

# Relevance of Heart Failure in Prevention, Treatment and Prognosis of Ischemic Stroke



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## ABSTRACT

About 1.2 million people in Germany suffer from heart failure (HF) and HF is present in about 13–29% of all patients with acute ischemic stroke. HF is a risk factor for ischemic stroke and it is accompanied by a comparably high morbidity and mortality after stroke. Only limited data are available regarding the relevance of HF in acute ischemic stroke. The hypothesis has emerged that an acute ischemic stroke may contribute to deterioration and occurrence of heart failure. Stroke prevention by oral anticoagulation is only recommended for HF patients with concomitant atrial fibrillation. This article is based on a selective literature review summarizing the present knowledge as well as current guideline recommendations and provides recommendations for clinical practice.

## Introduction

According to current estimates, about 1.2 million people in Germany suffer from heart failure (HF). According to data from the German Federal Statistical Office, HF was the second most frequent reason for inpatient treatment in Germany with 432 900 patients treated for HF in 2014 [1]. Chronic HF is also associated with a mortality rate of about 50% within 5 years [2] and is ranked fourth as the cause of death in the German mortality statistics of 2014 [3]. Besides HF with a reduced ejection fraction (HFrEF, ejection fraction <40%, “systolic” heart failure) and HF with preserved ejection fraction (HFpEF; ejection fraction ≥50% “diastolic” heart failure) the current European guidelines introduced the category of heart failure with mid-range ejection fraction (HFmrEF, ejection fraction 40–49%) [4]. HF is found in 13–29% of all patients with acute ischemic stroke and is recognized as the most relevant cardiac cause of ischemic stroke besides atrial fibrillation (AF). This article on the relevance of HF for stroke prevention, acute therapy and prognosis after ischemic stroke is based on a selective literature review and previous publications by the authors [5–7].

## Heart Failure as a Risk Factor for Stroke

HF is defined as the inability of the heart to provide the organism with sufficient blood and oxygen to ensure the systemic metabolism at rest and during activity. In addition to impaired left ventricular contractility, HF is associated with a wide range of pathophysiolog-

ic features including increased platelet activation, reduced fibrinolysis, endothelial dysfunction and increased coagulability, which favor cardiac thrombus formation [5]. Thromboembolic etiology is considered the predominant mechanism of stroke in patients with HF. HF-related hypotension may also contribute to the occurrence of border zone infarctions in the presence of relevant arteriosclerosis. Due to overlapping risk factors of HF and ischemic stroke, however, there are also lacunar strokes or strokes due to large-artery atherosclerosis in HF patients with concomitant arterial hypertension and/or diabetes mellitus [8].

In addition to advanced age, arterial hypertension, diabetes mellitus and previous stroke, an impaired left ventricular ejection fraction (LVEF) and concomitant AF have to be considered as risk factors for ischemic stroke in HF patients [6, 9]. AF is detected in 5–50% of all HF patients depending on LVEF [10]. Accordingly, a retrospective evaluation of a national registry-based Danish cohort study demonstrated a correlation between stroke risk in HF patients with the CHA<sub>2</sub>DS<sub>2</sub>-VASc score [11], which is relevant for stroke prevention in AF patients [12]. However, due to the moderate predictive value in HF patients with no AF, the CHA<sub>2</sub>DS<sub>2</sub>-VASc score is of no practical relevance for medication-based stroke prevention in this patient group [4]. A recently published prognostic model to estimate the risk of stroke and mortality in patients with HFrEF used clinical parameters (advanced age, diastolic blood pressure, diabetes mellitus, previous stroke, LVEF) and laboratory parameters (uric acid, hemoglobin) [13]. An increased NT-proBNP

level also correlated with increased stroke risk in the pooled analysis of the CORONA and GISSI-HF studies [9]. According to a meta-analysis, the risk of recurrent stroke is doubled in stroke patients with pre-existing HF (RR 1.96; 95 % CI: 1.49–2.60) [14]. The underlying, mostly prospective (cohort) studies, however, did not have a uniform definition of HF, reducing the significance of the meta-analysis.

Based on present data, HF<sub>rEF</sub> has to be considered as independent risk factor for ischemic stroke increasing the risk 2–3-fold. In addition, the risk of recurrent stroke is apparently doubled in (chronic) HF. Comparable data for HF<sub>m</sub>rEF or HF<sub>p</sub>rEF are not yet available.

## Stroke Prevention in Patients with Heart Failure

In four randomized trials on stroke prevention in patients with HF<sub>rEF</sub> (defined as LVEF < 35 %) and maintained sinus rhythm (WARCEF, WATCH, HELAS and WASH), an annual stroke rate of 0.3–1.4 % was found in patients treated with warfarin, acetylsalicylic acid or clopidogrel. However, trial designs were heterogeneous and the HF cohorts were only partially comparable (for overview: 7, 10). According to a meta-analysis of these four studies, oral anticoagulation with the vitamin-K antagonist (VKA) warfarin reduced the risk of stroke by 41 % (RR 0.59, 95 % CI 0.41–0.85) compared to acetylsalicylic acid. Oral anticoagulation, however, almost doubled the risk of bleeding (RR 2.02, 95 % CI 1.45–2.80) thus canceling the assigned benefit. In addition, there was no difference in mortality, the incidence of myocardial infarction or the rate of hospitalization in this group of patients [15], in which the majority had not suffered from a stroke before enrolment. Further analyses of the WARCEF study showed an increasing risk of (recurrent) stroke in patients with an increasingly reduced LVEF, reaching statistical significance only in patients with LVEF < 15 % [16]. In these patients, there was a trend towards more effective stroke prevention by using acetylsalicylic acid [17]. Due to the low event rates in the WARCEF study, this finding has to be validated in further HF studies. Since no subgroup analyses with regard to the etiology of HF were reported for WARCEF, WATCH, HELAS or WASH, no statement can be made on the importance of HF etiology in stroke prevention.

In the absence of a control group (without a platelet inhibitor or VKA) in all four randomized studies, the importance of platelet inhibitors for primary stroke prevention in HF<sub>rEF</sub> of non-ischemic etiology remains unanswered, and the recently updated guidelines of the European Society of Cardiology (ESC) do not provide a respective recommendation [4]. Primary stroke prevention by means of acetylsalicylic acid intake should therefore be decided upon in each case and should depend on the existing cardiovascular risk profile [18]. So far, there are no published randomized studies on secondary stroke prevention in patients with (chronic) HF.

The randomized double-blind COMMANDER HF trial [19] is ongoing to investigate in patients with HF the efficacy and safety of rivaroxaban (2.5 mg twice daily) compared to placebo with respect to the combined primary endpoint of death, myocardial infarction and stroke. The study will enroll up to 5 000 patients with symptomatic HF and concomitant coronary heart disease (who did not receive oral anticoagulation).

Pre-specified subgroup analyses of the four randomized phase III trials on stroke prevention in non-valvular AF (RE-LY, Rocket-AF, ARISTOTLE and ENGAGE AF-TIMI 48) on the safety and efficacy of non-vitamin K-dependent oral anticoagulants (NOACs) compared to the VKA warfarin showed a similar efficacy and safety profile in patients with and without HF, respectively [20]. However, the definition of HF in these phase III trials varied and (serial) LVEF assessment was not regularly done at baseline or during follow-up [10]. A subgroup analysis of the AVERROES trial demonstrated the superiority of apixaban compared to acetylsalicylic acid in preventing the combined endpoint of stroke and systemic embolism in AF patients with HF (39 % of all study patients) or without HF, respectively. There were no significant differences regarding bleeding complications in both treatment arms [21]. Notably, pre-existing HF was named as a reason to withhold the VKA warfarin in nearly 7 % of the participants in this randomized trial.

The guidelines of the European Society of Cardiology (ESC) for the diagnosis and treatment of HF [4] refer to the ESC guidelines for the management of AF [11], which recommend oral anticoagulation with highest degree of evidence in AF patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score ≥ 2 (for men) and a CHA<sub>2</sub>DS<sub>2</sub>-VASc score ≥ 3 (for women), which is also in line with the ACCF/AHA recommendations of 2013 [22]. Due to the subsequent therapeutic implications and the given prevalence of AF, HF patients should be screened for AF. In accordance with applicable guidelines, ECG screening for AF is recommended in patients above 65 years of age, independent of co-existing HF [11].

Until now, recent data on improved care of HF patients have not demonstrated any benefit in stroke prevention. However, present studies (like TIM-HF, BEAT-HF, CHAMPION, IN-TIME) were not powered for this endpoint. No effective treatment for primary prevention of stroke can be identified in the current studies on HF, even if, for example, the PARADIGM HF study – comparing the neprilysin-inhibitor sacubitril to enalapril – demonstrated reduced mortality and a lower hospitalization rate in sacubitril treated patients with HF<sub>rEF</sub> [23]. Relevant data for stroke prevention regarding the use of cardioverter/defibrillators or left ventricular assist devices are not yet available.

Medical primary prevention of stroke in HF patients should be applied according to the individual cardiovascular risk profile. For secondary stroke prevention in HF, acetylsalicylic acid 100 mg once daily should be given in patients with maintained sinus rhythm, while oral anticoagulation is recommended in HF patients with AF.

## Relevance of Heart Failure for Acute Stroke Treatment

Cohort studies have shown that 13–29 % of all patients with acute stroke have HF<sub>rEF</sub> and about 9 % of all ischemic strokes are caused by HF [24]. The presence of HF is relevant for cerebral perfusion in the acute phase of stroke since cerebral autoregulation can be impaired and cerebral perfusion is linearly correlated to cardiac output and may be insufficient in the presence of HF<sub>rEF</sub>. In general, inconsiderate discontinuation of cardiovascular treatment such as antihypertensive drugs or heart rate lowering drugs (in particular β-blockers) should be avoided. Uncontrolled effects such as a sym-

pathomimetic rebound effect can result in worsening of cardiac function without increasing blood pressure. To date, no randomized study is available focusing on the efficiency of systemic thrombolysis using rt-PA in stroke patients with HF. However, a retrospective analysis of the VISTA database [25] suggests a similar efficiency of systemic thrombolysis in patients with HF as in patients without. Notably, the risk of rt-PA-associated bleeding appears to be approximately doubled in HF patients according to a meta-analysis [26]. In stroke patients undergoing (additional) mechanical recanalization, no subgroup analyses for HF have been published so far. A recent report from the IMS-III study showed a significantly lower baseline degree of collateral vascularization in HF patients, which correlated with clinical outcome [27].

A recent meta-analysis on the efficacy of acetylsalicylic acid in secondary stroke prevention in the acute phase after ischemic stroke [28] did not focus on patients with pre-existing HF. Surprisingly, there are apparently no published data on the efficacy of stroke unit treatment in patients with pre-existing HF, which can be assumed to be likely.

It is worth mentioning that stroke-related damage to certain areas of the brain (such as the insula region) may lead to autonomic dysfunction specifically affecting central control of cardiac function and may therefore promote decompensation of pre-existing HF [29]. There are publications postulating a comparably high prevalence of HFrEF or HFpEF after ischemic stroke, with less than 20% of these patients having a pre-existing HF [30]. The SICFAIL study, which is currently enrolling stroke patients at the University Hospital in Würzburg, will provide further insight on this aspect. A total of 750 stroke patients is planned to be enrolled and followed-up over a period of five years. Patients with HF in the acute phase of stroke will be monitored by echocardiography for 6 months after stroke for the course of HF.

Due to limited data, no HF-specific recommendations can be given for acute stroke treatment, which do not comply with present standard of care. In general, inconsiderate discontinuation of medical treatment of HF should be avoided during the acute phase of stroke.

## Relevance of Heart Failure for Prognosis after Stroke

Previous cohort studies suggest that stroke patients with pre-existing HF have a two- to three-times higher probability to suffer severe stroke compared to patients without HF [7]. Moreover, in the majority of studies mortality has been observed to be 2–2.5-fold higher in patients with HF compared to patients without HF [5, 31]. Notably, in stroke patients with HF, the risk of dying – which is about 80% over a period of five years – is not further increased in the presence of AF [8, 32]. In turn, the presence of a stroke has relevant implications for the prognosis of HF patients. In patients with HFrEF (in the CORONA study) as well as in patients with HFpEF (in the I-Preserve study) mortality after stroke was significantly higher compared to HF patients without stroke or to patients hospitalized due to worsening of HF [33].

The presence and the characteristics of HF are highly relevant for the prognosis after stroke. Therefore, evaluation of present car-

diac function appears to be necessary in patients with acute ischemic stroke. Moreover, attention should be paid to the clinical course of HF. Optimized interdisciplinary care of (stroke) patients with HF is necessary in order to optimize acute therapy and prognosis after stroke.

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