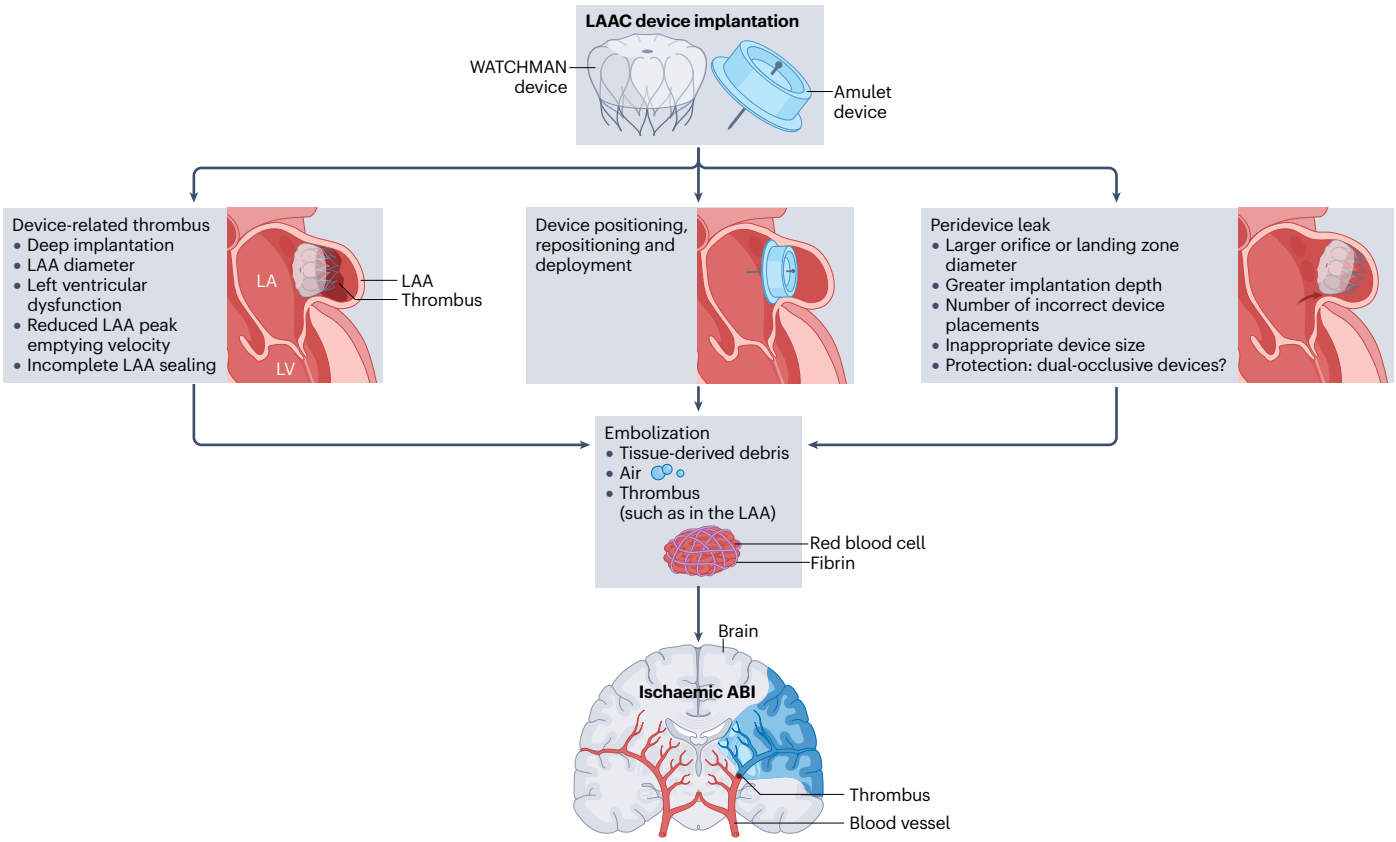

Fig. 3 | Specific pathophysiological pathways by which LAAC causes ABI. Positioning and repositioning of the left atrial (LA) appendage (LAA) closure (LAAC) device in the appendage is associated with the release of potentially thrombogenic material (tissue-derived debris, air or thrombus), which can lead to ischaemic acute brain injury (ABI). Incomplete appendage closure and residual peridevice leak are common after LAAC, with rates ranging from 26% to 57% depending on the imaging technique used[73,76]. Any peridevice leak detected by transoesophageal echocardiography (as opposed to CT), regardless of size, is associated with an increased risk of thromboembolism, major bleeding and all-cause death[76]. LAAC carries a 2–5% risk of device-related thrombus, which typically occurs within 180 days of implantation[71,77]. CT scans can classify device-related thrombus as having low-grade or high-grade hypoattenuated thickening, the latter being associated with an increased risk of stroke (HR 4.6)[79]. LV, left ventricle.

Smaller studies reported PDL rates as high as 68% at 3 months after LAAC[88], and a meta-analysis of more than 60,000 patients reported TEE-detected PDL in 26.1% of patients and CT-detected PDL in 57.3% of patients[76].

The overall prevalence of DRT is approximately 2–5% and depends on the imaging-guided follow-up protocol[71,80,82,89,90] but was not significantly different between single-seal and dual-seal devices[90]. The occurrence of DRT in the PROTECT AF and PREVAIL trials and their nested registries was 3.74%[80]. In a meta-analysis of more than 10,000 patients, the pooled incidence of DRT was 3.8%, with the majority occurring in the first year after LAAC[89]. DRT or high-grade hypoattenuated thickening is associated with a fourfold to fivefold increase in ischaemic events[71,79,80,89,90], which was similar for single-seal and dual-seal devices[90]. Up to 33–45% of ischaemic events occurred within 1 month of DRT diagnosis, indicating a potential temporal association[77,91].

Transcatheter mitral valve replacement or repair

Pathophysiology. The risk of stroke during transcatheter edge-to-edge repair (TEER) of the mitral valve is mainly associated with air embolization and thrombus formation at the delivery catheters or the devices themselves. Blood stasis, in combination with missing atrial contraction, can lead to a thrombogenic status, which predisposes to thrombus formation at the puncture site, on the mitral annulus or on the TEER device itself[92]. The prothrombotic state of each patient determines the risk of thrombosis and the need for subsequent anticoagulation, especially in patients with very low cardiac output. By contrast, transcatheter mitral valve replacement, especially in patients with annular or leaflet calcifications or degenerated bioprostheses, is related to a higher risk of embolization of microthrombi, calcific particles or debris.

Prevalence. Transcatheter mitral valve interventions are less commonly associated with ABI than aortic valve procedures. The incidence of overt stroke at 30 days after TEER is 0.2–2.6%, although higher rates have been reported in older studies or those that include high-risk patients[93] (Table 1). Although the numbers of mitral valve implantations with dedicated prostheses are considerably lower than the numbers of TEERs, the rate of stroke in registries of selected patients is 3–5%[93]. As expected, the use of an aortic valve prosthesis in calcified mitral valve disease was associated with a higher rate of stroke (6.9%), and the level of manipulation in a severely calcified valve has been reported to be a strong predictor of neurological complications[94]. The same applies to valve implantations in degenerated and, therefore, usually calcified, bioprostheses[95].

Transcatheter aortic valve replacement or repair

Pathophysiology. TAVI pertains to the introduction of large-bore catheters and delivery systems into the arterial system, navigation through the thoracic aorta, and crossing and eventual deployment of a transcatheter valve within a degenerated (calcific) native or bioprosthetic aortic valve. Mechanistic studies have unequivocally established the embolization of debris particles into the brain throughout the procedure. Transcranial Doppler studies detected high-intensity transient signals as a surrogate for (micro)embolization in all patients undergoing TAVI with a self-expanding or balloon-expandable transcatheter valve throughout the procedure and predominantly during aortic valve crossing and transcatheter valve deployment[96,97]. A seminal histopathology study of filters that had been placed in the brachiocephalic trunk and left common carotid artery revealed the presence of debris in 75% of TAVI procedures[98]. Debris consisting of fibrin, amorphous calcium and connective tissue derived from leaflet and aortic wall tissue was found in 98–99% of patients undergoing TAVI[99–101]. Interestingly, valve repositioning features were associated with higher debris volume, and bicuspid aortic valve disease was linked to larger debris particles[101].

Thrombogenic and gaseous emboli can also occur because of inadequate periprocedural anticoagulation and inarticulate de-airing techniques, respectively. Fast or rapid pacing techniques during transcatheter valve deployment can result in cerebral hypoperfusion and create watershed infarcts in the brain. The specific pathways that lead to ABI associated with the TAVI procedure are summarized in Fig. 4.

Prevalence. A series of brain MRI studies performed within 5 days after TAVI reported the presence of ABI in 58–100% of the patients[102,103] (Table 1). The clinical effect of these new lesions remains unclear, and most had disappeared on follow-up MRI performed 3 months later. The first randomized controlled trial (RCT) on patients at high operative risk suggested numerically more strokes after TAVI with early-generation devices than with surgical aortic valve replacement[104]. Conversely, the rates of stroke in RCTs involving patients at lower operative risk were numerically lower with contemporary transcatheter valve platforms than with surgical aortic valve replacement[105–108]. Operator experience, improved implantation techniques, shorter procedure time and smaller-profile devices might contribute to the overall low stroke rate in contemporary TAVI practice.

The risk of overt ABI seems to be independent of geographical location[109]. An Australian prospective, observational study in patients at intermediate surgical risk undergoing isolated TAVI with the SAPIEN-XT valve (Edwards Lifesciences) revealed minor stroke in 2.5%, postoperative delirium in 2.5% and clinically significant postoperative cognitive dysfunction in 5% of the patients[110]. In a retrospective analysis of 689 patients who underwent TAVI with a self-expanding prosthesis at six tertiary academic centres in Argentina, no periprocedural stroke was reported in the 33 patients who were aged ≥90 years[111]. However, ethnic differences in body habitus observed in some regions (such as the shorter stature and, therefore, smaller sizes of the aorta and sinus of Valsalva and smaller annulus area and coronary ostia heights in Asian individuals[112]) raised concerns about the safety of TAVI in specific populations, especially in older individuals[113]. Additionally, ethnicity-specific differences in anatomy (such as a higher prevalence of bicuspid aortic valves in native Chinese individuals, but not in Chinese individuals outside China[114]) might increase the risk of certain complications (possibly including ABI) and might require different tools (for example, a smaller valve size) and precautions in some groups of patients.

Interventions for congenital heart defects

Pathophysiology. Congenital heart defects are linked to specific pathophysiological pathways that predispose individuals to ABI during interventions. Some congenital heart defects (especially single ventricle with shunts, Fontan circulation and coronary aneurysms) are considered a prothrombotic state for multiple reasons[115,116]. Erythrocytosis, microcytosis and blood hyperviscosity (slow flow)[117], and also the presence of shunts, restricted inflow–outflow, and atrial or ventricular dilatation (turbulent flow), predispose patients to rheological abnormalities and coagulation[118]. Protein S or protein C deficiency[119], hyperproduction of coagulation factors, endothelial dysfunction (owing to hypoxia and shear stress)[120,121] and the presence of sutures or stents facilitate clotting[118,122]. The coagulation cascade is also accelerated by reactionary systemic inflammation in patients with congenital heart

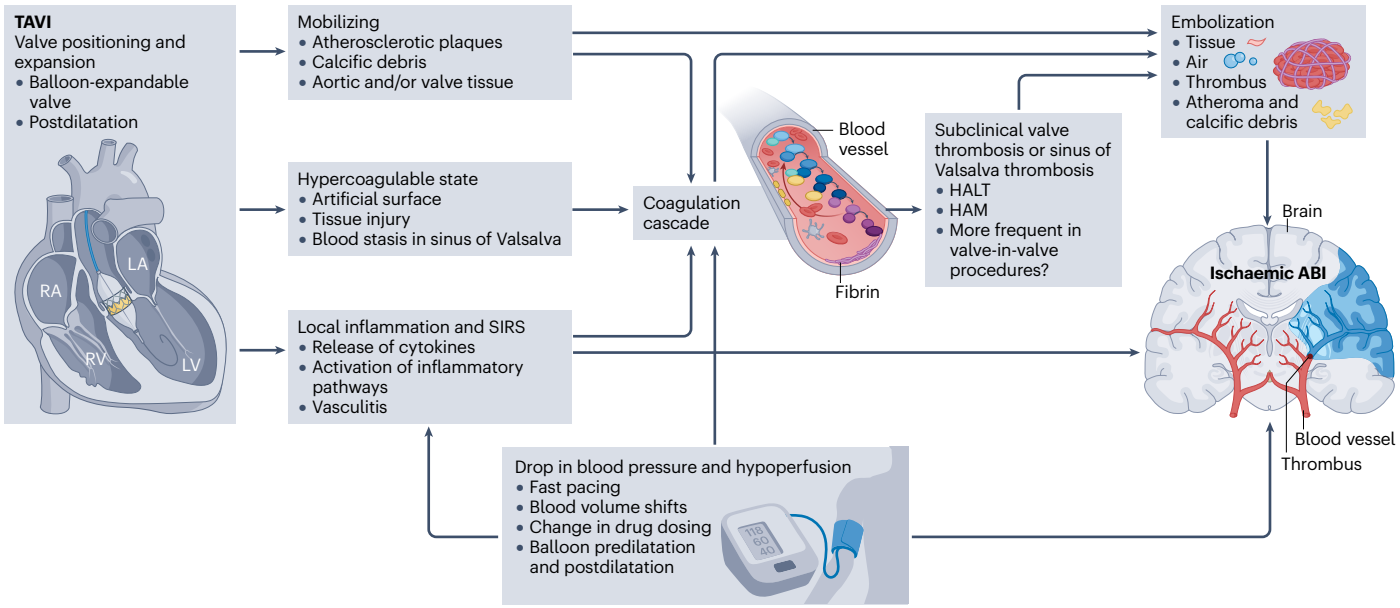

Fig. 4 | Specific pathophysiological pathways by which TAVI induces ABI. Positioning, repositioning and expansion of the artificial valve can result in the release of tissue or atherosclerotic plaque fragments or calcified debris from the native valve, aortic wall or arterial vascular system, leading to embolization and acute brain injury (ABI). Tissue injury caused by valve implantation and foreign material leads to a hypercoagulable state and can initiate a local inflammatory process, with release of inflammatory mediators and local vasculitis, further activating the coagulation cascade and leading to thrombus formation and cerebral embolization. Subclinical valve thrombosis, manifested on imaging as hypoattenuating leaflet thickening (HALT) with or without hypoattenuation affecting motion (HAM), occurs in up to 20–40% of patients after transcatheter aortic valve implantation (TAVI)[397,398]. Similar to sinus of Valsalva thrombosis, HALT and HAM are proposed risk factors for TAVI-related ABI. A drop in blood pressure during valve inflation or rapid pacing can lead to hypoperfusion and consequent brain damage. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; SIRS, systemic inflammatory response syndrome.

defects[123]. Cardiac shunts (such as atrial septal defect, patent foramen ovale (PFO) or single ventricle physiology) and extracardiac shunts predispose individuals to paradoxical embolism[124,125]. Conversely, haemorrhagic risk (including the risk of haemorrhagic stroke) is increased by a propensity to aneurysm formation (hypertension and shear stress in coarctation of the aorta, bicuspid aortic valve or tetralogy of Fallot)[126] and haemostatic abnormalities in congenital heart defects (owing to thrombocytopenia, platelet abnormalities, hypofibrinogenaemia and coagulation factor deficiency)[115,127,128]. Arteriovenous and cavernous malformations and aneurysms are anatomical substrates for haemorrhagic stroke, and haemodynamic fluctuations (hypotension and hypertension) and the use of postprocedural anticoagulants are acquired risk factors for haemorrhagic stroke[129].

Several risk factors associated with periprocedural stroke have been reported in the paediatric population, such as low intraprocedural haematocrit, periprocedural high or low blood pressure, and changes in the haemostatic balance[130]. Additionally, adult patients might have a high burden of conventional vascular risk factors, such as hypertension and impaired glucose metabolism[131]. Patients with cyanotic heart disease require repeat procedures, and 68% of neurological events occur within the procedural period[132]. The most frequent location of ischaemic stroke is the anterior circulation[133], with more than 30% including multiple territories[132].

Prevalence. The overall incidence of ischaemic stroke in children is estimated at 6 per 100,000 children per year, and although the stroke is usually of multifactorial origin, 10–30% are associated with a cardiac aetiology[134]. Stroke (predominantly ischaemic stroke) occurs in the paediatric population with congenital heart defects at a rate of 0.13% per year[135]. The risk of stroke in individuals with congenital heart defects is almost 20-fold higher than in general paediatric populations and 10- to 20-fold higher than in general adult populations, depending on age[136,137]. The cumulative risk of ischaemic stroke in individuals with congenital heart defects up to the age of 65 years is 6.1% in women and 7.7% in men[138]. Approximately 30% of ischaemic strokes occur in the periprocedural period, and stroke occurs during 1 in 500 to 1 in 600 cardiac catheterizations for congenital heart defects[133,139]. The highest risk of stroke in either adults or children with congenital heart defects is posed by cyanotic heart disease and right-to-left shunt on the atrial level (three times higher than in patients without right-to-left shunt), previous palliative and corrective surgery, rheological disturbances and dysrhythmias (particularly patients with Fontan circulation or palliative single ventricle)[140].

Patients with congenital heart defects also have an increased likelihood of peripheral vascular malformations[141]. Haemorrhagic stroke is caused by structural lesions in more than 75% of arteriovenous malformations, and more than 10% are idiopathic.

Patent foramen ovale closure

Pathophysiology. Closure of a persistent PFO is a common treatment for patients with 'cryptogenic' stroke in whom PFO is identified as an aetiological factor. After a period of controversy, several trials showed the superiority of percutaneous PFO closure over the use of antiplatelet and/or anticoagulation medication[142–144]. The procedure involves

a catheter crossing the atrial septum via the PFO and manipulating an implantable device on the left and right side of the heart, typically under heparinization.

Prevalence. The PFO closure procedure is fairly straightforward but requires some manipulation in the left side of the heart and crossing the atrial septum, which confers a risk of ABI. In clinical trials[143,144], the incidence of neurological events was reported as 0–0.4% (depending on clinical definitions), whereas in a US registry[22], the reported incidence of neurological events was 6.7% (95% CI 2.5–16.7%). An older study showed a higher incidence of covert injuries (detected on diffusion-weighted MRI)[145] (Table 1). Larger studies with contemporary devices are not available.

DRT-related phenomena, which were observed at a rate of 0–7% with some early designs of PFO closure device, suggest the potential for longer-term events[146,147], but these outcomes were not studied systematically. In initial clinical trials, DRT events typically occurred during the early period after implantation at a rate of <1%[148]. Factors influencing DRT occurrence could be technology-related, patient non-adherence to antiplatelet medication, possible left atrial disc separation from the septum or even improper stratification of patients at high risk of developing DRT.

Cardiovascular surgery

Pathophysiology. The risk of clinically evident ABI is highly related to the procedure performed, which determines the extent of manipulation at high-risk anatomical areas, such as the ascending aorta and the aortic arch. Perioperative ischaemic stroke has been associated with one or combinations of the following conditions: pre-existing disease of the ascending aorta or the aortic arch, pre-existing disease of the extracranial and intracranial cerebral vessels, hypoperfusion in terms of low blood pressure periods or related to the absence of pulsatile flow during cardiopulmonary bypass, and uncontrollable coagulation changes that result in a transient hypercoagulable state. Perioperative cardiac rhythm disturbances, such as AF, affect up to 30% of the patients, especially those undergoing valvular procedures, and have been associated with central thromboembolism in the early postoperative period[149]. Moreover, perioperative blood pressure alterations, especially hypotension, can aggravate lesions caused by microembolism, by impaired clearing of the embolus. This situation can transform an initially limited thromboembolic episode from a subclinical to a clinically evident brain lesion[150]. The occurrence of prolonged periods of hypoperfusion, particularly during cardiopulmonary bypass, can exacerbate brain low-flow in the presence of stenotic brain-related vessels and is another relevant cause of ABI. The complex interplay of pathophysiological mechanisms leading to ABI in cardiac surgical procedures is summarized in Fig. 5.

Prevalence. The prevalence of permanent stroke varies from 0.9% in the low-risk population of patients undergoing mitral valve repair to 3.1% in the higher-risk group of patients with ischaemic cardiomyopathy undergoing combined coronary and mitral valve surgery[42] (Table 1). The risk varies by surgical technique. In the group undergoing CABG surgery, the risk of stroke was 1.5% in patients undergoing aortic clamp but only 0.6% in those operated on using the no-touch technique[151]. Off-pump coronary artery bypass technique seems to protect against stroke[152]; however, the benefits in terms of neurocognitive outcomes have been questioned[153].

Geographical variation in the risk of ABI associated with surgery is low, and the type of surgery (higher risk with complex procedures and with valvular or aortic procedures than with CABG surgery), the technique used (highest risk with deep hypothermic circulatory arrest[154]) and patient profile determine the risk of ABI. In the Japan Cardiovascular Surgery Database, which encompasses more than 68,000 operations of all types, postoperative stroke occurred in 6.8% after thoracic aortic surgery, 1.8% after valve surgery and 1.5% after isolated CABG surgery[155]. A single-centre registry of 626 Chinese patients found permanent neurological dysfunction in 1.9% and transient neurological dysfunction in 13.9% after aortic arch surgery with deep hypothermic circulatory arrest and antegrade selective cerebral perfusion[156]. In a Chinese, propensity-matched, single-centre registry, postoperative stroke occurred in 1.11% and 3.33% of high-risk patients (EuroSCORE >6) undergoing off-pump coronary artery bypass or on-pump CABG surgery, respectively[157]. In a retrospective, single-centre analysis of 53 patients operated on in Argentina for type A aortic dissection, ABI occurred in 6%[158]. A small, single-centre study of patients in New Zealand undergoing valvular surgery (17% with additional CABG surgery) reported perioperative stroke in 5% and new ischaemic brain lesions on postprocedural MRI in 43%[159]. Of note, cognitive decline was seen in 100% of patients with ischaemic brain lesions and 35% of those without ischaemic brain lesions[159].

Preventive measures

Percutaneous coronary interventions

Antithrombotic pretreatment is a cornerstone of modern therapy for acute coronary syndromes, independent of invasive management. The optimal regimen, developed through numerous RCTs, has improved patient outcomes[160]. However, trials directly comparing different pretreatment regimens to reduce brain injury are lacking, and the effect of pretreatment on neurological outcomes might differ from the effects on other end points. For instance, the landmark PLATO RCT comparing ticagrelor and clopidogrel in 18,624 patients with acute coronary syndrome showed a lower composite end point of death from vascular causes, myocardial infarction or stroke in the ticagrelor group (HR 0.84, 95% CI 0.77–0.92, $P < 0.001$)[161]. However, the incidence of stroke alone was similar in the two groups (1.5% versus 1.3%; $P = 0.22$), with more haemorrhagic stroke in the ticagrelor group[161].

Although RCT data are lacking, observational studies suggest that the administration of protamine (a drug used to reverse the anticoagulant effect of heparin) is safe, reducing the incidence of haematoma and shortening the length of hospital stay after PCI[162,163]. However, heparin reversal with protamine is rare after PCI owing to the low bleeding risk associated with the radial route, the small-calibre catheters (up to 6F) used and the fear of provoking in-stent thrombosis.

Antiplatelet therapy after PCI is crucial for patient outcomes, with optimal regimens recommended by current guidelines[160,164]. Patients receiving oral anticoagulants (OACs) are at high risk of bleeding, thromboembolism and stroke after PCI. In 153 patients undergoing PCI from the ROCKET AF trial[165], the rate of stroke was 3.1 per 100 patient-years (versus 2.1 per 100 patient-years in patients not undergoing PCI) and higher in the vitamin K antagonist (VKA) group (4.1 per 100 patient-years) than in the direct OAC (DOAC) group (1.6 per 100 patient-years). For patients receiving OAC, dual therapy with an OAC plus clopidogrel might be optimal for reduction of cerebrovascular events. A meta-analysis of 32,825 patients showed that triple therapy increased the risk of all-cause death (OR 2.11, 95% CI 1.10–4.06, $P = 0.02$) compared with OAC plus clopidogrel, but reduced the risk of all-cause death and stroke, TIA or peripheral embolism compared with OAC plus aspirin (OR 0.29, 95% CI 0.09–0.96, $P = 0.04$) in patients needing OAC

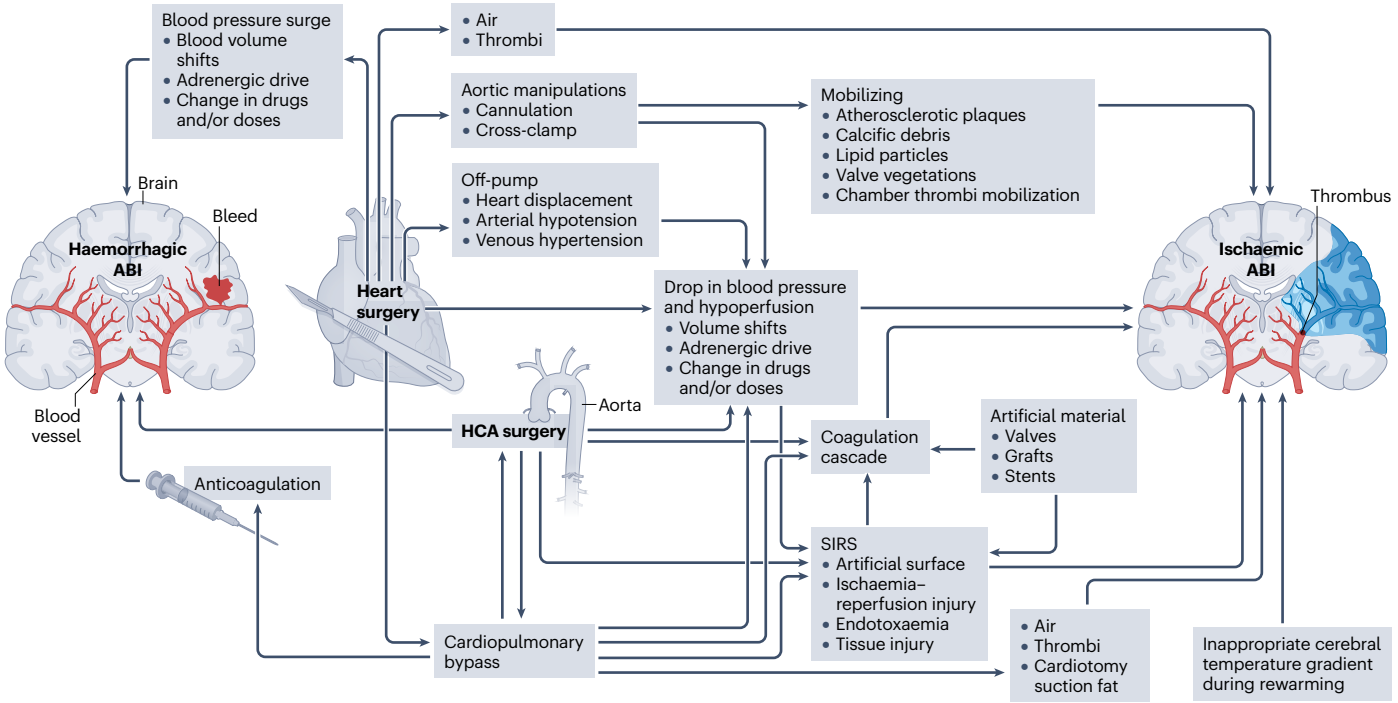

Fig. 5 | Specific pathophysiological pathways by which cardiac surgery induces ABI. Off-pump cardiac surgery requires mechanical displacement, rotation and compression of the ventricles (particularly the right ventricle), resulting in systolic–diastolic ventricular dysfunction, reduced cardiac output, arterial hypotension and watershed brain injury. Periodically reduced cardiac output with similar consequences can also be caused by hypothermic circulatory arrest (HCA). Open-heart surgery and the use of cardiopulmonary bypass carry the risk of air bubbles, blood clots or fat from cardiothoracic suction entering the bloodstream and causing cerebral embolism. Manipulation of arterial vessels, particularly the aorta (cannulation and cross-clamping), carries a risk of detachment of atherosclerotic plaques, calcific deposits, lipid-laden particles, vegetations or tissue fragments, which can cause cerebral embolism. Exposure to the artificial materials of grafts, prosthetic valves or cardiopulmonary bypass systems, but also intraoperative ischaemia or reperfusion, surgical tissue damage or endotoxins, create the conditions for local and systemic inflammation and activation of the coagulation cascade, increasing the risk of thrombus formation and cerebral embolism. Systemic anticoagulation (for example, during cardiopulmonary bypass) and episodes of high blood pressure (caused by large volume shifts, medication change or adrenergic drive during stress) can cause intracerebral haemorrhage. ABI, acute brain injury; SIRS, systemic inflammatory response syndrome.

after coronary intervention[166]. The best long-term antiplatelet regimen after PCI for protection against brain injury is yet to be established.

Catheter ablation

Despite the lack of specific data, a European Heart Rhythm Association consensus document on AF ablation suggests ≥3 weeks of pretreatment before catheter ablation in patients with a low CHA_2DS_2-VASc score (0 in men and 1 in women) who are considered at high risk of thrombosis owing to persistent AF or specific heart disease (hypertrophic cardiomyopathy, rheumatic heart disease or cardiac amyloidosis)[167]. In other OAC-naive patients, the first dose of heparin is typically given just before or after access to the arterial bed (after trans-septal puncture or arterial sheath insertion). The OAC regimen in patients already receiving OAC before catheter ablation depends on the type of anticoagulant, the bleeding risk associated with the procedure and the overall risk of the patient (including thrombotic bleeding risk, concomitant medications and renal function). Stopping the VKA treatment before catheter ablation is linked to a higher risk of stroke than continuing the VKA treatment[168], and many RCTs have shown that an uninterrupted DOAC strategy is as safe as an uninterrupted VKA strategy in terms of all-cause death, stroke or major bleeding[169–172]. Two meta-analyses indicate that uninterrupted DOAC treatment might reduce bleeding by 50% compared with uninterrupted VKA treatment before catheter ablation[173,174]. Of note, the rates of stroke or TIA (0.08% with DOAC and 0.16% with VKA) and covert cerebral embolic events (8% with DOACs and 9.6% with VKA) were similar between DOAC and VKA (OR 0.86, 95% CI 0.42–1.76)[174]. A meta-analysis of eight studies (six randomized, two observational) with 2,168 patients showed no significant difference in major bleeding or thromboembolic events between catheter ablation of AF with minimally interrupted DOAC therapy compared with continuous DOAC therapy[175]. Covert cerebral embolism was equally common with either strategy in the three studies that reported data, with moderate heterogeneity (OR 2.62, 95% CI 0.54–12.61, $P = 0.12$)[175]. Therefore, performing catheter ablation during an interruption to OAC (or minimally interrupted DOAC, with one or two doses skipped), which is the recommended strategy before ablation for AF, might also protect against cerebrovascular events[167]. Bypass therapy with unfractionated or low-molecular-weight heparin should be avoided and limited to exceptional situations (patients at very high thrombotic risk, such as any mitral valve prosthesis or recent stroke and high-bleeding-risk catheter ablation)[176]. Data on pretreatment regimens before catheter ablation of other arrhythmias are lacking.

Mitigation measures to prevent the formation of heating-induced coagulum historically relied on termination of the delivery of radiofrequency energy if impedance rose. Then, with the advent of electrode temperature monitoring, energy delivery could be automatically titrated to avoid exceeding a threshold temperature (temperature-controlled radiofrequency delivery). The development of open-tip irrigated radiofrequency catheters effectively prevented the generation of coagulum by actively cooling the electrode–tissue interface. Similarly, continuous low-flow irrigation of long left-sided sheath introducers with a heparinized saline solution has been shown to prevent intraluminal stasis and thrombus generation[177]. Irrigation of diagnostic multi-electrode catheters has also been useful in preventing blood stasis.

In clinical practice, pre-existing intracardiac thrombi are routinely excluded by TEE before pulmonary vein isolation or left atrial ablations and also before transeptally accessed left ventricular tachycardia ablations in at-risk patients. Anticoagulation is initiated 4 weeks before the ablation and maintained for at least 2 months afterwards, without interruption for the procedure. Standardized intraprocedural anticoagulation with intravenous heparin titrated according to the activated clotting time is also routine. The combination of uninterrupted preprocedural anticoagulation, a heparin bolus even before trans-septal puncture and procedural activated clotting times >300 s is effective in reducing covert brain lesions, whereas better sheath management can reduce gaseous emboli[60].

Protamine administration after catheter ablation rapidly reverses the effect of heparin and is recommended by cardiology societies (class IIa)[178,179]. Observational studies, RCTs and a meta-analysis suggest that adding protamine to standard haemostatic manoeuvres (mainly a figure-of-eight suture or the stopcock technique) for heparin reversal after AF ablation reduces time to haemostasis and accelerates ambulation (by ~3 h), but has a similar rate of vascular complications, minor haematomas or cerebrovascular events when compared with not administering protamine[180–182]. One observational study found that protamine use was associated with fewer occurrences of haematoma, pseudoaneurysm or femoral fistula requiring surgical or interventional repair at the femoral access site (1.1% versus 6.3%; $P = 0.01$), although thromboembolic complications did not significantly differ between the two groups[183]. Data on the use of protamine after catheter ablation for ventricular arrhythmias are scarce; a single-centre study found that prophylactic protamine administration did not affect thrombotic or bleeding complication rates[184]. Potential benefits must be weighed against the risks of serious anaphylactic reactions (up to 1.2% of patients[185]) or non-immunological reactions with shock, ventricular arrhythmias and fatal consequences[186].

Recommended regimens are at least 2 months of OAC (DOAC preferred to VKA) after catheter ablation of AF, starting the DOAC 3–5 h after sheath removal in patients who did not receive anticoagulant treatment or those undergoing ablation with minimally interrupted OAC[167]. After left ventricular endocardial catheter ablation, antiplatelet treatment (class IIa) for less extensive procedures or OAC (class IIb) for more extensive procedures (for example, >3 cm between ablation sites) is recommended for 4–6 weeks if antiplatelet treatment is used and 3 months if OAC is used[187]. Optimal therapy after AF ablation has not been evaluated in RCTs. The need for OAC during the blanking period (first 2–3 months) is mainly based on mechanism-based data on the time course of atrial tissue healing and endothelialization[188]. Long-term discontinuation of OAC after successful AF ablation remains controversial. Evidence suggests that decisions on long-term anticoagulation should be based on the individual patient's risk of stroke rather than rhythm status[189]. However, contradictory data exist[190], and trials are ongoing to clarify this issue[191]. For patients undergoing ablation for ventricular arrhythmias, recommendations are based on trial regimens. In trials evaluating anticoagulation protocols for catheter ablation of ischaemic ventricular tachycardia, no stroke or cerebrovascular events occurred, regardless of whether single antiplatelet therapy (SAPT) or dual antiplatelet therapy (DAPT) was used[192]. A multicentre observational study of 231 patients undergoing ablation for ventricular tachycardia after myocardial infarction found no procedure-related thromboembolic complications or stroke in patients discharged with a prescription for aspirin 325 mg per day for 3 months or for warfarin if the ablation had been extensive[193].

Left atrial appendage closure

Specific complications of LAAC that increase the thromboembolic risk can limit the success of a procedure. An imaging-guided follow-up protocol after LAAC helps to detect these complications promptly. No data are available on the efficacy of pretreatment before LAAC to prevent ABI. A 2014 European Heart Rhythm Association expert consensus document recommends a loading dose of 500 mg of aspirin or 300–600 mg of clopidogrel before the LAAC procedure if the patient is not taking the drug already[194].

Procedure-related preventive measures are similar to those for other procedures involving catheter manipulation in the left side of the heart, including adequate periprocedural anticoagulation and device preparation. Precise sizing, device selection and a careful implantation technique, minimizing manipulation in the left atrium, are important for general safety and to avoid complications. Postprocedural antiplatelet or anticoagulation medication is individualized, given that most patients are referred because of adverse effects in response to anticoagulation rather than the recurrence of embolic events despite anticoagulation. Close collaboration in multispecialty teams is desirable to decide on postprocedural management. Given that dedicated randomized studies have not been conducted, antiplatelet or low-dose anticoagulant medication is used[195].

Deep implantation of the device can leave trabeculated portions of the LAA exposed to stagnant blood, increasing the risk of thrombus formation[80]; therefore, shallower implantation might be protective. DAPT (HR 0.10) or OAC (HR 0.26) at hospital discharge were protective against the occurrence of DRT[84].

Data on protamine use after LAAC are limited and inconclusive. In a propensity-matched, observational study of 40,278 patients who underwent LAAC at 243 hospitals, protamine was used in ~50% of procedures and its use was associated with less-frequent major bleeding rates (2.4% versus 2.8%; $P = 0.03$)[196]. Conversely, major vascular complications (0.8% versus 0.6%; $P = 0.04$) and pericardial tamponade (1.0% versus 0.8%; $P = 0.01$) were higher in the protamine group, without significant differences in the rates of ischaemic or haemorrhagic stroke, all-cause mortality or the rate of any major adverse events[196]. However, higher rates of vascular complication and cardiac tamponade were probably attributable to the more frequent use of protamine as a reversal agent in patients with these complications.

The postulated theoretical advantage of utilizing cerebral protection devices (CPDs) has not been studied in these procedures and cannot be recommended. CPD use during LAAC is being investigated in an ongoing study[197].

A consensus statement recommends DAPT for 6 months after LAAC[194], but some studies suggest similar safety with SAPT in the group with a high risk of bleeding[194,198]. Moreover, a platelet-independent

coagulation cascade might be operative after LAAC[199], and reduced[200] or even long-term, half-dose[201] DOAC therapy might provide protection against DRT after LAAC that is similar to (or better than) that with DAPT or SAPT, with a lower risk of bleeding[201]. Of note, the risks associated with any antiplatelet therapy might be too great in patients with a history of major bleeding, limiting their eligibility for this procedure.

Transcatheter mitral valve replacement or repair

Air embolization can be prevented by meticulous de-airing of all delivery components, minimization of the manipulations and low-flow continuous saline flushing after entering the left atrium. In addition, maintenance of sufficient intraprocedural anticoagulation (activated clotting time 200–300 s) minimizes the risk of thrombus formation. Whether the use of a CPD mitigates the risk of overt stroke remains to be determined. Debris analysis in small studies revealed that the embolic material commonly consisted of acute thrombus and not calcified particles[202].

No data are available on protamine use during or after TEER, so it should be used only in emergent situations (such as cardiac perforation or tamponade). Although no formal recommendations are available to guide antithrombotic therapy after TEER, it has been suggested that OAC should not be initiated after the procedure because of the low thrombogenicity of the device (in contrast to transcatheter mitral valve implantation)[203]. Conversely, the continuation of OAC is safe in patients who are already receiving OAC and, in an observational study of 609 patients, the rates of cerebral and thromboembolic events after TEER were similar with the use of DAPT, OAC, OAC plus SAPT and OAC plus DAPT (0% versus 1% versus 1% versus 0%; $P = 1.0$)[204]. In OAC-naive patients, DAPT should be used for at least 1–6 months, followed by aspirin for up to 12 months[203,205].

Transcatheter aortic valve replacement or repair

Antithrombotic therapy before TAVI is not standardized, and evidence on the effects of various preprocedural regimens on cerebral events is limited. Extrapolating data from PCI trials[206], a loading dose of 300 mg of clopidogrel before TAVI, followed by 3–6 months of DAPT, was commonly used until recently. However, the OCEAN TAVI trial[207] in 2017 showed that the absence of preprocedural antiplatelet therapy or the use of SAPT did not significantly increase the rate of thrombotic complications, including stroke (3.6% versus 1.7%; $P = 0.16$), compared with the use of DAPT. Additionally, DAPT before TAVI increased the bleeding risk compared with either SAPT (32.4% versus 24.7%; $P = 0.048$) or no preprocedural antiplatelet therapy (34.1% versus 25.5%; $P = 0.030$), leading to the general consensus that DAPT should be avoided before TAVI[207]. Maintaining OAC during TAVI in patients with pre-existing indications has been shown to be safe[208], but data on the de novo initiation of OAC in patients without other indications are lacking. According to a consensus document from a European Society of Cardiology working group, low-dose aspirin (or clopidogrel if aspirin is contraindicated) should be started before TAVI in patients without an indication for OAC, whereas the continuation of a VKA or DOAC treatment during TAVI seems to be safe in patients already receiving OAC[209].

Three types of CPD are available for use during TAVI procedures: filters, deflectors and a hybrid of the two, with the most clinical data available for filter-based embolic protection. Relatively underpowered RCTs found a nonsignificant reduction in new lesions on brain MRI with the use of CPDs in patients undergoing TAVI[100,210,211]. RCTs did not demonstrate clinically meaningful reductions in the occurrence of stroke with the use of filters. The largest RCT recruited 3,000 patients and did not achieve the primary end point of a reduction in all-cause stroke but did find a significant reduction in disabling stroke[212]. Trials with deflectors also suggested fewer new brain lesions after TAVI and preserved cognitive function in some domains of neurocognitive testing[213,214]. Collectively, CPDs are safe and will capture or deflect debris in almost all TAVI procedures, despite challenges in demonstrating clinically meaningful benefits in RCTs. Furthermore, it has not been possible to identify patient phenotypes that might particularly benefit from the use of CPDs.

Data on heparin reversal after TAVI are limited and inconsistent. An observational study of 897 patients compared full-dose with half-dose (0.5 mg per 100 units) protamine after TAVI, where the half-dose was used only in patients undergoing PCI concurrently with TAVI, most of whom were treated with DAPT. The combined end point of death, life-threatening bleeding and major vascular complications was significantly higher in the low-dose group, persisting in multivariable analysis (OR 3.07, 95% CI 1.17–8.08, $P = 0.023$)[215]. The incidence of stroke after TAVI was similar in the full-dose and half-dose groups in both the raw data (1.6% versus 2.1%; $P = 0.6$) and the propensity-matched groups (1.5% versus 2.3%; $P = 0.55$)[215]. Univariate regression showed that half-dose administration did not affect the risk of stroke (HR 1.35, 95% CI 0.42–4.29)[215]. Another observational study of 873 patients undergoing TAVI, with 677 receiving protamine, found that protamine use was independently associated with reduced 30-day all-cause mortality and major bleeding and shorter hospital stays, but no significant difference was observed in the rates of stroke and myocardial infarction[216]. By contrast, a small RCT with 100 patients randomly assigned to protamine or saline showed no significant difference in the primary composite end point of major bleeding or neurological events between the two groups; TIA occurred in 0% and 4% of patients in each group ($P = 0.5$) and stroke occurred in 0% and 2% of patients in each group ($P = 1.0$)[217].

Clinical guidelines recommend long-term, low-dose aspirin after TAVI in patients without an indication for OAC (class IIa); DAPT with aspirin and clopidogrel might be reasonable for 3–6 months in patients with a low risk of bleeding (class IIb)[209,218]. However, the effect of aspirin on cerebrovascular events differs from its effect on the primary end points. The ARTE RCT[219] suggested that 3 months of aspirin therapy alone reduced the rate of major adverse events (the composite of all-cause death, myocardial infarction, ischaemic stroke, TIA, and major or life-threatening bleeding) after TAVI compared with DAPT, without significant differences in the 30-day and 90-day rates of stroke or TIA. The POPULAR TAVI RCT[220] reported that aspirin alone reduced the 12-month incidence of all bleeding, including non-procedure-related bleeding, compared with 3 months of DAPT, but did not reduce the risk of stroke (5.1% versus 5.7%; risk ratio 0.90, 95% CI 0.48–1.71). Although postprocedural continuation of OAC in patients with a pre-existing indication is safe[208], the de novo initiation of OAC is debatable. The ATLANTIS 4D-CT trial[221] showed a lower incidence of valve leaflet thrombosis with apixaban than with antiplatelet therapy, but similar clinical outcomes. The GALILEO trial[222] found higher rates of death with rivaroxaban (10 mg) than with aspirin after TAVI. Therefore, no evidence supports the use of a VKA or DOACs after TAVI in patients who do not have a pre-existing indication for OAC. No compelling data favour one antithrombotic therapy over another to prevent cerebral thromboembolic events after TAVI.

Interventions for congenital heart disease and PFO closure

Patients with cryptogenic stroke who are candidates for PFO closure are typically treated with antithrombotic therapy until the procedure

is performed. Despite the rationale that anticoagulants might be more effective than antiplatelets in preventing recurrent stroke in patients with PFO, the data supporting OAC over antiplatelet agents are weak[223]. A meta-analysis found no significant difference between anticoagulant and antiplatelet therapy for the prevention of ischaemic stroke in patients with PFO and embolic stroke of undetermined source (OR 0.70, 95% CI 0.43–1.14)[224].

No formal recommendations are available on periprocedural or postprocedural antithrombotic treatment in patients undergoing transcatheter interventions for congenital heart disease[225,226]. Management depends on the defect type, procedure type and patient characteristics (such as bleeding and thrombotic risk and the presence of comorbidities). After PFO closure, 1–6 months of DAPT is recommended, followed by SAPT for up to 5 years (prolongation beyond 5 years should be determined by the stroke and bleeding risks of the patient)[227]. This recommendation is based on observations of device endothelialization and residual shunts. In an observational study of 660 patients undergoing PFO closure after embolic stroke of undetermined source, thromboembolic events occurred in 25 patients (3.8%) within 5 years of follow-up (TIA 1.5%, stroke 1.8% and cerebral death 0.5%), with the latest stroke occurring 56 months after the procedure[146]. Of note, the recommendations indicate that the choice of antiplatelet drug type is empirical[227]. Additionally, data suggest that all patients with a history of ischaemic stroke might be candidates for lifelong antithrombotic treatment, regardless of PFO closure[203]. Optimal antithrombotic treatment after PFO closure remains to be assessed.

Cardiovascular surgery

Several methods can be used to prevent ABI during cardiac surgery. Prevention starts from the preoperative assessment and extends up to the first weeks after hospital discharge. Carotid ultrasonography has been used for years as a preoperative screening method. However, current practice limits its use to patients with a history of cerebral events, severe peripheral atherosclerosis or clinical symptoms of carotid disease.

Whereas perioperative hypotension is a well-recognized risk factor for cerebral hypoperfusion and ABI, a higher nadir of the mean arterial pressure during surgery has been identified as a risk factor for stroke[228]. More importantly, the ascending aorta is used to apply aortic clamping and declamping, place the arterial perfusion cannula, access the aortic valve, connect proximal bypass grafts, and it is the area of interest for aortic operations. Important information on the anatomy and extent of atherosclerotic disease is provided by CT scan. Being aware of the presence of diseased areas, surgeons can modify the operative plan to reduce or even avoid risky manipulations. This strategy has been shown to reduce the risk of perioperative stroke substantially[229]. The application of a single cross-clamp compared with the double clamp technique for coronary surgery and the use of the aortic no-touch technique can reduce the incidence of ABI, especially in patients with aortic calcifications[230,231]. Intraoperative cerebral oxygen desaturation increases the risk of early cognitive decline[232] and can worsen long-term cognitive function and survival[233]. Approximately 10% of intraoperative oxygen desaturation events can go unnoticed by clinicians, and continuous monitoring of regional cerebral oximetry might be a more effective method of detecting oxygen desaturation[234]. However, the value of monitoring in a therapeutic context remains debatable. Although some observational studies[234] and RCTs[235,236] indicated that a protocol aimed at maintaining proper cerebral oxygen saturation resulted in fewer desaturations and improved long-term outcomes, other RCTs did not report such positive effects[232,237] or found that cerebral desaturation was not associated with postoperative cognitive changes[238].

Long-term antithrombotic treatment depends on the type of surgery and can also depend on clinical presentation and the patient profile (bleeding versus thrombotic risk and other indications requiring anticoagulation). Appropriate treatment regimens are provided in other expert documents[209,239–241] and are beyond the scope of this Consensus Statement.

Diagnosis

Imaging

Cardiac procedures are performed with patients under conscious sedation, deep sedation or general anaesthesia. Consequently, the onset of neurological complications during the procedure can remain undetected until full awakening. However, asymmetry of motor response to pain, altered pupillary responses or unexpected changes in respiratory patterns or blood pressure can provide early clues. Delayed awakening, neurological deficits or abnormal neurological signs should prompt a complete evaluation and complementary imaging investigations. Neurological deficits related to posterior circulation stroke can be more challenging to recognize than those of anterior circulation stroke because of the variety of signs, such as diplopia, isolated vertigo, dysarthria or impaired consciousness[242]. Whether routine and standardized clinical neurological examination is superior to occasional assessment has not been proved. Guidelines recommend establishing standardized protocols to assess for stroke (such as code stroke algorithms) to increase awareness by nurses and physicians of the signs of stroke and reduce time delays[243–245].

Non-contrast cranial CT and CT angiography of the craniocervical vasculature, including the aortic arch, should be performed emergently in response to clinical suspicion of brain injury after invasive cardiovascular interventions[10]. Neuroimaging is necessary to inform clinicians about the most likely type of ABI (ischaemic versus haemorrhagic lesions) and the extent of brain lesions. This information is crucial to guide the selection of potential therapeutic options (see the section on ‘Treatment’). In addition to diagnosing ischaemic stroke (with or without proximal cerebral large-vessel occlusion) and haemorrhagic stroke, neuroimaging can be helpful to identify changes in cerebral haemodynamics, impaired vasoregulation or disturbance of the blood–brain barrier (such as hyperperfusion syndrome), contrast-induced encephalopathy or posterior reversible encephalopathy syndrome.

Cerebral MRI can be helpful in certain circumstances if ABI is clinically suspected, but CT imaging is inconclusive. CT perfusion can additionally be performed in patients with neurological deficits persisting for more than 6 h to evaluate for the presence of tissue that could be salvageable with mechanical thrombectomy or to improve the identification of disorders of cerebral vasoregulation and blood–brain barrier disturbance. A proposed workflow for diagnostic and therapeutic procedures is shown in Fig. 6.

Biomarkers

The use of biomarkers to identify ABI and predict postoperative cognitive dysfunction is a fairly new field of research, with the first studies published in 2000 (Table 2). The most-studied biomarkers of brain injury associated with cardiovascular interventions are protein S100B, glial fibrillary acidic protein (GFAP), microtubule-associated protein tau, neurofilament light polypeptide (NFL) and γ-enolase (also known as neuron-specific enolase)[246] (Fig. 7).

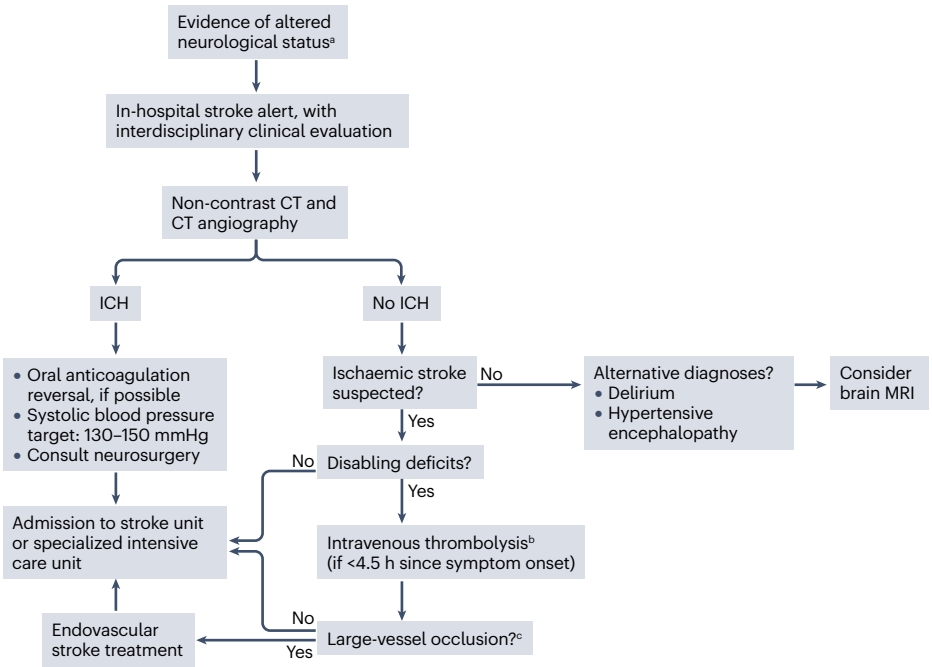

Fig. 6 | Diagnostic and therapeutic pathways depending on type of periprocedural acute brain injury. When the neurological status of a patient raises the suspicion of brain injury, a stroke alert and multidisciplinary assessment should be initiated. CT without contrast and CT angiography are recommended as the initial imaging, and further management depends on the presence or absence of intracranial haemorrhage (ICH). If ICH is diagnosed, oral anticoagulation should be reversed, blood pressure should be maintained within recommended limits and neurosurgical consultation should be sought. The patient should be admitted to the stroke unit and endovascular or neurosurgical treatment options should be considered. In patients without ICH and with suspected ischaemic stroke, intravenous thrombolysis should be initiated if disabling deficits are present, and endovascular treatment should be performed in patients with large-vessel occlusion. [a]Focal signs, delayed awakening, seizures or unexplained delirium. [b]Check for contraindications. [c]Localized to the following cerebral arteries: the carotid artery T, the basilar artery, or the M1 or proximal M2 segments of the cerebral middle artery.

Of these, the glia-derived cytosolic protein S100B is the most widely studied[247]. Among patients undergoing CABG surgery, a significant postoperative rise in the serum S100B level was predictive of postoperative stroke or neurocognitive decline[248,249]. A small, prospective RCT in which patients who required revascularization were randomly assigned to on-pump or off-pump CABG surgery showed that whereas on-pump CABG surgery was associated with a greater rise in serum S100B levels within 30 min of surgery, the levels were similar by 4 h after surgery, and there was no significant difference in neuropsychiatric deterioration between the two groups by 12 weeks[250]. A meta-analysis showed that postoperative serum S100B and γ-enolase levels were significantly higher in patients with postoperative cognitive dysfunction than in those without[251]. A similar association was shown between higher postoperative serum S100B levels after thoracic aorta repair and postoperative neurological events[252]. In patients undergoing radiofrequency catheter ablation of AF, serial assessment of serum S100B levels might improve the detection of asymptomatic ABI[253]. Studies measuring serum S100B levels before and after carotid artery stenting or carotid endarterectomy indicate that S100B might be a useful biomarker for covert brain injury and neurological deficit after carotid revascularization[254,255]. In a small study, serum S100B levels increased in all patients after TAVI, peaking at 1 h after the procedure and normalizing by 4 h, with a positive correlation between the area under the curve for S100B and the number of cerebral microemboli detected on transcranial Doppler imaging ($r = 0.68$, $P < 0.001$)[256].

Some studies in patients undergoing cardiac surgery have shown that elevated postoperative serum levels of tau protein and GFAP were associated with an increased incidence of postoperative cognitive dysfunction[257,258], whereas others showed that a postoperative rise in plasma levels of neuroserpin, but not GFAP, was predictive of cognitive dysfunction[259]. The serum levels of several biomarkers of ABI have been shown to increase significantly even after uncomplicated cardiac surgery (S100B +1.145%, GFAP +17%, tau +456%, NFL +57% and γ-enolase +168%)[260,261].

Although the levels of some biomarkers are clearly increased in patients undergoing cardiac intervention and seem to be associated with the occurrence of ABI and postoperative cognitive dysfunction, most biomarkers have very modest predictive ability[257]. In addition, the specificity of these biomarkers for neurological injury is questionable, given that some are also released from extracerebral tissues such as fat, muscle and bone marrow. Therefore, potential nonspecific release from extracerebral sites might limit the usefulness of these biomarkers[246,247]. Currently, no biomarkers of sufficient sensitivity or specificity have been identified to reliably detect ABI after cardiovascular interventions, and further research is warranted.

Treatment

Symptomatic brain injury

Ischaemic stroke. The decision to administer recombinant tissue plasminogen activator (rTPA) to a patient with an ischaemic stroke during an invasive cardiovascular procedure is always difficult because the benefit–risk ratio is borderline. An individualized approach is necessary, taking into consideration the well-established inclusion and exclusion criteria of rTPA administration, the bleeding risk associated with the cardiovascular intervention (the technical parameters and the administration of antithrombotic drugs such as heparin or bivalirudin), the bleeding risk associated with the patient (based on age and comorbidities) and the severity of the symptoms. The related evidence is scarce and comes from case reports, small case series and retrospective analyses with the inherent risk of bias. In the retrospective ASTRO-TAVI cohort of patients who had an ischaemic stroke after TAVI, the rate of severe or life-threatening bleeding among patients treated with rTPA was twice that of patients treated with mechanical thrombectomy, supporting the argument that mechanical thrombectomy is preferable if both treatment modalities

Table 2 | Biomarkers of acute brain injury after cardiovascular interventions

Study	Cohort	Study design	Serum biomarkers	Main findings	Comments	Ref.
Brightwell et al. (2007)	54 patients with internal carotid artery stenosis undergoing CEA or CAS	Prospective observational study	S100B and γ-enolase	γ-Enolase levels declined after revascularization by CAS but not by CEA (P=0.002); S100B levels increased in patients with higher numbers of HITSs (P=0.002); S100B level increased significantly at 24 h in patients with a postoperative neurological deficit (P=0.015)	Postoperative rise in S100B level associated with cerebral embolization and POCD	255
Wiberg et al. (2022)	168 patients undergoing elective or subacute on-pump CABG surgery and/or AVR	Post-hoc analysis of data collected prospectively in a randomized controlled trial in a single centre	γ-Enolase, tau, NFL and GFAP	Patients with POCD at hospital discharge had significantly higher levels of tau (P=0.02) and GFAP (P=0.01) from baseline to discharge; the biomarkers with the highest AUC for prediction of POCD at discharge were NFL at discharge (AUC 0.64, 95% CI 0.54–0.73), GFAP at 48 h after induction (AUC 0.64, 95% CI 0.55–0.73) and GFAP at discharge (AUC 0.64, 95% CI 0.54–0.74)	Postoperative tau and GFAP levels were significantly elevated in patients with POCD at discharge, but had only modest predictive power for POCD; postoperative γ-enolase level not associated with POCD	257
Barbu at al. (2022)	61 patients undergoing elective CABG surgery	Secondary analysis of a randomized controlled trial	S100B, GFAP, tau, NFL, γ-enolase and β-trace protein	Levels of all biomarkers of brain injury increased significantly after surgery (tau +456%, NFL +57%, S100B +1,145%, GFAP +17% and γ-enolase +168%), whereas β-trace protein level was reduced (−11%); tau, S100B and γ-enolase levels peaked at 2 h and NFL and GFAP levels peaked at 24 h after the procedure	–	260
Reinsfelt et al. (2012)	21 patients undergoing TAVI	Prospective, observational study	S100B	S100B level increased in all patients with a peak at 1 h after the procedure and returned to baseline after 4 h; the total amount of cerebral microemboli correlated with the AUC at 24 h for S100B (r=0.68, P<0.001); no patients developed neurological impairment	Rise in S100B level associated with cerebral microemboli after TAVI	256
Alifier et al. (2020)	25 patients undergoing cardiac surgery and 25 undergoing otolaryngeal surgery	Prospective, observational study	Tau, NFL, Aβ40 and Aβ42	Tau level increased during surgery (1,752%; P=0.0001) and NFL level increased 7 days after the procedure (1,090%; P<0.0001) in patients undergoing cardiac surgery; the increase was greater with on-pump than with off-pump surgery; no changes observed in patients undergoing otolaryngeal surgery; only minor fluctuations in the levels of Aβ40 and Aβ42	Cardiac surgery is associated with neuronal injury exacerbated by extracorporeal circuit	261
Sramko et al. (2014)	58 patients undergoing radiofrequency catheter ablation of paroxysmal or persistent AF	Prospective, observational study	S100B	No symptomatic neurological complications observed; S100B levels increased after ablation above upper reference limit of 105 ng/l in three patients, one of whom developed a new ischaemic lesion on DW-MRI; no acute lesions emerged on DW-MRI in patients with normal S100B level after ablation; the incidence of asymptomatic brain injury was 1.7% when evaluated only by DW-MRI, but 5% when measuring S100B level	Serial assessment of S100B level might improve detection of asymptomatic acute brain injury during AF ablation	253
Wu et al. (2018)	268 patients undergoing CAS	Multicentre, prospective cohort study	TMAO (a proatherosclerotic gut microbiota metabolite)	TMAO level was higher in patients with new lesions (DW-MRI-detected) than in patients without lesions (5.2 μmol/l versus 3.2 μmol/l; P<0.001); increased TMAO level associated with more new lesions on DW-MRI after CAS (adjusted OR 3.85, 95% CI 1.37–7.56, P<0.001 for highest versus lowest quartile; adjusted OR 1.86, 95% CI 1.09–4.66, P=0.02 for third versus lowest quartile); AUC of TMAO 0.706 for new lesions on DW-MRI; optimal cut-off: 4.29 μmol/l; sensitivity, specificity, PPV and NPV of TMAO levels ≥4.29 μmol/l for predicting new lesions on DW-MRI were 61.5%, 74.8%, 65.5% and 65.5%, respectively	High TMAO levels are associated with cerebral microembolization after CAS	395
LeMaire et al. (2001)	39 patients undergoing thoracic aortic repair during hypothermic circulatory arrest	Prospective, observational cohort study	S100B	Neurological complications occurred in three patients (8%), who had higher S100B levels after bypass (7.17±1.01 mg/l) than those without neurological complications (3.63±2.31 mg/l; P=0.013); S100B levels ≥6.0 mg/l were associated with a higher incidence of neurological complications (3 of 7 patients, 43%) than lower S100B levels (0 of 30 patients; P=0.005)	Serum S100B level ≥6.0 mg/l is associated with a higher risk of postoperative neurological complications	252

Table 2 (continued) | Biomarkers of acute brain injury after cardiovascular interventions

Study	Cohort	Study design	Serum biomarkers	Main findings	Comments	Ref.
Szwed et al. (2020)	100 patients undergoing elective off-pump CABG surgery[a]	Prospective, observational cohort study	GFAP, neuroserpin, phosphorylated axonal neurofilament subunit H and visinin-like protein 1	Increased neuroserpin levels at end of surgery versus baseline predicted the occurrence of both POCD (AUC 0.655, 95% CI 0.54–0.77) and delirium (AUC 0.643, 95% CI 0.52–0.77); neuroserpin levels were significantly higher on postoperative day 7 than at the end of surgery or on postoperative day 1 in all groups; levels of GFAP, phosphorylated axonal neurofilament subunit H and visinin-like protein 1 were not associated with neurological complications	Neuroserpin might be a predictor of type 2 neurological complications after off-pump CABG surgery	259
Georgiadis et al. (2000)	190 patients undergoing elective cardiac surgery (CABG surgery, valve replacement or both)	Prospective, observational cohort study	S100B and γ-enolase	S100B and γ-enolase levels were associated with the severity of postoperative neurological complications and had diagnostic specificity of 89% and 79%, respectively, in identifying patients with stroke, coma or stupor outcomes; S100B (but not γ-enolase) level was an independent predictor of adverse neurological outcome (OR 16.2, $P<0.0004$)	S100B is a predictor of adverse neurological outcome	249
Lloyd et al. (2000)	60 patients with known neurological abnormality undergoing CABG surgery (randomly assigned to on-pump or off-pump)	Prospective, randomized controlled trial	S100B	S100B level was higher in the on-pump group than the off-pump group at 30 min after the procedure, but this difference was no longer apparent at 4 h postoperatively; the extent of changes in S100B level was unrelated to the index of neuropsychological deterioration	S100B level unrelated to postoperative neurological deterioration	250
Lazibat et al. (2012)	62 men undergoing elective aortocoronay bypass	Prospective, observational study	S100B	Perioperative cerebral microembolization was significantly more pronounced with on-pump than with off-pump surgery but was not associated with early postoperative neurocognitive function; increase in S100B level immediately postoperatively and 48 h after surgery correlated with the number of HITS ($r=0.708$, $P<0.0001$ and $r=0.269$, $P=0.0359$) and was a significant predictor of POCD ($r=-0.337$, $P=0.0098$)	S100B level is associated with HITS and POCD	248
Alserr et al. (2019)	30 patients undergoing CAS or CEA	Prospective, observational cohort study	S100B	S100B level was higher after CAS than after CEA (331.3 pg/ml versus 76.3 pg/ml; $P=0.01$); type I and type II plaques were associated with higher S100B levels in CAS than in CEA ($P=0.048$); S100B level increased in patients undergoing CEA whose contralateral cerebral hemisphere oximetry value was <60% ($P=0.043$), which is a marker of hypoperfusion probably attributable to embolization	S100B level is a useful biomarker for silent brain injury in carotid revascularization	396
Nurcahyo et al. (2022)	56 patients undergoing on-pump CABG surgery	Retrospective cohort study	GFAP	POCD was related to longer cardiopulmonary bypass and cross-clamp surgery times ($P=0.002$ and $P=0004$); postoperative GFAP level in patients with POCD was significantly higher than in patients without POCD (12.95±7.47 versus 3.80±2.77 pg/ml; $P<0.001$); the difference (delta change) between preoperative and postoperative GFAP levels was significantly greater in patients with POCD than in patients without POCD (8.28±7.24 versus −1.5±3.03 pg/ml; $P<0.001$); AUC value of GFAP against POCD was 0.887; GFAP cut-off level: 4.750 pg/ml, with 92.9% sensitivity and 71.4% specificity	Postoperative GFAP levels and rise in GFAP levels preoperatively to postoperatively are associated with POCD after CABG surgery	258

Aβ40, amyloid-β protein 40; Aβ42, amyloid-β protein 42; AF, atrial fibrillation; AUC, area under the receiver operating characteristic curve; AVR, aortic valve replacement; CABG, coronary artery bypass graft; CAS, carotid artery stenting; CEA, carotid endarterectomy; DW-MRI, diffusion-weighted MRI; GFAP, glial fibrillary acidic protein; HITS, high-intensity transient signal; NFL, neurofilament light polypeptide; NPV, negative predictive value; POCD, postoperative cognitive decline; PPV, positive predictive value; tau, microtubule-associated protein tau; TAVI, transcatheter aortic valve implantation; TMAO, trimethylamine *N*-oxide. [a]Patients with postoperative POCD or delirium were compared with a control group of patients without neurological complications ($n=48$).

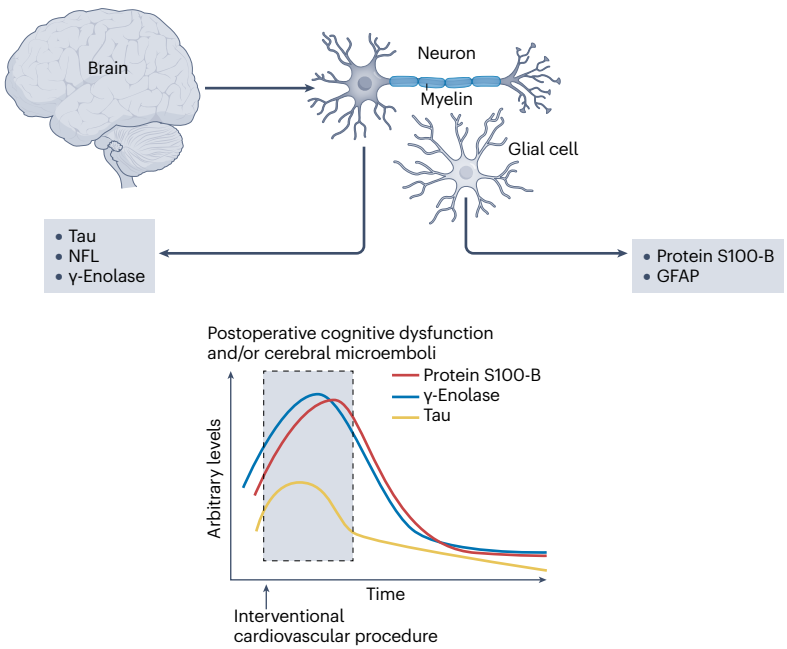

Fig. 7 | Biomarkers of brain damage and cognitive dysfunction after cardiovascular interventional procedures. Protein S100B regulates intracellular calcium levels and is concentrated in glial cells (mainly astrocytes), but it is also detectable in pulmonary alveolar cells, cardiomyocytes, chondrocytes and adipocytes. Glial fibrillary acidic protein (GFAP) is found in astrocytes in the central nervous system but also in non-myelinating Schwann cells in the peripheral nervous system and in enteric glial cells. GFAP is responsible for the cytoskeletal structure of glia and the blood–brain barrier. Microtubule-associated protein tau promotes the self-assembly of tubulin into microtubules (protein polymers of the cytoskeleton that act to stabilize the shape of the cell, mitosis and intracellular transport) and is found mainly in the axons of the central nervous system. Neurofilament light polypeptide (NFL) is a scaffold protein that is mainly concentrated in myelinated axons. NFL supports the structural stability of the neuron and improves the speed of nerve conduction. γ-Enolase is found in the cytoplasm of neurons but also in cells with neuroendocrine differentiation, lymphocytes, platelets and erythrocytes. γ-Enolase might have a role in promoting both neuroinflammation and neuroprotection.

are available[262]. An integrated, multidisciplinary approach including the stroke physician, interventional cardiologist, internist, coagulation specialist, neurologist, radiologist, anaesthesiologist and potentially other physicians is of utmost importance to decide on the optimal treatment[263].

In patients with periprocedural embolism and subsequent cerebral large-vessel occlusion accompanied by a functionally relevant neurological deficit (NIH Stroke Scale ≥6), emergent endovascular thrombectomy with a stent retriever or primary thrombus aspiration is indicated[10,264]. Seminal RCTs demonstrated the efficacy of endovascular thrombectomy in occlusions of the distal internal carotid artery and the first (M1) and proximal part of the second (M2) segments of the middle cerebral artery[265]. Benefit is greatest in patients treated within 6 h of symptom onset, but data support the benefits of endovascular thrombectomy even in patients with severely disabling deficits and who already have signs of extensive infarction[266,267]. Advanced neuroimaging can guide the selection of treatment candidates with relevant salvageable tissue. In selected patients, endovascular thrombectomy of more distal vessels might be an option, with careful consideration of the procedural risks, the likelihood of recanalization and the severity of the clinical deficits[268]. High-quality evidence to support this approach is lacking, but clinical trials are under way[269,270].

RCT data suggest the efficacy of endovascular thrombectomy in basilar artery occlusions up to 24 h after the onset of symptoms, especially in patients with severe neurological deficits[271,272]. Evidence supports the administration of intravenous thrombolysis to otherwise-eligible patients, even if endovascular thrombectomy is planned[273]. If cerebral vessel occlusion is evident before completion of the cardiovascular intervention, the vascular sheath should be left in place for endovascular thrombectomy access.

Intracranial haemorrhage. Patients undergoing invasive cardiovascular procedures are commonly receiving, or receive loading doses of, antithrombotic agents, including antiplatelets, anticoagulants and thrombolytics. Therefore, ICH can (spontaneously) occur during or early after the procedure. Given the high mortality (approximately 20–50%) early after ICH, immediate treatment is required[40,274,275]. Haematoma expansion is the only modifiable predictor of ICH outcome[276,277]. Therefore, immediate blood pressure stabilization is required because elevated blood pressure levels are associated with greater haematoma expansion[11,278]. Blood pressure-lowering drugs with rapid onset and short duration of action should be used to facilitate titration and sustained blood pressure control, aiming at a systolic blood pressure of 130–150 mmHg[11]. Of note, very intense and rapid blood pressure lowering below this threshold is potentially harmful and should be avoided[11,279]. Another preventive measure to counteract haematoma expansion is immediate interruption and reversal of action of ongoing antithrombotic agents. With (single or dual) antiplatelet therapy involving aspirin, clopidogrel, ticagrelor and/or prasugrel, no specific reversal therapy has been approved[278]. Platelet transfusion with or without desmopressin has been discussed, but RCT data suggest worse outcomes in patients with ICH who are receiving antiplatelet therapy and are treated with platelet infusion[280]. Therefore, guidelines recommend not to use platelet infusions in this setting[11,278].

In patients receiving OAC with a VKA, four-factor prothrombin complex concentrate is recommended when the international normalized ratio is ≥2.0 (ref. 11). Intravenous vitamin K should be administered directly after the four-factor prothrombin complex concentrate to prevent a later increase in the international normalized ratio and associated haematoma expansion[11]. In patients receiving a DOAC (dabigatran or the factor Xa inhibitors apixaban, edoxaban or rivaroxaban), the specific antidote should be immediately administered[11]. If the specific antidote is unavailable, (activated) prothrombin complex concentrate can be used instead[11]. Haemodialysis can be considered for the removal of dabigatran only[11].

With either unfractionated or low-molecular-weight heparin, reversal of action should be achieved with intravenous administration of protamine sulfate[11]. No specific measures have been recommended for

Table 3 | Consensus statements and recommendations

Consensus statements and recommendations	Level of evidence
Perioperative assessment	
A careful preoperative assessment of the patient is necessary to ensure the best clinical conditions in haemodynamic, coagulative and metabolic terms to control the perioperative and postoperative risk of brain injury	5
For surgical procedures, an adequate preoperative assessment and an appropriate postoperative assessment will reduce the risk of brain injury	5
Procedural technique	
Careful device preparation and proper procedural technique are pivotal to minimize the risk of brain injuries in all invasive procedures	5
For left-sided heart ablation procedures, use continuous, high-flow perfusion of sheaths placed in the left cardiac chambers and mitigation measures to control radiofrequency energy delivery to reduce overheating	3
Minimization of left-sided heart and aortic manipulation is recommended	4
Replacement of a severely atherosclerotic ascending aorta (porcelain aorta) can be considered before manipulation in cardiac surgical procedures	4
Preventive measures	
Standardized, comprehensive training programmes for health-care professionals performing transcatheter interventions can improve procedural safety and reduce the risk of complications, including stroke	5
Collaborative decision-making involving multidisciplinary teams comprising cardiologists, cardiac surgeons, neurologists and imaging specialists can optimize patient care and minimize the risk of complications when planning complex cardiovascular interventions	5
Prescribe uninterrupted preprocedural anticoagulation if feasible; otherwise, timely interruption of oral anticoagulation, based on the individual agent and renal function; combine heparin bolus with continuous heparin treatment to achieve adequate activated clotting times during left atrial and other cardiovascular procedures with relevant embolic risk	3
Use of antithrombotic therapies could be beneficial in reducing the risk of brain injury in patients undergoing left atrial appendage closure	3
CT scans of the ascending aorta should be considered in patients aged >70 years and/or with signs of extensive generalized atherosclerosis before surgical procedures involving aortic manipulation	4
In the absence of a CT scan, epi-aortic ultrasonography should be considered to identify atheromatous plaques and select the optimal surgical strategy	4
Routine use of cerebral protection devices during transcatheter aortic valve implantation is not recommended	2
Diagnostics	
Implementation of a standardized postprocedural protocol, including early recognition of neurological deficits, appropriate and timely imaging, and a subsequent accurately coded procedure, is crucial to the detection and management of procedure-related acute brain injury	4
Routine measurement of biomarkers to detect and monitor acute brain injury is not recommended	3
Treatment	
An integrated, multidisciplinary approach is needed to optimize treatment choice, based on the specific characteristics of the patient	5
Decisions about performing thrombolysis in patients with a brain injury after an invasive cardiovascular procedure need to consider the bleeding risk related to the index procedure and the individual patient	4
In patients undergoing planned endovascular thrombectomy, intravenous thrombolysis is a reasonable bridging strategy, if the individual bleeding risk of the patient allows its application	1
In patients with large-vessel occlusion with relevant neurological deficit (NIH Stroke Scale ≥6), endovascular thrombectomy or thrombus aspiration is indicated	1
The benefit of endovascular thrombectomy is greatest when patients are treated within 6 h of symptom onset, but in patients with severe disabling deficits and extensive brain infarct signs, treatment could be indicated for longer-lasting symptoms of periprocedural embolism	1
Use of endovascular thrombectomy in more distal vessels should be based on the careful consideration of procedural risks, likelihood of recanalization and severity of clinical deficits	4
Immediate blood pressure control and stabilization are recommended in patients with intracranial haemorrhage and hypertension, with the goal of achieving a systolic blood pressure of 130–150 mmHg	3
Very intense and rapid blood pressure lowering below the optimal range is potentially harmful and should be avoided in the acute phase of intracranial haemorrhage	3
Platelet transfusions in patients receiving single or dual antiplatelet therapy are not recommended	3
Immediate reversal of ongoing anticoagulant treatment with dedicated reversal agents is recommended in patients with intracranial haemorrhage	3
After revascularization procedures are completed, admission of patients with brain injury to a stroke unit to provide a multidisciplinary approach to care is pivotal to reduce disability and mortality	1
In patients with asymptomatic brain injury, the adequate management of comorbidities and concomitant risk factors is indicated to reduce the risk of long-term detrimental effects	5
Quality of life after a brain injury caused by a major cerebrovascular event is essential from the perspective of patients, given the impact of such events	5

patients treated with thrombolytics. Reversal of associated coagulopathy by the administration of cryoprecipitates, antifibrinolytic agents (tranexamic acid or aminocaproic acid), platelets, fresh frozen plasma, prothrombin complex concentrate or factor VIIa can be considered[281].

Stroke unit treatment. After treatment decisions about revascularization are completed, all patients with stroke should be admitted to a stroke unit (a dedicated ward with organized inpatient stroke care) to reduce disability and mortality[282]. Care in the stroke unit is provided by a multidisciplinary team and entails regular neurological assessments to detect clinical deterioration, awareness of neurological and medical post-stroke complications, establishment of individual secondary prevention measures and early rehabilitation[283].

Asymptomatic brain injury

No therapies have been established for patients who develop covert ABI after cardiovascular procedures. Nevertheless, emerging evidence suggests that asymptomatic, MRI-detected injuries, whether ischaemic or haemorrhagic, could potentially contribute to cognitive deterioration and functional decline in the long term and elevate the risk of future stroke[26]. To mitigate long-term detrimental effects, the incidence of covert ABI should be reported. Comorbidities should be managed, and cardiovascular risk factors should be controlled by increasing physical activity; controlling blood pressure, hypercholesterolaemia and diabetes mellitus; adopting a Mediterranean diet; and abstaining from smoking and excessive alcohol consumption[263,284–286]. Educational programmes and social engagement are instrumental in supporting individuals to reach these health objectives[287–289].

Box 4 | Gaps in knowledge and future directions

- The clinical consequences of covert brain lesions are uncertain.
- The use of cerebral protection devices in left atrial appendage closure is being tested in a randomized controlled trial (RCT) to elucidate their role in reducing the risk of acute brain injury.
- Data on the efficacy and safety of antithrombotic drugs are needed to elucidate the best treatment strategies.
- Data from RCTs are needed to determine the benefits and optimal strategy for reversing anticoagulation in patients with intracranial haemorrhage who are taking oral anticoagulants.
- New transcatheter devices with enhanced design features are needed to reduce the risks of embolization and thrombus formation.
- Advances in minimally invasive surgical techniques, such as off-pump procedures and less-invasive access routes, could continue to lower the likelihood of perioperative stroke during cardiovascular surgeries.
- More evidence is needed to identify whether radiofrequency ablation guided by tissue temperature or newer ablation techniques such as pulsed-field ablation reduce the risk of symptomatic and asymptomatic acute brain injury compared with conventional modalities.
- Cerebral protection devices in patients undergoing transcatheter aortic valve implantation have a good safety profile but have not shown clinically meaningful benefits.
- More data are needed to identify patient phenotypes that are likely to benefit from cerebral embolic protection strategies.
- Data on the use of biomarkers to identify acute brain injuries are debated, and more research is needed to identify those biomarkers with sufficient sensitivity and specificity and how to integrate them into clinical management.
- More evidence is needed from RCTs to elucidate the benefit–risk ratio for the use of endovascular treatment in distal vessels.
- Further data are needed from RCTs on the role of the ABC_{stroke} pathway in reducing the burden of acute brain injury on quality of life and the risk of long-term adverse outcomes.

Patient perspectives

In patients undergoing a major cerebrovascular event, whether an ischaemic stroke or a major bleed, the main interest in terms of patient perspective is the overall quality of life (QoL) after recovery from the acute phase. A systematic review and meta-analysis comprised 39 studies enrolling a total of 30,853 patients with ischaemic stroke[290]. In the meta-analysis, which included 17 of the 39 studies, impairment of QoL was high after 1 month of follow-up, with a pooled utility value of 0.42 (95% CI 0.13–0.71)[290], with higher values indicating a better quality of health, and a theoretical maximum value of 1.00 indicating the best possible QoL[290]. This value slightly increased to 0.55 (95% CI 0.43–0.68) after 3 months and to 0.65 (95% CI 0.52–0.78) after 6 months of follow-up[290]. The overall values of QoL then plateaued at 12 months and 24 months, with no further increase[290].

The researchers then investigated the dynamics of QoL according to the functional outcome of patients with ischaemic stroke, showing that self-reported QoL is related to the functional outcome at discharge from hospital after the ischaemic stroke had occurred. Indeed, patients who recovered from ischaemic stroke with no disability (modified Rankin Scale score of 0 out of 6) at hospital discharge had a higher level of QoL (pooled utility value of 0.91, 95% CI 0.85–0.97), but QoL progressively decreased as the level of disability increased[290]. Patients with moderate disability at hospital discharge (modified Ranking Scale score of 3) had an impairment in QoL, with a utility value of 0.54 (95% CI 0.47–0.61)[290].

In the evaluation of which aspects of QoL were impaired in patients with ischaemic stroke, 'usual activity' was most impaired, whereas 'self-care' was least impaired, emphasizing how these patients are heavily compromised in their daily activities[290]. In a trial of rehabilitation for patients with ischaemic stroke, longitudinal changes in QoL were assessed using a specific stroke-related questionnaire[291]. Despite an initial improvement in QoL in the short-term and mid-term follow-up, overall QoL deteriorated over the longer-term (6-year) follow-up, with reductions in the strength, mobility and hand-function domains[291].

Patients with major ICH have been the focus of less research, but similar evidence is available. In a study investigating 657 patients with haemorrhagic stroke, one-third of the study population had a severely reduced utility score (<0.50) at 90 days, and 87% reported a utility score lower than that of the general population[292]. Again, the functional outcome according to modified Rankin Scale positively correlated with the overall QoL[292].

Rehabilitation programmes are crucial in achieving a substantial improvement in the overall QoL in patients with a major cerebrovascular event. A systematic review and meta-analysis of 1,451 patients with stroke or TIA showed a significant beneficial effect of exercise interventions on overall QoL at hospital discharge, in both physical and mental health dimensions[293]. However, the mean difference in utility

values was numerically but not significantly increased compared with baseline after 3–9 months of follow-up[293].

Integrated care management, going beyond the pharmacological treatment of the disease, seems to achieve greater reductions in the risk of major adverse outcomes. An integrated care management approach should consider the main evidence-based pharmacological therapies, the symptomatic and/or functional status and the evidence-based management of associated comorbidities at the same time. This approach has been proposed and validated in AF, through the Atrial fibrillation Better Care (ABC) pathway, which was shown to reduce all the major adverse outcomes in this clinical context[294] and is now recommended by international clinical guidelines[295].

A consensus paper from the European Society of Cardiology Council on Stroke proposed an ABC_{stroke} pathway to optimize the clinical management of these patients[263]. The ABC_{stroke} pathway is based on three main pillars: appropriate antithrombotic therapy, better functional and psychological status, and cardiovascular risk factors and comorbidity optimization (including lifestyle changes)[263]. In a holistic, integrated care management strategy, achieving an improvement in QoL and functional outcomes is at the centre of the clinical needs of patients with a major cerebrovascular event[263]. In a retrospective evaluation of a clinical strategy that resembles the ABC_{stroke} pathway, adherence to the integrated approach was associated with reduced risks of stroke recurrence (HR 0.61), major adverse cardiovascular events (HR 0.59) and all-cause death (HR 0.22)[296]. The magnitude of risk reduction correlated with the number of ABC_{stroke} criteria attained.

Consensus statements, limitations and future research

Our consensus statements and recommendations are presented in Table 3. Notwithstanding, we identify several limitations and opportunities for future research.

We acknowledge that, despite the extensive and thorough literature search conducted, some relevant studies might not have been captured by this search and, consequently, not included in this document. Furthermore, despite using a formal recommendations system, applying the Oxford Centre for Evidence-Based Medicine method can be difficult in complex and multidisciplinary topics with limited high-quality evidence. Although we tried to identify and report as much data as possible on worldwide cohorts, most of the available data are from European and American cohorts, which limits the knowledge on this topic and the generalizability of our statements.

Other general aspects of the available studies on ABI represent limitations to this Consensus Statement. Most of the studies focused on short-term follow-up, with longer-term studies needed to understand the persistence of subclinical lesions and the effect of ABI on cognitive function, delayed complications and overall prognosis. Greater patient awareness of the symptoms of ABI is needed, and the involvement of patient-reported outcomes in future studies would improve the knowledge in this field and produce more solid recommendations.

We collected extensive data on risk factors (Boxes 2 and 3), but information on patient profiles and phenotypes in terms of specific factors (such as anatomical considerations and calcification burden) that are more prone to develop ABI is scarce and needs further research. We have given overviews of antithrombotic drug management in the various sections of this Consensus Statement, but more data are needed, and the optimal regimens remain areas of ongoing research. Modification of anticoagulation protocols based on patient-specific factors could improve safety.

The main gaps in knowledge and the future research needed in this clinical field are presented in Box 4. Implementation of our recommendations, together with advances in research, will improve the assessment and management of ABI in patients undergoing invasive cardiovascular procedures, with the aim of improving their care and outcomes.

Conclusions

ABI after invasive cardiovascular procedures remains a clinically relevant entity. Across the various procedures, a broad spectrum of risk factors can predispose patients to the onset of ABI. The pathophysiological mechanisms differ substantially according to the procedure, although some mechanistic pathways are shared. The clinical presentation of patients can vary, with a high prevalence of asymptomatic ABI. The use of mitigating strategies is crucial to reduce the risk of ABI, but more evidence is needed from RCTs on the use of CPDs. Regarding therapeutic approaches, evidence for the use of thrombolysis in patients with ABI after cardiovascular procedures is limited, necessitating an individualized and multidisciplinary approach to identify the benefit–risk ratio. Conversely, the use of endovascular treatment is more evidence based, particularly within the first 6 h of the onset of symptoms, but more evidence is needed on the use of endovascular procedures in more distal vessels. Optimization of care in patients with ABI is pivotal to improve QoL and reduce the risk of future adverse outcomes. The ABC_{stroke} pathway might be the best option to streamline holistic or integrated care management in these patients.

Published online: 11 October 2024

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Acknowledgements
R. Lenarczyk receives funding from the European Union (EU)'s Horizon 2020 research and innovation programme under grant agreement No. 847999 — PROFID-EHRA Project. M.P. is the Italian national leader of the AFFIRMO project on multimorbidity in atrial fibrillation, which has received funding from the EU's Horizon 2020 research and innovation programme under grant agreement No. 899871. W.D. has received research support to his Institute from the EU (Horizon 2020), the German Ministry of Education and Research and the German Center for Cardiovascular Research. G.Y.H.L. is a National Institute for Health and Care Research Senior Investigator and co-principal investigator of the AFFIRMO project on multimorbidity in atrial fibrillation, which has received funding from the EU's Horizon 2020 research and innovation programme under grant agreement No. 899871.

Author contributions
The authors contributed substantially to all aspects of the article.

Competing interests
R. Lenarczyk has received consultant and lecture fees from Abbott and Boston Scientific. J.K. has received lecture fees from AstraZeneca and Pfizer. W.D. has received consulting fees and speaker honoraria from Aimediq, Bayer, Boehringer Ingelheim, Boston Scientific, Cardiomatics, Medtronic and Vifor Pharma; travel support from Pharmacosmos; and research support from Boehringer Ingelheim and Vifor Pharma. N.M.V.M. has received research grant support from Abbott Vascular, Boston Scientific, Daiichi–Sankyo, Medtronic, Meril, PulseCath BV and Teleflex; and has received advisory board fees from Abbott Vascular, Amgen, Anteris, Boston Scientific, Daiichi–Sankyo, JenaValve, Luma Vision, Medtronic, Pie Medical, PulseCath BV, Siemens and Teleflex. J.K. is a proctor and consultant and has a research contract for Boston Scientific. R. Lorusso is a consultant for LivaNova and Medtronic; is a member of the medical advisory board of Eurosets and Xenios; has received research grants from LivaNova and Medtronic; and has received a fee for presentation from Abiomed. J.M.R.-C. is a consultant for Idorsia Pharmaceuticals. A.C. is a speaker and consultant for Abbott Vascular, Abiomed, Boston Scientific, Biosensors, Medtronic and Menarini. G.Y.H.L. is a consultant and speaker for Anthos, BMS–Pfizer, Boehringer Ingelheim, Daiichi–Sankyo; no fees are received personally. The other authors declare no competing interests.

Additional information
Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41569-024-01076-0.

Peer review information *Nature Reviews Cardiology* thanks Raul Moreno and Giuseppe Tarantini for their contribution to the peer review of this work.

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