BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-025525
Article Type:	Research
Date Submitted by the Author:	19-Jul-2018
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Keywords:	comorbidity, psychosocial, rehospitalizations, mortality

Heart failure patients with and without a history of stroke: psychosocial, behavioural and clinical outcomes up to three years

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Word Count: 3805

ABSTRACT

Objectives Stroke in heart failure is common with poor prognosis, yet little is known about psychosocial and behavioral outcomes. This study aims to identify differences between patients with heart failure, with and without stroke across psychosocial, behavioral and clinical outcomes.

Design and participants We conducted a secondary analysis of 1023 patients with heart failure (n=1023) enrolled in the Coordinating study evaluating Outcomes of Advising and Counselling in Heart failure (COACH).

Outcomes and measures Depressive symptoms measured by the Centre for Epidemiological Studies Depression Scale; quality of life measured by the Minnesota Living with Heart Failure Questionnaire; self-care measured by the European Heart Failure Self-Care Behaviour Scale; adherence to HF management measured by the Revised Heart Failure Compliance Scale; and readmission for HF, CV- and all-cause hospitalizations at 18-months, and all-cause mortality at 18-months and 3 years.

Results Compared to those without stroke, patients with a history of stroke (10.3%; n=105) had: twice the likelihood of severe depressive symptoms at 12-months post-discharge (*OR*=2.83; 95% CI=1.27-6.28, *p*=0.011); twice the likelihood of poorer quality of life at 12 and 18 months; poorer self-care at 12-months and 18-months (*OR*=2.87, 95% CI=1.61-5.11, *p*=0.001); poorer heart failure management adherence at 12 and 18 months; higher rates of hospitalizations and mortality at 18-months; and higher 3-year all-cause mortality adjusted for age, sex, severity of disease and comorbidities (*HR*=1.43, 95% CI=1.07-1.91, *p*=0.016).

Conclusions Patients with heart failure and stroke have worse psychosocial, behavioural and clinical outcomes, notably from 12-months post-discharge, than those without stroke. Long-term, integrated disease management of heart failure and stroke involving lifestyle and behavioural change is warranted.

Strengths and limitations of this study

- Participants enrolled in a multi-centre (n=17) randomised controlled trial
- Cardiovascular risk data inclusive of psychosocial, behavioural and clinical factors
- Absence of a measure of stroke severity may have impeded interpretation of clinical outcomes
- Limited generalisability due to small proportion of patients with severe heart failure

Heart failure patients with and without a history of stroke: psychosocial, behavioural and clinical outcomes up to three years

INTRODUCTION

Heart failure (HF) is an increasing pandemic characterized by high morbidity, mortality and poor quality of life.[1] Stroke, the second leading global cause of death (11.8%), is a frequent comorbidity in patients with HF.[2] Stroke and HFHF and Stroke commonly coexist because of shared vascular risk factors.[3-4] Furthermore, HF is an established risk factor for cerebral embolism; associated with a 2 to 3-fold increased risk of ischaemic stroke.[5-8] Ultimately, having both HF and stroke contribute to a worse prognosis.

Recent cohort studies highlight the enormity of the issue. One study (n=12,396), found that HF among stroke patients (9.1%) was an independent predictor of death and disability, and hospital readmissions, after stroke at 30 days.[6] Another large-scale (n=1,736,118) 30-year population-based cohort study (of which 16.6% had HF) found HF to be associated with increased short- and long-term risk of all stroke subtypes.[7] In addition, a recent meta-analysis identified HF as a major risk factor for ischaemic stroke with a continuous two-fold increase for risk of ischaemic stroke recurrence.[8] The increasing proportion of patients with heart failure and stroke is highlighted, for example, by a recent Danish HF registry study (n = 210,430) which identified that 13 to 16% of patients with HF seen in HF clinics on a regular basis had a history of stroke.[9]

To date, research has focused on the etiology and pathophysiology of this comorbidity and subsequent management predominantly by anticoagulant and/or antiplatelet therapies.[3,4,8,10] This draws attention to an absence of studies investigating the psychosocial and behavioural characteristics of patients with HF and stroke. Strong evidence exists linking psychosocial factors, such as depression and lack of social support, to adverse outcomes in patients with cardiovascular (CV) disease including stroke[11,12] and HF.[13,14] Subsequently,

psychosocial and behavioural interventions targeting psychological adjustment, social support and lifestyle changes to reduce CV risk have gained much attention.[15-17] Further, attaining optimal levels of ideal cardiovascular health metrics such as smoking status, physical activity, healthy dietary intake, body mass index, and total cholesterol has been shown to prevent up to 80% of CV disease,[18] lower risk of total and CV disease mortality,[19] and lower rates of stroke, incident HF and lifetime risk of HF.[20]

Associations between lifestyle factors and HF and stroke, and their persistent poor prognosis, are well established. However, current evidence is deficient in psychosocial and behavioural comparisons of HF populations with and without stroke across the illness trajectory. Thus, the aim of our study was to identify differences between patients with HF, with and without a history of stroke in psychosocial (depression, wellbeing, quality of life), behavioural (self-care, treatment adherence) and clinical (rehospitalizations, mortality) outcomes at baseline, 6, 12 and 18 months (and mortality up to 3 years).

METHODS

Study patients and trial procedures

Briefly, COACH (Coordinating Study evaluating Outcome of Advising and Counselling in Heart failure) was a multicentre, prospective randomized HF disease management study. Patients who were admitted for HF were enrolled in the COACH study before discharge, and randomised to care as usual or basic or intensive care nurse-led interventions. Inclusion criteria were an admission for HF, evidence of a structural underlying heart disease and age ≥18 years. Exclusion criteria were participation in another study, a planned or recent invasive CV intervention or inability to complete questionnaires. The design and primary results of the COACH study have been described.[21,22] The study was performed in accordance with principles outlined in the Declaration of Helsinki and was approved by a

central medical ethical committee and also by the medical ethics committee in each participating centre. All participants provided informed consent.

Patients were interviewed and their medical record examined to obtain relevant demographic, clinical, psychosocial and behavioural data at baseline (hospital discharge), and at 6, 12 and 18 months thereafter. Additionally, all-cause mortality data were collected at 3 years after hospital discharge.

Data collection

Demographic and clinical data

Basic demographic (e.g. age, gender) and clinical data (e.g. comorbidities, CV risk factors, disease severity) were collated at baseline.

Psychosocial endpoints

Depressive symptoms were measured with the Centre for Epidemiological Studies Depression Scale (CES-D),[23] a 20-item clinically validated self-report questionnaire that assesses depressive symptoms in the general population and the medically ill. Scores range from 0 to 60; higher scores indicate increasing depressive symptoms. Cut-off scores of ≥16 indicating moderate depression and ≥24 for severe depression have been used extensively.[24]

Disease specific quality of life was measured with the Minnesota Living with Heart Failure Questionnaire (MLHFQ),[25] a 21-item self-report questionnaire that assesses patients' perceptions of the effects of their HF on quality of life. Degree of impairment on physical, social, psychological and socioeconomic domains is rated on a 6-point Likert scale from 0 (none) to 5 (very much); higher scores indicate poorer quality of life. A cut-off score of >45 indicates poor quality of life.[26]

Generic quality of life was measured with the Ladder of Life,[27] a 1-item measure of global wellbeing. Individuals are asked to place themselves on an 11-step ladder with 'worst possible life' representing the lowest rung (score = 0) and 'best possible life' the top rung (score = 10). The Ladder of Life has been used in various cardiovascular studies and is considered a valid measure of global well-being.

Behavioural endpoints

Self-care was measured with the European Heart Failure Self-Care Behaviour Scale (EHFScBS-9),[28] a 9-item self-report questionnaire. The nine items are answered on a 5-point Likert scale (1 = completely agree; 5 = completely disagree) and are converted to a standardised score ranging from 0 to 100 with a higher score indicating better self-care.[29] Inadequate self-care behaviour has been identified as a standardised score below 70. A clinically meaningful change is represented by a smallest real difference (SRD) of 5.75 points in EHFScBS-9 scores.[30] One internally consistent subscale can be identified in the EHFScBS, namely 'consulting behaviours'. Consulting behaviours investigate how often people with HF call their doctor/nurse in case of shortness of breath, ankle swelling, weight gain, and fatigue. The EHFScBS-9 has been implemented and validated across numerous countries world-wide.[31]

Adherence to HF management was measured with the Revised Heart Failure Compliance Scale (Evangelista)[32] that assesses adherence in: meeting appointments; taking medication; weighing; diet; fluid intake; and exercise. Items were rated on a 5-point Likert scale (0 = never; 1 = seldom; 2 = half of the time; 3 = mostly; 4 = always). Patients were classified as 'adherent' if they selected 'mostly' or 'always' and were defined as 'overall adherent' if they adhered to at least four of the six behaviours.[33]

Clinical endpoints

Readmission for HF, CV- and all-cause hospitalizations at 18-months, and all-cause mortality at 18-months and 3 years. Data at 18 months were adjudicated by an endpoint committee. Data on all-cause mortality were collected from the hospital registry, general practitioner and/or municipality up to three years for each patient.

Statistical analyses

A preliminary analysis using Chi-square statistic was conducted to identify differences in proportions of HF patients with, and without, stroke across intervention and control groups (care as usual, basic support; intensive support groups). Similar proportions were found across groups. Descriptive values are presented as mean (±SD) for continuous variables or as percentages for categorical variables. Continuous variables were compared between patients with and without a history of stroke at baseline, 6, 12 and 18 months using independent t-test or Mann-Whitney U tests where appropriate with Bonferroni correction to adjust for multiple comparisons (p<0.002).

Variables with a p value less than 0.05 in the analysis comparing patients with and without a history of stroke at baseline were consecutively subjected to a multivariate logistic regression model to assess the independent impact of each risk factor on major or severe depressive status (CES-D≥16 and CES-D≥24). The variables age and gender were chosen apriori as covariates in each model. A variance inflation factor (VIF) was calculated to ensure that two or more explanatory variables included in a multiple logistic regression model were not highly correlated. If two patient characteristics showed high multicollinearity (VIF>3) the least significant variable was excluded from the model. The model was estimated using the stepwise backward method (Wald) with a p value of less than 0.05 to enter and a p value of 0.10 to eliminate variables. This approach was repeated in order to identify significant predictors of: quality of life as measured by the MLHFQ[25] and

Ladder of Life[27], heart failure management adherence as measured by the Revised Heart Failure Compliance scale[32] and self-care behaviour as measured by the EHFScBS.[28]

Self-care subscale standardised scores of the EHFScBS were subjected to repeated measures analysis of covariance (RM-ANCOVA), with scores at baseline, 12 months and 18 months as the dependent variable, heart failure with a history of stroke as the between-subjects factor, and significantly different variables with a *p*-value less than 0.05 at baseline, with the addition of age and gender (chosen apriori) as covariates.

Event rates for clinical endpoints for HF patients with and without a history of stroke were analysed at 18 months for CV, HF and all-cause rehospitalizations (time to rehospitalization), and at 18-months and 3-years for all-cause mortality (time to death), using Kaplan-Meier curves and compared with the log-rank test. Hazard ratios (HRs) and 95% CI were calculated by means of the Cox proportional hazards regression model. The proportional hazard assumption was tested based on Schoenfeld residuals. Variables showing a *p*-value <0.1 derived from the univariate analysis, as well as sex and NYHA functional status, were included in multivariable Cox models. Data were analysed using SPSS version 22.

Patient and Public Involvement

This project involved secondary data analysis and thus did not involve patients. Details on the study design and primary analysis are described elsewhere. [21,22]

RESULTS

Differences in HF patient characteristics with and without stroke

Of the 1023 patients enrolled in the COACH study, 105 (10.3%) had a documented history of stroke. Baseline demographic and clinical (e.g. comorbidities, CV risk factors, disease severity, medications) characteristics are shown in Table 1. Significant differences were

identified for the comorbidities type 2 diabetes, peripheral artery disease and transient ischaemic attack, which were of higher proportion in HF patients with a history of stroke.

Table 1 Baseline characteristics as a function of heart failure and stroke comorbidity

	HF (N=918)	HF + stroke (N=105)	OR (95% CI) *Unadjusted*	*P*-value
Demographics				
Age mdn (IR)	73 (57-89)	75 (63-87)		0.069
Male	569 (62%)	70 (67%)	1.23 (0.80-1.88)	0.348
Married/living together	542 (60%)	63 (61%)	0.97 (0.64-1.46)	0.872
Comorbidities				
Type I & II diabetes mellitus	244 (27%)	45 (43%)	2.07 (1.37-3.13)	**<0.001**
Transient ischaemic attack	59 (6%)	24 (23%)	4.31 (2.55-7.30)	**<0.001**
COPD	238 (26%)	30 (29%)	1.14 (0.73-1.79)	0.559
History of atrial fibrillation	392 (43%)	59 (56%)	1.72 (1.15-2.59)	0.008
Asthma	36 (4%)	5 (5%)	1.23 (0.47-3.19)	0.678
Renal disease	68 (7%)	10 (10%)	1.32 (0.66-2.64)	0.440
Liver disease	23 (3%)	3 (3%)	1.15 (0.34-3.88)	0.828
Gastro-intestinal disease	105 (11%)	16 (15%)	1.39 (0.79-2.46)	0.255
Hypertension	385 (42%)	54 (51%)	1.47 (0.98-2.20)	0.064
Peripheral artery disease	139 (15%)	29 (28%)	2.14 (1.34-3.40)	**0.001**
CV risk factors				
Body Mass Index	27.1±5	26.3±5		0.219
Systolic blood pressure	118.2±21	119.3±19		0.623
Diastolic blood pressure	68.5±12	67.5±11		0.448
Disease severity				
LVEF	33.7±14.3	33.9±15.1		0.930
NYHA classification				0.650
II	465 (51%)	48 (47%)		
III	410 (45%)	51 (49%)		
IV	30 (3%)	4 (4%)		
Previous HF admission	296 (32%)	38 (36%)	1.19 (0.78-1.82)	0.414
Medications				
ACE Inhibitors	673 (73%)	71 (68%)	0.76 (0.49-1.17)	0.215
Angiotensin blockers	110 (12%)	14 (13%)	1.13 (0.62-2.05)	0.688
Beta-blockers	616 (67%)	61 (58%)	0.68 (0.45-1.03)	0.065
Diuretics	878 (96%)	102 (97%)	1.55 (0.47-5.10)	0.468
Coumarin	554 (60%)	71 (68%)	1.37 (0.89-2.11)	0.148
Anti-depressants	65 (7%)	6 (6%)	0.80 (0.34-1.88)	0.602

Nb. Bold *p*-values represent significant alpha after Bonferroni correction (p < .002). COPD, chronic obstructive pulmonary disease; CV, cardiovascular; HF, heart failure; IR, interquartile range; LVEF, left ventricular ejection; mdn, median

Differences in depressive symptoms

Table 2 shows the effect of the adjustment for multiple potential confounding variables (significant baseline characteristics, plus age and gender) on moderate and severe depression (CES-D). History of stroke was the only factor that remained in the model at both 12 and 18 months for risk of depression. This was most notable at the 12-month time-point that had more than a 2-fold increased risk for both moderate (OR=2.29; 95% CI=1.22-4.29) and severe (OR=2.83; 95% CI=1.27-6.28) depression. Only one other factor, type 2 diabetes, was found to have an independent association with depression; moderate depression at 18 months (OR=1.63; 95% CI=1.02-2.61).

Table 2 Predictors of moderate and severe depression in final model of multivariable logistic regression over 18 months.

Predictors in final step of model	OR (95%CI)	*P*-value
Moderate Depression (CES-D ≥16)		
Baseline		
Gender	1.60 (1.22-2.10)	**0.001**
Age	0.99 (0.97-0.99)	**0.037**
History of stroke	1.57 (1.03-2.41)	**0.036**
12-months		
History of stroke	2.29 (1.22-4.29)	**0.010**
18-months		
History of stroke	1.67 (0.92-3.04)	0.095
Comorbid type II diabetes	1.63 (1.02-2.61)	**0.040**
Severe Depression (CES-D ≥24)		
Baseline		
Gender	1.68 (1.22-2.32)	**0.002**
Age	0.98 (0.97-0.99)	**0.010**
12-months		
History of stroke	2.83 (1.27-6.28)	**0.011**
18-months		
Age	0.98 (0.96-1.00)	0.076
History of stroke	2.24 (1.03-4.88)	**0.043**

Nb. Bold *p*-values represent significant alpha, $p<0.05$. Covariates entered in each model: age at index hospitalisation; gender; comorbid transient ischaemic attack; comorbid peripheral arterial disease; comorbid type II diabetes mellitus; history of atrial fibrillation; and history of stroke. CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; SE, standard error; OR, odds ratio

Differences in quality of life

Similar findings to depression were found for both generic and disease specific quality of life, i.e. history of stroke was the only factor that remained in the model at both 12 and 18 months. The 12-month point was found to have the highest increased risk for disease specific (OR=2.80; 95% CI=1.61-4.84) and generic (OR=2.00, 95% CI=1.09-3.50) poor quality of life.

Differences in HF management adherence and HF self-care behaviour

Again, history of stroke was the only factor to show an independent association with inadequate HF management adherence total scores at both 12 (OR=0.39, 95% CI=0.18-0.81) and 18 (OR=0.35, 95% CI=0.17-0.72) month time-points (see Table 3). However, at 18-months comorbid TIA (OR=0.40, 95% CI=0.19-0.78) and history of atrial fibrillation (OR=1.79, 95% CI=1.04-3.07) also significantly increased risk of inadequate HF management adherence.

Also displayed on Table 3 is the consistent association between history of stroke and inadequate HF self-care at all time points that increased over time, e.g. a 1.8-fold increased risk at 12 months (OR=1.80, 95% CI=1.05-3.11), which increased to an almost 3-fold risk at 18 months (OR=2.87, 95% CI=1.61-5.11). Also identified as significant predictors of inadequate HF self-care was age at baseline and 12-months (~1-fold increased risk on both occasions) and comorbid peripheral arterial disease at 18 months (~1.7-fold increased risk).

Table 3 Predictors of inadequate heart failure management adherence and self-care behaviour in final model of logistic multivariable regression over 18 months.

Predictors in final step of model	OR (95% CI)	*P*-value
Inadequate HF management adherence (Evangelista; <3 of 6 behaviours[34])		
Baseline		
History of atrial fibrillation	1.30 (0.99-1.71)	0.060
12-months		
History of stroke	0.39 (0.18-0.81)	**0.012**
18-months		
History of stroke	0.35 (0.17-0.72)	**0.004**
Comorbid TIA	0.40 (0.19-0.78)	**0.008**
History of atrial fibrillation	1.79 (1.04-3.07)	**0.035**
Inadequate self-care behaviour (EHFScB-9; <70[30])		
Baseline		
Age	1.02 (1.01-1.03)	**0.001**
History of stroke	1.49 (0.97-2.29)	0.069
12-months		
Age	1.02 (1.01-1.03)	**0.009**
History of stroke	1.80 (1.05-3.11)	**0.034**
18-months		
History stroke	2.87 (1.61-5.11)	**<0.001**
Comorbid peripheral arterial disease	1.65 (1.05-2.60)	**0.030**

Nb. Bold *p*-values represent significant alpha, $p<0.05$. Covariates entered in each model: age at index hospitalisation; gender; comorbid transient ischaemic attack; comorbid peripheral arterial disease; comorbid type II diabetes mellitus; history of atrial fibrillation; and history of stroke. CI, confidence interval; EHFScB-9, European Heart Failure Self-care Behaviour scale; HF, heart failure; OR, odds ratio; SE, standard error; TIA, transient ischaemic attack

Differences in clinical outcomes

Table 4 shows HF patients with stroke fared worse across all rehospitalizations (HF, CV, all-cause) at 18 months compared to those without stroke; unadjusted hazard ratios indicated greater odds of all rehospitalizations (HF, CV, all-cause) at the 18-month endpoint ranging from 1.6 to 2.0. After adjusting for baseline age, sex, NYHA functional status and significant comorbidities (atrial fibrillation; peripheral artery disease; transient ischaemic attack; type 2 diabetes) HF patients with stroke were up to 1.7 times more likely to be rehospitalized and 1.5 times more likely to experience all-cause mortality than HF patients

without stroke. The odds of all-cause mortality at 18 months and 3 years remained significantly higher in HF patients with stroke compared to those without stroke (Table 4). For example, at 3 years HF patients with stroke had a 43% greater likelihood of dying from all-cause mortality, compared to those without stroke.

Table 4. Rehospitalization and mortality hazard ratios as a function of HF and stroke comorbidity.

	N (%)		Hazard ratio (95% CI) (unadjusted)	*P*-value	Hazard ratio (95% CI) adjusted: age, sex, NYHA, other comorbidities*	*P*-value
	HF (*n*=918)	HF + stroke (*n*=105)				
Clinical endpoints						
18 months post-discharge						
CV rehospitalization	373 (41%)	60 (57%)	1.74 (1.32-2.29)	**<0.001**	1.45 (1.09-1.94)	**0.012**
HF rehospitalization	218 (24%)	42 (40%)	1.99 (1.43-2.78)	**<0.001**	1.66 (1.17-2.36)	**0.005**
All-cause rehospitalization	495 (54%)	72 (69%)	1.57 (1.23-2.02)	**<0.001**	1.31 (1.01-1.70)	**0.044**
HF rehospitalization/ death	344 (38%)	67 (64%)	2.04 (1.57-2.66)	**<0.001**	1.68 (1.27-2.22)	**<0.001**
All-cause mortality	230 (25%)	42 (40%)	1.78 (1.28-2.48)	**<0.001**	1.46 (1.03-2.07)	**0.033**
3years post-discharge						
All-cause mortality	354 (39%)	59 (56%)	1.75 (1.33-2.31)	**<0.001**	1.43 (1.07-1.91)	**0.016**

Nb. *other comorbidities; Type 2 diabetes mellitus, transient ischemia attack, peripheral artery disease, history of atrial fibrillation. CI, confidence interval; CV, cardiovascular; HF, heart failure; NYHA, New York Heart Association

Figure 1 confirms significant differences between HF patients with and without stroke for days post-discharge to: CV, HF, and all-cause rehospitalizations up to 18-months; and all-cause mortality up to 3 years. Kaplan-Meier survival curves demonstrate HF patients with stroke fared worse than HF patients without stroke across all clinical outcomes. Compared to those without stroke, rehospitalizations at 18 months for patients with a history of stroke were on average: 84 days earlier for CV rehospitalizations (mean 310 days, 95% CI 265-355; mean 394 days, 95% CI 380-408); 61 days earlier for HF rehospitalizations (mean 404 days, 95% CI 363-444; mean 465 days, 95% CI 453-477); and 78 days earlier for all-cause

rehospitalizations (mean 261 days, 95%CI 218-304; mean 339 days, 95% CI 324-354). In regard to all-cause mortality, over the three years post-discharge HF patients with stroke died 167 days earlier (mean 702 days, 95% CI 615-788) than HF patients without stroke (mean 859 days, 95% CI 833-884), and had a median survival time of 99 days less.

Place Figure 1 about here

DISCUSSION

Overall, this secondary analysis of the COACH data revealed that HF patients with a history of stroke had greater and more complex needs as evidenced by more comorbidities, poorer psychosocial and behavioural outcomes, and increased risk and earlier rehospitalizations and mortality than HF patients without stroke. More specifically, HF patients with stroke demonstrated: a two-fold likelihood of being depressed; poorer HF management adherence; clinically meaningful differences in self-care; and almost twice the likelihood of earlier rehospitalizations and all-cause mortality after adjusting for demographics and comorbidities. Differences between the two groups across outcomes tended to exacerbate over time, most notably increasing from 12-months post-discharge, identifying this as a critical point of patient decline that necessitates early psychosocial intervention.

Comorbidities such as diabetes and peripheral artery disease greatly increase the physical and mental burden already experienced by HF patients with and without stroke.[17] In keeping with previous studies, our findings identified a higher prevalence of type 2 diabetes, peripheral artery disease and transient ischaemic attack in patients with HF and history of stroke.[34] Overall, patients were not severely impaired (96% had a NYHA classification of II or III; LVEF = 34%) with no differences noted between HF patients with and without stroke; these findings most likely the result of initial assessments for eligibility to participate in the

COACH study.[21] In populations experiencing more severe HF the likelihood is that they may experience even more severe outcomes.

Several meta-analyses have identified depression occurring as frequently as one in every three stroke patients.[17] In HF populations this estimate is known to be far greater.[14] Additionally, levels of depression are also known to increase alongside the number of comorbities.[11,17] This study serves to build on the evidence in this area, noting the proportion of patients with depressive symptoms (at baseline) was 38% for patients with HF, and 48% of all patients with comorbid HF and stroke. Significant differences between the two groups were present at baseline and 12-months post-discharge for both moderate (CES-D ≥ 16) and severe (CES-D ≥ 24) levels of depressive symptoms. This finding is aligned with a recent meta-analysis of 61 studies that identified depression being present in 33% of patients 12-months post-stroke, with a decline beyond 12-months.[12] In our study, there was almost a 3-fold likelihood of HF patients with a history of stroke having severe depressive symptoms at 12 months, which only reduced to over a 2-fold likelihood at 18 months. With its associated poor treatment adherence, lack of energy and motivation and social withdrawal,[11-13] sustained levels of depressive symptoms among HF patients with stroke draw attention to the vulnerability of this population and the need for screening, referral and engagement in evidence-based strategies to reduce depression. Although depression is known to increase the likelihood of mortality in HF[13,14] and stroke[11,17] populations, in the current study mortality rates did not differ for those with severe depressive symptoms, between HF patients with and without stroke. One possible explanation may be due to the low levels disease severity recorded across the two groups, as was the case in a recent population-based cohort study (n=204,523); depression was found to be an adverse prognostic factor for death in patients with severe LVEF dysfunction, but not in other patients with HF.[13]

Much evidence has attested to the negative impact of chronic disease on quality of life. For various reasons, inclusive of being more symptomatic and disabling, HF and stroke are commonly found to have the greatest impact on quality of life.[35] Thus, comorbidity of HF and stroke would likely augment any such impact, which was demonstrated in our study across both disease specific and generic quality of life. Similar to our findings on depression, patients with comorbid HF and stroke fared worse across both measures of quality of life at 12 and 18--months post discharge. This finding also aligns with previous studies of cardiovascular populations indicating the degree of the decrement in quality of life is often proportional to the severity of depressive symptoms.[35] The continuation of poorer physical quality of life at 18-months also supports findings in the current study, and of previous studies, of poor clinical outcomes e.g. increased rehospitalizations for this patient population.[6-9] In light of the poor prognosis of patients with comorbid HF and stroke, where symptoms can at best be controlled rather than cured, efforts to maintain and improve quality of life should be considered a primary goal in their disease management.

Achieving optimal self-care by HF patients is widely recognized as essential in the comprehensive disease management of their condition.[1,32,36] However, HF self-care behaviour is acknowledged as complicated due to ageing, comorbidities, cognitive impairment, frailty and limited social support.[36] The findings of our study demonstrate the difficulty of maintaining adequate HF self-care and management adherence. Patients with comorbid HF and stroke had poorer engagement in HF self-care and adherence to management from 12-months post-discharge, compared to those without stroke. Importantly, differences between the two groups in HF self-care reached that of clinical significance.[30] Essentially, this may be explained due to the nature of both HF and stroke being burdensome and progressive,[3,7] subsequently having both requires more intensive support. Also, patients with HF, compared to those without, had significantly more

comorbidities, a known barrier to successful engagement in self-care.[36] In view of these findings, and the extent of poor HF self-care and adherence to management found in the present study, interventions which focus on specific self-care behaviours may be more effective than general educational programs for patients dealing with burdensome comorbidities.

In regard to clinical outcomes, our findings of approximately twice the increased risk of hospitalization and mortality in HF patients with stroke concur with other studies demonstrating decreased odds of survival. [5,6-8] For example, a prospective four-year community-based cohort study showed that patients with stroke after HF had a 2.3 times higher risk of dying than patients without stroke.[5] Similarly, in a cohort of study of stroke patients the odds of dying within 30 days and 1 year since stroke diagnosis, was close to two times greater in patients who had pre-existing HF.[6] Additionally, in our study, comorbid HF and stroke was identified as a predictor of rehospitalizations at 18-months and all-cause mortality up to 3 years independent of age, gender, HF functional status, and presence of other comorbidities such as peripheral artery disease, transient ischmic attack and type 2 diabetes. Also identified, was that patients with both conditions were rehospitalized up to 84 days earlier and died an average of 5 months earlier, compared to those without stroke.

The findings of this study not only draw attention to the poor prognosis of patients with HF and stroke, they provide a more comprehensive understanding than was previously available by including psychosocial and behavioural factors. Unfortunately, these findings have attested to a culmination of adverse outcomes for patients with comorbid HF and stroke, which diminish the likelihood of successful functional recovery and long-term outcomes. Large-scale prospective studies are needed that focus on support strategies and lifestyle changes that can be implemented across the patient trajectory. Patient care and

education should encompass physical and mental functionality to help in dealing with the long-term consequences of this comorbidity. Consideration should also be given to psychosocial assessment for screening and ongoing monitoring of patients with comorbid HF and stroke.

Limitations

This secondary analysis of COACH data must be interpreted with caution. It should be noted that preliminary analysis identified no significant differences between proportions of HF patients with and without stroke across intervention and control groups. However, our study was limited in by the lack of patients with severe HF, which may have caused a bias. Additionally, the absence of a measure of stroke severity, a known predictor of functional dependency,[34] may have impeded our interpretation of clinical outcomes. Lastly, although clinical interview, the gold standard, was not used to diagnose depression, presence of depressive symptoms was assessed via the CES-D which has been well-validated, in both HF and stroke populations,[24] to identify patients who are at high risk of developing a depressive disorder.

Conclusions

To our knowledge, this is the first study to examine psychosocial, behavioural and clinical outcomes in HF patients with stroke compared to those without stroke. These findings not only add to the evidence-base establishing poor prognosis in HF patients with stroke, they have identified that: depression is more common; quality of life, HF self-care and HF management adherence are poorer; and risk of rehospitalization and mortality were greater in patients with comorbid HF and stroke. Further, 12 months post-discharge was identified as a point of heightened vulnerability for those experiencing this comorbidity that necessitates long-term disease management plans which integrate CV risk, psychosocial and

behavioural factors. This study has highlighted the clinical relevance of the complex interplay between HF and stroke that demands further investigation, and has reminded us of the importance of treating the 'whole' patient. Future management of patients with comorbid HF and stroke should be directed toward interdisciplinary models of care in hospital and at home.

Acknowledgements

None.

Competing interests

None declared.

Funding statement

The COACH study was supported by a program grant from the Netherlands Heart Foundation (grant 2000Z003); D.J.v.V. is a Clinical Established Investigator of the Netherlands Heart Foundation (grant D97.017)

Data sharing statement

The data that supports the findings of this study are available, on reasonable request, from the corresponding author.

Author contributions

CFS, TJ, DRT and MLG conceived, designed the study and drafted the manuscript. MLG, CFS, TJ and DJV analyzed and guided interpretation of data. MHLW, ILL, SM, JC critically advised on important intellectual content and contributed to drafting of the manuscript. All authors read and approved the manuscript. All authors approved the final version to be published. CFS and TJ are responsible for overall content as guarantors accountable to all aspects of the work.

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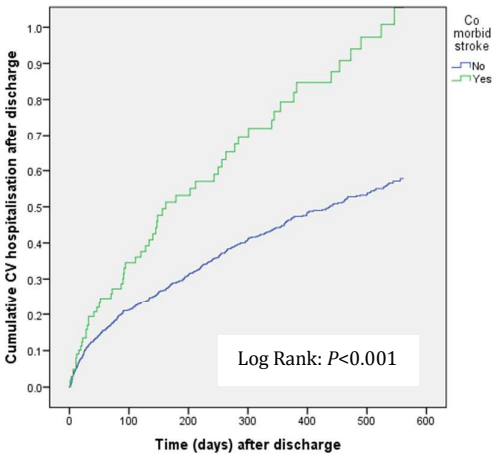
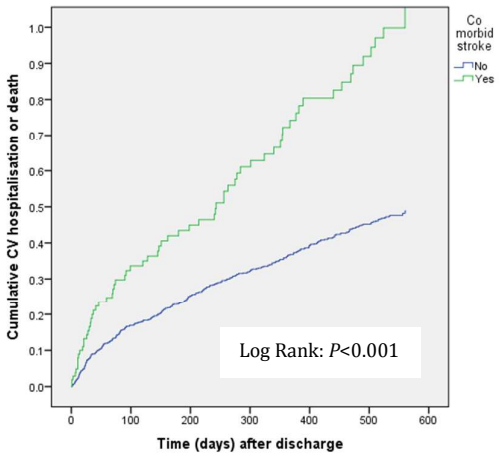
A. CV rehospitalisation by 18 months



Number at risk

Without Stroke	918	632	553	102
With Stroke	105	53	38	6

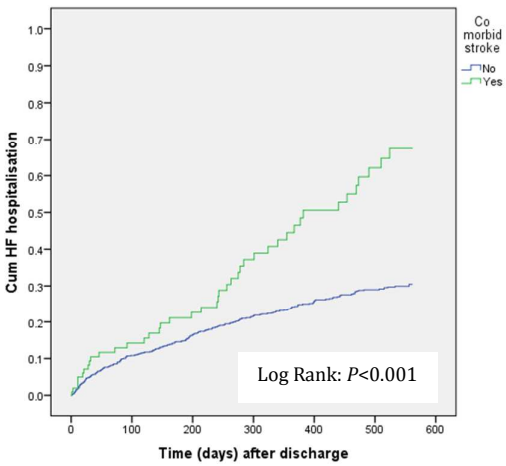
B. All-cause rehospitalisation by 18 months



Number at risk

Without Stroke	918	557	432	71
With Stroke	105	38	30	5

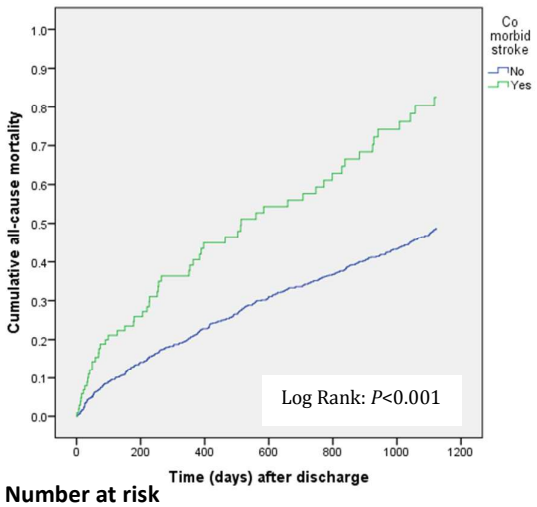
C. HF rehospitalisation by 18 months



Number at risk

Without Stroke	918	718	623	133
With Stroke	105	68	50	10

D. All-cause mortality by 3 years



Number at risk

Without Stroke	918	744	650	563
With Stroke	105	70	59	45

Figure 1. Kaplan–Meier event curves for HF patients with (n=105) and without (n=918) stroke across (A) CV rehospitalisation by 18 months, (B) HF rehospitalisation by 18 months, (C) CV rehospitalisation or death by 18 months, and (D) all-cause mortality by 3 years as a function of HF and stroke comorbidity. Kaplan-Meier curves represent a comparison of HF patients with (green) and without (blue) stroke, for days to rehospitalisation (A; B; C) or to death (D). Kaplan-Meier curves identified HF patients with stroke as significantly ($p < 0.001$) worse than HF patients without stroke across all clinical outcomes.

BMJ Open

Heart failure patients with and without a history of stoke in the Netherlands: secondary analysis of psychosocial, behavioural and clinical outcomes up to three years

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-025525.R1
Article Type:	Research
Date Submitted by the Author:	05-Mar-2019
Complete List of Authors:	Ski, Chantal; Queen's University, Belfast, School of Nursing and Midwifery van der Wal, Martje H.L; Linkopings universitet, Le Grande , Michael; Australian Centre for Heart Health van Veldhuisen, Dirk; University of Groningen, Groningen, The Netherlands Lesman-Leegte, Ivonne; University Medical Center Groningen, Epidemiology Thompson, David; Queen's University Belfast School of Medicine Dentistry and Biomedical Sciences, Nursing and Midwifery Middleton, Sandy; Nursing Research Institute, St Vincent's Health Australia (Syd) and Australian Catholic Univeristy, Cameron, Jan; Australian Centre for Heart Health Jaarsma, Tiny; of Health Sciences Linköping University, Department of Social and Welfare Studies
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	comorbidity, psychosocial, rehospitalizations, mortality, Heart failure < CARDIOLOGY, Stroke < NEUROLOGY

Heart failure patients with and without a history of stoke in the Netherlands: secondary analysis of psychosocial, behavioural and clinical outcomes up to three years

Short title: Heart failure patients with and without stroke

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ABSTRACT

Objective To identify differences between patients with heart failure (HF), with and without stroke across psychosocial, behavioural and clinical outcomes.

Design and participants A secondary analysis of 1023 patients with heart failure enrolled in the Coordinating study evaluating Outcomes of Advising and Counselling in Heart failure (COACH).

Setting Seventeen hospitals located across the Netherlands

Outcomes measures Depressive symptoms measured by the Centre for Epidemiological Studies Depression Scale; quality of life measured by the Minnesota Living with Heart Failure Questionnaire and Ladder of Life Scale; self-care measured by the European Heart Failure Self-Care Behaviour Scale; adherence to HF management measured by a modified version of the Heart Failure Compliance Questionnaire; and readmission for HF, cardiovascular- and all-cause hospitalizations at 18 months, and all-cause mortality at 18 months and 3 years.

Results Compared to those without stroke, HF patients with a history of stroke (10.3%; n=105) had: twice the likelihood of severe depressive symptoms at 12 months (*OR*=2.83; 95% CI=1.27-6.28, *p*=0.011); twice the likelihood of poorer quality of life at 12 and 18 months; poorer self-care at 12 and 18 months (*OR*=2.87, 95% CI=1.61-5.11, *p*=0.001); poorer HF management adherence at 12 and 18 months; higher rates of hospitalizations and mortality at 18 months; and higher all-cause mortality, adjusted for age, sex, severity of disease and comorbidities, at 3 years (*HR*=1.43, 95% CI=1.07-1.91, *p*=0.016).

Conclusions: Patients with HF and stroke have worse psychosocial, behavioural and clinical outcomes, notably from 12 months post-discharge, than those without stroke. Long-term, integrated disease management of HF and stroke involving lifestyle and behavioural change is warranted.

Key words: Comorbidity; psychosocial; rehospitalizations; mortality

Strengths and limitations of this study

- One of the largest multicentre (n=17) randomised controlled trials on disease management of HF patients
- Cardiovascular risk data inclusive of psychosocial, behavioural and clinical factors
- Absence of a measure of stroke severity may have impeded interpretation of clinical outcomes
- Limited generalisability due to small proportion of patients with severe heart failure

INTRODUCTION

Heart failure (HF) is an increasing pandemic characterized by high morbidity, mortality and poor quality of life.[1] Stroke, the second leading global cause of death (11.8%), is a frequent comorbidity in patients with HF.[2] Stroke and HF commonly coexist because of shared vascular risk factors.[3-4] Furthermore, HF is an established risk factor for cerebral embolism; associated with a 2- to 3-fold increased risk of ischemic stroke.[5-8] Ultimately, having both HF and stroke contributes to a worse prognosis.

Of recent cohort studies, one found that HF among stroke patients was an independent predictor of death and disability, and hospital readmissions, after stroke at 30 days,[6] and another found HF to be associated with increased short- and long-term risk of all stroke subtypes.[7] In addition, a recent meta-analysis identified HF as a major risk factor for ischemic stroke with a continuous two-fold increase for risk of ischemic stroke recurrence.[8] Further, a recent HF registry study identified that 13 to 16% of patients with HF seen in HF clinics on a regular basis had a history of stroke.[9]

To date, research has focused on the etiology and pathophysiology of this comorbidity and subsequent management predominantly by anticoagulant and/or antiplatelet therapies.[3,4,8,10] This draws attention to an absence of studies investigating the psychosocial and behavioural characteristics of patients with HF and stroke. Strong evidence exists linking psychosocial factors, such as depression and lack of social support, to adverse outcomes in patients stroke[11,12] and HF.[13,14] Subsequently, psychosocial and behavioural interventions targeting psychological adjustment, social support and lifestyle changes to reduce cardiovascular (CV) risk have gained much attention.[15-17] Further, attaining optimal levels of ideal CV health metrics such as smoking status, physical activity, healthy dietary intake, body mass index, and total cholesterol has been shown to prevent up to 80% of CV disease,[18] lower risk of total and CV disease mortality,[19] and lower rates of stroke, incident HF and

lifetime risk of HF.[20]

Associations between lifestyle factors and HF and stroke, and their persistent poor prognosis, are well established. However, current evidence is deficient in psychosocial and behavioural comparisons of HF populations with and without stroke across the illness trajectory. Thus, the aim of our study was to identify differences between patients with HF, with and without a history of stroke, in psychosocial (depression, wellbeing, quality of life), behavioural (self-care, treatment adherence) and clinical (rehospitalizations, mortality) outcomes at baseline, 6, 12 and 18 months and mortality at3 years.

METHODS

Study patients and trial procedures

COACH (Coordinating Study evaluating Outcome of Advising and Counselling in Heart failure) was a multicentre (17 hospitals in the Netherlands), prospective randomized HF disease management study. COACH was designed to compare basic support and intensive support in patients with chronic HF using blinded end-point evaluation. Patients who were admitted for HF were enrolled in COACH before discharge, and randomised to care as usual or basic or intensive care nurse-led interventions. Inclusion criteria were an admission for HF, evidence of a structural underlying heart disease and age ≥18 years. 'History of stroke' was confirmed by medical records. Only those patients with complete data were included.. The design and primary results of COACH have been described.[21,22] The COACH study was performed in accordance with principles outlined in the Declaration of Helsinki and was approved by a central medical ethical committee, Medical Ethical Committee Groningen (MEtC) 2002/047, and also by the medical ethics committee in each participating centre. All participants provided written informed consent.

Patients were interviewed and medical records were examined to obtain relevant demographic, clinical, psychosocial and behavioural data at baseline (hospital discharge), 6,

12 and 18 months thereafter. Additionally, all-cause mortality data were collected at 3 years.

Data collection

Demographic and clinical data

Basic demographic (e.g. age, gender) and clinical data (e.g. comorbidities, CV risk factors, disease severity) were collected at baseline.

Psychosocial endpoints

Depressive symptoms were measured with the Centre for Epidemiological Studies Depression Scale (CES-D),[23] a 20-item clinically validated self-report questionnaire that assesses depressive symptoms in the general population and the medically ill. Scores range from 0 to 60; higher scores indicate more severe depressive symptoms. Cut-off scores of ≥16 indicating moderate depression and ≥24 for severe depression have been used extensively.[24]

Disease specific quality of life was measured with the Minnesota Living with Heart Failure Questionnaire (MLHFQ),[25] a 21-item self-report questionnaire that assesses patients' perceptions of the effects of their HF on quality of life. Degree of impairment on physical, social, psychological and socioeconomic domains is rated on a 6-point Likert scale from 0 (none) to 5 (very much); higher scores indicate poorer quality of life. A cut-off score of >45 indicates poor quality of life.[26]

Generic quality of life was measured with the Ladder of Life Scale (LLS),[27] a 1-item measure of global wellbeing. Individuals are asked to place themselves on an 11-step ladder with 'worst possible life' representing the lowest rung (score = 0) and 'best possible life' the

top rung (score = 10). The Ladder of Life has been used in various cardiovascular studies and is considered a valid measure of subjective well-being.[28]

Behavioural endpoints

Self-care was measured with the European Heart Failure Self-Care Behaviour Scale (EHFScBS-9),[29] a 9-item self-report questionnaire. The nine items are answered on a 5-point Likert scale (1 = completely agree; 5 = completely disagree) and are converted to a standardised score ranging from 0 to 100 with a higher score indicating better self-care.[30] Inadequate self-care behaviour has been identified as a standardised score below 70. A clinically meaningful change is represented by a smallest real difference (SRD) of 5.75 points in EHFScBS-9 scores.[31] One internally consistent subscale can be identified in the EHFScBS, namely 'consulting behaviours'. Consulting behaviours investigate how often people with HF call their doctor/nurse in case of shortness of breath, ankle swelling, weight gain, and fatigue. The EHFScBS-9 has been implemented and validated across numerous countries world-wide.[32]

Adherence to HF management was measured with a modified version of the Heart Failure Compliance Questionnaire (HFCQ)[33] that assesses adherence in: meeting appointments; taking medication; weighing; diet; fluid intake; and exercise. Items were rated on a 5-point Likert scale (0 = never; 1 = seldom; 2 = half of the time; 3 = mostly; 4 = always). Content validity was established in a HF population (Cronbach's $\alpha = 0.68$).[33] Patients were classified as 'adherent' if they selected 'mostly' or 'always' and were defined as 'overall adherent' if they adhered to at least four of the six behaviours.[34]

Clinical endpoints

Readmission for HF, CV and all-cause hospitalizations at 18 months, and all-cause mortality at 18 months and 3 years. An end-point committee comprising two cardiologists

and a geriatrician adjudicated whether hospitalisations and death were related to HF, cardiovascular death or cardiovascular events.. Data on all-cause mortality were collected from the hospital registry, general practitioner and/or municipality at 3 years for each patient.

Statistical analyses

A preliminary analysis using Chi-square statistic was conducted to identify differences in proportions of HF patients with, and without, stroke across intervention and control groups (care as usual, basic support, intensive support groups). Descriptive values are presented as mean (±SD) for continuous variables or as percentages for categorical variables. Continuous variables were compared between patients with and without a history of stroke at baseline, 6, 12 and 18 months using independent t-test, unequal variances t-test or Mann-Whitney U test where appropriate. A Bonferroni correction was applied to adjust for multiple comparisons across all baseline variables (p<0.002).

Variables with a p value less than 0.05 in the analysis comparing HF patients with and without a history of stroke at baseline were consecutively subjected to a multivariate logistic regression model to assess the independent impact of each risk factor on major or severe depressive status (CES-D≥16 and CES-D≥24). The variables age and gender were chosen *a priori* as covariates in each model. A variance inflation factor (VIF) was calculated to ensure that two or more explanatory variables included in a multiple logistic regression model were not highly correlated. If two patient characteristics showed high multicollinearity (VIF>3) the least significant variable was excluded from the model. The model was estimated using the stepwise backward method (Wald) with a p value of less than 0.05 to enter and a p value of 0.10 to eliminate variables. This approach was repeated

in order to identify significant predictors of: quality of life (MLHFQ[25] and LLS[27]), HF management adherence (HFCQ[33]) and self-care behaviour (EHFScBS[29]).

Self-care subscale standardised scores of the EHFScBS were subjected to repeated measures analysis of covariance (RM-ANCOVA), with scores at baseline, 12 and 18 months as the dependent variable, HF with a history of stroke as the between-subjects factor, and significantly different variables with a *p*-value less than 0.05 at baseline, with the addition of age and gender (chosen a priori) as covariates.

Event rates for clinical endpoints for HF patients with and without stroke were analysed at 18 months for CV, HF and all-cause rehospitalizations (time to rehospitalization), and at 18 months and 3 years for all-cause mortality (time to death), using Kaplan-Meier curves and compared with the log-rank test. Hazard ratios (HRs) and 95% CI were calculated by means of the Cox proportional hazards regression model. The proportional hazard assumption was tested based on Schoenfeld residuals. Variables showing a *p* value <0.1 derived from the univariate analysis, as well as sex and NYHA functional status, were included in multivariable Cox models. A more conservative *p* value was used to avoid overfitting the model. Data were analysed using SPSS version 22. All data collected were part of the original COACH.

Patient and Public Involvement

This project involved secondary data analysis and thus did not involve patients. Details on the study design and primary analysis are described elsewhere.[21,22]

RESULTS

Preliminary analyses

No differences in proportions of HF patients with, and without, stroke across intervention and control groups were identified using Chi-square statistic.

Differences in HF patient characteristics with and without stroke

Of the 1023 patients enrolled in COACH, 105 (10.3%) had a documented history of stroke. Baseline demographic and clinical (e.g. comorbidities, CV risk factors, disease severity, medications) characteristics are shown in Table 1. No significant differences were identified for psychosocial or behavioural variables between HF patients with and without stroke. Significant differences were identified for the comorbidities type 2 diabetes, peripheral artery disease and transient ischemic attack (TIA), which were of higher proportion in HF patients with a history of stroke.

Place Table 1 about here

Differences in depressive symptoms

Table 2 shows the effect of the adjustment for multiple potential confounding variables (significant baseline characteristics, plus age and gender) on moderate and severe depression (CES-D). History of stroke was the only factor that remained in the model at both 12 and 18 months for risk of depression. This was most notable at 12 months with more than a 2-fold increased risk for both moderate (OR=2.29; 95% CI=1.22-4.29) and severe (OR=2.83; 95% CI=1.27-6.28) depression. Only one other factor, type 2 diabetes, was found to have an independent association with depression; moderate depression at 18 months (OR=1.63; 95% CI=1.02-2.61).

Place Table 2 about here

Differences in quality of life

Similar findings to depression were found for both generic and disease specific quality of life, i.e. history of stroke was the only factor that remained in the model at 12 and 18 months. The 12- month point was found to have the highest increased risk for disease-

specific (OR=2.80; 95% CI=1.61-4.84, *p*<0.001) and generic (OR=2.00, 95% CI=1.09-3.50, *p*=0.019) poor quality of life.

Differences in HF management adherence and HF self-care behaviour

Again, history of stroke was the only factor to show an independent association with inadequate HF management adherence total scores at both 12 (OR=0.39, 95% CI=0.18-0.81) and 18 (OR=0.35, 95% CI=0.17-0.72) months (Table 3). However, at 18 months comorbid TIA (OR=0.40, 95% CI=0.19-0.78) and history of atrial fibrillation (OR=1.79, 95% CI=1.04-3.07) also significantly increased risk of inadequate HF management adherence.

Also displayed in Table 3 is the consistent association between history of stroke and inadequate HF self-care at all time points that increased over time, e.g. a 1.8-fold increased risk at 12 months (OR=1.80, 95% CI=1.05-3.11), which increased to an almost 3-fold risk at 18 months (OR=2.87, 95% CI=1.61-5.11). Also identified as significant predictors of inadequate HF self-care was age at baseline and 12 months (~1-fold increased risk on both occasions) and comorbid peripheral arterial disease at 18 months (~1.7-fold increased risk).

Place Table 3 about here

Differences in clinical outcomes

Table 4 shows HF patients with stroke fared worse across all rehospitalizations (HF, CV, all-cause) at 18 months compared to those without stroke; unadjusted hazard ratios indicated greater odds of all rehospitalizations (HF, CV, all-cause) at 18 months ranging from 1.6 to 2.0. After adjusting for baseline age, sex, NYHA functional status and significant comorbidities (atrial fibrillation; peripheral artery disease; TIA; type 2 diabetes) HF patients with stroke were up to 1.7 times more likely to be rehospitalized and 1.5 times more likely to experience all-cause mortality than HF patients without stroke. The odds of all-cause

mortality at 18 months and 3 years remained significantly higher in HF patients with stroke compared to those without stroke (Table 4). For example, at 3 years HF patients with stroke had a 43% greater likelihood of dying from all-cause mortality, compared to those without stroke.

Place Table 4 about here

Figure 1 confirms significant differences between HF patients with and without stroke for days post-discharge to: CV, HF, and all-cause rehospitalizations up to 18 months; and all-cause mortality up to 3 years. Kaplan-Meier survival curves show HF patients with stroke fared worse than those without stroke across all clinical outcomes. Compared to those without stroke, rehospitalizations at 18 months for patients with a history of stroke were on average: 84 days earlier for CV rehospitalizations (mean 310 days, 95% CI 265-355; mean 394 days, 95% CI 380-408, Log Rank 16.48 p <0.001); 61 days earlier for HF rehospitalizations (mean 404 days, 95% CI 363-444; mean 465 days, 95% CI 453-477, Log Rank 17.39 p < 0.001); and 78 days earlier for all-cause rehospitalizations (mean 261 days, 95%CI 218-304; mean 339 days, 95% CI 324-354, Log Rank 13.31 p <0.001). In regard to all-cause mortality, over the three years post-discharge HF patients with stroke died 167 days earlier (mean 702 days, 95% CI 615-788) than HF patients without stroke (mean 859 days, 95% CI 833-884, Log Rank 15.78 p <0.001), and had a median survival time of 99 days less.

Place Figure 1 about here

DISCUSSION

This secondary analysis of COACH data revealed that HF patients with a history of stroke had greater and more complex needs as evidenced by more comorbidities, poorer psychosocial and behavioural outcomes, earlier rehospitalizations and increased CV risk and

mortality than HF patients without stroke. More specifically, HF patients with stroke demonstrated: a two-fold likelihood of being depressed; poorer HF management adherence; clinically meaningful differences in self-care; and almost twice the likelihood of earlier rehospitalizations and all-cause mortality after adjusting for demographics and comorbidities. Differences between the two groups across outcomes tended to exacerbate over time, most notably increasing from 12 months post-discharge, identifying this as a critical point of patient decline that necessitates early psychosocial intervention.

Comorbidities such as diabetes and peripheral artery disease greatly increase the physical and mental burden already experienced by HF patients with and without stroke.[17] In keeping with previous studies, our findings identified a higher prevalence of type 2 diabetes, peripheral artery disease and TIA in patients with HF and history of stroke.[35] Even so it should be noted that in our population, patients were not severely impaired with no differences noted between HF patients with and without stroke. These findings most likely the result of initial assessments for eligibility to participate in COACH.[21] In light of moderate disease severity and poor outcomes across psychosocial, behavioral and clinical factors, the likelihood is that populations with more severe HF may experience even more severe outcomes.

Several meta-analyses have identified depression occurring as frequently as one in every three stroke patients.[17] In HF populations this estimate is known to be far greater.[14] Additionally, levels of depression are also known to increase alongside the number of comorbities.[11,17] In our study, there was almost a 3-fold likelihood of HF patients with a history of stroke having severe depressive symptoms at 12 months, which only reduced to over a 2-fold likelihood at 18 months. With its associated poor treatment adherence, lack of energy and motivation and social withdrawal,[11-13] sustained levels of depressive symptoms

among HF patients with stroke draw attention to the vulnerability of this population and the need for screening, referral and engagement in evidence-based strategies to manage these symptoms. Our findings also demonstrated that comorbid type 2 diabetes were a stronger predictor of more severe depression among HF patients with stroke versus without stroke compared to other factors (e.g. history of atrial fibrillation, hypertension and peripheral artery disease). The reasons for this must remain speculative, though an additional comorbidity such as diabetes seems likely to increase the burden on patients and this may exacerbate depression which is known to be high in patients with diabetes alone. Further studies are warranted to test this association.

People with conditions such as HF and stroke are commonly found to report poor quality of life and wellbeing.[36] Together, HF and stroke would likely augment any such impact, as found in our study. Similar to our findings on depression, patients with HF and stroke fared worse across both measures of quality of life at 12 and 18- months, a finding aligned with previous studies, indicating the degree of the decrement in quality of life is often proportional to the severity of depressive symptoms.[36] The continuation of poor physical quality of life at 18 months may explain increased rehospitalizations for this patient population.[6-9] In light of the poor prognosis of patients with HF and stroke, where symptoms can at best be controlled rather than cured, efforts to maintain and improve quality of life should be considered a primary goal in their disease management.

Achieving optimal self-care by HF patients is widely recognized as essential in their disease management.[1,33,37] However, HF self-care behaviour is complicated due to ageing, comorbidities, cognitive impairment, frailty and limited social support.[37] Our study findings highlight the difficulty of maintaining adequate HF self-care and management adherence. Together with a history of stroke, factors including a history of atrial fibrillation, comorbid

TIA and peripheral artery disease contributed to inadequate HF management and self-care. This is likely due to the additive impact of major disabling conditions contributing to a more burdensome and complex HF management and self-care regimen. This issue needs to be considered carefully when planning with patients and carers how best to address such disease management strategies. Further, patients with HF and stroke had poorer engagement in both HF self-care and adherence to management from 12 months, compared to those without stroke. Importantly, differences between the two groups in HF self-care reached clinical significance according to interpretability of the EHFScBS-9.[31] This may be explained by both HF and stroke being established burdensome conditions,[3,7] both requiring more intensive support. Also, patients with HF and stroke, compared to those without, had significantly more comorbidities, a known barrier to successful self-care.[37] Thus, interventions which focus on prioritising specific self-care for HF and stroke independently may be more effective than general support for patients dealing with burdensome and complex comorbidities.

In regard to clinical outcomes, our findings of approximately twice the increased risk of hospitalization and mortality in HF patients with stroke concur with other studies. [5,6-8] For example, a cohort study showed that patients with stroke after HF had a 2.3 times higher risk of dying than patients without stroke.[5] Similarly, in another cohort study of stroke patients the odds of dying within 30 days and 1 year since stroke diagnosis, was close to two times greater for patients who had pre-existing HF.[6] Additionally, in our study, comorbid HF and stroke was identified as a predictor of rehospitalizations at 18 months and all-cause mortality up to 3 years independent of age, gender, HF functional status, and presence of other comorbidities such as peripheral artery disease, TIA and type 2 diabetes. Also, patients with both conditions were rehospitalized up to 84 days earlier and died an average of 5 months earlier, compared to those without stroke.

Our findings highlight not only poor clinical outcomes for patients with HF and stroke, but also their poor psychosocial and behavioural outcomes. Taken together they indicate a diminished likelihood of early and successful recovery. Studies are needed to examine the efficacy of support strategies and lifestyle changes that can be implemented for this patient group. Patient education and support strategies should encompass physical, mental and social aspects to help address the long-term consequences of this comorbidity. This will depend on a careful individual assessment of need, tailored intervention and systematic evaluation.

Limitations

This was a secondary analysis of COACH data and therefore was constrained to the methods employed in the original study design and methods.21,22 We did not employ additional statistical techniques such as multiple imputation to account for loss to follow up. Although we found no significant differences between proportions of HF patients with and without stroke across intervention and control groups, our study was limited by the lack of patients with severe HF, which may have caused a bias in terms of minimizing the magnitude of the effects on outcome. Also, the absence of a measure of stroke severity, a known predictor of functional dependency,[35] may have impeded our interpretation of clinical outcomes. Lastly, although clinical interview, the gold standard, was not used to diagnose depression, presence of depressive symptoms was assessed via the CES-D which has been well-validated, in both HF and stroke populations,[24] to identify patients who are at high risk of developing a depressive disorder.

Conclusions

To our knowledge, this is the first study to examine psychosocial, behavioural and clinical outcomes in HF patients with stroke compared to those without stroke. These findings not

only confirm the poor prognosis in HF patients with stroke, but also that: depression is more common; quality of life, HF self-care and HF management adherence are poorer; and risk of rehospitalization and mortality are greater in patients with comorbid HF and stroke. Further, 12 months post-discharge was identified as a point of heightened vulnerability for those experiencing this comorbidity that maybe ameliorated by strategies that address CV risk, and psychosocial and behavioural factors. This study highlights the clinical relevance of the complex interplay between HF and stroke that demands further investigation. Future management of patients with comorbid HF and stroke should be directed toward interdisciplinary models of care in hospital and at home.

Acknowledgements

None.

Competing interests

None declared.

Funding statement

The COACH study was supported by a program grant from the Netherlands Heart Foundation (grant 2000Z003); D.J.v.V. is a Clinical Established Investigator of the Netherlands Heart Foundation (grant D97.017)

Data sharing statement

The data that supports the findings of this study are available, on reasonable request, from the corresponding author.

Author contributions

CFS, TJ, DRT and MLG conceived, designed the study and drafted the manuscript. MLG, CFS, TJ and DJV analyzed and guided interpretation of data. MHLW, ILL, SM, JC critically advised on important intellectual content and contributed to drafting of the manuscript. All authors read and approved the manuscript. All authors approved the final version to be published. CFS and TJ are responsible for overall content as guarantors accountable to all aspects of the work.

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Table 1. Baseline characteristics as a function of heart failure and stroke comorbidity

	HF (N=918)	HF + stroke (N=105)	OR (95% CI) *Unadjusted*	*P*-value
Demographics				
Age mdn (IR)	73 (57-89)	75 (63-87)		0.069
Male	569 (62%)	70 (67%)	1.23 (0.80-1.88)	0.348
Married/living together	542 (60%)	63 (61%)	0.97 (0.64-1.46)	0.872
Comorbidities				
Type I diabetes mellitus	94 (10%)	14 (13%)	1.35 (0.74-2.46)	**0.330**
Type II diabetes mellitus	153 (17%)	33 (31%)	2.29 (1.47-3.58)	**<0.001**
Transient ischaemic attack	59 (6%)	24 (23%)	4.31 (2.55-7.30)	**<0.001**
COPD	238 (26%)	30 (29%)	1.14 (0.73-1.79)	0.559
History of atrial fibrillation	392 (43%)	59 (56%)	1.72 (1.15-2.59)	0.008
Asthma	36 (4%)	5 (5%)	1.23 (0.47-3.19)	0.678
Renal disease	68 (7%)	10 (10%)	1.32 (0.66-2.64)	0.440
Liver disease	23 (3%)	3 (3%)	1.15 (0.34-3.88)	0.828
Gastro-intestinal disease	105 (11%)	16 (15%)	1.39 (0.79-2.46)	0.255
Hypertension	385 (42%)	54 (51%)	1.47 (0.98-2.20)	0.064
Peripheral artery disease	139 (15%)	29 (28%)	2.14 (1.34-3.40)	**0.001**
CV risk factors				
Body Mass Index	27.1±5	26.3±5		0.219

Systolic blood pressure	118.2±21	119.3±19		0.623
Diastolic blood pressure	68.5±12	67.5±11		0.448
Disease severity				
LVEF	33.7±14.3	33.9±15.1		0.930
NYHA classification				0.650
II	465 (51%)	48 (47%)		
III	410 (45%)	51 (49%)		
IV	30 (3%)	4 (4%)		
Previous HF admission	296 (32%)	38 (36%)	1.19 (0.78-1.82)	0.414
Medications				
ACE Inhibitors	673 (73%)	71 (68%)	0.76 (0.49-1.17)	0.215
Angiotensin blockers	110 (12%)	14 (13%)	1.13 (0.62-2.05)	0.688
Beta-blockers	616 (67%)	61 (58%)	0.68 (0.45-1.03)	0.065
Diuretics	878 (96%)	102 (97%)	1.55 (0.47-5.10)	0.468
Coumarin	554 (60%)	71 (68%)	1.37 (0.89-2.11)	0.148
Anti-depressants	65 (7%)	6 (6%)	0.80 (0.34-1.88)	0.602

Nb. Bold *p*-values represent significant alpha after Bonferroni correction (p < .002). COPD, chronic obstructive pulmonary disease; CV, cardiovascular; HF, heart failure; IR, interquartile range; LVEF, left ventricular ejection; mdn, median

Table 2. Predictors of moderate and severe depression in final model of multivariable logistic regression over 18 months

Predictors in final step of model	OR (95%CI)	*P*-value
Moderate Depression (CES-D ≥16)		
Baseline		
Gender	1.60 (1.22-2.10)	**0.001**
Age	0.99 (0.97-0.99)	**0.037**
History of stroke	1.57 (1.03-2.41)	**0.036**
12 months		
History of stroke	2.29 (1.22-4.29)	**0.010**
18 months		
History of stroke	1.67 (0.92-3.04)	0.095
Comorbid type II diabetes	1.63 (1.02-2.61)	**0.040**
Severe Depression (CES-D ≥24)		
Baseline		
Gender	1.68 (1.22-2.32)	**0.002**
Age	0.98 (0.97-0.99)	**0.010**
12 months		
History of stroke	2.83 (1.27-6.28)	**0.011**

18 months		
Age	0.98 (0.96-1.00)	0.076
History of stroke	2.24 (1.03-4.88)	**0.043**

Nb. Bold *p*-values represent significant alpha, $p<0.05$. Covariates entered in each model: age at index hospitalisation; gender; comorbid transient ischaemic attack; comorbid peripheral arterial disease; comorbid type II diabetes mellitus; history of atrial fibrillation; and history of stroke. CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; SE, standard error; OR, odds ratio

Table 3. Predictors of inadequate heart failure management adherence and self-care behaviour in final model of logistic multivariable regression over 18 months

Predictors in final step of model	OR (95% CI)	*P*-value
Inadequate HF management adherence (HFCQ; <3 of 6 behaviours[32])		
Baseline		
History of atrial fibrillation	1.30 (0.99-1.71)	0.060
12 months		
History of stroke	0.39 (0.18-0.81)	**0.012**
18 months		
History of stroke	0.35 (0.17-0.72)	**0.004**
Comorbid TIA	0.40 (0.19-0.78)	**0.008**
History of atrial fibrillation	1.79 (1.04-3.07)	**0.035**
Inadequate self-care behaviour (EHFScB-9; <70[30])		
Baseline		
Age	1.02 (1.01-1.03)	**0.001**
History of stroke	1.49 (0.97-2.29)	0.069
12 months		
Age	1.02 (1.01-1.03)	**0.009**
History of stroke	1.80 (1.05-3.11)	**0.034**

18 months		
History stroke	2.87 (1.61-5.11)	**<0.001**
Comorbid peripheral arterial disease	1.65 (1.05-2.60)	**0.030**

Nb. Bold *p*-values represent significant alpha, $p<0.05$. Covariates entered in each model: age at index hospitalisation; gender; comorbid transient ischaemic attack; comorbid peripheral arterial disease; comorbid type II diabetes mellitus; history of atrial fibrillation; and history of stroke. CI, confidence interval; EHFScB-9, European Heart Failure Self-care Behaviour scale; HF, heart failure; HFCQ, Heart Failure Compliance Questionnaire; OR, odds ratio; SE, standard error; TIA, transient ischaemic attack

Table 4. Rehospitalization and mortality hazard ratios as a function of HF and stroke comorbidity

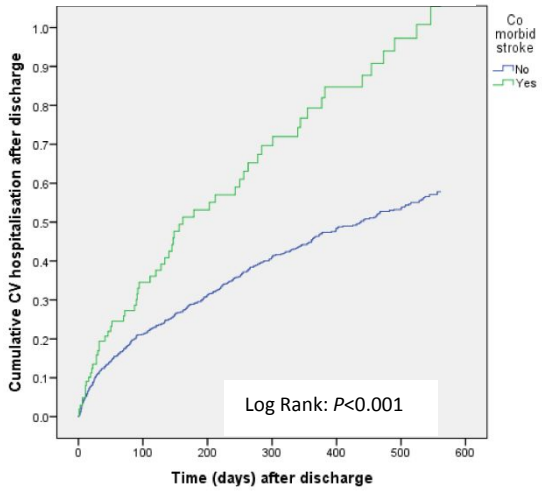
	N (%)		Hazard ratio (95% CI)		Hazard ratio (95% CI) adjusted: age, sex, NYHA, other comorbidities*	
	HF (*n*=918)	HF + stroke (*n*=105)	(unadjusted)	*P*-value		*P*-value
Clinical endpoints						
18 months post-discharge						
CV rehospitalization	373 (41%)	60 (57%)	1.74 (1.32-2.29)	**<0.001**	1.45 (1.09-1.94)	**0.012**
HF rehospitalization	218 (24%)	42 (40%)	1.99 (1.43-2.78)	**<0.001**	1.66 (1.17-2.36)	**0.005**
All-cause rehospitalization	495 (54%)	72 (69%)	1.57 (1.23-2.02)	**<0.001**	1.31 (1.01-1.70)	**0.044**
HF rehospitalization/ death	344 (38%)	67 (64%)	2.04 (1.57-2.66)	**<0.001**	1.68 (1.27-2.22)	**<0.001**
All-cause mortality	230 (25%)	42 (40%)	1.78 (1.28-2.48)	**<0.001**	1.46 (1.03-2.07)	**0.033**
3 years post-discharge						
All-cause mortality	354 (39%)	59 (56%)	1.75 (1.33-2.31)	**<0.001**	1.43 (1.07-1.91)	**0.016**

Nb. *other comorbidities; Type 2 diabetes mellitus, transient ischemia attack, peripheral artery disease, history of atrial fibrillation. CI, confidence interval; CV, cardiovascular; HF, heart failure; NYHA, New York Heart Association

Figure legend

Fig. 1. Kaplan–Meier event curves for HF patients with (n=105) and without (n=918) stroke across **(A)** CV rehospitalisation by 18 months, **(B)** HF rehospitalisation by 18 months, **(C)** CV rehospitalisation or death by 18 months, and **(D)** all-cause mortality by 3 years as a function of HF and stroke comorbidity. Kaplan-Meier curves represent a comparison of HF patients with (green) and without (blue) stroke, for days to rehospitalisation (A; B; C) or to death (D). Kaplan-Meier curves identified HF patients with stroke as significantly ($p < 0.001$) worse than HF patients without stroke across all clinical outcomes. 'Number at risk' columns are in 200 day increments for rehospitalization's, and 400 day increments for mortality.

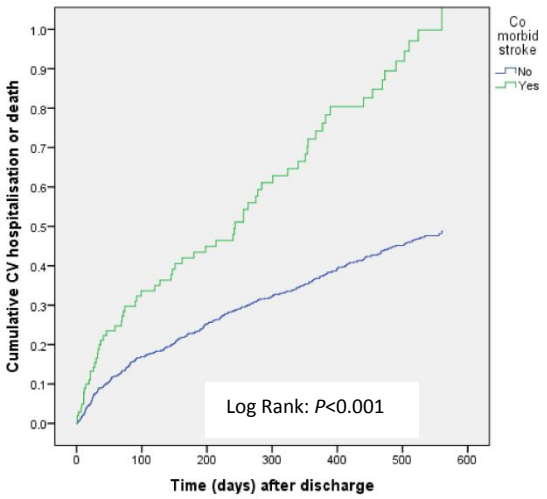
A. CV rehospitalisation by 18 months



Number at risk

Without Stroke	918	632	553	102
With Stroke	105	53	38	6

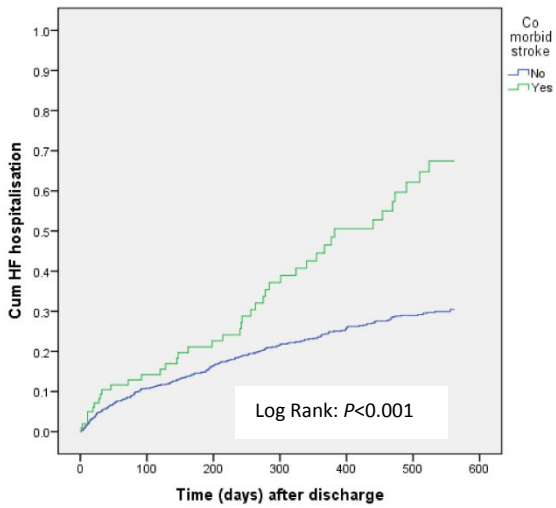
B. All-cause rehospitalisation by 18 months



Number at risk

Wit				
Wit				

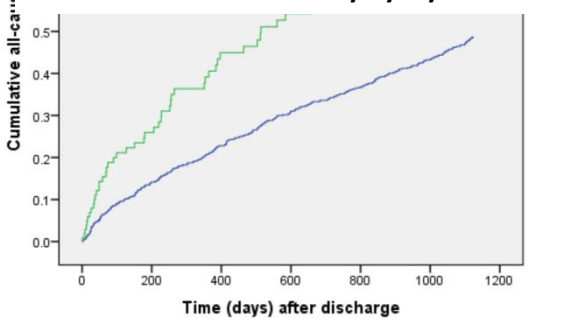
C. HF rehospitalisation by 18 months



Number at risk

Without Stroke	918	718	623	133
With Stroke	105	68	50	10

D. All-cause mortality by 3 years



Log Rank: P<0.001

Number at risk

Without Stroke	918	744	650	563
With Stroke	105	70	59	45

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-10
		(*c*) Explain how missing data were addressed	18
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	8-9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9-10
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	8-9
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-13

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-13
		(*b*) Report category boundaries when continuous variables were categorized	10-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17-19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	19-20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Heart failure patients with and without a history of stoke in the Netherlands: secondary analysis of psychosocial, behavioural and clinical outcomes up to three years from the COACH trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-025525.R2
Article Type:	Research
Date Submitted by the Author:	09-Apr-2019
Complete List of Authors:	Ski, Chantal; Queen's University, Belfast, School of Nursing and Midwifery van der Wal, Martje H.L; Linkopings universitet, Le Grande , Michael; Australian Centre for Heart Health van Veldhuisen, Dirk; University of Groningen, Groningen, The Netherlands Lesman-Leegte, Ivonne; University Medical Center Groningen, Epidemiology Thompson, David; Queen's University Belfast School of Medicine Dentistry and Biomedical Sciences, Nursing and Midwifery Middleton, Sandy; Nursing Research Institute, St Vincent's Health Australia (Syd) and Australian Catholic Univeristy, Cameron, Jan; Australian Centre for Heart Health Jaarsma, Tiny; of Health Sciences Linköping University, Department of Social and Welfare Studies
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	comorbidity, psychosocial, rehospitalizations, mortality, Heart failure < CARDIOLOGY, Stroke < NEUROLOGY

Heart failure patients with and without a history of stoke in the Netherlands: secondary analysis of psychosocial, behavioural and clinical outcomes up to three years from the COACH trial

Short title: Heart failure patients with and without stroke

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ABSTRACT

Objective To identify differences in psychosocial, behavioural and clinical outcomes between patients with heart failure (HF) with and without stroke.

Design and participants A secondary analysis of 1023 patients with heart failure enrolled in the Coordinating study evaluating Outcomes of Advising and Counselling in Heart failure (COACH).

Setting Seventeen hospitals located across the Netherlands

Outcomes measures Depressive symptoms (Centre for Epidemiological Studies Depression Scale), quality of life (Minnesota Living with Heart Failure Questionnaire, Ladder of Life Scale), self-care (European Heart Failure Self-Care Behaviour Scale), adherence to HF management (modified version of the Heart Failure Compliance Questionnaire) and readmission for HF, cardiovascular- and all-cause hospitalizations at 18 months, and all-cause mortality at 18 months and 3 years.

Results Compared to those without stroke, HF patients with a stroke (10.3%; n=105) had twice the likelihood of severe depressive symptoms (OR 2.83, 95% CI 1.27-6.28, *p*=0.011; OR 2.24, 95% CI 1.03-4.88, *p*=0.043) at 12 and 18 months, poorer disease-specific and generic quality of life (OR 2.80, 95% CI 1.61-4.84, *p*<0.001; OR 2.00, 95% CI 1.09-3.50, *p*=0.019) at 12 months, poorer self-care (OR 1.80, 95% CI 1.05-3.11, *p*=0.034; OR 2.87, 95% CI 1.61-5.11, *p*<0.0011) and HF management adherence (OR 0.39, 95% CI 0.18-0.81, *p*=0.012; OR 0.35, 95% CI 0.17-0.72, *p*=0.004) at 12 and 18 months, higher rates of hospitalizations and mortality at 18 months and higher all-cause mortality (HR 1.43, 95% CI 1.07-1.91, *p*=0.016) at 3 years.

Conclusions: Patients with HF and stroke have worse psychosocial, behavioural and clinical outcomes, notably from 12 months, than those without stroke. To ameliorate these poor outcomes long-term, integrated disease management pathways are warranted.

Key words: Comorbidity; psychosocial; rehospitalizations; mortality

Strengths and limitations of this study

- A secondary analysis of data from one of the largest multicentre (n=17) randomised controlled trials of heart failure disease management
- Comprehensive psychosocial, behavioural and clinical outcome data
- Absence of a measure of stroke severity may have impeded interpretation of clinical outcomes
- Limited generalisability due to small proportion of patients with severe heart failure

INTRODUCTION

Heart failure (HF) is an increasing pandemic characterized by high morbidity, mortality and poor quality of life.[1] Stroke, the second leading global cause of death (11.8%), is a frequent comorbidity in patients with HF.[2] Stroke and HF commonly coexist because of shared vascular risk factors,[3-4] and HF is associated with a 2- to 3-fold increased risk of ischemic stroke[5-8] and is an independent predictor of death and disability and hospital readmissions after stroke at 30 days.[6] Having both HF and stroke contributes to a worse prognosis: around 15% of patients with HF seen in HF clinics on a regular basis have a history of stroke.[9]

Research has focused on the etiology and pathophysiology of this comorbidity[3,4,8,10] rather than its psychosocial and behavioural characteristics. This is despite strong evidence linking factors such as depression and lack of social support to adverse outcomes in patients with stroke[11,12] and HF[13,14], and attesting to the efficacy of psychosocial and behavioural interventions on outcomes such as psychological adjustment, social support and lifestyle changes to reduce cardiovascular risk.[15-17] Attaining ideal cardiovascular health metrics such as quitting smoking and adopting a healthy diet can prevent up to 80% of cardiovascular disease,[18] lower risk of total and cardiovascular disease mortality[19] and lower rates of stroke, incident HF and lifetime risk of HF.[20]

Associations between lifestyle factors and HF and stroke, and their persistent poor prognosis, are well established, but evidence is deficient in psychosocial and behavioural comparisons of HF populations with and without stroke across the illness trajectory. Thus, we aimed to identify differences in psychosocial (depression, wellbeing, quality of life), behavioural (self-care, treatment adherence) and clinical (rehospitalizations, mortality)

outcomes at baseline, 6, 12 and 18 months and mortality at 3 years between patients with HF with and without a history of stroke.

METHODS

Study patients and trial procedures

COACH (Coordinating study evaluating Outcome of Advising and Counselling in Heart failure) was a multicentre (17 hospitals in the Netherlands), prospective randomized HF disease management trial designed to compare basic support and intensive support in patients with chronic HF using blinded end-point evaluation. Patients who were admitted for HF were enrolled in COACH before discharge, and randomised to care as usual or to one of two levels of care, basic or intensive, of nurse-led intervention. Inclusion criteria were an admission for HF, evidence of a structural underlying heart disease and age ≥18 years. 'History of stroke' was confirmed by medical records. Only those patients with complete data were included. The design and primary results of COACH have been described.[21,22] All data collected were part of the original COACH trial. The COACH trial was performed in accordance with principles outlined in the Declaration of Helsinki and was approved by a central medical ethical committee, Medical Ethical Committee Groningen (MEtC) 2002/047, and also by the medical ethics committee in each participating centre. This secondary analysis of data was exempt from further ethics approval as no additional data was collected and no significant additional harm was posed to patients. All participants provided written informed consent.

Patients were interviewed and medical records were examined to obtain relevant demographic, clinical, psychosocial and behavioural data at baseline (hospital discharge), 6,

12 and 18 months thereafter. Additionally, all-cause mortality data were collected at 3 years.

Data collection

Demographic and clinical data

Basic demographic (age, gender) and clinical data (comorbidities, cardiovascular risk factors, disease severity) were collected at baseline.

Psychosocial endpoints

Depressive symptoms were measured with the Centre for Epidemiological Studies Depression Scale (CES-D),[23] a 20-item clinically validated self-report questionnaire that assesses depressive symptoms in the general population and the medically ill. Scores range from 0 to 60; higher scores indicate more severe depressive symptoms. Cut-off scores of ≥16 indicating moderate depression and ≥24 for severe depression have been used extensively.[24]

Disease specific quality of life was measured with the Minnesota Living with Heart Failure Questionnaire (MLHFQ),[25] a 21-item self-report questionnaire that assesses patients' perceptions of the effects of their HF on quality of life. Degree of impairment on physical, social, psychological and socioeconomic domains is rated on a 6-point Likert scale from 0 (none) to 5 (very much); higher scores indicate poorer quality of life. A cut-off score of >45 indicates poor quality of life.[26]

Generic quality of life was measured with the Ladder of Life Scale (LLS),[27] a 1-item measure of global wellbeing. Individuals are asked to place themselves on an 11-step ladder

with 'worst possible life' representing the lowest rung (score = 0) and 'best possible life' the top rung (score = 10). The Ladder of Life has been used in various cardiovascular studies and is considered a valid measure of subjective well-being.[28]

Behavioural endpoints

Self-care was measured with the European Heart Failure Self-Care Behaviour Scale (EHFScBS-9),[29] a 9-item self-report questionnaire. The nine items are answered on a 5-point Likert scale (1 = completely agree; 5 = completely disagree) and are converted to a standardised score ranging from 0 to 100 with a higher score indicating better self-care.[30] Inadequate self-care behaviour has been identified as a standardised score below 70. A clinically meaningful change is represented by a smallest real difference (SRD) of 5.75 points in EHFScBS-9 scores.[31] One internally consistent subscale can be identified in the EHFScBS, namely 'consulting behaviours'. Consulting behaviours investigate how often people with HF call their doctor/nurse in case of shortness of breath, ankle swelling, weight gain, and fatigue. The EHFScBS-9 has been implemented and validated across numerous countries world-wide.[32]

Adherence to HF management was measured with a modified version of the Heart Failure Compliance Questionnaire (HFCQ)[33] that assesses adherence in: meeting appointments, taking medication, weighing, diet, fluid intake and exercise. Items were rated on a 5-point Likert scale (0 = never, 1 = seldom, 2 = half of the time, 3 = mostly, 4 = always). Content validity was established in a HF population (Cronbach's α = 0.68).[33] Patients were classified as 'adherent' if they selected 'mostly' or 'always' and were defined as 'overall adherent' if they adhered to at least four of the six behaviours.[34]

Clinical endpoints

Clinical endpoints comprised HF, cardiovascular and all-cause hospitalizations at 18 months, and all-cause mortality at 18 months and 3 years. An end-point committee comprising two cardiologists and a geriatrician adjudicated whether hospitalizations and death were related to HF, cardiovascular death or cardiovascular events. Data on all-cause mortality were collected from the hospital registry, general practitioner and/or municipality at 3 years for each patient.

Statistical analyses

A preliminary analysis using Chi-square statistic was conducted to identify differences in proportions of HF patients with, and without, stroke across intervention and control groups (care as usual, basic support, intensive support groups). Descriptive values are presented as mean (±SD) for continuous variables or as percentages for categorical variables. Continuous variables were compared between patients with and without a history of stroke at baseline, 6, 12 and 18 months using independent t-test, unequal variances t-test or Mann-Whitney U test where appropriate. A Bonferroni correction was applied to adjust for multiple comparisons across all baseline variables (p<0.002).

Variables with a p value less than 0.05 in the analysis comparing HF patients with and without a history of stroke at baseline were consecutively subjected to a multivariate logistic regression model to assess the independent impact of each risk factor on major or severe depressive status (CES-D≥16 and CES-D≥24). The variables age and gender were chosen *a priori* as covariates in each model. A variance inflation factor (VIF) was calculated to ensure that two or more explanatory variables included in a multiple logistic regression

model were not highly correlated. If two patient characteristics showed high multicollinearity (VIF>3) the least significant variable was excluded from the model. The model was estimated using the stepwise backward method (Wald) with a *p* value of less than 0.05 to enter and a *p* value of 0.10 to eliminate variables. This approach was repeated in order to identify significant predictors of: quality of life (MLHFQ[25] and LLS[27]), HF management adherence (HFCQ[33]) and self-care behaviour (EHFScBS[29]).

Self-care subscale standardised scores of the EHFScBS were subjected to repeated measures analysis of covariance (RM-ANCOVA), with scores at baseline, 12 and 18 months as the dependent variable, HF with a history of stroke as the between-subjects factor, and significantly different variables with a *p*-value less than 0.05 at baseline, with the addition of age and gender (chosen a priori) as covariates.

Event rates for clinical endpoints for HF patients with and without stroke were analysed for cardiovascular, HF and all-cause rehospitalizations at 18 months, and for all-cause mortality at 18 months and 3 years using Kaplan-Meier curves and compared with the log-rank test. Hazard ratios (HRs) and 95% CI were calculated by means of the Cox proportional hazards regression model. The proportional hazard assumption was tested based on Schoenfeld residuals. Variables showing a *p* value <0.1 derived from the univariate analysis, as well as sex and NYHA functional status, were included in multivariable Cox models. A more conservative *p* value was used to avoid overfitting the model. Data were analysed using SPSS version 22.

Patient and public Involvement

This project involved secondary data analysis and thus did not involve patients. The study design and primary analysis are described elsewhere.[21,22]

RESULTS

Preliminary analyses

No differences in proportions of HF patients with and without stroke across intervention and control groups were identified using Chi-square statistic.

Differences in HF patient characteristics with and without stroke

Of the 1023 patients enrolled in COACH, 105 (10.3%) had a documented history of stroke. Table 1 shows the baseline demographic and clinical characteristics. No significant differences were found for psychosocial or behavioural variables between HF patients with and without stroke. Significant differences were found for the comorbidities type 2 diabetes, peripheral artery disease and transient ischemic attack, with higher proportions among HF patients with a history of stroke.

Place Table 1 about here

Differences in depressive symptoms

Table 2 shows the effect of the adjustment for multiple potential confounding variables on moderate and severe depression (CES-D). History of stroke was the only factor that remained in the model at both 12 and 18 months for risk of depression. This was most notable at 12 months with more than a 2-fold increased risk for both moderate (OR 2.29; 95% CI 1.22-4.29, p=0.010) and severe (OR 2.83; 95% CI 1.27-6.28, p=0.011) depression.

Type 2 diabetes was found to have an independent association with moderate depression at 18 months (OR 1.63; 95% CI 1.02-2.61, *p*=0.040).

Place Table 2 about here

Differences in quality of life

History of stroke was the only factor that remained in the model at 12 and 18 months. The 12-month point was found to have the highest increased risk for disease-specific (OR 2.80; 95% CI 1.61-4.84, *p*<0.001) and generic (OR 2.00, 95% CI 1.09-3.50, *p*=0.019) poor quality of life.

Differences in HF management adherence and HF self-care behaviour

History of stroke was the only factor to show an independent association with inadequate HF management adherence total scores at both 12 (OR 0.39, 95% CI 0.18-0.81, *p*=0.012) and 18 (OR 0.35, 95% CI 0.17-0.72, *p*=0.004) months (Table 3). However, at 18 months comorbid transient ischaemic attack (OR 0.40, 95% CI 0.19-0.78) and history of atrial fibrillation (OR 1.79, 95% CI 1.04-3.07, *p*=0.035) also significantly increased risk of inadequate HF management adherence.

Table 3 shows the association between history of stroke and inadequate HF self-care at all time-points, with a 1.8-fold risk at 12 months (OR 1.80, 95% CI 1.05-3.11, *p*=0.034) increasing to an almost 3-fold risk at 18 months (OR 2.87, 95% CI 1.61-5.11, *p*<0.001). Other significant predictors of inadequate HF self-care were age at baseline and 12 months, ~1-fold increased risk on both occasions, and comorbid peripheral arterial disease at 18 months, ~1.7-fold increased risk.

Place Table 3 about here

Differences in clinical outcomes

Table 4 shows HF patients with stroke fared worse across all rehospitalizations at 18 months compared to those without stroke; unadjusted hazard ratios indicated greater odds of all rehospitalizations at 18 months, ranging from 1.6 to 2.0. After adjusting for baseline age, sex, NYHA functional status and significant comorbidities HF patients with stroke were up to 1.7 times more likely to be rehospitalized and 1.5 times more likely to experience all-cause mortality than HF patients without stroke. The odds of all-cause mortality at 18 months and 3 years remained significantly higher in HF patients with stroke compared to those without stroke (Table 4). For example, at 3 years HF patients with stroke had a 43% greater likelihood of dying from all-cause mortality, compared to those without stroke.

Place Table 4 about here

Figure 1 shows significant differences between HF patients with and without stroke for cardiovascular, HF and all-cause rehospitalizations up to 18 months and all-cause mortality up to 3 years. Kaplan-Meier survival curves show HF patients with stroke fared worse than those without stroke across all clinical outcomes. Compared to those without stroke, rehospitalizations at 18 months for patients with stroke were on average 84 days earlier for cardiovascular rehospitalizations (mean 310 days, 95% CI 265-355; mean 394 days, 95% CI 380-408, Log Rank 16.48 $p<0.001$), 61 days earlier for HF rehospitalizations (mean 404 days, 95% CI 363-444; mean 465 days, 95% CI 453-477, Log Rank 17.39 $p<0.001$) and 78 days earlier for all-cause rehospitalizations (mean 261 days, 95%CI 218-304; mean 339 days, 95%

CI 324-354, Log Rank 13.31 $p<0.001$). In regard to all-cause mortality, over the 3 years HF patients with stroke died 167 days earlier (mean 702 days, 95% CI 615-788) than HF patients without stroke (mean 859 days, 95% CI 833-884, Log Rank 15.78 $p<0.001$) and had a median survival time of 99 days less.

Place Figure 1 about here

DISCUSSION

This secondary analysis of COACH data showed an association between HF and stroke and psychosocial, behavioural and clinical outcomes. The HF patients with a history of stroke had more comorbidities, poorer psychosocial and behavioural outcomes, earlier rehospitalizations and increased cardiovascular risk and mortality than HF patients without stroke. Specifically, HF patients with stroke had a two-fold likelihood of being depressed, poorer HF management adherence and self-care and almost twice the likelihood of earlier rehospitalizations and all-cause mortality after adjusting for demographic variables and comorbidities. Differences between the two groups across outcomes tended to exacerbate over time, most notably from 12 months, indicating this as a critical point of patient decline that necessitates early intervention.

Comorbidities such as diabetes and peripheral artery disease greatly increase the physical and mental burden already imposed on HF patients with and without stroke.[17] Like other studies, we found a higher prevalence of type 2 diabetes, peripheral artery disease and transient ischaemic attack in patients with HF and stroke.[35] Even so, it should be noted that in our population, patients were not severely impaired (NYHA functional status) with no differences between HF patients with and without stroke. These findings are most likely the

result of initial assessments for eligibility to participate in COACH.[21] In light of moderate disease severity and poor psychosocial, behavioral and clinical outcomes, the likelihood is that populations with more severe HF may experience even more severe outcomes.

Depression may occur in one in every three stroke patients.[17] In HF populations this estimate is known to be far greater.[14] Additionally, levels of depression are also known to increase alongside the number of comorbidities.[11,17] In our study, there was almost a 3-fold likelihood of HF patients with stroke having severe depressive symptoms at 12 months, which declined only to over a 2-fold likelihood at 18 months. With its associated poor treatment adherence, lack of energy and motivation and social withdrawal,[11-13] sustained levels of depressive symptoms among HF patients with stroke draw attention to the vulnerability of this population and the need for screening, referral and engagement in management strategies. Our finding that comorbid type 2 diabetes was a stronger predictor of more severe depression than other factors (history of atrial fibrillation, hypertension and peripheral artery disease) among HF patients with stroke compared to those without is intriguing and warrants further study, though an additional comorbidity such as diabetes is likely to increase the burden on patients and may exacerbate depression, which is known to be high in patients with diabetes alone.[36]

People with conditions such as HF and stroke are commonly found to report poor quality of life and wellbeing.[37] Together, HF and stroke would likely augment any such impact, as found in our study. Similar to our findings on depression, patients with HF and stroke fared worse across both measures of quality of life at 12 and 18 months, a finding aligned with previous studies, indicating the degree of the decrement in quality of life is often

proportional to the severity of depressive symptoms.[37] The enduring continuation of increased rehospitalizations may explain poor physical quality of life at 18 months for this patient population.[6-9] In light of the poor prognosis of patients with HF and stroke, where symptoms can at best be controlled rather than cured, efforts to maintain and improve quality of life should be considered a primary goal in their disease management.

Achieving optimal self-care by HF patients is widely regarded as essential goal of disease management.[1,33,38] However, HF self-care behaviour is complicated by factors such as ageing, comorbidities, cognitive impairment, frailty and limited social support.[38] Our findings highlight the difficulty of maintaining adequate HF self-care and management adherence. Together with stroke, a history of atrial fibrillation, comorbid transient ischaemic attack and peripheral artery disease contributed to deficiencies in these aspects of care. This is likely due to the additive impact of major chronic disabling conditions contributing to a more burdensome and complex HF management and self-care regimen. This issue needs to be considered carefully when planning with patients and carers how best to optmise disease management strategies. Patients with HF and stroke had poorer engagement in HF self-care and management adherence from 12 months, compared to those without stroke, with differences between the two groups in HF self-care being clinically significant according to interpretability of the EHFScBS-9.[31] This may be explained by HF and stroke being established burdensome conditions,[3,7] both requiring intensive and enduring support. Also, patients with HF and stroke, compared to those without stroke, had significantly more comorbidities, a known barrier to successful self-care.[38] Thus, interventions which focus on prioritizing specific aspects of self-care for HF and stroke independently may be more

effective than general support for patients dealing with such burdensome and complex comorbidities.

In regard to clinical outcomes, our findings of approximately twice the increased risk of hospitalization and mortality in HF patients with stroke concur with those of other studies,[5,6-8] such as one showing patients with stroke after HF had a 2.3 times higher risk of dying than patients without stroke[5] and another showing the odds of dying within 30 days and 1 year since stroke diagnosis, was close to two times greater for patients who had pre-existing HF.[6] Additionally, in our study, comorbid HF and stroke was identified as a predictor of rehospitalizations at 18 months and all-cause mortality up to 3 years independent of age, gender, HF functional status and presence of other comorbidities such as peripheral artery disease, transient ischaemic attack and type 2 diabetes. Also, patients with HF and stroke were rehospitalized up to 84 days earlier and died an average of 5 months earlier compared to those without stroke.

Our findings highlight poor psychosocial, behavioural and clinical outcomes for patients with HF and stroke which, taken together, indicate a diminished likelihood of early and successful recovery. An assessment of the particular needs of this significant and growing patient group should inform the design of appropriately-tailored care management strategies, which can then be evaluated for effectiveness. Patient choice and preferences should be central to such efforts.

Limitations

This was a secondary analysis of COACH data and therefore was constrained by the methods employed in the original study.[21,22] Applicable to all observational trials,

correlation does not prove causation. Although we found no statistically significant differences between proportions of HF patients with and without stroke across intervention and control groups, our study was limited by the lack of patients with severe HF, which may have caused a bias in terms of minimizing the magnitude of the effects on outcome. Also, the absence of a measure of stroke severity, a known predictor of functional dependency,[35] may have impeded our interpretation of clinical outcomes. Another limitation is the absence of recurrent stroke or mortality due to stroke as a clinical outcome measure. It would be valuable information to know if patients with HF and stroke were more likely to have recurrent stroke, as this could potentially influence depression, quality of life, adherence to HF care and clinical outcomes. Using the medical record to determine the presence or absence of prior stroke does not capture severity and may be inaccurate due to poor history taking or documentation and this may have influenced the findings. This is an important consideration when patients with 'history of stroke' in their medical record were more likely to have severe stroke. Lastly, although clinical interview, the gold standard, was not used to diagnose depression, presence of depressive symptoms was assessed via the CES-D which has been well-validated, in both HF and stroke populations,[24] to identify patients who are at high risk of developing a depressive disorder.

Conclusions

To our knowledge, this is the first study to examine psychosocial, behavioural and clinical outcomes in HF patients with stroke compared to those without stroke. These findings not only confirm the poor prognosis in HF patients with stroke, but also that depression is more common, quality of life, HF self-care and HF management adherence are poorer and risk of rehospitalization and mortality are greater in these patients. Further, 12 months post-discharge was identified as a point of heightened vulnerability for those experiencing this

comorbidity that maybe ameliorated by strategies that address cardiovascular risk and psychosocial and behavioural factors. This study highlights the clinical relevance of the complex interplay between HF and stroke that requires further investigation and warrants the need for long-term, integrated disease management pathways for patients with comorbid HF and stroke which span the hospital-home interface.

Acknowledgements

None.

Competing interests

None declared.

Funding statement

The COACH study was supported by a program grant from the Netherlands Heart Foundation (grant 2000Z003); D.J.v.V. is a Clinical Established Investigator of the Netherlands Heart Foundation (grant D97.017)

Data sharing statement

The data that supports the findings of this study are available, on reasonable request, from the corresponding author.

Author contributions

CFS, TJ, DRT and MLG conceived and designed the study and drafted the manuscript. MLG, CFS, TJ and DJV analyzed and guided interpretation of data. MHLW, ILL, SM, JC critically advised on important intellectual content and contributed to drafting of the manuscript. All authors read and approved the manuscript. All authors approved the final version to be published. CFS and TJ are responsible for overall content as guarantors accountable to all aspects of the work.

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Table 1. Baseline characteristics as a function of heart failure and stroke comorbidity

	HF (N=918)	HF + stroke (N=105)	OR (95% CI) *Unadjusted*	*P*-value
Demographics				
Age mdn (IR)	73 (57-89)	75 (63-87)		0.069
Male	569 (62%)	70 (67%)	1.23 (0.80-1.88)	0.348
Married/living together	542 (60%)	63 (61%)	0.97 (0.64-1.46)	0.872
Comorbidities				
Type I diabetes mellitus	94 (10%)	14 (13%)	1.35 (0.74-2.46)	**0.330**
Type II diabetes mellitus	153 (17%)	33 (31%)	2.29 (1.47-3.58)	**<0.001**
Transient ischaemic attack	59 (6%)	24 (23%)	4.31 (2.55-7.30)	**<0.001**
COPD	238 (26%)	30 (29%)	1.14 (0.73-1.79)	0.559
History of atrial fibrillation	392 (43%)	59 (56%)	1.72 (1.15-2.59)	0.008
Asthma	36 (4%)	5 (5%)	1.23 (0.47-3.19)	0.678
Renal disease	68 (7%)	10 (10%)	1.32 (0.66-2.64)	0.440
Liver disease	23 (3%)	3 (3%)	1.15 (0.34-3.88)	0.828
Gastro-intestinal disease	105 (11%)	16 (15%)	1.39 (0.79-2.46)	0.255
Hypertension	385 (42%)	54 (51%)	1.47 (0.98-2.20)	0.064
Peripheral artery disease	139 (15%)	29 (28%)	2.14 (1.34-3.40)	**0.001**
Cardiovascular risk factors				
Body mass index	27.1±5	26.3±5		0.219

Systolic blood pressure	118.2±21	119.3±19		0.623
Diastolic blood pressure	68.5±12	67.5±11		0.448
Disease severity				
LVEF	33.7±14.3	33.9±15.1		0.930
NYHA classification				0.650
II	465 (51%)	48 (47%)		
III	410 (45%)	51 (49%)		
IV	30 (3%)	4 (4%)		
Previous HF admission	296 (32%)	38 (36%)	1.19 (0.78-1.82)	0.414
Medications				
ACE inhibitors	673 (73%)	71 (68%)	0.76 (0.49-1.17)	0.215
Angiotensin blockers	110 (12%)	14 (13%)	1.13 (0.62-2.05)	0.688
Beta-blockers	616 (67%)	61 (58%)	0.68 (0.45-1.03)	0.065
Diuretics	878 (96%)	102 (97%)	1.55 (0.47-5.10)	0.468
Coumarin	554 (60%)	71 (68%)	1.37 (0.89-2.11)	0.148
Anti-depressants	65 (7%)	6 (6%)	0.80 (0.34-1.88)	0.602

Nb. Bold *p*-values represent significant alpha after Bonferroni correction (p < .002). COPD, chronic obstructive pulmonary disease; HF, heart failure; IR, interquartile range; LVEF, left ventricular ejection; mdn, median

Table 2. Predictors of moderate and severe depression in final model of multivariable logistic regression over 18 months

Predictors in final step of model	OR (95%CI)	*P*-value
Moderate Depression (CES-D ≥16)		
Baseline		
Gender	1.60 (1.22-2.10)	**0.001**
Age	0.99 (0.97-0.99)	**0.037**
History of stroke	1.57 (1.03-2.41)	**0.036**
12 months		
History of stroke	2.29 (1.22-4.29)	**0.010**
18 months		
History of stroke	1.67 (0.92-3.04)	0.095
Comorbid type II diabetes	1.63 (1.02-2.61)	**0.040**
Severe Depression (CES-D ≥24)		
Baseline		
Gender	1.68 (1.22-2.32)	**0.002**
Age	0.98 (0.97-0.99)	**0.010**
12 months		
History of stroke	2.83 (1.27-6.28)	**0.011**

18 months		
Age	0.98 (0.96-1.00)	0.076
History of stroke	2.24 (1.03-4.88)	**0.043**

Nb. Bold *p*-values represent significant alpha, $p<0.05$. Covariates entered in each model: age at index hospitalization; gender; comorbid transient ischaemic attack; comorbid peripheral arterial disease; comorbid type II diabetes mellitus; history of atrial fibrillation; and history of stroke. CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; SE, standard error; OR, odds ratio

Table 3. Predictors of inadequate heart failure management adherence and self-care behaviour in final model of logistic multivariable regression over 18 months

Predictors in final step of model	OR (95% CI)	*P*-value
Inadequate HF management adherence (HFCQ; <3 of 6 behaviours[32])		
Baseline		
History of atrial fibrillation	1.30 (0.99-1.71)	0.060
12 months		
History of stroke	0.39 (0.18-0.81)	**0.012**
18 months		
History of stroke	0.35 (0.17-0.72)	**0.004**
Comorbid TIA	0.40 (0.19-0.78)	**0.008**
History of atrial fibrillation	1.79 (1.04-3.07)	**0.035**
Inadequate self-care behaviour (EHFScB-9; <70[30])		
Baseline		
Age	1.02 (1.01-1.03)	**0.001**
History of stroke	1.49 (0.97-2.29)	0.069
12 months		
Age	1.02 (1.01-1.03)	**0.009**
History of stroke	1.80 (1.05-3.11)	**0.034**

18 months		
History stroke	2.87 (1.61-5.11)	**<0.001**
Comorbid peripheral arterial disease	1.65 (1.05-2.60)	**0.030**

Nb. Bold *p*-values represent significant alpha, $p<0.05$. Covariates entered in each model: age at index hospitalization; gender; comorbid transient ischaemic attack; comorbid peripheral arterial disease; comorbid type II diabetes mellitus; history of atrial fibrillation; and history of stroke. CI, confidence interval; EHFScB-9, European Heart Failure Self-care Behaviour scale; HF, heart failure; HFCQ, Heart Failure Compliance Questionnaire; OR, odds ratio; SE, standard error; TIA, transient ischaemic attack

Table 4. Rehospitalization and mortality hazard ratios as a function of HF and stroke comorbidity

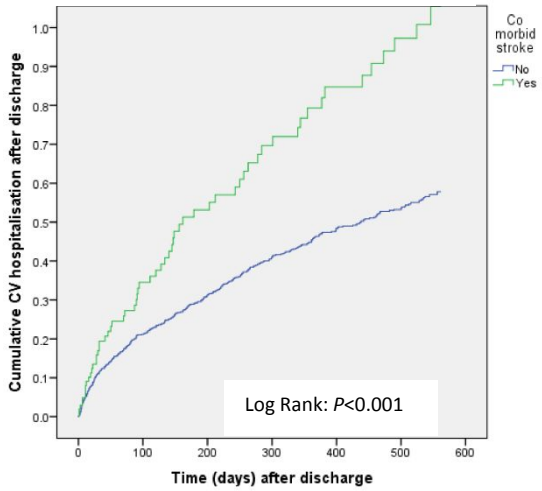
	N (%)		Hazard ratio (95% CI)		Hazard ratio (95% CI) adjusted: age, sex, NYHA, other comorbidities*	
	HF (*n*=918)	HF + stroke (*n*=105)	(unadjusted)	*P*-value		*P*-value
Clinical endpoints						
18 months post-discharge						
CV rehospitalization	373 (41%)	60 (57%)	1.74 (1.32-2.29)	**<0.001**	1.45 (1.09-1.94)	**0.012**
HF rehospitalization	218 (24%)	42 (40%)	1.99 (1.43-2.78)	**<0.001**	1.66 (1.17-2.36)	**0.005**
All-cause rehospitalization	495 (54%)	72 (69%)	1.57 (1.23-2.02)	**<0.001**	1.31 (1.01-1.70)	**0.044**
HF rehospitalization/ death	344 (38%)	67 (64%)	2.04 (1.57-2.66)	**<0.001**	1.68 (1.27-2.22)	**<0.001**
All-cause mortality	230 (25%)	42 (40%)	1.78 (1.28-2.48)	**<0.001**	1.46 (1.03-2.07)	**0.033**
3 years post-discharge						
All-cause mortality	354 (39%)	59 (56%)	1.75 (1.33-2.31)	**<0.001**	1.43 (1.07-1.91)	**0.016**

Nb. *other comorbidities; Type 2 diabetes mellitus, transient ischemia attack, peripheral artery disease, history of atrial fibrillation. CI, confidence interval; CV, cardiovascular; HF, heart failure; NYHA, New York Heart Association

Figure legend

Fig. 1. Kaplan–Meier event curves for HF patients with (n=105) and without (n=918) stroke across **(A)** CV rehospitalization by 18 months, **(B)** HF rehospitalization by 18 months, **(C)** CV rehospitalization or death by 18 months, and **(D)** all-cause mortality by 3 years as a function of HF and stroke comorbidity. Kaplan-Meier curves represent a comparison of HF patients with (green) and without (blue) stroke, for days to rehospitalization (A; B; C) or to death (D). Kaplan-Meier curves identified HF patients with stroke as significantly ($p < 0.001$) worse than HF patients without stroke across all clinical outcomes. 'Number at risk' columns are in 200 day increments for rehospitalization's, and 400 day increments for mortality.

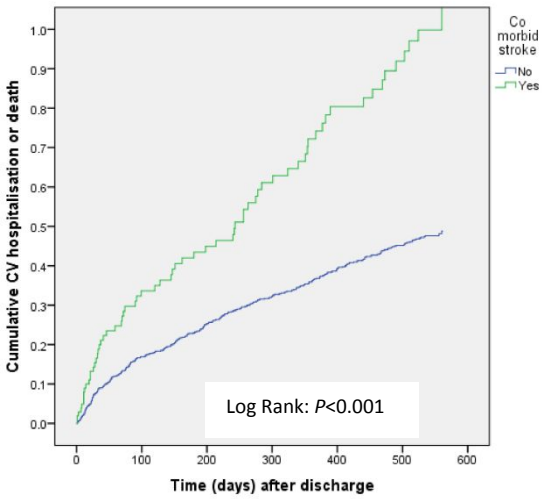
A. CV rehospitalisation by 18 months



Number at risk

Without Stroke	918	632	553	102
With Stroke	105	53	38	6

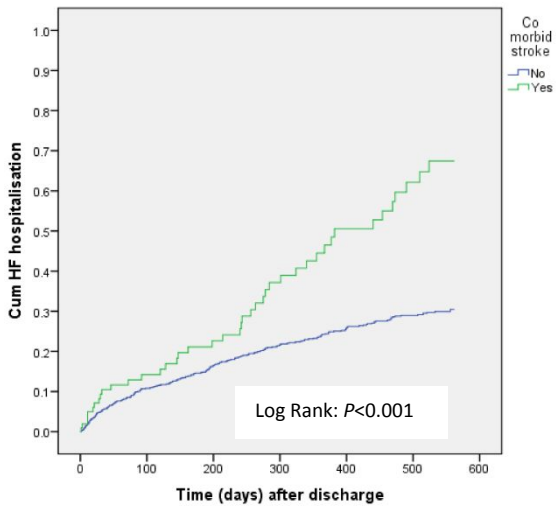
B. All-cause rehospitalisation by 18 months



Number at risk

Wit				
Wit				

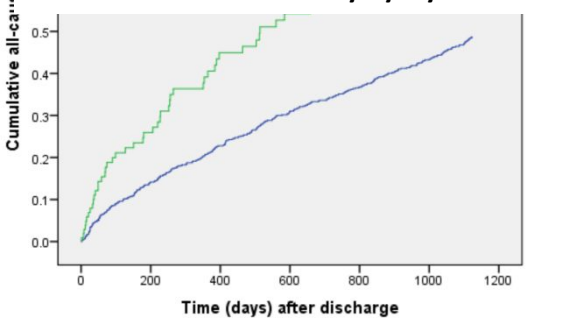
C. HF rehospitalisation by 18 months



Number at risk

Without Stroke	918	718	623	133
With Stroke	105	68	50	10

D. All-cause mortality by 3 years



Number at risk

Without Stroke	918	744	650	563
With Stroke	105	70	59	45

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-10
		(*c*) Explain how missing data were addressed	18
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	8-9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9-10
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	8-9
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-13

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-13
		(*b*) Report category boundaries when continuous variables were categorized	10-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17-19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	19-20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Heart failure patients with and without a history of stroke in the Netherlands: secondary analysis of psychosocial, behavioural and clinical outcomes up to three years from the COACH trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-025525.R3
Article Type:	Research
Date Submitted by the Author:	03-Jun-2019
Complete List of Authors:	Ski, Chantal; Queen's University Belfast, School of Nursing and Midwifery van der Wal, Martje H.L; Linkopings universitet, Le Grande , Michael; Deakin University van Veldhuisen, Dirk; University of Groningen, Department of Cardiology Lesman-Leegte, Ivonne; University of Groningen, Department of Epidemiology Thompson, David; Queen's University Belfast, School of Nursing and Midwifery Middleton, Sandy; Australian Catholic University, Nursing Research Institute Cameron, Jan; Monash University, School of Nursing Jaarsma, Tiny; Linköping University, Department of Social and Welfare Studies
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	comorbidity, psychosocial, rehospitalizations, mortality, Heart failure < CARDIOLOGY, Stroke < NEUROLOGY

Heart failure patients with and without a history of stroke in the Netherlands: secondary analysis of psychosocial, behavioural and clinical outcomes up to three years from the COACH trial

Short title: Heart failure patients with and without stroke

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ABSTRACT

Objective To identify differences in psychosocial, behavioural and clinical outcomes between patients with heart failure (HF) with and without stroke.

Design and participants A secondary analysis of 1023 patients with heart failure enrolled in the Coordinating study evaluating Outcomes of Advising and Counselling in Heart failure (COACH).

Setting Seventeen hospitals located across the Netherlands

Outcomes measures Depressive symptoms (Centre for Epidemiological Studies Depression Scale), quality of life (Minnesota Living with Heart Failure Questionnaire, Ladder of Life Scale), self-care (European Heart Failure Self-Care Behaviour Scale), adherence to HF management (modified version of the Heart Failure Compliance Questionnaire) and readmission for HF, cardiovascular- and all-cause hospitalizations at 18 months, and all-cause mortality at 18 months and 3 years.

Results Compared to those without stroke, HF patients with a stroke (10.3%; n=105) had twice the likelihood of severe depressive symptoms (OR 2.83, 95% CI 1.27-6.28, p=0.011; OR 2.24, 95% CI 1.03-4.88, p=0.043) at 12 and 18 months, poorer disease-specific and generic quality of life (OR 2.80, 95% CI 1.61-4.84, p<0.001; OR 2.00, 95% CI 1.09-3.50, p=0.019) at 12 months, poorer self-care (OR 1.80, 95% CI 1.05-3.11, p=0.034; OR 2.87, 95% CI 1.61-5.11, p<0.0011) and HF management adherence (OR 0.39, 95% CI 0.18-0.81, p=0.012; OR 0.35, 95% CI 0.17-0.72, p=0.004) at 12 and 18 months, higher rates of hospitalizations and mortality at 18 months and higher all-cause mortality (HR 1.43, 95% CI 1.07-1.91, p=0.016) at 3 years.

Conclusions: Patients with HF and stroke have worse psychosocial, behavioural and clinical outcomes, notably from 12 months, than those without stroke. To ameliorate these poor outcomes long-term, integrated disease management pathways are warranted.

Key words: Comorbidity; heart failure; stroke; psychosocial; rehospitalizations; mortality

Strengths and limitations of this study

- A secondary analysis of data from one of the largest multicentre (n=17) randomised controlled trials of heart failure disease management
- Comprehensive psychosocial, behavioural and clinical outcome data
- Absence of a measure of stroke severity may have impeded interpretation of clinical outcomes
- Limited generalisability due to small proportion of patients with severe heart failure

INTRODUCTION

Heart failure (HF) is an increasing pandemic characterized by high morbidity, mortality and poor quality of life.[1] Stroke, the second leading global cause of death (11.8%) is a frequent comorbidity in patients with HF.[2] Stroke and HF commonly coexist because of shared vascular risk factors,[3-4] and HF is associated with a 2- to 3-fold increased risk of ischemic stroke[5-8] and is an independent predictor of death and disability and hospital readmissions after stroke at 30 days.[6] Around 15% of patients with HF seen in HF clinics on a regular basis have a history of stroke.[9] Having both HF and stroke contributes to a worse prognosis.[3,6]

Research has focused on the etiology and pathophysiology of this comorbidity[3,4,8,10] rather than its psychosocial and behavioural characteristics. This is despite strong evidence linking factors such as depression and lack of social support to adverse outcomes in patients with stroke[11,12] and HF[13,14] , and attesting to the efficacy of psychosocial and behavioural interventions on outcomes such as psychological adjustment, social support and lifestyle changes to reduce cardiovascular risk.[15-17] Attaining ideal cardiovascular health metrics such as quitting smoking and adopting a healthy diet can prevent up to 80% of cardiovascular disease,[18] lower risk of total and cardiovascular disease mortality[19] and lower rates of stroke, incident HF and lifetime risk of HF.[20]

Associations between lifestyle factors and HF and stroke, and their persistent poor prognosis, are well established, but evidence is deficient in psychosocial and behavioural comparisons of HF populations with and without stroke across the illness trajectory. Thus, we aimed to identify differences in psychosocial (depression, wellbeing, quality of life), behavioural (self-care, treatment adherence) and clinical (rehospitalizations, mortality)

outcomes at baseline, 6, 12 and 18 months and mortality at 3 years between patients with HF with and without a history of stroke.

METHODS

Study patients and trial procedures

COACH (Coordinating study evaluating Outcome of Advising and Counselling in Heart failure) was a multicentre (17 hospitals in the Netherlands), prospective randomized HF disease management trial designed to compare basic support and intensive support in patients with chronic HF using blinded end-point evaluation. Patients who were admitted for HF were enrolled in COACH before discharge, and randomised to care as usual or to one of two levels of care, basic or intensive, of nurse-led intervention. Inclusion criteria were an admission for HF, evidence of a structural underlying heart disease and age ≥18 years. 'History of stroke' was confirmed by medical records. Only those patients with complete data were included. The design and primary results of COACH have been described.[21,22] All data collected were part of the original COACH trial. The COACH trial was performed in accordance with principles outlined in the Declaration of Helsinki and was approved by a central medical ethical committee, Medical Ethical Committee Groningen (MEtC) 2002/047, and also by the medical ethics committee in each participating centre. This secondary analysis of data was exempt from further ethics approval as no additional data was collected and no significant additional harm was posed to patients. All participants provided written informed consent.

Patients were interviewed and medical records were examined to obtain relevant demographic, clinical, psychosocial and behavioural data at baseline (hospital discharge), 6,

12 and 18 months thereafter. Additionally, all-cause mortality data were collected at 3 years.

Data collection

Demographic and clinical data

Basic demographic (age, gender) and clinical data (comorbidities, cardiovascular risk factors, disease severity) were collected at baseline.

Psychosocial endpoints

Depressive symptoms were measured with the Centre for Epidemiological Studies Depression Scale (CES-D),[23] a 20-item clinically validated self-report questionnaire that assesses depressive symptoms in the general population and the medically ill. Scores range from 0 to 60; higher scores indicate more severe depressive symptoms. Cut-off scores of ≥16 indicating moderate depression and ≥24 for severe depression have been used extensively.[24]

Disease specific quality of life was measured with the Minnesota Living with Heart Failure Questionnaire (MLHFQ),[25] a 21-item self-report questionnaire that assesses patients' perceptions of the effects of their HF on quality of life. Degree of impairment on physical, social, psychological and socioeconomic domains is rated on a 6-point Likert scale from 0 (none) to 5 (very much); higher scores indicate poorer quality of life. A cut-off score of >45 indicates poor quality of life.[26]

Generic quality of life was measured with the Ladder of Life Scale (LLS),[27] a 1-item measure of global wellbeing. Individuals are asked to place themselves on an 11-step ladder

with 'worst possible life' representing the lowest rung (score = 0) and 'best possible life' the top rung (score = 10). The Ladder of Life has been used in various cardiovascular studies and is considered a valid measure of subjective well-being.[28]

Behavioural endpoints

Self-care was measured with the European Heart Failure Self-Care Behaviour Scale (EHFScBS-9),[29] a 9-item self-report questionnaire. The nine items are answered on a 5-point Likert scale (1 = completely agree; 5 = completely disagree) and are converted to a standardised score ranging from 0 to 100 with a higher score indicating better self-care.[30] Inadequate self-care behaviour has been identified as a standardised score below 70. A clinically meaningful change is represented by a smallest real difference (SRD) of 5.75 points in EHFScBS-9 scores.[31] One internally consistent subscale can be identified in the EHFScBS, namely 'consulting behaviours'. Consulting behaviours investigate how often people with HF call their doctor/nurse in case of shortness of breath, ankle swelling, weight gain, and fatigue. The EHFScBS-9 has been implemented and validated across numerous countries world-wide.[32]

Adherence to HF management was measured with a modified version of the Heart Failure Compliance Questionnaire (HFCQ)[33] that assesses adherence in: meeting appointments, taking medication, weighing, diet, fluid intake and exercise. Items were rated on a 5-point Likert scale (0 = never, 1 = seldom, 2 = half of the time, 3 = mostly, 4 = always). Content validity was established in a HF population (Cronbach's α = 0.68).[33] Patients were classified as 'adherent' if they selected 'mostly' or 'always' and were defined as 'overall adherent' if they adhered to at least four of the six behaviours.[34]

Clinical endpoints

Clinical endpoints comprised HF, cardiovascular and all-cause hospitalizations at 18 months, and all-cause mortality at 18 months and 3 years. An end-point committee comprising two cardiologists and a geriatrician adjudicated whether hospitalizations and death were related to HF, cardiovascular death or cardiovascular events. Data on all-cause mortality were collected from the hospital registry, general practitioner and/or municipality at 3 years for each patient.

Statistical analyses

A preliminary analysis using Chi-square statistic was conducted to identify differences in proportions of HF patients with, and without, stroke across intervention and control groups (care as usual, basic support, intensive support groups). Descriptive values are presented as mean (±SD) for continuous variables or as percentages for categorical variables. Continuous variables were compared between patients with and without a history of stroke at baseline, 6, 12 and 18 months using independent t-test, unequal variances t-test or Mann-Whitney U test where appropriate. A Bonferroni correction was applied to adjust for multiple comparisons across all baseline variables (p<0.002).

Variables with a p value less than 0.05 in the analysis comparing HF patients with and without a history of stroke at baseline were consecutively subjected to a multivariate logistic regression model to assess the independent impact of each risk factor on major or severe depressive status (CES-D≥16 and CES-D≥24). The variables age and gender were chosen *a priori* as covariates in each model. A variance inflation factor (VIF) was calculated to ensure that two or more explanatory variables included in a multiple logistic regression

model were not highly correlated. If two patient characteristics showed high multicollinearity (VIF>3) the least significant variable was excluded from the model. The model was estimated using the stepwise backward method (Wald) with a *p* value of less than 0.05 to enter and a *p* value of 0.10 to eliminate variables. This approach was repeated in order to identify significant predictors of: quality of life (MLHFQ[25] and LLS[27]), HF management adherence (HFCQ[33]) and self-care behaviour (EHFScBS[29]).

Self-care subscale standardised scores of the EHFScBS were subjected to repeated measures analysis of covariance (RM-ANCOVA), with scores at baseline, 12 and 18 months as the dependent variable, HF with a history of stroke as the between-subjects factor, and significantly different variables with a *p*-value less than 0.05 at baseline, with the addition of age and gender (chosen a priori) as covariates.

Event rates for clinical endpoints for HF patients with and without stroke were analysed for cardiovascular, HF and all-cause rehospitalizations at 18 months, and for all-cause mortality at 18 months and 3 years using Kaplan-Meier curves and compared with the log-rank test. Hazard ratios (HRs) and 95% CI were calculated by means of the Cox proportional hazards regression model. The proportional hazard assumption was tested based on Schoenfeld residuals. Variables showing a *p* value <0.1 derived from the univariate analysis, as well as sex and NYHA functional status, were included in multivariable Cox models. A more conservative *p* value was used to avoid overfitting the model. Data were analysed using SPSS version 22.

Patient and public Involvement

This project involved secondary data analysis and thus did not involve patients. The study design and primary analysis are described elsewhere.[21,22]

RESULTS

Preliminary analyses

No differences in proportions of HF patients with and without stroke across intervention and control groups were identified using Chi-square statistic.

Differences in HF patient characteristics with and without stroke

Of the 1023 patients enrolled in COACH, 105 (10.3%) had a documented history of stroke. Table 1 shows the baseline demographic and clinical characteristics. No significant differences were found for psychosocial or behavioural variables between HF patients with and without stroke. Significant differences were found for the comorbidities type 2 diabetes, peripheral artery disease and transient ischemic attack, with higher proportions among HF patients with a history of stroke.

Place Table 1 about here

Differences in depressive symptoms

Table 2 shows the effect of the adjustment for multiple potential confounding variables on moderate and severe depression (CES-D). History of stroke was the only factor that remained in the model at both 12 and 18 months for risk of depression. This was most notable at 12 months with more than a 2-fold increased risk for both moderate (OR 2.29; 95% CI 1.22-4.29, p=0.010) and severe (OR 2.83; 95% CI 1.27-6.28, p=0.011) depression.

Type 2 diabetes was found to have an independent association with moderate depression at 18 months (OR 1.63; 95% CI 1.02-2.61, *p*=0.040).

Place Table 2 about here

Differences in quality of life

History of stroke was the only factor that remained in the model at 12 and 18 months. The 12-month point was found to have the highest increased risk for disease-specific (OR 2.80; 95% CI 1.61-4.84, *p*<0.001) and generic (OR 2.00, 95% CI 1.09-3.50, *p*=0.019) poor quality of life.

Differences in HF management adherence and HF self-care behaviour

History of stroke was the only factor to show an independent association with inadequate HF management adherence total scores at both 12 (OR 0.39, 95% CI 0.18-0.81, *p*=0.012) and 18 (OR 0.35, 95% CI 0.17-0.72, *p*=0.004) months (Table 3). However, at 18 months comorbid transient ischaemic attack (OR 0.40, 95% CI 0.19-0.78) and history of atrial fibrillation (OR 1.79, 95% CI 1.04-3.07, *p*=0.035) also significantly increased risk of inadequate HF management adherence.

Table 3 shows the association between history of stroke and inadequate HF self-care at all time-points, with a 1.8-fold risk at 12 months (OR 1.80, 95% CI 1.05-3.11, *p*=0.034) increasing to an almost 3-fold risk at 18 months (OR 2.87, 95% CI 1.61-5.11, *p*<0.001). Other significant predictors of inadequate HF self-care were age at baseline and 12 months, 1.02-fold increased risk on both occasions, and comorbid peripheral arterial disease at 18 months, 1.65-fold increased risk.

Place Table 3 about here

Differences in clinical outcomes

Table 4 shows HF patients with stroke fared worse across all rehospitalizations at 18 months compared to those without stroke; unadjusted hazard ratios indicated greater odds of all rehospitalizations at 18 months, ranging from 1.6 to 2.0. After adjusting for baseline age, sex, NYHA functional status and significant comorbidities HF patients with stroke were up to 1.7 times more likely to be rehospitalized and 1.5 times more likely to experience all-cause mortality than HF patients without stroke. The odds of all-cause mortality at 18 months and 3 years remained significantly higher in HF patients with stroke compared to those without stroke (Table 4). For example, at 3 years HF patients with stroke had a 43% greater likelihood of dying from all-cause mortality, compared to those without stroke.

Place Table 4 about here

Figure 1 shows significant differences between HF patients with and without stroke for cardiovascular, HF and all-cause rehospitalizations up to 18 months and all-cause mortality up to 3 years. Kaplan-Meier survival curves show HF patients with stroke fared worse than those without stroke across all clinical outcomes. Compared to those without stroke, rehospitalizations at 18 months for patients with stroke were on average 84 days earlier for cardiovascular rehospitalizations (mean 310 days, 95% CI 265-355; mean 394 days, 95% CI 380-408, Log Rank 16.48 $p<0.001$), 61 days earlier for HF rehospitalizations (mean 404 days, 95% CI 363-444; mean 465 days, 95% CI 453-477, Log Rank 17.39 $p<0.001$) and 78 days earlier for all-cause rehospitalizations (mean 261 days, 95%CI 218-304; mean 339 days, 95%

CI 324-354, Log Rank 13.31 $p<0.001$). In regard to all-cause mortality, over the 3 years HF patients with stroke died 167 days earlier (mean 702 days, 95% CI 615-788) than HF patients without stroke (mean 859 days, 95% CI 833-884, Log Rank 15.78 $p<0.001$) and had a median survival time of 99 days less.

Place Figure 1 about here

DISCUSSION

This secondary analysis of COACH data showed an association between HF and stroke and psychosocial, behavioural and clinical outcomes. The HF patients with a history of stroke had more comorbidities, poorer psychosocial and behavioural outcomes, earlier rehospitalizations and increased cardiovascular risk and mortality than HF patients without stroke. Specifically, HF patients with stroke had a two-fold likelihood of being depressed, poorer HF management adherence and self-care and almost twice the likelihood of earlier rehospitalizations and all-cause mortality after adjusting for demographic variables and comorbidities. Differences between the two groups across outcomes tended to exacerbate over time, most notably from 12 months, indicating this as a critical point of patient decline that necessitates early intervention.

Comorbidities such as diabetes and peripheral artery disease greatly increase the physical and mental burden already imposed on HF patients with and without stroke.[17] Like other studies, we found a higher prevalence of type 2 diabetes, peripheral artery disease and transient ischaemic attack in patients with HF and stroke.[35] Even so, it should be noted that in our population, patients were not severely impaired (NYHA functional status) with no differences between HF patients with and without stroke. These findings are most likely the

result of initial assessments for eligibility to participate in COACH.[21] In light of moderate disease severity and poor psychosocial, behavioural and clinical outcomes, the likelihood is that populations with more severe HF may experience even more severe outcomes.

Depression may occur in one in every three stroke patients.[17] In HF populations this estimate is known to be far greater.[14] Additionally, levels of depression are also known to increase alongside the number of comorbidities.[11,17] In our study, there was almost a 3-fold likelihood of HF patients with stroke having severe depressive symptoms at 12 months, which declined only to over a 2-fold likelihood at 18 months. With its associated poor treatment adherence, lack of energy and motivation and social withdrawal,[11-13] sustained levels of depressive symptoms among HF patients with stroke draw attention to the vulnerability of this population and the need for screening, referral and engagement in management strategies. Our finding that comorbid type 2 diabetes was a stronger predictor of more severe depression than other factors (history of atrial fibrillation, hypertension and peripheral artery disease) among HF patients with stroke compared to those without is intriguing and warrants further study, though an additional comorbidity such as diabetes is likely to increase the burden on patients and may exacerbate depression, which is known to be high in patients with diabetes alone.[36]

People with conditions such as HF and stroke are commonly found to report poor quality of life and wellbeing.[37] Together, HF and stroke would likely augment any such impact, as found in our study. Similar to our findings on depression, patients with HF and stroke fared worse across both measures of quality of life at 12 and 18 months, a finding aligned with previous studies, indicating the degree of the decrement in quality of life is often

proportional to the severity of depressive symptoms.[37] The enduring continuation of increased rehospitalizations may explain poor physical quality of life at 18 months for this patient population.[6-9] In light of the poor prognosis of patients with HF and stroke, where symptoms can at best be controlled rather than cured, efforts to maintain and improve quality of life should be considered a primary goal in their disease management.

Achieving optimal self-care by HF patients is widely regarded as essential goal of disease management.[1,33,38] However, HF self-care behaviour is complicated by factors such as ageing, comorbidities, cognitive impairment, frailty and limited social support.[38] Our findings highlight the difficulty of maintaining adequate HF self-care and management adherence. Together with stroke, a history of atrial fibrillation, comorbid transient ischaemic attack and peripheral artery disease contributed to deficiencies in these aspects of care. This is likely due to the additive impact of major chronic disabling conditions contributing to a more burdensome and complex HF management and self-care regimen. This issue needs to be considered carefully when planning with patients and carers how best to optimize disease management strategies. Patients with HF and stroke had poorer engagement in HF self-care and management adherence from 12 months, compared to those without stroke, with differences between the two groups in HF self-care being clinically significant according to interpretability of the EHFScBS-9.[31] This may be explained by HF and stroke being established burdensome conditions,[3,7] both requiring intensive and enduring support. Also, patients with HF and stroke, compared to those without stroke, had significantly more comorbidities, a known barrier to successful self-care.[38] Thus, interventions which focus on prioritizing specific aspects of self-care for HF and stroke independently may be more

effective than general support for patients dealing with such burdensome and complex comorbidities.

In regard to clinical outcomes, our findings of approximately twice the increased risk of hospitalization and mortality in HF patients with stroke concur with those of other studies,[5,6-8] such as one showing patients with stroke after HF had a 2.3 times higher risk of dying than patients without stroke[5] and another showing the odds of dying within 30 days and 1 year since stroke diagnosis, was close to two times greater for patients who had pre-existing HF.[6] Additionally, in our study, comorbid HF and stroke was identified as a predictor of rehospitalizations at 18 months and all-cause mortality up to 3 years independent of age, gender, HF functional status and presence of other comorbidities such as peripheral artery disease, transient ischaemic attack and type 2 diabetes. Also, patients with HF and stroke were rehospitalized up to 84 days earlier and died an average of 5 months earlier compared to those without stroke.

Our findings highlight poor psychosocial, behavioural and clinical outcomes for patients with HF and stroke which, taken together, indicate a diminished likelihood of early and successful recovery. An assessment of the particular needs of this significant and growing patient group should inform the design of appropriately-tailored care management strategies, which can then be evaluated for effectiveness. Patient choice and preferences should be central to such efforts.

Limitations

This was a secondary analysis of COACH data and therefore was constrained by the methods employed in the original study.[21,22] Applicable to all observational trials,

correlation does not prove causation. Although we found no statistically significant differences between proportions of HF patients with and without stroke across intervention and control groups, our study was limited by the lack of patients with severe HF, which may have caused a bias in terms of minimizing the magnitude of the effects on outcome. Also, the absence of a measure of stroke severity, a known predictor of functional dependency,[35] may have impeded our interpretation of clinical outcomes. Another limitation is the absence of recurrent stroke or mortality due to stroke as a clinical outcome measure. It would be valuable information to know if patients with HF and stroke were more likely to have recurrent stroke, as this could potentially influence depression, quality of life, adherence to HF care and clinical outcomes. Using the medical record to determine the presence or absence of prior stroke does not capture severity and may be inaccurate due to poor history taking or documentation and this may have influenced the findings. This is an important consideration when patients with 'history of stroke' in their medical record were more likely to have severe stroke. Lastly, although clinical interview, the gold standard, was not used to diagnose depression, presence of depressive symptoms was assessed via the CES-D which has been well-validated, in both HF and stroke populations,[24] to identify patients who are at high risk of developing a depressive disorder.

Conclusions

To our knowledge, this is the first study to examine psychosocial, behavioural and clinical outcomes in HF patients with stroke compared to those without stroke. These findings not only confirm the poor prognosis in HF patients with stroke, but also that depression is more common, quality of life, HF self-care and HF management adherence are poorer and risk of rehospitalization and mortality are greater in these patients. Further, 12 months post-discharge was identified as a point of heightened vulnerability for those experiencing this

comorbidity that may be ameliorated by strategies that address cardiovascular risk and psychosocial and behavioural factors. This study highlights the clinical relevance of the complex interplay between HF and stroke that requires further investigation and warrants the need for long-term, integrated disease management pathways for patients with comorbid HF and stroke which span the hospital-home interface.

Acknowledgements

None.

Competing interests

None declared.

Funding statement

The COACH study was supported by a program grant from the Netherlands Heart Foundation (grant 2000Z003); D.J.v.V. is a Clinical Established Investigator of the Netherlands Heart Foundation (grant D97.017)

Data sharing statement

The data that supports the findings of this study are available, on reasonable request, from the corresponding author.

Author contributions

CFS, TJ, DRT and MLG conceived and designed the study and drafted the manuscript. MLG, CFS, TJ and DJV analyzed and guided interpretation of data. MHLW, ILL, SM, JC critically advised on important intellectual content and contributed to drafting of the manuscript. All authors read and approved the manuscript. All authors approved the final version to be published. CFS and TJ are responsible for overall content as guarantors accountable to all aspects of the work.

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Table 1. Baseline characteristics as a function of heart failure and stroke comorbidity

	HF (N=918)	HF + stroke (N=105)	OR (95% CI) *Unadjusted*	*P*-value
Demographics				
Age mdn (IR)	73 (57-89)	75 (63-87)		0.069
Male	569 (62%)	70 (67%)	1.23 (0.80-1.88)	0.348
Married/living together	542 (60%)	63 (61%)	0.97 (0.64-1.46)	0.872
Comorbidities				
Type I diabetes mellitus	94 (10%)	14 (13%)	1.35 (0.74-2.46)	**0.330**
Type II diabetes mellitus	153 (17%)	33 (31%)	2.29 (1.47-3.58)	**<0.001**
Transient ischaemic attack	59 (6%)	24 (23%)	4.31 (2.55-7.30)	**<0.001**
COPD	238 (26%)	30 (29%)	1.14 (0.73-1.79)	0.559
History of atrial fibrillation	392 (43%)	59 (56%)	1.72 (1.15-2.59)	0.008
Asthma	36 (4%)	5 (5%)	1.23 (0.47-3.19)	0.678
Renal disease	68 (7%)	10 (10%)	1.32 (0.66-2.64)	0.440
Liver disease	23 (3%)	3 (3%)	1.15 (0.34-3.88)	0.828
Gastro-intestinal disease	105 (11%)	16 (15%)	1.39 (0.79-2.46)	0.255
Hypertension	385 (42%)	54 (51%)	1.47 (0.98-2.20)	0.064
Peripheral artery disease	139 (15%)	29 (28%)	2.14 (1.34-3.40)	**0.001**
Cardiovascular risk factors				
Body mass index	27.1±5	26.3±5		0.219

Systolic blood pressure	118.2±21	119.3±19		0.623
Diastolic blood pressure	68.5±12	67.5±11		0.448
Disease severity				
LVEF	33.7±14.3	33.9±15.1		0.930
NYHA classification				0.650
II	465 (51%)	48 (47%)		
III	410 (45%)	51 (49%)		
IV	30 (3%)	4 (4%)		
Previous HF admission	296 (32%)	38 (36%)	1.19 (0.78-1.82)	0.414
Medications				
ACE inhibitors	673 (73%)	71 (68%)	0.76 (0.49-1.17)	0.215
Angiotensin blockers	110 (12%)	14 (13%)	1.13 (0.62-2.05)	0.688
Beta-blockers	616 (67%)	61 (58%)	0.68 (0.45-1.03)	0.065
Diuretics	878 (96%)	102 (97%)	1.55 (0.47-5.10)	0.468
Coumarin	554 (60%)	71 (68%)	1.37 (0.89-2.11)	0.148
Anti-depressants	65 (7%)	6 (6%)	0.80 (0.34-1.88)	0.602

Nb. Bold *p*-values represent significant alpha after Bonferroni correction (p < .002). COPD, chronic obstructive pulmonary disease; HF, heart failure; IR, interquartile range; LVEF, left ventricular ejection; mdn, median

Table 2. Predictors of moderate and severe depression in final model of multivariable logistic regression over 18 months

Predictors in final step of model	OR (95%CI)	*P*-value
Moderate Depression (CES-D ≥16)		
Baseline		
Gender	1.60 (1.22-2.10)	**0.001**
Age	0.99 (0.97-0.99)	**0.037**
History of stroke	1.57 (1.03-2.41)	**0.036**
12 months		
History of stroke	2.29 (1.22-4.29)	**0.010**
18 months		
History of stroke	1.67 (0.92-3.04)	0.095
Comorbid type II diabetes	1.63 (1.02-2.61)	**0.040**
Severe Depression (CES-D ≥24)		
Baseline		
Gender	1.68 (1.22-2.32)	**0.002**
Age	0.98 (0.97-0.99)	**0.010**
12 months		
History of stroke	2.83 (1.27-6.28)	**0.011**

18 months		
Age	0.98 (0.96-1.00)	0.076
History of stroke	2.24 (1.03-4.88)	**0.043**

Nb. Bold *p*-values represent significant alpha, $p<0.05$. Covariates entered in each model: age at index hospitalization; gender; comorbid transient ischaemic attack; comorbid peripheral arterial disease; comorbid type II diabetes mellitus; history of atrial fibrillation; and history of stroke. CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; SE, standard error; OR, odds ratio

Table 3. Predictors of inadequate heart failure management adherence and self-care behaviour in final model of logistic multivariable regression over 18 months

Predictors in final step of model	OR (95% CI)	*P*-value
Inadequate HF management adherence (HFCQ; <3 of 6 behaviours[32])		
Baseline		
History of atrial fibrillation	1.30 (0.99-1.71)	0.060
12 months		
History of stroke	0.39 (0.18-0.81)	**0.012**
18 months		
History of stroke	0.35 (0.17-0.72)	**0.004**
Comorbid TIA	0.40 (0.19-0.78)	**0.008**
History of atrial fibrillation	1.79 (1.04-3.07)	**0.035**
Inadequate self-care behaviour (EHFScB-9; <70[30])		
Baseline		
Age	1.02 (1.01-1.03)	**0.001**
History of stroke	1.49 (0.97-2.29)	0.069
12 months		
Age	1.02 (1.01-1.03)	**0.009**
History of stroke	1.80 (1.05-3.11)	**0.034**

18 months		
History stroke	2.87 (1.61-5.11)	**<0.001**
Comorbid peripheral arterial disease	1.65 (1.05-2.60)	**0.030**

Nb. Bold *p*-values represent significant alpha, $p<0.05$. Covariates entered in each model: age at index hospitalization; gender; comorbid transient ischaemic attack; comorbid peripheral arterial disease; comorbid type II diabetes mellitus; history of atrial fibrillation; and history of stroke. CI, confidence interval; EHFScB-9, European Heart Failure Self-care Behaviour scale; HF, heart failure; HFCQ, Heart Failure Compliance Questionnaire; OR, odds ratio; SE, standard error; TIA, transient ischaemic attack

Table 4. Rehospitalization and mortality hazard ratios as a function of HF and stroke comorbidity

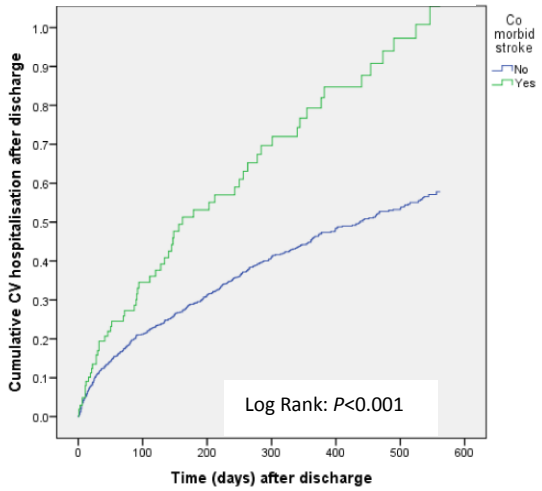
	N (%)		Hazard ratio (95% CI)		Hazard ratio (95% CI) adjusted: age, sex, NYHA, other comorbidities*	
	HF (*n*=918)	HF + stroke (*n*=105)	(unadjusted)	*P*-value		*P*-value
Clinical endpoints						
18 months post-discharge						
CV rehospitalization	373 (41%)	60 (57%)	1.74 (1.32-2.29)	**<0.001**	1.45 (1.09-1.94)	**0.012**
HF rehospitalization	218 (24%)	42 (40%)	1.99 (1.43-2.78)	**<0.001**	1.66 (1.17-2.36)	**0.005**
All-cause rehospitalization	495 (54%)	72 (69%)	1.57 (1.23-2.02)	**<0.001**	1.31 (1.01-1.70)	**0.044**
HF rehospitalization/ death	344 (38%)	67 (64%)	2.04 (1.57-2.66)	**<0.001**	1.68 (1.27-2.22)	**<0.001**
All-cause mortality	230 (25%)	42 (40%)	1.78 (1.28-2.48)	**<0.001**	1.46 (1.03-2.07)	**0.033**
3 years post-discharge						
All-cause mortality	354 (39%)	59 (56%)	1.75 (1.33-2.31)	**<0.001**	1.43 (1.07-1.91)	**0.016**

Nb. *other comorbidities; Type 2 diabetes mellitus, transient ischemia attack, peripheral artery disease, history of atrial fibrillation. CI, confidence interval; CV, cardiovascular; HF, heart failure; NYHA, New York Heart Association

Figure legend

Fig. 1. Kaplan–Meier event curves for HF patients with (n=105) and without (n=918) stroke across **(A)** CV rehospitalization by 18 months, **(B)** HF rehospitalization by 18 months, **(C)** CV rehospitalization or death by 18 months, and **(D)** all-cause mortality by 3 years as a function of HF and stroke comorbidity. Kaplan-Meier curves represent a comparison of HF patients with (green) and without (blue) stroke, for days to rehospitalization (A; B; C) or to death (D). Kaplan-Meier curves identified HF patients with stroke as significantly ($p < 0.001$) worse than HF patients without stroke across all clinical outcomes. 'Number at risk' columns are in 200 day increments for rehospitalization's, and 400 day increments for mortality.

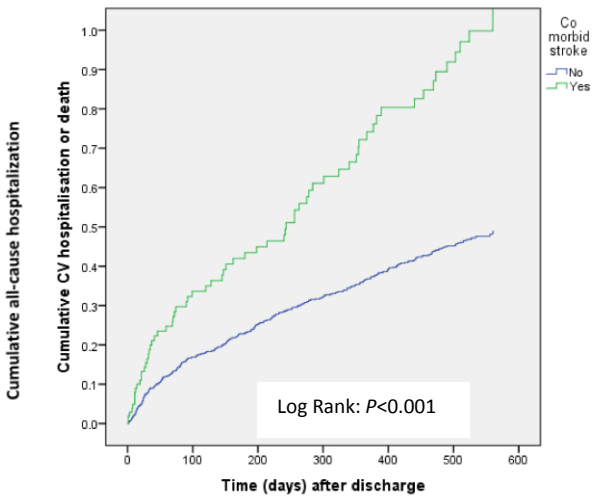
A. CV rehospitalisation by 18 months



Number at risk

Without Stroke	918	632	553	102
With Stroke	105	53	38	6

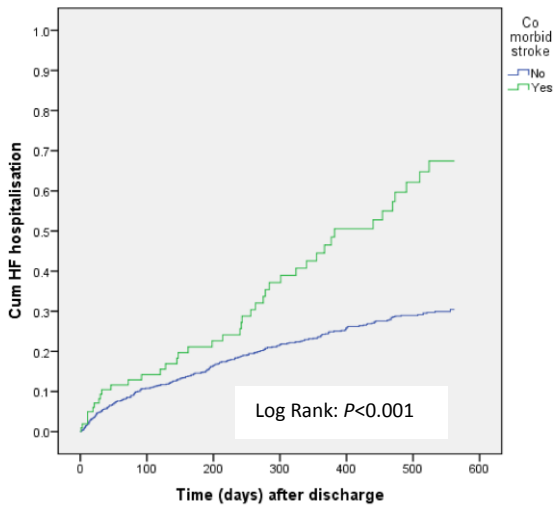
B. All-cause rehospitalisation by 18 months



Number at risk

Without Stroke	918	557	432	71
With Stroke	105	38	30	5

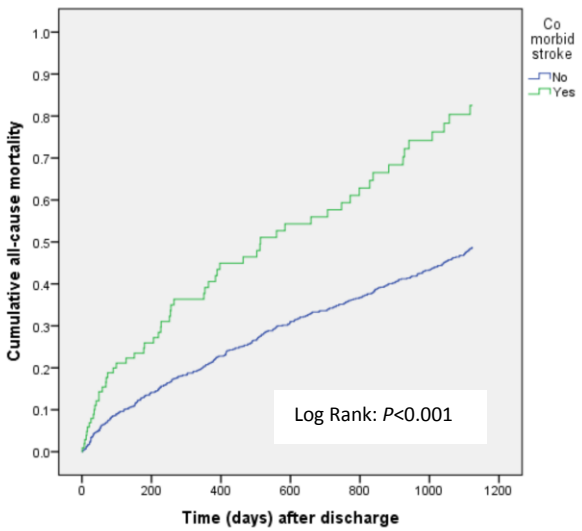
C. HF rehospitalisation by 18 months



Number at risk

Without Stroke	918	718	623	133
With Stroke	105	68	50	10

D. All-cause mortality by 3 years



Number at risk

Without Stroke	918	744	650	563
With Stroke	105	70	59	45

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-10
		(*c*) Explain how missing data were addressed	18
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	8-9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9-10
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	8-9
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-13

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-13
		(*b*) Report category boundaries when continuous variables were categorized	10-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17-19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	19-20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.