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Heart failure and the risk of stroke: The Rotterdam Study

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ABSTRACT

Patients with heart failure used to have an increased risk of stroke, but this may have changed with current treatment regimens. We assessed the association between heart failure and the risk of stroke in a population-based cohort that was followed since 1990. The study uses the cohort of the Rotterdam Study and is based on 7546 participants who at baseline (1990-1993) were aged 55 years or over and free from stroke. The associations between heart failure and risk of stroke were assessed using time-dependent Cox proportional hazards models, adjusted for cardiovascular risk factors (smoking, diabetes mellitus, BMI, ankle brachial index, blood pressure, atrial fibrillation, myocardial infarction and relevant medication). At baseline, 233 participants had heart failure. During an average follow-up time of 9.7 years, 1014 persons developed heart failure, and 827 strokes (470 ischemic, 75 hemorrhagic, 282 unclassified) occurred. The risk of ischemic stroke was more than five-fold increased in the first month after diagnosis of heart failure (age and sex adjusted HR 5.79, 95% CI 2.15-15.62), but attenuated over time (age and sex adjusted HR 3.50 [95% CI 1.96-6.25] after 1-6 months and 0.83 [95% CI 0.53-1.29] after 0.5-6 years). Additional adjustment for cardiovascular risk factors only marginally attenuated these risks. In conclusion, the risk of ischemic stroke is strongly increased shortly after the diagnosis of heart failure but returns to normal within 6 months after onset of heart failure.

Key words: Stroke, Heart Failure, Elderly, Cohort Study

INTRODUCTION

Almost one out of three persons of 55-year and over will develop heart failure during their remaining lifespan [1-5]. Because of its high incidence, heart failure may have an important impact on the incidence of other diseases, including stroke.[6]

Previous studies found that the risk of stroke among heart failure patients is almost 7 times higher than in the general population [7-13]. However, most population-based studies were performed before the 1990s when ACE inhibitors were introduced on a large scale. Current guidelines recommend the use of ACE inhibitors in all patients with symptomatic systolic heart failure [14]. The survival rate of heart failure has improved significantly over the past decades, and also the risk of stroke in heart failure patients was higher in studies performed before 1990 than in more recent ones [9, 15]. This makes it hard to extrapolate findings from previous population-based studies to the present day; in addition, most previous studies did not adjust for confounders other than age and sex [8, 11, 12, 16]. In 2006, Witt et al found a 17.4-fold increased risk of stroke in the fist 30 days after heart failure diagnosis, which was reduced to 2.9-fold after five years [16]. This suggests that the risk of stroke varies with time after the diagnosis of heart failure.

We investigated the association between heart failure and the risk of stroke in a large prospective population-based cohort study that started in 1990. To compare our results with previous studies, which almost invariably focused on the short-term prognosis of heart failure, we also wished to investigate the longer term-prognosis of heart failure and assessed the risk of stroke in various time intervals after the diagnosis of heart failure.

METHODS

Population

The present study is part of the Rotterdam Study, a population-based prospective cohort study on chronic and disabling diseases. All inhabitants of Ommoord, a district in the city of Rotterdam in the Netherlands, who were 55 years or older were invited to participate. Of all 10 275 invited subjects, 7983 were entered into the study (78%) [17]. The Medical Ethics Committee of the Erasmus Medical Center approved the study. Baseline examinations, which consisted of a home interview and clinical workup at the research center, were conducted between 1990 and 1993. Subsequently, participants were continuously monitored for major events, including stroke and heart failure, through automated linkage of the study database with files from general practitioners. Information on vital status is obtained regularly from municipal health authorities in Rotterdam. Furthermore, all drug prescriptions dispensed to participants by all pharmacies in the study area are routinely stored in the database. After exclusion of participants who refused informed consent (n=174), participants with missing data (n=20), or who had a stroke before baseline (n=243), 7546 persons were included in this study.

Assessment of heart failure

Prevalent heart failure at baseline was assessed using a validated score, that was based on the heart failure definition of the European Society of Cardiology [18]. More details of the assessment have been described previously [1, 19]. Prevalent heart

failure cases were obtained through a database containing hospital discharge diagnoses from all hospitals in the Rotterdam area as of January 1, 1991 [20]. Furthermore, all medical records were screened in retrospect for the occurrence of heart failure in most (97%) participants of the Rotterdam Study. With these three methods, information on the presence of heart failure at baseline was available for all participants.

Cases of incident heart failure were obtained by continuously monitoring participants of the Rotterdam Study for the occurrence of heart failure during follow-up through automated linkage with files from general practitioners. Also, we used verified hospital discharge diagnoses for case finding, gathered from all hospitals in the Rotterdam area. The date of incident heart failure was defined as the day of the first occurrence of symptoms suggestive of heart failure, obtained from the medical records, or the day of receipt of a first prescription for a loop diuretic or an ACE-inhibitor indicated for treatment of heart failure, whichever came first.

The diagnosis of heart failure was classified as definite, probable, possible, or unlikely. Only definite and probable cases were considered in the analyses. In accordance with the criteria of the European Society of Cardiology, definite heart failure was defined as a combination of heart failure diagnosed by a medical specialist and the presence of typical symptoms of heart failure, such as breathlessness at rest or during exertion, ankle edema, and pulmonary crepitations, confirmed by objective evidence of cardiac dysfunction (chest x-ray, echocardiography) [18]. Probable heart failure was defined as heart failure diagnosed by a general practitioner, with at least 2 typical symptoms suggestive of heart failure, and at least 1 of the following: history of cardiovascular

disease, response to treatment of heart failure, or objective evidence of cardiac dysfunction, whereas symptoms could not be attributed to another underlying disease.

Two research physicians independently classified all information on potential heart failure events. If there was disagreement, a consensus was reached in a separate session. Finally, a cardiologist verified all probable cases, and all cases in which the 2 physicians could not reach consensus. If the cardiologist disagreed with the research physicians, the cardiologist's judgment was considered decisive.

Assessment of stroke

History of stroke at baseline was assessed and verified as described previously [21]. In summary, during the baseline interview, a previous stroke was assessed by asking, "Did you ever suffer from a stroke, diagnosed by a physician?" Medical records of patients who answered yes were checked to verify the diagnosis [22, 23]. Once subjects are enrolled in the Rotterdam Study, they are monitored continuously for major events through automated linkage of the study database with files from general practitioners and the municipality. In addition, nursing home physicians' files are scrutinized. For reported events, additional information (including brain imaging) is obtained from hospitals. Stroke research physicians reviewed information on all possible strokes; an experienced stroke neurologist (P.J.K.) verified all diagnoses.

Ischemic strokes were diagnosed when a patient had typical symptoms and a CT or MRI within 4 weeks that ruled out other diagnoses or when indirect evidence (deficit limited to 1 limb or completely resolved within 72 hours, atrial fibrillation in the absence of anticoagulants) pointed at an ischemic nature of the stroke. Hemorrhagic stroke was

diagnosed when a relevant hemorrhage was shown on CT or MRI. If a stroke did not match any of these criteria, it was classified as unspecified.

Possible confounders

Blood pressure was measured twice in sitting position on the right arm with a random-zero sphygmomanometer. We used the average of these measurements. A single systolic blood pressure reading was taken at both the left and the right posterior tibial arteries with a Doppler ultrasound 8-MHz transducer while the subject was in the supine position. Ankle-Brachial index was calculated by dividing tibial blood pressure by brachial blood pressure. We considered diabetes mellitus to be present if a random or postload glucose level was more than 11.0 mmol/L or if a person used antidiabetic medication. Quetelet body mass index (calculated as weight in kilograms divided by the square of height in meters) was assessed at the research center. During the home interview, smoking status (classified as ever or never) and medication use were assessed. Occurrence of myocardial infarction and atrial fibrillation before baseline and during follow-up was assessed and verified as described previously [24, 25].

Statistical analysis

We calculated hazard ratios with 95% confidence intervals (95% CIs) for the associations between heart failure and the risk of stroke, with Cox proportional hazards models. Hazard ratios were calculated for any stroke, ischemic stroke, and hemorrhagic stroke. Furthermore, we assessed whether the association between heart failure and risk of stroke was different in various time intervals (0 to 30 days, 30 days to 6 months

and 6 months to 5 years) after the diagnosis of heart failure. For the 30 days to 6 months period and 6 months to 5 years period, the time between diagnosis of heart failure and start of the period of interest was not counted as person-time at risk. We only used first-ever strokes. Subjects were censored at the time of death, end of study or, in case of loss to follow-up, at the date last known to be alive. Follow-up was complete for all participants until January 1, 2005, for 97.1 % of potential person years [26].

All hazard ratios were adjusted for age and sex (model A) and additionally for smoking, diabetes mellitus, BMI, ankle-brachial index, systolic blood pressure, use of antihypertensive drugs, use of antithrombotic drugs and for occurrence of atrial fibrillation and myocardial infarction before baseline and during follow-up (model B) [27-31]. Heart failure, systolic blood pressure, BMI, diabetes mellitus, atrial fibrillation and myocardial infarction were entered as time-dependent covariates. We had <1% missings for all variables during the baseline examination except for blood pressure (n=799), ankle brachial index (n=1343) and BMI (n=858). Mean values were imputed to missing values for blood pressure, ankle brachial index and BMI. Analyses were performed using SPSS 11.0.1 for Windows.

RESULTS

At baseline, the median age of the study population was 69 years. Of all 7546 participants, 4596 were female and 233 had heart failure (baseline characteristics are presented in Table 1). During 73147 person years of follow-up, 827 first-ever strokes occurred. Of all strokes, 470 were ischemic, 75 hemorrhagic, and 282 could not be specified. Additionally, 1014 participants developed heart failure.

Participants with heart failure had a higher risk of subsequent stroke than participants without heart failure (table 2) with no significant differences between men and women (P interaction = 0.69). When adjusted for cardiovascular risk factors, this association disappeared (HR 1.07, 95% CI 0.86 to 1.32; model B). For ischemic strokes, the age and sex adjusted hazard ratio was 1.51 (95% CI 1.15 to 1.98), which disappeared after adjustment for possible cardiovascular risk factors (HR 1.02, 95% CI 0.77 to 1.37). In particular the inclusion of atrial fibrillation in model B caused the association to disappear. Heart failure was not associated with the risk of hemorrhagic stroke (age- and sex adjusted HR 1.02, 95% CI 0.49 to 2.16). The risk of stroke was highest in the first 30 days after the diagnosis of heart failure (age- and sex-adjusted HR 4.27 (95% CI 1.90-9.60) for stroke, HR 5.79, (95% CI 2.15 15.62) for ischemic stroke (table 3) and decreased significantly with increasing time since first diagnosis of heart failure: P for interaction between time since diagnosis and heart failure, 0.004 for stroke, and 0.003 for ischemic stroke. The risk remained increased during the first half year after diagnosis of heart failure (table 3), but was no longer increased thereafter. Adjustments for cardiovascular risk factors (model B) modestly attenuated these hazard ratios, and showed a decreased risk of ischemic stroke after 0.5-6 years (age and sex adjusted HR 0.58, 95% CI 0.37-0.92).

DISCUSSION

Men and women with heart failure had a higher risk of stroke than those without heart failure in this population-based cohort study. The risk of stroke was more than four-fold

increased during the month following the diagnosis of heart failure, but had returned to normal by the time people had survived 6 months after the diagnosis of heart failure.

Strengths of our study are its population-based design, the large study population (N=7546), a mean follow-up of approximately 10 years, and the meticulous ascertainment of heart failure and stroke cases. The follow-up of our cohort started in 1990, so after the introduction of current treatment regimens for heart failure. Our stringent stroke monitoring procedures enabled the ascertainment of stroke cases that had not been referred to a hospital and hence would have been missed had we only relied on hospital records, as is the case in many cohort studies. However, since in these non-hospitalized patients neuroimaging was lacking, 34% of all strokes could not be subclassified into ischemic or hemorrhagic. Although we adjusted for potential cardiovascular confounders, residual confounding may remain.

Several previous studies reported an increased risk of stroke shortly after the diagnosis of heart failure [7, 8, 10, 16]. Most of these studies had a short follow-up of several months, did not adjust for confounders other than age and sex or were based on hospitalized patients only [7, 8, 10]. In 2006, a study from Rochester followed 630 persons with incident heart failure for a longer period (median follow-up 4.3 years) and reported a 17.4-fold increased risk of stroke in the first 30 days after heart failure diagnosis, which decreased to 2.9-fold after five years [16]. In line with the earlier studies we found a 4.3-fold increase for the risk of stroke in the first month after diagnosis of heart failure and an almost six-fold increased risk for ischemic stroke in this period, that only slightly attenuated when adjusted for cardiovascular risk factors. However, in our study these increased risks returned to normal within 6 months after

onset of heart failure, and the risk of ischemic stroke was even slightly decreased after 0.5 to 5 years after the diagnosis of heart failure. This is either a chance finding or may possibly be explained by competing risk or medication effect. A possible explanation for the discrepant findings between our study and the study from Rochester is that our patients developed heart failure after 1991 and most of them were treated with ACE inhibitors, whereas the inclusion period of the Rochester study was stretched over 20 years, from 1979 till 1999, and many persons did not receive current standard treatment.

Heart failure may cause stroke through cardioembolism. Due to the increased risk of stroke in heart failure patients, these persons might benefit from antithrombotic treatment, in particular during the first month after heart failure diagnosis. Currently, a large trial is being undertaken to examine the effect of antithrombotic therapy in patients with heart failure, but this trial assesses the 3-to-5 year survival while ignoring the first month after heart failure [32, 33]. With an increased risk of stroke after heart failure, and in particular in the first month after onset of heart failure, our results suggest that this study may miss an important window of opportunity to prevent stroke in persons with recent heart failure.

In conclusion, the risk of stroke is strongly increased in the early phase after the diagnosis of heart failure and attenuates over time. Investigating whether a more rigorous treatment of newly diagnosed heart failure patients may result in a decreased incidence of stroke is warranted.

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TABLE 1. Baseline characteristics of the Study Population (n=7546)

Characteristic	Median (interquartile range) or number (percentage)
Age (years)	69.0 (62.3–76.7)
Female sex	4596 (60.9 %)
Ever smoking	4649 (61.6 %)
Diabetes mellitus	756 (10.0 %)
Body mass index (kg/m²)	26.3 (24.1–28.0)
Systolic blood pressure (mmHg)	139 (125–152)
Ankle brachial index	1.05 (1.00–1.18)
Antihypertensive drug use	2466 (32.7 %)
ACE-inhibitor use	466 (8.5%)
Antithrombotic drug use	369 (4.9 %)
Heart failure (at baseline)	233 (3.1 %)

TABLE 2. Hazard Ratios and 95% CIs for the Associations Between Heart Failure and Risk of Subsequent Stroke.

		Hazard Ratio (95% CI)		
		All stroke	Ischemic stroke	Hemorrhagic stroke
Presence of heart failure		(n=827)	(n=470)	(n=75)
No heart failure (N=6299)		1 (reference)	1 (reference)	1 (reference)
Heart failure (N=1247)	Model A	1.41 (1.15–1.72)	1.51 (1.15–1.98)	1.02 (0.49–2.16)
	Model B	1.07 (0.86–1.32)	1.02 (0.77–1.37)	0.80 (0.37–1.76)

Model A: adjusted for age and sex

Model B: adjusted for age, sex, smoking, diabetes mellitus, BMI, ankle-brachial index, blood pressure, use of antihypertensives, use of antithrombotics, incident and prevalent atrial fibrillation and incident and prevalent myocardial infarction.

TABLE 3. Hazard Ratios and 95% CIs for the Association Between Heart Failure and the Risk of Subsequent Stroke and Ischemic Stroke for Various Time Intervals After the Diagnosis of Heart Failure.

Outcome	Presence of heart failure	Hazard Ratio (95% CI)			
			0 – 30 days	30 days – 6 months	6 months – 5 years
All stroke	No heart failure (N=6299, 749 strokes)		1 (reference)	1 (reference)	1 (reference)
	Heart failure (N=1247, 78 strokes)*	Model A	4.27 (1.90–9.60)	1.94 (1.14–3.31)	0.99 (0.74–1.33)
		Model B	3.59 (1.59–8.10)	1.60 (0.93–2.73)	0.78 (0.58–1.05)
Ischemic stroke	No heart failure (N=6299, 428 ischemic strokes)		1 (reference)	1 (reference)	1 (reference)
	Heart failure (N=1247, 42 ischemic strokes)*	Model A	5.79 (2.15-15.62)	3.50 (1.96-6.25)	0.83 (0.53-1.29)
		Model B	4.60 (1.70-12.49)	2.75 (1.53-4.94)	0.58 (0.37-0.92)

Model A: adjusted for age and sex

Model B: adjusted for age, sex, smoking, diabetes mellitus, BMI, ankle-brachial index, blood pressure, use of antihypertensives, use of antithrombotics, incident and prevalent atrial fibrillation and incident and prevalent myocardial infarction.

* 11 strokes, of which 7 ischemic, occurred between 0 and 30 days after the diagnosis of heart failure, 15 strokes of which 12 ischemic, between 30 days and 6 months, and 52 strokes, of which 23 ischemic, between 6 months and 5 years.