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EDITORIAL

Ischemic stroke and heart failure: facts and numbers

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Abstract

Heart failure (HF) is pandemic in the modern society. Comorbidities of HF come increasingly to the fore in today's patient presentation and demand multidisciplinary treatment concepts. Ischemic stroke is a major comorbidity in HF patients and frequently contributes to the adverse outcome and functional dependency. Patients with HF are two-fold to three-fold more likely to suffer an ischemic stroke, have more than two times higher mortality and show worse functional outcome after stroke compared with non-HF subjects. The risk of recurrent stroke is about two-fold elevated in patients with HF. The risk of stroke increased with time duration of HF from 18 per 100 cases in the first year of HF to 47 per 1000 patients within the next 4-5 years. Moreover, so called 'silent' strokes (clinically asymptomatic brain lesions) are two to four times more likely in HF patients. In turn, 10–24% of stroke patients have HF. Specific characteristics of the interaction between ischemic stroke and HF have been uncovered in recent years. However, gaps in present knowledge need to be addressed in future studies. What are the detailed pathophysiologic links beyond atrial fibrillation, stroke patterns, and time courses in the interaction? What implication has HF with preserved versus reduced ejection fraction? Does treatment of HF prevents ischemic stroke or reduces stroke-related sequelae? This editorial provides a condensed overview on current insights and presents facts and numbers on the interaction between heart failure and ischemic stroke.

Keywords HFrEF; HFpEF; stroke; risk factors; prevalence; TOAST

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Introduction

Heart failure (HF) has a prevalence rate over 23 million per year and belongs to one of the leading causes of mortality and morbidity worldwide.[1] Shifting demographic patterns (ageing populations) and improved acute and chronic medical care account for the increasing numbers of patients with chronic HF, sustaining for extending periods in a state of stable, compensated HF. Long-term complications of HF and multimorbid disease interactions are of increasing importance and demand multidisciplinary concepts. Ischemic stroke is a frequent neurological complication of HF and a significant comorbidity with mutual interaction.

Prevalence, mortality, and morbidity of ischemic stroke in HF

The increased risk of ischemic stroke among HF patients varies widely in the literature due to heterogeneity of the patients' cohorts, study designs, and definition of stroke. In general, a two-fold to three-fold increased risk of stroke for HF patients has recently been summarized.[2] However, within the first 30 days after HF diagnosis, the risk of ischemic stroke was 17-fold increased compared with the general population.[3] The strong association between HF and stroke is underscored in the $CHADS_2$ score and the CHA_2DS_2-VASc score. These scores for risk assessment in patients with Atrial fibrillation (AFib) list heart failure ('C' for congestion) as the first additional factor that increases the risk of stroke.[4]

Heart failure not only increases the risk of stroke incidence, but also mortality and morbidity after stroke are increased in HF compared with non-HF subjects. So literally, this comorbidity adds insult to injury:

A prospective community-based cohort study has shown that patients with stroke after HF had a 2.3 times higher risk of dying than patients without stroke.[3] In turn, a number of retrospective trials showed stroke mortality being two to four times higher if HF as a comorbidity is present.[5–7] Symptomatic status of HF according to the New York Heart Association (NYHA) class was observed as the strongest predictor for survival after

stroke.[8] Patients with HF have significantly worse symptomatic stroke severity according to scores of functional independence (modified Rankin Scale score).[5,9] Indeed, the best predictors of functional dependency 1 year after stroke were HF, stroke severity, and old age.[5] Moreover, ischemic brain lesions with seemingly no apparent consequence, termed as 'silent strokes', are more prevalent in HF patients (20–42%) compared with non-HF (0–12%).[10–13] The debate is ongoing that these brain lesions are not truly 'silent', but rather indicate a subtle and with time progressing deterioration of cognitive and other cerebral functions. Of note, the risk of recurrent stroke is roughly doubled in stroke patients with HF compared with those without HF.[2]

Risk factors of stroke in heart failure

Present knowledge is primarily based on retrospective studies, cohort studies, or post hoc analyses of large clinical trials. The incidence of stroke in patients with HF depends on several factors. The severity of HF has been shown as the most powerful independent risk factor for stroke. Thus, in more severe HF in the Prospective Randomized Milrinone Survival trial (PROMISE trial, median NYHA class 3.4) the incidence of stroke was about three-fold higher compared with patients with mild HF in the Studies of Left Ventricular Dysfunction (SOLVED trial, median NYHA class 1.7). Indeed, a stepwise increase of stroke risk may be observed in parallel to increasing NYHA class and decreasing Left Ventricular Ejection Fraction (LVEF).[14] Moreover, the prospective observational Survival and Ventricular Enlargement trial (SAVE trial) showed an increase of stroke incidence from 4.1% to 8.9% in patients with LVEF $>$35% compared with patients with LVEF $\leq$28%.[15] In addition, the risk of stroke increases with the duration of HF. A previous meta-analysis indicated an incidence of ischemic stroke of 18.4 per 1000 cases during the first year of the HF presence, that increased up to 47.4 per 1000 cases within next 4–5 years of follow-up.[16]

AFib has firmly been established as an independent risk factor for stroke, and clearly, HF patients are prone to develop AFib in the course of the disease. The Framingham Heart study—analysing a cohort of general population over 30 years—revealed that 12% of all stroke cases were related to AFib.[17] A more recent prospective study following patients after the first stroke for 10 years showed that AFib was present in 51% of patients with HF and stroke.[8]

Moreover, arterial hypertension, old age, prior stroke, and diabetes have been identified as additional risk factors for stroke in HF.[18]

Prevention of stroke in patients with HF

The value of anticoagulation in the context of AFib is clearly established regardless of the presence of HF. However, less is known about adequate antithrombotic therapy for stroke prevention in HF patients with maintained sinus rhythm. For decades, clinicians had to decide mostly on empiric grounds between vitamin K antagonists, anti platelet drugs, or no anticoagulant therapy due to the lack of sufficient evidence. Recently, the WARCEF trial, a double-blind randomized multicenter study comparing aspirin 325 mg and warfarin (INR 2.0 to 3.5), tried to answer this pressing question. The complicated design (blinding of anticoagulant therapy) and recruitment problems resulted in prolonged timing (8 years enrolment period) and reduced enrolment numbers. The study revealed no overall difference between warfarin and aspirin regarding the primary outcome (ischemic stroke, hemorrhagic stroke, or death from any cause) in 2305 HF patients with reduced LVEF ($<$35%) and sinus rhythm.[19] A reduced risk of ischemic stroke by taking warfarin was offset by increased risk of major bleedings. A borderline significant benefit of warfarin on the primary outcome was observed only after 4 years. The analysis of two smaller previous randomized controlling trials, Heart failure Long-term Antithrombotic Study 2006 (HELAS) and Warfarin/Aspirin study of Heart Failure 2004 (WASH), demonstrated no benefit of antithrombotic therapy compared with placebo regarding vascular events and mortality in HF patients with sinus rhythm.[20] Accordingly, a position paper of the relevant European Society of Cardiology (ESC) working groups was published that does not support the routine use of warfarin in patients with HF and sustained sinus rhythm. It should be noted that the novel anticoagulants may change the benefit/risk ratio of anticoagulation in HF with sinus rhythm. Respective clinical research is ongoing (ie. COMMANDER HF). There is a need of prospective studies to demonstrate whether optimal treatment of HF prevents ischemic stroke or reduces stroke-related sequelae.

Stroke aetiology in heart failure

Thrombus formation due to AFib or impaired contractility of the left ventricle are the main reasons for ischemic stroke in HF. However, several further mechanisms may be involved, particularly the activation of a range of coagulant factors, thrombocytes, and pro-inflammatory factors.[2] Endothelium dysfunction is a key characteristic of HF also contributing to the classical Virchow Trias of pro-coagulant activation (impaired flow, activation of endothelium and of plasma coagulant factors) with clot formation becoming imminent.

Reduced cerebral blood flow (CBF) may as well contribute to cerebral ischemia, particularly in watershed areas of brain-supplying arteries. Low CBF has been investigated in several studies in HF patients with AFib, in patients with mild to moderate HF, and patients with severe HF (NYHA class III–IV) in association with cognitive impairment.[21–23] Reduced CBF is considered as a causal factor of white matter lesions in the brain.[24–26] Notably, impaired auto-regulation of cerebral vessels after ischemic stroke may increase the impact of low tissue perfusion due to cardiac pumping failure.[27]

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Expectedly, the aetiology of HF impacts on the mechanisms and, hence, the aetiology and clinical patterns of stroke. A recent study analysing 2904 patients with the first-ever ischemic stroke showed variable stroke mechanisms according to HF aetiology.[8] Using the TOAST classification for etiologic categories of stroke,[28] AFib was predominantly associated to cardioembolic events (82%). Also, vascular heart disease and dilated cardiomyopathy were related more to cardioembolism (60% and 67%, respectively). However, HF due to coronary artery disease and hypertension was related to stroke due to large-artery atherosclerosis and lacunar stroke (41% and 62%, respectively).

Ischemic stroke and heart failure with preserved and reduced systolic function

The etiologic entity of HF with preserved EF (HFpEF) has recently gathered much attention, and common and distinct characteristics with HF with reduced EF (HFrEF) have been established.[29,30] About half of the patients with chronic HF are HFpEF patients.[31] Present knowledge is based on very limited evidence from retrospective studies or cohort studies. No difference in stroke prevalence according to the type of HF has been suggested in a cohort of 503 patients with acute ischemic stroke.[9] HFrEF was observed in 10% of the patients and HFpEF in 8% of the patients. Both types of HF have been observed as an independent risk factor for poor outcome at 3 months after acute ischemic stroke. The current Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events trial (ACTIVE trial) included over 3400 patients with HF. This trial showed a similar risk (hazard ration 1.01; 95% confidence interval, 0.78–1.31) of 4.3% and 4.4% per 100 person years for embolic events in non-coagulated patients with HFpEF and in HFrEF, respectively.[18] This is fully in line with a post hoc analysis of the Atrial Fibrillation Follow-up Investigation of Rhythm Management trial (AFFIRM trial).[31] This study demonstrated, despite higher $CHADS_2$ score in HFpEF patients, similar prevalence of ischemic stroke, major bleeding, NYHA progression, and use of antithrombotic therapy in both HF types. A surprising gender discrepancy has been reported in the community-based study in Olmsted county in over 1300 patients with HF.[32] The study of comorbidities of HF revealed similar prevalence of stroke in men with HFpEF and with HFrEF, while in woman, the stroke prevalence was higher in patients with HFpEF than with HFrEF.

Conclusions

Ischemic stroke is a common complication in HF regardless of HFpEF or HFrEF. Cardioembolism is the most frequent mechanism of stroke, but multiple factors like pro-coagulant state, endothelial dysfunction, cerebral hypoperfusion, vascular auto-regulation, and sympathetic activation may contribute to the overall increased risk of ischemic stroke in HF.

The incidence of ischemic stroke in HF depends on the duration and severity of HF, on the cardiac contractile ability, and cardiac rhythm. Stroke-related mortality and morbidity are more severe in HF patients compared with non-HF subjects. Anticoagulation therapy is firmly established in HF patients with AFib; however, in HF with sustained sinus rhythm, vitamin K antagonists cannot be recommended. Whether there is a benefit of novel anticoagulants has to be clarified by adequate clinical trials.

Declaration of interest

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