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

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Abstract

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 via imbalanced neural and neurovegetative control of cardiovascular regulation may induce or aggravate HF.

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 pathophysiologic interactions of the heart and the brain in the comorbidity of HF and stroke. Principal aspects of diagnostic workup, pathophysiologic 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 heart failure and stroke.

1 Introduction

Heart failure (HF) is commonly presenting as a systemic clinical syndrome associated with multiple organ dysfunctions and various co-morbidities. Co-morbidities 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 co-morbidities, 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 hospitalisation, 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 feed-back 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 ESC Council on Stroke has emphasised 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 optimisation (including lifestyle changes)

Antithrombotic therapy (A) and CV risk factor optimisation (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 programs and continued home-care and social services [4]. Such an integrated care approach requires standardized post stroke care concepts with multi-disciplinary collaboration and coordination of care. Adequate diagnostic work up 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 European Society of Cardiology (ESC)-Council on Stroke together with the Heart Failure Association of the ESC (HFA) 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: a) on HF patients with increased risk of stroke or with acute stroke including transient ischaemic attack (TIA), and b) 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 pathophysiologic 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.

2 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 ca 1% at the age <55 years to >10% at the ager >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 HF in patients with stroke

HF is present in about 10-24% of patients with ischemic stroke [7, 8, 9, 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 ischemic stroke patients have systolic and additional 23% have diastolic dysfunction [13]. Among stroke patients, those with heart failure tend to have higher overall comorbidity level that includes more frequent diabetes mellitus, coronary artery disease, valvular heart disease, and AF compared to those without HF [7]. In a nationwide analysis in the U.S.A., the proportion of stroke patients with HF increased from 10.8% of all stroke admissions in 1995 to 12.3% in 2005 [10].

Prevalence of stroke in patients with HF

Numerous studies have provided evidence that patients with HF are at increased risk of ischemic stroke compared to the general population [14]. The prevalence of stroke in clinical trials and registries of HF ranges between 8% and 11% [14, 15, 16, 17, 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 Chapter 3). Some studies suggested that the stroke rate was related to NYHA class and inversely to left ventricular ejection fraction [19, 20, 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, 24, 25, 26, 27, 28, 29] or even higher [30, 31] risk of stroke for patients with HFpEF compared to 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, 16, 17, 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 also in HF patients in sinus rhythm compared to non-HF subjects [34, 35], while atrial fibrillation (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 sinus rhythm 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. Ischemic 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, 40, 41, 42, 43, 44].

Stroke outcomes in HF 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 are 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 ischemic lesions in different vascular regions due to fragmentation of the embolus. Mortality after stroke was observed between 2.2 to 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 to 3 times more likely to present with severe functionally 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.

3 Mechanisms of interaction of heart failure and stroke

Mechanisms of HF to cause stroke

Cardioembolism is the most common aetiology of stroke in HF. Haemodynamic strokes due to hypoperfusion may result from low cardia 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**).

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-anti thrombin complexes, and fibrinopeptide A [55, 56]. The fibrinolytic system is also altered, irrespectively of preserved or reduced ejection fraction, which results in higher levels of D-dimer, tPA and PAI-1 [56, 57]

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 of vascular integrity can be measured as 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 (NO) deficiency thus promoting immune activation and endothelium dysfunction. Leukocyte adherence to the endothelial surface is activated and together with endothelial cells release of inflammatory cytokines is increased, such as IL-6 and TNF 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].

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, endothelium dysfunction. Progressing decrease of left ventricular ejection fraction together with the above discussed mechanisms has led to recognise a particular cardiac thrombogenicity with a high risk of cardioembolic stroke [19, 64].

Ischemic stroke due to large artery atherosclerosis may occur in ischaemic HF with generalised atherosclerosis, as atherosclerotic diseases is associated with systemic activation of both inflammation and coagulation [43, 65, 66] A haemodynamic stroke may particularly result from HF with low cardiac output 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 Chapter 6). Furthermore, antiplatelet therapy increases the risk of haemorrhagic stroke.

Mechanisms of stroke to cause or aggravate HF

The heart as a major *cause* of stroke is widely understood in the heart-brain interaction. There are as well reciprocal cerebral-cardiac effects [Figure 3] [69]. 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 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, atrial fibrillation, arrhythmias, ventricular dysfunction and may ultimately trigger cardiac decompensation (Figure 4). The systematic interaction**s** 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 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 to 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].

4 Stratification of stroke risk in HF patients

The individual stroke risk of patients with HF depends on clinical variables of the HF plus additional clinical characteristics and comorbidities (**Table Chapter 4-A**). The *temporal association* of a particular 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). 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 Chapter 3, Virchow's triad). **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 NT-

proBNP was shown to be predictive of increased stroke risk in acute HF. In 3,261 patients hospitalised with acute HF in the APEX trial, elevated NT-proBNP was associated with a 3.6-fold higher risk of stroke (adjusted HR 3.64, 95% CI 1.35-9.83) [73].

Left ventricular thrombus is not a rare finding in HF patients particularly in connection to LV regional akinetic segments or aneurysms and has an obvious mechanistic association with ischemic stroke [38]. Patients with left ventricular thrombus identified in cardiac MRI 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, atrial fibrillation, 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 sinus rhythm [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, 80, 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 (dichotomised at the threshold of 60 years), sex, haemoglobin, blood urea nitrogen, ejection fraction, diastolic blood pressure, diabetes status, and prior stroke or transient ischemic attack **(Table Chapter 4-B)** [83]. It showed a C-index of 0.63 for the prediction of the overall risk of ischemic 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 3 variables (history of prior stroke, insulin-treated diabetes, and plasma N-terminal pro-B-type natriuretic peptide 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.

5 Primary & secondary stroke prevention in HF

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 [**Figure 5**][87, 88]. **Preventive measures should be addressed as primary and 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 patient 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 artery 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 this 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.

AF detection 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 HF progression *and* prevention of stroke. The comprehensive concept of management of AF in HF includes a) identification and treatment of triggers of AF, b) prevention of embolic events, c) rate control **to prevent HF progression**, d) 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 ≥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 patient with or without HF (see chapter 6, below).

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, 100, 101]. A number of echocardiographic parameters have been associated with an increased risk of stroke in AF patients, with or without HF (Table Chapter 5), but it remains unclear which incremental value these parameters may carry on top of the widely used CHA_2DS_2VASc 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 [102]. 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 disease in general [102, 103]. This concept should imply joint efforts to improve social and environmental conditions, as well as individual behaviours for a wider adoption of healthy lifestyles [103, 104].

6 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, i.e. when sinus rhythm 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 OAC apply and DOACs are the preferred choice for patients with non-valvular AF [75]. Randomised 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 or 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 in secondary prevention of 14 within 1 year [105]. Comparing anticoagulation strategies in AF, direct oral anticoagulatns (DOAC's) significantly reduced the risk of stroke compared with warfarin by 19% (RR, 0.81; 95% CI, 0.73-0.91) [106]. 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 etiological factors of HF, such as CAD, hypertension, diabetes, and advance 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 it prevents strokes also in patients with subclinical (i.e. device-detected) AF is currently unknown and assessed in ongoing randomized controlled trials [107, 108].

In contrast, **in patients with HF and with maintained sinus rhythm** the benefit of anticoagulation for stroke prevention is less clear. Four RCTs have assessed oral anticoagulation in HF with SR comparing warfarin with aspirin or placebo (Table Chapter 6). All these studies were restricted to HFrEF. Two small studies (WASH and HELAS) did not have adequate statistical power [109]. In the larger WARCEF trial (n=2,305), warfarin did not improve the composite primary outcome of ischemic stroke, intracerebral haemorrhage, or death from any cause (HR 0.93, 95% CI 0.79-1.10). Notably, warfarin reduced the rate of ischemic strokes (HR 0.52, 95% CI 0.33-0.82) [110]. However, treatment with warfarin resulted in more major haemorrhages (adjusted rate ratio 2.05, 95% CI 1.36-3.12) with no significant difference the rate of intracerebral haemorrhage. A Cochrane meta-analysis showed similar all-cause mortality for warfarin vs aspirin (RR 1.00, 95% CI 0.89-1.13) with a 2-fold increase in major bleeding with warfarin (RR 2.00, 95% CI 1.44-2.78) [111]. 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 (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 [113]. In this trial, 5022 participants with HF and background coronary artery disease (CAD) were randomised to rivaroxaban 2.5 mg bd. 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 ischemic 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 the rivaroxaban on the primary outcome. A similar result was reported from a recent meta-analysis including 15,794 patients from 7 controlled trials [114]. 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, NNH 58). In the subgroup analysis according to the type of OAC, 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 differences between groups for the outcomes of myocardial infarction, all-cause mortality, and heart failure 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 OAC therapy [115]**

Overall, oral anticoagulation in HFrEF with SR did not improve mortality, and the stroke events were relatively few in all groups **(Table Ch6)**. A consistent increase in bleeding events offsets the potential benefits of anticoagulation on thromboembolism reduction [116]. 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 atrial fibrillation has been diagnosed (**Figure 6**). However, low-dose rivaroxaban may be considered in HF patients with CAD 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 [117]

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 for stroke prevention in patients with nonvalvular 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 subgroup. However, higher incidence of noncardiac complications such as acute kidney injury and respiratory failure were noted for the HF subgroup [118]. Another study observed during a 3 year follow up a higher rate of MACCE (31% vs 15% and of death (24% vs 7%) [119]. 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.

7 Specific aspects of HF 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 no therapy is a given a class 1A Guideline recommendation although it is important to control congestion with diuretic treatment and to treat common co-morbidities 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 current 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 suspension of some of the standard HF treatments might be needed. Notably, any reduction of β-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 SCD. An early re-initiation/up-titration of HF treatment in the post-acute phase is beneficial for both the secondary prevention of stroke, i.e. 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 mortality after ischaemic stroke follows a U- or J-shape, with an optimal blood pressure range of 130-150 mmHg [120, 121]. 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 ischemia-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 ischemic 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 [122, 123].

The occurrence of stroke may be associated with **tachycardia and with** new-onset AF as stroke is also associated with increased sympathetic activity [124]: A high ventricular rate might contribute to worsening HF and, therefore, initiation/up-titration of beta-blockers might be particularly helpful (see below, stroke unit care). **Ivabradine might be considered in patients with tachycardia without AF**.

8 Specific aspects of acute stroke treatment in HF patients

Reduced cardiac output is observed in 10-24% of all patients with acute ischemic 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 borderzone 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 [125] 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 below, stroke unit care) [126].

Regarding interventional treatments for acute ischaemic stroke, to date, no randomized data are available focusing on the efficiency and safety of (systemic) thrombolysis using rt-PA or mechanical recanalization in stroke patients with HF [127]. Moreover, HF patients were often excluded from randomized stroke trials. A retrospective analysis of the VISTA database comparing HF vs. non-HF patients suggests a similar efficiency [46] and safety of thrombolysis, while rt-PA-associated bleeding was almost doubled in HF patients [128] in a meta-analysis including 55 studies. In a German single-center cohort study, recanalization rate and the rate of rt-PA-associated secondary intracranial haemorrhage was not different in HF vs. non-HF patients [127].

The same holds true for (HF vs. non-HF) patients undergoing (additional) mechanical recanalization [127]. 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 [129]. 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 [130]. Nevertheless, in a single-center prospective registry on acute stroke treatment a similar outcome in HF vs. non-HF patients after mechanical recanalization was observed [127].

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.

9 Cardiac complications and HF 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 [131]. As outlined above, an increased risk of cardiac complications (like HF, myocardial infarction, Takotsubo cardiomyopathy cardiomyopathy, acute hypertensive episodes, atrial fibrillation, ventricular arrhythmias, change of repolarization, Table Chapter 9), arises in acute stroke, peaking within the first 3 days [132, 133, 134, 135, 136]. Cardiac complications in acute stroke imply poor short- and long-term prognosis [137, 138, 139, 140]. It is therefore consensus that cardiologists should be consistently integrated in stroke unit care to address cardiovascular aspects of acute stroke in selected patients [141]. The systematic cardiologic workup of patients on a stroke unit should address the three main targets **(Figure 8)** [141]:

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

The rate of cardiac complications differs to some extent between ischemic stroke, haemorrhagic stroke or subarachnoid haemorrhage (**Table Ch9**). 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 patients' characteristics, such as age, risk profile and underlying comorbidities [142].

Key factors of cardiac monitoring on a stroke unit are **(Figure 8)**

- preventing haemodynamic decompensation and ADHF
- ECG-monitoring for AF, heart rate, severe ventricular and supraventricular **arrhythmias**
- fluid status monitoring
- blood pressure monitoring,
- blood-based biomarkers
- cardiac imaging,

to identify stroke patients at higher risk of cardiac complications (**Table Chapter 9**)[52, 133, 139, 143, 144].

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 [134, 136, 145]. A first episode of AF is detected in up to 10% of stroke patients and account for the majority of arrhythmias in acute stroke [133]. 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 sensitive cardiac troponin (hs-cTn) are frequently found in patients with stroke and even transient increased hs-cTn are related to worse prognosis [139, 146], a dynamic change of hs-cTn is associated with an early increased risk of mortality [139]. 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 [144]. The ongoing PRAISE trial evaluates when a coronary angiography should be performed in these high-risk patients in the subacute phase of stroke [147]. A complication in the management of subarachnoid haemorrhage (SAH) 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 [131]. There is apparently no published data on the efficacy of stroke unit treatment in HF patients. However, the hemodynamically 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 [148].

10 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 [149]. As discussed above, the risk of stroke in acute HF is excessively high [17], even among patients in sinus rhythm i.e. without pre-existing AF [150].

In line, Asian HF registries show a particular high stroke risk during hospitalization or shortly after discharge [151, 152, 153]. In the Kyoto Congestive HF (KCHF) registry including 4.056 patients with acute HF, 1.6% of patients developed an ischemic stroke during a hospitalization for acute HF [154]. The stroke risk in acute HF can be predicted by the CHA_2DS_2-VASc score [155], which also can predict rehospitalization for acute HF [156]. 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 [157].

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 [158]. 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 [159].

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 [160]. This may in part explain the very high risk of ischemic 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 [161], ROS accumulation and inflammatory activation [162]. 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 [163, 164]. Furthermore, pathophysiological and clinical changes in acute HF such as high heart rate, new onset of AF [165], low blood pressure [166] or comorbidities and polypharmacy [167] 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 [154]. Indeed, the degree of *acute* ventricular dysfunction seems to relate 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 classes compared to the lowest Killip class amounting to a relative risk of 4.85 [168]. In turn, acute HF worsens the risk for death and cardiovascular complications as well in the follow-up after acute stroke [169].

There is sound evidence comparing acute HF with reduced vs. preserved ejection fraction regarding the risk of stroke. Data from the Nationwide US Readmission Database (NRD) including over 2.5 Mio patients with acute HF

showed higher event rates of stroke in acute HF with reduced (4.7%) vs. preserved (2.5%) ejection fraction [170]. A study in 2.922 patients admitted with acute HF and AF showed that the predictive power of the CHA_2DS_2VASc Score for stroke risk prediction was similarly valid in HF patients with reduced as with preserved ejection fraction [155]. However, only a modest predictive power of the CHA_2DS_2VASc Score in patients with acute HF was observed in a HF registry from Korea [156]

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 [171]. Also, silent cerebral infarctions, that are known to relate to subtle functional deficits, are significantly more prevalent in patients with HF [40, 172]. Depression is a prevalent comorbidity in HF and may further accelerate in acute HF. Clinically significant depressive symptoms affect 20 to 50% of HF patients depending on HF severity [173]. Depression in HF is associated with advanced HF severity, and poor prognosis [174]. **To date anti-depressive treatment in HF has not convincingly shown efficacy. Selective serotonin reuptake inhibitors (SSRI) have shown to improve depressive symptoms and to be safe but have failed to improve prognosis [175]. 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 [176]**

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 cardiologist 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 complication of acute HF.

11 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 [177, 178]. 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 [179]. Rehabilitation is recommended for patients living with cardiovascular disease [180]. Notably, fewer than 1:5 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 [181]. Unlike cardiac patients (including HF and a range of other cardiac conditions) who are recognised as chronic patients and usually referred for long-term cardiac monitoring and ambulatory management, no such long-term care exists in most health care 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 [182]. Limited information, resources and a lack of access to psychological support are common [183].

In the absence of proper support, cardiac and stroke patients rely on informal caregivers [184] who provide a crucial role providing patients with motivation, hope and meaning [185]. They help manage medicines, provide personal care, facilitate conversations with healthcare professionals, aid symptom recognition and promote lifestyle change [186]. 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 [187]. Hendriks et al. suggests that a personalised 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 QoL and life expectancy [188]. Whilst this approach is welcomed, these benefits will only be realised if the patient and their care giver play an active role in the decision-making process.

12 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 statement of the authors may inform clinicians on diagnostic workup, prevention and treatment of the comorbidity of HF and stroke.

Epidemiology:

Patients with HF:

- The prevalence of stroke among patients with HF is 8 to 11 %.
- The risk of stroke is highest in the first 30 days of initial diagnosis of HF
- The risk of stroke is elevated during episodes of ADHF
- HF-related factors contributing to the risk of stroke are advanced 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 triad (slow blood flow, endothelium 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 LV 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 LV functional status (TTE).
- **Echocardiographic imaging should be performed if structural and functional abnormalities are suspected. The selection of the appropriate type of echocardiography (i.e. transthoracic vs transoesophageal echo) 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 hospitalisation.**

Treatment and prevention

<u>The HF perspective</u>

- 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_2VASc score. In HF patients with maintained sinus rhythm, 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.

<u>The stroke perspective</u>

- 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 optimisation (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 ACE inhibitor, or angiotensin receptor antagonists or angiotensin receptor antagonists/neprilyin inhibitor (ARNI), ß-blockers, SGLT2-inhibitors. If needed, titration (particularly of β-blockers) should be done carefully and with continued monitoring of haemodynamic stability. Early re-initiation of HF treatment should be pursued.
- Blood pressure control is particularly challenging and requires careful 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.
- 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 GP or basic health care 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.

Table Chapter 4: A) Clinical parameters which are known to affect the stroke risk in HF patients, B) 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: - impaired contractile function - enlarged left atrial diameter/volume - enlarged left ventricular diameter/volume - low cardiac output - left ventricular thrombus	Left ventricular ejection fraction
Atrial fibrillation	
Cardiovascular comorbidities	Prior stroke or transient ischemic attack Diabetes mellitus Diastolic blood pressure
Renal function	Blood urea nitrogen
Prothrombotic conditions	Haemoglobin

Table Chapter 5. Echocardiographic parameters associated with an increased risk of stroke in AF patients (with or without HF) [189].

Echocardiographic parameters associated with an increased risk of stroke in AF patients (with or without HF).
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

Table Chapter 6. Randomised controlled trials of oral anticoagulation in heart failure with sinus rhythm

	WASH [190]	HELAS Post- MI arm [191]	HELAS DCM arm [191]	WATCH [112]	WARCEF [110]	COMMANDER-HF [113]
Year published	2004	2006	2006	2009	2012	2018
Randomised Patients, n	279	115	82	1587	2,305	5,022
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/d or no treatment	Aspirin 325 mg/d	Placebo	Aspirin 162 mg/d Clopidogrel 75 mg/d	Aspirin 325 mg/d	Placebo
HF-related criteria	Diuretic required	NYHA II-IV Previous MI	NYHA II-IV DCM	NYHA II-IV Diuretic and ACEI use	NYHA I-IV	CAD, High (NTpro)BNP*
EF 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)‡ vs 11 clopidogrel‡	0.52 (0.33-0.82)‡	0.66 (0.47–0.95)‡
Major bleeding, n or HR (95% CI)	4 vs 0 (placebo) vs 1 (aspirin)‡	4 vs 0 (aspirin)	3 vs 0 (placebo)	28 vs 19 (aspirin) vs 11 clopidogrel‡	2.21 (1.42–3.47)‡	1.68 (1.18–2.39)‡

ACEI, angiotensin converting enzyme inhibitor; CAD, coronary artery disease; CI, confidence interval; DCM, dilated cardiomyopathy; EF, left ventricular ejection fraction; HF, heart failure; HR, hazard ratio; INR, international normalised ratio; MI, myocardial infarction; na, data not available; (NT-pro)BNP, brain natriuretic peptide or N-terminal pro-brain natriuretic peptide; NYHA, New Your Heart Association class;

*After the recruitment of 23% of patients the protocol amendment required patients to have plasma BNP ≥200 pg/ml or N-terminal pro–BNP) ≥800 pg/ml.

‡p<0.05 vs. anticoagulation group on antithrombotic therapy in a patient with heart failure depending on heart rhythm.

Table Chapter 9: Cardiac complications in acute stroke patients

	Ischemic Stroke	Subarachnoid haemorrhage	Intracerebral haemorrhage	What to do if…
Heart failure [9, 13,192]	-5% clinical HF -10% systolic dysfunction -23% diastolic dysfunction	3-26%	3.8% [193]	Echocardiography when suspicion of impaired heart function. Avoid inconsiderate discontinuation of HF drugs (in particular β-blockers). Sympathomimetic rebound effect can worsen cardiac function without increasing blood pressure.
Troponin elevation and myocardial infarction [132, 140, 143, 144, 194]	-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 β-blockers).
Takotsubo cardiomyopathy [135]	1.3%	0.8-8% [195, 196]	1.2%	Echocardiography/cardiac MRI to identify apical ballooning. Cardiac biomarkers (TnT, BNP). Coronary angiogram may be indicated.
ECG repolarisation disturbance [134, 197, 198]	15-40%	75%	60-70%	Continuous rhythm monitoring for at least 72 hours. Avoid inconsiderate discontinuation of β-blockers.
Heart rhythm disturbances [133, 199, 200]	25%, AF as most common arrhythmia	5%, AF as most common arrhythmia	2.9%, new onset AF [201]	Continuous rhythm monitoring for at least 72 hours 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 [125]	7.5-15%	40%	15-20%	Blood pressure (BP) reduction according to recommendations considering stroke aetiology, acute stroke intervention strategy. Continued BP monitoring while on stroke unit.

Figure legends:

Figure 1: Stroke aetiology according to TOAST classification and respective cardiological input in diagnostic workup and in acute and subacute stroke care

Figure 2: Virchow trial of thrombus formation and stroke risk in patients with heart failure

Figure3: Bidirectional interaction of heart failure and stroke

Figure 4: Signalling pathways in acute and subacute stroke to provoke cardiac injury and to induce or aggravate heart failure [modified from 69].

Figure 5: Sequence of prevention concepts in preventing the HF – stroke comorbidity

Figure 6: Example of anticoagulation treatment decision in the course of HF disease progression

Figure 7: Shifting treatment targets for HF in the acute, subacute and chronic phases after stroke.

Figure 8: Flowchart of cardiovascular management of stroke patients (1) diagnostic workup, (2) monitoring for CV complications and (3) secondary prevention and subsequent CV management

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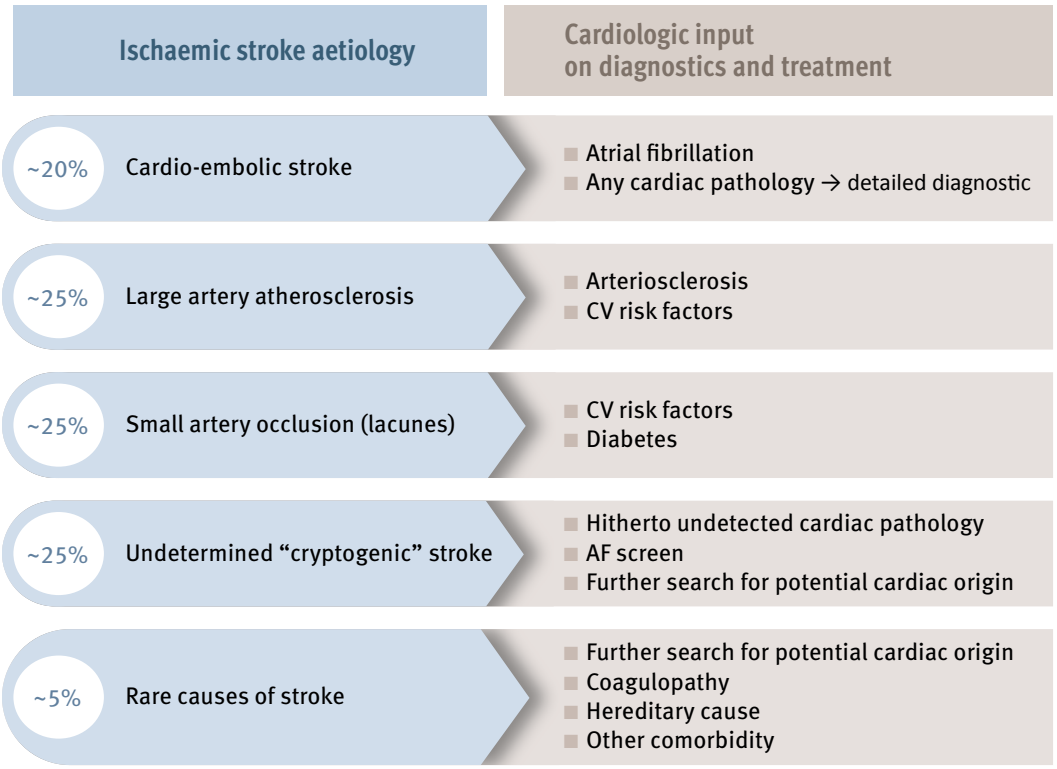
Figure 1



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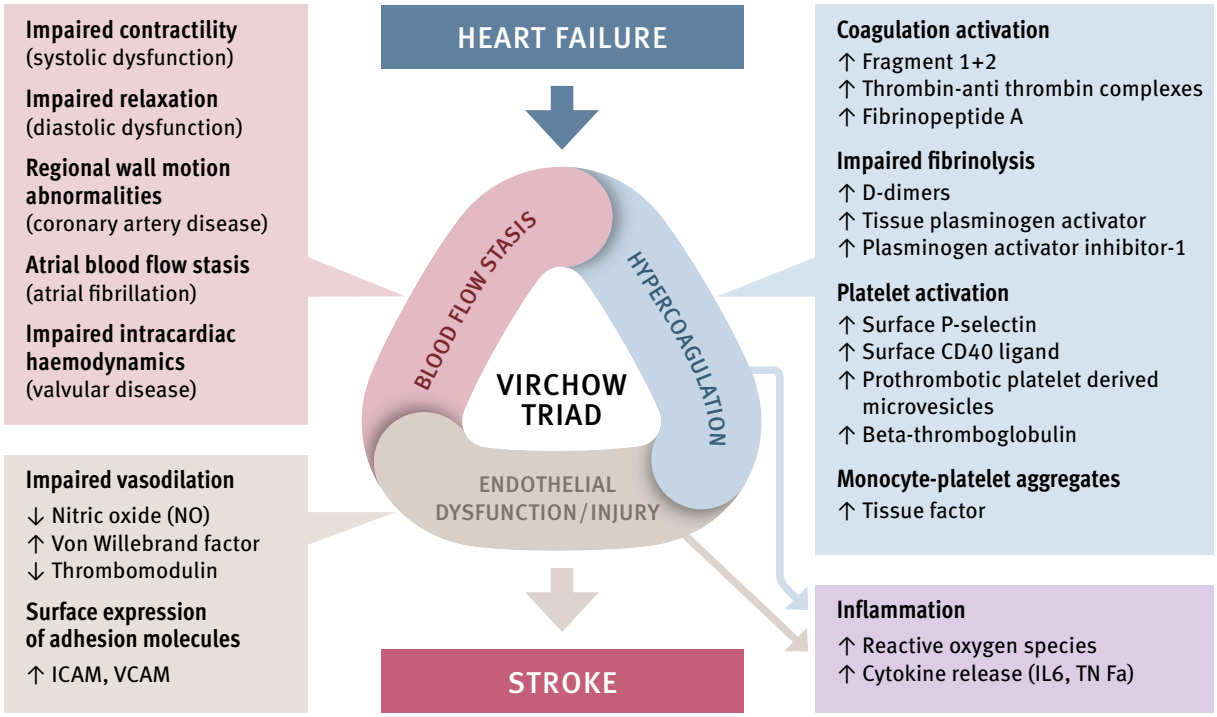

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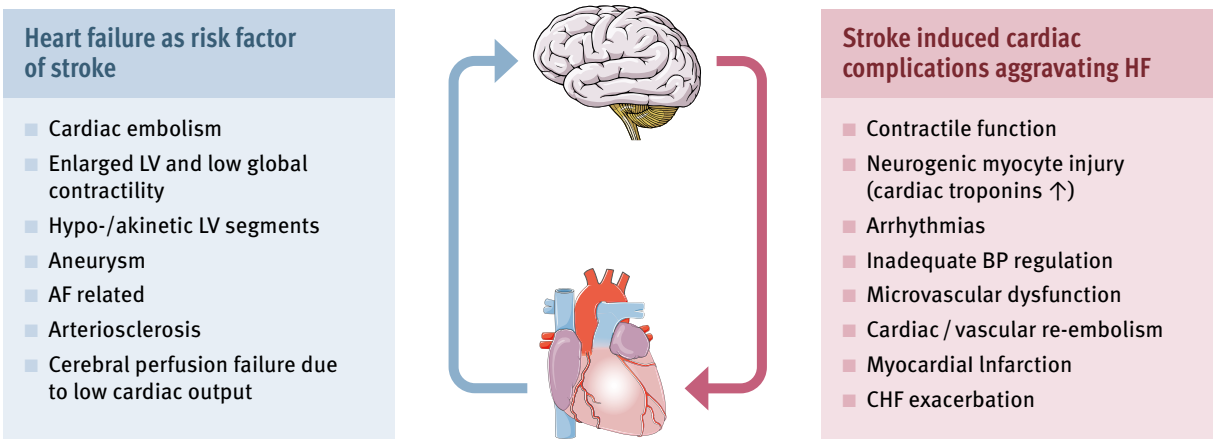

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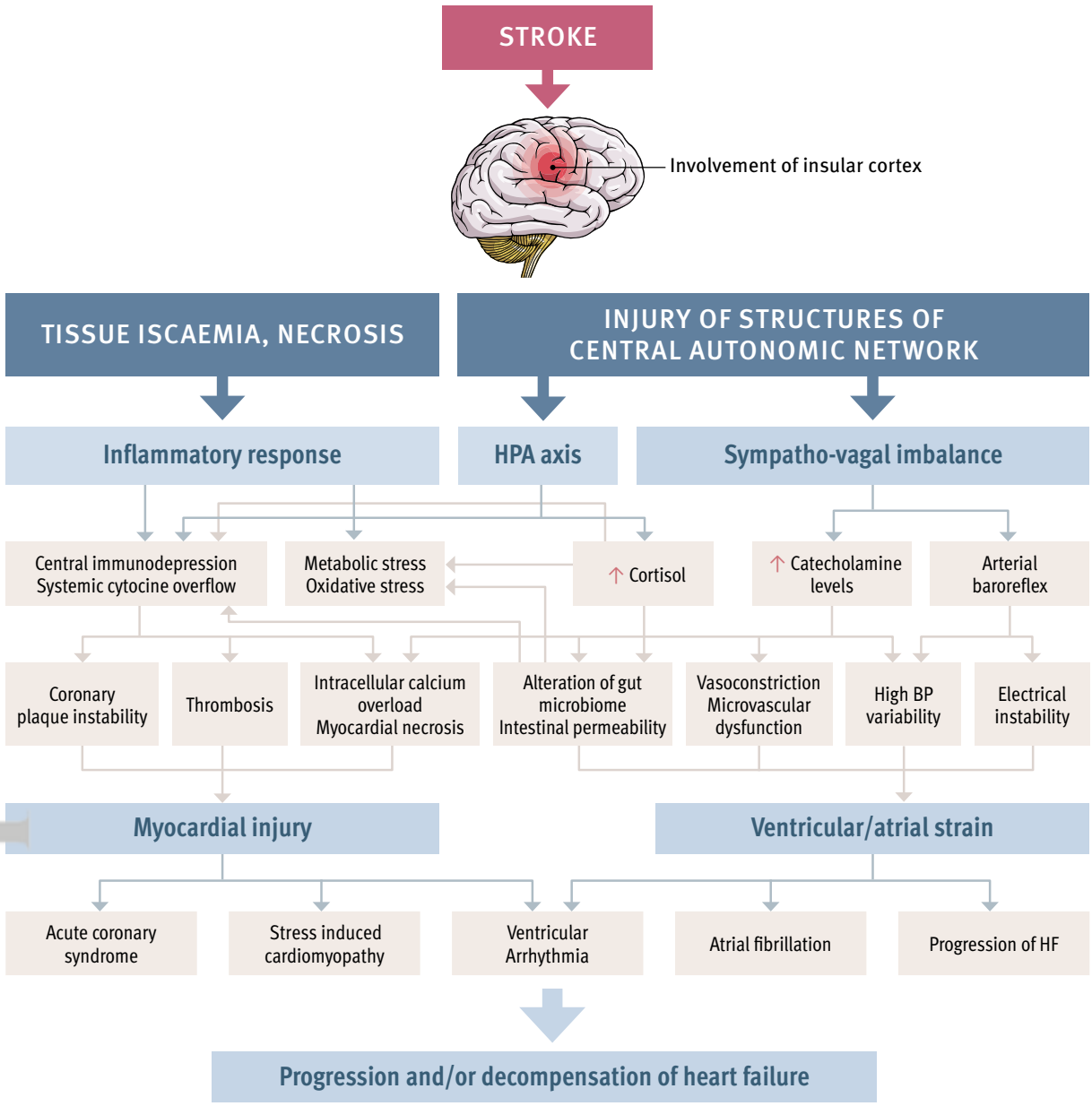

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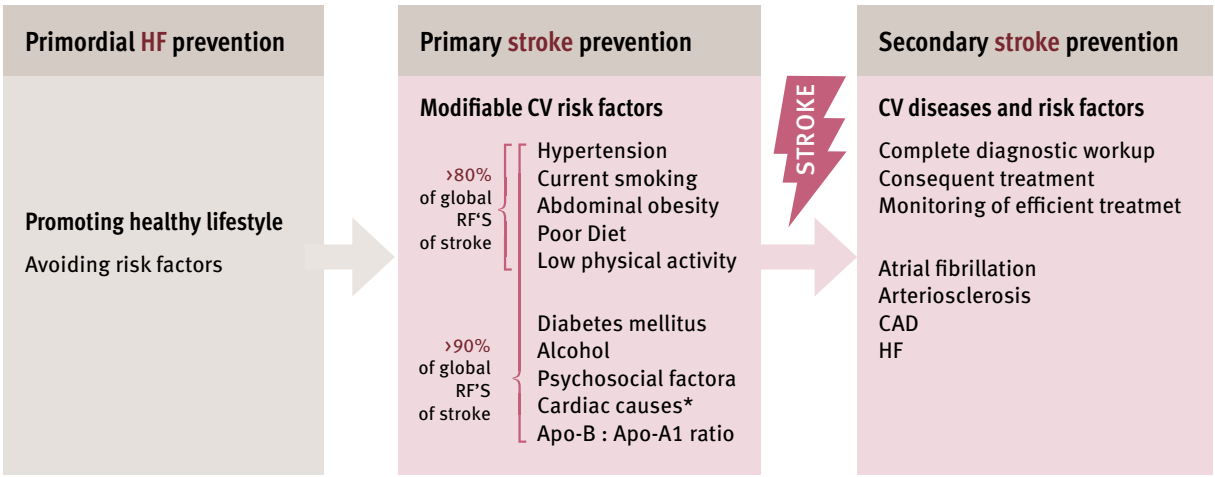

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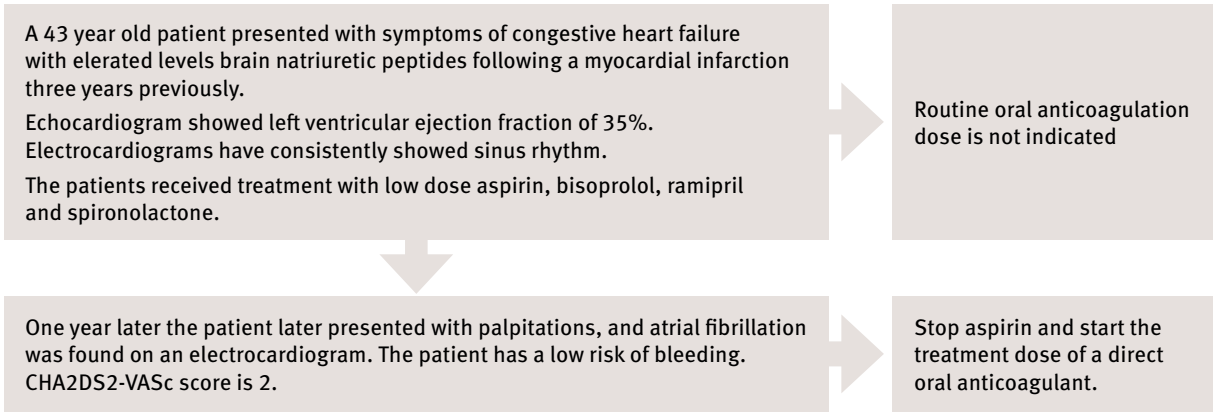

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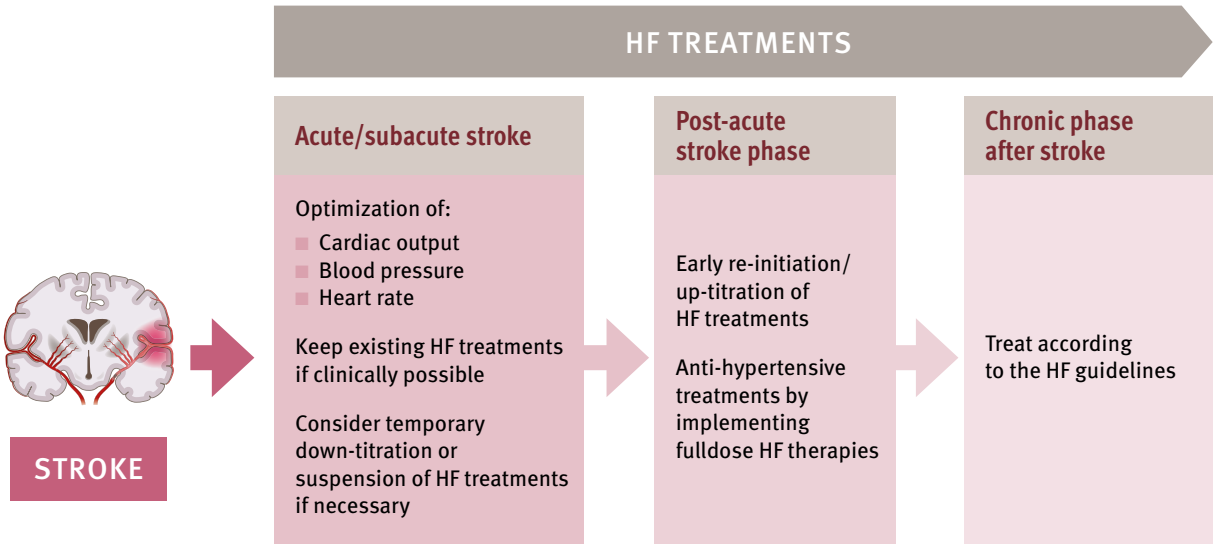

Figure 8: Flowchart of cardiovascular management of stroke patients (1) diagnostic workup, (2) monitoring for CV complications and (3) secondary prevention and subsequent CV management
*as clinically indicated, ECG electrocardiogram, TTE transthoracic echocardiography, TOE transoesophageal echocardiography, CAG coronary angiography, CMR cardiac magnet resonance tomography