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Clinical Characteristics, Precipitating Factors, Management and Outcome of Patients with Prior Stroke Hospitalized With Heart Failure: A Contemporary Observational Report

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Abstract:

Objective: The purpose of this study is to report the prevalence, clinical characteristics, precipitating factors, management and outcome of patients with prior stroke hospitalized 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, multicenter study of consecutive patients hospitalized with acute HF in 2012 in 7 Middle Eastern countries and analyzed according to the presence or absence of prior stroke. Demographics, management and outcomes were compared.

Participants: A total of 5005 HF patients.

Primary and secondary outcome measures: In-hospital and one-year outcome.

Results: The prevalence of prior stroke in HF patients was 8.1 %. When compared with non-stroke patients, stroke patients were more likely to be older and to be admitted under the care of internists rather than cardiologists. Stroke patients were more likely to have diabetes mellitus, hypertension, atrial fibrillation, hyperlipidemia, chronic kidney disease, ischemic heart disease, peripheral arterial disease and left ventricular dysfunction (P=0.001 for all) and they were less likely to be smokers (0.003). No significant differences in term of precipitating risk factors for HF hospitalization between the 2 groups. Stroke patients with HF had longer hospital stay (mean ± SD days; 11±14 vs. 9±13, p= 0.03), higher risk of recurrent strokes and 1-year mortality rates (32.7% vs. 23.2%, P=0.001). Stroke was independent predictor of in hospital and 1 year mortality rates.

Conclusion: This observational study from a contemporary acute HF registry reports high prevalence of prior stroke in hospitalized HF patients. Internists rather than cardiologists were the predominant care givers in this high risk group. Stroke patients had higher risk of in-hospital recurrent strokes and higher long-term mortality rates and prior stroke was independent predictor of in-hospital and one-year mortality rates in patients hospitalized with HF.

ARTICLE SUMMARY:

Article focus: To explore the baseline clinical characteristics managements precipitating factors and outcome and short and long term outcome in Middle East population.

Key messages:

*The prevalence of prior stroke in hospitalized HF patients around 8.1 % which relatively high compared to other studies from different part of the world.

* Stroke patients had higher risk of in-hospital recurrent strokes and higher long-term mortality rates and prior stroke was independent predictor of in-hospital and one-year mortality rates in patients hospitalized with HF.

* Stroke patients hospitalized with HF were more likely admitted under the care of internists rather than cardiologists resulting in less use of evidence based medications for HF and stroke.

Strength: This is the first study to provide multinational estimates of prevalence and demographics management in correlation for care giver internist vs. cardiologist in terms short and long-term outcome of stroke and in heart failure patients from the Middle East with well-designed electronic data collection with accurate and complete information with few missing data.

Limitations: 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 stroke patients that major impact on morbidity and mortality in addition no information available regarding the cause of stroke , embolic versus thrombotic, future studies need to overcome this limitation. In addition not all hospitals in each country participated. Hence, the results should not be generalized.

Key words: **Stroke, Heart failure, morbidity, and mortality.**

1. Introduction:

Heart failure (HF) is one of the leading causes of hospitalization, morbidity, and mortality worldwide. HF is also one of the major risk factors for the development of ischemic stroke with 2-3 fold-increased risk of stroke when compared to non-HF patients [1]. Several pathophysiologic mechanisms can contribute to the development of stroke in HF patients including; 1) cardioembolic stroke through thrombus formation as a result of atrial fibrillation or left ventricular dysfunction [2, 3]. 2) The hypercoagulable state; increased aggregation of thrombocytes, and reduced fibrinolysis in patients with HF as an effect of the activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system [4,5]. 3) Endothelial dysfunction in HF patients, rheological alterations consistent with increased blood velocity, and malfunctioning of cerebral auto-regulation[6, 7]. Hypotension may be an additional risk factor for stroke as a result of heart failure [8]. In addition to the causal relationship, HF and ischemic stroke represent manifestations of similar underlying risk factors, such as hypertension and diabetes mellitus [9]. Therefore, patients with HF are at risk for stroke of large-artery atherosclerosis and small-vessel thrombosis [10].

The prevalence and incidence of stroke in patients with HF is unclear because of heterogeneous nature of the limited published studies where most of them were subset analysis of randomized trials rather than epidemiologic studies with variation of the clinical characteristics of HF patients [11-17]. Furthermore, data on the prevalence and outcome of stroke in patients hospitalized for HF is mainly limited to studies conducted in the Western world. Gulf CARE (Gulf aCute heArt failure) registry [18], a multinational multicenter prospective observational acute heart failure (AHF) survey based on cases admitted to various hospitals in 7 countries from the Gulf Middle East, namely, Oman, Saudi Arabia, United Arab Emirates (UAE), Qatar, Bahrain, Yemen, and Kuwait gives an opportunity to study this association in this part of the world. The aim of this study is to define the prevalence, clinical characteristics, precipitating factors, management and outcome of stroke patients hospitalized with HF, using data from Gulf CARE.

2. Patients and Methods;

2.1. Registry design

Gulf CARE is a prospective, multinational multi-center registry that recruited patients from February, 2012 to November 2012 who were admitted with the final diagnosis of AHF in 47 hospitals in 7 Middle Eastern Arab countries in the Gulf [18]. Data were collected on episodes of hospitalization 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 one 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 with number NCT01467973.

Patient included from both genders aged above 18 year of age and admitted to the participating hospitals admitted with AHF. AHF was defined based on the European Society of Cardiology (ESC) definition [2]. AHF was further classified as either acute decompensated chronic heart failure (ADCHF) or new-onset AHF (de novo AHF) based on ESC guidelines. ADCHF was defined as worsening of HF in patients with a previous diagnosis or hospitalization for HF. New-onset AHF (de novo AHF) was defined as AHF in patients with no prior history of HF.

Patient excluded from Gulf CARE if: 1) discharged from the emergency room without admission. 2) Transferred from non-registry hospital. 3) Failure to obtain informed consent.4) Patients whose final diagnosis was not heart failure were also excluded from the final analyses. Registry organization and Data Collection and Validation mentioned in published article of Gulf CARE[18].

Definitions of data variables in the CRF are based on the ESC guidelines 2008 and the American College of Cardiology clinical data standards 2005 [19,20]. A 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 [20]. Diastolic heart failure was defined as presence of symptoms and/or signs of HF and a preserved left ventricular ejection fraction (LVEF) >40% [19]. Stroke/TIA defined as History of cerebrovascular disease, documented by any one of the following: **1)** Cerebrovascular ischemic or hemorrhagic stroke: patient has a history of stroke (i.e., any focal neurological deficit of abrupt onset caused by a disturbance in blood supply that did not resolve within 24 hours) confirmed by a standard neurological examination with or without a positive imaging study, or an event of presumed ischemic origin that did not resolve within 24 hours, but the imaging showed a new lesion**. 2)** Transient ischemic attack (TIA): patient has a history of any sudden new focal neurological deficit of presumed ischemic origin as determined by a standard neurological exam that resolved completely within 24 hours, with a brain image study not revealing a new lesion. **3)** Noninvasive/invasive carotid test with greater than or equal to 75% occlusion. **4)** Previous carotid artery surgery **5)** Previous carotid angioplasty [19]. Diabetes mellitus was defined as having a history of diabetes diagnosed and treated with medication and/or insulin or fasting blood glucose 7.0mmol/l (126 mg/dl) or HBA1c ≥6.5%. Hypertension defined as having a history of hypertension diagnosed and treated with medication, blood pressure greater than 140 mmHg systolic or 90 mmHg diastolic on at least 2 occasions or greater than 130 mm Hg systolic or 80 mm Hg diastolic on at least 2 occasions for patients with diabetes or chronic kidney disease (CKD). Hyperlipidemia defined as history of dyslipidemia diagnosed and/or treated by a physician or total cholesterol greater than 5.18mmol/l (200mg/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 smoking cigarettes, water pipe, cigar or chewing tobacco within 1 month of index admission. Khat chewing was defined as chewing khat plant/leaves (Catha edulis containing cathionine, an amphetamine-like stimulant which can cause euphoria, hypertension, myocardial infarction, dilated cardiomyopathy) within 1 month of the index admission.

CKD was defined as GFR <60 mL per minute per 1.73 m2 for three months or more, with or without kidney damage or on dialysis. If no GFR is available, serum creatinine >177 mmol/L or 2 mg/dL was

marked as CKD. Obesity was defined as body mass index (BMI) greater than 25 kg/m^2. Infection definition in the registry: Any systemic infection needing antibiotics [20].

3. Statistical Analysis:

Baseline and outcome data are presented in frequency and percentages for categorical variables and interval variables are presented in mean and standard deviations or median and range as appropriate. Chi-square tests are applied to see association between stroke vs. Non-stroke groups for categorical variables whereas; student t tests or Wilcoxon rank sum tests are used for interval variables as appropriate between the two the group. Multivariate logistic regression analysis is performed at in-hospital and one year mortality for important risk factors. Adjusted OR and 95% C.I. with p values are presented in tables. P value 0.05(two tailed) is considered as statistical significant level. SPSS 21.0 Statistical package is used for the analysis [21].

4. Results:

4.1. Patients demographic (Table1):

Out of the total of 5005 patients included in the Gulf CARE registry; 8.1% had history of stroke/TIA. Stroke patients were more likely to present with ADCHF with more frequent recent hospitalization (≤ 6 months) for HF (0.001) when compared to non-stroke patients. Stroke patients with HF were more likely to be admitted under internists rather than cardiologists care. There was no significant gender or racial differences between the 2 groups. Stroke patients with HF were older (66.5 years vs. 59 years P=0.001) and more likely to have diabetes mellitus, hypertension, atrial fibrillation, coronary artery disease and LV dysfunction (0.001) chronic kidney disease and to be on renal replacement therapy than non-stroke patients (0.001) and were less likely to be smokers (0.003) or have history of asthma /COPD. Stroke patients were more likely to have thyroid disease (6.2% vs. 3.4%, P= 0.001) and previous CABG when compared to non-stroke patients (7% vs. 10.9%, P=0.004).

4.2. Clinical presentation (Table2):

No significant differences between the 2 groups in regards to NYHA class on presentation or other classical heart failure symptoms and sign, with the 2 exceptions; stroke patients more likely to have had syncope in the last one year (4.7% vs. 11.1%, P=0.001) and had more frequently palpable tender liver (27.4% vs. 19.3%, P=0.001) when compared to non-stroke patients.

4.3.Treatments and interventions before admission (Table 3);

Stroke patients were more likely to be on digoxin, oral nitrates, hydralazine, aspirin, clopidogrel, oral anti-coagulants, statin and ARBs (P=0.001) when compared to non-stroke patients

4.4. Investigations during hospitalization (Table 4):

Stroke patient were more likely to have lower glomerular filtration rate (GFR) (mean±SD; 58±36.6, vs. 69±35.7 P=0.001 and as result higher serum creatinine (mean±SD; 146±111 vs.129±117, P=0.003) and blood urea (mean±SD: 12.8±9 vs. 11±8.4 vs., P=0.002) and may be as a result have lower First hemoglobin (mean ±SD 11.9±2.3, vs.12.7±2.4; P=0.001). Stroke patients were more frequently to have atrial arrhythmias on admission; AF/Flutter (12.7 % vs. 24.9%, P=0.001), Stroke patients were also more likely to have concentric LVH (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.

4.5. Precipitating factors, hospitalization course and outcomes (Table5):

No significant differences between the two groups in terms of precipitating risk factors for hospitalization with heart failure including medication and diet noncompliance between the 2 groups.

Stroke patient were more likely to require invasive and non-invasive ventilation (12.4% vs. 8.1%, P=0.003), (15.3% vs. 8.9%, P=0.001) respectively, they were also more likely to require more 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 transfusion (9.2% vs. 4.7%, P=0.001) when compared to non-stroke patients. Stroke patients also were more likely to develop recurrent strokes and have systemic infections that require antibiotic treatment (34.9% vs. 23.2%, p=0.001) **(Table 5)**. IHD, HHD and primary VHD were the common etiologies in both groups. The clinical work up of stroke patients showed that they were more likely to have ischemic 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), more specifically idiopathic cardiomyopathy (9.2% vs. 13.1%p=0.02) **(Table5)**.

Stroke patient were more likely to be discharged on oral nitrates, hydralazine, statin, ACE-inhibitors, aldosterone antagonists (P=0.001), oral anticoagulants (P=0.02), and clopidogrel (P=0.01) when compared to non-stroke patients **(Table 3)**. At discharge more non-stroke patients had undergone PCI [0.02].

Stroke patients had longer hospital stay (mean±SD days; 11±14 vs. 9±13, p= 0.03) and had higher but statistically non-significant in hospital (8.4% vs. 6.1%, P=0.06) and statistically significant higher 1-year mortality rate (32.7% vs. 23.2%, P=0.001). **(Table5)**. On Multivariate logistic regression analysis stroke was an independent mortality predictors for both in hospital and 1 year follow up **(Table 6)**. Age, hypertension, peripheral vascular disease and atrial fibrillation were independent risk factors for stroke in heart failure patients **(Table 6)**.

4.7: Cardiologist vs. internist care: Sub-analysis done according to the primary care provider (as cardiologist vs. internist); showed that patient admitted to cardiologists were more likely to be on antiplatelet clopidogrel (48.2% vs. 30.3%, P=0.001) and ACEI (51.8 vs. 38.1%, P=0.007) and with less occurrence of in-hospital -stroke (2% vs.11% P=0.001). They also had less incidence of major bleed (0% vs. 1.9%, P=0.03) and thus less blood transfusion requirement (6.4% vs. 13.5%, P=0.02). Patients with stroke, heart failure and systemic infection requiring antibiotics were more likely to be admitted under internal medicine care (46.5% vs. 27.7%, P=0.001) There was higher in hospital mortality (13.5% vs. 5.2%P=0.009) in this group when compared stroke patients admitted under cardiologist care with no

difference in Hospital stay(11±17 vs. 10±10(days), P=0.33). On one year follow up there is non-significant marginally higher hospitalization for patients cared for by internist (19.3% vs.24.5%, P=0.07), but significantly higher mortality when compared to patients cared by cardiologists (69.9% vs. 63.2%, P=0.002) **(Table 7).**

5. Discussion:

The current contemporary registry of hospitalized patients for HF demonstrates the followings: 1. Stroke prevalence is relatively common among Middle-East patients hospitalized with HF. 2. Stroke patients hospitalized with HF were more likely to be admitted under the care of internists rather than cardiologists with less use of evidence based medications. There was under use of anticoagulation therapy in patients with atrial fibrillation, stroke and HF. 3. Stroke patients had higher risk of in-hospital recurrent strokes and higher long-term mortality rates. 4. Stroke was an independent predictor of in-hospital and one-year mortality rates.

HF is a common disease and is a major risk factor for ischemic stroke. Stroke-related morbidity and mortality are considerably higher in HF patients compared with stroke patients without CHF[22]. Data on the prevalence and outcome of stroke in patients hospitalized 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 world that explores this issue. We had previously reported the incidence of stroke in acute myocardial infarction using acute coronary syndrome (ACS) registries from Middle-East, that showed relatively low prevalence of history of stroke in patients with ACS in the Middle east [23, 24]**.** On the other hand**,** the current study reports relatively high prevalence of stroke in patients hospitalized with HF in 7 Middle eastern countries suggesting HF as important risk factor for stroke, more than ACS in this region.

5.1: Prevalence of stroke in heart failure patients: Approximately 1.8 % persons will experience an ischemic stroke during the first year after diagnosis of HF and subsequently the rate rises to nearly 5% cases of HF by 5 years [25]. This prevalence varied according the type and design of the studies (26-31) (table 12). Data from the Framingham Study [11] and a recent cohort study[12] indicated that the risk of ischemic stroke is 2 to 3 times higher for patients with ЄHF than it is for those without HF. According to epidemiologic data, cohort studies, and case series, ≈10% to 24% of all stroke patients have ЄHF, whereas ЄHF is thought to be the likely cause of stroke in ≈9% of all patients [13-17]**.** A meta-analysis including 15 clinical studies and 11 cohort studies published before 2006 [25] reported a rate of 1.8 % and 4.7% within 1 or 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 heart failure that normalized within 6 months [32]**.**

The current contemporary study reports high prevalence of stroke of 8.1% in HF patients from Middle-East. This high prevalence may be due to associated risk factors for stroke such as severe LV systolic dysfunction (44.6 % had EF < 35%) and Atrial fibrillation (25%). Even though there was relatively high prevalence of associated risk factors like LV dysfunction and atrial fibrillation only 20% of patients pre-

admission and 22.5% of stroke patients at discharge were anti-coagulated with warfarin. Use of clopidogrel was 29% pre-admission and 41% at discharge. In comparison, the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) that had not pre-specified stroke as a primary end point through subgroup analysis demonstrated an average annual stroke rate of 1% in 2114 CHF patients without atrial fibrilation of which 33% of all patients received anticoagulation and the other two thirds received antiplatelet agents [33]. In the WATCH trial (Warfarin and Antiplatelet Therapy in Chronic Heart Failure) a prospective, randomized (enrolled 1587 patients with CHF, an LVEF 35%, but had sinus rhythm trial, open-label warfarin was associated with fewer nonfatal strokes than was either aspirin or clopidogrel (0.6% vs. 2.3%) during an average follow-up of 21 months [34].

In the current study we reported the use of anticoagulant (20-22%) and antiplatelet (29-41%) during hospitalization and discharge respectively in stroke patient this rate may be much lower than has been reported in EUROASPIRE III survey where antiplatelet drugs or oral anticoagulants were used by 87.2%, of stroke patients [35]. This lower use of anticoagulants and antiplatelet in this study may have contributed to their increased risk of recurrent strokes and mortality

5.2: Risk factors for stroke in heart failure patients: Present facts concerning other risk factors for stroke in heart failure (apart from AF as the major one) is primarily grounded on retrospective studies, cohort studies, or post hoc analyses of large clinical trials with significant inconsistencies [36]. The current study reported age (OR, 1.02, 95%CI: 1.01-1.03,P=0.001), diabetes mellitus, hypertension, hyperlipidemia and peripheral vascular disease in addition to atrial fibrillation to independently associate with stroke in heart failure patients in addition to atrial fibrillation (OR, 2.20,95%CI: 1.67-2.89,P=0.001). The Olmsted County cohort demonstrated that prior stroke, advanced age, and diabetes were relevant stroke risk factors in 630 heart failure patients [12] whereas a history of AFib 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 CHF patients [37]. In contrast to these reports, the prospective SCD-HeFT-study revealed a hazard ratio of 1.9 (95% CI, 1.1–3.1) for stroke when hypertension was present at randomization of 2144 heart failure patients without atrial fibrillation [38] In addition, a medical history of hypertension was associated with an increased risk of hospitalization for stroke (hazard ratio1.4; 95% CI, 1.01–1.8) in 7788 heart failure patients of the Digitalis Investigation Group trial [39]. Furthermore our result is compatible from age point of view with Olmsted Country data that revealed a significant but modest association between stroke risk and advanced age (relative risk 1.04; 95% CI, 1.02–1.06)[12] In addition, an exploratory analysis of the SAVE study showed similar results (relative risk1.18; 95% CI, 1.05–1.3, for each increase of 5 years)[36] while these results contradict the result of Framingham Study that indicated that advanced age does not account for the increased risk of stroke in ~~C~~HF patients[40,41.]

5.3: Morbidity and mortality of stroke in heart failure:, The severity of cardiac dysfunction is pertinent to structural brain changes and neuropsychological alterations, as demonstrated for the rate of silent strokes within a small cohort study [42]. Cardiac index may be positively related to total brain volume and information processing speed but inversely related to lateral ventricular volume that can be explained by impaired cerebrovascular reactivity that inversely related to systolic dysfunction [43,44]. Many

retrospective database analyses have shown that stroke increases the disability and mortality of heart failure patients through the alteration in neuropsychological status, like decreased attention and concentration, memory loss, diminished psychomotor speed, and decreased executive function and this ranged approximately 25% to 80% of all patients with CHF experience [45–48]. The current study had shown that heart failure patient with stroke had 30% higher in hospital mortality with longer hospital stay (8.4% vs. 6.1%, P=0.06) and they are less likely to stay alive on one-year follow up probably explained by multiple comorbidities in this patient population . The current study failed to record the cognitive status of heart failure patients and failed to show the prevalence of silent infarcts in this group of patients.

5.4: Cardiologist vs. internist care: The management of heart failure by cardiologists may be better than that of other physicians in that cardiologists' treatment choices more frequently conform to published guidelines and the results of clinical trials [49, 50]. From the current observational study we noticed that stroke/heart failure patient had less in-hospital-stroke with significant lower in-hospital and one year mortality for stroke / heart failure patient managed by cardiologist as the rate of use of antiplatelet and ACEI are higher, this may be explained that patient under internist care are more ill with higher incidence of major bleed requiring blood transfusion and this may result in bias so such conclusion should be interpreted with care though is compatible with other registries result , as expected, and that patient under cardiologist care had been treated more frequently with clopidogrel.

6. Conclusion: This observational study from a contemporary acute HF registry reports high prevalence of history of stroke in Middle-East HF patients. Stroke patients hospitalized with HF were more likely admitted under the care of internists rather than cardiologists resulting in less use of evidence based medications for HF and stroke. There was under use of anticoagulation therapy in patients with atrial fibrillation, stroke and HF. Stroke patients had higher risk of in-hospital recurrent strokes and higher long-term mortality rates. History of stroke was independent predictor of in-hospital and one-year mortality rates in patients hospitalized with HF. There is lot of evidence for using preventive oral anticoagulation or antiplatelet therapy in HF patients with AF, there is need for large trials to find therapeutic options in preventing stroke in HF patients who are in sinus rhythm.

7. Study limitations: This study is sub-analysis of The Gulf CARE study. Like any observational study, the possibility for unmeasured confounding biases exists. In addition not all hospitals in each country participated. Hence, the results should not be generalized. In addition this study has not recorded the cognitive status and the disability status in stroke patients that major impact on morbidity and mortality in addition no information available regarding the cause of stroke , embolic versus thrombotic, future studies need to overcome this limitation. However, this study's main strength lies in the fact that it is the first study to provide multinational estimates of prevalence and demographics of stroke in heart failure patients from the Middle East with well-designed electronic data collection with accurate and complete information with few missing data.

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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 ±SD)		59±14.9	66.5±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 Care Giver	Cardiologist (%)	3326(72.3)	249(61.6)	
	Internist (%)	1275(27.7)	155(38.4)	0.001
Previous CV History				
HF previous admission (%)	≤ 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 hyperlipidemia (%)	1572(34.2)	227(56.2)	0.001
CKD/Dialysis (%)	631(13.7)	113(28)	0.001
Sleep apnea 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, PVD=peripheral vascular disease, TIA=transient ischemic attack, CKD=chronic kidney disease, COPD=chronic obstructive pulmonary disease, HTN=hypertension, DM=diabetes mellitus.

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
ClinicalSymptoms				
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
Orthopnea (%)		3618(78.6)	324(80.2)	0.46
Paroxysmal nocturnal dyspnea (%)		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 one year (%)		218(4.7)	45(11.1)	0.001
Clinical Signs				
HR (mean ±SD)		97±23	95±22.9	0.
BP(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)		92±15	93±16.7	0.84
BMI(mean ±SD)		28±6	29±6.3	0.03
Raised JVP>6 cm (%)		2323(56.5)	203(50.2)	0.93

Peripheral edema (%)	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
HR=heart rate, BP=blood pressure, RR=respiratory rate, BMI=body mass index, JVP=jugular venous pressure			

Table 3. Medications and interventions (Stroke/TIA vs. No Stroke/TIA).

			Before Admission			On discharge		
Variable			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 anticogulants (%)			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
Allpurinol			121(2.6)	14(3.5)	0.32	219(4.8)	20(5)	0.86
Ivabridine (%)			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
Anti-depressnats (%)			57(1.2)	9(2.2)	0.10	82(1.8)	10(2.5)	0.32
BB	Cardvidolol		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			148(3.2)	19(4.7)	0.11	88(1.9)	6(1.5)	0.54

(yes) (%)						

Table 4. Investigations during hospitalization (Stroke/TIA vs. No Stroke/TIA).

Variable	No-Stroke/TIA	Stroke/TIA,	P-Value

		N=4601(91.9%)	N =404(8.1%)	
Pulse oximetry saturation(mean ±SD)		93±6.9	93±6.2	0.86
Troponin	Elevated (%)	1726(37.5)	176(43.6)	
	Normal (%)	2453(53.3)	198(49)	
	Not done (%)	422(9.2)	30(7.4)	0.05
First BNP or NT-Pro BNP		780(17)	70(17.3)	0.85
HBA1C(mean ±SD)		7.2±2.2	7.6±2.0	0.03
Total cholesterol(mean ±SD)		4.8±2.3	4.5±2.2	0.02
First hemoglobin(mean ±SD)		12.7±2.4	11.9±2.3	0.001
First WBC (mean ±SD)		10.4±8	10±7	0.89
First Urea(mean ±SD)		11±8.4	12.8±9	0.002
First Creatinine		129±117	146±111	0.003
E-GFR		69±35.7	58±36.6	0.001
First serum sodium(mean±SD)				
First serum potassium(mean ±SD)		4.3±0.7	4.3±0.69	0.06
First ALT(mean ±SD)		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
	LV hypertrophy (%)	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 msec	-		

	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		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

MS=mitral stenosis, MR=mitral regurgitation, AS=aortic stenosis, AR=aortic regurgitation, TR=tricuspid regurgitation, PA=pulmonary artery, SVD=single vessel disease, DVD=double vessel disease, TVD=tripe vessel disease, LMSD=left main disease, GFR=glomerular filtration rate.

Table 5. Course in the Hospital & 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 noncompliance (%)	878(19.1)	86(21.3)	0.28
	Noncompliance 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
	Anemia (%)	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)		9±13	11±14	0.03
Alive (yes)		3532(76.8)	272(67.3)	0.001
HF re-hospitalization (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

NIV=Non-invasive ventilation, IABP=intra-aortic balloon pump insertion, VT=ventricular tachycardia, VF=ventricular fibrillation, AF=atrial fibrillation. HHD=hypertensive heart disease, IHD=ischemic heart disease, HOCM=hypertophic cardiomyopathy, CM=cardiomyopathy, DCM=dilated cardiomyopathy, ARVD-arrhythmogenic right ventricular dysplasia

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Table 6 : Multivariate logistic regression analysis for In hospital mortality

Variable	Adjusted OR	95% C.I.	P value

Age	0.99	0.98 – 1.03	0.16
Male gender	0.78	0.59 – 1.04	0.09
DM II	1.06	0.79 – 1.41	0.70
CKD	1.31	0.91 – 1.89	0.15
COPD/Asthma	0.64	0.37 – 1.10	0.11
STEMI	2.25	1.57 – 3.23	0.001
LVEF ≥35%	0.77	0.59 – 1.01	0.06
LVEF <35	1.30	0.99 – 1.70	0.06
VHD	1.59	1.12 – 2.25	0.009
Stroke	1.71	1.13 – 2.60	0.01
PVD	1.52	0.89 – 2.62	0.13
Multivariate logistic regression analysis for one year mortality			
Age	1.04	1.03 – 1.05	0.001
Male gender	1.12	0.90 – 1.40	0.31
DM II	1.18	0.95 – 1.46	0.13
CKD	1.53	1.19 – 1.96	0.001
COPD/Asthma	1.22	0.91 – 1.65	0.19
STEMI	0.89	0.62 – 1.29	0.55
LVEF≥35	0.74	0.60 – 0.91	0.005
LVEF <35	1.35	1.10 – 1.67	0.005
VHD	1.46	1.10 – 1.93	0.009
Stroke	1.34	0.98 – 1.84	0.07
PVD	1.20	0.79 – 1.82	0.41
Risk factors for stroke in heart failure			
Age	1.02	1.01-1.03	0.001
Gender	1.02	0.81-1.28	0.88

DM	1.30	1.01-1.69	0.045
HTN	2.10	1.50-2.80	0.001
Systolic BP	1.0	0.99 – 1.01	0.51
Diastolic BP	1.0	0.99 – 1.01	0.65
NYHA I	0.64	0.19 – 2.14	0.33
NYHA II	0.98	0.42 – 2.25	0.46
NYHA III	1.24	0.55 – 2.80	0.95
NYHA IV	1.24	0.54 – 2.81	0.61
hyperlipidemia	1.30	1.02-1.65	0.03
CKD	1.31	1.05-1.75	0.045
Systolic LV dysfunction	1.08	0.85-1.37	0.52
Known CAD	1.14	0.89-1.47	0.30
PVD (%)	2.97	2.06 -4.12	0.001
AF	2.20	1.67-2.89	0.001
Thyroid disease	0.91	0.56-1.49	0.71

DM; Diabetes Mellitus CKD: Chronic kidney disease, VHD: Valvular heart disease, PVD: Peripheral vascular disease PVD: Peripheral vascular disease.

Table 7: HF patient with Stroke/TIA as per care provider

Variable	Cardiologist care 249(61.6%)	Internist care 155(38.4%)	P-Value

Acute new-onset heart failure (%)	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
Atrial fibrillation	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 anticogulants (%)	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)		11±17	10±10	0.33
1 Year follow up	Alive (yes)	174(69.9)	98(63.2)	0.002
	HF hospitalization (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

Table 8: Prevalence of stroke in heart failure patients / studies from different parts of the world

Study Name	Study Period	Patient	Mean Age	Female Sex	Strokes%	F/U* (Days)

(Reference		No.	(years)	(%)		
Granger [26] North America Europe	CHARM-Alternative trial 1999-2001	2028	66.5	31.9	3.8 %	1011
Mathew [27] North America	DIG trial 1991-1993	7788	63.9	24.7	4.2 %	1110
Pfeffer[28] North America Europe	CHARM-Overall programme 1999-2001	7599	66	31.6	1.4 %	1131
Dries [29] North America	SOLVD trial 1986-1989	6378	60	4.4	3.5 %	1197
McMurray [30] 26 countries world wide	CHARM-Added trial 1999	2548	64	21.3%	3.4 %	1230
Remme[31] Europe	COMET Trial 1996-1999	3029	62	0.2%	4.7 %	1740
Khafaji et al Current study Middle east	Gulf CARE 2012-2013	5005	66.5	40.8%	8.1 %	360

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **(mentioned in the tile as well as the abstract and the main manuscript)**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **(done)**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **(done)**
Objectives	3	State specific objectives, including any prespecified hypotheses**(done)**
Methods		
Study design	4	Present key elements of study design early in the paper**(done)**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection**(done)**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up**(done)** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed**(done)** *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable**(done)**
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
Bias	9	Describe any efforts to address potential sources of bias**(done)**
Study size	10	Explain how the study size was arrived at**(done)**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding**(done)**
		(*b*) Describe any methods used to examine subgroups and interactions**(done)**
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed**(done)** *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

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**(done)**
		(b) Give reasons for non-participation at each stage**(done)**
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders**(done)**
		(b) Indicate number of participants with missing data for each variable of interest**(done)**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time**(done)**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
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**(done)**
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives**(done)**
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**(done)**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results**(done)**
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**(done)**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.

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Clinical Characteristics, Precipitating Factors, Management and Outcome of Patients with Prior Stroke Hospitalized With Heart Failure: Observational Report from Middle East

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Clinical Characteristics, Precipitating Factors, Management and Outcome of Patients with Prior Stroke Hospitalized With Heart Failure: Observational Report from 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 hospitalized 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, multicenter study of consecutive patients hospitalized with acute HF in 2012 in 7 Middle Eastern countries and analyzed according to the presence or absence of prior stroke; demographics, management and outcomes were compared.

Participants: A total of 5005 HF patients.

Outcome measures: In-hospital and one-year outcome.

Results: The prevalence of prior stroke in HF patients was 8.1 %. Stoke patient with HF were more likely to be admitted under the care of internists rather than cardiologists. When compared with non-stroke patients, stroke patients were more likely to be older and to have diabetes mellitus, hypertension, atrial fibrillation, hyperlipidemia, chronic kidney disease, ischemic heart disease, peripheral arterial disease and left ventricular dysfunction (P=0.001 for all). Stroke patients were less likely to be smokers (0.003). No significant differences in term of precipitating risk factors for HF hospitalization between the 2 groups. Stroke patients with HF had longer hospital stay (mean ± SD days; 11±14 vs. 9±13, p= 0.03), higher risk of recurrent strokes and 1-year mortality rates (32.7% vs. 23.2%, P=0.001). Stroke was independent predictor of in hospital and 1 year mortality rates.

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

ARTICLE SUMMARY:

Article focus: To explore the baseline clinical characteristics, management and outcome of patients hospitalized with heart failure in the Middle East and the presence or absence of prior stroke history.

Key messages:

*The prevalence of prior stroke in hospitalized HF patients around 8.1 %.

* Patients with prior stroke when hospitalized with HF were more likely to be admitted under the care of internists rather than cardiologists resulting in less use of evidence based medications.

* Patients with prior stroke when hospitalized with HF had higher risk of recurrent strokes and higher long-term mortality rates.

* Prior stroke was independent predictor of in-hospital and one-year mortality rates in patients hospitalized with HF.

Strength: This is the first multicenter, multinational study in the Middle East to provide report the prevalence, demographics, management and one-year outcome of patients hospitalized with HF in relation to prior history of stroke.

Limitations: 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 stroke patients which have major impact on morbidity. Furthermore no information are available regarding the cause of stroke (embolic versus thrombotic), future studies need to overcome these limitations.

Key words: **Stroke, Heart failure, morbidity, and mortality.**

1. Introduction:

The prevalence and incidence of stroke in patients with HF and the temporal relation of these two diseases in term of increasing morbidity and mortality has been scarcely reported from around the world and never from the Middle East. Heart failure (HF) is one of the leading causes of hospitalization, and is a significant factor for morbidity and mortality worldwide. Moreover HF is a major risk factor for the development of ischemic stroke with 2-3 fold-increased risk of stroke when compared to patients without HF [1]. Several pathophysiologic mechanisms can contribute to the development of stroke in HF patients including; atrial fibrillation or left ventricular dysfunction that are potential source embolization [2, 3]. The hyper-coagulable state and reduced fibrinolysis as a consequence of the activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system [4,5]. In addition to endothelial dysfunction in HF [6, 7]. Hypotension may also be an additional risk factor for stroke as a result of heart failure [8]. Moreover underlying risk factors for the development of HF, such as hypertension and diabetes mellitus[9] can also predispose to large-artery atherosclerosis and small-vessel thrombosis and hence stroke [10].

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 analysis of randomized trials rather than epidemiologic studies [11-17]. Furthermore, most of the available data is mainly limited to studies conducted in the Western world and data about the prevalence of prior stroke among patients hospitalized with HF is lacking. The aim of this study is to define the prevalence, clinical characteristics, precipitating factors, management and outcome of stroke patients hospitalized with HF, using data from Gulf CARE[18]. It is hypothesized that patients with prior stroke when hospitalized with HF have worse outcome when compared with HF and without prior stroke.

2. Patients and Methods;

2.1. Registry design

Gulf CARE is a prospective, multinational multi-center registry that recruited patients from February, 2012 to November 2012 who were admitted with the final diagnosis of AHF in 47 hospitals in 7 Middle Eastern Arab countries in the Gulf [18]. Data were collected on episodes of hospitalization 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 one 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 with number NCT01467973.

Patient included from both genders aged above 18 year of age and admitted to the participating hospitals admitted with AHF. AHF was defined based on the European Society of Cardiology (ESC) definition [2]. AHF was further classified as either acute decompensated chronic heart failure (ADCHF) or new-onset AHF (de novo AHF) based on ESC guidelines. ADCHF was defined as worsening of HF in patients with a previous diagnosis or hospitalization for HF. New-onset AHF (de novo AHF) was defined as AHF in patients with no prior history of HF.

Patient excluded from Gulf CARE if: 1) discharged from the emergency room without admission. 2) Transferred from non-registry hospital. 3) Failure to obtain informed consent.4) Patients whose final diagnosis was not heart failure were also excluded from the final analyses. Registry organization and Data Collection and Validation mentioned in published article of Gulf CARE[18].

Definitions of data variables in the CRF are based on the ESC guidelines 2008 and the American College of Cardiology clinical data standards 2005 [19,20]. A 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 [20]. Diastolic heart failure was defined as presence of symptoms and/or signs of HF and a preserved left ventricular ejection fraction (LVEF) >40% [19]. Stroke/TIA defined as History of cerebrovascular disease, documented by any one of the following: **1)** Cerebrovascular ischemic or hemorrhagic stroke: patient has a history of stroke (i.e., any focal neurological deficit of abrupt onset caused by a disturbance in blood supply that did not resolve within 24 hours) confirmed by a standard neurological examination with or without a positive imaging study, or an event of presumed ischemic origin that did not resolve within 24 hours, but the imaging showed a new lesion**. 2)** Transient ischemic attack (TIA): patient has a history of any sudden new focal neurological deficit of presumed ischemic origin as determined by a standard neurological exam that resolved completely within 24 hours, with a brain image study not revealing a new lesion. **3)** Noninvasive/invasive carotid test with greater than or equal to 75% occlusion. **4)** Previous carotid artery surgery **5)** Previous carotid angioplasty [19]. Diabetes mellitus was defined as having a history of diabetes diagnosed and treated with medication and/or insulin or fasting blood glucose 7.0mmol/l (126 mg/dl) or HBA1c ≥6.5%. Hypertension defined as having a history of hypertension diagnosed and treated with medication, blood pressure greater than 140 mmHg systolic or 90 mmHg diastolic on at least 2 occasions or greater than 130 mm Hg systolic or 80 mm Hg diastolic on at least 2 occasions for patients with diabetes or chronic kidney disease (CKD). Hyperlipidemia defined as history of dyslipidemia diagnosed and/or treated by a physician or total cholesterol greater than 5.18mmol/l (200mg/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 smoking cigarettes, water pipe, cigar or chewing tobacco within 1 month of index admission.

CKD was defined as Glomerular filtration rate (GFR) <60 mL per minute per 1.73 m2 for three months or more, with or without kidney damage or on dialysis. If no GFR is available, serum creatinine >177 mmol/L or 2 mg/dl was marked as CKD. Obesity was defined as body mass index (BMI) greater than 25 kg/m^2. Infection definition in the registry: Any systemic infection needing antibiotics [20].

3. Statistical Analysis:

Baseline and outcome data are presented in frequency and percentages for categorical variables and interval variables are presented in mean and standard deviations or median and range as appropriate. Chi-square tests are applied to see association between strokes vs. Non-stroke groups for categorical variables whereas; student t tests or Wilcoxon rank sum tests are used for interval variables as appropriate between the two the group. Multivariate logistic regression analysis is performed at in-hospital and one year mortality for important risk factors. Adjusted OR and 95% C.I. with p values are presented in tables. P value 0.05(two tailed) is considered as statistical significant level. SPSS 21.0 Statistical package is used for the analysis [21].

4. Results:

4.1. Patients demographics (Table1, 2&3):

8.1% of Gulf CARE patients (total 5005 patients) had prior history of stroke, with no significant gender or racial differences between stroke and non-stroke groups. Stroke patients with HF were older (66.5 vs. 59 years, P=0.001) and more likely to have diabetes mellitus, hypertension, atrial fibrillation, coronary artery disease and LV dysfunction (P=0.001). Stroke patients were also more likely to have chronic kidney disease and to be on renal replacement therapy than non-stroke patients (P=0.001) and to have thyroid disease (6.2% vs. 3.4%, P= 0.001) and previous coronary artery bypass grafting (CABG) (7% vs. 10.9%, P=0.004) and were less likely to be smokers (P=0.003) or have history of asthma / chronic obstructive pulmonary disease (COPD). Stroke patients were more likely to present with ADCHF with more frequent recent (≤6 months) HF hospitalizations (P=0.001), and more likely to be admitted under internists rather than cardiologists care when compared to non-stroke patients.

4.2. Investigations during hospitalization (Table 4):

Stroke patients were more likely to be admitted with atrial arrhythmias when compared to non-stroke patients; atrial fibrillation (AF)/Flutter (12.7 % vs. 24.9%, P=0.001). Stroke patients were also more likely to have concentric left ventricular hypertrophy (LVH) (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 2 groups.

Stroke patient were more likely to have lower GFR (mean±SD; 58±36.6, vs. 69±35.7 P=0.001 and as a result higher serum creatinine (mean±SD; 146±111 vs.129±117 mg/dL, P=0.003) and blood urea (mean±SD: 12.8±9 vs. 11±8.4 mg/dL, P=0.002). Stroke patients were also more likely to have lower admission hemoglobin levels (mean ±SD 11.9±2.3, vs.12.7±2.4 mg/dL; P=0.001).

4.3. Precipitating factors, hospitalization course and outcomes (Table: 5&6):

No significant differences in terms of precipitating factors for heart failure hospitalization between the 2 groups **(Table5).**

Stroke patient 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 to non-stroke patients. Stroke patients also were 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 hospitalization when compared to non-stroke patients **(Table 5)**. The clinical work up of stroke patients showed that they were more likely to have ischemic 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) **(Table5)**.

Stroke patient were more likely to be discharged on oral nitrates, hydralazine, statin, angiotensin-converting enzyme (ACE)-inhibitors, aldosterone antagonists (P=0.001), oral anticoagulants (P=0.02), and clopidogrel (P=0.01) when compared to non-stroke patients **(Table 3)**. At discharge more non-stroke patients had undergone PCI [0.02].

Stroke patients had longer hospital stay (mean±SD days; 11±14 vs. 9±13, p= 0.03) and had higher but statistically non-significant in hospital (8.4% vs. 6.1%, P=0.06) and significant higher 1-year mortality rate (32.7% vs. 23.2%, P=0.001). **(Table5)**. On Multivariate logistic regression analysis stroke was an independent mortality predictor for both in hospital and 1 year follow up **(Table 6)**. Age, hypertension, peripheral vascular disease and atrial fibrillation were independent risk factors for stroke in heart failure patients **(Table 6)**.

4.4: Cardiologist vs. internist care: Sub-analysis of prior stroke patients according to whether the primary care provider is cardiologist versus internist showed the followings; 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) and 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 to prior stroke patients hospitalized under the care of internists. Prior stroke patients 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±17 vs. 10±10 (days), P=0.33) when compared to those admitted under cardiologist care. One year follow up showed non-significant marginally higher re-hospitalization for patients under internist care (19.3% vs. 24.5%, P=0.07) with significantly higher mortality when compared to patients under cardiologists care (69.9% vs. 63.2%, P=0.002) **(Table 7).**

5. Discussion:

The current registry of patients hospitalized for HF demonstrates the followings: 1) Prior-stroke history is relatively common among Middle-Eastern patients. 2) Stroke patients had higher risk of recurrent in-hospital strokes and higher long-term mortality rates. 3) Prior stroke was an independent predictor of both in-hospital and one-year mortality. 4) Stroke patients hospitalized with HF were more

likely to be admitted under the internists care rather than cardiologists with less use of evidence based medications.

HF is a common disease and is a major risk factor for ischemic stroke. Stroke-related morbidity and mortality are considerably higher in HF patients compared with stroke patients without HF[22]. Data on the prevalence and outcome of stroke in patients hospitalized 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 world that explores this issue. We had previously reported low prevalence of prior stroke in patients hospitalized with acute coronary syndrome (ACS) in the Middle-east [23, 24]. On the other hand, the current study reports relatively higher prevalence of stroke in patients hospitalized with HF in 7 Middle Eastern countries, suggesting prior stroke is more prevalent among patients hospitalized with HF rather than ACS in this region.

5.1: Prevalence of stroke in heart failure patients: The reported prevalence of stroke in HF patients is variable because of the heterogeneous and limited number of published studies **(table 8)**. [25-31]. One study reported 1.8 % risk of development of an ischemic stroke during the first year after diagnosis of HF and subsequently the rate rises to nearly 5% by 5 years [25]. Data from the Framingham Study [11] and a recent cohort study[12] indicated that the risk of ischemic stroke is 2 to 3 times higher for patients with HF than it is for those without HF. According to epidemiologic data, cohort studies, and case series, ≈10% to 24% of all stroke patients have HF, whereas HF is thought to be the likely cause of stroke in ≈9% of all patients [13-17]. A meta-analysis including 15 clinical studies and 11 cohort studies published before 2006 [25] 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 heart failure that normalized within 6 months [32].

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

5.2: Risk factors for stroke in heart failure patients and outcome: Present facts concerning other risk factors for stroke in heart failure (apart from AF as the major one) is primarily grounded on retrospective studies, cohort studies, or post hoc analyses of large clinical trials with significant inconsistencies [34]. The current study reported age, diabetes mellitus, hypertension, hyperlipidemia, peripheral vascular disease and AF to be independently associated with recurrent stroke risk in HF patients. The Olmsted County cohort demonstrated that prior stroke, advanced age, and diabetes were

relevant stroke risk factors in 630 HF patients [12] whereas a history of atrial Fibrillation 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 HF patients [35]. In contrast to these reports, the SCD-HeFT-study revealed a hazard ratio of 1.9 (95% CI, 1.1–3.1) for stroke when hypertension was present at randomization of 2144 heart failure patients without atrial fibrillation [36] In addition, a medical history of hypertension was associated with an increased risk of hospitalization for stroke (hazard ratio1.4; 95% CI, 1.01–1.8) in 7788 heart failure patients of the Digitalis Investigation Group trial [37]. Furthermore our result is compatible from the age point of view with Olmsted Country data that revealed a significant but modest association between stroke risk and advanced age (relative risk 1.04; 95% CI, 1.02–1.06)[12] **.** An exploratory analysis of the SAVE study also showed similar results (relative risk of stroke 1.18; 95% CI, 1.05–1.3, for each increase of 5 years in age)[36] while these results contradict the result of Framingham Study that indicated that advanced age does not account for the increased risk of stroke in HF patients[38,39.]

The current study had shown that heart failure patient with stroke had higher in hospital mortality with longer hospital stay and they are less likely to stay alive on one-year follow up probably explained by multiple comorbidities in this patient population. Many retrospective database analyses have shown that stroke increases the disability and mortality of heart failure patients through the alteration in neuropsychological status, like decreased attention and concentration, memory loss, diminished psychomotor speed, and decreased executive function and this ranged approximately 25% to 80% of all patients with CHF [40–43].

5.3: Cardiologist vs. internist care of HF patients with Prior Stroke: Cardiologists when compared to internists may provide more evidence-based therapies for the treatment of HF patients [44, 45]. This is supported by the current study, where patients under the care of cardiologists had lower risk of recurrent in-hospital stroke, major bleeding, the need for blood transfusion and lower in-hospital and one-year mortality rates when compared to patients managed by internists. This suggests that prior stroke patients are higher risk group and may benefit from specialized care. On the other hand, the observational nature of the current study does not adjust for the possibility of selection bias in that "lower" risk stroke patients were "preferentially" admitted under the care of cardiologists rather than internists.

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

7. Conclusion: This observational study reports high prevalence of prior stroke in Middle-East HF patients. There was under use of anticoagulation therapy in stroke and HF patients with atrial fibrillation. Stroke patients hospitalized 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. Stroke patients had higher risk of in-hospital recurrent strokes and higher long-term mortality rates. History of stroke was independent predictor of in-hospital and one-year mortality rates in patients hospitalized with HF. Future studies are needed to evaluate wither aggressive evidence based therapies to this high risk group will improve outcome.

a. Contributors: KS, KA, NA, AA, MA, BB, WA, MR, NB, HA, AA, HA, AA, PP and JA were involved in the design of Gulf CARE registry and patients enrollment and ensuring quality control of the study. RS carried out the statistical analyses. All authors contributed to drafting of the article and approved the final version of the manuscript.

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d. **Data sharing statement:** No additional data available.

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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 ±SD)		59±14.9	66.5±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 Care Giver	Cardiologist (%)	3326(72.3)	249(61.6)	
	Internist (%)	1275(27.7)	155(38.4)	0.001
Previous CV History				
HF previous admission (%)	≤ 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 hyperlipidemia (%)	1572(34.2)	227(56.2)	0.001
CKD/Dialysis (%)	631(13.7)	113(28)	0.001
Sleep apnea 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, PVD=peripheral vascular disease, TIA=transient ischemic attack, CKD=chronic kidney disease, COPD=chronic obstructive pulmonary disease, HTN=hypertension, DM=diabetes mellitus.

Table 2. Clinical presentation (symptoms, signs) (Stroke/TIA vs. No Stroke/TIA).

Variable	**No-Stroke/TIA N=4601(91.9%)**	**Stroke/TIA,**	**P-Value**

		N =404(8.1%)	
ClinicalSymptoms			
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
Orthopnea (%)	3618(78.6)	324(80.2)	0.46
Paroxysmal nocturnal dyspnea (%)	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 one year (%)	218(4.7)	45(11.1)	0.001
Clinical Signs			
HR (mean ±SD)	97±23	95±22.9	0.
BP mm Hg (mean ±SD) Systolic	137±34	142±33	0.01
BP mm Hg (mean ±SD) 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)	92±15	93±16.7	0.84
BMI(mean ±SD)	28±6	29±6.3	0.03
Raised JVP>6 cm (%)	2323(56.5)	203(50.2)	0.93
Peripheral edema (%)	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
HR=heart rate, BP=blood pressure, RR=respiratory rate, BMI=body mass index, JVP=jugular venous pressure			

Table 3. Medications and interventions (Stroke/TIA vs. No Stroke/TIA).

		Before Admission			On discharge		
Variable		**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 anticogulants (%)		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
Allpurinol		121(2.6)	14(3.5)	0.32	219(4.8)	20(5)	0.86
Ivabridine (%)		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
Anti-depressnats (%)		57(1.2)	9(2.2)	0.10	82(1.8)	10(2.5)	0.32
BB	Cardvidolol	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

Table 4. Investigations during hospitalization (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 done (%)	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 hemoglobin gm /dL(mean ±SD)		12.7±2.4	11.9±2.3	0.001
First WBC (mean ±SD)		10.4±8	10±7	0.89
First Urea(mean ±SD) mmol/L		11±8.4	12.8±9	0.002
First Creatinine mmol/L		129±117	146±111	0.003
E-GFR		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
	LV hypertrophy (%)	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 msec	-		
	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		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

MS=mitral stenosis, MR=mitral regurgitation, AS=aortic stenosis, AR=aortic regurgitation, TR=tricuspid regurgitation, PA=pulmonary artery, SVD=single vessel disease, DVD=double vessel disease, TVD=tripe vessel disease, LMSD=left main disease, GFR=glomerular filtration rate.

Table 5. Course in the Hospital & 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 noncompliance (%)	878(19.1)	86(21.3)	0.28
	Noncompliance 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
	Anemia (%)	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)		9±13	11±14	0.03
Alive (yes)		3532(76.8)	272(67.3)	0.001
HF re-hospitalization (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

NIV=Non-invasive ventilation, IABP=intra-aortic balloon pump insertion, VT=ventricular tachycardia, VF=ventricular fibrillation, AF=atrial fibrillation. HHD=hypertensive heart disease, IHD=ischemic heart disease, HOCM=hypertophic cardiomyopathy, CM=cardiomyopathy, DCM=dilated cardiomyopathy, ARVD-arrhythmogenic right ventricular dysplasia

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Table 6 : Multivariate logistic regression analysis for In hospital mortality			
Variable	**Adjusted OR**	**95% C.I.**	**P value**
Age	0.99	0.98 – 1.03	0.16
Male gender	0.78	0.59 – 1.04	0.09
DM II	1.06	0.79 – 1.41	0.70
CKD	1.31	0.91 – 1.89	0.15
COPD/Asthma	0.64	0.37 – 1.10	0.11
STEMI	2.25	1.57 – 3.23	0.001
LVEF ≥35%	0.77	0.59 – 1.01	0.06
LVEF <35	1.30	0.99 – 1.70	0.06
VHD	1.59	1.12 – 2.25	0.009
Stroke	1.71	1.13 – 2.60	0.01
PVD	1.52	0.89 – 2.62	0.13
Multivariate logistic regression analysis for one year mortality			
Age	1.04	1.03 – 1.05	0.001
Male gender	1.12	0.90 – 1.40	0.31
DM II	1.18	0.95 – 1.46	0.13
CKD	1.53	1.19 – 1.96	0.001
COPD/Asthma	1.22	0.91 – 1.65	0.19
STEMI	0.89	0.62 – 1.29	0.55
LVEF≥35	0.74	0.60 – 0.91	0.005
LVEF <35	1.35	1.10 – 1.67	0.005
VHD	1.46	1.10 – 1.93	0.009
Stroke	1.34	0.98 – 1.84	0.07
PVD	1.20	0.79 – 1.82	0.41
Risk factors for stroke in heart failure			

Age	1.02	1.01-1.03	0.001
Gender	1.02	0.81-1.28	0.88
DM	1.30	1.01-1.69	0.045
HTN	2.10	1.50-2.80	0.001
Systolic BP	1.0	0.99 – 1.01	0.51
Diastolic BP	1.0	0.99 – 1.01	0.65
NYHA I	0.64	0.19 – 2.14	0.33
NYHA II	0.98	0.42 – 2.25	0.46
NYHA III	1.24	0.55 – 2.80	0.95
NYHA IV	1.24	0.54 – 2.81	0.61
hyperlipidemia	1.30	1.02-1.65	0.03
CKD	1.31	1.05-1.75	0.045
Systolic LV dysfunction	1.08	0.85-1.37	0.52
Known CAD	1.14	0.89-1.47	0.30
PVD (%)	2.97	2.06 -4.12	0.001
AF	2.20	1.67-2.89	0.001
Thyroid disease	0.91	0.56-1.49	0.71

DM; Diabetes Mellitus CKD: Chronic kidney disease, VHD: Valvular heart disease, PVD: Peripheral vascular disease PVD: Peripheral vascular disease.

Table 7: HF patient with Stroke/TIA as per care provider			
Variable	**Cardiologist care 249(61.6%)**	**Internist care 155(38.4%)**	**P-Value**
Acute new-onset heart failure (%)	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
Atrial fibrillation	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 anticogulants (%)	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)		11±17	10±10	0.33
1 Year follow up	Alive (yes)	174(69.9)	98(63.2)	0.002
	HF hospitalization (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

Table 8: Prevalence of stroke in heart failure patients / studies from different parts of the world

Study Name (Reference	Study Period	Patient No.	Mean Age (years)	Female Sex (%)	Strokes%	F/U* (Days)
Granger [26] North America Europe	CHARM-Alternative trial 1999-2001	2028	66.5	31.9	3.8 %	1011
Mathew [27] North America	DIG trial 1991-1993	7788	63.9	24.7	4.2 %	1110
Pfeffer [28] NorthAmerica Europe	CHARM-Overall program 1999-2001	7599	66	31.6	1.4 %	1131
Dries [29] North America	SOLVD trial 1986-1989	6378	60	4.4	3.5 %	1197
McMurray [30] 26 countries world wide	CHARM-Added trial 1999	2548	64	21.3%	3.4 %	1230
Remme [31] Europe	COMET Trial 1996-1999	3029	62	0.2%	4.7 %	1740
Khafaji et al Current study Middle east	Gulf CARE 2012-2013	5005	66.5	40.8%	8.1 %	360

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **(mentioned in the tile as well as the abstract and the main manuscript) page 1 and 2.**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **(done) page 2.**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **(done) page 2.**
Objectives	3	State specific objectives, including any prespecified hypotheses**(done)** **Page 2, the hypothesis is as follows "**It is hypothesized that patients with prior stroke when hospitalized with HF have worse outcome when compared with HF and without prior stroke."
Methods		
Study design	4	Present key elements of study design early in the paper **1 & 2.**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **page 4 in the registry design and details of which are also available in the methodology reference of the Gulf CARE registry reference no 18 in the references section page 14.**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **page 4 in the registry design and details of which are also available in the methodology reference of the Gulf CARE registry reference no 18 in the references section page 14.** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed **outlined in the statistical section and details are available in the tables section of the manuscript.** *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **results section pages no 6 & 7.**
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
Bias	9	Describe any efforts to address potential sources of bias **in the limitation section page 10.**
Study size	10	Explain how the study size was arrived at **in the methodology section study design page 4.**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why

Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **in the statistical section page 5 & 6.**
		(*b*) Describe any methods used to examine subgroups and interactions **in the statistical section page 5 & 6.**
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed **page 4 in the registry design and details of which are also available in the methodology reference of the Gulf CARE registry reference no 18 in the references section page 14.** *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

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**(done)**
		(b) Give reasons for non-participation at each stage**(done)**
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders**(done)**
		(b) Indicate number of participants with missing data for each variable of interest**(done)**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time**(done)**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
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**(done)**
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives**(done)**
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**(done)**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results**(done)**
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**(done)**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.