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POSITION PAPER

Interaction of heart failure and stroke: A clinical consensus statement of the ESC Council on Stroke, the Heart Failure Association (HFA) and the ESC Working Group on Thrombosis

Wolfram Doehner[1,2,3]*, Michael Böhm[4], Giuseppe Boriani[5], Christina Christersson[6], Andrew J.S. Coats[7], Karl Georg Haeusler[8], Ian D. Jones[9], Gregory Y.H. Lip[10,11], Marco Metra[12], George Ntaios[13], Gianluigi Savarese[14], Eduard Shantsila[15,16], Gemma Vilahur[17], and Giuseppe Rosano[18]

[1]Berlin Institute of Health Center for Regenerative Therapies, Charité–Universitätsmedizin Berlin, Berlin, Germany; [2]Deutsches Herzzentrum der Charité, Department of Cardiology (Campus Virchow) and German Centre for Cardiovascular Research (DZHK) partner site Berlin, Charité–Universitätsmedizin Berlin, Berlin, Germany; [3]Center for Stroke Research Berlin, Charité–Universitätsmedizin Berlin, Berlin, Germany; [4]Universitätsklinikum des Saarlandes, Klinik für Innere Medizin III, Saarland University (Kardiologie, Angiologie und Internistische Intensivmedizin), Homburg, Germany; [5]Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Policlinico di Modena, Modena, Italy; [6]Department of Medical Sciences, Cardiology, Uppsala University, Uppsala, Sweden; [7]Heart Research Institute, Sydney, Australia; [8]Department of Neurology, Universitätsklinikum Würzburg (UKW), Würzburg, Germany; [9]Liverpool Centre for Cardiovascular Science, School of Nursing and Allied Health, Liverpool John Moores University, Liverpool, UK; [10]Liverpool Centre for Cardiovascular Science, University of Liverpool, Liverpool John Moores University and Liverpool Heart & Chest Hospital, Liverpool, UK; [11]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark; [12]Cardiology, ASST Spedali Civili and Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy; [13]Department of Internal Medicine, School of Health Sciences, Faculty of Medicine, University of Thessaly, Larissa, Greece; [14]Division of Cardiology, Department of Medicine, Karolinska Institutet, Heart and Vascular and Neuro Theme, Karolinska University Hospital, Stockholm, Sweden; [15]Department of Primary Care, University of Liverpool, Liverpool, UK; [16]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, UK; [17]Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau and CIBERCV, Barcelona, Spain; and [18]St George's University Hospital, London, UK, San Raffaele Cassino, Rome, Italy

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Heart failure (HF) is a major disease in our society that often presents with multiple comorbidities with mutual interaction and aggravation. The comorbidity of HF and stroke is a high risk condition that requires particular attention to ensure early detection of complications, efficient diagnostic workup, close monitoring, and consequent treatment of the patient. The bi-directional interaction between the heart and the brain is inherent in the pathophysiology of HF where HF may be causal for acute cerebral injury, and – in turn – acute cerebral injury may induce or aggravate HF via imbalanced neural and neurovegetative control of cardiovascular regulation. The present document represents the consensus view of the ESC Council on Stroke, the Heart Failure Association and the ESC Working Group on Thrombosis to summarize current insights on pathophysiological interactions of the heart and the brain in the comorbidity of HF and stroke. Principal aspects of diagnostic workup, pathophysiological mechanisms, complications, clinical management in acute conditions and in long-term care of patients with the comorbidity are presented and state-of-the-art clinical management and current evidence from clinical trials is discussed. Beside the physicians perspective, also the patients values and preferences are taken into account. Interdisciplinary cooperation of cardiologists, stroke specialists, other specialists and primary care physicians is pivotal to ensure optimal treatment in acute events and in continued long-term treatment of these patients. Key consensus statements are presented in a concise overview on mechanistic insights, diagnostic workup, prevention and treatment to inform clinical acute and continued care of patients with the comorbidity of HF and stroke.

Keywords Heart failure • Stroke • Cognition • Mood • Muscle • Cardiac reflex

*Corresponding author. Berlin Institute of Health Center for Regenerative Therapies, Charité Universitätsmedizin, Augustenburger Platz 1, 13353 Berlin, Germany. Tel: +49 30 450553507, Email: wolfram.doehner@charite.de

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Introduction

Heart failure (HF) is commonly presenting as a systemic clinical syndrome associated with multiple organ dysfunctions and various comorbidities. Comorbidities can complicate the diagnosis of HF, worsen symptomatic status, accelerate disease progression and can make treatment more difficult and more expensive. Among these HF related comorbidities, brain disorders are some of the most prevalent and most difficult to manage.[1] The comorbidity of HF and stroke is of particular importance as this comorbidity substantially impacts on adverse outcome, delayed recovery, prolonged hospitalization, and chronically impaired quality of life. Moreover, the comorbidity of HF and stroke is driven by common cardiovascular risk factors such as hypertension, atherosclerosis, diabetes mellitus, dyslipidaemia but also by mutually affecting pathophysiological mechanisms such as thromboembolic activation, haemodynamic failure, and neuroendocrine feedback activation.

This tight and mechanistic interaction of both diseases has been acknowledged in the concepts of a 'cardio-cerebral syndrome' addressing brain injuries induced by HF[2] and the 'stroke–heart syndrome", addressing myocardial injuries and further cardiovascular complications induced by acute stroke.[3] Despite the clinical and socioeconomic impact of the HF–stroke comorbidity, evidence on specific diagnostic and treatment recommendations in this high-risk setting are limited and therapeutic options are often empirical with little specific guidance from relevant clinical practice guidelines.

A recent position paper from the European Society of Cardiology (ESC) Council on Stroke has emphasized the need for a holistic or integrated approach to stroke and heart disease, including HF.[4] This approach would include the following three pillars of management:

- A: Appropriate antithrombotic therapy.
- B: Better functional and psychological status.
- C: Cardiovascular risk factors and comorbidity optimization (including lifestyle changes).

Antithrombotic therapy (A) and cardiovascular risk factor optimization (C) are discussed in subsequent chapters. Better functional and psychological status (B) includes prolonged and multidisciplinary efforts along a long-term stroke care pathway that ought to combine multiple medical specialties, psychological support in both acute care and rehabilitation programmes and continued home care and social services.[4] Such an integrated care approach requires standardized post-stroke care concepts with multidisciplinary collaboration and coordination of care. Adequate diagnostic workup and treatment of patients with the comorbidity of HF and stroke require interdisciplinary management concepts involving cardiologists, stroke specialists, internists, neurologists, radiologists with expertise in cardiovascular and brain imaging and others.

To address this complex medical condition, the ESC Council on Stroke together with the Heart Failure Association (HFA) of the ESC and the Working Group on Thrombosis (WGT) of the ESC have convened a task force with the remit to review current evidence on the complex condition and interplay of HF and stroke comorbidity. In this clinical consensus document we address both clinical perspectives: (i) on HF patients with increased risk of stroke or with acute stroke including transient ischaemic attack (TIA), and (ii) on stroke patients with existing HF or at risk of acute decompensated HF (ADHF). We also evaluate epidemiologic data, present mechanistic insights and discuss state-of-the-art diagnostic principles and treatment approaches of this high-risk comorbidity.

A better understanding of the pathophysiological mechanisms linking HF and stroke in mutual interaction and aggravation may help to inform the clinical work on early diagnosing, efficient diagnostic workup and optimal treatment of patients at risk or with the comorbidity of HF and stroke.

Epidemiology of the comorbidity heart failure and stroke

The global prevalence of stroke is about 100 million patients, whereas stroke accounts for up to 6.6 million deaths per year worldwide.[5] In European countries stroke is the second most common cause of death[6] and the most common cause of disability in adult life. HF is, too, a leading disease in developed countries with an incidence in Europe of about 5/1000 person-years and a prevalence of about 1–2% in adults (all age groups). HF is a particular disease of advanced age and prevalence increases from ~1% at the age <55 years to >10% at the age >70 years. The frequent comorbidity of HF and stroke is determined by the mutual mechanistic interaction between both syndromes: HF represents a major risk factor for stroke and, in turn, stroke may induce acute HF to trigger haemodynamic decompensation, even more so in case of pre-existing HF.[3]

Prevalence of heart failure in patients with stroke

Heart failure is present in about 10–24% of patients with ischaemic stroke,[7–10] which reflects either pre-existing HF or *de novo* acute HF secondary to the acute stroke. The latter can present as stress-induced cardiomyopathy (see below) which may develop in about 1% of acute stroke patients.[11,12] The most frequent cause of HF among stroke patients is ischaemic heart disease in about 50% of patients, followed by dilated cardiomyopathy (23%), valvular heart disease (17%) and hypertension (11%).[7] Based on echocardiography, 10% of all ischaemic stroke patients have systolic and additional 23% have diastolic dysfunction.[13] Among stroke patients, those with HF tend to have a higher overall comorbidity level that includes more frequent diabetes mellitus, coronary artery disease, valvular heart disease, and atrial fibrillation (AF) compared to those without HF.[7] In a nationwide analysis in the U.S., the proportion of stroke patients with HF increased from 10.8% of all stroke admissions in 1995 to 12.3% in 2005.[10]

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Prevalence of stroke in patients with heart failure

Numerous studies have provided evidence that patients with HF are at increased risk of ischaemic stroke compared to the general population.[14] The prevalence of stroke in clinical trials and registries of HF ranges between 8% and 11%.[14–18] In Europe, about 85% of all strokes are ischaemic strokes on populational level, while haemorrhagic strokes (including subarachnoid haemorrhage and intracerebral haemorrhage) account for about 15% of all strokes. Among patients with HF, cardioembolic aetiology is the main cause of stroke due to activation of multiple pathways of thrombus formation (see Section 'Mechanisms of interaction of heart failure and stroke'). Some studies suggested that the stroke rate was related to New York Heart Association class and inversely to left ventricular ejection fraction[19–21] but this was not confirmed in later studies.[22] In fact, comparison of the stroke risk according to the category of HF showed a similar[23–29] or even higher[30,31] risk of stroke for patients with HF with preserved ejection fraction (HFpEF) compared to HF with reduced ejection fraction (HFrEF). The higher stroke rate in HFpEF is not fully understood but several factors such as higher prevalence of AF, higher age and comorbidity level are discussed as contributing factors.[32,33]

There is a clear temporal factor in the interaction of HF and stroke with clinical relevance: the risk of stroke is highest (between 5-fold and 17-fold) within the first 30 days after newly diagnosed HF.[15–18] In turn, a cumulative risk of stroke over time living with HF has been shown in a meta-analysis: stroke prevalence increased from 18 per 1000 HF patients in the first year to 47 strokes per 1000 HF patients after 5 years.[14] An elevated risk of stroke is present as well in HF patients in sinus rhythm (SR) compared to non-HF subjects,[34,35] while AF confers a further increased risk. As such, the annualized stroke risk was 2.00 per 100 person-years in patients with chronic HF and SR compared to 2.87 for patients with chronic HF and AF in a 2003–2012 cohort.[36,37] Assessment of the attributable risk of HF alone to the overall stroke risk is, however, challenging. Ischaemic stroke is attributable to several pathologies including cardioembolic (left atrial, ventricular or valvular pathologies), atherosclerosis, small artery disease, or less frequent causes such as arterial dissection, paradox embolism (involving a persistent foramen ovale), vasculitis, and cardiac tumours, most of which being tightly interrelated with HF[38] (*Figure 1*).

Moreover, not only this risk for clinically overt stroke but also the prevalence of so-called silent brain infarcts is higher in patients with HF (20–35% vs. <5% without HF).[39–44]

Stroke outcomes in heart failure patients

Outcome of stroke is worse in patients with HF compared to non-HF patients. Cardioembolic stroke is the predominant aetiology of stroke in HF and is known to be often larger, multilocal, and more severe than other types of strokes, leading to more significant brain damage and disability. The larger strokes result from the cardiac thrombus causing occlusion of larger vessels and inducing multiple ischaemic lesions in different vascular regions due to fragmentation of the embolus. Mortality after stroke was observed between 2.2 and 4.5 times higher in patients with HF compared to non-HF patients.[9,10,45] Patients with HF experience higher stroke recurrence risk during follow-up[46] and have higher death rates.[7,47,48] Not only mortality of stroke is higher in HF patients. Patients with comorbid HF compared to non-HF patients are 2.5–3 times more likely to present with severe functional disability after stroke (modified Rankin scale 3–6)[9,49,50] with more severe short-term and long-term disability.[7,47,51] A direct relation between impaired left ventricular function and poor functional outcome after stroke has been reported.[52] In the COMMANDER-HF trial, 47.5% of strokes were either disabling (16.5%) or fatal (31%).[35] This unfavourable outcome in HF-related stroke resembles the findings in AF-related strokes, which further underlines that cardioembolic origin may be a predominating mechanism in these patients.

Mechanisms of interaction of heart failure and stroke

Mechanisms of heart failure to cause stroke

Cardioembolism is the most common aetiology of stroke in HF. Haemodynamic strokes due to hypoperfusion may result from low cardiac output and other stroke aetiologies may apply due to the interrelation of HF with other cardiovascular diseases (i.e. AF, hypertension, arteriosclerosis, and valvular disease). The principal concept of thrombus formation applies particularly in HF, as all three components of Virchow's triad are fulfilled, namely hypercoagulation, endothelial activation and a low-flow state with risk of blood stasis[53] (*Figure 2*).

(1) The hypercoagulation state in HF is complex. HF is associated with higher platelet activity and thrombin generation.[54] Patients with HF have elevated levels of soluble markers of platelet activity; beta-thromboglobulin, P-selectin, and CD40 ligand, as well as coagulation activity; fragment 1 + 2, thrombin-antithrombin complexes, and fibrinopeptide A.[55,56] The fibrinolytic system is also altered, irrespective of preserved or reduced ejection fraction, which results in higher levels of D-dimer, tissue-type plasminogen activator and plasminogen activator inhibitor-1.[56,57]

(2) Endothelial dysfunction is a characteristic feature of HF pathophysiology characterized by functional and structural impairment of the endothelium that results in impaired organ- and regional blood flow, and reduced vascular adaptability to perfusion demands.[56] The change in vascular integrity can be measured by higher concentrations of von Willebrand factor and reduced thrombomodulin in patients with HF.[58] In both HF with preserved or reduced ejection fraction, neurohormonal activation leads to production of reactive oxygen species (ROS) and results in nitric oxide deficiency thus promoting immune activation and endothelial dysfunction. Leucocyte adherence to the endothelial surface is activated and together with endothelial cells release

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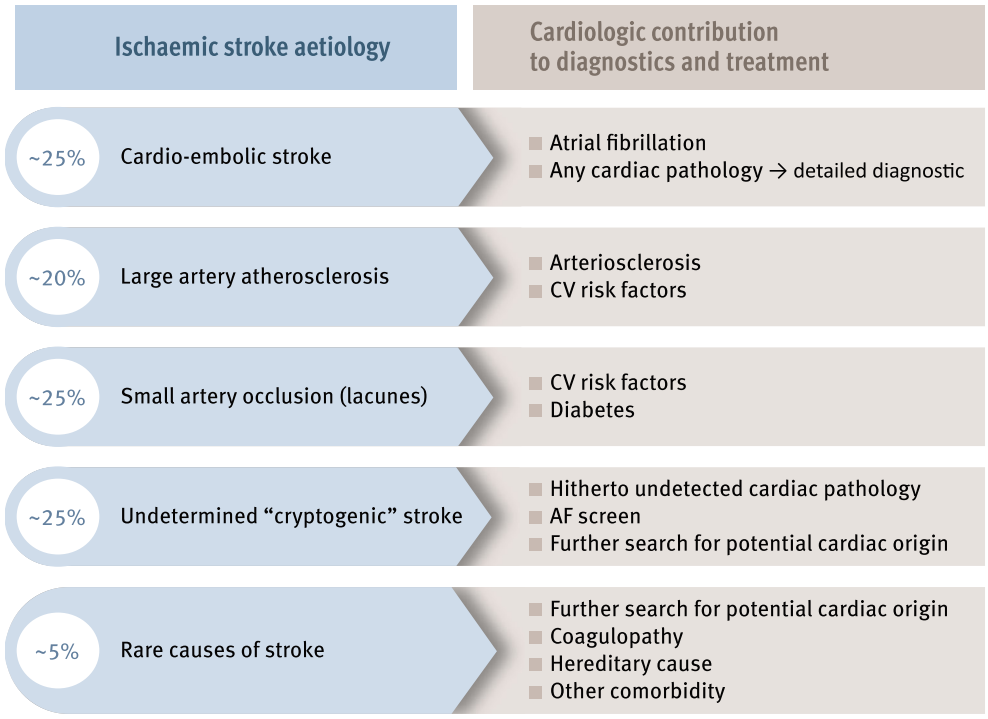

Figure 1 Stroke aetiology according to TOAST classification and respective cardiological input in diagnostic work-up and in acute and subacute stroke care. AF, atrial fibrillation; CV, cardiovascular.

of inflammatory cytokines is increased, such as interleukin-6 and tumour necrosis factor alpha, which are associated with the severity of HF.[59,60] Activated platelets expressing P-selectin and CD40 ligand form aggregates with monocytes and promote the inflammatory process and initiate production of tissue factor.[61,62] Extracellular vesicles released from activated platelets and endothelial cells can also express tissue factor, and together with their negatively charged phospholipid surfaces facilitate thrombin generation.[63]

(3) The intracardiac flow may be reduced when the left ventricle is enlarged and contractility is reduced. Blood flow may be further slowed in patients with concomitant AF. When HF is accompanied by valvular diseases, abnormal regional left ventricular morphology (aneurysm) or contractility (dys-akinetic segments), blood flow may be further compromised.[7] The impaired contractility with subsequent myocardial remodelling processes contributes further to increased myocardial fibrosis, and, again, endothelial dysfunction. Progressing decrease of left ventricular ejection fraction together with the above discussed mechanisms has led to recognize a particular cardiac thrombogenicity with a high risk of cardioembolic stroke.[19,64]

Ischaemic stroke due to large artery atherosclerosis may occur in ischaemic HF with generalized atherosclerosis, as atherosclerotic disease is associated with systemic activation of both inflammation and coagulation[43,65,66] A haemodynamic stroke may result from HF with low cardiac output particularly when combined with significant stenosis of carotid and cerebral arteries due to atherosclerosis.[67,68]

Haemorrhagic stroke may occur in patients with HF in the context of anticoagulation therapy, which contributes to the attenuated beneficial effect of oral anticoagulation in patients with HF without AF (see Section 'Anticoagulation for stroke prevention in heart failure'). Furthermore, antiplatelet therapy increases the risk of haemorrhagic stroke.

Mechanisms of stroke to cause or aggravate heart failure

The heart as a major cause of stroke is widely understood in the heart–brain interaction. There are as well reciprocal cerebral-cardiac effects[69] (*Figure 3*). An acute stroke can trigger an imbalance of the autonomic nervous system, of the hypothalamic–pituitary–adrenal axis and immune activation which all contribute to an exaggerated cardiovascular stress response.[3] The autonomic dysfunction includes impairment of the baroreceptor sensitivity, the stress response results in elevated catecholamine levels and cortisol levels.[70] This contributes to systemic microvascular vasoconstriction and systemic vascular resistance, increased heart rate and arrhythmogenic potential with

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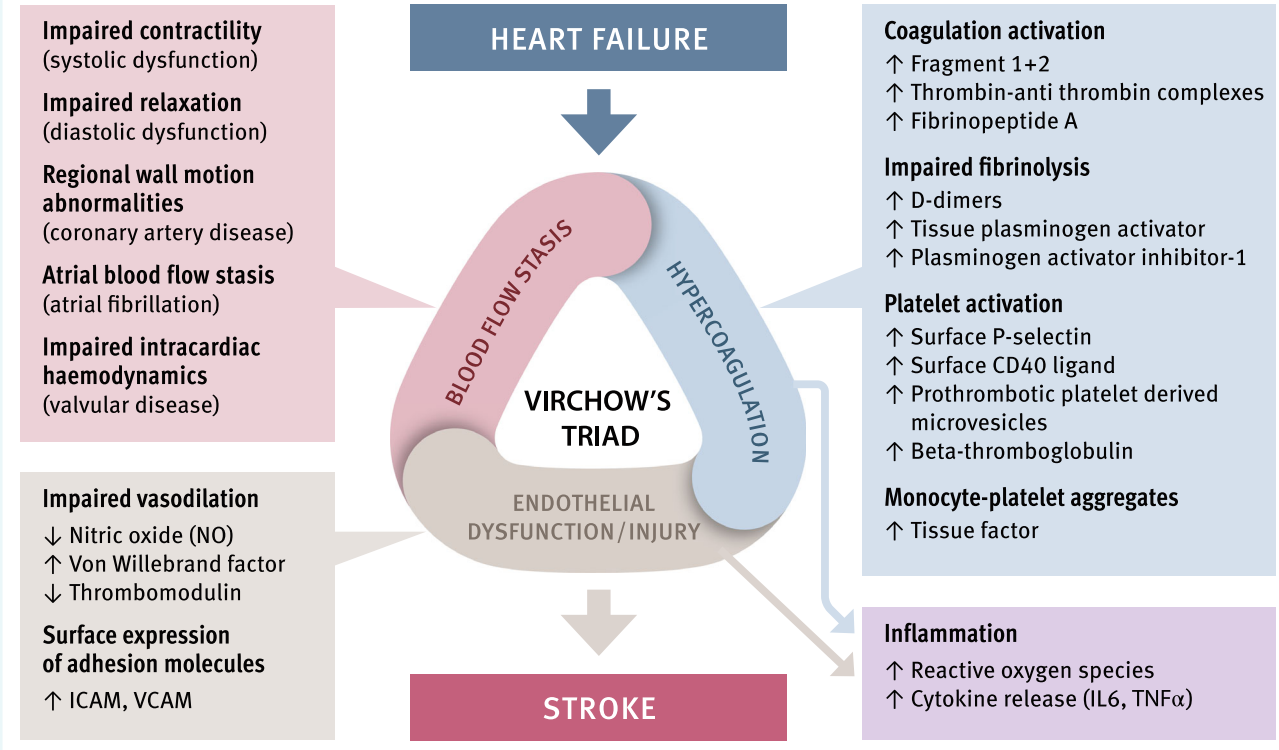

Figure 2 Virchow's triad of thrombus formation and stroke risk in patients with heart failure. ICAM, intercellular adhesion molecule; IL6, interleukin-6; TNFα, tumour necrosis factor alpha; VCAM, vascular cell adhesion molecule.

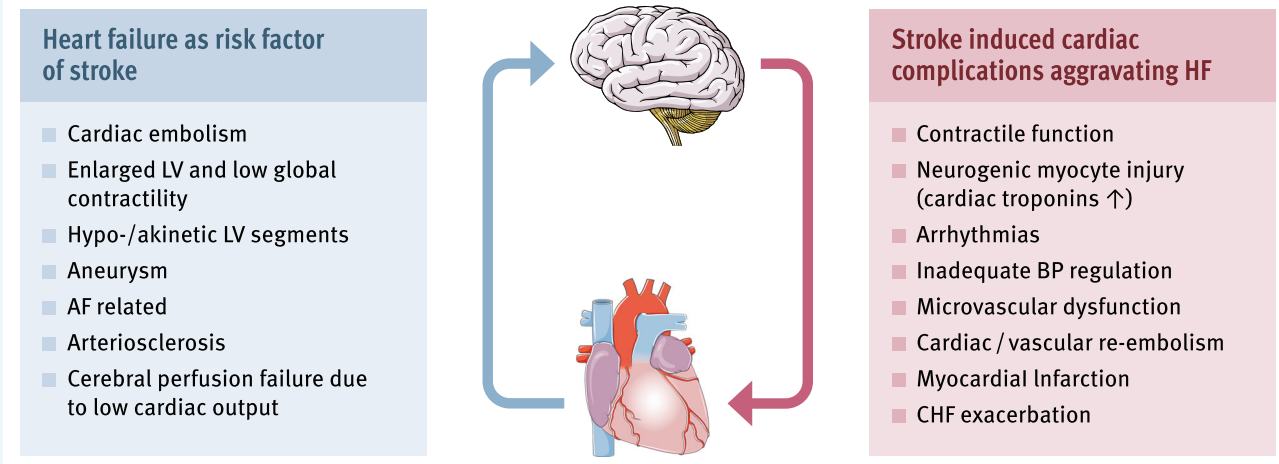

Figure 3 Bidirectional interaction of heart failure and stroke. AF, atrial fibrillation; BP, blood pressure; CHF, congestive heart failure; HF, heart failure; LV, left ventricle.

subsequent myocardial injuries, disturbed calcium homoeostasis, and accelerated oxidative and metabolic stress.[3] The cumulative cardiovascular effects of a stroke may thus result in clinical complications of acute hypertensive episodes, acute myocardial ischaemia, AF, arrhythmias, ventricular dysfunction and may ultimately trigger cardiac decompensation (*Figure 4*).[69] The systematic interactions of acute stroke to induce cardiovascular complications have been summarized as stroke–heart syndrome.[3] Such cardiac complications may be more pronounced and prolonged in conditions of pre-existing cardiac diseased since an add-on

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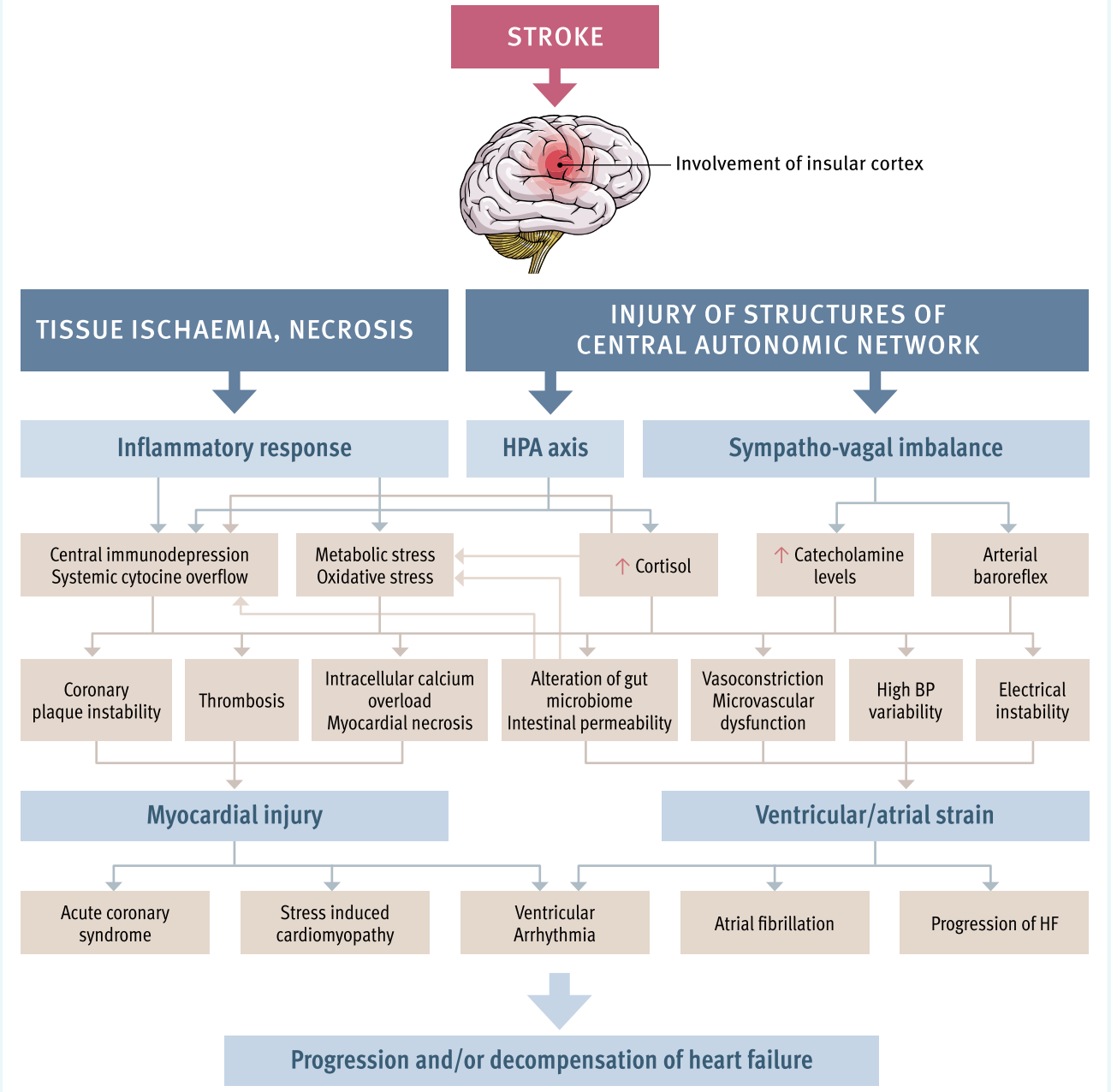

Figure 4 Signalling pathways in acute and subacute stroke to provoke cardiac injury and to induce or aggravate heart failure. BP, blood pressure; HF, heart failure; HPA, hypothalamic–pituitary–adrenal. Modified from[69].

effect may results in more severe complications than in case of a previously healthy heart. Of note, the intensity of the autonomic dysfunction and subsequent myocardial injury are not related to age, the severity of the stroke or the volume of brain injury but are associated with injury of certain cerebral regions (including the insula region, the anterior cingulate gyrus and the amygdala).[71]

Although stroke-related cardiac changes are typically transient within the subacute phase of 2–5 days after a stroke, some stroke survivors may experience long-term deterioration of left ventricular function.[72] Even though further research is needed, these mechanisms can contribute to progression of prevalent HF or new onset of HF.[15]

Stratification of stroke risk in heart failure patients

The individual stroke risk of patients with HF depends on clinical variables of the HF plus additional clinical characteristics and comorbidities (*Table 1A*). The temporal association of a particular

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Table 1 Clinical parameters which are known to affect the stroke risk in heart failure patients and clinical parameters included in a prognostic model to predict risk of stroke

A. Clinical characteristics	B. Prognostic model[83]
Age	Age (</> 60 years)
	Sex
Timing of HF diagnosis	
Myocardial factors	Left ventricular ejection fraction
- Impaired contractile function	
- Enlarged left atrial diameter/volume	
- Enlarged left ventricular diameter/volume	
- Low cardiac output	
- Left ventricular thrombus	
Atrial fibrillation	
Cardiovascular comorbidities	Prior stroke or transient ischaemic attack
	Diabetes mellitus
	Diastolic blood pressure
Renal function	Blood urea nitrogen
Prothrombotic conditions	Haemoglobin

high stroke risk early after the *de-novo* diagnosis of HF (<30 days) or related to an episode of ADHF has been discussed above (see Section 'Epidemiology of the comorbidity heart failure and stroke'). In turn, the risk of stroke is accumulating over years of chronic HF. In a 30-year Danish nationwide cohort study between 1980 and 2021, the 1-, 3- and 5-year risk of stroke among HF patients was 1.4%, 2.9% and 3.9%, respectively.[17]

Age is an important determinant of stroke risk in HF, and both HF and stroke have a strong association with increasing age. The mean age of diagnosis is >71 years in both HF and stroke patients.[1]

Myocardial factors are related to HF: impaired contractile function, enlarged left atrial and left ventricular diameter and low cardiac blood flow contribute to the increased thromboembolic risk in HF (see Section 'Mechanisms of interaction of heart failure and stroke'). Notably, while a reduced left ventricular systolic function does not seem to be a strong determinant of stroke risk in HF patients, a high E/e' value was observed as an independent risk factor for stroke.[31] The latter may also support the finding of a higher stroke rate in patients with HFpEF. Elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) was shown to be predictive of increased stroke risk in acute HF. In 3261 patients hospitalized with acute HF in the APEX trial, elevated NT-proBNP was associated with a 3.6-fold higher risk of stroke (adjusted hazard ratio [HR] 3.64, 95% confidence interval [CI] 1.35–9.83).[73]

A *left ventricular thrombus* is not a rare finding in HF patients particularly in connection to left ventricular regional akinetic segments or aneurysms and has an obvious mechanistic association with ischaemic stroke.[38] Patients with left ventricular thrombus identified on cardiac magnetic resonance imaging have a 9% short-term risk of stroke,[74] and should be considered for oral anticoagulation.[75]

It is evident that multiple cardiac pathologies are related to HF and carry in addition a direct or indirect risk of stroke. Such comorbidities include anatomical abnormalities, ventricular aneurysm, valvular pathologies, AF, storage diseases and others. Those diseases may require specific diagnostic workup and treatments that is beyond the scope of this document.

Atrial fibrillation as a major cause of stroke has a strong bidirectional association with HF with interchangeable roles as cause and consequence. Patients with HF and AF have worse prognosis and higher stroke risk compared to patients with SR.[34,76,77] Notably, a pooled analysis of the PARADIGM-HF and the ATMOSPHERE trials has shown that among patients with HF and AF, those with paroxysmal AF were at greater stroke risk compared to patients with persistent or permanent AF,[76] which seems to be in contrast to the association seen in non-HF AF patients.[78]

Cardiovascular comorbidities are associated with the risk of stroke in patients with HF. Notably, the CHA_2DS_2-VASc score, which is used to assess stroke risk and guide treatment decisions explicitly in patients with AF, shows a similar stepwise increase of stroke risk in HF patients, even in the absence of AF.[79–81] Although the CHA_2DS_2-VASc score may predict stroke in HF patients without AF,[82] prescription of oral anticoagulants regularly requires the documentation of clinical AF.

A prognostic algorithm for stroke prediction was developed specifically for patients with systolic HF based on the WARCEF cohort which included the following parameters: age (dichotomized at the threshold of 60 years), sex, haemoglobin, blood urea nitrogen, ejection fraction, diastolic blood pressure, diabetes status, and prior stroke or TIA (*Table 1B*).[83] It showed a C-index of 0.63 for the prediction of the overall risk of ischaemic stroke or death in HF patients. A recent analysis used pooled data from HF cohorts of three clinical trials, to test a simple risk model based on three variables (history of prior stroke, insulin-treated diabetes, and plasma NT-proBNP level).[84] This model was able to identify a subset of HFrEF patients without AF which had a stroke risk equivalent to that of patients with AF who are not anticoagulated.

Renal function is related to higher stroke risk in patients with HF.[85] In the Danish nationwide registry, among patients with HF, those with chronic renal disease had a 30% higher stroke risk compared to patients without.[86]

Beside these risk factors, any (systemic) clinical characteristics that may increase the likelihood of thrombus formation may further add to the HF-related risk of stroke, including chronic inflammatory diseases and venous vascular comorbidities.

Primary and secondary stroke prevention in heart failure

Prevention has a key role in reducing the burden of stroke globally, since it is generally assumed that up to 90% of all strokes could be preventable, and attributable to 10 modifiable risk factors[87,88] (*Figure 5*). Preventive measures should be addressed as primary and

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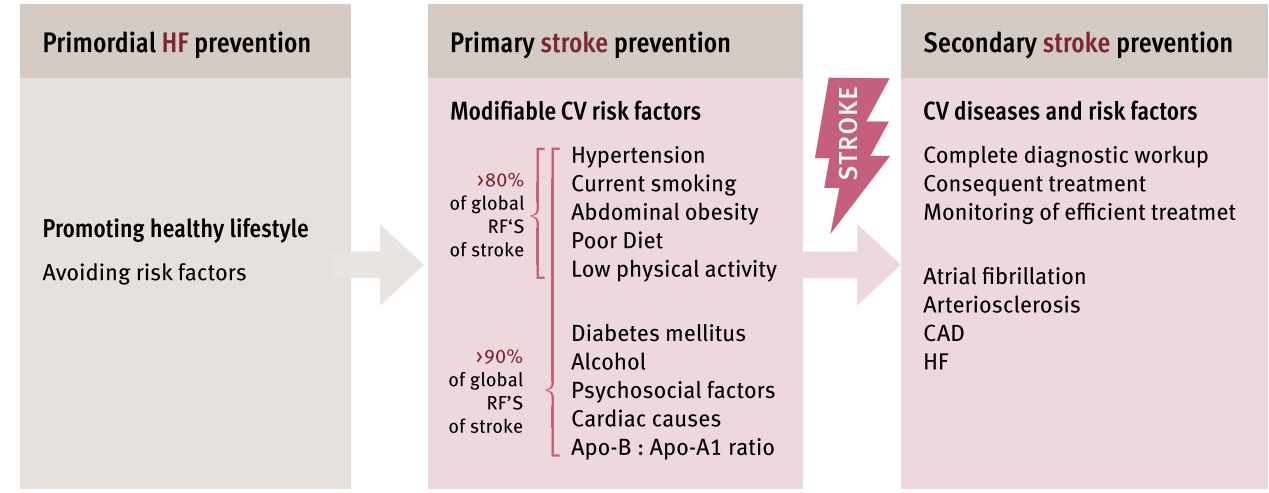

Figure 5 Sequence of prevention concepts in preventing the heart failure–stroke comorbidity. Apo, apolipoprotein; CAD, coronary artery disease; CV, cardiovascular; HF, heart failure; RF, risk factor.

secondary prevention but also primordial prevention may exert important benefits towards risk reduction.

Primary and secondary prevention of stroke are not particularly different in HF patients compared to non-HF patients following principles to reduce cardio-cerebro-vascular risk factors. Prevention of stroke involves both screening for and treatment of major risk factors including hypertension, AF, atherosclerotic disease, lipid disorders, as well as lifestyle factors such as smoking, alcohol, physical inactivity, or abdominal obesity; and other risk factors such as diabetes mellitus or a family history of stroke or AF. However, once HF has been established, an increased risk of stroke should be acknowledged as motivation for further diagnostic assessment and monitoring of these patients. Accordingly, thorough echocardiographic assessment of the left atrium and left ventricle should be pursued in patients with HF for both primary and secondary prevention of stroke.[89]

Prevention of stroke (primary and secondary) in patients with HF is supported by optimization of HF treatment according to guideline recommendations.[75] Given the known association of a particular high risk of stroke with ADHF (see above), avoiding such decompensation will likely reduce the risk of stroke. Meticulous monitoring and careful (slow) rebalancing of volume status in the treatment of ADHF, avoiding infections and other complications during recompensation may therefore be particularly relevant for stroke prevention.

Detection of AF is a major factor for stroke prevention and there are mutual interactions between AF and HF.[82,90,91] Silent AF is detected in approximately one-third of embolic strokes of undetermined source, although its causal association with stroke seems to be less important than initially thought.[92,93] Therefore, prevention and treatment of AF in HF is important for both prevention of HF progression *and* prevention of stroke. The comprehensive concept of management of AF in HF includes (i) identification and treatment of triggers of AF, (ii) prevention of embolic events, (iii) rate control to prevent HF progression, and (iv) rhythm control to improve outcome.[75] Catheter ablation of AF has been shown to improve outcome in patients with HF[94] and even in patients with end-stage HF.[95] Screening for AF should be pursued according to the guideline-recommended principles with opportunistic screening in elderly patients aged ≥65 years and systematic screening in patients aged ≥75 years.[96] For this screening, implanted devices with rhythm recording capacity should be utilized where possible. If AF is detected, anticoagulation is the cornerstone for preventing stroke and this is not different in patients with or without HF (see Section 'Anticoagulation for stroke prevention in heart failure').

In secondary stroke prevention (i.e. in patients after stroke), a thorough diagnostic workup of potential cardiac involvement is particularly recommended, if risk profile, family history or hitherto unclear (and undiagnosed) symptoms may hint towards a cardiac origin of the cerebral injury. Notably, secondary prevention after stroke benefits as well the prevention of myocardial infarction, peripheral artery disease and HF.[97,98] Taking into account the mechanistic interrelation of HF and AF, detection of abnormalities of the left atrium may be of particular value for stroke risk assessment in patients with concomitant HF.[99–101] A number of echocardiographic parameters have been associated with an increased risk of stroke in AF patients, with or without HF (*Table 2*),[102] but it remains unclear which incremental value these parameters may carry on top of the widely used CHA_2DS_2-VASc score for improved stroke risk stratification.

An important impact to reduce the burden of stroke could be achieved through a paradigm shift in prevention towards so-called 'primordial prevention', defined as prevention of the development of risk factors in the first place.[103] This approach is even upstream to primary prevention and aims at avoiding the penetration of risk factors into the population rather than treating them, and has been proposed for the prevention of cardiovascular

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Table 2 Echocardiographic parameters associated with an increased risk of stroke in atrial fibrillation patients (with or without heart failure)[102]

- Enlarged left atrial dimension
- Enlarged left atrial volume
- Spontaneous echo contrast
- Left atrial appendage non-chicken wing shape
- Left atrial appendage peak velocity <20 cm/s at pulsed-wave Doppler
- Abnormal left atrial longitudinal strain at speckle tracking echocardiography

disease in general.[103,104] This concept should imply joint efforts to improve social and environmental conditions, as well as individual behaviours for a wider adoption of healthy lifestyles.[104,105]

Anticoagulation for stroke prevention in heart failure

Anticoagulation treatment is the cornerstone for prevention of cardioembolic stroke in HF. The concept of anticoagulation in HF needs to be addressed separately for the two main situations of HF with AF, and HF without AF, that is, when SR is maintained.

In patients with HF and concomitant AF the ESC guidelines for the diagnosis and treatment of HF clearly recommend oral anticoagulation, unless contraindications for oral anticoagulation apply and direct oral anticoagulants (DOACs) are the preferred choice for patients with non-valvular AF.[75] Randomized controlled trials (RCTs) of DOACs for stroke prevention in non-valvular AF included a significant proportion of patients with HF to support this anticoagulation choice.[91] A relative risk reduction of recurrent stroke by 64% and all-cause mortality by 26% can be achieved by anticoagulation compared to placebo or control, yielding a number needed to treat (NNT) in secondary prevention of 14 within 1 year.[106] Comparing anticoagulation strategies in AF, DOACs significantly reduced the risk of stroke compared with warfarin by 19% (relative risk 0.81, 95% CI 0.73–0.91).[107] HF is one risk factor of the CHA_2DS_2-VASc score and hence patients with HF but with no other risk factors for stroke should be considered for oral anticoagulation.[96] However, this would apply only to a small number of HF patients as the common aetiological factors of HF, such as coronary artery disease, hypertension, diabetes, and older age further increase the CHA_2DS_2-VASc score to ≥2 where oral anticoagulation is recommended. Of note, the beneficial effect of oral anticoagulation for stroke prevention has been confirmed only in patients with clinical AF. Whether anticoagulation improves outcome as well in patients with subclinical (i.e. device-detected) AF is currently undecided as recent trials reported conflicting results.[108,109]

In contrast, in patients with HF and with maintained SR, the benefit of anticoagulation for stroke prevention is less clear. Five RCTs have assessed oral anticoagulation in HF with SR comparing warfarin with aspirin or placebo (*Table 3*).[110–114] All these studies were restricted to HFrEF. Two small studies (WASH and HELAS) did not have adequate statistical power.[115] In the larger WARCEF trial ($n = 2305$), warfarin did not improve the composite primary outcome of ischaemic stroke, intracerebral haemorrhage, or death from any cause (HR 0.93, 95% CI 0.79–1.10). Notably, warfarin reduced the rate of ischaemic strokes (HR 0.52, 95% CI 0.33–0.82).[113] However, treatment with warfarin resulted in more major haemorrhages (adjusted rate ratio 2.05, 95% CI 1.36–3.12) with no significant difference in the rate of intracerebral haemorrhage. A Cochrane meta-analysis showed similar all-cause mortality for warfarin versus aspirin (risk ratio 1.00, 95% CI 0.89–1.13) with a two-fold increase in major bleeding with warfarin (risk ratio 2.00, 95% CI 1.44–2.78).[116] Comparison of warfarin with clopidogrel in the WATCH trial showed similar findings.[112] There were fewer non-fatal cardiovascular events, including non-fatal strokes in the warfarin group (odds ratio [OR] 0.79, 95% CI 0.63–1.00).

The double-blind COMMANDER-HF trial is the only clinical trial to assess the efficacy of a DOAC in the setting of HF with maintained SR.[114] In this trial, 5022 participants with HF and background coronary artery disease were randomized to rivaroxaban 2.5 mg twice daily or placebo on top of usual care including aspirin in 93% of patients. There was no significant difference in the primary composite efficacy outcome of death from any cause, myocardial infarction, or stroke (HR 0.94, 95% CI 0.84–1.05), nor in overall mortality (HR 0.98, 95% CI 0.87–1.10), or in any prespecified secondary outcome. A detailed post-hoc analysis, however, showed a 32% reduction in strokes and TIAs in the rivaroxaban arm (HR 0.68, 95% CI 0.49–0.94; $p = 0.02$), due to a lower rate of ischaemic strokes.[35] In turn, rivaroxaban led to more major bleeding events (HR 1.68, 95% CI 1.18–2.38), but there was no significant difference in the primary composite safety outcome of fatal bleeding or bleeding into a critical space with a potential for causing permanent disability (HR 0.80, 95% CI 0.43–1.49). The outcome in the study population was mainly driven by HF deterioration rather than thrombotic events, which explains the net neutral effect of rivaroxaban on the primary outcome. A similar result was reported from a recent meta-analysis including 15 794 patients from seven controlled trials.[117] It was found that the reduced rate of stroke or systemic embolism (OR 0.57, 95% CI 0.39–0.82, NNT 65) was outweighed by a higher rate of major bleeding (OR 1.86, 95% CI 1.32–2.63, number needed to harm 58). In the subgroup analysis according to the type of oral anticoagulation, rivaroxaban was associated with a significantly reduced rate of stroke or systemic embolism (1.24 vs. 1.97 events per 100 patient-years, respectively; OR 0.63, 95% CI 0.45–0.88, NNT 82) without excess risk of major bleeding (OR 1.66, 95% CI 0.26–10.59) compared to antiplatelets or placebo. There was no significant difference between groups for the outcomes of myocardial infarction, all-cause mortality, and HF hospitalization. The accumulated data emphasize that further biomarkers and individualized risk profiles may be taken into account and structured decision pathways may be pursued to identify patients at high risk of recurrent stroke and who may benefit from oral anticoagulant therapy.[118]

Overall, oral anticoagulation in HFrEF with SR did not improve mortality, and the stroke events were relatively few in all groups

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Table 3 Randomized controlled trials of oral anticoagulation in heart failure with sinus rhythm

Study characteristic	WASH[110]	HELAS Post-MI arm[111]	HELAS DCM arm[111]	WATCH[112]	WARCEF[113]	COMMANDER-HF[114]
Year published	2004	2006	2006	2009	2012	2018
Randomized patients, *n*	279	115	82	1587	2305	5022
Study design	Open label	Double-blind	Double-blind	APT: Double-blind Warfarin: open-label	Double-blind	Double-blind
Trial intervention	Warfarin	Warfarin	Warfarin	Warfarin	Warfarin	Rivaroxaban
Target INR	2–3	2–3	2–3	2.5–3	2–3.5	No INR
Control group	Aspirin 300 mg/day or no treatment	Aspirin 325 mg/day	Placebo	Aspirin 162 mg/day Clopidogrel 75 mg/day	Aspirin 325 mg/day	Placebo
HF-related criteria	Diuretic required	NYHA class II–IV Previous MI	NYHA class II–IV DCM	NYHA class II–IV Diuretic and ACEI use	NYHA class I–IV	CAD, high (NT-pro)BNP[a]
LVEF criteria, %	≤35	<35	<35	≤35	≤35	≤40
Follow-up, months	27 (mean)	19 (mean)	20 (mean)	23 (mean)	42 (mean)	21 (median)
All-cause death, *n*, HR (95% CI)	22 vs. 21 (placebo) vs. 27 (aspirin)	11 vs. 9 (aspirin)	2 vs. 6 (placebo)	0.98 (0.85–1.13) vs. aspirin 0.92 (0.69–1.23) vs. clopidogrel	1.05 (0.86–1.27)	0.98 (0.87–1.10)
Non-fatal stroke, *n*, HR (95% CI)	0 vs. 2 (placebo) vs. 2 (aspirin)	2 vs. 2 (aspirin)	0 vs. 2 (placebo)	1 vs. 9 (aspirin)[b] vs. 11 clopidogrel[b]	0.52 (0.33–0.82)[b]	0.66 (0.47–0.95)[b]
Major bleeding, *n*, HR (95% CI)	4 vs. 0 (placebo) vs. 1 (aspirin)[b]	4 vs. 0 (aspirin)	3 vs. 0 (placebo)	28 vs. 19 (aspirin) vs. 11 clopidogrel[b]	2.21 (1.42–3.47)[b]	1.68 (1.18–2.39)[b]

ACEI, angiotensin-converting enzyme inhibitor; APT, antiplatelet therapy; CAD, coronary artery disease; CI, confidence interval; DCM, dilated cardiomyopathy; HF, heart failure; HR, hazard ratio; INR, international normalized ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; na, data not available; (NT-pro)BNP, N-terminal pro-(B-type natriuretic peptide); NYHA, New York Heart Association.

[a]After recruitment of 23% of patients, the protocol amendment required patients to have plasma BNP ≥200 pg/ml or NT-proBNP ≥800 pg/ml.

[b]$p < 0.05$ vs. anticoagulation group on antithrombotic therapy in a patient with HF depending on heart rhythm.

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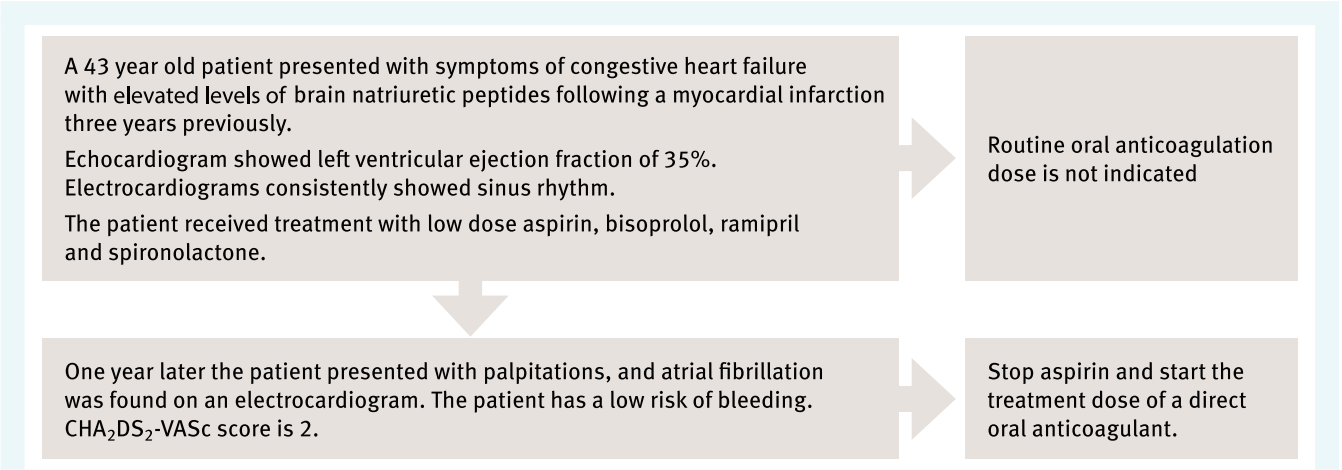

Figure 6 Example of anticoagulation treatment decision in the course of heart failure (HF) disease progression. [Correction added on 15 January 2024, after first online publication: Figure 6 image has been corrected in this version.]

(*Table 3*). A consistent increase in bleeding events offsets the potential benefits of anticoagulation on thromboembolism reduction.[119] RCTs on oral anticoagulation for HFpEF with SR are lacking. The ESC guidelines for the diagnosis and treatment of HF point out that the lack of data does not support the routine use of anticoagulation in HFrEF with SR and recommend anticoagulation once AF has been diagnosed (*Figure 6*). However, low-dose rivaroxaban may be considered in HF patients with coronary artery disease or peripheral artery disease, a high risk of stroke and no major haemorrhagic risk. This recommendation is based on a subgroup analysis of the COMPASS trial where a low dose of rivaroxaban, on top of aspirin, reduced ischaemic events in patients with HF, mainly HF with moderately reduced or preserved ejection fraction.[120]

Oral anticoagulation treatment may be prohibited in case of increased risk of bleeding and other options to prevent cardiac embolism may be pursued. Left atrial appendage closure (LAAC) has been established as a safe and effective procedure for stroke prevention in patients with non-valvular AF. Observational data from over 34 000 LAAC procedures have shown that the use in patients with AF and HF (25% of the LAAC cohort) is safe and there is no difference in inpatient mortality and cardiac complications between the HF and non-HF subgroups. However, higher incidence of non-cardiac complications such as acute kidney injury and respiratory failure were noted for the HF subgroup.[121] Another study observed during a 3-year follow-up a higher rate of major adverse cardiac and cerebrovascular events (31% vs. 15%) and of death (24% vs. 7%).[122] The impaired outcome was, however, attributed by the authors to the overall adverse outcome due to the HF comorbidity compared to the non-HF group.

Specific aspects of heart failure treatment after stroke

Treatment of HF after stroke needs to be separately addressed for acute stroke and the subacute phase after stroke and for the chronic treatment long-term after stroke (*Figure 7*). It also needs to take into account the specific background and guideline-recommended therapy for HFrEF and HFpEF which are materially different. Currently, for HFpEF a class IA guideline recommendation is given only for the treatment with SGLT2 inhibitor, although it is important to control congestion with diuretic treatment and to treat common comorbidities such as hypertension and AF. This treatment will apply independent of the presence of stroke. The rest of this section will concentrate on the management of HFrEF.

The chronic treatment of HF after a stroke should follow the HF management guidelines.[75] However, certain specific aspects may need adaptation in the setting of an acute stroke event. Optimization of cardiac output, blood pressure and heart rate is of crucial importance during the vulnerable phase following acute stroke for both improving outcome after stroke and preventing episodes of ADHF.

As a general rule, existing treatment for HF should be maintained if clinically possible and titration or interruption of medical treatment should be done slowly and under close clinical supervision. Most HF guideline-recommended medical treatments reduce blood pressure. In acute stroke, whether there is clinically evident hypotension or not, a temporary down-titration or discontinuation of some of the standard HF treatments might be needed. Notably, any reduction of beta-blocker needs to be done with great caution and sudden cessation of such therapy should be avoided given the risk of neuroendocrine rebound and the consequent increased risk of arrhythmias and sudden cardiac death. An early reinitiation/uptitration of HF treatment in the post-acute phase is beneficial for both the secondary prevention of stroke, that is, as anti-hypertensive treatments, and for the reduction of mortality/morbidity in patients with HF with reduced and mildly reduced ejection fraction.[75] In the post-acute phase, when required, anti-hypertensive treatment can be performed by first re-implementing full-dose HF therapies.

Maintaining optimum blood pressure control in acute stroke is crucial for outcome and may be particularly challenging in stroke patients with HF. The relationship of systolic blood pressure with

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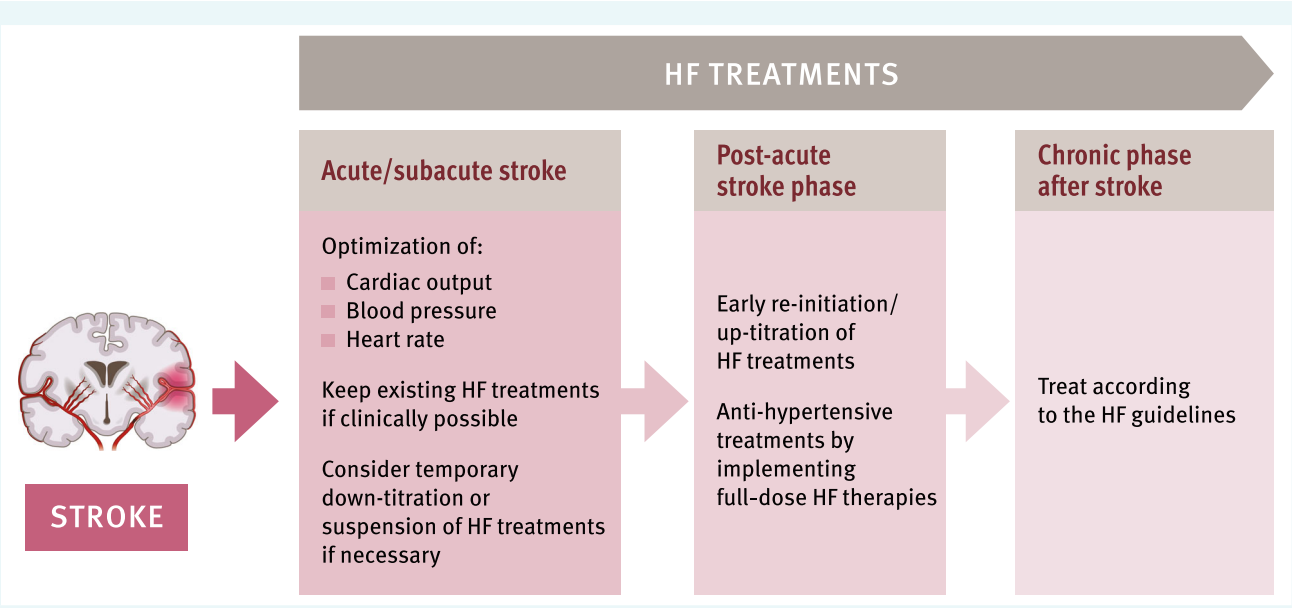

Figure 7 Shifting treatment targets for heart failure (HF) in the acute, subacute and chronic phases after stroke.

mortality after ischaemic stroke follows a U- or J-shape, with an optimal blood pressure range of 130–150 mmHg.[123,124] The interaction of blood pressure and stroke is indeed complex and time-dependent: While hypertension is a major risk factor for ischaemic stroke, severe elevation of blood pressure may occur secondary to the acute stroke due to imbalanced neurovegetative vascular control. Acute hypertensive episodes may not only increase cerebral oedema or foster a haemorrhagic transformation in the acute phase, it can as well worsen HF by increasing afterload. Despite this, a moderately higher blood pressure during the acute phase of stroke is understood to improve outcome by maintaining adequate brain perfusion in the presence of ischaemia-induced cerebral oedema. Maintaining adequate cerebral perfusion may be further complicated when concomitant HF accounts for low blood pressure and low cardiac output with the risk of aggravated ischaemic cerebral injury in the border infarct zone. Therefore, both hypotension and hypertension should be avoided in acute stroke, with chronic blood pressure lowering strategies being progressively re-established in hypertensive patients after the acute phase of a stroke.[125,126]

The occurrence of stroke may be associated with tachycardia and with new-onset AF as stroke is also associated with increased sympathetic activity[127]. A high ventricular rate might contribute to worsening HF and, therefore, initiation/uptitration of beta-blockers might be particularly helpful (see Section 'Cardiac complications and heart failure management on the stroke unit'). Ivabradine might be considered in patients with tachycardia without AF.

Specific aspects of acute stroke treatment in heart failure patients

Reduced cardiac output is observed in 10–24% of all patients with acute ischaemic stroke.[13,69] As the normal vascular autoregulation in the brain is impaired in acute stroke, cerebral perfusion will linearly be correlated to cardiac output.

Maintaining adequate cerebral perfusion in acute stroke is particularly complicated in patients with HF when low ejection fraction and low blood pressure inhibit sufficient cerebral perfusion pressure, thus increasing the risk of border zone infarction. In these patients, rehydration may support blood pressure and hence cerebral perfusion pressure. However, fluid management for improved blood pressure control has to be carefully balanced in HF due to risk of volume overload which may lead to haemodynamic decompensation. On the other hand, blood pressure lowering is key in hypertensive patients with haemorrhagic stroke[128] and will as well prevent cardiac decompensation due to acute hypertensive episodes. Blood pressure management should therefore be adapted to the individual (HF) patient requirements that include type of stroke, cardiac comorbidity, spontaneous blood pressure level, and the use of fibrinolytic therapy. Therefore, cardiac function and clinical signs of cardiac decompensation should be tightly monitored in HF patients in the acute phase of stroke, taking into account proactive management of associated comorbidities (see also Section 'Cardiac complications and heart failure management on the stroke unit').[129]

Regarding interventional treatments for acute ischaemic stroke, to date, no randomized data are available focusing on the efficiency and safety of (systemic) thrombolysis using recombinant tissue-type plasminogen activator (rt-PA) or mechanical recanalization in stroke patients with HF.[130] Moreover, HF patients were often excluded from randomized stroke trials. A retrospective analysis of the VISTA database comparing HF versus non-HF patients suggests a similar efficiency[46] and safety of thrombolysis, while rt-PA-associated bleeding was almost doubled in HF patients[131] in a meta-analysis including 55 studies. In a German single-centre cohort study, recanalization rate and the rate of rt-PA-associated

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secondary intracranial haemorrhage was not different in HF versus non-HF patients.[130]

The same holds true for (HF vs. non-HF) patients undergoing (additional) mechanical recanalization.[130] In stroke patients undergoing mechanical recanalization, HF may impact on anaesthesiological management during the procedure that should aim to maintain certain blood pressure levels, as this correlates with clinical outcome.[132] A report from the Interventional Management of Stroke (IMS) III study showed a significantly lower baseline degree of collateral vascularization in HF patients, which correlated with clinical outcome.[133] Nevertheless, in a single-centre prospective registry on acute stroke treatment, a similar outcome in HF versus non-HF patients after mechanical recanalization was observed.[130]

Taken together, available data on patients with HF and with acute stroke are limited and despite the higher risk of these patients, no curtailment of state-of-the-art stroke care should be accepted. Special attention must be paid on blood pressure management in HF patients during the acute phase of stroke.

Cardiac complications and heart failure management on the stroke unit

Stroke unit care for patients with acute stroke has been shown to result in better short-term and long-term outcome, greater independence and lower mortality by applying multidisciplinary treatment concepts, close monitoring and prevention or fast treatment of complications.[134] As outlined above, an increased risk of cardiac complications (like HF, myocardial infarction, takotsubo cardiomyopathy, acute hypertensive episodes, AF, ventricular arrhythmias, change of repolarization; *Table 4*[9,13,128,135–151]) arises in acute stroke, peaking within the first 3 days.[137,142,145,148,152] Cardiac complications in acute stroke imply poor short- and long-term prognosis.[138,153–155] It is therefore consensus that cardiologists should be consistently integrated in stroke unit care to address cardiovascular aspects of acute stroke in selected patients.[156] The systematic cardiologic workup of patients on a stroke unit should address three main targets[156] (*Figure 8*):

- Diagnostic workup to establish the stroke aetiology (cardioembolism related to HF; evaluation of cardiac structure and function, other cardiovascular causes).
- Cardiovascular monitoring for prevention of cardiac complications in (sub-)acute stroke (high risk of ADHF and HF-related complications, other cardiovascular complications).
- Initiation of continued cardiovascular management for secondary prevention (as well as optimizing HF treatment).

The rate of cardiac complications differs to some extent between ischaemic stroke, haemorrhagic stroke, or subarachnoid haemorrhage (*Table 4*). Pre-existing HF will inevitably account for a more vulnerable heart to neuronal injury which may explain both a particular high risk of cardiac complications and a worse outcome with these complications in HF patients. In addition, the risk of cardiac complications is related to patient characteristics, such as age, risk profile and underlying comorbidities.[157]

Key factors of cardiac monitoring on a stroke unit are (*Figure 8*) (i) preventing haemodynamic decompensation and ADHF, (ii) electrocardiographic (ECG) monitoring for AF, heart rate, severe ventricular and supraventricular arrhythmias, (iii) fluid status monitoring, (iv) blood pressure monitoring, (v) blood-based biomarkers, (vi) cardiac imaging, to identify stroke patients at higher risk of cardiac complications (*Table 4*).[52,139,140,148,155]

Pathological ECG findings are observed in a relevant proportion of stroke patients even when accounting for pre-existing heart disease. Changes of repolarization appear early, indicating a higher risk of arrhythmias and increased mortality.[145,152,158] A first episode of AF is detected in up to 10% of stroke patients and account for the majority of arrhythmias in acute stroke.[148] Whether AF is the underlying cause of stroke or stroke-induced is difficult to disentangle in individual cases but adequate treatment of AF in acute stroke, including rate control and antithrombotic therapy, should follow guideline recommendations in any case.[96]

While elevated levels of high-sensitivity cardiac troponin (hs-cTn) are frequently found in patients with stroke and even transient increased hs-cTn are related to worse prognosis,[155,159] a dynamic change in hs-cTn is associated with an early increased risk of mortality.[155] However, in patients with troponin elevation, a culprit coronary lesion is found in a mere 25%, especially in such patients with dynamic rise and fall of hs-cTn.[140] The PRAISE trial is ongoing and will evaluate when a coronary angiography should be performed in these high-risk patients in the subacute phase of stroke.[160] A complication in the management of subarachnoid haemorrhage is the occurrence of cerebral vasospasms. The acute treatment by nimodipine infusion and volume expansion requires careful blood pressure management which may, again, be particularly susceptible in patients with HF.

Taken together, acute stroke patients should be treated in a stroke unit, as this treatment has been shown to improve outcome after stroke.[134] There are apparently no published data on the efficacy of stroke unit treatment in HF patients. However, the haemodynamically vulnerable state of HF patients suggests a particular benefit of stroke unit care for patients with HF as they have a particularly high risk for cardiac complications and a higher risk of recurrent stroke.[161]

Cerebral complications including stroke and cognitive decline in acute heart failure

The strong mutual interaction between brain and heart in functional and structural injury is particularly pronounced in ADHF. In general, 6.5–15% of all strokes occur in patients while in hospital, and cardiac disorders besides perioperative settings are a main underlying condition in these patients.[162] As discussed above, the risk of stroke in acute HF is excessively high,[17] even among patients in SR that is, without pre-existing AF.[163]

In line, Asian HF registries show a particular high stroke risk during hospitalization or shortly after discharge.[164–166] In the Kyoto

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Table 4 Cardiac complications in acute stroke patients

	Ischemic stroke	Subarachnoid haemorrhage	Intracerebral haemorrhage	What to do if…
Heart failure[9,13,135]	- 5% clinical HF - 10% systolic dysfunction - 23% diastolic dysfunction	3–26%	3.8%[136]	Echocardiography when suspicion of impaired heart function. Avoid inconsiderate discontinuation of HF drugs (in particular beta-blockers). Sympathomimetic rebound effect can worsen cardiac function without increasing blood pressure.
Troponin elevation and myocardial infarction[137–141]	- 20–34% troponin elevation - Whereof 25% with significant coronary stenosis	11–71% troponin elevation	0.4–2.0% MI	Assess dynamic changes of troponin levels, as this indicates high-risk patients. Combine with clinical evaluation and other diagnostic tests (ECG, Echo, history). Avoid inconsiderate discontinuation of HF drugs (in particular beta-blockers).
Takotsubo cardiomyopathy[142]	1.3%	0.8–8%[143,144]	1.2%	Echocardiography/cardiac MRI to identify apical ballooning. Cardiac biomarkers (TnT, BNP). Coronary angiogram may be indicated.
ECG repolarization disturbance[145–147]	15–40%	75%	60–70%	Continuous rhythm monitoring for at least 72 h. Avoid inconsiderate discontinuation of beta-blockers.
Heart rhythm disturbances[148–150]	25%, AF as most common arrhythmia	5%, AF as most common arrhythmia	2.9%, new-onset AF[151]	Continuous rhythm monitoring for at least 72 h with sufficient quality for confirmation by a health professional. AF detection rate is related to ECG duration and quality of analysis, and patient characteristics.
Hypertensive crisis[128]	7.5–15%	40%	15–20%	BP reduction according to recommendations considering stroke aetiology, acute stroke intervention strategy. Continued BP monitoring while on stroke unit.

AF, atrial fibrillation; BNP, B-type natriuretic peptide; BP, blood pressure; ECG, electrocardiogram; Echo, echocardiography; HF, heart failure; MRI, magnetic resonance imaging; TnT, troponin T.

Congestive HF (KCHF) registry including 4056 patients with acute HF, 1.6% of patients developed an ischaemic stroke during a hospitalization for acute HF.[167] The stroke risk in acute HF can be predicted by the CHA_2DS_2-VASc score,[168] which also can predict rehospitalization for acute HF.[169] In turn, acute HF has been observed to occur in 5% of patients within 7 days after admission for stroke and is shown to affect survival.[170]

A history of cerebrovascular disease has significant impact on the outcome of acute HF episodes. In the ASCEND-HF trial population, enrolling patients with acute HF, a pre-existing cerebrovascular disease was associated with an 80% higher risk of death or HF rehospitalization.[171] Consistently, in the Euro Heart Failure Survey II, a history of cerebrovascular disease was associated with higher mortality at 3 months and 1 year after the ADHF event.[172]

Mechanistically, a number of factors contribute to the high risk of stroke in ADHF. Low cardiac output, procoagulant properties of activated endothelium and of circulating thrombogenic factors (Virchow's triad, see above) are particularly pronounced in ADHF, compared to chronic HF.[173] This may in part explain the very high risk of ischaemic stroke in close timely relation to the *de-novo* diagnosis of HF.[15,17] ADHF results in systemic tissue hypoxia with subsequent activation of pathogenic signalling cascades such as neuroendocrine activation,[174] ROS accumulation and inflammatory activation.[175] Moreover, the initiation of haemodynamic recompensation therapy including enforced diuresis to achieve euvolaemia and haemorheological changes may contribute to the increased stroke risk in ADHF.[176,177] Furthermore, pathophysiological and clinical changes in acute HF such as high heart rate, new onset of AF,[178] low blood pressure[179] or comorbidities and polypharmacy[180] predispose to temporal (TIA) or persisting brain injury (stroke).

Cardioembolism is the main cause of stroke as well in patients with ADHF (64%), with first-time hospitalization for HF and high natriuretic peptides being predictors of stroke in these patients.[167] Indeed, the degree of acute ventricular dysfunction seems to relate

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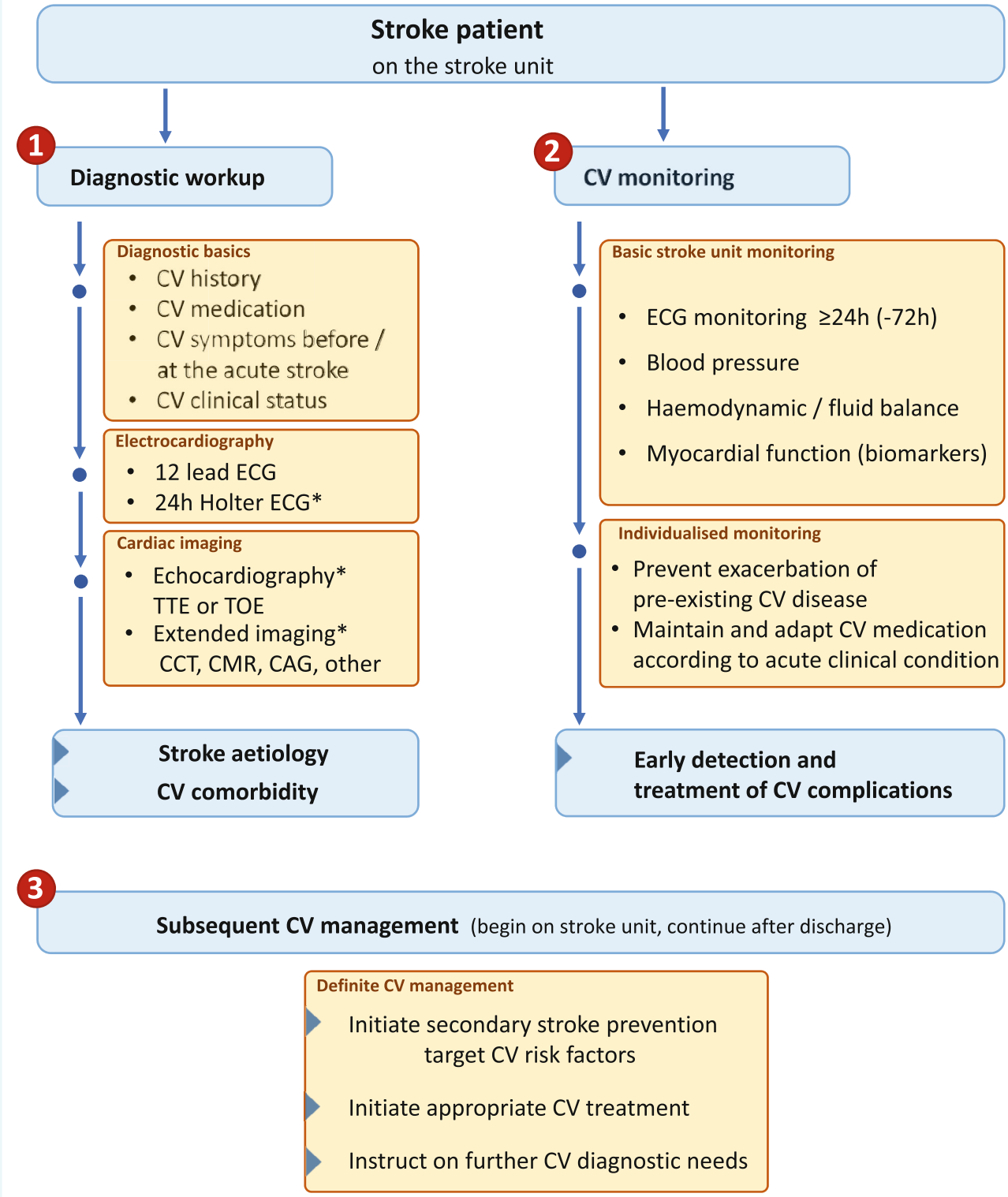

Figure 8 Flowchart of cardiovascular management of stroke patients: (1) diagnostic work-up, (2) monitoring for cardiovascular complications, and (3) secondary prevention and subsequent cardiovascular management. CAG, coronary angiography; CCT, cardiac computer tomography; CMR, cardiac magnetic resonance; CV, cardiovascular; ECG, electrocardiogram; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography. *As clinically indicated.

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directly to the risk of stroke. In the VALIANT study in patients after myocardial infarction with compromised left ventricular function, the stroke rate was directly related to a higher risk class compared to the lowest Killip class amounting to a relative risk of 4.85.[181] In turn, acute HF worsens the risk for death and cardiovascular complications as well in the follow-up after acute stroke.[182]

There is sound evidence comparing acute HF with reduced versus preserved ejection fraction regarding the risk of stroke. Data from the Nationwide US Readmission Database (NRD) including over 2.5 million patients with acute HF showed higher event rates of stroke in acute HF with reduced (4.7%) versus preserved (2.5%) ejection fraction.[183] A study in 2922 patients admitted with acute HF and AF showed that the predictive power of the CHA_2DS_2-VASc score for stroke risk prediction was similarly valid in HF patients with reduced as with preserved ejection fraction.[168] However, only a modest predictive power of the CHA_2DS_2-VASc score in patients with acute HF was observed in a HF registry from Korea.[169]

Beside a stroke, other cerebral functional and structural alterations may occur in acute HF such as cognitive decline or depression. Cognitive impairment is augmented in episodes of haemodynamic decompensation and partially reversible after recompensation.[184] Also, silent cerebral infarctions, that are known to relate to subtle functional deficits, are significantly more prevalent in patients with HF.[40,185] Depression is a prevalent comorbidity in HF and may further accelerate in acute HF. Clinically significant depressive symptoms affect 20–50% of HF patients depending on HF severity.[186] Depression in HF is associated with advanced HF severity, and poor prognosis.[187] To date anti-depressive treatment in HF has not convincingly shown efficacy. Selective serotonin reuptake inhibitors have been shown to improve depressive symptoms and to be safe but failed to improve prognosis.[188] Tricyclic antidepressants may cause cardiovascular side effects including hypotension, arrhythmias and worsening of HF and should therefore be avoided in patients with HF. A recent meta-analysis has suggested that the use of antidepressants could increase all-cause death, although this might simply be reflection of disease severity.[189]

Taken together, acute HF represents a high-risk condition for stroke, transient cognitive decline and depression. During treatment for acute HF, particular attention should be paid on the neurological, cognitive and psychological status of the patients and its potential changes. Clinical signs of stroke should trigger immediate diagnostic clarification (brain imaging) and fast-track stroke treatment. The interdisciplinary care of cardiologists and stroke specialists are pivotal to ensure optimum treatment for both clinical conditions. Avoiding abrupt haemodynamic changes in the course of the treatment of acute HF with careful titration of diuretic therapy and close monitoring of fluid and haemodynamic balance of the patients may help to prevent thromboembolic activation and stroke as complications of acute HF.

Patient values and preferences

The long-term management of stroke and HF focuses on the patient's ability to adopt complex lifestyle changes and adhere to treatment regimens whilst suffering increasing levels of cognitive and/or functional impairment.[190,191] Cardiac rehabilitation as a multi-factorial and comprehensive secondary prevention intervention is designed to limit cardiovascular disease's physiological and psychological effects, manage symptoms, and reduce the risk of future cardiovascular events.[192] Rehabilitation is recommended for patients living with cardiovascular disease.[193] Notably, fewer than one out of five HF patients are referred to cardiac rehabilitation according to recent UK data. A systematic review reported that few cardiac rehabilitation studies focused on stroke care.[194] Unlike cardiac patients (including HF and a range of other cardiac conditions) who are recognized as chronic patients and usually referred for long-term cardiac monitoring and ambulatory management, no such long-term care exists in most healthcare systems for a patient with stroke. Indeed, in a recent systematic review, stroke patients discharged into the community and their carers reported a feeling of abandonment and an inability to re-engage with healthcare services.[195] Limited information, resources and a lack of access to psychological support are common.[196]

In the absence of proper support, cardiac and stroke patients rely on informal caregivers[197] who play a crucial role in providing patients with motivation, hope and meaning.[198] They help manage medicines, provide personal care, facilitate conversations with healthcare professionals, aid symptom recognition and promote lifestyle change.[199] However, the responsibility placed on the caregiver can cause deleterious effects on their own health with sustained levels of anxiety and depression being witnessed in this population.[200]

Hendriks *et al.*[201] suggest that a personalized care model that considers the aims for treatment and care of patients with co-existing morbidities would result in significant benefits in terms of improved quality of life and life expectancy. Whilst this approach is welcomed, these benefits will only be realized if the patient and their caregiver play an active role in the decision-making process.

Consensus statements

The comorbidity of HF and stroke represents a high-risk condition that requires particular attention to ensure early detection, efficient diagnostic workup, consequent and careful treatment and close monitoring of the patient. Interdisciplinary cooperation of cardiologists, stroke specialists, other specialists and primary care physicians is pivotal to ensure optimal treatment in acute disease events and during long-term care of these patients. The following consensus statements of the authors may inform clinicians on diagnostic workup, prevention and treatment of the comorbidity of HF and stroke.

Epidemiology

Patients with heart failure

- The prevalence of stroke among patients with HF is 8–11%.
- The risk of stroke is highest in the first 30 days of initial diagnosis of HF.

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- The risk of stroke is elevated during episodes of ADHF.
- HF-related factors contributing to the risk of stroke are older age, HF duration, HF severity and the comorbidity of AF.
- Patients with HF have not only an increased risk of stroke, but also an increased risk of silent brain lesions.

Patients with stroke

- The prevalence of HF in patients with ischaemic stroke is about 10–24%, either as pre-existing HF or as acute haemodynamic decompensation secondary to the acute stroke.
- The outcome after stroke is worse in patients with HF (higher mortality and worse functional outcomes) compared to stroke patients without HF.

Mechanistic interaction

- Cardioembolism is the most common aetiology of stroke in HF (at 40–50%) but also haemodynamic stroke due to hypoperfusion as well as other stroke aetiologies may apply due to the interrelation of HF with other cardiovascular diseases (i.e. AF, hypertension, arteriosclerosis).
- All factors of the Virchow's triad (slow blood flow, endothelial activation and coagulation system activation) are activated in HF indicating a high-risk procoagulant state.
- Stroke-induced cardiac complications ('stroke–heart syndrome') present often as a clinical pattern of acute HF, stress-induced cardiomyopathy, (micro-)vascular dysfunction, arrhythmias, and blood pressure deviations. The vulnerability may be particularly pronounced in patients with pre-existing HF.
- Impaired left ventricular function with low cardiac output may contribute to reduced cerebral perfusion pressure and may worsen cerebral ischaemia and functional outcome.

Cardiac diagnostic workup in stroke patients

- Cardiovascular workup should include the patients' cardiovascular history, current and previous symptoms and medications, cardiac rhythm (12-lead ECG on admission) and left ventricular functional status (transthoracic echocardiography).
- Echocardiographic imaging should be performed if structural and functional abnormalities are suspected. The appropriate type of echocardiography (i.e. transthoracic vs. transoesophageal echocardiography) should be selected according to the intended information.
- Cardiac biomarkers may be helpful to inform clinicians on dynamic cardiac functional status in the subacute phase of stroke and are mandatory for the evaluation of suspected myocardial injury including myocardial infarction.
- Subsequent diagnostic workup for cardiac comorbidity may be extended as appropriate and may be continued after discharge from stroke hospitalization.

Treatment and prevention

The heart failure perspective

- Optimal treatment of HF and avoidance of episodes of acute cardiac decompensation are important to prevent stroke in HF.
- During treatment for cardiac recompensation of acute HF patients, abrupt haemodynamic changes should be avoided, titration of diuretic therapy should be done carefully and with close monitoring of fluid status to prevent thromboembolic complications.
- In acute HF, close monitoring of the patient should include the neurological status (prompt stroke detection), cognitive and psychological status.
- Anticoagulation is applicable to prevent thromboembolic complications in patients with HF and AF according to the CHA_2DS_2-VASc score. In HF patients with maintained SR, there is no evidence for improved outcome in HF patients receiving anticoagulant therapy, since a reduction in ischaemic stroke in anticoagulated patients is outweighed by an increased risk of major bleeding.

The stroke perspective

- Management principles aligned with the concept of integrated care for stroke and heart disease should be applied including three pillars of management:
  - A: Appropriate Antithrombotic therapy.
  - B: Better functional and psychological status.
  - C: Cardiovascular risk factors and Comorbidity optimization (including lifestyle changes).
- Data on systemic thrombolysis and mechanical thrombectomy in patients with concomitant HF are limited. Observational data suggest a similar effect in HF patients and non-HF patients. Therefore, systemic thrombolysis and mechanical thrombectomy should be performed according to licensed indication and irrespective of HF status.
- Patients with acute stroke should be treated in a stroke unit, irrespective of HF status.
- Patients with acute stroke and pre-existing HF are at risk of cardiac decompensation in the (sub-)acute phase after stoke, requiring careful monitoring for cardiovascular complications.
- Cardiologists should be consistently integrated in stroke unit care for selected patients.
- Chronic HF treatment should be continued in the acute phase of stroke if clinically possible including angiotensin-converting enzyme inhibitors, or angiotensin receptor antagonists or angiotensin receptor–neprilysin inhibitor, beta-blockers, mineralocorticoid receptor antagonists, and sodium–glucose cotransporter 2 inhibitors. If needed, titration (particularly of beta-blockers) should be done carefully and with continued monitoring of haemodynamic stability. Early reinitiation of HF treatment should be pursued.
- Blood pressure control is particularly challenging and requires careful monitoring as hypertensive episodes may cause cardiac decompensation and maintaining cerebral perfusion pressure may be limited by low systemic blood pressure due to low cardiac output in HF.

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- Elevation of troponin levels are frequently observed in acute stroke. The decision on invasive coronary diagnostics needs to be based on individual considerations taking into account a comprehensive cardiovascular diagnostic workup (troponin dynamics, symptoms, ECG, echocardiography, risk profile, disease history).
- There is a lack of continued and long-term (cardiovascular) care for stroke patients as most patients are discharged to their general practitioner or basic healthcare service.
- After discharge from the stroke centre, systematic completion of cardiovascular diagnostic workup should be pursued as clinically required.
- Optimal treatment of HF and cardiovascular secondary prevention should be initiated without delay.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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References

1. Scherbakov N, Doehner W. Heart-brain interactions in heart failure. *Card Fail Rev* 2018;**4**:87–91. https://doi.org/10.15420/cfr.2018.14.2
2. Havakuk O, King KS, Grazette L, Yoon AJ, Fong M, Bregman N, *et al.* Heart failure-induced brain injury. *J Am Coll Cardiol* 2017;**69**:1609–1616. https://doi.org/10.1016/j.jacc.2017.01.022
3. Scheitz JF, Nolte CH, Doehner W, Hachinski V, Endres M. Stroke-heart syndrome: Clinical presentation and underlying mechanisms. *Lancet Neurol* 2018;**17**:1109–1120. https://doi.org/10.1016/S1474-4422(18)30336-3
4. Lip GYH, Lane DA, Lenarczyk R, Boriani G, Doehner W, Benjamin LA, *et al.* Integrated care for optimizing the management of stroke and associated heart disease: A position paper of the European Society of Cardiology Council on Stroke. *Eur Heart J* 2022;**43**:2442–2460. https://doi.org/10.1093/eurheartj/ehac245
5. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, *et al.*; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2021 update: A report from the American Heart Association. *Circulation* 2021;**143**:e254–e743. https://doi.org/10.1161/CIR.0000000000000950
6. Timmis A, Vardas P, Townsend N, Torbica A, Katus H, De Smedt D, *et al.* European Society of Cardiology: Cardiovascular disease statistics 2021: Executive summary. *Eur Heart J Qual Care Clin Outcomes* 2022;**8**:377–382. https://doi.org/10.1093/ehjqcco/qcac014
7. Vemmos K, Ntaios G, Savvari P, Vemmou AM, Koroboki E, Manios E, *et al.* Stroke aetiology and predictors of outcome in patients with heart failure and acute stroke: A 10-year follow-up study. *Eur J Heart Fail* 2012;**14**:211–218. https://doi.org/10.1093/eurjhf/hfr172
8. Hays AG, Sacco RL, Rundek T, Sciacca RR, Jin Z, Liu R, *et al.* Left ventricular systolic dysfunction and the risk of ischemic stroke in a multiethnic population. *Stroke* 2006;**37**:1715–1719. https://doi.org/10.1161/01.STR.0000227121.34717.40
9. Ois A, Gomis M, Cuadrado-Godia E, Jimenez-Conde J, Rodriguez-Campello A, Bruguera J, *et al.* Heart failure in acute ischemic stroke. *J Neurol* 2008;**255**:385–389. https://doi.org/10.1007/s00415-008-0677-1
10. Divani AA, Vazquez G, Asadollahi M, Qureshi AI, Pullicino P. Nationwide frequency and association of heart failure on stroke outcomes in the United States. *J Card Fail* 2009;**15**:11–16. https://doi.org/10.1016/j.cardfail.2008.09.001
11. Jung JM, Kim JG, Kim JB, Cho KH, Yu S, Oh K, *et al.* Takotsubo-like myocardial dysfunction in ischemic stroke: A hospital-based registry and systematic literature review. *Stroke* 2016;**47**:2729–2736. https://doi.org/10.1161/STROKEAHA.116.014304
12. Yoshimura S, Toyoda K, Ohara T, Nagasawa H, Ohtani N, Kuwashiro T, *et al.* Takotsubo cardiomyopathy in acute ischemic stroke. *Ann Neurol* 2008;**64**:547–554. https://doi.org/10.1002/ana.21459
13. Heuschmann PU, Montellano FA, Ungethüm K, Rücker V, Wiedmann S, Mackenrodt D, *et al.* Prevalence and determinants of systolic and diastolic cardiac dysfunction and heart failure in acute ischemic stroke patients: The SICFAIL study. *ESC Heart Fail* 2021;**8**:1117–1129. https://doi.org/10.1002/ehf2.13145
14. Witt BJ, Gami AS, Ballman KV, Brown RD Jr, Meverden RA, Jacobsen SJ, *et al.* The incidence of ischemic stroke in chronic heart failure: A meta-analysis. *J Card Fail* 2007;**13**:489–496. https://doi.org/10.1016/j.cardfail.2007.01.009
15. Alberts VP, Bos MJ, Koudstaal P, Hofman A, Witteman JC, Stricker B, *et al.* Heart failure and the risk of stroke: The Rotterdam study. *Eur J Epidemiol* 2010;**25**:807–812. https://doi.org/10.1007/s10654-010-9520-y
16. Lip GY, Rasmussen LH, Skjoth F, Overvad K, Larsen TB. Stroke and mortality in patients with incident heart failure: The Diet, Cancer and Health (DCH) cohort study. *BMJ Open* 2012;**2**:e000975. https://doi.org/10.1136/bmjopen-2012-000975
17. Adelborg K, Szepligeti S, Sundboll J, Horvath-Puho E, Henderson VW, Ording A, *et al.* Risk of stroke in patients with heart failure: A population-based 30-year cohort study. *Stroke* 2017;**48**:1161–1168. https://doi.org/10.1161/STROKEAHA.116.016022
18. Witt BJ, Brown RD Jr, Jacobsen SJ, Weston SA, Ballman KV, Meverden RA, *et al.* Ischemic stroke after heart failure: A community-based study. *Am Heart J* 2006;**152**:102–109. https://doi.org/10.1016/j.ahj.2005.10.018
19. Freudenberger RS, Hellkamp AS, Halperin JL, Poole J, Anderson J, Johnson G, *et al.*; SCD-HeFT Investigators. Risk of thromboembolism in heart failure: An analysis from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). *Circulation* 2007;**115**:2637–2641. https://doi.org/10.1161/CIRCULATIONAHA.106.661397
20. Di Tullio MR, Qian M, Thompson JL, Labovitz AJ, Mann DL, Sacco RL, *et al.*; WARCEF Investigators. Left ventricular ejection fraction and risk of stroke and cardiac events in heart failure: Data from the Warfarin Versus Aspirin in

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Reduced Ejection Fraction trial. *Stroke* 2016;**47**:2031–2037. https://doi.org/10.1161/STROKEAHA.116.013679
21. Pullicino PM, Halperin JL, Thompson JL. Stroke in patients with heart failure and reduced left ventricular ejection fraction. *Neurology* 2000;**54**:288–294. https://doi.org/10.1212/WNL.54.2.288
22. Sobue Y, Watanabe E, Lip GYH, Koshikawa M, Ichikawa T, Kawai M, *et al.* Thromboembolisms in atrial fibrillation and heart failure patients with a preserved ejection fraction (HFpEF) compared to those with a reduced ejection fraction (HFrEF). *Heart Vessels* 2018;**33**:403–412. https://doi.org/10.1007/s00380-017-1073-5
23. Zile MR, Gaasch WH, Anand IS, Haass M, Little WC, Miller AB, *et al.*; I-Preserve Investigators. Mode of death in patients with heart failure and a preserved ejection fraction: Results from the Irbesartan in Heart Failure With Preserved Ejection Fraction Study (I-Preserve) trial. *Circulation* 2010;**121**:1393–1405. https://doi.org/10.1161/CIRCULATIONAHA.109.909614
24. Solomon SD, Anavekar N, Skali H, McMurray JJ, Swedberg K, Yusuf S, *et al.*; Candesartan in Heart Failure Reduction in Mortality (CHARM) Investigators. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. *Circulation* 2005;**112**:3738–3744. https://doi.org/10.1161/CIRCULATIONAHA.105.561423
25. McManus DD, Hsu G, Sung SH, Saczynski JS, Smith DH, Magid DJ, *et al.*; Cardiovascular Research Network PRESERVE Study. Atrial fibrillation and outcomes in heart failure with preserved versus reduced left ventricular ejection fraction. *J Am Heart Assoc* 2013;**2**:e005694. https://doi.org/10.1161/JAHA.112.005694
26. Banerjee A, Taillandier S, Olesen JB, Lane DA, Lallemand B, Lip GY, *et al.* Ejection fraction and outcomes in patients with atrial fibrillation and heart failure: The Loire Valley Atrial Fibrillation Project. *Eur J Heart Fail* 2012;**14**:295–301. https://doi.org/10.1093/eurjhf/hfs005
27. Badheka AO, Rathod A, Kizilbash MA, Bhardwaj A, Ali O, Afonso L, *et al.* Comparison of mortality and morbidity in patients with atrial fibrillation and heart failure with preserved versus decreased left ventricular ejection fraction. *Am J Cardiol* 2011;**108**:1283–1288. https://doi.org/10.1016/j.amjcard.2011.06.045
28. Kotecha D, Chudasama R, Lane DA, Kirchhof P, Lip GY. Atrial fibrillation and heart failure due to reduced versus preserved ejection fraction: A systematic review and meta-analysis of death and adverse outcomes. *Int J Cardiol* 2016;**203**:660–666. https://doi.org/10.1016/j.ijcard.2015.10.220
29. Sandhu RK, Hohnloser SH, Pfeffer MA, Yuan F, Hart RG, Yusuf S, *et al.* Relationship between degree of left ventricular dysfunction, symptom status, and risk of embolic events in patients with atrial fibrillation and heart failure. *Stroke* 2015;**46**:667–672. https://doi.org/10.1161/STROKEAHA.114.007140
30. Chung S, Kim TH, Uhm JS, Cha MJ, Lee JM, Park J, *et al.* Stroke and systemic embolism and other adverse outcomes of heart failure with preserved and reduced ejection fraction in patients with atrial fibrillation (from the COmparison study of Drugs for symptom control and complication prEvention of Atrial Fibrillation [CODE-AF]). *Am J Cardiol* 2020;**125**:68–75. https://doi.org/10.1016/j.amjcard.2019.09.035
31. Uhm JS, Kim J, Yu HT, Kim TH, Lee SR, Cha MJ, *et al.* Stroke and systemic embolism in patients with atrial fibrillation and heart failure according to heart failure type. *ESC Heart Fail* 2021;**8**:1582–1589. https://doi.org/10.1002/ehf2.13264
32. Carlisle MA, Fudim M, DeVore AD, Piccini JP. Heart failure and atrial fibrillation, like fire and fury. *JACC Heart Fail* 2019;**7**:447–456. https://doi.org/10.1016/j.jchf.2019.03.005
33. Marra AM, Bencivenga L, D'Assante R, Rengo G, Cittadini A. Heart failure with preserved ejection fraction: Squaring the circle between comorbidities and cardiovascular abnormalities. *Eur J Intern Med* 2022;**99**:1–6. https://doi.org/10.1016/j.ejim.2022.01.019
34. Abdul-Rahim AH, Perez AC, Fulton RL, Jhund PS, Latini R, Tognoni G, *et al.*; Investigators of the Controlled Rosuvastatin Multinational Study in Heart Failure (CORONA); GISSI-Heart Failure (GISSI-HF) Committees and Investigators. Risk of stroke in chronic heart failure patients without atrial fibrillation: Analysis of the Controlled Rosuvastatin in Multinational Trial Heart Failure (CORONA) and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca-Heart Failure (GISSI-HF) trials. *Circulation* 2015;**131**:1486–1494. https://doi.org/10.1161/CIRCULATIONAHA.114.013760
35. Mehra MR, Vaduganathan M, Fu M, Ferreira JP, Anker SD, Cleland JGF, *et al.* A comprehensive analysis of the effects of rivaroxaban on stroke or transient ischaemic attack in patients with heart failure, coronary artery disease, and sinus rhythm: The COMMANDER HF trial. *Eur Heart J* 2019;**40**:3593–3602. https://doi.org/10.1093/eurheartj/ehz427
36. Kang SH, Kim J, Park JJ, Oh IY, Yoon CH, Kim HJ, *et al.* Risk of stroke in congestive heart failure with and without atrial fibrillation. *Int J Cardiol* 2017;**248**:182–187. https://doi.org/10.1016/j.ijcard.2017.07.056
37. Ling LH, Kistler PM, Kalman JM, Schilling RJ, Hunter RJ. Comorbidity of atrial fibrillation and heart failure. *Nat Rev Cardiol* 2016;**13**:131–147. https://doi.org/10.1038/nrcardio.2015.191
38. Ntaios G, Perlepe K, Lambrou D, Sirimarco G, Strambo D, Eskandari A, *et al.* Prevalence and overlap of potential embolic sources in patients with embolic stroke of undetermined source. *J Am Heart Assoc* 2019;**8**:e012858. https://doi.org/10.1161/JAHA.119.012858
39. Kozdag G, Ciftci E, Ural D, Sahin T, Selekler M, Agacdiken A, *et al.* Silent cerebral infarction in chronic heart failure: Ischemic and nonischemic dilated cardiomyopathy. *Vasc Health Risk Manag* 2008;**4**:463–469. https://doi.org/10.2147/VHRM.S2166
40. Kozdag G, Ciftci E, Vural A, Selekler M, Sahin T, Ural D, *et al.* Silent cerebral infarction in patients with dilated cardiomyopathy: Echocardiographic correlates. *Int J Cardiol* 2006;**107**:376–381. https://doi.org/10.1016/j.ijcard.2005.03.055
41. Schmidt R, Fazekas F, Offenbacher H, Dusleag J, Lechner H. Brain magnetic resonance imaging and neuropsychologic evaluation of patients with idiopathic dilated cardiomyopathy. *Stroke* 1991;**22**:195–199. https://doi.org/10.1161/01.str.22.2.195
42. Siachos T, Vanbakel A, Feldman DS, Uber W, Simpson KN, Pereira NL. Silent strokes in patients with heart failure. *J Card Fail* 2005;**11**:485–489. https://doi.org/10.1016/j.cardfail.2005.04.004
43. Vogels RL, van der Flier WM, van Harten B, Gouw AA, Scheltens P, Schroeder-Tanka JM, *et al.* Brain magnetic resonance imaging abnormalities in patients with heart failure. *Eur J Heart Fail* 2007;**9**:1003–1009. https://doi.org/10.1016/j.ejheart.2007.07.006
44. Hassell ME, Nijveldt R, Roos YB, Majoie CB, Hamon M, Piek JJ, *et al.* Silent cerebral infarcts associated with cardiac disease and procedures. *Nat Rev Cardiol* 2013;**10**:696–706. https://doi.org/10.1038/nrcardio.2013.162
45. Sharma JC, Fletcher S, Vassallo M, Ross I. Cardiovascular disease and outcome of acute stroke: Influence of pre-existing cardiac failure. *Eur J Heart Fail* 2000;**2**:145–150. https://doi.org/10.1016/s1388-9842(00)00067-2
46. Abdul-Rahim AH, Fulton RL, Frank B, McMurray JJ, Lees KR; VISTA Collaborators. Associations of chronic heart failure with outcome in acute ischaemic stroke patients who received systemic thrombolysis: Analysis from VISTA. *Eur J Neurol* 2015;**22**:163–169. https://doi.org/10.1111/ene.12548
47. Milionis H, Faouzi M, Cordier M, D'Ambrogio-Remillard S, Eskandari A, Michel P. Characteristics and early and long-term outcome in patients with acute ischemic stroke and low ejection fraction. *Int J Cardiol* 2013;**168**:1082–1087. https://doi.org/10.1016/j.ijcard.2012.11.036
48. Byun JI, Jung KH, Kim YD, Kim JM, Roh JK. Cardiac function and outcome in patients with cardio-embolic stroke. *PLoS One* 2014;**9**:e95277. https://doi.org/10.1371/journal.pone.0095277
49. Burkot J, Kopec G, Pera J, Slowik A, Dziedzic T. Decompensated heart failure is a strong independent predictor of functional outcome after ischemic stroke. *J Card Fail* 2015;**21**:642–646. https://doi.org/10.1016/j.cardfail.2015.03.008
50. Appelros P, Nydevik I, Viitanen M. Poor outcome after first-ever stroke: Predictors for death, dependency, and recurrent stroke within the first year. *Stroke* 2003;**34**:122–126. https://doi.org/10.1161/01.STR.0000047852.05842.3C
51. Sennfalt S, Pihlsgard M, Petersson J, Norrving B, Ullberg T. Long-term outcome after ischemic stroke in relation to comorbidity – An observational study from the Swedish Stroke Register (Riksstroke). *Eur Stroke J* 2020;**5**:36–46. https://doi.org/10.1177/2396987319883154
52. Kim WJ, Nah HW, Kim DH, Cha JK. Association between left ventricular dysfunction and functional outcomes at three months in acute ischemic stroke. *J Stroke Cerebrovasc Dis* 2016;**25**:2247–2252. https://doi.org/10.1016/j.jstrokecerebrovasdis.2016.05.004
53. Lip GY, Gibbs CR. Does heart failure confer a hypercoagulable state? Virchow's triad revisited. *J Am Coll Cardiol* 1999;**33**:1424–1426. https://doi.org/10.1016/s0735-1097(99)00033-9
54. Yamamoto K, Ikeda U, Furuhashi K, Irokawa M, Nakayama T, Shimada K. The coagulation system is activated in idiopathic cardiomyopathy. *J Am Coll Cardiol* 1995;**25**:1634–1640. https://doi.org/10.1016/0735-1097(95)00049-a
55. O'Connor CM, Gurbel PA, Serebruany VL. Usefulness of soluble and surface-bound P-selectin in detecting heightened platelet activity in patients with congestive heart failure. *Am J Cardiol* 1999;**83**:1345–1349. https://doi.org/10.1016/S0002-9149(99)00098-3
56. Shantsila E, Wrigley BJ, Blann AD, Gill PS, Lip GY. A contemporary view on endothelial function in heart failure. *Eur J Heart Fail* 2012;**14**:873–881. https://doi.org/10.1093/eurjhf/hfs066
57. Jug B, Vene N, Salobir BG, Sebestjen M, Sabovic M, Keber I. Procoagulant state in heart failure with preserved left ventricular ejection fraction. *Int Heart J* 2009;**50**:591–600. https://doi.org/10.1536/ihj.50.591

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58. Chong AY, Freestone B, Patel J, Lim HS, Hughes E, Blann AD, *et al.* Endothelial activation, dysfunction, and damage in congestive heart failure and the relation to brain natriuretic peptide and outcomes. *Am J Cardiol* 2006;**97**:671–675. https://doi.org/10.1016/j.amjcard.2005.09.113
59. Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. *N Engl J Med* 1990;**323**:236–241. https://doi.org/10.1056/NEJM199007263230405
60. Chin BS, Blann AD, Gibbs CR, Chung NA, Conway DG, Lip GY. Prognostic value of interleukin-6, plasma viscosity, fibrinogen, von Willebrand factor, tissue factor and vascular endothelial growth factor levels in congestive heart failure. *Eur J Clin Invest* 2003;**33**:941–948. https://doi.org/10.1046/j.1365-2362.2003.01252.x
61. Wrigley BJ, Shantsila E, Tapp LD, Lip GY. Increased formation of monocyte-platelet aggregates in ischemic heart failure. *Circ Heart Fail* 2013;**6**:127–135. https://doi.org/10.1161/CIRCHEARTFAILURE.112.968073
62. Stumpf C, Lehner C, Eskafi S, Raaz D, Yilmaz A, Ropers S, *et al.* Enhanced levels of CD154 (CD40 ligand) on platelets in patients with chronic heart failure. *Eur J Heart Fail* 2003;**5**:629–637. https://doi.org/10.1016/s1388-9842(03)00110-7
63. Kerris EWJ, Hoptay C, Calderon T, Freishtat RJ. Platelets and platelet extracellular vesicles in hemostasis and sepsis. *Clin Res* 2020;**68**:813–820. https://doi.org/10.1136/jim-2019-001195
64. Bäck M, Doehner W. Cardiac thrombogenicity in stroke: Mechanisms and evaluation. *Eur J Vasc Endovasc Surg* 2022;**64**:150–152. https://doi.org/10.1016/j.ejvs.2022.09.004
65. Petrovic-Djergovic D, Goonewardena SN, Pinsky DJ. Inflammatory disequilibrium in stroke. *Circ Res* 2016;**119**:142–158. https://doi.org/10.1161/CIRCRESAHA.116.308022
66. Briasoulis A, Androulakis E, Christophides T, Tousoulis D. The role of inflammation and cell death in the pathogenesis, progression and treatment of heart failure. *Heart Fail Rev* 2016;**21**:169–176. https://doi.org/10.1007/s10741-016-9533-z
67. Pullicino PM, McClure LA, Wadley VG, Ahmed A, Howard VJ, Howard G, *et al.* Blood pressure and stroke in heart failure in the REasons for Geographic and Racial Differences in Stroke (REGARDS) study. *Stroke* 2009;**40**:3706–3710. https://doi.org/10.1161/STROKEAHA.109.561670
68. Klijn CJ, Kappelle LJ. Haemodynamic stroke: Clinical features, prognosis, and management. *Lancet Neurol* 2010;**9**:1008–1017. https://doi.org/10.1016/S1474-4422(10)70185-X
69. Doehner W, Ural D, Haeusler KG, Celutkiene J, Bestetti R, Cavusoglu Y, *et al.* Heart and brain interaction in patients with heart failure: Overview and proposal for a taxonomy. A position paper from the Study Group on Heart and Brain Interaction of the Heart Failure Association. *Eur J Heart Fail* 2018;**20**:199–215. https://doi.org/10.1002/ejhf.1100
70. Yperzeele L, van Hooff RJ, Nagels G, De Smedt A, De Keyser J, Brouns R. Heart rate variability and baroreceptor sensitivity in acute stroke: A systematic review. *Int J Stroke* 2015;**10**:796–800. https://doi.org/10.1111/ijs.12573
71. Krause T, Werner K, Fiebach JB, Villringer K, Piper SK, Haeusler KG, *et al.* Stroke in right dorsal anterior insular cortex is related to myocardial injury. *Ann Neurol* 2017;**81**:502–511. https://doi.org/10.1002/ana.24906
72. Scheitz JF, Mochmann HC, Erdur H, Tutuncu S, Haeusler KG, Grittner U, *et al.* Prognostic relevance of cardiac troponin T levels and their dynamic changes measured with a high-sensitivity assay in acute ischaemic stroke: Analyses from the TRELAS cohort. *Int J Cardiol* 2014;**177**:886–893. https://doi.org/10.1016/j.ijcard.2014.10.036
73. Chi G, Januzzi JL, Korjian S, Daaboul Y, Goldhaber SZ, Hernandez AF, *et al.* N-terminal pro-B-type natriuretic peptide and the risk of stroke among patients hospitalized with acute heart failure: An APEX trial substudy. *J Thromb Thrombolysis* 2017;**44**:457–465. https://doi.org/10.1007/s11239-017-1552-7
74. Merkler AE, Alakbarli J, Gialdini G, Navi BB, Murthy SB, Goyal P, *et al.* Short-term risk of ischemic stroke after detection of left ventricular thrombus on cardiac magnetic resonance imaging. *J Stroke Cerebrovasc Dis* 2019;**28**:1027–1031. https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.12.025
75. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, *et al.*; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2022;**24**:4–131. https://doi.org/10.1002/ejhf.2333
76. Mogensen UM, Jhund PS, Abraham WT, Desai AS, Dickstein K, Packer M, *et al.*; PARADIGM-HF and ATMOSPHERE Investigators and Committees. Type of atrial fibrillation and outcomes in patients with heart failure and reduced ejection fraction. *J Am Coll Cardiol* 2017;**70**:2490–2500. https://doi.org/10.1016/j.jacc.2017.09.027
77. Swedberg K, Olsson LG, Charlesworth A, Cleland J, Hanrath P, Komajda M, *et al.* Prognostic relevance of atrial fibrillation in patients with chronic heart failure on long-term treatment with beta-blockers: Results from COMET. *Eur Heart J* 2005;**26**:1303–1308. https://doi.org/10.1093/eurheartj/ehi166
78. Vanassche T, Lauw MN, Eikelboom JW, Healey JS, Hart RG, Alings M, *et al.* Risk of ischaemic stroke according to pattern of atrial fibrillation: Analysis of 6563 aspirin-treated patients in ACTIVE-A and AVERROES. *Eur Heart J* 2015;**36**:281–288. https://doi.org/10.1093/eurheartj/ehu307
79. Melgaard L, Gorst-Rasmussen A, Lane DA, Rasmussen LH, Larsen TB, Lip GY. Assessment of the CHA_2DS_2-VASc score in predicting ischemic stroke, thromboembolism, and death in patients with heart failure with and without atrial fibrillation. *JAMA* 2015;**314**:1030–1038. https://doi.org/10.1001/jama.2015.10725
80. Wolsk E, Lamberts M, Hansen ML, Blanche P, Køber L, Torp-Pedersen C, *et al.* Thromboembolic risk stratification of patients hospitalized with heart failure in sinus rhythm: A nationwide cohort study. *Eur J Heart Fail* 2015;**17**:828–836. https://doi.org/10.1002/ejhf.309
81. Ye S, Qian M, Zhao B, Buchsbaum R, Sacco RL, Levin B, *et al.* CHA_2DS_2-VASc score and adverse outcomes in patients with heart failure with reduced ejection fraction and sinus rhythm. *Eur J Heart Fail* 2016;**18**:1261–1266. https://doi.org/10.1002/ejhf.613
82. Renda G, Ricci F, Patti G, Aung N, Petersen SE, Gallina S, *et al.* CHA_2DS_2VASc score and adverse outcomes in middle-aged individuals without atrial fibrillation. *Eur J Prev Cardiol* 2019;**26**:1987–1997. https://doi.org/10.1177/2047487319868320
83. Freudenberger RS, Cheng B, Mann DL, Thompson JL, Sacco RL, Buchsbaum R, *et al.*; WARCEF Investigators. The first prognostic model for stroke and death in patients with systolic heart failure. *J Cardiol* 2016;**68**:100–103. https://doi.org/10.1016/j.jjcc.2015.09.014
84. Kondo T, Abdul-Rahim AH, Talebi A, Abraham WT, Desai AS, Dickstein K, *et al.* Predicting stroke in heart failure and reduced ejection fraction without atrial fibrillation. *Eur Heart J* 2022;**43**:4469–4479. https://doi.org/10.1093/eurheartj/ehac487
85. Ferreira JP, Girerd N, Gregson J, Latar I, Sharma A, Pfeffer MA, *et al.*; High-Risk Myocardial Infarction Database Initiative. Stroke risk in patients with reduced ejection fraction after myocardial infarction without atrial fibrillation. *J Am Coll Cardiol* 2018;**71**:727–735. https://doi.org/10.1016/j.jacc.2017.12.011
86. Melgaard L, Overvad TF, Skjoth F, Christensen JH, Larsen TB, Lip GYH. Risk of stroke and bleeding in patients with heart failure and chronic kidney disease: A nationwide cohort study. *ESC Heart Fail* 2018;**5**:319–326. https://doi.org/10.1002/ehf2.12256
87. O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, *et al.*; INTERSTROKE Investigators. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): A case-control study. *Lancet* 2016;**388**:761–775. https://doi.org/10.1016/S0140-6736(16)30506-2
88. Diener HC, Hankey GJ. Primary and secondary prevention of ischemic stroke and cerebral hemorrhage: JACC focus seminar. *J Am Coll Cardiol* 2020;**75**:1804–1818. https://doi.org/10.1016/j.jacc.2019.12.072
89. Tufano A, Galderisi M. Can echocardiography improve the prediction of thromboembolic risk in atrial fibrillation? Evidences and perspectives. *Intern Emerg Med* 2020;**15**:935–943. https://doi.org/10.1007/s11739-020-02303-5
90. Boriani G, Palmisano P, Malavasi VL, Fantecchi E, Vitolo M, Bonini N, *et al.* Clinical factors associated with atrial fibrillation detection on single-time point screening using a hand-held single-lead ECG device. *J Clin Med* 2021;**10**:729. https://doi.org/10.3390/jcm10040729
91. Schumacher K, Kornej J, Shantsila E, Lip GYH. Heart failure and stroke. *Curr Heart Fail Rep* 2018;**15**:287–296. https://doi.org/10.1007/s11897-018-0405-9
92. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, *et al.*; CRYSTAL AF Investigators. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med* 2014;**370**:2478–2486. https://doi.org/10.1056/NEJMoa1313600
93. Diener HC, Easton JD, Hart RG, Kasner S, Kamel H, Ntaios G. Review and update of the concept of embolic stroke of undetermined source. *Nat Rev Neurol* 2022;**18**:455–465. https://doi.org/10.1038/s41582-022-00663-4
94. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, *et al.*; CASTLE-AF Investigators. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med* 2018;**378**:417–427. https://doi.org/10.1056/NEJMoa1707855
95. Sohns C, Fox H, Marrouche NF, Crijns HJGM, Costard-Jaeckle A, Bergau L, *et al.*; CASTLE HTx Investigators. Catheter ablation in end-stage heart failure with atrial fibrillation. *N Engl J Med* 2023;**389**:1380–1389. https://doi.org/10.1056/NEJMoa2306037
96. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, *et al.*; ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2021;**42**:373–498. https://doi.org/10.1093/eurheartj/ehaa612

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97. Doehner W, Mazighi M, Hofmann BM, Lautsch D, Hindricks G, Bohula EA, *et al.* Cardiovascular care of patients with stroke and high risk of stroke: The need for interdisciplinary action: A consensus report from the European Society of Cardiology Cardiovascular Round Table. *Eur J Prev Cardiol* 2020;**27**:682–692. https://doi.org/10.1177/2047487319873460
98. Piepoli MF, Adamo M, Barison A, Bestetti RB, Biegus J, Bohm M, *et al.* Preventing heart failure: A position paper of the Heart Failure Association in collaboration with the European Association of Preventive Cardiology. *Eur J Heart Fail* 2022;**24**:143–168. https://doi.org/10.1002/ejhf.2351
99. Santhanakrishnan R, Wang N, Larson MG, Magnani JW, McManus DD, Lubitz SA, *et al.* Atrial fibrillation begets heart failure and vice versa: Temporal associations and differences in preserved versus reduced ejection fraction. *Circulation* 2016;**133**:484–492. https://doi.org/10.1161/CIRCULATIONAHA.115.018614
100. Al-Khatib SM, Benjamin EJ, Albert CM, Alonso A, Chauhan C, Chen PS, *et al.* Advancing research on the complex interrelations between atrial fibrillation and heart failure: A report from a US National Heart, Lung, and Blood Institute Virtual Workshop. *Circulation* 2020;**141**:1915–1926. https://doi.org/10.1161/CIRCULATIONAHA.119.045204
101. Boriani G, Vitolo M, Lane DA, Potpara TS, Lip GY. Beyond the 2020 guidelines on atrial fibrillation of the European Society of Cardiology. *Eur J Intern Med* 2021;**86**:1–11. https://doi.org/10.1016/j.ejim.2021.01.006
102. Delgado V, Di Biase L, Leung M, Romero J, Tops LF, Casadei B, *et al.* Structure and function of the left atrium and left atrial appendage: AF and stroke implications. *J Am Coll Cardiol* 2017;**26**:3157–3172. https://doi.org/10.1016/j.jacc.2017.10.063
103. Weintraub WS, Daniels SR, Burke LE, Franklin BA, Goff DC Jr, Hayman LL, *et al.*; American Heart Association Advocacy Coordinating Committee; Council on Cardiovascular Disease in the Young; Council on the Kidney in Cardiovascular Disease; Council on Epidemiology and Prevention; Council on Cardiovascular Nursing; Council on Arteriosclerosis; Thrombosis and Vascular Biology; Council on Clinical Cardiology, and Stroke Council. Value of primordial and primary prevention for cardiovascular disease: A policy statement from the American Heart Association. *Circulation* 2011;**124**:967–990. https://doi.org/10.1161/CIR.0b013e3182285a81
104. Vaduganathan M, Venkataramani AS, Bhatt DL. Moving toward global primordial prevention in cardiovascular disease: The heart of the matter. *J Am Coll Cardiol* 2015;**66**:1535–1537. https://doi.org/10.1016/j.jacc.2015.08.027
105. Pandian JD, Gall SL, Kate MP, Silva GS, Akinyemi RO, Ovbiagele BI, *et al.* Prevention of stroke: A global perspective. *Lancet* 2018;**392**:1269–1278. https://doi.org/10.1016/S0140-6736(18)31269-8
106. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;**146**:857–867. https://doi.org/10.7326/0003-4819-146-12-200706190-00007
107. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, *et al.* Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: A meta-analysis of randomised trials. *Lancet* 2014;**383**:955–962. https://doi.org/10.1016/S0140-6736(13)62343-0
108. https://clinicaltrials.gov/ct2/show/NCT02618577 .
109. ClinicalTrials.gov. Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Related Sub-Clinical Atrial Fibrillation (ATRESIA). https://clinicaltrials.gov/ct2/show/NCT01938248 (last accessed 3 November 2023).
110. Cleland JG, Findlay I, Jafri S, Sutton G, Falk R, Bulpitt C, *et al.* The Warfarin/Aspirin Study in Heart Failure (WASH): A randomized trial comparing antithrombotic strategies for patients with heart failure. *Am Heart J* 2004;**148**:157–164. https://doi.org/10.1016/j.ahj.2004.03.010
111. Cokkinos DV, Haralabopoulos GC, Kostis JB, Toutouzas PK; HELAS Investigators. Efficacy of antithrombotic therapy in chronic heart failure: The HELAS study. *Eur J Heart Fail* 2006;**8**:428–432. https://doi.org/10.1016/j.ejheart.2006.02.012
112. Massie BM, Collins JF, Ammon SE, Armstrong PW, Cleland JG, Ezekowitz M, *et al.* Randomized trial of warfarin, aspirin, and clopidogrel in patients with chronic heart failure: The Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial. *Circulation* 2009;**119**:1616–1624. https://doi.org/10.1161/CIRCULATIONAHA.108.801753
113. Homma S, Thompson JL, Pullicino PM, Levin B, Freudenberger RS, Teerlink JR, *et al.*; WARCEF Investigators. Warfarin and aspirin in patients with heart failure and sinus rhythm. *N Engl J Med* 2012;**366**:1859–1869. https://doi.org/10.1056/NEJMoa1202299
114. Zannad F, Anker SD, Byra WM, Cleland JGF, Fu M, *et al.*; COMMANDER HF Investigators. Rivaroxaban in patients with heart failure, sinus rhythm, and coronary disease. *N Engl J Med* 2018;**379**:1332–1342. https://doi.org/10.1056/NEJMoa1808848
115. Shantsila E, Koziel M, Lip GY. Anticoagulation versus placebo for heart failure in sinus rhythm. *Cochrane Database Syst Rev* 2021;**5**:CD003336. https://doi.org/10.1002/14651858.CD003336.pub4
116. Shantsila E, Lip GY. Antiplatelet versus anticoagulation treatment for patients with heart failure in sinus rhythm. *Cochrane Database Syst Rev* 2016;**9**:CD003333. https://doi.org/10.1002/14651858.CD003333.pub3
117. Li W, Seo J, Kokkinidis DG, Palaiodimos L, Nagraj S, Korompoki E, *et al.* Efficacy and safety of vitamin-K antagonists and direct oral anticoagulants for stroke prevention in patients with heart failure and sinus rhythm: An updated systematic review and meta-analysis of randomized clinical trials. *Int J Stroke* 2023;**18**:392–399. https://doi.org/10.1177/17474930221109149
118. Lin AY, Dinatolo E, Metra M, Sbolli M, Dasseni N, Butler J, *et al.* Thromboembolism in heart failure patients in sinus rhythm: Epidemiology, pathophysiology, clinical trials, and future direction. *JACC Heart Fail* 2021;**9**:243–253. https://doi.org/10.1016/j.jchf.2021.01.009
119. Saeed O, Zhang S, Patel SR, Jorde UP, Garcia MJ, Bulcha N, *et al.* Oral anticoagulation and adverse outcomes after ischemic stroke in heart failure patients without atrial fibrillation. *J Card Fail* 2021;**27**:857–864. https://doi.org/10.1016/j.cardfail.2021.02.017
120. Branch KR, Probstfield JL, Eikelboom JW, Bosch J, Maggioni AP, Cheng RK, *et al.* Rivaroxaban with or without aspirin in patients with heart failure and chronic coronary or peripheral artery disease. *Circulation* 2019;**140**:529–537. https://doi.org/10.1161/CIRCULATIONAHA.119.039609
121. Das S, Lorente-Ros M, Wu L, Mehta D, Suri R. Safety of left atrial appendage closure in heart failure patients. *J Cardiovasc Electrophysiol* 2022;**33**:2578–2584. https://doi.org/10.1111/jce.15682
122. Saad M, Osman M, Hasan-Ali H, Abdel Ghany M, Alsherif A, Risha O, *et al.* Atrial appendage closure in patients with heart failure and atrial fibrillation: Industry-independent single-centre study. *ESC Heart Fail* 2022;**9**:648–655. https://doi.org/10.1002/ehf2.13698
123. Leonardi-Bee J, Bath PM, Phillips SJ, Sandercock PA; IST Collaborative Group. Blood pressure and clinical outcomes in the international stroke trial. *Stroke* 2002;**33**:1315–1320. https://doi.org/10.1161/01.STR.0000014509.11540.66
124. Vemmos KN, Tsivgoulis G, Spengos K, Zakopoulos N, Synetos A, Manios E, *et al.* U-shaped relationship between mortality and admission blood pressure in patients with acute stroke. *J Intern Med* 2004;**255**:257–265. https://doi.org/10.1046/j.1365-2796.2003.01291.x
125. Sandset EC, Anderson CS, Bath PM, Christensen H, Fischer U, Gasecki D, *et al.* European Stroke Organisation (ESO) guidelines on blood pressure management in acute ischaemic stroke and intracerebral haemorrhage. *Eur Stroke J* 2021;**6**:XLVIII–LXXXIX. https://doi.org/10.1177/23969873211012133
126. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, *et al.* Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2019;**50**:e344–e418. https://doi.org/10.1161/STR.0000000000000211
127. Naredi S, Lambert G, Eden E, Zall S, Runnerstam M, Rydenhag B, *et al.* Increased sympathetic nervous activity in patients with nontraumatic subarachnoid hemorrhage. *Stroke* 2000;**31**:901–906. https://doi.org/10.1161/01.str.31.4.901
128. Haeusler KG, Huttner HB, Kuramatsu JB. Comment on 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J* 2019;**40**:2092. https://doi.org/10.1093/eurheartj/ehz126
129. Lip GYH, Genaidy A, Tran G, Marroquin P, Estes C, Sloop S. Improving stroke risk prediction in the general population: A comparative assessment of common clinical rules, a new multimorbid index, and machine-learning-based algorithms. *Thromb Haemost* 2022;**122**:142–150. https://doi.org/10.1055/a-1467-2993
130. Siedler G, Sommer K, Macha K, Marsch A, Breuer L, Stoll S, *et al.* Heart failure in ischemic stroke: Relevance for acute care and outcome. *Stroke* 2019;**50**:3051–3056. https://doi.org/10.1161/STROKEAHA.119.026139
131. Whiteley WN, Slot KB, Fernandes P, Sandercock P, Wardlaw J. Risk factors for intracranial hemorrhage in acute ischemic stroke patients treated with recombinant tissue plasminogen activator: A systematic review and meta-analysis of 55 studies. *Stroke* 2012;**43**:2904–2909. https://doi.org/10.1161/STROKEAHA.112.665331
132. Rasmussen M, Schönenberger S, Hendèn PL, Valentin JB, Espelund US, Sørensen LH, *et al.*; SAGA collaborators. Blood pressure thresholds and neurologic outcomes after endovascular therapy for acute ischemic stroke: An analysis of individual patient data from 3 randomized clinical trials. *JAMA Neurol* 2020;**77**:622–631. https://doi.org/10.1001/jamaneurol.2019.4838
133. Liebeskind DS, Tomsick TA, Foster LD, Yeatts SD, Carrozzella J, Demchuk AM, *et al.*; IMS III Investigators. Collaterals at angiography and outcomes in the Interventional Management of Stroke (IMS) III trial. *Stroke* 2014;**45**:759–764. https://doi.org/10.1161/STROKEAHA.113.004072

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134. Langhorne P, Ramachandra S; Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke: Network meta-analysis. *Cochrane Database Syst Rev* 2020;**4**:CD000197. https://doi.org/10.1002/14651858.CD000197.pub4
135. Schnabel RB, Camen S, Knebel F, Hagendorff A, Bavendiek U, Bohm M, *et al.* Expert opinion paper on cardiac imaging after ischemic stroke. *Clin Res Cardiol* 2021;**110**:938–958. https://doi.org/10.1007/s00392-021-01834-x
136. Putaala J, Lehto M, Meretoja A, Silvennoinen K, Curtze S, Kääriäinen J, *et al.* In-hospital cardiac complications after intracerebral hemorrhage. *Int J Stroke* 2014;**9**:741–746. https://doi.org/10.1111/ijs.12180
137. Jensen JK, Ueland T, Aukrust P, Antonsen L, Kristensen SR, Januzzi JL, *et al.* Highly sensitive troponin T in patients with acute ischemic stroke. *Eur Neurol* 2012;**68**:287–293.
138. Wrigley P, Khoury J, Eckerle B, Alwell K, Moomaw CJ, Woo D, *et al.* Prevalence of positive troponin and echocardiogram findings and association with mortality in acute ischemic stroke. *Stroke* 2017;**48**:1226–1232. https://doi.org/10.1161/STROKEAHA.116.014561
139. Haeusler KG, Jensen C, Scheitz JF, Krause T, Wollboldt C, Witzenbichler B, *et al.* Cardiac magnetic resonance imaging in patients with acute ischemic stroke and elevated troponin: A TRoponin ELevation in Acute Ischemic Stroke (TRELAS) sub-study. *Cerebrovasc Dis Extra* 2019;**9**:19–24. https://doi.org/10.1159/000498864
140. Mochmann HC, Scheitz JF, Petzold GC, Haeusler KG, Audebert HJ, Laufs U, *et al.*; TRELAS Study Group. Coronary angiographic findings in acute ischemic stroke patients with elevated cardiac troponin: The Troponin Elevation in Acute Ischemic Stroke (TRELAS) study. *Circulation* 2016;**133**:1264–1271. https://doi.org/10.1161/CIRCULATIONAHA.115.018547
141. Memar Montazerin S, Chi G, Marandi R, Najafi H, Shojaei F, Lee JJ, *et al.* Evaluation of cardiac troponin and adverse outcomes after aneurysmal subarachnoid hemorrhage: A systematic review and meta-analysis. *Neurocrit Care* 2021;**36**:650–661. https://doi.org/10.1007/s12028-021-01368-0
142. Morris NA, Chatterjee A, Adejumo OL, Chen M, Merkler AE, Murthy SB, *et al.* The risk of takotsubo cardiomyopathy in acute neurological disease. *Neurocrit Care* 2019;**30**:171–176. https://doi.org/10.1007/s12028-018-0591-z
143. Kaculini C, Sy C, Lacci JV, Jafari AA, Mirmoeeni S, Seifi A. The association of takotsubo cardiomyopathy and aneurysmal subarachnoid hemorrhage: A U.S. nationwide analysis. *Clin Neurol Neurosurg* 2022;**215**:107211. https://doi.org/10.1016/j.clineuro.2022.107211
144. Molnár C, Gál J, Szántó D, Fülöp L, Szegedi A, Siró P, *et al.* Takotsubo cardiomyopathy in patients suffering from acute non-traumatic subarachnoid hemorrhage-a single center follow-up study. *PLoS One* 2022;**17**:e0268525. https://doi.org/10.1371/journal.pone.0268525
145. Khechinashvili G, Asplund K. Electrocardiographic changes in patients with acute stroke: A systematic review. *Cerebrovasc Dis* 2002;**14**:67–76. https://doi.org/10.1159/000064733
146. Takeuchi S, Nagatani K, Otani N, Wada K, Mori K. Electrocardiograph abnormalities in intracerebral hemorrhage. *J Clin Neurosci* 2015;**22**:1959–1962. https://doi.org/10.1016/j.jocn.2015.04.028
147. Lele A, Lakireddy V, Gorbachov S, Chaikittisilpa N, Krishnamoorthy V, Vavilala MS. A narrative review of cardiovascular abnormalities after spontaneous intracerebral hemorrhage. *J Neurosurg Anesthesiol* 2019;**31**:199–211. https://doi.org/10.1097/ANA.0000000000000493
148. Kallmunzer B, Breuer L, Kahl N, Bobinger T, Raaz-Schrauder D, Huttner HB, *et al.* Serious cardiac arrhythmias after stroke: incidence, time course, and predictors – A systematic, prospective analysis. *Stroke* 2012;**43**:2892–2897. https://doi.org/10.1161/STROKEAHA.112.664318
149. Frontera JA, Parra A, Shimbo D, Fernandez A, Schmidt JM, Peter P, *et al.* Cardiac arrhythmias after subarachnoid hemorrhage: Risk factors and impact on outcome. *Cerebrovasc Dis* 2008;**26**:71–78. https://doi.org/10.1159/000135711
150. Schnabel RB, Haeusler KG, Healey JS, Freedman B, Boriani G, Brachmann J, *et al.* Searching for atrial fibrillation poststroke: A white paper of the AF-SCREEN International Collaboration. *Circulation* 2019;**140**:1834–1850. https://doi.org/10.1161/CIRCULATIONAHA.119.040267
151. Gabet A, Olié V, Béjot Y. Atrial fibrillation in spontaneous intracerebral hemorrhage, Dijon Stroke Registry (2006-2017). *J Am Heart Assoc* 2021;**10**:e020040. https://doi.org/10.1161/JAHA.120.020040
152. Prosser J, MacGregor L, Lees KR, Diener HC, Hacke W, Davis S; VISTA Investigators. Predictors of early cardiac morbidity and mortality after ischemic stroke. *Stroke* 2007;**38**:2295–2302. https://doi.org/10.1161/STROKEAHA.106.471813
153. Wira CR 3rd, Rivers E, Martinez-Capolino C, Silver B, Iyer G, Sherwin R, *et al.* Cardiac complications in acute ischemic stroke. *West J Emerg Med* 2011;**12**:414–420. https://doi.org/10.5811/westjem.2011.2.1785
154. He L, Wang J, Dong W. The clinical prognostic significance of hs-cTnT elevation in patients with acute ischemic stroke. *BMC Neurol* 2018;**18**:118. https://doi.org/10.1186/s12883-018-1121-5
155. Scheitz JF, Lim J, Broersen LHA, Ganeshan R, Huo S, Sperber PS, *et al.* High-sensitivity cardiac troponin T and recurrent vascular events after first ischemic stroke. *J Am Heart Assoc* 2021;**10**:e018326. https://doi.org/10.1161/JAHA.120.018326
156. Doehner W, Leistner DM, Audebert HJ, Scheitz JF. The role of cardiologists on the stroke unit. *Eur Heart J Suppl* 2020;**22**:M3–M12. https://doi.org/10.1093/eurheartj/suaa160
157. Ahn SH, Kim YH, Shin CH, Lee JS, Kim BJ, Kim YJ, *et al.* Cardiac vulnerability to cerebrogenic stress as a possible cause of troponin elevation in stroke. *J Am Heart Assoc* 2016;**5**:e004135. https://doi.org/10.1161/JAHA.116.004135
158. Hjalmarsson C, Bokemark L, Fredriksson S, Antonsson J, Shadman A, Andersson B. Can prolonged QTc and cTNT level predict the acute and long-term prognosis of stroke? *Int J Cardiol* 2012;**155**:414–417. https://doi.org/10.1016/j.ijcard.2010.10.042
159. von Rennenberg R, Siegerink B, Ganeshan R, Villringer K, Doehner W, Audebert HJ, *et al.* High-sensitivity cardiac troponin T and severity of cerebral white matter lesions in patients with acute ischemic stroke. *J Neurol* 2019;**266**:37–45. https://doi.org/10.1007/s00415-018-9085-3
160. Nolte CH, von Rennenberg R, Litmeier S, Scheitz JF, Leistner DM, Blankenberg S, *et al.* PRediction of acute coronary syndrome in acute ischemic StrokE (PRAISE) – Protocol of a prospective, multicenter trial with central reading and predefined endpoints. *BMC Neurol* 2020;**20**:318. https://doi.org/10.1186/s12883-020-01903-0
161. Haeusler KG, Endres M, Doehner W. Relevance of heart failure in prevention, treatment and prognosis of ischemic stroke. *Neurol Int Open* 2017;**01**:E61–E64. https://doi.org/10.1055/s-0043-102208
162. Blacker DJ. In-hospital stroke. *Lancet Neurol* 2003;**2**:741–746. https://doi.org/10.1016/s1474-4422(03)00586-6
163. Ivanescu AC, Dan GA. Stroke risk scores to predict hospitalization for acute decompensated heart failure in atrial fibrillation patients. *Rom J Intern Med* 2021;**59**:73–82. https://doi.org/10.2478/rjim-2020-0032
164. Hamatani Y, Iguchi M, Nakamura M, Ohtani R, Yamashita Y, Takagi D, *et al.* Incidence and predictors of ischemic stroke during hospitalization for congestive heart failure. *Heart Vessels* 2016;**31**:1154–1161. https://doi.org/10.1007/s00380-015-0719-4
165. Sato N, Kajimoto K, Keida T, Mizuno M, Minami Y, Yumino D, *et al.*; TEND Investigators. Clinical features and outcome in hospitalized heart failure in Japan (from the ATTEND Registry). *Circ J* 2013;**77**:944–951. https://doi.org/10.1253/circj.cj-13-0187
166. Hamaguchi S, Kinugawa S, Tsuchihashi-Makaya M, Goto D, Yamada S, Yokoshiki H, *et al.* Characteristics, management, and outcomes for patients during hospitalization due to worsening heart failure-a report from the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). *J Cardiol* 2013;**62**:95–101. https://doi.org/10.1016/j.jjcc.2013.03.009
167. Iguchi M, Kato T, Yaku H, Morimoto T, Inuzuka Y, Tamaki Y, *et al.* Ischemic stroke in acute decompensated heart failure: From the KCHF registry. *J Am Heart Assoc* 2021;**10**:e022525. https://doi.org/10.1161/JAHA.121.022525
168. Berkovitch A, Mazin I, Younis A, Shlomo N, Nof E, Goldenberg I, *et al.* CHA_2DS_2-VASc score performance to predict stroke after acute decompensated heart failure with and without reduced ejection fraction. *Europace* 2019;**21**:1639–1645. https://doi.org/10.1093/europace/euz192
169. Son MK, Lim NK, Park HY. Predicting stroke and death in patients with heart failure using CHA_2DS_2-VASc score in Asia. *BMC Cardiovasc Disord* 2019;**19**:193. https://doi.org/10.1186/s12872-019-1178-0
170. Shima S, Shinoda M, Takahashi O, Unaki A, Kimura T, Okada Y, *et al.* Risk factors for acute heart failure and impact on in-hospital mortality after stroke. *J Stroke Cerebrovasc Dis* 2019;**28**:1629–1635. https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.02.030
171. Bhatt AS, Ambrosy AP, Dunning A, DeVore AD, Butler J, Reed S, *et al.* The burden of non-cardiac comorbidities and association with clinical outcomes in an acute heart failure trial – Insights from ASCEND-HF. *Eur J Heart Fail* 2020;**22**:1022–1031. https://doi.org/10.1002/ejhf.1795
172. Harjola VP, Follath F, Nieminen MS, Brutsaert D, Dickstein K, Drexler H, *et al.* Characteristics, outcomes, and predictors of mortality at 3 months and 1 year in patients hospitalized for acute heart failure. *Eur J Heart Fail* 2010;**12**:239–248. https://doi.org/10.1093/eurjhf/hfq002
173. Popovic B, Zannad F, Louis H, Clerc-Urmes I, Lakomy C, Gibot S, *et al.* Endothelial-driven increase in plasma thrombin generation characterising a new hypercoagulable phenotype in acute heart failure. *Int J Cardiol* 2019;**274**:195–201. https://doi.org/10.1016/j.ijcard.2018.07.130
174. Haeusler KG, Laufs U, Endres M. Chronic heart failure and ischemic stroke. *Stroke* 2011;**42**:2977–2982. https://doi.org/10.1161/STROKEAHA.111.628479

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175. Sabit R, Thomas P, Shale DJ, Collins P, Linnane SJ. The effects of hypoxia on markers of coagulation and systemic inflammation in patients with COPD. *Chest* 2010;**138**:47–51. https://doi.org/10.1378/chest.09-2764
176. Yetkin E, Topal E, Yanik A, Ozten M. Thromboembolic complications in patients with newly diagnosed dilated cardiomyopathy immediately after initiation of congestive heart failure treatment: Just a coincidence or should we pay more attention? *Clin Appl Thromb Hemost* 2010;**16**:480–482. https://doi.org/10.1177/1076029609335520
177. Gillum RF, Sempos CT. Hemoglobin, hematocrit, and stroke incidence and mortality in women and men. *Stroke* 1996;**27**:1910 PMID: 8841352.
178. Böhm M, Cotton D, Foster L, Custodis F, Laufs U, Sacco R, *et al.* Impact of resting heart rate on mortality, disability and cognitive decline in patients after ischaemic stroke. *Eur Heart J* 2012;**33**:2804–2812. https://doi.org/10.1093/eurheartj/ehs250
179. Böhm M, Brueckmann M, Eikelboom JW, Ezekowitz M, Fräßdorf M, Hijazi Z, *et al.* Cardiovascular outcomes, bleeding risk, and achieved blood pressure in patients on long-term anticoagulation with the thrombin antagonist dabigatran or warfarin: Data from the RE-LY trial. *Eur Heart J* 2020;**41**:2848–2859. https://doi.org/10.1093/eurheartj/ehaa247
180. Millenaar D, Schumacher H, Brueckmann M, Eikelboom JW, Ezekowitz M, Slawik J, *et al.* Cardiovascular outcomes according to polypharmacy and drug adherence in patients with atrial fibrillation on long-term anticoagulation (from the RE-LY trial). *Am J Cardiol* 2021;**149**:27–35. https://doi.org/10.1016/j.amjcard.2021.03.024
181. Szummer KE, Solomon SD, Velazquez EJ, Kilaru R, McMurray J, Rouleau JL, *et al.* Heart failure on admission and the risk of stroke following acute myocardial infarction: The VALIANT registry. *Eur Heart J* 2005;**26**:2114–2119. https://doi.org/10.1093/eurheartj/ehi352
182. Pana TA, Wood AD, Perdomo-Lampignano JA, Tiamkao S, Clark AB, Kongbunkiat K, *et al.* Impact of heart failure on stroke mortality and recurrence. *Heart Asia* 2019;**11**:e011139. https://doi.org/10.1136/heartasia-2018-011139
183. Mir T, Uddin M, Qureshi WT, Shanah L, Soubani A, Saydain G, *et al.* Trends and complications associated with acute new-onset heart failure: A national readmissions database-based cohort study. *Heart Fail Rev* 2021;**27**:399–406. https://doi.org/10.1007/s10741-021-10152-3
184. Kindermann I, Fischer D, Karbach J, Link A, Walenta K, Barth C, *et al.* Cognitive function in patients with decompensated heart failure: The Cognitive Impairment in Heart Failure (CogImpair-HF) study. *Eur J Heart Fail* 2012;**14**:404–413. https://doi.org/10.1093/eurjhf/hfs015
185. Suzuki H, Matsumoto Y, Ota H, Sugimura K, Takahashi J, Ito K, *et al.* Hippocampal blood flow abnormality associated with depressive symptoms and cognitive impairment in patients with chronic heart failure. *Circ J* 2016;**80**:1773–1780. https://doi.org/10.1253/circj.CJ-16-0367
186. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *J Am Coll Cardiol* 2006;**48**:1527–1537. https://doi.org/10.1016/j.jacc.2006.06.055
187. Holm H, Bachus E, Jujic A, Nilsson ED, Wadström B, Molvin J, *et al.* Cognitive test results are associated with mortality and rehospitalization in heart failure: Swedish prospective cohort study. *ESC Heart Fail* 2020;**7**:2948–2955. https://doi.org/10.1002/ehf2.12909
188. Sbolli M, Fiuzat M, Cani D, O'Connor CM. Depression and heart failure: The lonely comorbidity. *Eur J Heart Fail* 2020;**22**:2007–2017. https://doi.org/10.1002/ejhf.1865
189. He W, Zhou Y, Ma J, Wei B, Fu Y. Effect of antidepressants on death in patients with heart failure: A systematic review and meta-analysis. *Heart Fail Rev* 2020;**25**:919–926. https://doi.org/10.1007/s10741-019-09850-w
190. Sun JH, Tan L, Yu JT. Post-stroke cognitive impairment: Epidemiology, mechanisms and management. *Ann Transl Med* 2014;**2**:80. https://doi.org/10.1002/ehf2.12909
191. Cannon JA, Moffitt P, Perez-Moreno AC, Walters MR, Broomfield NM, McMurray JJV, *et al.* Cognitive impairment and heart failure: Systematic review and meta-analysis. *J Card Fail* 2017;**23**:464–475. https://doi.org/10.1016/j.cardfail.2017.04.007
192. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, *et al.* 2016 European Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2016;**37**:2315–2381. https://doi.org/10.1093/eurheartj/ehw106
193. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, *et al.*; ESC National Cardiac Societies; ESC Scientific Document Group. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021;**42**:3227–3337. https://doi.org/10.1093/eurheartj/ehab484
194. Jeffares I, Merriman NA, Rohde D, McLoughlin A, Scally B, Doyle F, *et al.* A systematic review and meta-analysis of the effects of cardiac rehabilitation interventions on cognitive impairment following stroke. *Disabil Rehabil* 2021;**43**:773–788. https://doi.org/10.1080/09638288.2019.1641850
195. Pindus DM, Mullis R, Lim L, Wellwood I, Rundell AV, Abd Aziz NA, *et al.* Stroke survivors' and informal caregivers' experiences of primary care and community healthcare services – A systematic review and meta-ethnography. *PLoS One* 2018;**13**:e0192533. https://doi.org/10.1371/journal.pone.0192533
196. Guo Y, Zhang Z, Lin B, Mei Y, Liu Q, Zhang L, *et al.* The unmet needs of community-dwelling stroke survivors: A systematic review of qualitative studies. *Int J Environ Res Public Health* 2021;**18**:2140. https://doi.org/10.3390/ijerph18042140
197. Ski CF, Castle DJ, Lautenschlager NT, Moore G, Thompson DR. Caring for caregivers after a stroke. *Int Psychogeriatr* 2015;**27**:1–4. https://doi.org/10.1017/S1041610214002385
198. Loft MI, Martinsen B, Esbensen BA, Mathiesen LL, Iversen HK, Poulsen I. Call for human contact and support: An interview study exploring patients' experiences with inpatient stroke rehabilitation and their perception of nurses' and nurse assistants' roles and functions. *Disabil Rehabil* 2019;**41**:396–404. https://doi.org/10.1080/09638288.2017.1393698
199. Wingham J, Frost J, Britten N, Jolly K, Greaves C, Abraham C, *et al.*; REACH-HF Research Investigators. Needs of caregivers in heart failure management: A qualitative study. *Chronic Illn* 2015;**11**:304–319. https://doi.org/10.1177/1742395315574765
200. Pont W, Groeneveld I, Arwert H, Meesters J, Mishre RR, Vliet Vlieland T, *et al.*; SCORE Study Group. Caregiver burden after stroke: Changes over time? *Disabil Rehabil* 2020;**42**:360–367. https://doi.org/10.1080/09638288.2018.1499047
201. Hendriks J, Andreae C, Ågren S, Eriksson H, Hjelm C, Walfridsson U, *et al.* Cardiac disease and stroke: Practical implications for personalised care in cardiac-stroke patients. A state of the art review supported by the Association of Cardiovascular Nursing and Allied Professions. *Eur J Cardiovasc Nurs* 2020;**19**:495–504. https://doi.org/10.1177/1474515119895734

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