Biomarkers for advancing diagnosis and prognosis in stroke

Steffen Tiedt, Alejandro Bustamante, Alan Cameron, Pol Camps-Renom, Gerrit M Grosse, Johanna Ospel, Bastian Volbers, Heinrich J Audebert, Julia Aulin, Bastian Cheng, Charlotte Cordonnier, Jonathan M Coutinho, Ana Catarina Fonseca, Michael D Hill, Märit Jensen, Christina Jern, Joseph Kamtchum-Tatuene, Mira Katan, Peter J Kelly, Anna Kopczak, Robin Lemmens, Arne G Lindgren, James J M Loan, Christian H Nolte, Laurent Puy, Luca Saba, Rustam Al-Shahi Salman, Else Charlotte Sandset, Magdy H Selim, Pierre Seners, Nikola Sprigg, Hsin-Hsi Tsai, Karen M Doyle, Joan Montaner, Floris H B M Schreuder, Luciano Sposato, Neshika Samarasekera, John J McCabe*, on behalf of the BIOSTROKE investigators†*

Lancet Neurol 2026; 25: 406–20

See **Comment** page 333

*Joint corresponding authors

†Study group members are listed in the appendix (pp 3–7)

Institute for Stroke and Dementia Research, LMU University Hospital, LMU Munich, Munich, Germany (S Tiedt PhD, A Kopczak MD); **Stroke Unit, Department of Neurology, Hospital Universitari Germans Trias i Pujol** (A Bustamante PhD), **Neurovascular Research Laboratory, Vall d'Hebron Institute of Research (VHIR)** (J Montaner MD), **Universitat Autònoma de Barcelona, Barcelona, Spain; School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, UK** (A Cameron PhD); **Stroke Unit, Neurology Department, Institut de Recerca Sant Pau, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain** (P Camps-Renom MD); **Department of Neurology, Hannover Medical School, Hannover, Germany** (G M Grosse PhD); **Department of Neurology and Stroke Center, University and University Hospital Basel, Basel, Switzerland** (G M Grosse, Prof M Katan MD); **Department of Radiology** (J Ospel PhD), **Department of Clinical Neurosciences and Hotchkiss Brain Institute, Cumming School of Medicine** (Prof M D Hill MD), **University of Calgary, Calgary, Canada; Department of Neurology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland** (B Volbers MD); **Center for Stroke Research Berlin** (Prof H J Audebert MD, Prof C H Nolte MD), **Klinik und Hochschulambulanz für Neurologie mit experimenteller Neurologie** (Prof H J Audebert, Prof C H Nolte), **Berlin Institute of Health** (Prof C H Nolte), **Charité–Universitätsmedizin Berlin, Berlin, Germany; Department of Medical**

The complexity and incomplete understanding of the pathophysiology of stroke poses substantial challenges to personalised medicine and the development of novel therapies, as reflected in the neutral results of many randomised trials. Current clinical algorithms lack the precision to diagnose stroke before hospital admission, predict disease progression and recovery, or assess recurrence risk. Biomarkers are urgently needed, yet the absence of a robust evidence base hinders their clinical translation. To lay the groundwork for addressing this knowledge gap, an international multidisciplinary panel of stroke experts conducted a literature review that informed a Delphi consensus process. The stroke experts panel proposes 17 research priorities and five minimum reporting datasets for stroke biomarker studies, each corresponding to a key domain of stroke care: prehospital diagnosis, ischaemic stroke progression, atrial cardiopathy, plaque vulnerability, and intracerebral haemorrhage. This framework will promote consistency and collaboration towards the discovery, validation, and clinical translation of biomarkers to improve stroke care.

Introduction

Stroke is a leading cause of death and disability worldwide.[1] Despite progress in stroke care, particularly with reperfusion strategies, treatment options for both the acute phase and secondary prevention remain scarce, with numerous clinical trials—evaluating different interventions from prehospital blood pressure lowering,[2] to neuroprotection in ischaemic stroke,[3,4] or anticoagulation in suspected atrial cardiopathy[5,6]—unable to show benefit. A major barrier to therapeutic advancements is the limited understanding of the biological mechanisms driving the progression of acute ischaemic stroke and intracerebral haemorrhage, and those contributing to secondary events, including major adverse cardiovascular and cerebrovascular events and post-stroke cognitive impairment. The development of targeted treatments will remain a considerable challenge without deeper insights into stroke pathophysiology in patients. Although preclinical studies have revealed potential molecular pathways involved in infarct progression,[7] haematoma expansion,[8] and stroke recurrence,[9] these discoveries are yet to translate into actionable tools for patient care.

Biomarkers are measurable indicators of biological processes or disease states and can be fluid-based (eg, blood or CSF), electrophysiological, or imaging-derived. In stroke, the most widely used biomarkers are derived from brain and neurovascular imaging and inform treatment decisions, such as thrombolysis.[10] In contrast, biomarkers from blood, other bodily fluids, or tissue are not yet integrated into routine clinical care because of the absence of robust evidence to support their use, in part stemming from small and heterogeneous study cohorts and methodological variability. There is now both a pressing need and opportunity to develop biomarkers to characterise the pathophysiological mechanisms of stroke with greater precision, underscored by several recent neutral trials in stroke and rapid advances in high-throughput biomarker technologies. Biomarkers are needed to enable earlier diagnosis, monitor infarct or intracerebral haemorrhage progression, and identify atrial cardiopathy or culprit atherosclerotic plaques. Ultimately, biomarkers could improve stroke aetiological classification, risk stratification, guide personalised treatment, and accelerate targeted therapy development. In this Personal view, we report a Delphi consensus process that defines 17 research priorities and five minimum reporting datasets for stroke biomarker studies that are aligned to key domains of care. Our goal was to provide a practical framework for designing, analysing, and reporting studies aimed at the discovery and validation of biomarkers that can improve stroke care.

Delphi consensus process

Experts with a background of clinical neurology, neuroimaging, molecular biology, clinical trials, and neuroscience met at the inaugural BIOSTROKE Conference (Munich, Nov 7–8, 2024), where the need for research priorities and minimum reporting datasets was identified and domain-specific discussions were initiated. After the meeting, we constituted dedicated working groups for each domain: prehospital diagnosis; ischaemic stroke (progression and recovery, atrial cardiopathy, and plaque vulnerability); and intracerebral haemorrhage. The working group leads selected members based on their scientific contribution to the field, with due consideration for balance in sex, geography, and disciplinary expertise. Using a Delphi approach informed by a targeted literature review, working group members anonymously proposed research priorities and reporting dataset items, discussed them in conference calls, and completed anonymous voting to select final priorities and dataset items (ie, minimum, preferred, or optional). To ensure global relevance, each priority and minimum dataset item was validated internally by all authors and

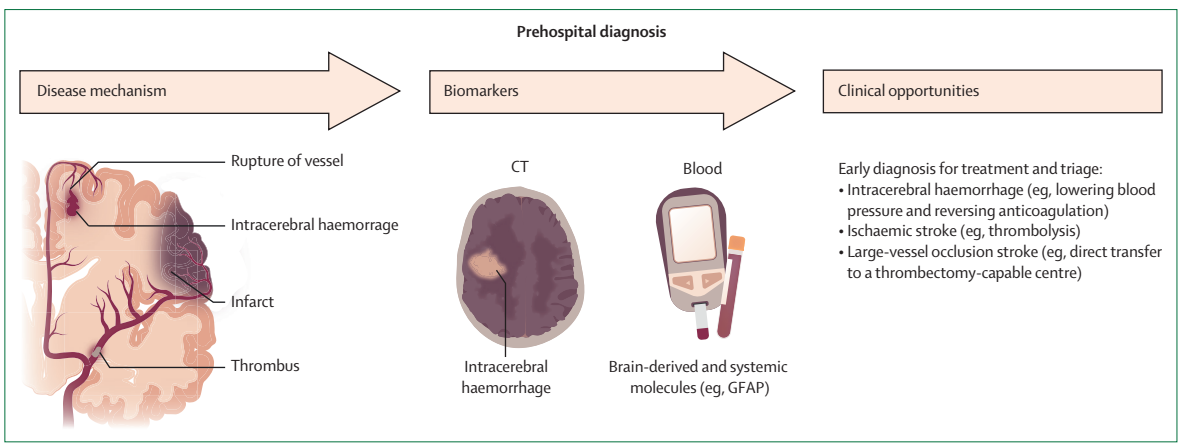


Figure 1: **Biomarker-driven clinical opportunities for prehospital diagnosis**
Intracerebral haemorrhage and ischaemic stroke—primarily caused by vessel rupture or occlusion—define the underlying disease mechanisms (left) that guide biomarker research. Candidate biomarkers could be derived from imaging, primarily CT, and from blood, including both systemic and brain-derived molecules, such as GFAP (centre). Developing biomarkers for stroke subtype diagnosis in the prehospital setting could shorten times to treatment; for example, by enabling early therapy initiation or optimising patient triage and transfer pathways (right). GFAP=glial fibrillary acidic protein.

externally by an independent expert panel. Further details on panel selection and Delphi methodology, including a summary of proposed and standardised definitions of covariates and endpoints are provided in the appendix (pp 10–12 and 37–40). The domain-specific sections present the results of the targeted literature review and the Delphi consensus process.

Prehospital diagnosis

For both ischaemic stroke and intracerebral haemorrhage, reducing the time to treatment is essential for improving outcome.[11,12] A major challenge to implementing effective prehospital stroke treatment is the difficulty in establishing a rapid and accurate diagnosis of stroke and its subtypes. This challenge applies to various prehospital settings that lack neuroimaging capability, including ambulances, small hospitals, and urgent-care facilities. Currently, prehospital stroke care relies almost exclusively on clinical assessment. Yet, established scales, such as the Face-Arm-Speech-Time test, the National Institutes of Health Stroke Scale, and the Rapid Arterial Occlusion Evaluation lack sufficient accuracy to distinguish stroke from stroke mimics, differentiate stroke subtypes, or detect large-vessel occlusion on scene.[13–15] Recent trials using clinical assessment to select patients for prehospital triage or treatment have been neutral: in the Fourth Intensive Ambulance-Delivered Blood Pressure Reduction in Hyper-Acute Stroke (INTERACT4) trial,[2] blood pressure reduction in patients with motor deficits showed worse outcomes for ischaemic stroke but better outcomes for intracerebral haemorrhage, while in the Transfer to the Closest Local Stroke Center vs Direct Transfer to Endovascular Stroke Center of Acute Stroke Patients With Suspected Large Vessel Occlusion in the Catalan Territory (RACECAT) trial,[16] direct transfer to thrombectomy-capable centres for patients with a Rapid Arterial Occlusion Evaluation score of 5 or higher did not improve functional outcome for ischaemic stroke and worsened outcome for intracerebral haemorrhage.[17]

Multiple promising biomarkers—derived from blood, EEG, and ultrasound (figure 1)—have been proposed to differentiate between ischaemic stroke, intracerebral haemorrhage, transient ischaemic attack, and stroke mimics. These tools could enable earlier treatment decisions and prehospital triage. Astrocyte-derived glial fibrillary acidic protein (GFAP) is the most studied blood-based biomarker for intracerebral haemorrhage and improves diagnostic accuracy alone or in combination with other biomarkers, such as the N-terminal pro-B-type natriuretic peptide (NT-proBNP).[18,19] The diagnostic value of GFAP is greatest in the hyperacute phase when intracerebral haemorrhage causes more abrupt blood–brain barrier disruption and astrocytic injury leading to higher GFAP levels than in ischaemic stroke. However, the usefulness of GFAP is low for small-volume intracerebral haemorrhage and when stroke onset time is uncertain. D-dimer and troponin could improve the accuracy of large-vessel occlusion detection when added to clinical scores,[20] but they do not indicate the presence or location of vessel occlusion directly and are unlikely to have clinical use without complementary information. Overall, evidence for these emerging biomarkers remains scarce, largely coming from selected cohorts (ie, cohorts were not representative of all emergency medical service stroke code activations.), and many studies use blood samples obtained only after hospital arrival rather than in true prehospital settings. Studies evaluating the feasibility of implementation, diagnostic performance, and clinical value of point-of-care devices are ongoing.[21] EEG has shown feasibility for its integration into workflows for rapid prehospital large-vessel occlusion detection,[22] but its limitations include the indirect nature of the EEG signal reflecting downstream cortical effects rather than vessel

Sciences, Cardiology and Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden (J Aulin PhD); **Department of Neurology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany** (B Cheng, M Jensen MD); **University of Lille, INSERM, CHU Lille, U1172–Lille Neuroscience and Cognition, Lille, France** (Prof C Cordonnier PhD, L Puy PhD); **Department of Neurology, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands** (Prof J M Coutinho MD); **Department of Neurology, Stroke Unit, Hospital de Santa Maria, Lisbon, Portugal** (A C Fonseca MD); **Institute of Pharmacology and Neurosciences, Centro de Estudos Egas Moniz, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal** (A C Fonseca); **Department of Laboratory Medicine, Institute of Biomedicine, the Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden** (Prof C Jern PhD); **Department of Clinical Genetics and Genomics, Sahlgrenska University Hospital, Gothenburg, Region Västra Götaland, Sweden** (Prof C Jern); **Wolfson Centre for Prevention of Stroke and Dementia, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK** (J Kamtchum-Tatuene PhD); **Stroke Clinical Trials Network Ireland, Dublin, Ireland** (Prof P J Kelly MD, J J McCabe PhD); **School of Medicine, University College Dublin, Ireland** (Prof P J Kelly, J J McCabe); **Stroke Service, Department of Neurology** (Prof P J Kelly), **Stroke Service, Department of Geriatric Medicine** (J J McCabe), **Mater Misericordiae University Hospital, Dublin, Ireland; Department of Neurosciences, Experimental Neurology, KU Leuven–University of Leuven, Belgium** (Prof R Lemmens MD); **Department of Neurology, Leuven University Hospital, Belgium** (Prof R Lemmens); **Department of Neurology, Skåne University Hospital** (Prof A G Lindgren MD); **Department of Clinical Sciences Lund, Neurology, Lund University, Lund, Sweden** (Prof A G Lindgren); **Centre for**

Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK (J J M Loan PhD, Prof R Al-Shahi Salman FMedSci, N Samarasekera PhD); **Deutsches Zentrum für Herz-Kreislaufforschung DZHK, Berlin, Germany** (Prof C H Nolte); **Department of Radiology, Azienda Ospedaliero Universitaria, Cagliari, Italy** (Prof L Saba MD); **Department of Neurology, Oslo University Hospital, Oslo, Norway** (E C Sandset MD); **The Norwegian Air Ambulance Foundation, Oslo, Norway** (E C Sandset); **Institute of Clinical Medicine, University of Oslo, Oslo, Norway** (E C Sandset); **Department of Neurology, Stroke Division, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts, USA** (Prof M H Selim MD); **Neurology Department, Hôpital Fondation A de Rothschild, Paris, France** (P Seners MD); **Université Paris Cité, Institute of Psychiatry and Neurosciences of Paris, INSERM U1266, Team Turc, Paris, France** (P Seners); **Stroke Trials Unit, Division of Mental Health and Clinical Neuroscience, Faculty of Medicine and Health Sciences, University of Nottingham, Nottingham, UK** (Prof N Sprigg PhD); **Department of Neurology, National Taiwan University Hospital, Taipei, Taiwan** (H-H Tsai PhD); **Department of Physiology and Galway Neuroscience Centre, School of Medicine and CÚRAM Research Ireland Centre for Medical Devices, University of Galway, Galway, Ireland** (Prof K M Doyle PhD); **Stroke Research Program, Institute of Biomedicine of Seville, IBiS/Hospital Universitario Virgen del Rocío/CSIC/University of Seville & Department of Neurology Hospital Universitario Virgen Macarena, Seville, Spain** (J Montaner); **Department of Neurology, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, Netherlands** (F H B M Schreuder MD); **Departments of Clinical Neurological Sciences, Epidemiology and Biostatistics, and Anatomy and Cell Biology, Schulich School of Medicine and Dentistry, Heart & Brain Laboratory and Robarts**

Panel: **Research priorities for stroke biomarker development**

Priority order within each domain reflects the clinical care continuum rather than consensus scores.

Prehospital diagnosis

- Biomarkers for diagnosing stroke subtypes to enable treatments (eg, blood pressure lowering in intracerebral haemorrhage) or triage (eg, transfer of large-vessel occlusion stroke)
- Diagnostic biomarkers in cohorts representative of all emergency medical service stroke code activations
- Biomarkers compatible with prehospital constraints, including portability, rapid turnaround time, and cost-effectiveness

Ischaemic stroke progression and recovery

- Biomarkers for guiding clinical decision making in acute ischaemic stroke (eg, for selecting patients for recanalisation strategies)
- Treatment-responsive biomarkers for predicting long-term clinical outcome
- Biomarkers specific to the underlying pathophysiological mechanisms of stroke progression and recovery

Atrial cardiopathy

- Biomarkers for detecting atrial cardiopathy
- Biomarkers for detecting atrial fibrillation after stroke
- Biomarkers for predicting major adverse cardiovascular and cerebrovascular events or cognitive impairment in individuals with atrial cardiopathy

Plaque vulnerability

- Biomarkers for detecting culprit atherosclerotic plaques after acute ischaemic stroke
- Biomarkers for improving vascular risk stratification in individuals with atherosclerotic plaques of the brain-supplying arteries
- Biomarkers to improve patient selection for stroke and cardiovascular prevention therapies in individuals with atherosclerotic plaques of the brain-supplying arteries

Intracerebral haemorrhage

- Biomarkers for differentiating between the underlying causes of intracerebral haemorrhage (ie, macrovascular, microvascular, and non-vascular)
- Surrogate markers for predicting responses to acute interventions (eg, minimally invasive surgery, acute blood pressure lowering, and reversal of anticoagulation)
- Biomarkers of parenchymal or intraventricular haematoma expansion
- Biomarkers of perihaematomal oedema evolution and haematoma resorption
- Biomarkers for predicting intracerebral haemorrhage recurrence, major adverse cardiovascular and cerebrovascular events, or cognitive impairment

status leading to reduced specificity and a high frequency of insufficient quality of data recordings. Novel technologies, including point-of-care ultrasound[23] or volumetric impedance phase shift spectroscopy,[24] have also yielded encouraging results for large-vessel occlusion detection, but findings need to be validated in larger prehospital cohorts of consecutive stroke code activations. Additional limitations include modest sensitivity and specificity of both technologies for detecting large-vessel occlusion and interrater variability for ultrasound.

Building on this evidence, the Delphi consensus process yielded three research priorities that were endorsed by internal and external experts (median agreement 99%, range 86–100%; panel and appendix pp 13–14). The first priority focuses on diagnosing stroke types to enable ultra-early interventions (eg, blood pressure lowering in intracerebral haemorrhage or prehospital thrombolysis in ischaemic stroke) and to support triage decisions (eg, transfer of patients with large-vessel occlusion for endovascular therapy[25] or avoidance of unnecessary transfers of patients with stroke mimics). While GFAP shows promise for intracerebral haemorrhage identification, an equally sensitive and specific biomarker for ischaemic stroke remains to be identified. The second and third priorities highlight methodological challenges specific to the prehospital setting, including patient heterogeneity (eg, high rate of stroke mimics) and requirements for implementation of biomarkers into the prehospital setting. Prospective studies with point-of-care devices in the prehospital setting are needed, followed by trials that base triage or treatment decisions on biomarker results to test the effects on time-to-treatment and patient outcomes. The successful implementation of biomarkers in prehospital care depends on combining diagnostic accuracy with operational simplicity, delivery of rapid and easily interpretable results, portability, and affordability to enable their use across various prehospital scenarios, including ambulances and small urgent-care centres. Given the technological constraints in the prehospital setting, expectations regarding diagnostic performance need to be weighed against what is clinically acceptable in specific scenarios. Differences in health-care systems and the heterogeneous prehospital population that includes a high rate of stroke mimics represent obstacles to biomarker development.[26] To facilitate future collaborative alignment, a minimum reporting dataset was proposed and endorsed, comprising information related to diagnosis, disease severity, and procedural times (table and appendix pp 15–16). Additional items were assigned to preferred and optional reporting datasets.

	Index event and baseline function	Medical history	Medication	Neurovascular imaging	Laboratory and biomarker tests	Cardiac evaluation	Outcomes*
Prehospital diagnosis	Interval from onset and whether known onset; baseline NIHSS; baseline blood pressure; IVT or EVT; blood pressure-lowering acutely; OAC reversal (and agents used)	Atrial fibrillation	None	Brain imaging modality performed (eg, CT or MRI); vascular imaging modality performed (eg, CT angiography or magnetic resonance angiography); LVO, MeVO/DVO	Duration of biomarker measurement; glucose	None	Final diagnosis (eg, ischaemic stroke, intracerebral haemorrhage, TIA, or stroke mimic); in-hospital mortality
Ischaemic stroke: progression and recovery	NIHSS (with subitem scores); pre-stroke mRS; IVT or EVT (and interval to treatment); TOAST	Cardiovascular system risk factors†; alcohol intake; previous stroke or TIA	None	LVO, MeVO/DVO; mTICI score (if EVT)	Glucose	None	Infarct volume at 24 h; functional outcome (ie, mRS 90 days); all-cause death
Atrial cardiopathy	Index event subtype; pre-stroke mRS; EVT; NIHSS; ABCD2 (for TIAs)	Atrial fibrillation on ECG; atrial fibrillation known before stroke *vs* AFDAS; cardiovascular system risk factors†; previous stroke or TIA; peripheral artery disease; chronic kidney disease	Antiplatelets; OAC; statins; anti-hypertensives	LVO	eGFR; LDL; NT-proBNP, or brain natriuretic peptide; Troponin-T or Troponin-I	Transthoracic echocardiography performed; left atrial thrombus; patent foramen ovale; 12-lead ECG	Atrial fibrillation; recurrent ischaemic stroke; intracerebral haemorrhage; myocardial infarction; MACCE‡; cardiovascular death; all-cause death
Plaque vulnerability	Index event subtype; earlier event before presenting (<6 months) and time interval since this earlier event; IVT or EVT; TOAST; pre-stroke mRS; NIHSS; interval from onset	Cardiovascular system risk factors†; active solid organ malignancy; heart failure; alcohol intake; peripheral artery disease; previous stroke or TIA; atrial fibrillation known before stroke *vs* AFDAS; atrial fibrillation on ECG	Antiplatelets; OAC; statins or other lipid-lowering therapy; anti-hypertensives	Imaging modality used to evaluate neuroimaging data and cervico-cranial arteries; presence of acute infarct on imaging, laterality, and territorial pattern; chronic infarct and subtype (lacunar *vs* non-lacunar); maximal wall thickness of the extracranial internal carotid artery plaque; luminal stenosis (%) of the extracranial internal carotid artery plaque; extracranial vertebral artery (V1–V3) luminal stenosis; presence of a suspected culprit plaque (irrespective of stenosis severity) in the intracranial circulation (specify location and stenosis severity)	eGFR; C-reactive protein or high-sensitivity C-reactive protein; HbA_{1c}; lipid parameters; interval from stroke to sample measurement	Echocardiography performed (and modality); cardiac rhythm monitoring during follow-up and if AFDAS detected	Recurrent ischaemic stroke; recurrent stroke within the territory of the culprit plaque that caused the index stroke; TIA; intracerebral haemorrhage; myocardial infarction; MACCE‡; cardiovascular death; all-cause death; non-fatal (resuscitated) cardiac arrest; sudden cardiac death; functional outcome (mRS) at 90 days; carotid revascularisation since index stroke, procedure type, and side

(Table continues on next page)

Ischaemic stroke

Progression and recovery

The evolution of brain injury in the hours and days following an ischaemic event, together with subsequent neural reorganisation, are key determinants of clinical outcome. Biomarkers that capture the dynamics of tissue injury and recovery are crucial for informing treatment decisions. In the acute phase, brain injury is determined by imaging. Non-contrast CT-based biomarkers, such as Alberta stroke program early CT score, CT perfusion-derived penumbra and core volumes, and diffusion-weighted imaging lesions on MRI estimate reversible and irreversible injury (figure 2A). These imaging biomarkers inform crucial decisions, including thrombolysis in patients with unknown time of onset.[10] However, current imaging approaches account for only a portion of the observed variability in clinical severity, progression risk, and recovery, leaving key biological processes unmeasured. For example, ischaemic core volume—a cornerstone of clinical treatment decisions—is commonly derived from perfusion imaging but does not capture tissue-level pathophysiology and only has moderate predictive value regarding clinical outcomes.[27] Furthermore, uncertainties remain regarding the benefit of endovascular therapy in medium-vessel occlusions or proximal occlusions with mild symptoms and thrombolysis in extended time windows after stroke onset. In recovery, biomarkers are predominantly functional, reflecting motor, sensory, cognitive, and speech outcomes. Functional neuroimaging and neurophysiological modalities—including functional MRI, PET, EEG, and transcranial magnetic stimulation—could provide insights into neural reorganisation and guide rehabilitation but large multicentre observational studies and clinical trials are currently lacking. For example, the integrative Predict Recovery Potential-2 algorithm based on transcranial magnetic stimulation predicts upper-limb recovery but transcranial magnetic stimulation access is rare.[28,29] As a major dimension of long-term outcomes, post-stroke cognitive impairment is

Research Institute, Western University, London, ON, Canada (Prof L Sposato MD); **Lawson Health Research Institute, London, ON, Canada** (Prof L Sposato)

Correspondence to:
Steffen Tiedt, Institute for Stroke and Dementia Research, LMU University Hospital, LMU Munich, 81377 Munich, Germany
steffen.tiedt@med.uni-muenchen.de

or

John J McCabe, Geriatric Medicine, Mater Misericordiae University Hospital, Dublin 7, Ireland
JohnMcCabe@mater.ie

See **Online** for appendix

	Index event and baseline function	Medical history	Medication	Neurovascular imaging	Laboratory and biomarker tests	Cardiac evaluation	Outcomes*
(Continued from previous page)							
Intracerebral haemorrhage: diagnosis and aetiology	Interval from onset to admission; admission GCS	Cardiovascular system risk factors†; previous intracerebral haemorrhage	Antiplatelets; OAC	Interval from onset to imaging and subsequent scans; intracerebral haemorrhage location; intracerebral haemorrhage volume on initial and subsequent imaging; intraventricular haemorrhage	None	None	None
Intracerebral haemorrhage: progression	Interval from onset to admission; acute blood pressure-lowering; haemostatic therapy (and type) and OAC reversal; osmotic therapy (and type); any acute surgical intervention and type; admission GCS	Cardiovascular system risk factors†; previous intracerebral haemorrhage	Antiplatelets; OAC	Interval from onset to imaging and subsequent scans; intraventricular haemorrhage; intracerebral haemorrhage volume of initial and subsequent imaging; intracerebral haemorrhage location	None	None	Functional outcome (mRS)
Intracerebral haemorrhage: recovery, recurrence, and complications	Interval from onset to admission; acute blood pressure-lowering; haemostatic therapy (and type) and OAC reversal; osmotic therapy (and type); any acute surgical intervention and type; admission GCS	Cardiovascular system risk factors†; previous intracerebral haemorrhage	Antiplatelets; OAC	Interval from onset to imaging and subsequent scans; intraventricular haemorrhage; intracerebral haemorrhage volume of initial and subsequent imaging; intracerebral haemorrhage location	..	..	Functional outcome (mRS); recurrent intracerebral haemorrhage; ischaemic stroke; myocardial infarction; all-cause death; cardiovascular death; MACCE‡; non-cardiovascular death; dementia; cognitive impairment

The interval from index event to biomarker measurement is considered a minimum dataset item across domains. ABCD2=age, blood pressure, clinical features, duration of transient ischaemic attack, and presence of diabetes. AFDAS=atrial fibrillation detected after stroke. eGFR=estimated glomerular filtration rate. EVT=endovascular thrombectomy. GCS=Glasgow Coma Scale. HbA_{1c}=glycated haemoglobin. IVT=intravenous thrombolysis. LVO=large vessel occlusion. MeVO/DVO=medium vessel occlusion/distal vessel occlusion. mRS=modified Rankin scale. mTICI=modified thrombolysis in cerebral infarction score. MACCE=major adverse cardiovascular and cerebrovascular events. NIHSS=National Institutes of Health Stroke Scale. NTproBNP=N-terminal prohormone of brain natriuretic peptide. OAC=oral anticoagulant. TIA=transient ischaemic attack. TOAST=The Trial of Org 10172 in Acute Stroke Treatment. *For each outcome, the time interval between index event and outcome should be reported. †The minimum set of cardiovascular risk factors are defined variably across the domains, but generally refer to hypertension, diabetes, hyperlipidaemia, coronary artery disease, smoking status, and previous stroke or transient ischaemic attack. For further details, refer to the appendix (pp 15–36). ‡It is recommended that major adverse cardiovascular and cerebrovascular events should always at a minimum include the individual components of three-point major adverse cardiovascular and cerebrovascular events: recurrent non-fatal stroke (ie, ischaemic or intracerebral haemorrhage), non-fatal myocardial infarction, and cardiovascular death.

Table: **Minimum reporting dataset recommendations**

common but its onset, domain profile, and trajectory are heterogeneous and difficult to predict.[30,31] Current tools for prediction and monitoring (eg, neuroimaging and neuropsychological testing) are resource intensive and lack stratification thresholds.

Whereas imaging provides only a single snapshot and is often logistically challenging to perform repeatedly, molecular biomarkers offer the opportunity for high-frequency and dynamic monitoring of brain injury and recovery. Novel technologies, such as single-molecule assays, now enable the detection of low-abundance brain-derived proteins, allowing for the quantification of cellular injury with unprecedented sensitivity. Emerging examples include neuronal and glial markers, such as neurofilament light chain (NfL),[32,33] S100B,[34] and brain-derived tau.[35,36] However, head-to-head comparisons of biomarkers with imaging remain scarce and most studies are small, single-centre observational cohorts, and robust validation in large, longitudinal, multicentre studies is lacking. The frequent assessment required for clinical use of biomarkers might depend on the availability of point-of-care technologies. Beyond injury quantification, molecular biomarkers could complement imaging by providing insights into functional multiorgan states preceding structural changes. Biomarkers reflecting experimentally established local and systemic mechanisms—including oxidative stress, excitotoxicity, neuroinflammation, reperfusion injury, gut dysbiosis, and catabolism—could improve the prediction and monitoring of stroke progression and guide treatment development. Promising biomarkers include matrix metalloprotease-9 for reperfusion injury,[37] indole metabolites for gut dysbiosis,[38] and glucose and ketone bodies for catabolism. In recovery, BDNF has the potential to guide timing and modalities of rehabilitation.[39] Higher concentrations of NfL and C-reactive protein during acute stroke have been linked to a greater risk for post-stroke cognitive impairment in observational studies but require validation in large, well-phenotyped cohorts.

Building on this evidence, the Delphi consensus process yielded three research priorities (median agreement 95%, range 89–100%; panel and appendix pp 13–14) directed towards (1) clinical decision making, (2) outcome prediction, and (3) stroke pathophysiological

mechanisms. Together, they offer an analytical framework for the development of meaningful biomarkers. In vitro, animal experiments, and omics studies are required to identify novel biomarkers with subsequent large prospective clinical studies for validation. Future clinical studies should integrate serial blood and imaging assessments to longitudinally characterise disease progression and recovery.[40] The most informative time-point-specific biomarker signatures could then guide patient selection for treatment and rehabilitation trials.[29,41] Ideally, biomarker development is guided by relevant biological mechanisms and aligned with broad, evolving clinical needs. In contrast, focusing on a single, highly specific intended clinical application can carry a higher risk of becoming outdated, as treatment algorithms often evolve more rapidly than the time required to bring a biomarker into clinical use. To facilitate studies combining biomarker modalities, a minimum reporting dataset was proposed and endorsed (table and appendix pp 17–19), incorporating pre-stroke status, acute treatments, procedural time intervals, imaging findings, and long-term functional outcomes.

Atrial cardiopathy

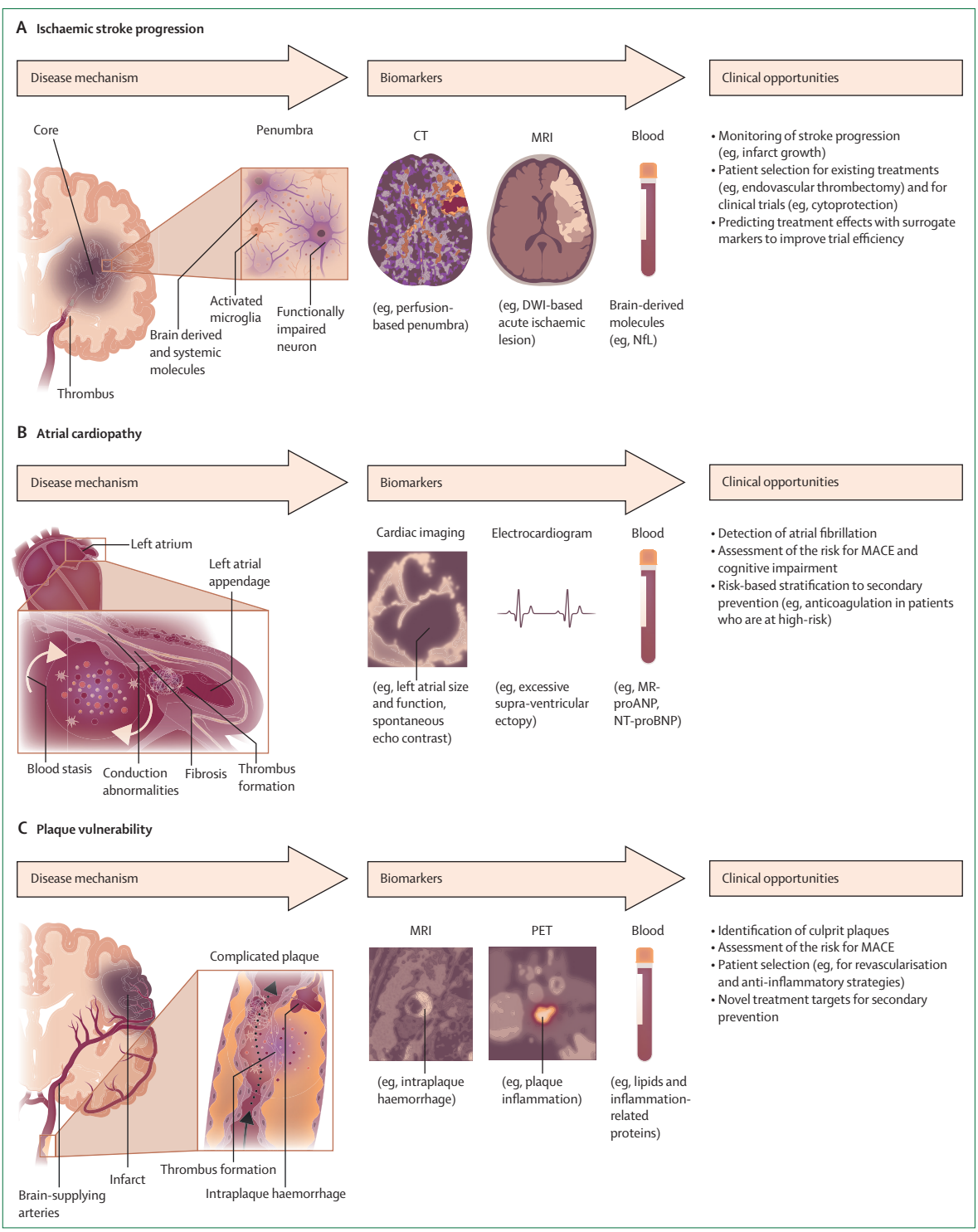
Atrial fibrillation is implicated in one-third of ischaemic strokes. Atrial fibrillation-related stroke carries a high risk of recurrent stroke despite anticoagulation,[42] highlighting an urgent need to improve our understanding of biological processes driving recurrence in patients with atrial cardiopathy, with and without manifest atrial fibrillation.

Atrial cardiopathy is characterised by atrial fibrosis, inflammation, and endothelial dysfunction, with atrial fibrillation as an overt clinical manifestation. Atrial cardiopathy encompasses structural, electrical, and functional left atrial abnormalities that create a prothrombotic state (dependent or independent of atrial fibrillation) leading to stroke and post-stroke cognitive impairment.[43] Atrial cardiopathy biomarkers include findings from cardiac imaging (eg, left atrial fibrosis, size, geometry, strain, and thrombus), ECG (eg, excessive supraventricular ectopy, PR prolongation, and P-wave terminal force in V_1 [$PTFV_1$]), and blood (eg, mid-regional pro-atrial natriuretic peptide [MR-proANP], NT-proBNP, and troponin; figure 2B). Identifying atrial cardiopathy is clinically important because it could justify anticoagulation for secondary prevention, even without documented atrial fibrillation. The Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke (ARCADIA)[5] and Apixaban for Treatment of Embolic Stroke of Undetermined Source (ATTICUS)[6] trials used broad atrial cardiopathy criteria (eg, NT-proBNP >250 pg/mL and indexed left atrial diameter ≥3 cm/m²) to select individuals who might benefit from anticoagulation. Neither trial showed superiority of anticoagulation over aspirin to prevent new ischaemic events. It is possible that the criteria used did not sufficiently enrich for individuals with the highest risk or burden of atrial cardiopathy (without atrial fibrillation) who might derive greatest benefit from anticoagulation. These challenges are amplified by variability in biomarker definitions and thresholds, often due to an absence of internal and external validation,[44] limiting comparability across studies. Internal validation exists for MR-proANP, which can stratify the probability of atrial fibrillation detection in patients with ischaemic stroke[45,46] and might help guide cardiac monitoring.[47] The Midregional Proatrial Natriuretic Peptide to Guide Secondary Stroke Prevention (MOSES; NCT03961334) trial is evaluating the efficacy of anticoagulation for stroke prevention in individuals with elevated MR-proANP levels and recent stroke without atrial fibrillation. The Optimising Atrial fibrillation screening to prevent Second Ischaemic Strokes (OASIS) study is evaluating a care pathway with NT-proBNP to guide patient selection for 28 days of cardiac monitoring after stroke. The Find Atrial Fibrilation 2 (Find-AF 2; NCT04371055) study is evaluating whether ECG-based risk stratification using excessive supra-ventricular ectopy to guide the intensity of cardiac rhythm monitoring is more effective than standard care in preventing recurrent stroke and systemic embolism.[48] The DAYLIGHT trial showed that hyperacute extended CT angiography 6 cm or more below the carina improves detection of cardioaortic thrombi, with implications for use of anticoagulation.[49] Opportunities to discover novel biomarkers of atrial cardiopathy and atrial fibrillation are expanding with technological advances, including smartphone-based atrial fibrillation screening.[50] Emerging ECG, echocardiographic, neuroimaging, and blood-based biomarkers of myocardial or cerebral injury show potential for risk stratification to facilitate earlier, personalised diagnostic and therapeutic approaches to improve outcomes.[46,51,52] For most of these emerging approaches, data are still restricted to few studies, often with modest sample sizes, and evidence that biomarker-guided strategies reduce recurrent stroke is lacking.

Building on this evidence, the Delphi consensus process yielded three research priorities (median agreement 92%, range 86–100%; panel and appendix pp 13–14). These priorities are interrelated and could be addressed by the same or complementary biomarkers, contributing to mechanistic understanding while ensuring clinical relevance. Future studies should assess implementation strategies for atrial cardiopathy biomarkers to guide personalised diagnostic and therapeutic approaches in clinical practice. Identification of optimal biomarker thresholds, combinations, feasibility, and cost-effectiveness is crucial and should be assessed in implementation studies where possible. To support such studies, a minimum reporting dataset was recommended to include pre-existing atrial fibrillation, vascular risk factors, findings from ECG, echocardiography, and blood, and data on secondary prevention (table and appendix pp 20–23).

Plaque vulnerability

Atherosclerosis accounts for at least 20% of all ischaemic stroke. Perhaps unsurprising given the systemic nature of the disease, atherosclerotic stroke is consistently associated with a very high risk of long-term major adverse cardiovascular and cerebrovascular events.[53] Traditional stroke aetiological classification systems have primarily relied on luminal stenosis as the main biomarker for determining stroke aetiology and recurrence risk.[54] However, there is overwhelming evidence indicating that inflammation, neovascularisation, and intraplaque haemorrhage substantially determine plaque



vulnerability.[55–57] Increasing data supports the role of non-stenosing atherosclerotic plaque in the aetiology of embolic stroke of undetermined source and recurrent stroke,[58] which might explain neutral results in trials of anticoagulation in these patients.[5,6,59,60] Indeed, it is highly probable that current aetiological classification algorithms underreport the burden and contribution of atherosclerosis to stroke aetiology and recurrence. Better tools are needed to accurately assign causality to atherosclerosis where present. Moreover, despite the high residual risk of vascular recurrence after atherosclerotic stroke, existing prediction scores for identifying individuals at greatest risk show modest performance and were derived before the advent of modern prevention.[61] Improved risk stratification tools are needed to identify patients who are at high risk for stroke recurrence, patient counselling, clinical decision making, and individualising treatment decisions.

Although carotid revascularisation has proven added benefit compared with best medical therapy alone, the pivotal trials were performed in the 1990s and since then, best medical therapy has advanced substantially.[62] Recent trial data in groups who are at low to intermediate risk of stroke have questioned the benefit of revascularisation over best medical therapy.[63] These data indicate that patient selection based on luminal stenosis alone could be insufficient to identify those at higher risk of stroke who could benefit from revascularisation. MRI or PET imaging can help by capturing high-risk plaque features, such as intraplaque haemorrhage or inflammation (figure 2C) and are an example of how biomarkers could inform patient selection and be incorporated into future randomised controlled trial design. However, clinical use is still restricted by availability and costs[57,64] and simpler imaging modalities and protocols are both needed to tailor treatments with greater precision.

The availability of biomarkers that accurately identify culprit plaques would assist clinicians in assigning causality, thereby also differentiating between competing causes and guiding treatment decisions. Efforts to standardise carotid plaque phenotyping procedures are an important step in this process, but require rigorous validation to confirm improved performance compared with luminal stenosis, both for risk stratification for recurrent stroke and differentiating culprit from non-culprit plaque.[65] Biomarkers could also identify culprit plaques in the aortic arch and vertebral or intracranial arteries that have been relatively understudied so far.[66]

The pathophysiological mechanisms driving the high residual risk of recurrence after atherosclerotic stroke are poorly understood. However, experimental data suggest that innate immune responses to brain infarction, including neutrophil extracellular traps and cell-free DNA, trigger plaque inflammation that contributes to plaque vulnerability.[9] Advances in multiomics technologies might aid the discovery of novel molecular pathways mediating stroke risk and thereby also identify new therapeutic targets for prevention. In the meantime, several new treatment strategies for the prevention of atherosclerotic events have emerged, including anti-inflammatory therapies (eg, colchicine),[67] PCSK9 inhibitors, and lipoprotein(a) reduction. Unfortunately, these treatment strategies have not yet shown clear additional benefit for secondary prevention after stroke. Blood inflammatory markers[68] or direct lipoprotein(a)[69] measurements provide prognostic information for recurrence after stroke, but their clinical value might remain low without demonstrating their value for patient enrichment in trials targeting inflammation or lipoprotein(a), respectively.

Building on this evidence, the Delphi consensus process yielded three research priorities (median agreement 96%, range 86–100%; panel and appendix pp 13–14). To overcome the limitations of heterogeneous cohorts, inconsistent plaque characterisation, and variable outcome definitions, a minimum reporting dataset was proposed and endorsed (table and appendix pp 24–29), focusing on previous vascular events, risk factors, vascular imaging, blood-based biomarkers, and information on secondary prevention and major adverse cardiovascular and cerebrovascular events.

Intracerebral haemorrhage

Intracerebral haemorrhage is a major cause of stroke-related mortality and disability,[70] yet effective treatments remain scarce due to diverse causes and complex pathophysiology. Novel biomarkers to identify the underlying cause and monitor intracerebral haemorrhage progression could help predict complications and enable more targeted treatment and prevention strategies.

Figure 2: **Biomarker-driven clinical opportunities for ischaemic stroke**
(A) Progression: the dynamic evolution of the primary core to a final infarct—a key element of stroke progression—is a major determinant of functional outcome. Mechanisms, such as excitotoxicity, oxidative stress, neuroinflammation, and blood–brain barrier dysfunction influence whether neurons of the penumbra die or survive (left). Routinely used imaging biomarkers, including CT perfusion-based penumbra assessment and MRI-based ischaemic lesion characterisation, already inform clinical decision making. Emerging biomarkers (eg, NfL) reflecting the underlying pathophysiology (centre), could enable high-frequency monitoring, improve patient selection for treatments, and predict treatment responses in clinical trials (right). (B) Atrial cardiopathy: pathophysiological mechanisms, such as blood stasis, atrial wall fibrosis, and conduction abnormalities drive thrombus formation in the left atrium, particularly in the atrial appendage (left). Candidate biomarkers include structural and functional cardiac imaging features (eg, left atrial size, left atrial flow, and spontaneous echo contrast), electrocardiographic biomarkers (eg, excessive supraventricular ectopy, P-terminal force in V1, and advanced interatrial block), and blood-based biomarkers (eg, natriuretic peptides; centre). These biomarkers could improve risk stratification for MACE and guide targeted secondary prevention (right). (C) Plaque vulnerability: complex plaques in brain-supplying arteries—characterised by intraplaque haemorrhage, inflammation, and thin fibrous caps—are rupture-prone and can lead to thrombosis and ischaemic stroke (left). Imaging-based biomarkers from MRI and PET (eg, for intraplaque haemorrhage or inflammation) and blood-based biomarkers (eg, lipid profiles and inflammation-related proteins from the IL-6–C-reactive protein axis), are being explored (centre). These biomarkers could enable early identification of culprit plaques, refine patient selection for secondary prevention strategies, and identify novel treatment targets (right). DWI=diffusion-weighted imaging. MACE=major adverse cardiovascular and cerebrovascular events. MR-proANP=midregional pro-atrial natriuretic peptide. NfL=neurofilament light chain. NT-proBNP=N-terminal pro-B-type natriuretic peptide.

Diagnosis and causes

Intracerebral haemorrhage can result from a range of causes, most commonly microvascular (eg, arteriolosclerosis or cerebral amyloid angiopathy) and, less frequently, macrovascular (eg, arteriovenous malformations or aneurysms) or non-vascular pathologies (eg, metastases; figure 3). Identifying the cause is essential for acute and long-term management, yet even with validated classification schemes and prediction models, the cause remains undetermined in up to 30% of spontaneous intracerebral haemorrhage cases.[71,72] In many other cases, classification remains associative rather than definitive and often requires clinicians to assign a single presumed cause despite the possibility of multiple contributing mechanisms and precipitating factors. Available biomarkers are predominantly imaging-based; blood-based biomarkers are largely lacking. Non-contrast CT provides information on haematoma characteristics, the perihaematomal area, and brain parenchyma. Haematoma features include location,[71] shape (eg, finger-like projections in cerebral amyloid angiopathy),[73,74] and convexity subarachnoid extension.[74] Extensive perihaematomal oedema can indicate an underlying tumour, while calcifications might suggest an arteriovenous malformation. In the parenchyma, white matter lesions and lacunes reflect small vessel disease. Vascular imaging can identify macrovascular lesions or venous sinus thrombosis. MRI detects cavernous malformations, metastases, and small vessel disease-related intracerebral haemorrhage, especially cerebral amyloid angiopathy. The updated MRI-based Boston 2.0 criteria incorporate both haemorrhagic and non-haemorrhagic features with 80% sensitivity and 85% specificity for diagnosing cerebral amyloid angiopathy.[75] As cerebral amyloid angiopathy and arteriolosclerosis often coexist,[76] distinguishing their respective contributions remains challenging. Integrating imaging with other biomarker modalities could improve aetiological assessment and progression prediction, guiding treatment and prevention. Promising biomarker candidates have emerged from genotyping,[73] CSF analyses,[77] and PET imaging;[78] and blood-based biomarkers have been proposed to identify cavernous angioma-related intracerebral haemorrhage.[79] Most of these candidate biomarkers are supported by relatively small, often single-centre cohort studies. Larger diagnostic accuracy studies with external validation are needed before clinical adoption.

Progression

Multidimensional care bundles have reduced early intracerebral haemorrhage mortality,[80] yet outcomes remain poor. A major contributor for poor outcomes is intracerebral haemorrhage progression—defined as clinical deterioration after onset—with haematoma expansion and perihaematomal oedema growth as key drivers (figure 3).[81,82] Haematoma expansion is associated with coagulation biomarkers (eg, activated partial thromboplastin-time), non-contrast CT features (eg, haematoma volume and island sign),[83] and CT angiography-based spot sign. However, haematoma volume only moderately predicts long-term functional outcome, and tools to monitor underlying tissue injury or evolving secondary injury in the perihaematomal area are lacking. Experimental and human ex vivo data suggest multiple mechanisms—including mass effect, inflammation,[84–86] blood product toxicity, and excitotoxicity—contribute to injury.[8] While these processes present potential therapeutic targets, no clinically established biomarkers exist to monitor them. Inflammatory biomarkers (eg, neutrophil-to-lymphocyte ratio) correlate with larger perihaematomal oedema volumes, but findings are inconsistent across heterogeneous study designs and populations and no blood-based biomarker consistently correlates with both oedema and long-term functional outcome.[87] Also, the potential of tau isoforms and NfL to map brain-injury trajectories in intracerebral haemorrhage for early patient stratification remains underexplored. Overall, data on blood-based biomarkers in intracerebral haemorrhage progression are restricted to small observational studies, and robust prognostic or monitoring biomarkers to identify susceptible patients, track progression, and guide trials remain an urgent unmet need. To discover novel biomarkers, approaches integrating serial blood and CSF biomarker profiling with imaging are promising. Such studies can leverage standardised pipelines for repeated volumetric assessments while accounting for intraventricular extension, oedema, and location. Longitudinal studies exploring local and systemic pathophysiology, including inflammation (eg, body temperature and cytokines), could improve understanding of the biological processes driving intracerebral haemorrhage progression and recovery and identify subgroups that might benefit from targeted therapies.

Long-term complications

People who have recovered from intracerebral haemorrhage are at elevated risk of both haemorrhagic and ischaemic major adverse cardiovascular and cerebrovascular events and post-stroke cognitive impairment.[88,89] Current prognostic biomarkers are largely imaging-based. MRI-based biomarkers of cerebral amyloid angiopathy, such as superficial siderosis and convexity subarachnoid haemorrhage, are associated with increased risk of post-stroke cognitive impairment[89] and recurrent intracerebral haemorrhage.[90] Non-haemorrhagic MRI biomarkers, including lacunes and asymptomatic diffusion-weighted imaging lesions, can also predict recurrent intracerebral haemorrhage and ischaemic stroke.[91] The global cerebral small vessel disease score combines haemorrhagic and non-haemorrhagic MRI biomarkers to predict post-stroke cognitive impairment with 83% sensitivity and 91% specificity,[92] although

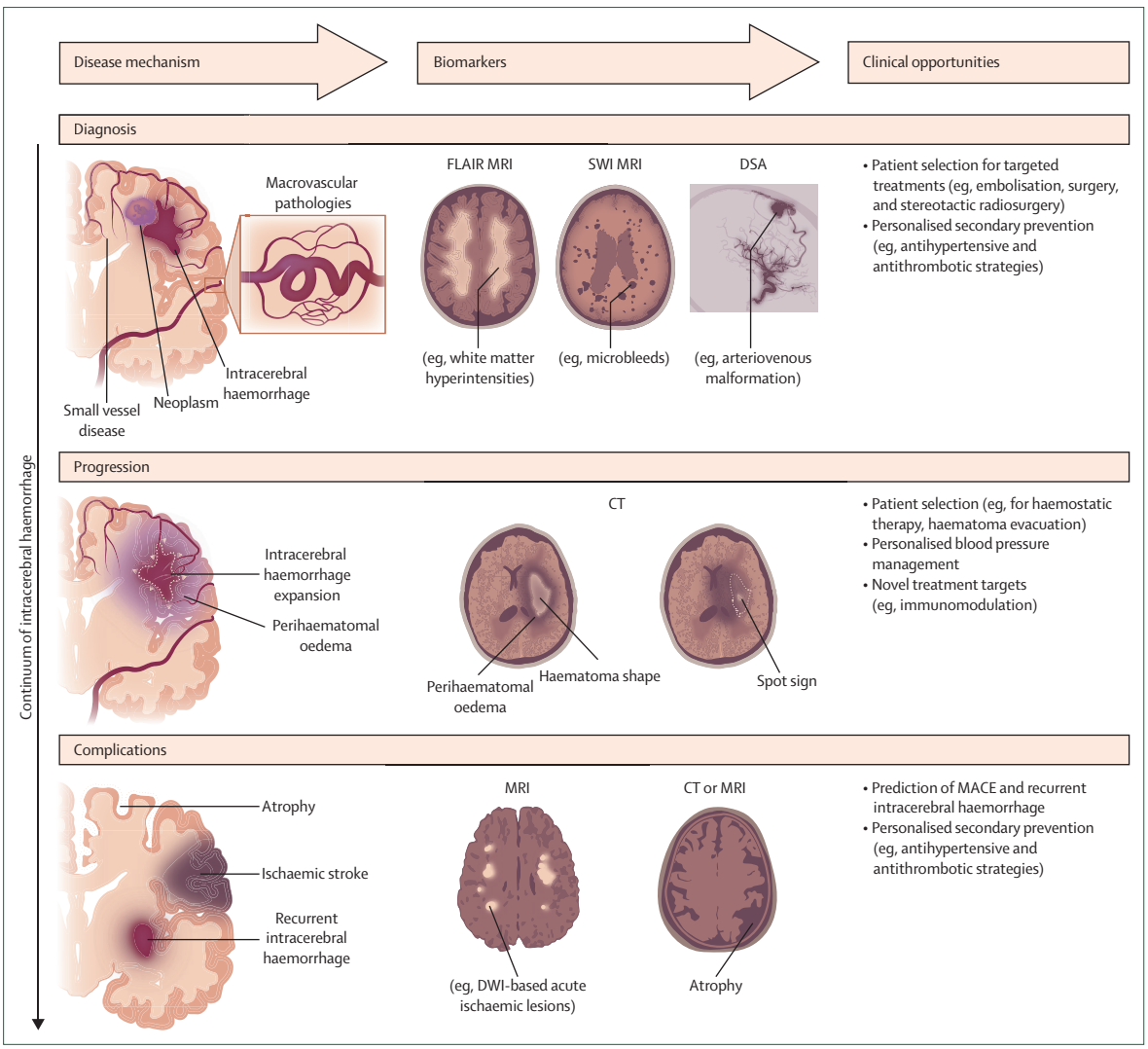


Figure 3: **Biomarker-driven clinical opportunities for intracerebral haemorrhage**
Top row: diagnosis. Intracerebral haemorrhage can result from a range of causes, including small vessel disease, macrovascular abnormalities, and non-vascular pathologies, such as neoplasms (left). Several imaging-derived biomarkers are routinely used to support aetiological classification (centre). Novel biomarkers could help resolve currently undetermined cases and guide personalised treatment and secondary prevention strategies (right). Middle row: progression. Haematoma expansion and perihaematomal oedema are key drivers of intracerebral haemorrhage progression (left), yet the underlying mechanisms (eg, neuroinflammation) remain incompletely understood. Routinely used imaging-based biomarkers, including the spot sign support prediction of disease trajectories (centre), while novel biomarkers reflecting the underlying mechanisms could provide opportunities for patient selection, personalised acute management, and identify novel treatment targets (right). Bottom row: complications. Long-term complications of intracerebral haemorrhage include recurrent haemorrhage, ischaemic stroke, and brain atrophy (left). Whereas imaging-based biomarkers exist (centre), they are not routinely used for long-term longitudinal monitoring. Translating emerging biomarkers into clinical care could improve prediction of MACE and cognitive decline and enable targeted secondary prevention (right). DSA=digital subtraction angiography. DWI=diffusion-weighted imaging. FLAIR=fluid attenuated inversion recovery. MACE=major adverse cardiovascular and cerebrovascular events. SWI=susceptibility-weighted imaging.

external validation is missing. CT biomarkers of cerebral amyloid angiopathy, such as subarachnoid haemorrhage and finger like projections,[73] inform intracerebral haemorrhage recurrence risk,[93] but their association with post-stroke cognitive impairment or major adverse cardiovascular and cerebrovascular events is underexplored.[94] Blood-based biomarkers for predicting post-stroke cognitive impairment and major adverse cardiovascular and cerebrovascular events after intracerebral haemorrhage have not been systematically studied. Inflammation might be a driver of post-stroke cognitive impairment,[95] but studies of inflammatory biomarkers, such as C-reactive protein, have been small and heterogeneous, often combining intracerebral haemorrhage and ischaemic stroke populations.[96] Our understanding of the mechanisms driving complications, such as post-stroke cognitive impairment and major adverse cardiovascular and cerebrovascular events,

Search strategy and selection criteria

References for this Personal view were identified from searches of OVID MEDLINE for papers published between Jan 1, 2015, to Jan 1, 2025, and references from relevant articles. Various keywords, including for stroke, imaging markers, blood markers, diagnosis, and prognosis were used (appendix pp 8–9). Original research articles and, when appropriate, high-impact reviews were included. Case series or abstracts were excluded. Language was restricted to English (appendix p 41). The final reference list was generated based on the relevance to topics covered in this Personal view.

remains limited. Although recurrent intracerebral haemorrhage is commonly attributed to cerebral amyloid angiopathy or hypertension,[97] it might result from a broader interplay of vessel and tissue pathologies—including arteriolosclerosis, diabetic vasculopathy, impaired blood-brain barrier integrity, and chronic inflammation—all of which could shape the phenotype and relative risk of haemorrhagic versus ischaemic complications.[98] Importantly, the observed associations between imaging findings and post-stroke cognitive impairment might reflect shared underlying processes, such as co-evolving cerebral amyloid angiopathy and Alzheimer's disease, rather than direct causality, highlighting the need for mechanistically informed biomarkers. Existing prognostic models rely predominantly on imaging, and there is a paucity of validated blood-based biomarkers or multimodal signatures to predict post-stroke cognitive impairment and major adverse cardiovascular and cerebrovascular events after intracerebral haemorrhage. Prediction models incorporating biomarkers that directly reflect relevant pathophysiology could improve risk stratification, enable identification of individuals at high-risk, and support the selection of patients for antithrombotic medications and other preventive strategies. Longitudinal studies integrating clinical, imaging, and blood-based data are needed to enable a comprehensive understanding of the biology underlying intracerebral haemorrhage-related complications. Given the lower prevalence of intracerebral haemorrhage compared with ischaemic stroke, large international collaborations are essential to generate datasets of sufficient size.[81]

For **BIOSTROKE** see www.biostroke.org

Building on the presented evidence, the Delphi consensus process yielded five research priorities (median agreement 91%, range 81–100%; panel and appendix pp 13–14). These priorities span the intracerebral haemorrhage clinical care continuum, from diagnosis to long-term outcomes, with a focus on developing biomarkers that provide mechanistic insights and inform treatment. Biologically plausible surrogate markers could accelerate early-phase trials. To promote harmonisation and collaborations, minimum reporting datasets were proposed and endorsed (table and appendix pp 30–36) that covered risk factors, medication, and imaging findings, and items specific to diagnosis, progression, or complications.

Conclusions and future directions

Biomarkers could increase biological precision in research and clinical care and support the development of more targeted therapeutic strategies. The framework presented here—consensus-based research priorities for biomarker development, spanning discovery to clinical translation, and minimum reporting datasets—lays the groundwork for more aligned and mechanistically informed stroke biomarker studies, complementing patient-identified priorities to improve patient outcomes.[99] By promoting standardisation, this framework aims to reduce heterogeneity between studies and to support efficient data aggregation. To facilitate feedback, collaboration, and future updates, the priorities and reporting datasets are available on the BIOSTROKE website.

Moving biomarkers into clinical use will require a structured pathway from discovery to clinical translation. Candidates should first show that they reflect the relevant pathophysiology, including with artificial intelligence-based analyses that can integrate clinical, imaging, and molecular omics data, then show added value beyond existing clinical and imaging markers using decision-focused performance metrics and external validation in diverse populations. Eventual adoption in care will depend on standardised assays and sampling protocols, together with demonstration of cost-effectiveness, regulatory approval, and feasibility in different health-care systems.

We acknowledge limitations. The research priorities reflect the views of the participating experts, but we sought to minimise bias with validation by an independent global panel. Revisions of the recommendations will be required as new evidence emerges. Minimum reporting datasets differ between domains, and some items might not be routinely available, but they are intended to support adequate phenotyping aligned with key priorities and drive excellence in biomarker research. The final application of the datasets should be guided by the investigators, based on study objectives and design. Important areas of stroke care, such as cerebral small vessel disease, were not covered and warrant future work.

We expect this framework to support biomarker studies that capture dynamic stroke biology, improve diagnosis and patient stratification, and inform the evaluation of surrogate endpoints. Progress will depend on coordinated multicentre efforts, shared data standards, and integration of biomarker research with therapeutic development to deliver more targeted interventions.

Contributors

ST and JMC conceptualised this Personal view, conducted the literature search, coordinated the Delphi process, provided the structure of the manuscript, and contributed to drafting the manuscript. AB and JM

served as leads of the working group on prehospital diagnosis, KMD and JO served as leads of the working group on stroke progression and recovery, AC and LSp served as leads of the working group on atrial cardiopathy, GMG and PC-R served as leads of the working group on plaque vulnerability, and NSa, FHBMS, and BV served as leads of the working group on intracerebral haemorrhage and coordinated work within the groups. HJA, MDH, MK, PJK, and RA-SS acted as internal reviewers for the prehospital diagnosis, stroke progression and recovery, atrial cardiopathy, plaque vulnerability, and intracerebral haemorrhage working groups, respectively. JMC, ECS, and NSp were members of the working group on prehospital diagnosis. AGL, BC, CJ, PS, and ST were members of the working group on stroke progression and recovery. CHN, JA, MJ, and ACF were members of the working group on atrial cardiopathy. AK, JK-T, LSa, and RL were members of the working group on plaque vulnerability. CC, JJML, LP, H-HT, and MHS were members of the working group on intracerebral haemorrhage. Within each working group, all members contributed to the systematic review, Delphi rounds, and drafting of section content. All authors contributed intellectual content, were involved in drafting or revising the manuscript, and agreed to submit the manuscript.

Declaration of interests

AC received grants from Pfizer; support from Novacor, Icentia, and Technomed; speaker honoraria from Bristol Myers Squibb, Pfizer, AstraZeneca, and Boehringer Ingelheim; travel support from Medtronic; consultancy fees from TriVirum; and is the chair of the Brain and Heart Council of the European Stroke Organization. AGL received consulting fees from Arega; speaker honoraria from Novo Nordisk; and serves as the Co-chair for the Global Alliance for International Stroke Genetics Consortium on Acute and Long-term Outcome studies. BC received consulting and speaker fees from Boehringer Ingelheim and Bayer. BV received non-financial support from AbbVie; personal fees from Ipsen Pharma; personal fees from CSL Behring; personal fees from AstraZeneca; non-financial support from AbbVie; grants from the Bangerter Rhyner Foundation; and personal fees from Boehringer Ingelheim, AbbVie, Athersys, Sivantos, Bristol Myers Squibb, and from the University of Bern (outside the submitted work). CC received speaker fees from Bristol Myers Squibb; was a randomised controlled trial steering committee member for Biogen and Bayer; and served as an associate editor for *Stroke*. CHN received personal fees from Alexion, AstraZeneca, Bayer, Bristol Myers Squibb, Novartis, and Pfizer. ECS served on the data safety monitoring board of the ASPIRING trial and on the steering committee of the OCEANIC trial funded by Bayer; of the ANNEXAi trial funded by Portola, Alexion, and AstraZeneca; and of the MOSES trial; and was the chair of the working group of the European Stroke Organisation Guidelines on Blood Pressure Management in Acute Ischaemic Stroke and Intracerebral Haemorrhage. FHBMS received support from Swedisch Orphan Biovitrum. GMG received honoraria for advisory boards by Boehringer Ingelheim and Bayer. HJA reports speaker fees from Boehringer Ingelheim and EVER Pharma; and served as a member and chair of data monitoring committees for Novo Nordisk; served as a member of the steering board of the FASTEST trial funded by National Institutes of Health; served as a chair of the telemedicine in acute stroke committee of the German Stroke Society; and served as a coordinator of scientific and managerial activities of the Berlin Stroke Emergency Mobile. H-HT served as a board member for the international CAA Association. JA received speaker honoraria from Alnylam. JMC received support from Bayer, AstraZeneca, and Eli Lilly (all fees were paid to the employer); and is co-founder and shareholder of TrianecT. JJM received support from Roche Diagnostics. JM holds the patent for "Method for selecting a patient for a reperfusion therapy" EP19382384.6; and is a co-founder and shareholder of ABCDx. JO received speaker fees and travel support from Cerenovus; is a steering committee member for a clinical study funded by Penumbra; and is a guideline committee member for ESO-ESMINT. LP received speaker fees from Novo Nordisk. MDH receievd grants from NoNo and Medtronic LLC; consulting fees from Sun Pharma, Brainsgate, and Merck; has patents for US patent office numbers: 62/086,077 and 10/916,346 issued and licensed; has served as data and safety monitoring board Chair for the Oncovir hiltonel trial and the DUMAS trial; served as a data and safety monitoring member of the ARTESIA trial, the BRAIN-AF trial, and the LAAOS-4 trial; is Director at and holds stocks of Circle NVI; is Director of the Canadian Stroke Consortium; and is the President of the Canadian Neuroscience Federation. MJ served on an advisory board for Bristol Myers Squibb. MK received speaker fees from Bayer, Bristol Myers Squibb, Pfizer, Jansen, and Novartis; research support from Roche Diagnostics and BRAHMS Thermofisher Scientific; and served on advisory boards for AstraZeneca, Bayer, Bristol Myers Squibb, Pfizer, Jansen and Medtronic. MHS is the Principal Investigator for the SATURN (Statins Use in Intracerebral Hemorrhage Patients) trial (ClinicalTrials.gov ID: NCT0393636); serves on an advisory board for MedRhythms; received royalties from UpToDate Inc and Cambridge University Press; and received consulting fees from Alnylam Pharmaceuticals, Aegis CN LLC, Bioxodes, and NeuGel. NSa received consulting fees from Bioxodes. RA-SS received consulting fees from Recursion Pharmaceuticals and Bioxodes; served on endpoint adjudication committees for Novo Nordisk (NN9931-4553 and NN9931-4554); is on an advisory board for the DO-IT trial; and has served as the Clinical Director of the UK Clinical Research Collaboration network of registered Clinical Trials Unit. RL received consultancy fees (paid to institution) from Bayer, Boehringer Ingelheim, iSchemiaView, and Pfizer. ST received a grant from CSL Behring; has a patent on the "Means and methods for determining the potential extent of brain injury" (WO 2025/056634); and received consulting fees from Quanterix. The other authors declare no competing interests.

Acknowledgments

We thank the somersault18:24 studio for illustrating the figures. This study did not receive any specific funding. The following authors report funding support independent of this Personal view. AB received financial support from the Spanish Ministry of Science and Innovation (RD24/0009/0015 and PI21/00939) and from the JMC Legacy Research Fund of Germans Trias I Pujol University Hospital (LC2307). AK received funding from the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy within the framework of the Munich Cluster for Systems Neurology (EXC 2145 SyNergy – ID 390857198). CJ received support from the Swedish Heart and Lung Foundation (20220184), the Swedish Research Council (2021-01114), and the Swedish state under the agreement between the Swedish government and the county councils, the ALF agreement (ALFGBG-965328). PC-R received financial support from the Spanish Ministry of Science and Innovation (RD24/0009/0010). JJML received research grants from the British Heart Foundation, the UK Dementia Research Institute, the UKE Chief Scientist Office, and the British Irish Association of Stroke Physicians. JK-T is recipient of a Wellcome Trust Early Career Award (304532/Z/23/Z). KMD received research support from Research Ireland (grant number 13/RC/2073_P2). AGL received funding (paid to institution) from The Swedish Government (under the "Avtal om Läkarutbildning och Medicinsk Forskning, ALF"), The Swedish Heart and Lung Foundation, The Swedish Brain Foundation, The FGS Fang foundation, The Swedish Stroke Association, Region Skåne, Lund University, the National Institutes of Health (1R01-NS114045), and the Fremasons Lodge of Instruction Eos in Lund (all paid to institution). BC received support from EBRAINS, the European digital research infrastructure for neuroscience (Horizon Europe: 101147319); and travel grants from the European Academy of Neurology, the European Stroke Organization, the German Stroke Organization, and the German Neurological Organization. CHN received a research grant from the Berlin Institute of Health. FHBMS received a NWO ZonMw Veni grant from the Dutch Scientific Council (09150162310154). GMG received research support from the German Research Foundation (grant number: DFG, ME 3696/3-1), the European Commission, the Ministry of Science and Culture Lower Saxony, and the German Federal Ministry of Education and Research. H-HT received a stipend for a presentation at the International Society on Thrombosis and Haemostasis; and travel support from the Taiwan National Science and Technology Council. JA received support from The Bissen Brainwalk Foundation, Uppsala County Association Against Heart and Lung Diseases, Hjärt-Lungfonden (The Swedish Heart Lung Foundation), Uppsala University Hospital, and Uppsala University, Sweden. JMC received financial support from the Dutch Heart Foundation. JJM received research grants from the Irish Institute of Clinical Neuroscience and the University College Dublin. JM received financial support from the Spanish Ministry of Science,

Innovation and Universities (AEI 2021-TED2021-131742B-I00 G-MC), the Instituto de Salud Carlos III (PI21/01158, DTS22/00078), the General Secretariat for research, development and innovation in biomedicine and health sciences in Andalusia (PIP-0009-2021), and ERA-NET NEURON (CV_056 CRESCENDO). JO received research fellowship grants from the Radiological Society of North America (RSNA) and the Canadian Association of Radiologists. MDH received grants from the Canadian Institutes of Health Research and the Heart & Stroke Foundation of Canada. MK received grants from the Swiss National Science Foundation (142422), the Swiss Heart Foundation, and Horizon Europe (ERANET-NEURON). NSa received grants from The Stroke Association (SA SCLM 23\100002) and NHS Research. MHS received grants from the National Institute of Neurological Disorders and Stroke (U01NS102289) and the National Institute of Aging (UF1NS120871). RA-SS received research grants from the British Heart Foundation, the Chief Scientist Office Health Improvement, Protection and Services Research committee, and from the European Stroke Masters of the European Stroke Organization. ST received research grants from the Corona foundation, the Leducq foundation (21CVD04), the German Federal Ministry of Education and Research (European Joint Program for Rare Diseases, EJPRD23-010), and the LMU (LMUexcellent: NFF-1507; Medical & Clinician Scientist Program (MCSP): ACS-16).

References

1 Naghavi M, Ong KL, Aali A, et al. Global burden of 288 causes of death and life expectancy decomposition in 204 countries and territories and 811 subnational locations, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet* 2024; **403:** 2100–32.

2 Li G, Lin Y, Yang J, et al. Intensive Ambulance-Delivered Blood-Pressure Reduction in Hyperacute Stroke. *N Engl J Med* 2024; **390:** 1862–72.

3 Hill MD, Goyal M, Demchuk AM, et al. Efficacy and safety of nerinetide in acute ischaemic stroke in patients undergoing endovascular thrombectomy without previous thrombolysis (ESCAPE-NEXT): a multicentre, double-blind, randomised controlled trial. *Lancet* 2025; **405:** 560–70.

4 O'Collins VE, Macleod MR, Donnan GA, Horky LL, van der Worp BH, Howells DW. 1,026 experimental treatments in acute stroke. *Ann Neurol* 2006; **59:** 467–77.

5 Kamel H, Longstreth WT Jr, Tirschwell DL, et al. Apixaban to prevent recurrence after cryptogenic stroke in patients with atrial cardiopathy: the ARCADIA randomized clinical trial. *JAMA* 2024; **331:** 573–81.

6 Geisler T, Keller T, Martus P, et al. Apixaban versus aspirin for embolic stroke of undetermined source. *NEJM Evid* 2024; **3:** EVIDoa2300235.

7 Tiedt S, Buchan AM, Dichgans M, Lizasoain I, Moro MA, Lo EH. The neurovascular unit and systemic biology in stroke – implications for translation and treatment. *Nat Rev Neurol* 2022; **18:** 597–612.

8 Puy L, Parry-Jones AR, Sandset EC, Dowlatshahi D, Ziai W, Cordonnier C. Intracerebral haemorrhage. *Nat Rev Dis Primers* 2023; **9:** 14.

9 Cao J, Roth S, Zhang S, et al. DNA-sensing inflammasomes cause recurrent atherosclerotic stroke. *Nature* 2024; **633:** 433–41.

10 Thomalla G, Boutitie F, Ma H, et al. Intravenous alteplase for stroke with unknown time of onset guided by advanced imaging: systematic review and meta-analysis of individual patient data. *Lancet* 2020; **396:** 1574–84.

11 Li Q, Warren AD, Qureshi AI, et al. Ultra-early blood pressure reduction attenuates hematoma growth and improves outcome in intracerebral hemorrhage. *Ann Neurol* 2020; **88:** 388–95.

12 Saver JL, Goyal M, van der Lugt A, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. *JAMA* 2016; **316:** 1279–88.

13 Scheitz JF, Abdul-Rahim AH, MacIsaac RL, et al. Clinical selection strategies to identify ischemic stroke patients with large anterior vessel occlusion: results from SITS-ISTR (Safe Implementation of Thrombolysis in Stroke International Stroke Thrombolysis Registry). *Stroke* 2017; **48:** 290–97.

14 Schlemm L, Ebinger M, Nolte CH, Endres M. Impact of prehospital triage scales to detect large vessel occlusion on resource utilization and time to treatment. *Stroke* 2018; **49:** 439–46.

15 Dekker L, Daems JD, Ali M, et al. Prehospital large-vessel occlusion stroke detection scales: a pooled individual patient data analysis of 2 prospective cohorts. *Neurology* 2025; **104:** e213570.

16 Pérez de la Ossa N, Abilleira S, Jovin TG, et al. Effect of direct transportation to thrombectomy-capable center vs local stroke center on neurological outcomes in patients with suspected large-vessel occlusion stroke in nonurban areas: the RACECAT randomized clinical trial. *JAMA* 2022; **327:** 1782–94.

17 Ramos-Pachón A, Rodríguez-Luna D, Martí-Fàbregas J, et al. Effect of bypassing the closest stroke center in patients with intracerebral hemorrhage: a secondary analysis of the RACECAT randomized clinical trial. *JAMA Neurol* 2023; **80:** 1028–36.

18 Bustamante A, Penalba A, Orset C, et al. Blood biomarkers to differentiate ischemic and hemorrhagic strokes. *Neurology* 2021; **96:** e1928–39.

19 Kalra LP, Zylyftari S, Blums K, et al. Rapid diagnosis of intracerebral hemorrhage in patients with acute stroke by measuring prehospital GFAP levels on a point-of-care device (DETECT). *Neurology* 2025; **105:** e213823.

20 Ramos-Pachón A, López-Cancio E, Bustamante A, et al. D-dimer as predictor of large vessel occlusion in acute ischemic stroke. *Stroke* 2021; **52:** 852–58.

21 Kaffes M, Bondi F, Geisler F, et al. Optimization of sensitivity and specificity of a biomarker-based blood test (LVOCheck-Opti): a protocol for a multicenter prospective observational study of patients suspected of having a stroke. *Front Neurol* 2024; **14:** 1327348.

22 van Stigt MN, Groenendijk EA, van Meenen LCC, et al. Prehospital detection of large vessel occlusion stroke with EEG. *Neurology* 2023; **101:** e2522–32.

23 Habib P, Dimitrov I, Pinho J, et al. Point-of-care ultrasound to detect acute large vessel occlusions in stroke patients: a proof-of-concept study. *Can J Neurol Sci* 2023; **50:** 656–61.

24 Kellner CP, Sauvageau E, Snyder KV, et al. The VITAL study and overall pooled analysis with the VIPS non-invasive stroke detection device. *J Neurointerv Surg* 2018; **10:** 1079–84.

25 Schlemm L, Endres M, Nolte CH. Bypassing the closest stroke center for thrombectomy candidates: what additional delay to thrombolysis is acceptable? *Stroke* 2020; **51:** 867–75.

26 Richards CT, Oostema JA, Chapman SN, et al. Prehospital stroke care part 2: on-scene evaluation and management by emergency medical services practitioners. *Stroke* 2023; **54:** 1416–25.

27 Goyal M, Ospel JM, Menon B, et al. Challenging the ischemic core concept in acute ischemic stroke imaging. *Stroke* 2020; **51:** 3147–55.

28 Boyd LA, Hayward KS, Ward NS, et al. Biomarkers of stroke recovery: consensus-based core recommendations from the Stroke Recovery and Rehabilitation Roundtable. *Int J Stroke* 2017; **12:** 480–93.

29 Stinear CM, Lang CE, Zeiler S, Byblow WD. Advances and challenges in stroke rehabilitation. *Lancet Neurol* 2020; **19:** 348–60.

30 Filler J, Georgakis MK, Dichgans M. Risk factors for cognitive impairment and dementia after stroke: a systematic review and meta-analysis. *Lancet Healthy Longev* 2024; **5:** e31–44.

31 Filler J, Georgakis MK, Janowitz D, et al. Risk factors for dementia and cognitive impairment within 5 years after stroke: a prospective multicentre cohort study. *Lancet Reg Health Eur* 2025; **56:** 101428.

32 Gendron TF, Badi MK, Heckman MG, et al. Plasma neurofilament light predicts mortality in patients with stroke. *Sci Transl Med* 2020; **12:** eaay1913.

33 Tiedt S, Duering M, Barro C, et al. Serum neurofilament light: a biomarker of neuroaxonal injury after ischemic stroke. *Neurology* 2018; **91:** e1338–47.

34 Luger S, Koerbel K, Martinez Oeckel A, et al. Role of S100B serum concentration as a surrogate outcome parameter after mechanical thrombectomy. *Neurology* 2021; **97:** e2185–94.

35 Varela R, Gonzalez-Ortiz F, Dias A, et al. Plasma brain-derived tau in prognosis of large vessel occlusion ischemic stroke. *Stroke* 2024; **55:** 2353–58.

36 Vlegels N, Knuth NL, Steiner KA, et al. Brain-derived tau for monitoring brain injury in acute ischemic stroke. *Sci Transl Med* 2026; **18:** eadz1280.

37 Kollikowski AM, Pham M, März AG, et al. MMP-9 release into collateral blood vessels before endovascular thrombectomy to assess the risk of major intracerebral haemorrhages and poor outcome for acute ischaemic stroke: a proof-of-concept study. *EBioMedicine* 2024; **103:** 105095.

38 Peesh P, Blasco-Conesa MP, El Hamamy A, et al. Benefits of equilibrium between microbiota- and host-derived ligands of the aryl hydrocarbon receptor after stroke in aged male mice. *Nat Commun* 2025; **16:** 1767.

39 Ashcroft SK, Ironside DD, Johnson L, Kuys SS, Thompson-Butel AG. Effect of exercise on brain-berived neurotrophic factor in stroke survivors: a systematic review and meta-analysis. *Stroke* 2022; **53:** 3706–16.

40 Brännmark C, Klasson S, Stanne TM, et al. FIND Stroke Recovery Study (FIND): rationale and protocol for a longitudinal observational cohort study of trajectories of recovery and biomarkers poststroke. *BMJ Open* 2023; **13:** e072493.

41 Stinear CM, Smith MC, Byblow WD. Prediction tools for stroke rehabilitation. *Stroke* 2019; **50:** 3314–22.

42 McCabe JJ, Cheung Y, Foley M, et al. Residual risk of recurrent stroke despite anticoagulation in patients with atrial fibrillation: a systematic review and meta-analysis. *JAMA Neurol* 2025; **82:** 696–705.

43 Bisbal F, Baranchuk A, Braunwald E, Bayés de Luna A, Bayés-Genís A. Atrial failure as a clinical entity: JACC review topic of the week. *J Am Coll Cardiol* 2020; **75:** 222–32.

44 Fonseca AC, Coelho P. Update on biomarkers associated to cardioembolic stroke: a narrative review. *Life* 2021; **11:** 448.

45 Schweizer J, Arnold M, König IR, et al. Measurement of midregional pro-atrial natriuretic peptide to discover atrial fibrillation in patients with ischemic stroke. *J Am Coll Cardiol* 2022; **79:** 1369–81.

46 Cameron AC, Arnold M, Katsas G, et al. Natriuretic peptides to classify risk of atrial fibrillation detection after stroke: analysis of the BIOSIGNAL and PRECISE cohort studies. *Neurology* 2024; **103:** e209625.

47 Meinel T, Arnold M, Roten L, et al. Swiss Stroke Society position paper on atrial fibrillation monitoring and management after ischaemic stroke: a shift from understanding the index stroke to preventing the next one. *Swiss Med Wkly* 2025; **155:** 4170.

48 Uhe T, Wasser K, Weber-Krüger M, et al. Intensive heart rhythm monitoring to decrease ischemic stroke and systemic embolism-the Find-AF 2 study-rationale and design. *Am Heart J* 2023; **265:** 66–76.

49 Sposato LA, Ayan D, Ahmed M, et al. Extended CT angiography versus standard CT angiography for the detection of cardioaortic thrombus in patients with ischaemic stroke and transient ischaemic attack (DAYLIGHT): a prospective, randomised, open-label, blinded end-point trial. *Lancet Neurol* 2025; **24:** 489–99.

50 Rizas KD, Freyer L, Sappler N, et al. Smartphone-based screening for atrial fibrillation: a pragmatic randomized clinical trial. *Nat Med* 2022; **28:** 1823–30.

51 Aulin J, Sjölin K, Lindbäck J, et al. Neurofilament light chain and risk of stroke in patients with atrial fibrillation. *Circulation* 2024; **150:** 1090–100.

52 Cheung Y, Foley M, Bradley D, et al. Clinical and biomarker determinants for recurrent stroke in patients with atrial fibrillation: a systematic review and meta-analysis. *Neurology* 2025; **104:** e210061.

53 Lavallée PC, Charles H, Albers GW, et al. Effect of atherosclerosis on 5-year risk of major vascular events in patients with transient ischaemic attack or minor ischaemic stroke: an international prospective cohort study. *Lancet Neurol* 2023; **22:** 320–29.

54 Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in acute stroke treatment. *Stroke* 1993; **24:** 35–41.

55 Redgrave JNE, Lovett JK, Gallagher PJ, Rothwell PM. Histological assessment of 526 symptomatic carotid plaques in relation to the nature and timing of ischemic symptoms: the Oxford plaque study. *Circulation* 2006; **113:** 2320–28.

56 Marnane M, Prendeville S, McDonnell C, et al. Plaque inflammation and unstable morphology are associated with early stroke recurrence in symptomatic carotid stenosis. *Stroke* 2014; **45:** 801–06.

57 Nies KPH, Smits LJM, van Kuijk SMJ, et al. Individualized MRI-based stroke prediction score using plaque vulnerability for symptomatic carotid artery disease patients (IMPROVE). *Stroke* 2025; **56:** 2068–78.

58 Savastano L, Brinjikji W, Lutsep H, Chen H, Chaturvedi S. Symptomatic nonstenotic carotids: a topical review. *Stroke* 2024; **55:** 2921–31.

59 Hart RG, Sharma M, Mundl H, et al. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. *N Engl J Med* 2018; **378:** 2191–201.

60 Diener HC, Sacco RL, Easton JD, et al. Dabigatran for prevention of stroke after embolic stroke of undetermined source. *N Engl J Med* 2019; **380:** 1906–17.

61 Weimar C, Diener H-C, Alberts MJ, et al. The Essen stroke risk score predicts recurrent cardiovascular events: a validation within the REduction of Atherothrombosis for Continued Health (REACH) registry. *Stroke* 2009; **40:** 350–54.

62 Rothwell PM, Eliasziw M, Gutnikov SA, et al. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet* 2003; **361:** 107–16.

63 Donners SJA, van Velzen TJ, Cheng SF, et al. Optimised medical therapy alone versus optimised medical therapy plus revascularisation for asymptomatic or low-to-intermediate risk symptomatic carotid stenosis (ECST-2): 2-year interim results of a multicentre randomised trial. *Lancet Neurol* 2025; **24:** 389–99.

64 McCabe JJ, Camps-Renom P, Giannotti N, et al. Carotid plaque inflammation imaged by PET and prediction of recurrent stroke at 5 years. *Neurology* 2021; **97:** e2282–91.

65 Saba L, Cau R, Murgia A, et al. Carotid Plaque-RADS: a novel stroke risk classification system. *JACC Cardiovasc Imaging* 2024; **17:** 62–75.

66 Song JW, Pavlou A, Xiao J, Kasner SE, Fan Z, Messé SR. Vessel wall magnetic resonance imaging biomarkers of symptomatic intracranial atherosclerosis: a meta-analysis. *Stroke* 2021; **52:** 193–202.

67 Kelly P, Lemmens R, Weimar C, et al. Long-term colchicine for the prevention of vascular recurrent events in non-cardioembolic stroke (CONVINCE): a randomised controlled trial. *Lancet* 2024; **404:** 125–33.

68 McCabe JJ, Walsh C, Gorey S, et al. C-reactive protein, interleukin-6, and vascular recurrence after stroke: an individual participant data meta-analysis. *Stroke* 2023; **54:** 1289–99.

69 Arnold M, Schweizer J, Nakas CT, et al. Lipoprotein(a) is associated with large artery atherosclerosis stroke aetiology and stroke recurrence among patients below the age of 60 years: results from the BIOSIGNAL study. *Eur Heart J* 2021; **42:** 2186–96.

70 GBD 2021 Stroke Risk Factor Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet Neurol* 2024; **23:** 973–1003.

71 Hilkens NA, van Asch CJJ, Werring DJ, et al. Predicting the presence of macrovascular causes in non-traumatic intracerebral haemorrhage: the DIAGRAM prediction score. *J Neurol Neurosurg Psychiatry* 2018; **89:** 674–79.

72 Raposo N, Zanon Zotin MC, Seiffge DJ, et al. A causal classification system for intracerebral hemorrhage subtypes. *Ann Neurol* 2023; **93:** 16–28.

73 Rodrigues MA, Samarasekera N, Lerpiniere C, et al. The Edinburgh CT and genetic diagnostic criteria for lobar intracerebral haemorrhage associated with cerebral amyloid angiopathy: model development and diagnostic test accuracy study. *Lancet Neurol* 2018; **17:** 232–40.

74 Sembill JA, Knott M, Xu M, et al. Simplified Edinburgh CT criteria for identification of lobar intracerebral hemorrhage associated with cerebral amyloid angiopathy. *Neurology* 2022; **98:** e1997–2004.

75 Charidimou A, Boulouis G, Frosch MP, et al. The Boston criteria version 2·0 for cerebral amyloid angiopathy: a multicentre, retrospective, MRI-neuropathology diagnostic accuracy study. *Lancet Neurol* 2022; **21:** 714–25.

76 Goeldlin MB, Mueller M, Siepen BM, et al. CADMUS: a novel MRI-based classification of spontaneous intracerebral hemorrhage associated with cerebral small vessel disease. *Neurology* 2024; **102:** e207977.

77 van Etten ES, Verbeek MM, van der Grond J, et al. β-amyloid in CSF: biomarker for preclinical cerebral amyloid angiopathy. *Neurology* 2017; **88:** 169–76.

78 Romoli M, Marinoni G, Tagliabue L, et al. ^{18F}Flutemetamol-PET aided classification of cerebral amyloid angiopathy: a multicenter study. *Neurology* 2024; **103:** e209719.

79 Lyne SB, Girard R, Koskimäki J, et al. Biomarkers of cavernous angioma with symptomatic hemorrhage. *JCI Insight* 2019; **4:** e128577.

80 Ma L, Hu X, Song L, et al. The third Intensive Care Bundle with Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT3): an international, stepped wedge cluster randomised controlled trial. *Lancet* 2023; **402:** 27–40.

81 Al-Shahi Salman R, Frantzias J, Lee RJ, et al. Absolute risk and predictors of the growth of acute spontaneous intracerebral haemorrhage: a systematic review and meta-analysis of individual patient data. *Lancet Neurol* 2018; **17:** 885–94.

82 Volbers B, Giede-Jeppe A, Gerner ST, et al. Peak perihemorrhagic edema correlates with functional outcome in intracerebral hemorrhage. *Neurology* 2018; **90:** e1005–12.

83 Law ZK, Ali A, Krishnan K, et al. Noncontrast computed tomography signs as predictors of hematoma expansion, clinical outcome, and response to tranexamic acid in acute intracerebral hemorrhage. *Stroke* 2020; **51:** 121–28.

84 Puy L, Perbet R, Figeac M, et al. Brain peri-hematomal area, a strategic interface for blood clearance: a human neuropathological and transcriptomic study. *Stroke* 2022; **53:** 2026–35.

85 Loan JJ, Kirby C, Emelianova K, et al. Secondary injury and inflammation after intracerebral haemorrhage: a systematic review and meta-analysis of molecular markers in patient brain tissue. *J Neurol Neurosurg Psychiatry* 2022; **93:** 126–32.

86 Askenase MH, Goods BA, Beatty HE, et al. Longitudinal transcriptomics define the stages of myeloid activation in the living human brain after intracerebral hemorrhage. *Sci Immunol* 2021; **6:** eabd6279.

87 Kirby C, Barrington J, Sondag L, et al. Association between circulating inflammatory biomarkers and functional outcome or perihaematomal oedema after ICH: a systematic review & meta-analysis. *Wellcome Open Res* 2023; **8:** 239.

88 Li L, Poon MTC, Samarasekera NE, et al. Risks of recurrent stroke and all serious vascular events after spontaneous intracerebral haemorrhage: pooled analyses of two population-based studies. *Lancet Neurol* 2021; **20:** 437–47.

89 Moulin S, Labreuche J, Bombois S, et al. Dementia risk after spontaneous intracerebral haemorrhage: a prospective cohort study. *Lancet Neurol* 2016; **15:** 820–29.

90 Raposo N, Charidimou A, Roongpiboonsopit D, et al. Convexity subarachnoid hemorrhage in lobar intracerebral hemorrhage: a prognostic marker. *Neurology* 2020; **94:** e968–77.

91 Gokcal E, Horn MJ, van Veluw SJ, et al. Lacunes, microinfarcts, and vascular dysfunction in cerebral amyloid angiopathy. *Neurology* 2021; **96:** e1646–54.

92 Pasi M, Sugita L, Xiong L, et al. Association of cerebral small vessel disease and cognitive decline after intracerebral hemorrhage. *Neurology* 2021; **96:** e182–92.

93 Rodrigues MA, Seiffge D, Samarasekera N, et al. Association between the Edinburgh CT and genetic diagnostic criteria for cerebral amyloid angiopathy-associated lobar intracerebral haemorrhage and recurrent intracerebral haemorrhage: an individual patient data meta-analysis. *Lancet Neurol* 2025; **24:** 828–39.

94 Ball EL, Sutherland R, Squires C, et al. Predicting post-stroke cognitive impairment using acute CT neuroimaging: a systematic review and meta-analysis. *Int J Stroke* 2022; **17:** 618–27.

95 Shi K, Tian DC, Li ZG, Ducruet AF, Lawton MT, Shi FD. Global brain inflammation in stroke. *Lancet Neurol* 2019; **18:** 1058–66.

96 Ma Y, Chen Y, Yang T, et al. Blood biomarkers for post-stroke cognitive impairment: a systematic review and meta-analysis. *J Stroke Cerebrovasc Dis* 2024; **33:** 107632.

97 Fandler-Höfler S, Ambler G, Goeldlin MB, et al. MRI-based prediction of macrovascular causes of intracerebral hemorrhage: the MACRO score. *Neurology* 2024; **103:** e209950.

98 El Husseini N, Katzan IL, Rost NS, et al. Cognitive impairment after ischemic and hemorrhagic stroke: a scientific statement from the American Heart Association/American Stroke Association. *Stroke* 2023; **54:** e272–91.

99 Hill G, Regan S, Francis R, et al. Research priorities to improve stroke outcomes. *Lancet Neurol* 2022; **21:** 312–13.

Copyright © 2026 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license