BMJ Open

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Stroke and mortality in patients with incident heart failure: the Diet, Cancer and Health (DCH) cohort study

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ABSTRACT

Objective: The objective was to test the hypothesis that the risk of stroke, death and the composite of 'stroke and death' would be increased among patients with incident heart failure (HF). While HF increases the risk of mortality, stroke and thromboembolism in general, the 'extreme high-risk' nature of incident HF is perhaps under-recognised in everyday clinical practice.

Design: Prospective cohort study.

Setting: Large Danish prospective epidemiological cohort.

Participants: Subjects in the Diet, Cancer and Health study.

Outcome measures: Stroke, death and the composite of 'stroke and death' among patients with incident cases of HF, without concomitant atrial fibrillation.

Results: From the original cohort, 1239 patients with incident HF were identified. Incidence rates show a higher incidence in the initial period following the diagnosis of HF, with a markedly higher rate of death and stroke (ischaemic or haemorrhagic) in the initial 30 days following the diagnosis of incident HF. While lower than the risk at 0—30 days, the higher risk did not return to normal at 6+ months after the diagnosis of incident HF. This risk increase was apparent for the end points of stroke (ischaemic or haemorrhagic or both) whether or not a vitamin K antagonist (VKA) was used. With VKA use, there was a lower adjusted HR for death and the composite of 'death or stroke' compared to non-VKA use at the three time intervals following diagnosis of HF, whether 0—30 days, 30 days to 6 months and 6+ months. On multivariate analysis, previous stroke/transient ischaemic attack/thromboembolism was a predictor of higher risk of stroke, death and the composite of 'stroke and death', while VKA treatment was a highly significant predictor of a lower risk for death (adjusted HR 0.46, 95% CI 0.28 to 0.74, p<0.001) and the combined end point of death or stroke (adjusted HR 0.64, 95% CI 0.43 to 0.96, p=0.003).

Conclusions: Based on relative hazards, incident HF is clearly a major risk factor for stroke, death and the composite of 'stroke and death', especially in the initial 30 days following initial diagnosis. The use of VKA therapy was associated with a lower risk of these end points. These findings would have major implications for the approach to management of patients presenting with incident HF, given the high risk of this population

ARTICLE SUMMARY

Article focus
- While HF increases the risk of mortality, stroke and thromboembolism in general, the 'extreme high-risk' nature of incident HF is perhaps under-recognised in everyday clinical practice.
- We tested the hypothesis that the risk of stroke, death and the composite of 'stroke and death' would be increased among patients with incident HF.

Key messages
- Incident HF is clearly a major risk factor for stroke, death and the composite of 'stroke and death', especially in the initial 30 days following initial diagnosis.
- The use of VKA therapy was associated with a lower risk of these end points.
- These findings would have major implications for our approach to management of patients presenting with incident HF, given the high risk of this population for death and stroke, which may be ameliorated by VKA therapy.

Strengths and limitations of this study
- Our 'real-world' study focused on incident HF, this reflects the new development of 'clinically significant' HF requiring the need for hospital case contact.
- Some deaths could be due to undiagnosed stroke, and some patients with HF could have undiagnosed AF, where the benefits of VKA therapy on stroke and mortality have been clearly shown in clinical trials.
- The incidence of stroke was defined by the Danish National Patient Register, and not all stroke end points were defined by cerebral imaging.
- The choice of VKA therapy was non-randomised and could be biased by a selective preference for VKA therapy and variance in use over time.

for death and stroke, which may be ameliorated by VKA therapy.

INTRODUCTION

Heart failure (HF) is a major healthcare burden and is increasing in incidence and prevalence.[1] Despite efforts with various pharmacological interventions, mortality and morbidity remain high in patients with this common condition.

When associated with atrial fibrillation, the presence of HF is also associated with a higher risk of stroke and thromboembolism.[2] However, the impact of HF per se, in the absence of atrial fibrillation, on stroke and mortality is less clear. Recent cohort data suggest that the risk of stroke and thromboembolism is greatest in the initial period (<30 days) following the diagnosis of HF, although the risk may still be evident until 6 months.[3] Indeed, postmortem studies suggest that many sudden deaths in HF have an aetiology related to thromboembolism.[4] Even studies from >50 years ago suggest that anticoagulation with warfarin may have an impact on mortality and thromboembolism, while the benefits of antiplatelet therapy are less evident.[5 6] While antithrombotic therapy has limited impact on mortality in contemporary trials,[7] there is some evidence that warfarin reduces the risk of HF hospitalisations and thromboembolism.[2 8 9]

We hypothesised that incident HF would predict the risk of stroke, death and the composite of 'stroke and death'. To test this hypothesis, we analysed data from a large Danish prospective cohort, the Diet, Cancer and Health (DCH) study, to assess the RR of stroke and/or death according to the exposure to incident HF with no concomitant atrial fibrillation. Furthermore, among participants who developed HF, the predictors of stroke and/or death were explored.

METHODS

The DCH study cohort was established between 1993 and 1997. The study design has been reported in detail elsewhere.[10] The primary objective of this prospective study was to investigate the aetiological role of diet and lifestyle in the development of cancer, and 57 053 participants were enrolled (27 178 men and 29 876 women, respectively) in the cohort. The study participants were aged between 50 and 64 years, living in the urban areas of Copenhagen and Aarhus, and without a cancer diagnosis registered in the Danish Cancer Registry at baseline. Participants were, for this study, followed from January 1995 until December 2009. The DCH cohort has detailed information on demographics, existing comorbidities and individual risk factors, including myocardial infarction (MI) and peripheral artery disease (PAD). Cross linkage between the DCH cohort and the Danish National Patient Register provides detailed information on incident HF, stroke/thromboembolism (TE) and death and specific information about censoring from emigration and death during follow-up until December 2009. The study was conducted in accordance with the Helsinki Declaration II and approved by the regional ethics committees.

Figure 1 Flowchart describing case exclusion for the two data sets used for analysis. DCH, Diet, Cancer and Health; HF, heart failure.
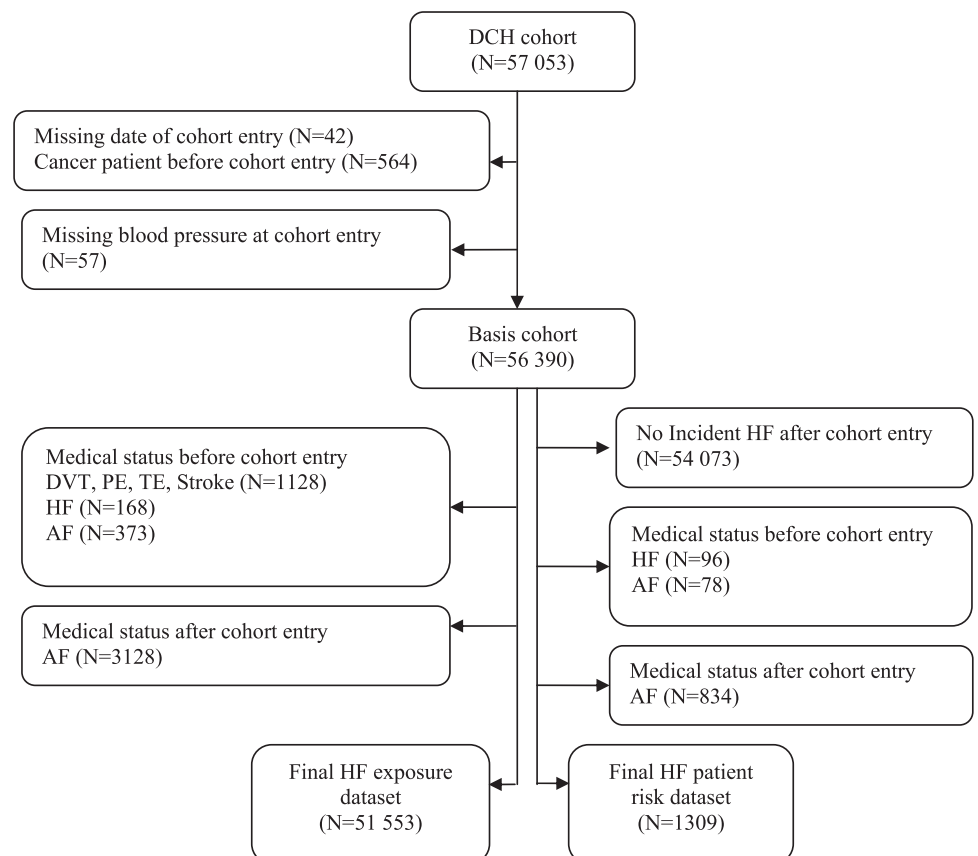
Case finding

The DCH cohort subjects were linked to the National Registry of Patients, dating back to 1976, using the Danish Personal Identification number. This is a unique and national identification number, which is part of the personal information stored in the Civil Registration System.

Codes from the International Classification of Diseases (ICD) were used to extract admissions for baseline clinical diagnoses from the Danish National Patient Register,[11] stroke end points, AF and HF. ICD-8 was used until 1994 and replaced by ICD-10 thereafter. The ICD codes used are given in web only table X1. Information on drug use was extracted from the Danish National Prescription Registry.[12] Drug categories and ATC codes used are listed in web only table X. Based on the prescription information on amount and time lap between individual prescriptions treatment periods were estimated for each subject and drug.

Study subjects were selected from the DCH cohort following the criteria as described in figure 1, which were essentially DCH participants without selected cardiovascular diseases before study entry. Two sets of data were created. The first set was used for estimating the risk for an outcome if exposed to an incident HF event. The second set was used for investigating potential risk factors for an outcome if having experienced a HF event.

Outcomes

We determined our outcomes as stroke, death or 'death and stroke' during follow-up. Given the nature of the data set, some deaths could have been due to (undiagnosed) stroke, and the coding of 'stroke' refers to all strokes, consistent with recommendations on outcomes in AF studies.[13] Rehospitalisation for HF was considered in a subanalysis. Rehospitalisation was defined as a subsequent re-admission to hospital with HF. Re-entry should be at least 4 days from discharge and should not be within a treatment period where the patient was seeing regularly the hospital for ambulant control for HF.

Statistical methods

Descriptive analysis with proportions for discrete covariates and means and SDs for continuous covariates was used to describe the baseline distributions (ie, at time of entry into DCH cohort and at HF diagnosis). HF exposure was analysed both as a constant effect, from the time of incident HF event, and as a piecewise constant effect, allowing for a separate hazard rate in the periods: 0−1, 1−6 and 6+ months after incident HF event. Incidence rates of the outcomes were calculated for each level of the exposure groups. Cox proportional hazards models with age as time scale were used to estimate the HRs for HF exposure and reported as crude and adjusted measures of association. Primary

Table 1 Clinical characteristics of the study cohorts

Clinical characteristic	Whole cohort, n (%) or mean±SD	Incident HF, n (%) or mean±SD	Incident HF patients without prior stroke or VTE, n (%) or mean±SD	No HF, n (%) or mean±SD
N	51 553	1309	1239	50 314
Age, years	56.6±4.3	67.1±5.5	58.7±4.3	56.5±4.3
Age ≥75 years at heart failure diagnosis		86 (6.6)	80 (6.5)	
Women	27 722 (53.8)	495 (37.8)	463 (37.4)	27 259 (54.2)
Past medical history before entry				
MI	633 (1.3)	450 (34.4)	143 (11.5)	490 (1.0)
CAD	293 (0.6)	328 (25.1)	67 (5.4)	226 (0.4)
Peripheral vascular disease	185 (0.4)	119 (9.1)	22 (1.8)	163 (0.3)
Hypertension	1022 (2.0)	486 (37.1)	91 (7.3)	931 (1.8)
Diabetes type I	244 (0.5)	83 (6.3)	16 (1.3)	227 (0.5)
Type II	469 (0.9)	208 (15.9)	49 (0.0)	419 (0.8)
Restrictive cardiomyopathy	13 (0.03)	32 (2.4)	2 (0.2)	11 (0.02)
Thyroid disease	383 (0.7)	33 (2.5)	13 (1.0)	370 (0.7)
Systolic blood pressure, mm Hg	139.1±20.3		148.3±21.7	138.8±20.3
Drugs				
ACEI	1469 (2.9)		103 (8.3)	1336 (2.7)
ARB	210 (0.4)		9 (0.7)	201 (0.4)
ACEI/ARB	1663 (3.2)		111 (9.0)	1552 (3.1)
Statins	626 (1.2)		76 (6.3)	550 (1.1)
Antiplatelet drugs	1102 (2.1)		117 (9.4)	985 (2.0)
Warfarin	40 (0.1)		9 (0.7)	31 (0.1)

Baseline for patients with incident HF was at time of HF diagnosis.
ACEI, ACE inhibitor; ARB, angiotensin II receptor blocker; CAD, coronary artery disease; HF, heart failure; TIA, transient ischaemic attack; VKA, vitamin K antagonist.

adjustment was vitamin K antagonist (VKA) treatment modelled as a time-varying covariate. The analysis was further adjusted for sex and systolic blood pressure (linear effect) as confounders. Linearity assumption for systolic blood pressure was tested by fitting alternative models using fractional polynomials.[14] Test for VKA treatment acting as an effect modifier was performed by likelihood ratio tests. The risk factor analysis was performed using a Cox proportional hazards model with time since HF event as time scale. Included a priori defined risk factors were, age >75 at HF event, sex, previous stroke (stroke, transient ischaemic attack (TIA) or TE), known hypertension, previous vascular diseases (coronary artery disease, PAD, DVT, PE or MI) and restrictive cardiomyopathy. All risk factors were analysed and the results reported as crude measures of association and as measures adjusted for VKA treatment. Eventually, a multivariate model with all risk factors including VKA treatment was estimated. VKA treatment was included as a time-varying covariate. The prognostic value of the risk factors was investigated by calculating c-statistics as area under the ROC curves using the method of Heagerty et al[15] to account for censored survival data. The reported c-statistics are averages of 200 cross-validations using 75% of the data for estimation balanced for sex and the remaining for validation. Rehospitalisation rate was estimated as the cumulative incidence rate from a competing risk survival analysis, treating death as a competing risk. A p value <0.05 was considered as statistically significant. Stata/SE V.12 was used for data analysis.

RESULTS

Patient characteristics are summarised in table 1. Of the original cohort of 51 553 subjects without prior HF or AF, we identified 1239 patients with incident HF (figure 1). Patients with HF were older, more likely to be male and had more comorbidities (previous MI, coronary artery disease, PAD, hypertension, diabetes and thyroid disease). Mean blood pressure at baseline was also higher among HF patients. Drug therapies were different between HF patients and the non-HF subjects and may partly reflect their associated comorbidities.

Incidence rates (per 100 person-year) of death and stroke for HF and for three periods after HF are shown in table 2. This clearly shows the higher incidence of death and stroke in the initial period following the diagnosis of HF, with a markedly higher rate of death, stroke (ischaemic or haemorrhagic) in the initial 30 days following the diagnosis of incident HF (figure 2A,B). While lower than the risk at 0–30 days, a higher risk was also observed at 6+ months after the diagnosis of incident HF.

This higher risk was apparently independent of VKA use for the end points of stroke (ischaemic or haemorrhagic or both) (table 3). VKA use was associated with a lower mortality and a lower combined end point of 'death and stroke'.

Table 2 Observed event frequencies and incidence rates (pr 100 person-year) of death and stroke for no HF/HF and for three periods after incident HF

|	Death		All stroke		Ischaemic stroke		Haemorrhagic stroke		Death and stroke	
	N	Rate (95% CI)	N	Rate (95% CI)	N	Rate (95% CI)	N	Rate (95% CI)	N	Rate (95% CI)
No HF	5238	0.77 (0.74 to 0.79)	2519	0.38 (0.37 to 0.40)	2186	0.33 (0.32 to 0.34)	481	0.07 (0.07 to 0.08)	7068	1.07 (1.05 to 1.10)
HF	390	7.64 (6.92 to 8.44)	66	1.42 (1.1 to 1.81)	63	1.35 (1.06 to 1.73)	12	0.24 (0.13 to 0.42)	383	8.25 (7.47 to 9.12)
HF 0–30 days	52	50.90 (38.79 to 66.80)	10	10.66 (5.73 to 19.80)	9	9.52 (4.95 to 18.30)	1	0.98 (0.13 to 7.00)	57	60.74 (46.85 to 78.74)
HF 30 days–6 months	69	14.95 (11.80 to 18.92)	7	1.65 (0.79 to 3.47)	7	1.64 (0.77 to 3.45)	2	0.43 (0.11 to 1.74)	61	14.41 (11.21 to 18.52)
HF 6+ months	269	5.92 (5.26 to 6.68)	49	1.19 (0.90 to 1.57)	47	1.14 (0.85 to 1.51)	9	0.20 (0.10 to 0.38)	265	6.42 (570 to 7.25)
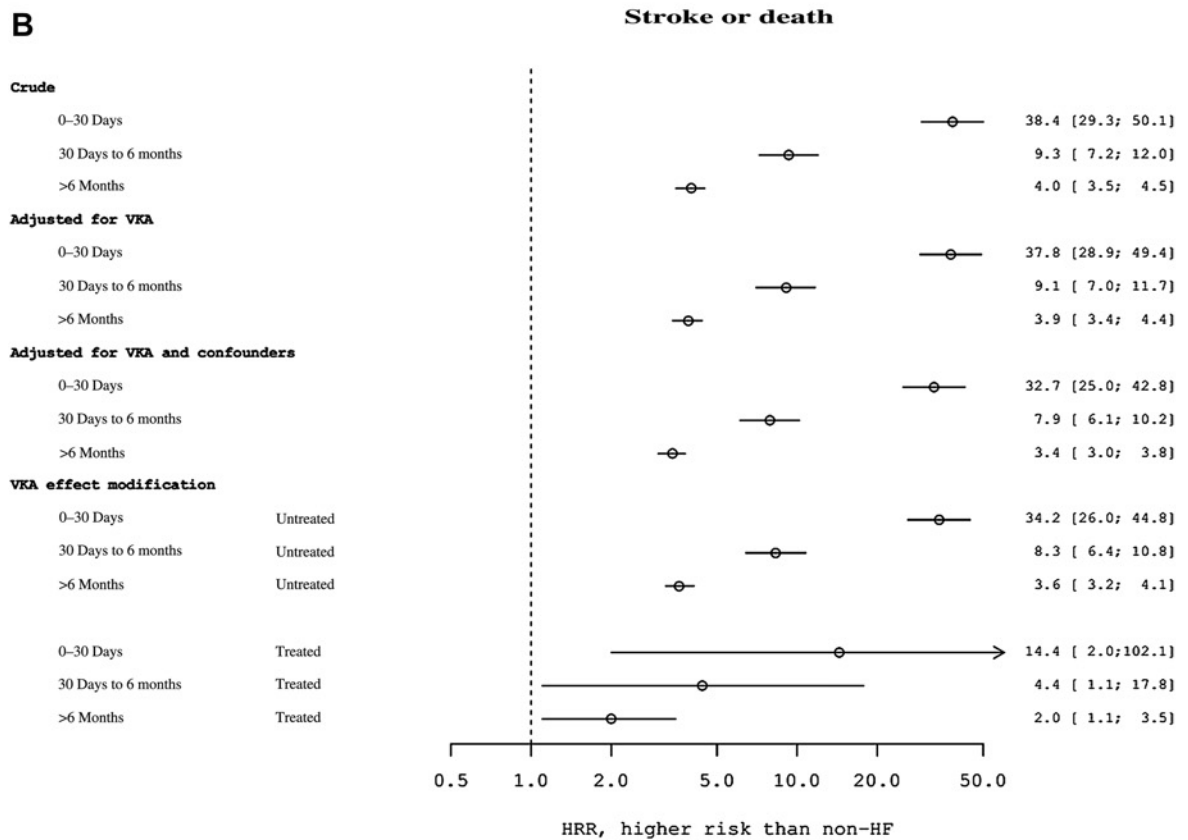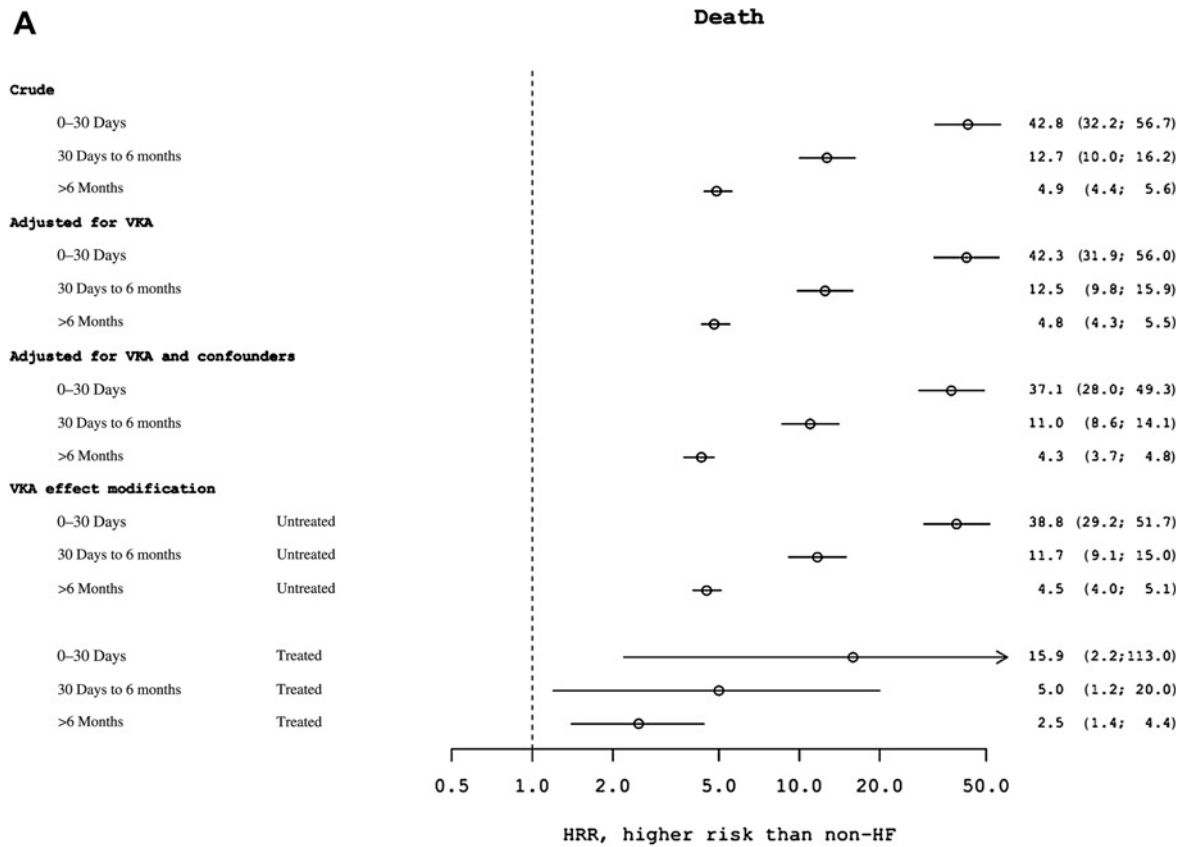
Figure 2 Hazard rate ratios of time after incident heart failure (HF) relative to non-HF exposed. VKA, vitamin K antagonist.

Table 3 HRs and 95% CIs for the associations between incident heart failure (HF) and risk of subsequent death and stroke

		Death HR (95% CI)	All stroke HR (95% CI)	Ischaemic stroke HR (95% CI)	Haemorrhagic stroke HR (95% CI)	Death and stroke HR (95% CI)
	No HF	Ref	Ref	Ref	Ref	Ref
Crude	HF	6.5 (5.9 to 7.2)	2.7 (2.0 to 3.4)	2.9 (2.2 to 3.7)	2.5 (1.4 to 4.5)	5.2 (4.7 to 5.8)
Model 1	HF	6.4 (5.8 to 7.1)	2.6 (2.0 to 3.3)	2.8 (2.2 to 3.7)	2.1 (1.2 to 3.8)	5.1 (4.6 to 5.7)
Model 2	HF	5.6 (5.0 to 6.2)	2.1 (1.7 to 2.7)	2.3 (1.8 to 3.0)	1.8 (1.0 to 3.3)	4.4 (4.0 to 4.9)
Model 2*	HF/−VKA	6.0 (5.3 to 6.6)	2.2 (1.7 to 2.8)	2.3 (1.8 to 3.0)	2.0 (1.0 to 3.7)	4.7 (4.2 to 5.2)
	HF/+VKA	2.9 (1.7 to 4.8)	2.4 (1.0 to 5.8)	3.2 (1.4 to 7.1)	5.4 (1.3 to 21.0)	2.3 (1.3 to 3.8)
	Test effect modification of VKA treatment	p<0.0001	p=0.383	p=0.648	p=0.616	p<0.0001

In some individuals, both ischaemic and haemorrhagic stroke may occur, while in 'all stroke' only first event (whether ischaemic or haemorrhagic) is counted. In the combined end point analysis, we model the association between the outcome events and the status of HF exposure and vitamin K antagonist (VKA) treatment without distinguishing between the type of stroke (ischaemic or haemorrhagic). Constant effect of HF exposure: crude: no adjustment, model 1: adjusted for VKA treatment, model 2: adjusted for VKA treatment, sex, systolic blood pressure. All models use age as time scale.
*Effect modification term added to the model. Test for effect modification is a likelihood ratio test between main effects model and model with interaction term. Expected risks are calculated as in the multiplicative model.

The time interaction is shown in table 4. With VKA use, there was a lower adjusted HR for death and the composite of 'death or stroke' compared with non-VKA use at the three time intervals following diagnosis of HF, whether 0−30 days, 30 days to 6 months and 6+ months (table 4).

Table 5 shows univariate and multivariate predictors for end points in patients with incident HF. Based on the multivariate model, the c-statistics were only modest at 1 year (death 0.57, stroke 0.68 and 'death or stroke' 0.60) and 10 years (0.56, 0.57 and 0.60, respectively). On multivariate analysis, previous stroke/TIA/TE was positively associated with stroke, death and the composite of 'stroke and death', while VKA treatment was a highly significant predictor of a lower risk for death (adjusted HR 0.46, p<0.001) and the combined end point of death or stroke (adjusted HR 0.56, p=0.003).

Figure 3 shows the cumulative incidence rate of readmission to hospital for HF patients, within 5 years 37% (95% CI 34% to 40%) was again having a further HF event that required hospitalisation.

DISCUSSION

In this large 'real-world' cohort study, we demonstrate a significantly greater risk of mortality and/or stroke in the initial 30 days after diagnosis of incident HF and also show that previous stroke/TIA/TE was an independent predictor of mortality and adverse outcomes (stroke) among these patients. In addition, we show that VKA use was associated with statistically significant lower risk of 'death or stroke', which was most apparent in the first 30 days after the diagnosis of incident HF.

Unsurprisingly, patients with HF were older and had more comorbidities, in keeping with previous

Table 4 HRs and 95% CIs for the association between incident heart failure (HF) and the risk of subsequent stroke and ischaemic stroke for various time intervals after the diagnosis of HF

	Presence of HF		HR (95% CI)		
	Possibly modified by VKA		0−30 days	30 days to 6 months	6+ months
Death	No HF		Ref	Ref	Ref
	HF	Crude	47.6 (36.2 to 62.6)	13.9 (11.0 to 17.7)	5.0 (4.4 to 5.6)
		Model 1	47.0 (35.7 to 61.9)	13.7 (10.8 to 17.4)	4.9 (4.3 to 5.5)
		Model 2	41.2 (31.3 to 54.2)	12.0 (9.5 to 15.3)	4.3 (3.7 to 4.9)
	HF/−VKA	Model 2*	43.2 (32.8 to 57.0)	12.9 (10.1 to 16.4)	4.5 (4.0 to 5.2)
	HF/+VKA		15.9 (2.2 to 113.1)	5.0 (1.2 to 20.0)	2.5 (1.4 to 4.5)
Death and stroke	No HF		Ref	Ref	Ref
	HF	Crude	42.0 (32.3 to 54.5)	9.9 (7.7 to 12.8)	4.0 (3.5 to 4.5)
		Model 1	41.3 (31.8 to 53.7)	9.7 (7.5 to 12.5)	3.9 (3.4 to 4.4)
		Model 2	35.7 (27.5 to 46.4)	8.4 (6.5 to 10.8)	3.4 (3.0 to 3.8)
	HF/−VKA	Model 2*	37.4 (28.7 to 48.7)	8.9 (6.9 to 11.5)	3.6 (3.2 to 4.1)
	HF/+VKA		14.3 (2.0 to 101.4)	4.4 (1.1 to 17.4)	1.9 (1.1 to 3.5)

Piecewise constant effect of HF exposure: crude: no adjustment (apart from age), model 1: adjusted for vitamin K antagonist (VKA) treatment, model 2 adjusted for VKA treatment, sex, systolic blood pressure. All models use age as time scale.
*Effect modification term added to the model.

Table 5 Univariate and multivariate predictive power of risk factors for end points

	With risk factor		Without risk factor		HR (95% CI) crude	HR (95% CI) adjusted*	HR (95% CI) multivariate
	N	Event rate (95% CI) (per 100)	N	Event rate (95% CI) (per 100)			
(a) Death (417 events)†							
Age >75 at HF diagnosis	11	11.0 (6.1 to 19.9)	406	7.7 (7.0 to 8.5)	0.90 (0.49 to 1.64)	0.91 (0.50 to 1.67)	0.90 (0.49 to 1.64)
Female	147	7.1 (6.0 to 8.3)	270	8.2 (7.2 to 9.2)	0.87 (0.71 to 1.06)	0.86 (0.70 to 1.05)	0.86 (0.70 to 1.05)
Stroke/TIA/TE	84	14.0 (11.3 to 17.4)	333	7.0 (6.2 to 7.7)	1.89 (1.48 to 2.40)	2.00 (1.57 to 2.54)	2.01 (1.57 to 2.57)
Hypertension	139	8.0 (6.8 to 9.4)	278	7.6 (6.8 to 8.6)	0.99 (0.80 to 1.21)	0.99 (0.80 to 1.21)	0.87 (0.70 to 1.08)
Diabetes	83	10.4 (8.4 to 12.9)	334	7.3 (6.5 to 8.1)	1.36 (1.07 to 1.73)	1.32 (1.04 to 1.68)	1.28 (1.00 to 1.65)
Vascular disease‡	205	7.5 (6.6 to 8.6)	212	8.0 (7.0 to 9.1)	0.94 (0.77 to 1.13)	0.95 (0.78 to 1.15)	0.89 (0.73 to 1.08)
RC	8	5.5 (2.7 to 11.1)	409	7.8 (7.1 to 8.6)	0.72 (0.36 to 1.44)	0.76 (0.38 to 1.53)	0.76 (0.38 to 1.54)
VKA treatment							0.46 (0.28 to 0.74)
(b) All stroke (105 events)§							
Age >75 at HF diagnosis	1	1.0 (0.1 to 7.3)	104	2.1 (1.7 to 2.5)	0.32 (0.04 to 2.33)	0.32 (0.04 to 2.30)	0.29 (0.04 to 2.08)
Female	37	1.9 (1.4 to 2.6)	68	2.1 (1.7 to 2.7)	0.88 (0.58 to 1.31)	0.89 (0.59 to 1.32)	0.87 (0.58 to 1.30)
Stroke/TIA/TE	45	9.2 (6.9 to 12.3)	60	1.3 (1.0 to 1.7)	6.48 (4.38 to 9.58)	6.43 (4.33 to 9.55)	6.43 (4.29 to 9.65)
Hypertension	42	2.6 (1.9 to 3.5)	63	1.8 (1.4 to 2.3)	1.34 (0.91 to 1.99)	1.34 (0.91 to 1.99)	1.05 (0.69 to 1.59)
Diabetes	20	2.7 (1.7 to 4.1)	85	1.9 (1.6 to 2.4)	1.30 (0.80 to 2.11)	1.34 (0.82 to 2.20)	1.06 (0.63 to 1.77)
Vascular disease‡	54	2.0 (1.6 to 2.7)	51	2.0 (1.5 to 2.7)	1.02 (0.69 to 1.49)	1.00 (0.69 to 1.48)	0.90 (0.61 to 1.32)
RC	2	1.5 (0.4 to 2.5)	103	2.1 (1.7 to 2.5)	0.71 (0.17 to 2.87)	0.68 (0.17 to 2.76)	0.72 (0.17 to 2.93)
VKA treatment							1.07 (0.58 to 2.00)
(c) Death or stroke (471 events)¶							
Age >75 at HF diagnosis	11	11.3 (6.2 to 20.2)	460	9.2 (8.4 to 10.1)	0.76 (0.42 to 1.39)	0.77 (0.42 to 1.41)	0.74 (0.40 to 1.35)
Female	168	8.6 (7.4 to 10.0)	303	9.7 (8.6 to 10.8)	0.89 (0.74 to 1.06)	0.88 (0.73 to 1.07)	0.88 (0.73 to 1.06)
Stroke/TIA/TE	106	21.6 (17.9 to 26.2)	365	7.9 (7.2 to 8.8)	2.43 (1.96 to 3.03)	2.53 (2.03 to 3.14)	2.52 (2.02 to 3.52)
Hypertension	163	10.1 (8.6 to 11.7)	308	8.9 (8.0 to 9.9)	1.06 (0.87 to 1.28)	1.06 (0.87 to 1.28)	0.92 (0.75 to 1.12)
Diabetes	96	12.7 (10.4 to 15.6)	375	8.7 (7.8 to 9.6)	1.40 (1.12 to 1.76)	1.38 (1.10 to 1.73)	1.30 (1.03 to 1.65)
Vascular disease‡	234	9.1 (8.0 to 13.3)	237	9.5 (8.3 to 10.7)	0.95 (0.79 to 1.14)	0.95 (0.80 to 1.14)	0.88 (0.73 to 1.06)
RC	8	5.9 (3.0 to 11.8)	463	9.4 (8.5 to 10.2)	0.64 (0.32 to 1.28)	0.62 (0.32 to 1.31)	0.67 (0.33 to 1.34)
VKA treatment							0.64 (0.43 to 0.96)

*Adjusted for VKA treatment.
†Based on the multivariate model, c-statistic at 1 year 0.57, 5 years 0.58, 10 years 0.60.
‡Coronary artery disease, peripheral vascular disease or a previous thromboembolism other than stroke/TIA.
§Based on the multivariate model, c-statistic at 1 year 0.69, 5 years 0.66, 10 years 0.56.
¶Based on the multivariate model, c-statistic at 1 year 0.60, 5 years 0.61, 10 years 0.60.
HF, heart failure; TE, thromboembolism; TIA, transient ischaemic attack; LVEF, left ventricular ejection fraction; VKA, vitamin K antagonist.
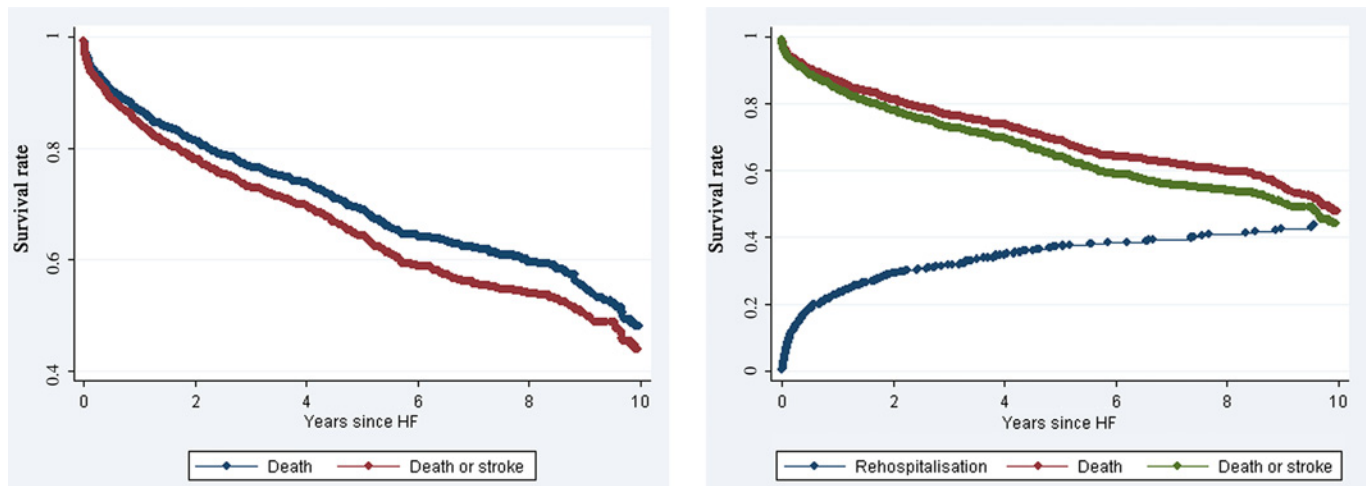
Figure 3 Baseline survival curve for heart failure (HF) patients, time (years) since incident HF. Additionally the cumulative incidence rate of HF events that required rehospitalisation.

epidemiological studies. Of note, average systolic blood pressure at baseline was also higher among patients with incident HF, consistent with epidemiological observations of a strong association between HF and hypertension.[16]

While HF increases the risk of mortality, stroke and thromboembolism in general, the 'extreme high-risk' nature of incident HF is perhaps under-recognised in everyday clinical practice. Our data in this large cohort study very clearly show a higher incidence of death and stroke in the initial period following the diagnosis of HF, with a markedly higher rate of death, stroke (ischaemic or haemorrhagic) in the initial 30 days following the diagnosis of incident HF. This confirms recent observations from the Rotterdam study,[3] which showed that the risk of ischaemic stroke was more than fivefold higher in the first month after diagnosis of HF (age and sex adjusted HR 5.79, 95% CI 2.15 to 15.62) but attenuated over time (age and sex, adjusted HR 3.50 (95% CI 1.96 to 6.25) after 1−6 months and 0.83 (95% CI 0.53 to 1.29) after 0.5−6 years). Our data extend several previous studies of short follow-up that reported a higher risk of stroke shortly after the diagnosis of HF.[17−19] Most of these studies did not adjust for possible confounders other than age and sex or were based on hospitalised patients only. In contrast to the Rotterdam study, the association was still present even at 6+ months after the diagnosis of incident HF.

With VKA use, we found a significantly lower adjusted HR for death and the composite end point of 'death or stroke' compared with non-VKA use. While recent contemporary clinical trials in stable HF patients have suggested that VKA therapy does not impact on mortality, there was a significant reduction in secondary trial end points such as stroke.[7 20] In the recently published WARCEF trial,[20] the rates of the primary outcome (ischemic stroke, intracerebral hemorrhage, or death) were not significantly different between warfarin and aspirin treatment groups (hazard ratio with warfarin, 0.93; 95% CI 0.79 to 1.10; P = 0.40), although ischaemic stroke was significantly reduced (and major

bleeding increased) with warfarin. In a time-varying analysis, the hazard ratio changed over time, slightly favoring warfarin over aspirin by the fourth year of follow-up, for the primary endpoint (P = 0.046).[20] The present cohort includes patients with incident HF, who are clearly at much higher risk than those with stable prior HF. Of note, historical trials of anticoagulation in HF did suggest a beneficial effect on mortality and stroke, although these trials are considered to be less robust by contemporary standards.[5 6] Also, the use of oral anticoagulation in acute medically ill patients, including the subset of patients with HF, did reduce stroke but with a significant increase in risk of bleeding compared with placebo.[21]

The possibility remains that some patients with incident HF have incident (and undiagnosed) atrial fibrillation, which is a well-recognised cause of higher mortality, stroke and TE that is significantly reduced by VKA therapy.[22 23] Indeed, the presence of HF adds to a higher risk of stroke and is incorporated into contemporary stroke risk stratification schemes for AF.[24] The development of atrial fibrillation may be asymptomatic and could have contributed to episodes of incident HF.

We found that on multivariate analysis, previous stroke/TIA/TE was a predictor of higher risk of stroke, death and the composite of 'stroke and death', while VKA treatment was a highly significant predictor of a lower risk for death and the combined end point of death or stroke. The predictive value of risk factors derived from the multivariate analysis was modest, with c-statistics approximately 0.60—this would reflect the multifactorial nature of HF and the many comorbidities that could impact on outcomes, as well as treatment options (eg, ACE inhibitors, devices, etc), which could not be considered in our study. Our observation would also suggest that development of a simple risk stratification score (similar to those seen in atrial fibrillation) would be difficult, and even so, a (potentially complicated) multivariable risk equation derived from

a multivariate analysis may not even have good predictive value in HF populations.

Nonetheless, our study shows that incident HF patients with prior stroke represent a very high-risk category of patients, who could be targeted for oral anticoagulation, given the potential reduction in mortality shown by the present analysis. This hypothesis would need to be tested in a clinical trial of patients with HF who have prior stroke, who may benefit from aggressive thromboprophylaxis.

Limitations

Some deaths could be due to undiagnosed stroke, and some patients with HF could have undiagnosed AF, where the benefits of VKA therapy on stroke and mortality have been clearly shown in clinical trials.[22] One small study using ambulatory ECG monitoring did show that patients with systolic HF did have a high prevalence of asymptomatic arrhythmias, including AF.[25] Also, the incidence of stroke was defined by the Danish National Patient Register, and not all stroke end points were defined by cerebral imaging. Indeed, silent strokes may be quite prevalent in HF patients.[26] Also, the choice of VKA therapy was non-randomised and could be biased by a selective preference for VKA therapy and variance in use over time. Indeed, this cohort study is not a randomised trial, and patients may be treated with multiple drugs for varying periods of time, at different doses and by multiple clinicians.

We also did not have detailed data on HF by the New York Heart Failure Association class (although this would clearly vary over time and with treatments), but since our study focused on incident HF, this reflects the new development of 'clinically significant' HF requiring the need for hospital case contact. Finally, we have used a clinical coding diagnosis of HF, and thus, we did not have echocardiographic or biomarker (eg, BNP) data to confirm the proportions with systolic HF or those with HF and preserved ejection fraction. While the latter patients have better mortality outcomes than those with systolic HF, the morbidity appears to be similar with similar rates of ischaemic stroke, rehospitalisation or progression to New York Heart Association class III−IV.[27]

Conclusions

Incident HF is a major risk factor for death and/or stroke and especially in the initial 30 days following initial diagnosis. Previous stroke/TIA/TE was associated with a higher the risk of stroke, death and the composite of 'stroke and death', while VKA treatment was associated with a lower risk for death and the combined end point of death or stroke. These findings would have major implications for our approach to management of patients presenting with incident HF, given the high risk of this population for death and stroke, which may be ameliorated by VKA therapy.

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