

CONTEMPORARY REVIEW

Stroke–Heart Syndrome: Recent Advances and Challenges

Jan F. Scheitz , MD; Luciano A. Sposato , MD; Jeanette Schulz-Menger, MD; Christian H. Nolte , MD; Johannes Backs, MD; Matthias Endres , MD

ABSTRACT: After ischemic stroke, there is a significant burden of cardiovascular complications, both in the acute and chronic phase. Severe adverse cardiac events occur in 10% to 20% of patients within the first few days after stroke and comprise a continuum of cardiac changes ranging from acute myocardial injury and coronary syndromes to heart failure or arrhythmia. Recently, the term *stroke–heart syndrome* was introduced to provide an integrated conceptual framework that summarizes neurocardiogenic mechanisms that lead to these cardiac events after stroke. New findings from experimental and clinical studies have further refined our understanding of the clinical manifestations, pathophysiology, and potential long-term consequences of the stroke–heart syndrome. Local cerebral and systemic mediators, which mainly involve autonomic dysfunction and increased inflammation, may lead to altered cardiomyocyte metabolism, dysregulation of (tissue-resident) leukocyte populations, and (micro-) vascular changes. However, at the individual patient level, it remains challenging to differentiate between comorbid cardiovascular conditions and stroke-induced heart injury. Therefore, further research activities led by joint teams of basic and clinical researchers with backgrounds in both cardiology and neurology are needed to identify the most relevant therapeutic targets that can be tested in clinical trials.

Key Words: brain–heart axis ■ heart ■ inflammation ■ outcomes ■ stroke

Ischemic stroke patients are at substantial risk of heart disease, and, vice versa, heart disease increases the risk of ischemic stroke. Randomized controlled trials and observational studies reported severe adverse cardiac events in ≈10% to 20% of patients with acute ischemic stroke.^{1–7} These clinically severe cardiac complications are more common in patients with severe stroke and may even occur in patients without known comorbid cardiac disease.^{1,2,4,6} Stroke patients with early severe cardiac complications are at a 2- to 3-fold increased risk of short-term mortality.^{1,8} Beyond these acute neurocardiogenic alterations, the occurrence of cardiovascular events and cardiac death are the main drivers of long-term prognosis after stroke.^{9,10} Nearly one-third of deaths in stroke survivors can be attributed to a cardiac cause.^{10,11} Both short-term and long-term cardiac events after stroke happen despite contemporary secondary prevention measures. Thus, there is a medical need to reduce the burden of both

acute and long-term cardiovascular complications after stroke.

Within the past years, it is increasingly recognized that the interactions between heart disease and ischemic stroke are more than a mere consequence of traditional vascular risk factors that affect both organs. Based upon the evidence from preclinical and clinical studies that acute ischemic stroke can have immediate deleterious effects on the heart, the concept of a distinct stroke–heart syndrome was introduced in 2018 (see Box and Figure 1 for definition).^{1,3,12–15} The intention of the concept was to provide an integrated view of stroke-related cardiac complications to increase the clinical awareness, generate a common mechanistic framework, and facilitate the development of research collaborations and clinical management pathways. The stroke–heart syndrome concept summarizes the full spectrum of cardiac changes newly observed within the first 30 days after an acute ischemic stroke.^{3,7} Its pathophysiological

Correspondence to: Matthias Endres, MD, Department of Neurology, Charité-Universitätsmedizin Berlin, Charitéplatz 1, Berlin 10117, Germany.
Email: matthias.endres@charite.de

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Nonstandard Abbreviations and Acronyms

AFDAS	AF detected after stroke
BDNF	brain-derived neurotrophic factor
CaMKII	Ca ²⁺ /calmodulin-dependent kinase II
CAN	central autonomic network
CORONA-IS	Cardiomyocyte Injury Following Acute Ischemic Stroke
MACE	major adverse cardiovascular events
MCAo	middle cerebral artery occlusion
NLRP3	NLR family pyrin domain containing 3
Nr4a1	nuclear receptor subfamily 4 group a member 1
PPARα	peroxisome proliferator-activated receptor α
PRAISE	Prediction of Acute Coronary Syndrome in Acute Ischemic Stroke
SICFAIL	Stroke-Induced Cardiac Failure in Mice and Men
TTS	Takotsubo syndrome

model views ischemic stroke as a specific event triggering neurocardiogenic heart injury and is based on both preclinical and clinical data suggesting a strong overlap between the continuum of clinical phenotypes and underlying mechanisms.^{1,3} The biggest controversy around this concept relates to the underlying pathophysiologic mechanisms: Is cardiac dysfunction following ischemic stroke caused by vascular comorbidity along the cardiovascular risk continuum, is it a specific event triggered by the stroke, or both? On an individual patient level, physicians are challenged by the clinical problem whether acute cardiac injury in a patient with stroke represents a critical event requiring urgent cardiac diagnostics and potentially harmful intervention.

In this review, we aimed to provide an updated overview of the experimental phenotype and clinical manifestations of the stroke–heart syndrome, and to extend the existing pathophysiological model, focusing on the most relevant stroke characteristics, key mediators, as well as downstream cardiac signaling pathways. Finally, we aimed to derive the most challenging questions and promising directions for future research.

MANIFESTATIONS OF STROKE–HEART SYNDROME

Evidence From Animal Models

Rodent models of experimental stroke provide a unique opportunity to study both the immediate short-term and

longer-term effects of ischemic stroke on the heart. In the late 1980s and early 1990s, there was an initial period of flourishing animal research on deleterious heart–brain interactions following stroke. Ground-breaking experiments in cats and rats demonstrated that stroke can impair physiological autonomic cardiac function and provoke proarrhythmogenic electrocardiographic changes.^{16,17} In recent years, several well-designed experimental studies have helped to refine our knowledge of the stroke–heart syndrome phenotype in rodent models (Figure 2).^{18–24} To study the acute cardiac effects of stroke, Veltkamp and colleagues induced an experimental ischemic stroke via transient (60 minutes) filament occlusion of the left middle cerebral artery (MCAo) in mice.¹⁸ This paradigm resulted in large cerebral infarcts and was paralleled by early cardiac dysfunction and damage. Serial echocardiographic measurements showed that MCAo reduced left ventricular (LV) ejection fraction and LV fractional shortening by 10% to 15% as compared with sham-operated animals. These effects began on the first day after experimental stroke and persisted for up to 14 days. These findings were accompanied by myocardial injury as reflected by transiently 3- to 5-fold increase in levels of high-sensitivity cardiac troponin (hs-cTn), bradycardia, rapid cardiomyocyte atrophy, and cardiac weight loss.¹⁸ Vornholz and colleagues were able to reproduce this phenotype of acute cardiac dysfunction also after right-sided MCAo.¹⁹ A similar study in rats demonstrated that embolic strokes resulting in large brain infarcts and severe neurologic deficits induced early and persistent reduction in LV fractional shortening.²³

Beyond these immediate cardiac effects, there is evidence that ischemic stroke produces a chronic heart failure phenotype. Bieber and colleagues performed short-term, right-sided MCAo in mice resulting in small ischemic lesions in the basal ganglia and the rodent analogue of the insular cortex.²¹ Eight weeks after surgery, MCAo resulted in a significant reduction of LV ejection fraction of about 15% compared with sham-operated and control animals. This was accompanied by a significantly higher heart rate, increased LV end-systolic and end-diastolic volumes, cardiac hypertrophy, and adverse cardiac remodeling as measured by increased LV collagen content.²¹ Similarly, in several murine stroke models that induced right-sided small to intermediate cortical lesions, a progressive 10% to 25% reduction in LV ejection fraction was found over a 3-day to 4-week period along with cardiac interstitial fibrosis.^{20,22,24} There is evidence that cardiac alterations are not limited to the left ventricle, but also include the left atrium. In a rat model with selective ischemic lesions of the left and right insular cortex stroke by local endothelin-1 injection, stroke resulted in left atrial remodeling and fibrosis, particularly in atrial regions with rich autonomic innervation.²⁵

BOX Updated Criteria and Features of the Stroke–Heart Syndrome*

Clinical definition

- New evidence of cardiac alterations or documented worsening of premorbid cardiac function after ischemic stroke.

Clinical phenotype[†]

- Acute myocardial injury (elevation of cardiac troponin with rise/fall pattern).
- Acute coronary syndrome (via coronary demand ischemia or coronary plaque destabilization).
- Left ventricular systolic and diastolic dysfunction including Takotsubo syndrome secondary to stroke.
- ECG changes (especially repolarization disorders like QTc prolongation), cardiac arrhythmias, and atrial fibrillation detected after stroke.
- Sudden cardiac death.

Time course

- Cardiac alterations usually peak within 72 hours after ischemic stroke onset and are considered to be part of stroke–heart syndrome if they occur within 30 days after the index event.
- Potential long-term consequences of stroke–heart syndrome occur later than 30 days after stroke.

Risk factors

- General: age, burden of cardiovascular risk factors.
- Stroke-specific: stroke severity, involvement of central autonomic network (especially the insular cortex).
- Heart specific: preexisting coronary or structural heart disease.

Differential diagnoses

- Other systemic or cardiac conditions: in particular sepsis, chronic but stable heart failure, pulmonary embolism, pulmonary hypertension, acute kidney injury, chronic kidney disease, myocarditis, and recent cardiac intervention.
- Causes of coronary demand ischemia not directly attributable to stroke (eg, anemia and reduced blood oxygenation).

Recent key advances

- Animal models established and characterized an acute and chronic phenotype of stroke-induced cardiac dysfunction.
- More clinical evidence supports a time-dependent trajectory of poststroke cardiac events with a highest prevalence (10%–20%) within the time-frame of 30 days after stroke.
- More evidence supports the role of systemic and local cardiac inflammation as drivers of stroke–heart syndrome.
- More clinical evidence supports that patients with stroke–heart syndrome are at increased risk of long-term major cardiac events.

*Adapted from Scheitz et al and Sposato et al.^{1,3} †Note that manifestations may overlap in the individual patient.

A potential drawback of animal research is that experimental stroke models usually use young, male, and healthy animals.^{18,25,26} This may hamper translation into clinical practice, because ischemic stroke is typically a disease of the elderly with a high burden of chronic cardiovascular comorbidities.^{27,28} To improve clinical translation, international guidelines recommend repeating experiments in aged and animals of both sexes as well as animals with comorbidities such as diabetes or hypertension.²⁹ Of note, there is evidence that the stroke–heart syndrome is more pronounced in diabetic mice and similar in young and aged mice.^{20,21,30} This underscores the notion that modeling the stroke–heart syndrome in rodents can be achieved under clinically relevant conditions. If these aspects are further considered in the future, streamlined rodent models will remain highly valuable tools to probe neurocardiogenic mechanisms of stroke–heart syndrome, identify causal mediators, and test promising interventions.

Spectrum, Severity, and Time Course of Clinical Manifestations

The stroke–heart syndrome encompasses a broad clinical spectrum of cardiovascular changes including (1) acute myocardial injury (as evidenced by acute elevation of hs-cTn), (2) acute coronary syndromes (ACS; including type 1 and type 2 myocardial infarction [MI]), (3)

systolic and diastolic LV dysfunction including Takotsubo syndrome (TTS), (4) cardiac arrhythmias including atrial fibrillation (AF) and relevant ECG changes, and (5) neurogenic sudden cardiac death (Box, Figure 2).^{1,3} Importantly, these categories are not mutually exclusive, and there is substantial overlap between these manifestations.^{1,31,32} Established risk factors include older age, premorbid cardiac disease, and stroke characteristics such as stroke severity, infarct size, and lesion site in the insular cortex.^{1,2} The stroke–heart syndrome apparently affects women and men equally, although certain phenotypes, such as TTS secondary to stroke, mainly affect women.^{33–35} In the original description of the stroke–heart syndrome, we proposed the differentiation of stroke–heart syndrome from myocardial ischemia because of coronary plaque rupture or plaque thrombosis (ie, type 1 MI). Recent evidence from experimental studies in humans and mice, however, suggest that acute mental stress and neuroinflammation may lead to destabilization of atherosclerotic plaques via activation of the neuroendocrine axis and subsequent uptake of inflammatory leucocyte populations.^{36,37} Thus, we now propose that also type 1 MI may occur as part of the spectrum of the stroke–heart syndrome. Given the high frequency of atypical clinical presentation of ACS in the elderly, especially those with neurological deficits (such as aphasia), the accurate diagnosis of ACS has to rely on strict and systematic clinical examination, typical

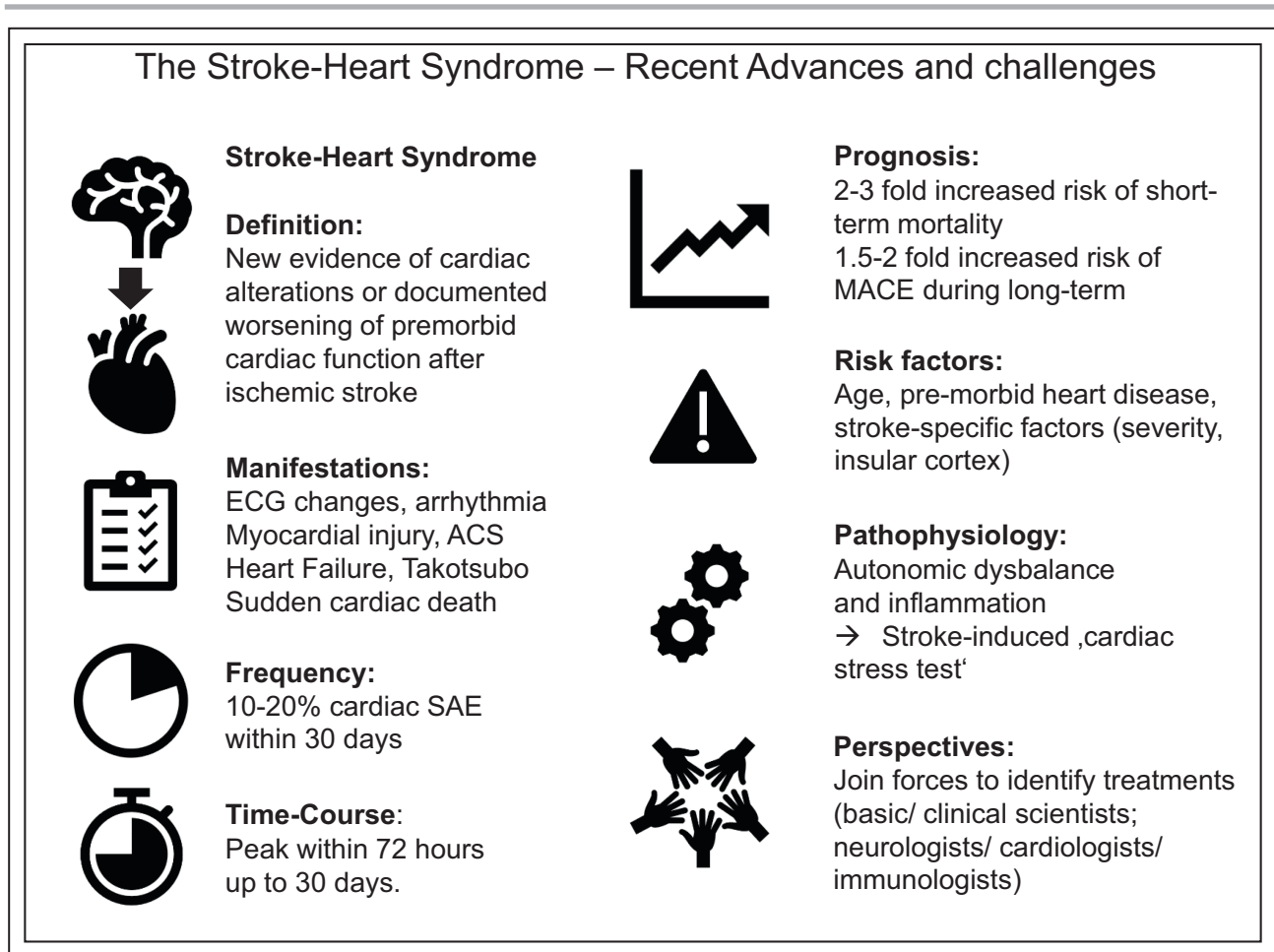


Figure 1. Summary of key criteria and of the stroke–heart syndrome.

ACS indicates acute coronary syndrome; MACE, major adverse cardiovascular events; and SAE, severe adverse events.

ECG findings, and cardiac imaging showing regional wall-motion abnormalities or coronary lesions.^{3,38}

With the introduction of increasingly sensitive and specific cardiac diagnostic tests within the past decades, it became clear that the manifestations of the stroke–heart syndrome range from oligo- or even asymptomatic laboratory or ECG findings to severe clinical manifestations requiring urgent cardiac diagnostics and treatments. The most common cardiac changes include myocardial injury (ie, elevated hs-cTn levels above assay-specific reference limits), ECG alterations such as QTc prolongation, and LV diastolic dysfunction, which are observed in up to 60% of patients with acute ischemic stroke, typically during the initial in-hospital workup.^{8,31,38} These patients are at increased risk of death and more likely to leave the hospital with more severe stroke-related disabilities.^{8,39} Because the individual pre-morbid cardiac status is usually unknown, thorough clinical assessment and serial diagnostic tests are required to distinguish comorbid and clinically stable heart disease from stroke–heart syndrome. Several observational studies documented

that myocardial injury and prolonged QTc time are associated with the incidence of more severe forms of stroke–heart syndrome.^{2,4,32,39–41} Therefore, it is reasonable and also recommended by current guidelines to measure hs-cTn and perform a standard 12-lead ECG to screen for subclinical early cardiac involvement after ischemic stroke.⁴² In case of pathological findings, prolonged ECG monitoring, thorough clinical cardiac assessment, and serial measurement of hs-cTn are warranted to identify patients at higher risk of developing severe or fatal cardiovascular complications. Data from systematic evaluations of adverse events documented in high-quality randomized controlled trial settings have shown that 10% to 20% of patients with acute ischemic stroke suffer a severe cardiac adverse event requiring urgent evaluation and treatment.^{2,5–7} These mainly include acute myocardial injury (characterized by a distinctive rise or fall pattern of hs-cTn levels),^{8,38,43} LV systolic dysfunction,^{31,40,44,45} and arrhythmia including atrial fibrillation.^{4,46} In 1% to 5% of patients, even more severe manifestations, such as myocardial infarction,^{5,47,48} overt heart failure

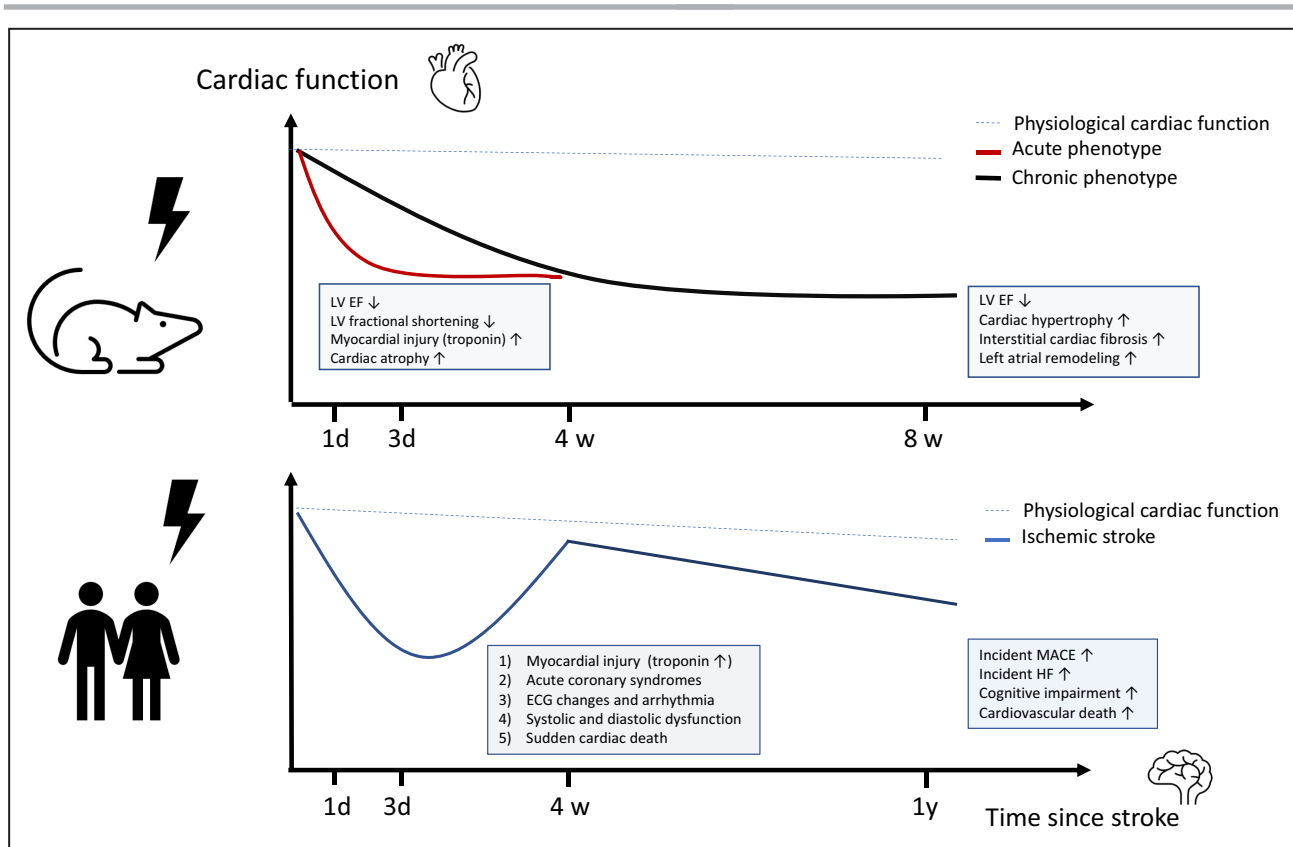


Figure 2. Phenotypes and time course of the stroke–heart syndrome in rodent models and clinical practice.

(Top) Phenotype observed in rodent ischemic stroke models. The dashed blue line indicates physiological cardiac function. The red line indicates the severity of acute cardiac dysfunction that peaks within 24 to 72 hours and persists up to 14 days after experimental stroke. Note that this phenotype was most consistently inducible by severe brain ischemia. The black line indicates a phenotype of chronic cardiac dysfunction starting 4 to 8 weeks after experimental brain ischemia. Note that this phenotype was most consistently inducible by mild, right-sided brain ischemia. (Bottom) Spectrum and time-course of stroke–heart syndrome observed in human clinical studies. The dashed blue line indicates physiological trajectory of cardiac function during aging. The blue line indicates the trajectory of cardiac alterations after stroke observed in observational clinical studies. Note that there is large individual variability, and that further studies are needed to predict the incidence of long-term cardiovascular outcomes and heart failure. EF indicates ejection fraction; HF, heart failure; LV, left ventricular; and MACE, major adverse cardiovascular events.

including TTS,^{1,3,7,34,45} and malignant tachycardia or cardiac arrest, have to be expected.^{4,5,7} The spectrum of severe forms of stroke–heart syndrome are associated with a 2- to 3-fold increased risk of mortality or poor functional outcome.^{1,5,48}

In regard to the time course, there is evidence that the acute manifestations of the stroke–heart syndrome peak within the first 72 hours after brain ischemia (Figures 1 and 2)^{1,2,4} but may not be limited to this early phase. A recent Canadian population-based study of adults aged ≥ 66 years, 9.1% of 21 931 patients with first-ever ischemic stroke had incident major adverse cardiovascular events (MACE) at 1 year (including ACS and MI, coronary interventions, incident congestive heart failure, or cardiovascular death).⁹ Compared with 71 696 matched individuals without stroke or heart disease, ischemic stroke was associated with a 4.5-times higher risk of MACE. Of note, patients with known heart disease at baseline were excluded from

this study, and the increased risk was strongly time dependent.^{9,33} Although adjusted risk of MACE was increased 25-fold in the first 30 days, it remained >2 times higher during the first year after ischemic stroke.⁹ Based on this time-dependent trajectory, it can be assumed that MACE occurring within the first 30 days after stroke may be directly attributable to the stroke–heart syndrome.³ After this phase, incident MACE and heart failure can be considered as possible long-term consequences of the initial cardiac injury attributable to stroke–heart syndrome.

Current Challenges

It remains challenging to differentiate whether post-stroke cardiac events are manifestations of stroke–heart syndrome, an expression of an underlying cardiac condition, or both. This is because the cardiac status before the stroke is usually not known when the

patient presents to the emergency department and because systematic cardiac evaluations by performing serial echocardiography or cardiovascular magnetic resonance (CMR) imaging during follow-up of stroke are lacking. As outlined above, however, there is strong evidence supporting a potential causal relationship between stroke and subsequent cardiac complications. In addition to the wealth of animal data that show experimental stroke can induce immediate and chronic cardiac dysfunction,^{13,18,22} clinical data provide evidence that there is a time-dependent occurrence of cardiac complications with a clear peak during the first few days after stroke.^{1,2,4,9,35} Major adverse cardiac events are also observed even when patients with known history of heart disease are excluded.^{9,49} Further evidence comes from observational studies that applied coronary angiography in stroke patients with elevation of hs-cTn, showing that the majority of these patients had no underlying obstructive coronary artery disease.^{47,50} Serial measurements of hs-cTn demonstrate a rise or fall pattern in 15% to 30% of patients,^{8,43} which means that myocardial injury is acute and not chronic in these patients. Finally, specific stroke characteristics like stroke severity and stroke lesion site promote the occurrence of poststroke cardiac events even when statistically accounting for premorbid cardiac conditions.^{32,41,51,52} These stroke characteristics linked to stroke–heart syndrome are discussed in more detail below.

To date, it remains also challenging to determine whether long-term vascular events and post-stroke cognitive dysfunction are prompted by stroke–heart syndrome or whether premorbid subclinical heart disease, or both, accounts for the observed associations. However, there is increasing evidence that this might be the case. As described earlier, a phenotype of chronic cardiac dysfunction with myocardial fibrosis can be induced 4 to 8 weeks after experimental stroke.^{21,24} Moreover, ex vivo experiments using rat hearts derived from animals that underwent an experimental stroke paradigm were more susceptible to second ischemic hits to the heart.²³ This suggests an increased susceptibility to secondary cardiac events poststroke. This presumption is supported by a recent retrospective analysis using a global (primarily US based) network of 365 383 health care records of patients with stroke and 5-year follow-up that compared the long-term cardiovascular outcomes of stroke patients with and without manifestations of stroke–heart syndrome (defined as new-onset cardiovascular complications within 30 days after stroke).⁷ Patients with stroke–heart syndrome had a 1.5- to 2-fold higher odds of 5-year mortality and MACE depending on the respective manifestation of stroke–heart syndrome.⁷ Although this study focused on substantial manifestations of stroke–heart syndrome diagnosed based on

International Classification of Diseases (ICD-10) codes, there is also evidence that more subtle manifestations may entail a higher cardiovascular risk. In a clinical study of 201 ischemic stroke patients, those who had evidence of autonomic imbalance (ie, lower high-frequency power in heart-rate variability analysis) within 48 hours after stroke had a higher risk of secondary ischemic events within 90 days.⁵³ However, most of the events detected in this study occurred early after stroke, highlighting the need for more confirmative data with regard to the longer term. Of 220 patients with first-ever, mild-to-moderate ischemic stroke and myocardial injury measured with hs-cTn within a median of 4 days after the event, but without clinical diagnosis of concurrent ACS, 27.3% experienced a cumulative end point of recurrent stroke, MI, or death within 3 years of follow-up.⁵⁴ This was significantly higher than in the control group of 342 patients with normal hs-cTn levels during the acute poststroke phase (10.2%; adjusted hazard ratio, 2.0).⁵⁴ Beyond the occurrence of cardiovascular events, there is also evidence that patients with (subclinical) myocardial injury in the acute phase after the ischemic stroke have a higher burden of cerebral small vessel disease and cognitive impairment than those without.^{55,56} Among 555 patients with first-ever ischemic stroke, global cognitive impairment was present in 43% of patients with hs-cTn values in the highest quartile.⁵⁶ This proportion was significantly higher than in the group of patients with hs-cTn in the lowest quartile (15%) and remained statistically significant after adjusting for potential confounders. Cognitive function remained worse in this group during the 3 years of follow-up.⁵⁶

Another challenging field of research includes the entity of AF detected after stroke (AFDAS), which may be considered a particular expression of the stroke–heart syndrome. According to a meta-analysis, previously unknown AF can be found in ≈10% of patients with ischemic stroke during the initial in-hospital workup and in ≈25% by sequentially combining cardiac monitoring methods during long-term follow-up.⁴⁶ The theoretical construct of AFDAS has evolved in recent years and addresses its distinctive characteristics when compared with AF known before stroke.^{57,58} Conceptually, AFDAS results from the interplay of underlying cardiogenic mechanisms and stroke-related neurogenic phenomena.⁵⁸ AFDAS seems to have a lower prevalence of cardiovascular comorbidities and less severe structural heart disease than AF known before stroke occurrence.^{58,59} These findings may explain why patients with AFDAS seem to have a lower risk of stroke recurrence than those with a known history of AF before stroke onset.^{60,61} AFDAS probably encompasses higher and lower risk phenotypes based on the severity of preexisting atrial cardiopathy and the prevalence of risk factors.⁵⁸ Within the spectrum

of AFDAS risk, patients with severe atrial cardiopathy (eg, dilated left atrium) are those who may bear the higher risk, whereas those with structurally healthy hearts and lower-burden AFDAS triggered by self-limited and short-lasting neurogenic mechanisms may have a lower embolic risk.^{3,62,63} Studies combining biomarkers, neuroimaging patterns, and cardiovascular comorbidities are needed to further characterize higher- and lower-risk AFDAS phenotypes. Characterizing these phenotypes may help improve the selection of ischemic stroke and transient ischemic attack patients who could benefit more from anticoagulation if AFDAS is found on prolonged cardiac monitoring.

PATHOPHYSIOLOGY OF STROKE–HEART SYNDROME

The pathophysiological model of stroke–heart syndrome considers the spectrum of clinical manifestations to be the result of neurocardiogenic mechanisms leading to stroke-induced heart injury (stroke-induced cardiac stress-test).^{1,3} Of note, neurocardiogenic injury is not restricted to an ischemic stroke cause and can be observed in other acute brain disorders such as seizures, traumatic brain injury, and intracranial hemorrhage (reviewed elsewhere).⁶⁴ Within the past few

years, further advances have been made that have helped to further elucidate the complex interplay of ischemic stroke-lesion characteristics, local cerebral and systemic mediators, and downstream cardiac mechanisms leading to the stroke–heart syndrome (Figure 3). The next paragraphs summarize these advances and describe promising future directions of research.

Impact of Stroke Characteristics

There is evidence that specific localizations of the ischemic lesion favor the occurrence of stroke–heart syndrome. A well-studied example is the association between ischemic lesions in the insular cortex and the occurrence of acute myocardial injury, TTS, and arrhythmia.^{8,34,41,51,52} In experimental studies, the extent of histological damage in the correlate of the insula in the mouse brain damage correlated with the severity of cardiac dysfunction and troponin elevation.^{19,26} The insular cortex is an integral part of central autonomic network (CAN) and is involved in both cardiac interoception and efferent cardiovascular response to emotional experience.^{65,66} Under physiological conditions, the CAN regulates sympathetic and parasympathetic neuronal outflow to the heart.^{3,66} Ischemic stroke may lead to abrupt changes in the physiological organization of the CAN, resulting in autonomic dysfunction.

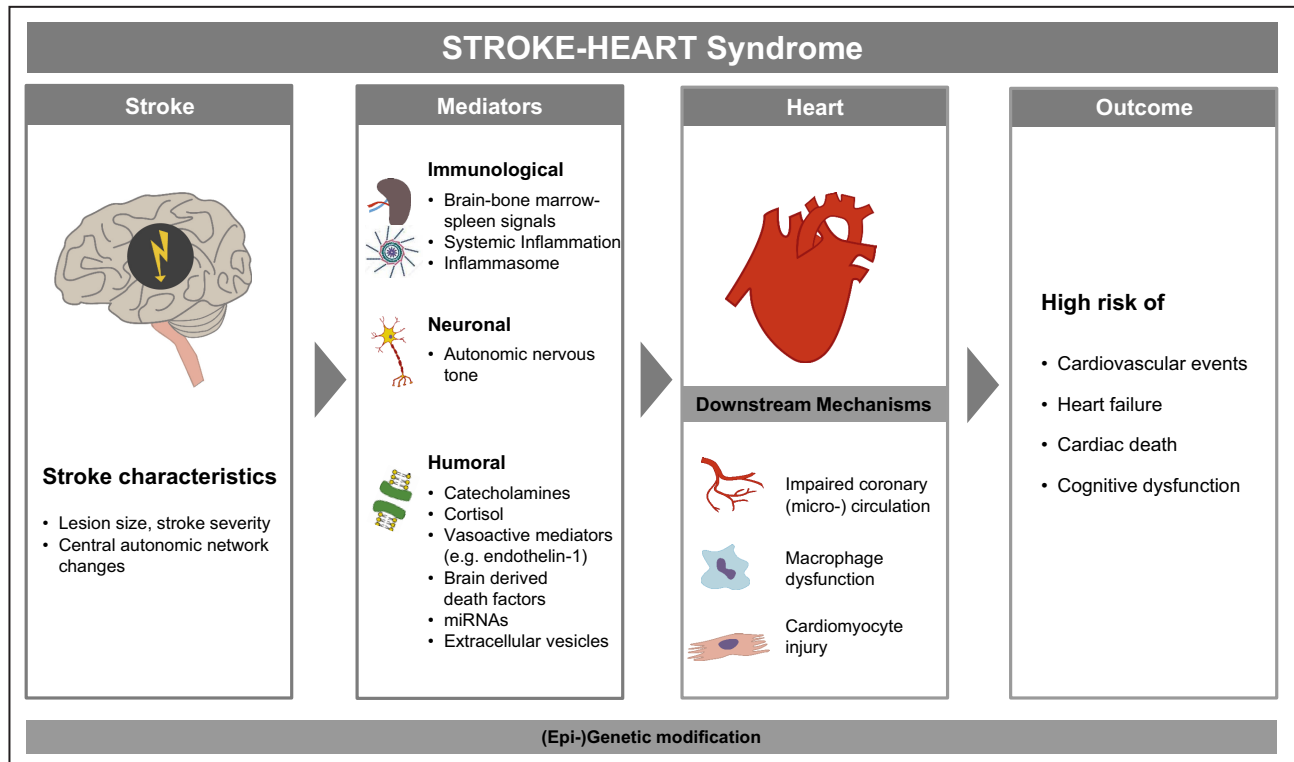


Figure 3. Overview about stroke-specific characteristics, mediators, downstream cardiac mechanisms, and outcomes of stroke–heart syndrome.

The 4 columns describe the most promising and well-studied stroke characteristics, mediators, cardiac mechanisms, and short-term and long-term outcomes of stroke–heart syndrome.

Importantly, the occurrence of the stroke–heart syndrome is not limited to ischemia within the insular cortex. Both in clinical and experimental settings, a phenotype of poststroke cardiac dysfunction can also be observed when the insular cortex itself is not affected.^{22,24,67} Other relevant regions of the CAN with documented impact on cardiac function include the amygdala, anterior cingulate cortex, ventromedial prefrontal cortex, hypothalamus, mediodorsal thalamus, hippocampus, and brainstem regions.^{3,66,68–70} With regard to the latter, QTc prolongation on ECG upon hospital admission was found in 9 out of 12 patients with acute medullary infarction.⁷¹ Lesion mapping revealed that QTc prolongation correlated with lesions in the right or left dorsal vagal nucleus. Remarkably, QTc time partially normalized during the in-hospital stay, suggesting a causal relationship with the stroke event. In addition, lateral medullary infarction can occasionally result in central sleep-related hypoventilation, which may lead to secondary cardiac injury (eg, via endothelial dysfunction) or coronary demand ischemia.^{72,73} Of note, stroke lesion sites in the insula and brain stem are associated with sleep-disordered breathing during the early poststroke phase.⁷⁴ In turn, sleep-disordered breathing after stroke was linked to impaired cardiac autonomic dynamics, endothelial dysfunction, ECG alterations like sinus brady- or tachycardia, and reduced LV function.^{73–75} Therefore, the interplay between the CAN and sleep-disordered breathing and its potential impact on the occurrence of the stroke–heart syndrome deserves further study.

Recent evidence from patients with TTS (synonymous with stress cardiomyopathy) highlights the role of the CAN in the occurrence of cardiac dysfunction. Compared with healthy controls, a surface- and voxel-based morphometry study revealed that patients with TTS related to emotional stress but unrelated to acute stroke have reduced cortical thickness in both insulae and reduced amygdala volume.⁷⁶ Moreover, a functional magnetic resonance imaging study demonstrated altered parasympathetic and sympathetic network activity in TTS patients versus matched controls.⁷⁷ In a case–control study of 104 individuals undergoing positron emission tomography–computed tomography imaging, higher activity in the amygdala was associated with the occurrence of TTS during a median follow-up of 2.5 years.⁷⁸ Interestingly, individuals with the highest activity within the amygdala developed TTS up to 2 years earlier than those with relatively lower activity.⁷⁸ Of note, higher resting activity of the amygdala and higher perceived stress was associated with arterial inflammation, bone marrow activity, and incident cardiovascular events in patients without known cardiovascular or cerebrovascular disease.⁷⁹ However, it remains challenging to determine whether inherited or acquired (eg, by epigenetic mechanisms) disturbance

of stress response and function of the CAN will before the stroke increase the individual's susceptibility to develop stroke–heart syndrome. Moreover, further clinical studies (eg, using lesion-network mapping approaches) are needed to determine the specificity of CAN dysfunction (beyond the insula and brain stem) for the occurrence of the stroke–heart syndrome.

Beyond specific lesion sites, observational clinical data provide compelling evidence that stroke severity is associated with the occurrence of virtually all manifestations of the stroke–heart syndrome.¹ This association has been shown most consistently in relation to the occurrence of myocardial injury, cardiac arrhythmia, and impaired LV function after stroke.^{4,8,60,67} In line with this data, animal studies provided evidence that the severity of acute and chronic cardiac dysfunction correlates with the size of brain ischemia.^{18,21,26} Larger ischemic brain injury not only increases the likelihood of CAN dysfunction, but also leads to more profound disruption of the blood–brain barrier and damage to the neurovascular unit. As a result, danger signals and extracellular vesicles enter the bloodstream, which results in a systemic activation of the immune system.⁸⁰ This is in line with the notion that the extent of cerebral injury and inflammation correlate with detrimental effects on the heart. Whether this can be targeted by therapeutic interventions remains to be proven.

Key Mediators

The knowledge about critical mediators of the stroke–heart syndrome is rather scarce. However, the way toward mechanistic studies is paved by combining experimental animal models such as MCAo with deeper cardiac phenotyping. Sympathetic overdrive and reduced parasympathetic activity as a cause for cardiac dysfunction in the stroke–heart syndrome are among the most consistently discussed mediators.^{1,3,81} MCAo-induced cardiac dysfunction in mice was associated with higher levels of norepinephrine in serum and the heart and linked to peripheral sympathetic overactivity.^{21,26} Seemingly contradicting, cardiac norepinephrine stores were enhanced 3 days after MCAo in the study of Veltkamp and colleagues, which could be interpreted as a decrease in sympathetic activity 3 days after stroke.¹⁸ However, unbiased RNA microarray analyses showed massive changes in expression of catecholamine-driven genes in the latter experimental setup. This suggests an early sympathetic overactivation in the heart persisting for at least 1 but not for 3 days after MCAo. In line with these considerations, it has been shown that already 2 hours after cerebral embolism in rats, circulating catecholamines were increased along with a reduction in cardiac function.²³ Therefore, local cardiac catecholamine homeostasis should, in particular, be examined and targeted in the

first hours after ischemia in the brain. Of note, MCAo-induced cardiac dysfunction could be attenuated by β -blockers.²¹ Moreover, different experiments found that monoamine oxidase inhibition resulted in both reduced local cerebral neuroinflammation and reduced catecholamine-induced cardiac dysfunction.^{82,83} This points to the potential of neuro-humoral blockade as therapeutic target. The role of autonomic dysfunction is supported by clinical evidence of impaired autonomic reflexes, and variability of blood pressure and heart rate in patients with ischemic stroke.^{84–86} High blood pressure variation, especially within the first 3 hours in the early critical phase of autonomic disbalance is associated with increased mortality at 90 days.⁸⁷ Both tachycardia and hypertensive blood pressure levels are established triggers of coronary demand ischemia, which can cause myocardial injury.⁸⁸ In addition, pressure overload can lead to reversible LV dysfunction with troponin release and myocyte apoptosis even without necrosis.⁸⁹

Recent experimental studies support an important role of inflammatory responses in the occurrence of stroke–heart syndrome.^{19,24} Stroke-induced cardiac dysfunction in mice was accompanied by a systemic inflammatory response, upregulation of proinflammatory cytokines within the myocardial tissue, and macrophage infiltration into the heart.^{19,24} Thus, besides sympathetic overactivation, proinflammatory pathways represent independent or perhaps interdependent mediators of the stroke–heart syndrome. In regard to the latter, sympathetic activation leads to the mobilization of inflammatory cells from the bone marrow or spleen.^{90,91} In a photothrombotic stroke model, splenectomy attenuated cardiac dysfunction along with interstitial cardiac fibrosis at 4 weeks.²⁴ This was preceded by an attenuation of proinflammatory cytokines and cardiac macrophage recruitment, suggesting that the spleen is critically involved in the development of subacute and long-term consequences of stroke–heart syndrome, eventually leading to chronic remodeling. Beyond the brain–bone marrow–spleen axis, further interorgan cross talks that involve the kidney and gut may be relevant drivers of inflammation and promote poststroke cardiac injury.^{92,93}

The directed recruitment of CD45+ leukocytes to the heart in response to injury has been shown to depend on cardiomyocyte-born cardiokines that serve as chemoattractant signaling molecules.^{94,95} Although the specific role of these cardiomyocyte-born signals in stroke–heart syndrome remains to be shown, similar pathophysiological roles have already been described for CC-chemokine ligands 2 (monocyte chemoattractant protein 1) and 3 (macrophage inflammatory protein) in ischemia–reperfusion injury of the heart.^{94,95} Importantly, this cascade was mediated by a catecholamine-sensitive protein kinase, namely CaMKII (Ca²⁺/calmodulin-dependent kinase II)

in cardiomyocytes, pointing to a model in which both peripheral sympathetic activation along with local cardiac sympathetic activation collectively orchestrate myocardial inflammation. Another candidate mediator in this particular context is BDNF (brain-derived neurotrophic factor), a neurotrophin involved in the development of (autonomic) neurons, angiogenesis, and maintenance of endothelial function.^{96,97} It has been demonstrated that BDNF improves cardiac muscle contraction and relaxation via the before-mentioned CaMKII pathway.⁹⁷ Circulating levels of BDNF are reduced after stroke, especially after severe stroke.⁹⁸ Therefore, BDNF signaling may represent a pathway mediating the interplay between autonomic tone, endothelial integrity, and myocardial dysfunction. Further experimental stroke studies in this direction are warranted in the future.

Both systemic inflammation and sympathetic overdrive can result in activation of coagulation, platelet hyperactivity, and endothelial dysfunction.^{99–101} This process of thromboinflammation has received scientific attention during the COVID-19 pandemic and has been proposed as an important mediator of myocardial injury, coronary microcirculatory dysfunction, and other extrapulmonary manifestations of COVID-19.^{101,102} The impact of thromboinflammation in the occurrence of the stroke–heart syndrome, however, has yet to be proven.

A potential contribution of cell–cell communication in combination with proinflammatory signals have recently been shown in experimental stroke models. Stroke-induced cardiac fibrosis and LV dysfunction was accompanied by decreased levels of the microRNA miR-126 in the serum and the heart.²² Mice specifically lacking miR-126 in endothelial cells showed an even more severe phenotype. This study demonstrates how a stroke-associated reduction in miR-126 and miR126-target genes may mediate the stroke–heart syndrome via the involvement of endothelial cells. Thus, it is possible that vascular injury after stroke might lead to long-distance cell–cell communication independent of the surrounding tissue. In this regard, metabolites or extracellular vesicles should also be considered.¹⁰³ Of note, administration of exosomes derived from cluster of differentiation 133+ umbilical cord blood cells attenuated cardiac dysfunction in a photothrombotic stroke model.²⁰ This was accompanied by reduced oxidative stress, reduced transforming growth factor- β expression, and reduced recruitment of proinflammatory macrophages. cluster of differentiation 133+ umbilical cells express miR-126, thereby providing a potential link to the aforementioned endothelial mechanism. The vasculature, with its enormous surface, may thereby serve as an amplifier of deleterious signals as was recently demonstrated in tumor biology.¹⁰⁴

Cardiac Downstream Pathways

The above-mentioned mediators affect various cardiac cell populations via induction of coronary demand ischemia (eg, via coronary vasoconstriction), microvascular dysfunction, metabolic switches, and cardiac inflammation (Figure 2). Within the past years, it is increasingly recognized that cardiomyocytes constitute less than half of the total cardiac cell population.¹⁰⁵ In response to acute injury, other cardiac-resident cells, including fibroblasts as well as the vasculature and immune cell compartments, also undergo phenotype changes that can trigger maladaptive cardiac remodeling. Interestingly, it has been shown that tissue-resident cardiac macrophages can be activated by remote injury processes including stroke.¹⁰⁶ Several downstream cardiac pathways have been established to mediate cardiac dysfunction.¹⁰⁷ However, signaling pathways to be potentially targeted by pharmacologic interventions that mediate acute cardiac dysfunction after stroke are largely elusive. Previous approaches to use calcium sensitizers in stroke models failed,¹⁰⁸ indicating that the underlying pathways may be more complex. Evidence for an important contribution of pro-inflammatory pathways was provided by a recent study in which an inhibitor of NLRP3 (NLR family pyrin domain containing 3), a key component of the inflammasome, restored cardiac function in mice after MCAo.³⁰ In a rat stroke model, increased oxidative stress and altered NO signaling were measured in the left atria. This was accompanied by the recruitment of neutrophils, T and B lymphocytes into the left atrium, as well as atrial fibrosis.²⁵ A detailed analysis of the recruitment of proinflammatory cells, receptor-ligand binding studies in combination with single cell, or even single nucleus sequencing may add to a better mechanistic understanding of these processes and their role in reducing the burden of stroke–heart syndrome.

In addition, recent discoveries highlight the role of the interface between metabolic and epigenetic processes. Nr4a1 (nuclear receptor subfamily 4 group a member 1) is a catecholamine-sensitive nuclear receptor that integrates cytokine signaling in inflammatory disorders by acting in nonmyocytes.¹⁰⁹ Nr4a1 was found to be upregulated 1 day after MCAo in the heart.¹⁸ Interestingly, Nr4a1 was also enhanced in cardiomyocytes derived from induced pluripotent stem cells of TTS patients,¹¹⁰ suggesting an overlapping molecular signature of these 2 brain-dependent forms of acute cardiac dysfunction. Interestingly, Nr4a1 was shown to be a key target of an epigenetic axis affecting cardiomyocyte calcium handling in response to stress.¹¹¹ Mechanistic experiments revealed that this process was causative for exercise-induced cardiac fatigue, which is reminiscent of the stroke–heart syndrome. Thus, it will be interesting to explore the potential

contribution of these epigenetic-metabolic signaling pathways to the stroke–heart syndrome. Supporting this notion, many of the genes acutely regulated after experimental stroke were found to depend on the activity of the transcription factor PPAR α (peroxisome proliferator-activated receptor α) that regulates fatty acid storage and glucose metabolism.¹⁸

Besides upregulation of metabolic pathways, Veltkamp and colleagues also reported that pathways that mediate muscle wasting were regulated following experimental stroke.¹⁸ These expression changes persisted over >3 days, pointing to more long-term consequences. Likewise, heart weight was reduced in the first days after MCAo, suggesting that these changes might impact the heart, resulting in pathological atrophy, a process that is also seen in muscle wasting diseases such as cancer-related cachexia. However, data that investigate the potential causal involvement are missing but may represent another new research direction.

OPEN QUESTIONS, ONGOING STUDIES, AND DIRECTIONS FOR FUTURE RESEARCH

Currently, there are many unanswered questions on the pathophysiology, long-term outcomes, and specific therapeutic approaches to stroke–heart syndrome, with many of them being addressed in ongoing studies (Table).^{40,67,112–120} Because elevation of serum markers of myocardial injury is associated with all other clinical categories of stroke–heart syndrome,^{4,32,40,41} it seems reasonable to measure hs-cTn in all patients to screen for early cardiac involvement after ischemic stroke and identify patients who are at risk for a more severe clinical course and further specific cardiac diagnostics. As described above, it is currently not clear how to differentiate causes of myocardial injury at the individual patient level and identify patients at high risk of ACS requiring timely coronary revascularization. It is therefore crucial to refine diagnostic algorithms to identify the corresponding underlying pathophysiology in the respective patient, in the future ideally without invasive diagnostics. This question is currently being answered by the PRAISE (Prediction of Acute Coronary Syndrome in Acute Ischemic Stroke) study, in which stroke patients with relevant hs-cTn elevation undergo coronary angiography in addition to standardized electrocardiography and echocardiographic assessment.¹¹⁹ In the future, other suitable diagnostic measures may routinely involve contrast-enhanced multislice cardiac computed tomography and/or comprehensive CMR to differentiate cardiac pathologies.^{121,122} In particular, CMR offers opportunities to distinguish causes

Table. Ongoing Clinical Studies Exploring the Pathophysiology or Targeting of Long-Term Consequences of Stroke–Heart Syndrome

Study	Title of study (registration)	Design	City, country	Target population	Target no. of patients	Outcomes of interest	Measures	Progress
1	Atrial Cardiomyopathy in Patients With Stroke of Undetected Mechanism ¹² (NCT03830983)	Prospective, observational, case-control-study (healthy age- and sex-matched controls)	Copenhagen, Denmark	Ischemic stroke (≤30 d before inclusion) without atrial fibrillation	150 (originally estimated enrolment=225)	Extent of LA fibrosis incidence of silent brain lesions, LA volume, LAEF	Gadolinium-enhanced CMR imaging	Active, recruiting
2	BEHABIS (The Bern Heart and Brain Interaction Study) ⁶⁷ (NCT03720522)	Prospective, observational, single-center cohort study	Bern, Switzerland	Acute ischemic stroke (<12 h after symptom onset) without severe renal failure (GFR <40)	220	TTS (prevalence of neurogenic stunned myocardium), subacute MI	CMR (gadolinium-enhanced with or without perfusion)	Active, recruiting
3	BeLOVE (Berlin Long-Term Observation of Vascular Events) ¹³ (DRKS00016852)	Prospective, observational, multicenter cohort study	Berlin, Germany	Hospitalization for: acute ischemic stroke; acute coronary syndrome, acute heart failure, acute kidney injury (4 study arms)	10 000, 2000 each study arm	MACE (cardiovascular mortality, nonfatal stroke, nonfatal myocardial infarction, hospitalization because of heart failure)	Clinical assessment, CMR, MRI (head), ECG, 3-dimensional echocardiography, ocular coherence tomography	Active, recruiting
4	CONVINCE (Colchicine for Prevention of Vascular Inflammation in Non-CardioEmbolic Stroke) ¹⁵ (NCT02898610)	Randomized controlled trial (colchicine vs placebo)	Several countries in Europe	Noncardioembolic ischemic stroke without major disability	2623	Recurrence of nonfatal ischemic stroke, nonfatal major cardiac event, vascular death	Clinical assessment	Active recruiting
5	CORONA-IS (Cardiomyocyte Injury Following Acute Ischemic Stroke) ¹⁶ (NCT03892226)	Prospective, observational, single-center cohort study	Berlin, Germany	Acute ischemic stroke with hospital admission <48 h after symptom onset	300	Quantify autonomic dysfunction and decipher downstream cardiac mechanisms leading to myocardial injury	Multimodal CMR, echocardiography, autonomic ECG markers, biobanking	Active, recruiting
6	Heart and Brain Study-Substudy of Whitehall II Imaging cohort ¹⁷ (NCT03335696)	Prospective, observational, cohort study	Oxford, United Kingdom	Retired British civil servants	775	Brain atrophy, cognitive decline	Vascular ultrasound, MRI (head)	Recruitment completed, extended follow-up

(Continued)

Table. Continued

Study	Title of study (registration)	Design	City, country	Target population	Target no. of patients	Outcomes of interest	Measures	Progress
7	InsuCor (Insular-Nominular Stroke Underlying Cardiac Failure (DRKS00012454)	Prospective, observational, case-control study	Würzburg, Germany	Acute ischemic stroke (onset <3d; with and without involvement of the insular lobe)	180	(New) systolic cardiac dysfunction, stroke, vascular events within 3mo	Echocardiography, blood biomarker	Active, recruiting
8	MIRACLE (MR Evidence of Cardiac Inflammation Post-Stroke Study)	Prospective, observational, cohort study	London, Ontario, Canada	Acute ischemic embolic stroke of undetermined source	44	NT-proBNP, systemic inflammation, myocardial infarction, LV function, LA fibrosis	NT-proBNP, inflammatory markers, gadolinium enhanced CMR imaging	Active, recruiting
9	Multifactorial Risk Stratification in Patients With Ischemic Stroke or Transient Ischemic Attack and Structural, Inflammatory, or Arrhythmic Cardiac Disease ¹⁸ (NCT04352790)	Prospective, observational, single-center cohort study	Tübingen, Germany	Ischemic stroke or TIA admitted to hospital	878	Any stroke, mortality, ischemic stroke, TIA, systemic embolism, myocardial infarction, intracranial hemorrhage, major bleeding	Clinical follow-up	Active, not recruiting
10	PRAISE (Prediction of Acute Coronary Syndrome After Acute Ischemic Stroke) ¹⁹ (NCT3609385)	Prospective, observational, multicenter cohort study	Multicenter, Germany	Acute ischemic stroke (<72 h) with troponin elevation	251	Presence of acute coronary syndrome, deaths, functional outcome, cardiovascular events	Coronary angiography, echocardiography, ECG	Recruitment completed. Follow-up ongoing
11	Predicting the Development of Myocardial Depression in Acute Neurological Patients (NCT03801694)	Prospective, observational, single-center cohort study	Columbus, Ohio, USA	Female patients with acute ischemic stroke or patients with SAH, >50y, predicted to be on norepinephrine infusion for at least 48h	10	Stress-induced cardiomyopathy	ST-T changes on ECG, echocardiography and measurement of catecholamines and troponin	Active and recruiting
12	PROSCIS (Prospective Cohort With Incident Stroke) ²⁰ (NCT01363856, NCT01364168)	Prospective, observational, hospital-based cohort study	Berlin (PROSCIS-B); Munich (PROSCIS-M), Germany	First ever acute stroke (including intracerebral hemorrhage in Berlin)	627 with first-ever ischemic stroke (Berlin), 850 (Munich)	Composite of stroke, myocardial infarction, and vascular death (within 3y)	Clinical follow-up including cerebral MRI, cognitive testing	Recruitment completed (Berlin); active (Munich).

(Continued)

Table. Continued

Study	Title of study (registration)	Design	City, country	Target population	Target no. of patients	Outcomes of interest	Measures	Progress
13	RIC-ACS (Protective Effects of Remote Ischemic Conditioning in Elderly With Acute Ischemic Stroke Complicating Acute Coronary Syndrome) (NCT03868007)	Randomized, controlled, double-blind, trial (sham procedure)	Beijing, China	Acute ischemic stroke (onset <24 h) plus acute coronary syndrome (onset <24 h), elderly patients (≤60y)	80	Any death and recurrence of cardiac and cerebrovascular ischemic events within 3mo	Remote ischemic conditioning (brief and transient limb ischemia)	Active and recruiting
14	SICFAIL (Stroke-Induced Cardiac Failure in Mice and Men) ¹⁰ (DRKS00011615)	Prospective, observational, single-center cohort study	Würzburg, Germany	Acute ischemic stroke with treatment on stroke unit	696	Heart failure, manifestation of cardiovascular disease	Follow-up by mail or telephone, echocardiography and ECG	Recruitment completed. First results published.

CMR indicates cardiovascular MRI; L.A, left atrium; LAEF, left atrial ejection fraction; LV, left ventricle; MACE, major adverse cardiovascular events; MI, myocardial infarction; MR, magnetic resonance; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SAH, subarachnoid hemorrhage; TIA, transient ischemic attack; and TTS, Takotsubo syndrome.

of myocardial injury after stroke and investigate long-term cardiac remodeling. The localization, pattern, and estimated reversibility of myocardial tissue changes enables the differentiation of ischemic and nonischemic injury. Focal fibrosis, as detected by CMR, may reflect unrecognized MI and has a prognostic impact in suspected ischemic heart disease.¹²³ Beyond focal fibrosis, diffuse fibrosis can be quantified by CMR and strongly correlates with histopathological findings of collagen content in the myocardium.¹²⁴ Diffuse fibrosis on CMR is associated with ventricular remodeling and event-free survival in patients aortic stenosis.¹²⁵ The role of CMR to differentiate mechanisms of myocardial injury after stroke is being addressed in the CORONA-IS (Cardiomyocyte Injury Following Acute Ischemic Stroke) study.¹¹⁶

Further open questions concern in particular the longer-term outcomes of stroke patients with stroke–heart syndrome, especially with regard to chronic cardiac function and vascular end points. At present, it is not clear if the high frequency of systolic and diastolic dysfunction detected in stroke patients is transient and recovers over time or whether this will result in clinically manifest heart failure. Approximately one-third of patients with early poststroke cardiac dysfunction have known heart failure before the stroke.⁴⁵ More longitudinal clinical studies are needed to determine the time-course, reversibility, and progression of heart failure in stroke patients. Among others, the SICFAIL (Stroke-Induced Cardiac Failure in Mice and Men) study aims to characterize and provide mechanistic understanding for long-term cardiac dysfunction after stroke.⁴⁰

The biggest task for the future will be to prove how to specifically treat stroke–heart syndrome and its long-term consequences. From our point of view, it seems conclusive that stroke patients with ACS should primarily be treated with coronary revascularization.^{126,127} In contrast, patients with other manifestations of stroke–heart syndrome may benefit from a pathophysiologically oriented drug therapy. This could consist of targeting the sympathetic nervous system (eg, with β -blockers), heart rate control, and improvement of blood pressure variability (eg, β -blockers, ivabradine, renin–angiotensin system inhibitors), anti-inflammatory approaches (eg, inhibition of the inflammasome or inflammatory cytokines like interleukin-1 β with colchicine or canakinumab), improvement of vascular endothelial function, and reduction of oxidative stress (eg, with statins, renin–angiotensin system inhibitors, antioxidants, new generation monoamine oxidase inhibitors), a combined antithrombotic medication (eg, temporary use of dual antiplatelets or adding low-dose anticoagulation), and avoiding proarrhythmic drugs (QTc prolongation). Until now, however, none of these candidates have formally been tested in appropriate randomized and blinded therapy studies. Joint research initiatives

led by interdisciplinary teams of cardiologists and neurologists from both preclinical and clinical perspectives are needed to reduce the knowledge gap and improve the clinical management of stroke-associated cardiac complications.

ARTICLE INFORMATION

Affiliations

Department of Neurology With Experimental Neurology (J.F.S., C.H.N., M.E.); and Center for Stroke Research Berlin (J.F.S., C.H.N., M.E.), Charité-Universitätsmedizin Berlin, Berlin, Germany; DZHK (German Centre for Cardiovascular Research), Partner Site Berlin, Berlin, Germany (J.F.S., C.H.N., M.E.); Berlin Institute of Health (BIH), Berlin, Germany (J.F.S., C.H.N., M.E.); World Stroke Organization Brain & Heart Task Force (J.F.S., L.A.S.); Department of Clinical Neurological Sciences, Schulich School of Medicine and Dentistry (L.A.S.); and Heart & Brain Laboratory (L.A.S.), Western University, London, Ontario, Canada; Working Group on Cardiovascular Magnetic Resonance, Experimental and Clinical Research Center, a Joint Cooperation Between the Charité-Universitätsmedizin Berlin, Department of Internal Medicine and Cardiology and the Max-Delbrueck Center for Molecular Medicine, DZHK (German Centre for Cardiovascular Research), Partner Site Berlin, Berlin, Germany (J.S.); Department of Cardiology and Nephrology, HELIOS Klinikum Berlin Buch, Berlin, Germany (J.S.); Institute of Experimental Cardiology, Heidelberg University, Heidelberg, Germany (J.B.); DZHK (German Centre for Cardiovascular Research), Partner Site Heidelberg/Mannheim, Heidelberg, Germany (J.B.); DZNE (German Center for Neurodegenerative Disease), Partner Site Berlin, Berlin, Germany (M.E.); and ExcellenceCluster NeuroCure, Berlin, Germany (M.E.).

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