

# BMJ Open Clinical characteristics, precipitating factors, management and outcome of patients with prior stroke hospitalised with heart failure: an observational report from the Middle East

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## ABSTRACT

**Objectives:** The purpose of this study is to report the prevalence, clinical characteristics, precipitating factors, management and outcome of patients with prior stroke hospitalised with acute heart failure (HF).

**Design:** Retrospective analysis of prospectively collected data.

**Setting:** Data were derived from Gulf CARE (Gulf aCute heArt failuRe rEgistry), a prospective multicentre study of consecutive patients hospitalised with acute HF in 2012 in seven Middle Eastern countries and analysed according to the presence or absence of prior stroke; demographics, management and outcomes were compared.

**Participants:** A total of 5005 patients with HF.

**Outcome measures:** In-hospital and 1-year outcome.

**Results:** The prevalence of prior stroke in patients with HF was 8.1%. Patients with stroke with HF were more likely to be admitted under the care of internists rather than cardiologists. When compared with patients without stroke, patients with stroke were more likely to be older and to have diabetes mellitus, hypertension, atrial fibrillation, hyperlipidaemia, chronic kidney disease, ischaemic heart disease, peripheral arterial disease and left ventricular dysfunction ( $p=0.001$  for all). Patients with stroke were less likely to be smokers (0.003). There were no significant differences in terms of precipitating risk factors for HF hospitalisation between the two groups. Patients with stroke with HF had a longer hospital stay (mean±SD days;  $11\pm14$  vs  $9\pm13$ ,  $p=0.03$ ), higher risk of recurrent strokes and 1-year mortality rates (32.7% vs 23.2%,  $p=0.001$ ). Multivariate logistic regression analysis showed that stroke is an independent predictor of in-hospital and 1-year mortality.

**Conclusions:** This observational study reports high prevalence of prior stroke in patients hospitalised with HF. Internists rather than cardiologists were the predominant caregivers in this high-risk group. Patients with stroke had higher risk of in-hospital recurrent strokes and long-term mortality rates.

## Strengths and limitations of this study

- This is the first multicentre multinational study in the Middle East to provide a report on the prevalence, demographics, management and 1-year outcome of patients hospitalised with HF in relation to a history of stroke that included a relatively large number of patients.
- As an observational study, the possibility for unmeasured confounding biases exists. The current study has not recorded the cognitive status and the disability status in patients with stroke, which have a major impact on morbidity.
- Furthermore, no information is available regarding the cause of stroke (embolic vs thrombotic), and future studies need to overcome these limitations.
- Mortality rates at follow-up were only recorded at 1 year without the specification of the exact date of death of each patient.

**Trial registration number:** NCT01467973.

## INTRODUCTION

The prevalence and incidence of stroke in patients with heart failure (HF) and the temporal relation of these two diseases in terms of increasing morbidity and mortality have scarcely been reported from around the world and never from the Middle East. HF is one of the leading causes of hospitalisation, and is a significant factor for morbidity and mortality worldwide. Moreover, HF is a major risk factor for the development of ischaemic stroke with a 2–3-fold increased risk of stroke when compared with patients without HF.<sup>1</sup> Factors that

may contribute to the occurrence of stroke in HF include: atrial fibrillation (AF) or left ventricular (LV) dysfunction that are potential source embolisation.<sup>2,3</sup> The hypercoagulable state and reduced fibrinolysis are a consequence of the activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system.<sup>4,5</sup> In addition to endothelial dysfunction in HF,<sup>6,7</sup> hypotension may also be an additional risk factor for stroke as a result of HF.<sup>8</sup> Moreover, underlying risk factors for the development of HF, such as hypertension and diabetes mellitus,<sup>9</sup> can also predispose to large-artery atherosclerosis and small-vessel thrombosis and hence stroke.<sup>10</sup>

The prevalence and incidence of prior and acute stroke in patients with HF is unclear because of the heterogeneous nature of the limited published studies, most of which were subset analyses of randomised trials rather than epidemiological studies.<sup>11–17</sup> Furthermore, most of the available data are mainly limited to studies conducted in the western world and data about the prevalence of prior stroke among patients hospitalised with HF are lacking. The aim of this study is to define the prevalence, clinical characteristics, precipitating factors, management and outcome of patients with stroke hospitalised with HF, using data from Gulf CARE (Gulf aCute heArt failuRe rEgistry).<sup>18</sup> It is hypothesised that patients with prior stroke when hospitalised with HF have worse outcomes when compared with patients with HF and without prior stroke.

## PATIENTS AND METHODS

### Registry design

Gulf CARE is a prospective multinational multicentre registry that recruited patients from February 2012 to November 2012 who were admitted with the final diagnosis of acute HF (AHF) in 47 hospitals in seven Middle Eastern Arab countries in the Gulf.<sup>18</sup> Data were collected on episodes of hospitalisation beginning with point of initial care, with patient's discharge, transfer out of hospital or in-hospital death, and for those discharged alive 3 and 12 months follow-up was obtained. Patients' recruitment was preceded by a pilot phase of 1 month in November 2011. Institutional or national ethical committee or review board approval was obtained in each of the seven participating countries, and all patients provided informed consent. Each patient was given a unique identification number to prevent double counting. The study is registered at [clinicaltrials.gov](http://clinicaltrials.gov) with the number NCT01467973.

Patients included in this registry were men and women aged 18 years and over with AHF who were admitted to participating hospitals. AHF was defined based on the European Society of Cardiology (ESC) definition<sup>2</sup> and was further classified as either acute decompensated chronic HF (ADCHF) or new-onset AHF (de novo AHF) based on the ESC guidelines. ADCHF was defined as worsening of HF in patients with a previous diagnosis or hospitalisation for HF. New-onset AHF (de novo AHF) was defined as AHF in patients with no history of HF.

Patients were excluded from Gulf CARE if: (1) they were discharged from the emergency room without admission. (2) They were transferred from a non-registry hospital. (3) There was a failure to obtain informed consent. (4) Their final diagnosis was not HF, in which case they were also excluded from the final analyses. Registry organisation and Data Collection and Validation are mentioned in Gulf CARE.<sup>18</sup>

Definitions of data variables in the chronic renal failure (CRF) are based on the ESC guidelines 2008 and the American College of Cardiology clinical data standards 2005.<sup>19,20</sup> Cardiomyopathy was defined as a myocardial disorder in which the heart muscle is structurally and functionally abnormal (in the absence of coronary artery disease, hypertension, valvular disease or congenital heart disease) sufficient to cause the observed myocardial abnormality.<sup>20</sup> Diastolic HF was defined as the presence of symptoms and/or signs of HF and a preserved LV ejection fraction (LVEF) >40%.<sup>19</sup> Stroke/transient ischaemic attack (TIA) was defined as a history of cerebrovascular disease, documented by any one of the following: (1) cerebrovascular ischaemic or haemorrhagic stroke: patient has a history of stroke (ie, any focal neurological deficit of abrupt onset caused by a disturbance in blood supply that did not resolve within 24 h) confirmed by a standard neurological examination with or without a positive imaging study, or an event of presumed ischaemic origin that did not resolve within 24 h, but the imaging showed a new lesion. (2) TIA: patient has a history of any sudden new focal neurological deficit of presumed ischaemic origin as determined by a standard neurological examination that resolved completely within 24 h, with a brain image study not revealing a new lesion. (3) Non-invasive/invasive carotid test with occlusion greater than or equal to 75%. (4) Previous carotid artery surgery. (5) Previous carotid angioplasty.<sup>19</sup> Diabetes mellitus was defined as having a history of diabetes diagnosed and treated with medication and/or insulin or fasting blood glucose 7.0 mmol/L (126 mg/dL) or glycated haemoglobin (HbA1c)  $\geq$ 6.5%. Hypertension was defined as having a history of hypertension diagnosed and treated with medication, blood pressure greater than 140 mm Hg systolic or 90 mm Hg diastolic on at least two occasions or greater than 130 mm Hg systolic or 80 mm Hg diastolic on at least two occasions for patients with diabetes or chronic kidney disease (CKD). Hyperlipidaemia was defined as a history of dyslipidemia diagnosed and/or treated by a physician or total cholesterol greater than 5.18 mmol/L (200 mg/dL), low-density lipoprotein greater than or equal to 3.37 mmol/L (130 mg/dL) or high-density lipoprotein less than 1.04 mmol/L (40 mg/dL). Current smoker was defined as a person smoking cigarettes, a water pipe, a cigar or chewing tobacco within 1 month of index admission.

CKD was defined as glomerular filtration rate (GFR) <60 mL/min/1.73 m<sup>2</sup> for 3 months or more, with or without kidney damage or on dialysis. If no GFR was available, serum creatinine >177 mmol/L or 2 mg/dL was marked as CKD. Obesity was defined as body mass

index greater than 25 kg/m<sup>2</sup>. In the registry, infection is defined as any systemic infection needing antibiotics.<sup>20</sup>

### Statistical analysis

Baseline and outcome data are presented in frequency and percentages for categorical variables and interval variables are presented in mean and SDs or median and range as appropriate. In order to establish the association between stroke and non-stroke groups  $\chi^2$  tests were applied. Student t tests or Wilcoxon rank sum tests were used for interval variables between the two groups as appropriate. Multivariate logistic regression analysis was performed at in-hospital and 1 year mortality for important risk factors. Adjusted OR and 95% CI with p values are presented in table 6. p Value  $\leq 0.05$  (two tailed) is considered statistically significant. SPSS V.21.0 Statistical package was used for the analysis.<sup>21</sup>

## RESULTS

### Patient demographics

Approximately 8.1% of Gulf CARE patients (total 5005 patients) had a history of stroke, with no significant gender or racial differences between stroke and non-stroke groups (tables 1–3). Patients with stroke with HF were older (66.5 vs 59 years,  $p=0.001$ ) and more likely to have diabetes mellitus, hypertension, AF, coronary artery disease and LV dysfunction ( $p=0.001$ ). Patients with stroke were also more likely to have chronic kidney disease and to be on renal replacement therapy than patients without stroke ( $p=0.001$ ) and to have thyroid disease (6.2% vs 3.4%,  $p=0.001$ ) and previous coronary artery bypass grafting (7% vs 10.9%,  $p=0.004$ ) and less likely to be smokers ( $p=0.003$ ) or have a history of asthma/chronic obstructive pulmonary disease. Patients with stroke were more likely to present with ADCHF

**Table 1** Baseline demographic and clinical characteristics (no stroke/TIA vs stroke/TIA)

Variable	No stroke/TIA N=4601 (91.9%)	Stroke/TIA N=404 (8.1%)	p Value
Acute new-onset heart failure (%)	2150 (46.7)	126 (31.2)	
Acute decompensated chronic heart failure (%)	2451 (53.3)	278 (68.8)	0.001
Age (mean $\pm$ SD)	59 $\pm$ 14.9	66.5 $\pm$ 13	0.001
Gender			
Male (%)	2892 (62.9)	239 (59.2)	
Female (%)	1709 (31.1)	165 (40.8)	0.14
Ethnicity			
Arab (%)	4130 (89.8)	386 (95.5)	
Asians (%)	455 (9.9)	18 (4.5)	
Others (%)	16 (0.3)	0 (0)	0.001
Main caregiver			
Cardiologist (%)	3326 (72.3)	249 (61.6)	
Internist (%)	1275 (27.7)	155 (38.4)	0.001
Previous CV history			
HF previous admission (%)			
$\leq 6$ months (%)	2439 (53)	278 (68.8)	0.001
Known systolic LV dysfunction (%)	2053 (44.6)	228 (56.4)	0.001
Known CAD (%)	2083 (45.3)	254 (62.9)	0.001
Valvular heart disease (%)	608 (13.2)	67 (16.6)	0.06
PVD (%)	162 (3.5)	61 (15.1)	0.001
Atrial fibrillation (%)	569 (11.1)	98 (24.3)	0.001
Current smoking (%)	1038 (22.6)	65 (16.1)	0.003
Type 1 DM (%)	160 (3.5)	25 (6.2)	
Type 2 DM (%)	2052 (44.6)	255 (63.1)	0.001
Known HTN (%)	2718 (59.1)	341 (84.4)	0.001
Known hyperlipidaemia (%)	1572 (34.2)	227 (56.2)	0.001
CKD/dialysis (%)	631 (13.7)	113 (28)	0.001
Sleep apnoea requiring therapy (%)	88 (1.9)	11 (2.7)	0.26
Family history of cardiomyopathy/heart failure (%)	244 (5.3)	15 (3.7)	0.17
Khat (%)	852 (18.5)	39 (9.7)	0.001
Alcohol (%)	165 (3.6)	11 (2.7)	0.63
Peripartum (at present) (%)	76 (1.7)	2 (0.5)	0.07
Radiation (%)	19 (0.4)	0 (0)	0.20
Chemotherapy (%)	29 (0.6)	3 (0.7)	0.79
Thyroid disease (%)	156 (3.4)	25 (6.2)	0.001
Asthma/COPD (%)	446 (9.7)	55 (13.6)	0.01

CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; DM, diabetes mellitus; HTN, hypertension; LV, left ventricular; PVD, peripheral vascular disease; TIA, transient ischaemic attack.

**Table 2** Clinical presentation (symptoms, signs; stroke/TIA vs no stroke/TIA)

Variable	No stroke/TIA N=4601 (91.9%)	Stroke/TIA, N=404 (8.1%)	p Value
Clinical symptoms			
Cardiac arrest (%)	138 (3)	19 (4.7)	0.06
NYHA I (%)	124 (2.7)	5 (1.2)	
NYHA II (%)	933 (20.3)	72 (17.8)	
NYHA III (%)	1973 (42.9)	188 (46.5)	
NYHA IV (%)	1471 (32)	132 (32.7)	0.22
Orthopnoea (%)	3618 (78.6)	324 (80.2)	0.46
Paroxysmal nocturnal dyspnoea (%)	2942 (63.9)	274 (67.8)	0.12
Abdominal/lower limb swelling (%)	2055 (44.7)	187 (46.3)	0.53
Weight gain (yes) (%)	1207 (26.2)	100 (24.8)	0.52
Chest pain (%)	2034 (44.2)	166 (41.1)	0.23
Palpitation (%)	1413 (30.7)	107 (26.5)	0.08
Easy fatigability (%)	2604 (56.6)	230 (56.9)	0.89
Syncope in the last 1 year (%)	218 (4.7)	45 (11.1)	0.001
Clinical signs			
Heart rate (mean±SD)	97±23	95±22.9	0
BP (mm Hg) (mean±SD)			
Systolic	137±34	142±33	0.01
Diastolic	81±20	80±19.5	0.37
RR (mean±SD)	24.6±5.9	24.9±5.8	0.32
Weight (kg) (mean±SD)	74±17	76±17.6	0.02
Height (cm) (mean±SD)	162±8.6	163±9	0.56
Waist circumference (cm) (mean±SD)	92±15	93±16.7	0.84
BMI (kg/m <sup>2</sup> ) (mean±SD)	28±6	29±6.3	0.03
Raised JVP>6 cm (%)	2323 (56.5)	203 (50.2)	0.93
Peripheral oedema (%)	2496 (54.2)	231 (57.2)	0.26
Ascites (%)	658 (14.3)	65 (16.1)	0.33
Enlarged tender liver (%)	1260 (27.4)	78 (19.3)	0.001
Gallop (%)	1747 (38)	129 (31.9)	0.02
Basal lung crepitation (%)	4214 (91.6)	383 (94.8)	0.02
Signs of pleural effusion (%)	847 (18.4)	77 (19.1)	0.75

BMI, body mass index; BP, blood pressure; JVP, jugular venous pressure; NYHA, New York Heart Association; RR, respiratory rate; TIA, transient ischaemic attack.

with more frequent recent ( $\leq 6$  months) HF hospitalisations ( $p=0.001$ ), and more likely to be admitted under the care of internists rather than cardiologists when compared with patients without stroke.

### Investigations during hospitalisation

Patients with stroke were more likely to be admitted with AF when compared with patients without stroke; atrial fibrillation/flutter (12.7% vs 24.9%,  $p=0.001$ ; table 4). Patients with stroke were also more likely to have concentric LV hypertrophy (26.8% vs 32.7%,  $p=0.02$ ), and less likely to have mitral regurgitation (30.4% vs 22.5%,  $p=0.001$ ) with no differences in the mean EF on echocardiographic assessment between the two groups.

Patients with stroke were more likely to have a lower GFR (mean±SD;  $58\pm 36.6$  vs  $69\pm 35.7$ ,  $p=0.001$  and, as a result, higher serum creatinine (mean±SD;  $146\pm 111$  vs  $129\pm 117$  mg/dL,  $p=0.003$ ) and blood urea (mean±SD;  $12.8\pm 9$  vs  $11\pm 8.4$  mg/dL,  $p=0.002$ ). Patients with stroke were also more likely to have lower admission haemoglobin levels (mean±SD;  $11.9\pm 2.3$  vs  $12.7\pm 2.4$  mg/dL,  $p=0.001$ ).

### Precipitating factors, hospitalisation course and outcomes

There were no significant differences in terms of precipitating factors for HF hospitalisation between the two groups (tables 5 and 6).

Patients with stroke were more likely to require invasive and non-invasive ventilations (12.4% vs 8.1%,  $p=0.003$ ), (15.3% vs 8.9%,  $p=0.001$ ), respectively, and were also more likely to require inotropic support (21.8% vs 15.1%,  $p=0.001$ ), AF therapy (11.4% vs 5.8%,  $p=0.001$ ), renal replacement therapy (2.5% vs 4.5%,  $p=0.02$ ) and blood transfusions (9.2% vs 4.7%,  $p=0.001$ ) when compared with patients without stroke. Patients with stroke were also more likely to suffer recurrent strokes and have systemic infections that require antibiotic treatment (34.9% vs 23.2%,  $p=0.001$ ) during the same hospitalisation when compared with patients without stroke (table 5). The clinical workup of patients with stroke showed that they were more likely to have ischaemic heart disease (59.2% vs 42.7%,  $p=0.01$ ) and less likely to have other types of cardiomyopathies (13.1% vs 18.7%  $p=0.005$ ), including idiopathic cardiomyopathy (9.2% vs 13.1%,  $p=0.02$ ; table 5).

**Table 3** Medications and interventions (stroke/TIA vs no stroke/TIA)

Variable	Before admission			On discharge		
	No stroke/TIA N=4601 (91.9%)	Stroke/TIA N=404 (8.1%)	p Value	No stroke/TIA N=4601 (91.9%)	Stroke/TIA N=404 (8.1%)	p Value
Digoxin	758 (16.5)	92 (22.8)	0.001	1112 (24.2)	95 (23.5)	0.77
Oral nitrates	1151 (25)	154 (38.1)	0.001	1636 (35.6)	186 (46)	0.001
Hydralazine	187 (4.1)	34 (8.4)	0.001	299 (6.5)	54 (13.4)	0.001
Aspirin	2781 (60.4)	308 (76.2)	0.001	3538 (76.9)	313 (77.5)	0.80
Clopidogrel	849 (18.5)	117 (29)	0.001	1631 (35.5)	167 (41.3)	0.02
Oral anticoagulants (%)	537 (11.7)	81 (20)	0.001	806 (17.5)	91 (22.5)	0.01
Statin	2269 (49.3)	286 (70.8)	0.001	311 (67.7)	319 (79)	0.001
Allopurinol	121 (2.6)	14 (3.5)	0.32	219 (4.8)	20 (5)	0.86
Ivabradine (%)	107 (2.3)	8 (2.0)	0.66	227 (4.9)	17 (4.2)	0.52
Antiarrhythmic (%)	116 (2.5)	10 (2.5)	0.96	208 (4.5)	15 (3.7)	0.45
Antidepressants (%)	57 (1.2)	9 (2.2)	0.10	82 (1.8)	10 (2.5)	0.32
BB						
Carvedilol	992 (49.6)	105 (50.2)	0.87	1600 (51.6)	140 (53.8)	0.48
Metoprolol	197 (9.9)	26 (12.4)	0.24	295 (9.5)	32 (12.3)	0.14
Bisoprolol	648 (32.4)	59 (28.2)	0.22	1151 (37.1)	80 (30.8)	0.04
ACE inhibitors	1968 (42.8)	164 (40.6)	0.40	2694 (58.6)	188 (46.5)	0.001
ARBs	563 (12.2)	84 (20.8)	0.001	725 (15.8)	77 (19.1)	0.08
Aldosterone antagonists	778 (16.9)	62 (15.3)	0.42	1921 (41.8)	135 (33.4)	0.001
Cardiac procedures						
PCI	484 (10.5)	55 (13.6)	0.05	2861 (6.2)	13 (3.2)	0.02
CABG	322 (7)	44 (10.9)	0.004	65 (1.4)	4 (1.0)	0.49
Device therapy (yes) (%)						
CRT-P	4 (0.1)	1 (0.2)		2 (0)	0 (0)	
CRT-D	52 (1.1)	4 (1.0)		26 (0.6)	3 (0.7)	
ICD	80 (1.7)	12 (3)	0.37	45 (1.0)	8 (2.0)	0.10
Valve repair/replacement (yes) (%)	148 (3.2)	19 (4.7)	0.11	88 (1.9)	6 (1.5)	0.54

ARBs, angiotensin receptors blockers; BB, B blockers; CABG, coronary artery bypass grafting; CRT, cardiac resynchronization therapy; ICD, International Classification of Diseases; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack.

Patients with stroke were more likely to be discharged on oral nitrates, hydralazine, statin, ACE inhibitors (ACEIs), aldosterone antagonists ( $p=0.001$ ), oral anticoagulants ( $p=0.02$ ) and clopidogrel ( $p=0.01$ ) when compared with patients without stroke (table 3). In comparison with stroke patients non-stroke patients had percutaneous coronary intervention during hospitalisation ( $p=0.02$ ).

Patients with stroke had a longer hospital stay (mean  $\pm$ SD days;  $11\pm 14$  vs  $9\pm 13$ ,  $p=0.03$ ) as well as a higher but statistically non-significant in-hospital (8.4% vs 6.1%,  $p=0.06$ ) and a significantly higher 1-year mortality rate (32.7% vs 23.2%,  $p=0.001$ ; table 5). On multivariate logistic regression analysis, stroke was an independent mortality predictor for in-hospital and 1-year follow-up (table 6). Age, hypertension, peripheral vascular disease and AF were independent risk factors for stroke in patients with HF (table 6).

### Cardiologist vs internist care

Subanalysis of patients with prior stroke according to whether the primary care provider is a cardiologist versus internist showed the following: patients admitted to cardiologists were more likely to be prescribed clopidogrel (48.2% vs 30.3%,  $p=0.001$ ) and ACEI (51.8 vs

38.1%,  $p=0.007$ ) and with less incidence of recurrent stroke (2% vs 11%,  $p=0.001$ ), less major bleeding (0% vs 1.9%,  $p=0.03$ ) and the need for blood transfusion (6.4% vs 13.5%,  $p=0.02$ ) when compared with patients with prior stroke hospitalised under the care of internists. Patients with prior stroke with systemic infection requiring antibiotics were more likely to be admitted under internal medicine care (46.5% vs 27.7%,  $p=0.001$ ) with higher in-hospital mortality (13.5% vs 5.2%,  $p=0.009$ ) with no significant differences in the duration of hospital stay ( $11\pm 17$  vs  $10\pm 10$  (days),  $p=0.33$ ) when compared with those admitted under cardiologist care. One year follow-up showed non-significant marginally higher rehospitalisation for patients under internist care (19.3% vs 24.5%,  $p=0.07$ ) with significantly higher mortality when compared with patients under cardiologist care (69.9% vs 63.2%,  $p=0.002$ ; table 7).

### DISCUSSION

The current registry of patients hospitalised for HF demonstrates the following: (1) stroke history is relatively common among Middle Eastern patients. (2) Patients with stroke had a higher risk of recurrent in-hospital

**Table 4** Investigations during hospitalisation (stroke/TIA vs no stroke/TIA)

Variable	No stroke/TIA N=4601 (91.9%)	Stroke/TIA N=404 (8.1%)	p Value
Pulse oximetry saturation (mean±SD)	93±6.9	93±6.2	0.86
Troponin, ng/mL			
Elevated (%)	1726 (37.5)	176 (43.6)	
Normal (%)	2453 (53.3)	198 (49)	
Not performed (%)	422 (9.2)	30 (7.4)	0.05
First BNP or NT-Pro BNP, pg/mL	780 (17)	70 (17.3)	0.85
HbA1c (mean±SD) (%)	7.2±2.2	7.6±2.0	0.03
Total cholesterol (mean±SD) mmol/L	4.8±2.3	4.5±2.2	0.02
First haemoglobin (mean±SD) g/dL	12.7±2.4	11.9±2.3	0.001
First WCC (mean±SD) cells/mL	10.4±8	10±7	0.89
First urea (mean±SD) mmol/L	11±8.4	12.8±9	0.002
First creatinine (mean±SD) mmol/L	129±117	146±111	0.003
E-GFR (mean±SD) mL/min	69±35.7	58±36.6	0.001
First serum potassium (mean±SD) mmol/L	4.3±0.7	4.3±0.69	0.06
First ALT (mean±SD) mmol/L	94±218	71±192	0.02
ECG rhythm			
Sinus (%)	3803 (83.2)	288 (71.8)	0.01
AF/flutter (%)	579 (12.7)	100 (24.9)	0.001
Paced (%)	69 (1.5)	10 (2.5)	0.13
Others (%)	62 (1.4)	1 (0.2)	0.05
LVH (%)	1377 (29.9)	144 (35.6)	0.02
STEMI (%)	495 (10.8)	31 (7.7)	0.05
AF	509 (11.1)	98 (24.3)	0.001
CHB	56 (1.2)	2 (0.5)	0.20
Pathological Q waves (old MI)	1072 (23.3)	106 (16.2)	0.18
QRS duration ≥0.12 ms	–		
LBBB	596 (13)	61 (15.1)	0.22
RBBB	203 (4.4)	19 (4.7)	0.79
IVCD	142 (3.1)	17 (4.2)	0.22
Echocardiography (available) (%)	4207 (91.4)	370 (91.6)	0.92
Left atrial enlargement (yes) (%)	2658 (63.2)	239 (64.6)	0.59
LVEF (mean±SD)	37±14	36.5±13	0.57
EF≤35%	1847 (43.9)	165 (44.6)	0.80
EF>35%	2360 (56.1)	205 (55.4)	0.80
Concentric LVH	1129 (26.8)	121 (32.7)	0.02
Moderate-to-severe valve disease			
MS	127 (2.8)	8 (2)	0.35
MR	1400 (30.4)	91 (22.5)	0.001
AS	115 (2.5)	8 (2.0)	0.52
AR	177 (3.8)	12 (3.0)	0.38
TR	646 (14)	49 (12.1)	0.29
PA systolic pressure (mean±SD)	55.7±16	53±11	0.03
Coronary angiogram (within 1 year) (%)	1017 (22.1)	74 (18.3)	0.08
SVD	183 (4)	10 (2.5)	0.13
DVD	204 (4.4)	10 (2.5)	0.06
TVD	313 (6.8)	30 (7.4)	0.64
LMSD	16 (0.3)	0 (0)	0.24
Blocked stent/graft	23 (0.5)	6 (1.5)	0.01

AF, atrial fibrillation; ALT, alanine transaminase; AR, aortic regurgitation; AS, aortic stenosis; BNP, brain natriuretic peptide; CHB, complete heart block; DVD, double vessel disease; EF, ejection fraction; GFR, glomerular filtration rate; HbA1c, glycated haemoglobin; IVCD, intra-ventricular conduction delay; LBBB, left bundle branch block; LMSD, left main disease; LVH, left ventricular hypertrophy; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MR, mitral regurgitation; MS, mitral stenosis; NT-Pro BNP, N-terminal Pro brain natriuretic peptide; PA, pulmonary artery; RBBB, right bundle branch block; STEMI, ST elevation myocardial infarction; SVD, single vessel disease; TIA, transient ischaemic attack; TR, tricuspid regurgitation; TVD, tripe vessel disease, WCC, white cell count.

strokes and higher long-term mortality rates. (3) Prior stroke was an independent predictor of in-hospital and 1-year mortality. (4) Patients with stroke hospitalised

with HF were more likely to be admitted under internist care rather than cardiologist care with less use of evidence-based medications.

**Table 5** Course in the hospital and in-hospital and 1-year outcome (stroke/TIA vs no stroke/TIA)

Variable	No stroke/TIA N=4601 (91.9%)	Stroke/TIA N=404 (8.1%)	p Value
Precipitating factors for HF			
Medications non-compliance (%)	878 (19.1)	86 (21.3)	0.28
Non-compliance with diet (%)	129 (2.8)	7 (1.7)	0.20
Salt retaining drugs (%)	26 (0.6)	0 (0)	0.13
Acute coronary syndrome (%)	1259 (27.4)	106 (26.2)	0.63
Uncontrolled hypertension (%)	374 (8.1)	36 (8.9)	0.58
Uncontrolled arrhythmia (%)	271 (5.9)	30 (7.4)	0.21
Anaemia (%)	138 (3)	16 (4)	0.28
Infection (%)	667 (14.5)	641 (15.8)	0.46
Unknown (%)	651 (14.1)	35 (8.7)	0.002
Worsening of renal failure	197 (4.3)	24 (5.9)	0.12
NIV	411 (8.9)	62 (15.3)	0.001
Intubation/ventilation	374 (8.1)	50 (12.4)	0.003
Inotropes	695 (15.1)	88 (21.8)	0.001
IABP	76 (1.7)	6 (1.5)	0.80
Acute dialysis/ultrafiltration	117 (2.5)	18 (4.5)	0.02
VT/VF requiring therapy (%)	202 (4.4)	20 (5.0)	0.60
AF requiring therapy (%)	265 (5.8)	46 (11.4)	0.001
Major bleeding (%)	37 (0.8)	3 (0.7)	0.90
Blood transfusion (%)	217 (4.7)	37 (9.2)	0.001
In-hospital new stroke (%)	46 (1)	22 (5.4)	0.001
Systemic infection requiring antibiotics (%)	1067 (23.2)	141 (34.9)	0.001
HHD	725 (15.8)	77 (19.1)	0.08
IHD	2424 (42.7)	239 (59.2)	0.01
Primary VHD	432 (9.4)	29 (7.2)	0.14
Viral myocarditis (%)	17 (0.4)	0 (0.0)	0.22
Cardiomyopathy (total)	862 (18.7)	53 (13.1)	0.005
CM subtype			
HCM	19 (0.4)	3 (0.7)	0.34
Infiltrative CM	12 (0.3)	1 (0.2)	0.96
Toxic CM	36 (0.8)	3 (0.7)	0.93
Pregnancy-related CM	63 (1.4)	2 (0.5)	0.14
Thyroid disease-related CM	10 (0.2)	0 (0)	0.35
Familial CM	9 (0.2)	0 (0)	0.37
Tachycardia-induced CM	30 (0.7)	1 (0.2)	0.32
Idiopathic DCM	605 (13.1)	37 (9.2)	0.02
Discharge home	4104 (89.2)	350 (86.6)	0.30
Transfer to another hospital	80 (1.7)	8 (2.0)	0.30
Death	279 (6.1)	34 (8.4)	0.06
Hospital stay (days) (mean±SD)	9±13	11±14	0.03
Alive (yes)	3532 (76.8)	272 (67.3)	0.001
HF rehospitalisation (yes) (%)	989 (28)	86 (31.6)	0.20
Cardiac intervention needed			
ICD	33 (0.7)	1 (0.2)	0.27
CRTD/P	12 (0.2)	2 (0.5)	0.33
PCI/CABG	358 (10.1)	22 (8.1)	0.28

AF, atrial fibrillation; CABG, coronary artery bypass grafting; CRTD, cardiac resynchronisation therapy, defibrillator; CRT, Cardiac resynchronization therapy; CM, cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HHD, hypertensive heart disease; IABP, intra-aortic balloon pump insertion; ICD, International Classification of Diseases; IHD, ischaemic heart disease; NIV, non-invasive ventilation; PCI, percutaneous coronary intervention; VF, ventricular fibrillation; VHD, valvular heart disease; VT, ventricular tachycardia.

HF is a common disease and is a major risk factor for ischaemic stroke. Stroke-related morbidity and mortality are considerably higher in patients with HF compared with patients with stroke without HF.<sup>22</sup> Data on the

prevalence and outcome of stroke in patients hospitalised for HF are very sparse and mainly conducted in the western world. To the best of our knowledge, this is the first study from the Middle East and the developing

**Table 6** Multivariate logistic regression analysis for in-hospital mortality

Variable	Adjusted OR	95% CI	p Value
Age	0.99	0.98 to 1.03	0.16
Male gender	0.78	0.59 to 1.04	0.09
DM II	1.06	0.79 to 1.41	0.70
CKD	1.31	0.91 to 1.89	0.15
COPD/asthma	0.64	0.37 to 1.10	0.11
STEMI	2.25	1.57 to 3.23	0.001
LVEF $\geq$ 35%	0.77	0.59 to 1.01	0.06
LVEF<35	1.30	0.99 to 1.70	0.06
VHD	1.59	1.12 to 2.25	0.009
Stroke	1.71	1.13 to 2.60	0.01
PVD	1.52	0.89 to 2.62	0.13
Multivariate logistic regression analysis for 1-year mortality			
Age	1.04	1.03 to 1.05	0.001
Male gender	1.12	0.90 to 1.40	0.31
DM II	1.18	0.95 to 1.46	0.13
CKD	1.53	1.19 to 1.96	0.001
COPD/asthma	1.22	0.91 to 1.65	0.19
STEMI	0.89	0.62 to 1.29	0.55
LVEF $\geq$ 35	0.74	0.60 to 0.91	0.005
LVEF<35	1.35	1.10 to 1.67	0.005
VHD	1.46	1.10 to 1.93	0.009
Stroke	1.34	0.98 to 1.84	0.07
PVD	1.20	0.79 to 1.82	0.41
Risk factors for stroke in heart failure			
Age	1.02	1.01 to 1.03	0.001
Gender	1.02	0.81 to 1.28	0.88
DM	1.30	1.01 to 1.69	0.045
HTN	2.10	1.50 to 2.80	0.001
Systolic BP	1.0	0.99 to 1.01	0.51
Diastolic BP	1.0	0.99 to 1.01	0.65
NYHA I	0.64	0.19 to 2.14	0.33
NYHA II	0.98	0.42 to 2.25	0.46
NYHA III	1.24	0.55 to 2.80	0.95
NYHA IV	1.24	0.54 to 2.81	0.61
Hyperlipidaemia	1.30	1.02 to 1.65	0.03
CKD	1.31	1.05 to 1.75	0.045
Systolic LV dysfunction	1.08	0.85 to 1.37	0.52
Known CAD	1.14	0.89 to 1.47	0.30
PVD (%)	2.97	2.06 to 4.12	0.001
AF	2.20	1.67 to 2.89	0.001
Thyroid disease	0.91	0.56 to 1.49	0.71

AF, atrial fibrillation; BP, blood pressure; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HTN, hypertension; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PVD, peripheral vascular disease; TIA, transient ischaemic attack; VHD, valvular heart disease.

world that explores this issue. We had previously reported a low prevalence of prior stroke in patients hospitalised with acute coronary syndrome (ACS) in the Middle East.<sup>23 24</sup> On the other hand, this study reports a relatively higher prevalence of stroke in patients hospitalised with HF in seven Middle Eastern countries, suggesting that prior stroke is more prevalent among patients hospitalised with HF rather than ACS in this region.

### Prevalence of stroke in patients with HF

The reported prevalence of stroke in patients with HF is variable because of the heterogeneous and limited number of published studies (table 8).<sup>25–31</sup> The initial risk of ischaemic stroke during the first year after diagnosis of HF was reported to be 1.8%; this compares with subsequent risk of nearly 5% at 5 years post-diagnosis.<sup>25</sup> Data from the Framingham Study<sup>11</sup> and a recent cohort study<sup>12</sup> indicated that the risk of ischaemic stroke is 2–3 times higher for patients with HF than it is for those without HF. According to epidemiological data, cohort studies and case series,  $\approx$ 10% to 24% of all patients with stroke have HF, whereas HF is thought to be the likely cause of stroke in  $\approx$ 9% of all patients.<sup>13–17</sup> A meta-analysis including 15 clinical studies and 11 cohort studies published before 2006<sup>25</sup> reported a stroke rate of 1.8% and 4.7% within 1 and 5 years, respectively. A recent report from the population-based, prospective Rotterdam Scan Study revealed that stroke risk is highest within 1 month after the diagnosis of HF that normalised within 6 months.<sup>32</sup>

This study complements previous reports by showing high prevalence of prior stroke among patients hospitalised with HF in the Middle East. Moreover, patients with a prior stroke had a higher risk of recurrent strokes during the index hospitalisation. This high prevalence may be due to associated risk factors for stroke such as severe LV systolic dysfunction (44.6% had EF <35%) and AF (25%), even though there was a relatively high prevalence of associated risk factors, including LV dysfunction and AF, while the use of anticoagulants and antiplatelet agents was low. In this study, we reported the use of anticoagulants (20–22%) and antiplatelets (29–41%) during hospitalisation at discharge, respectively, in patients with prior stroke; this rate may be much lower than has been reported in a EUROASPIRE III survey where antiplatelet drugs or oral anticoagulants were used by 87.2%, of patients with stroke.<sup>33</sup> This lower use of anticoagulants and antiplatelets in this study may have contributed to their increased risk of recurrent strokes and higher mortality rates.

### Risk factors for stroke in patients with HF and outcome

Present facts concerning other risk factors for stroke in HF (apart from AF as the major factor) are primarily grounded on retrospective studies, cohort studies or post-hoc analyses of large clinical trials with significant inconsistencies.<sup>34</sup> This study reported age, diabetes mellitus, hypertension, hyperlipidaemia, peripheral vascular disease and AF to be independently associated with recurrent stroke risk in patients with HF. The Olmsted County cohort demonstrated that prior stroke, advanced age and diabetes were relevant stroke risk factors in 630 patients with HF,<sup>12</sup> whereas a history of AF or hypertension did not reach statistical significance according to multivariable analysis. On the other side, a retrospective analysis of the prospective Survival and Ventricular Enlargement (SAVE) study also reported no significant impact of hypertension (and diabetes) in 2231 patients

**Table 7** Patient with HF with stroke/TIA as per care provider

Variable	Cardiologist care 249 (61.6%)	Internist care 155 (38.4%)	p Value
Acute new-onset HF (%)	83 (33.3)	43 (27.7)	
Acute decompensated chronic HF (%)	166 (66.7)	112 (72.3)	0.24
Age (mean±SD)	66±13	67±12	0.36
Male (%)	158 (63.5)	81 (52.3)	0.03
Previous admission for HF (%)	10 (4)	5 (3.2)	0.68
AF	60 (24.1)	38 (24.5)	0.92
CKD/dialysis (%)	71 (28.5)	42 (27.1)	0.76
PVD	44 (17.7)	17 (11)	0.07
CAD	164 (65.9)	90 (58.1)	0.12
NYHA III	106 (42.6)	82 (52.9)	0.04
NYHA IV	83 (33.3)	49 (31.6)	0.72
Clopidogrel	120 (48.2)	47 (30.3)	0.001
Oral anticoagulants (%)	60 (24.1)	31 (20)	0.34
ACE inhibitors	129 (51.8)	59 (38.1)	0.007
ARBs	43 (17.3)	34 (21.9)	0.25
Aldosterone antagonists	88 (35.3)	47 (30.3)	0.30
LVEF (mean±SD)	35±12.6	39±14	0.01
NIV	37 (14.9)	25 (16.1)	0.73
Intubation/ventilation	33 (13.3)	17 (11)	0.50
Inotropes	48 (19.3)	40 (25.8)	0.12
IABP	5 (2)	1 (0.6)	0.27
Acute dialysis/ultrafiltration	11 (4.4)	7 (4.5)	0.96
VT/VF requiring therapy (%)	14 (5.6)	6 (3.9)	0.43
AF requiring therapy (%)	27 (10.8)	19 (12.3)	0.66
Major bleeding (%)	0 (0)	3 (1.9)	0.03
Blood transfusion (%)	16 (6.4)	21 (13.5)	0.02
In-hospital stroke (%)	5 (2)	17 (11)	0.001
Systemic infection requiring antibiotics (%)	69 (27.7)	72 (46.5)	0.001
Death in-hospital	13 (5.2)	21 (13.5)	0.009
Hospital stay (days) (mean±SD)	11±17	10±10	0.33
1-year follow-up			
Alive (yes)	174 (69.9)	98 (63.2)	0.002
HF hospitalisation (yes) (%)	48 (19.3)	38 (24.5)	0.07
ICD	0 (0)	1 (0.6)	0.20
CRTD	2 (0.8)	0 (0)	0.26
PCI/CABG	13 (7.5)	9 (9.2)	0.62

AF, atrial fibrillation; ARBs, angiotensin receptors blockers; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; CRTD, Cardiac resynchronization therapy, defibrillator; HF, heart failure; IABP, intra-aortic balloon pump insertion; ICD, International Classification of Diseases; LVEF, left ventricular ejection fraction; NIV, non-invasive ventilation; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; TIA, transient ischaemic attack, VF, ventricular fibrillation; VT, ventricular tachycardia.

with HF.<sup>35</sup> In contrast to these reports, the SCD-HeFT-study revealed an HR of 1.9 (95% CI 1.1 to 3.1) for stroke when hypertension was present at randomisation of 2144 patients with HF without AF.<sup>9</sup> In addition, a medical history of hypertension was associated with an increased risk of hospitalisation for stroke (HR 1.4; 95% CI 1.01 to 1.8) in 7788 patients with HF of the Digitalis Investigation Group trial.<sup>36</sup> Furthermore, our result is compatible from the age point of view with the Olmsted County data that revealed a significant but modest association between stroke risk and advanced age (relative risk 1.04; 95% CI 1.02 to 1.06).<sup>12</sup> An exploratory analysis of the SAVE study also showed similar results (relative risk of stroke 1.18; 95% CI 1.05 to 1.3, for each increase of 5 years in age),<sup>9</sup> while these results contradict the

result of the Framingham Study that indicated that advanced age does not account for the increased risk of stroke in patients with HF.<sup>3, 37</sup>

This study has shown that patients with HF with stroke had higher in-hospital mortality with longer hospital stay and that they are less likely to stay alive at 1-year follow-up, probably explained by the multiple comorbidities in this patient population. Many retrospective database analyses have shown that stroke increases the disability and mortality of patients with HF through the alteration in neuropsychological status, like decreased attention and concentration, memory loss, diminished psychomotor speed and decreased executive function, and this ranged from approximately 25–80% of all patients with chronic HF.<sup>38–41</sup>

Table 8 Prevalence of stroke in patients with HF/studies from different parts of the world

Study name (reference)	Study period	Patient (n)	Mean age (years)	Female sex (%)	Strokes (%)	F/U* (days)
Granger <i>et al</i> <sup>6</sup>	CHARM-Alternative trial 1999–2001	2028	66.5	31.9	3.8	1011
North America Europe						
Mathew <i>et al</i> <sup>7</sup>	DIG trial 1991–1993	7788	63.9	24.7	4.2	1110
North America						
Pfeffer <i>et al</i> <sup>8</sup>	CHARM-Overall programme 1999–2001	7599	66	31.6	1.4	1131
North America Europe						
Dries <i>et al</i> <sup>9</sup>	SOLVD trial 1986–1989	6378	60	4.4	3.5	1197
North America						
McMurray <i>et al</i> <sup>10</sup>	CHARM-Added trial 1999	2548	64	21.3	3.4	1230
26 countries worldwide						
Remme <i>et al</i> <sup>11</sup>	COMET trial 1996–1999	3029	62	0.2	4.7	1740
Europe						
Khafaji <i>et al</i> /current study	Gulf CARE	5005	66.5	40.8	8.1	360
Middle East	2012–2013					

\*Included studies in the follow-up period.  
Gulf CARE, Gulf aCute heArt failuRe rEgistry.

### Cardiologist vs internist care of patients with HF with prior stroke

Cardiologists when compared with internists may provide more evidence-based therapies for the treatment of patients with HF.<sup>42 43</sup> This is supported by this study, where patients under the care of cardiologists had a lower risk of recurrent in-hospital stroke, major bleeding, the need for blood transfusion and lower in-hospital and 1-year mortality rates when compared with patients managed by internists. This suggests that patients with prior stroke are a higher risk group which may benefit from specialised care. On the other hand, the observational nature of this study does not adjust for the possibility of selection bias in that patients with “lower” risk stroke were “preferentially” admitted under the care of cardiologists rather than internists.

### STUDY LIMITATIONS

This study is a subanalysis of an observational study, which is like any observational study, where the possibility for unmeasured confounding variables exists. In addition, not all hospitals in each country participated; hence, the results cannot be generalised. This study did not record the cognitive status and the disability status in patients with stroke, which obviously have a major impact on morbidity and mortality and only 1-year mortality. Mortality rates at follow-up were only recorded at 1 year without the specification of the exact date of death of each patient, and hence the Kaplan-Meier curves could not have been done. Finally, no information was available regarding the cause of stroke (embolic vs thrombotic). Future studies need to overcome these limitations.

### CONCLUSION

This observational study reports a high prevalence of prior stroke in Middle Eastern patients with HF. There was underuse of anticoagulation therapy in patients with stroke and HF with AF. Patients with stroke hospitalised with HF were more likely to be admitted under the care of internists rather than cardiologists, resulting in less use of evidence-based medications and worse outcome. Patients with stroke had a higher risk of in-hospital recurrent strokes and higher long-term mortality rates. History of stroke was an independent predictor of in-hospital and 1-year mortality rates in patients hospitalised with HF. Future studies are needed to evaluate whether aggressive evidence based therapies to this high-risk group will improve outcome.

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