Major cardiovascular events in patients presenting with acute stroke: a 5-year follow-up study in patients who had ischaemic stroke and stroke mimics

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ABSTRACT

Objectives The long-term acute stroke outcome has not been well studied in the Middle-Eastern population. The primary objective of our study is to compare the long-term outcome of acute ischaemic stroke (IS) with/without previous cerebrovascular/cardiovascular disease (CVD) to stroke mimics (SM) with CVD.

Settings and participants The Qatar stroke database was reviewed for IS and SM admissions in Qatar Nationals between 2013 and 2019.

Outcomes Patients were prospectively assessed for development of recurrent stroke, myocardial infarction or death. Frequency of major cardiovascular events (MACEs) were compared between patients with or without a previous CVD.

Results There were 1114 stroke admissions (633 IS (prior CVD 211/18.9%), 481 SM (prior CVD 159/14.3%). Patients with IS/CVD were significantly older versus others (IS/CVD: 68.3±12.2; IS/no CVD: 63.3±14.4; SM/CVD: 67.6±13.1; SM/no CVD: 52.4±17.9. p<0.0001). Vascular risk factors were significantly higher in patients with IS and SM with previous CVD. Functional recovery (90-day mRS 0–2) was significantly better in SM/no CVD (IS/CVD: 55.0%; IS/no CVD: 64.2%; SM/CVD 59.7%; SM/no CVD: 88.8%, p<0.001). MACE occurred in 36% (76/211) IS/CVD, 24.9% (105/422) IS/no CVD, 22.0% (35/179) SM/CVD and only 6.8% (22/322) SM/no CVD. MACE occurred mostly during the first year of follow-up. Mortality 90 days was significantly higher in IS/CVD (IS/CVD 36%; IS/no CVD 24.9%; SM/CVD: 22%; SM/no CVD: 6.8%, p<0.0001).

Conclusions Prior CVD significantly increases the risk of MACE and early mortality in IS or SM patients. Age, male gender, obesity, atrial fibrillation and admission National Institute of Health Stroke Scale also increases risk of MACE during follow-up. Hence, aggressive vascular risk factor modification is needed even in patients with SM.

INTRODUCTION

Patients who suffer from an acute stroke (AS) are at an increased risk of major atherosclerotic cardiovascular events (MACEs) during follow-up. The risk of MACE is higher in the initial year following the stroke, especially in individuals with a previous history of cardio/cerebrovascular disease (CVD).1 This risk has decreased significantly during the last two decades, which is largely attributed to improved management of vascular risk factors.2

There are very few studies evaluating the risk of MACE in stroke mimics (SM).3 Similar to AS, the risk of vascular events during follow-up in SM also depends on the presence of underlying preexisting vascular disease and is higher in medical mimics compared with functional mimics.4 Additionally, in medical mimics, a higher cardiovascular event rate may occur in patients who experience ‘recrudescence of symptoms’ in the presence of a previous history of stroke.5

The long-term prognosis in patients who had an ischaemic stroke (IS) in the Middle East has received very little attention. We have previously studied the stroke subtypes, risk factors and early prognosis in patients who had an AS,6–8 SM9 and poststroke depression in Qatar.10 We have also evaluated the longterm prognosis and MACE in the ethnically distinct Qatari population. During the early
recovery phase following an AS, recovery is slower in
women and mortality is higher compared with men. 
However, during long-term follow-up, men tend to have 
higher MACE, especially in the presence of previous coro-
nary artery disease.11

The primary objective of the present research is to 
evaluate the short-term and long-term prognosis of AS 
and stroke mimic patients in an ethnically distinct Arab 
population in Qatar. We investigated the outcomes in 
patients who had an acute IS in the presence and absence
of previous CVD and similarly in SM with and without
previous CVD. We selected patients with SM without a
history of CVD both to serve as a control group and to
provide insight about the risk of MACE in this relatively
understudied population.

PATIENTS AND METHODS

Study population
All AS and stroke mimic patients admitted to the Hamad
General Hospital (HGH) from January 2014 to February
2019 were evaluated for the study. Patients or the public
were not involved in the design, or conduct, or reporting,
or dissemination plans of our research. SM included
both medical and functional mimics. The information
was obtained from the discharge diagnosis after patient
completed their in-hospital evaluation. Clinical informa-
tion including ethnicity, risk factors, clinical presenta-
tion and course in hospitalisation was entered prospectively
in a database. We also documented all investigations,
diagnosis and complications as previously published.6,7
The hospital has a dedicated stroke ward, admits 98% of
strokes in Qatar and is the only centre where AS treatment
with intravenous thrombolysis and mechanical thrombec-
tomy is offered. Patients of all ethnicities are admitted to
the HGH. All patients are evaluated by stroke neurolo-
gists or stroke physicians, and their stroke is confirmed
using neuroimaging (CT or MRI). For the purpose of the
current research, we only focused on Qatari nationals.
This allowed for accurate follow-up information on the
study subjects. Non-nationals who had a stroke typically
travel to their home countries for further treatment or
recovery, thus limiting accurate follow-up data. Patients
with a final diagnosis of IS and SM were reviewed for this
study. The prehospital modified Rankin Scale (mRS),
National Institutes of Health Stroke Scale (NIHSS) and
the mRS at discharge and 90-days follow-up were docu-
mented. We reviewed the state-wide Cerner medical
records of the patients to document any vascular compi-
lcations following discharge.

We did not include patients with transient ischaemic
attacks (TIAs) as the diagnosis is not always clear. There
is risk that SM may be wrongly classified as TIAs or
vice versa. We also did not review records of patients
admitted with intracranial haemorrhage (ICH) as
the mechanisms for most patients are not related to
atherosclerosis.

Study outcomes
The patients were categorised into four categories: isch-
aemic stroke with previous evidence of either stroke or
cardiac disease (CVD); ischaemic stroke with no previous
history of CVD; stroke mimic with previous CVD and stroke
mimic with no previous CVD. We reviewed the severity
of symptoms, hospital course, risk of medical complica-
tions in hospital and mortality during hospitalisation and
in the 90 days following discharge. The primary short-
term outcome was mRS score at 90 days. The primary
long-term outcome was occurrence of MACE. MACE was
defined as cardiovascular mortality, all-cause mortality,
fatal or non-fatal MI, recurrent stroke, congestive heart
failure and revascularisation procedure (CABG or PCI),
after the index event during follow-up.

Patient and public involvement
No patient involvement.

Statistical methods
Descriptive and inferential statistics were used to char-
acterise the study sample. Descriptive results (including
graphical displays) for all quantitative variables (eg, age)
are presented as the mean±SD for normally distrib-
uted data or median with IQR for data not normally distri-
uted. Bivariate analysis was performed using indepen-
dent sample t-test and the Mann Whitney U-test to
calculate the average for all quantitative variables (eg,
age) between stroke subtypes (IS vs SM), wherever appro-
priate, while the Pearson χ² test or Fisher’s exact test as
appropriate were used in comparing all the qualitative
variables (eg, presence or absence of CVD) between IS
and SM. The Kaplan-Meier survival analysis was applied
to compare differences in the cumulative incidence of
MACE in 5years among the four groups. The log rank
test (Mantel-Cox Method) was used to test the null
hypothesis that there was no difference between the four
groups in the probability of an event at any time point.
To understand the effect of age and other risk factors, HRs
for MACE were determined by multivariate Cox propor-
tional hazards regression analyses with data presented as
HR (compared with the lowest quartile) with 95% CIs.
The statistical tests were performed in IBM SPSS Statistics
V.26 (IBM, Armonk, USA).

RESULTS

Demographics
There were 8979 patients admitted with an AS to the
HGH during the study period. Of these, 1515 were Qatari
nationals. After excluding patients with ICH (n=179),
cerebral venous thrombosis (n=8) and TIAs (n=212),
we were left with 1114 patients who had an IS and SM
for analysis for our study (mean age 61.7±16.2; male:
610 (54.8), female: 504 (45.2)). These included IS with
previous CVD: 211 (18.9%); IS with no previous CVD
422 (37.9%), SM with previous CVD 159 (14.3%) and
SM with no previous CVD: 322 (28.9%). SM with no
Previous CVD were significantly younger than the other three groups (see Table 1). The incidence of hypertension and hyperlipidaemia were highest in patients with IS and previous CVD and lowest in SM with no previous CVD. The prestroke mRS was higher in both IS and SM patients with previous CVD (mRS 1.1±1.7; IS+CVD: 1.4±1.8; IS+no CVD: 0.8±1.5; SM+CVD: 2.1±1.9; SM+no CVD: 0.7±1.4; p=0.0001) (Table 1). Atrial fibrillation was significantly higher in the IS groups compared with the SM groups.

We evaluated if there were differences in outcome of functional and medical mimics. Functional mimics is made up of only 17% (82/481) of the SM patients, while medical mimics 83% (399/481) of the SM patients. Medical mimics constituted 133 (83.6%) of the SM patients with previous CVD and 266 (82.6%) of the SM patients without previous CVD. We found no differences in the clinical presentation and short-term outcome between the functional and medical mimics.

Clinical course and early prognosis following discharge

The mode of admission to the emergency department was similar in the four groups with slightly more than 50% transferred by the ambulance service. Overall, the severity of stroke (as measured on admission NIHSS) was mild in most strokes (3.9±5.3). Patients with IS and previous CVD had the most severe stroke (NIHSS 6.3±6.3) and those with SM and no previous CVD had the mildest symptoms (NIHSS 1.5±3.1) as shown in Table 1.

The percentage of patients admitted to the stroke unit was similar between patients with ischaemic stroke with and without CVD. Stroke-related investigations were significantly fewer in SMs compared with IS. Significantly fewer patients with SM received thrombolysis (IS+CVD: 8.5%; IS+no CVD:10.9%; SM+CVD: 1.3%; SM+no CVD: 1.2%; p=0.0001). At the time of discharge, the percentage of patients with mRS of 0–2 (functional independence) was low in IS with previous CVD (46.7%), IS with no previous SVD (52.8%) and SM with previous CVD (47.2%) compared with SM with no previous CVD (82.0%). These remained similar at 90-day follow-up as well with IS and CVD (55.0%), IS with no CVD (64.2%) and SM with CVD (59.7%) compared with SM with no CVD (88.8%). There were 51 (4.60%) deaths in hospital and within 90 days, of which 22 (10.4%) were patients with IS and previous CVD as shown in Table 1.

MACES during follow-up

Follow-up information was available on the electronic medical system for all patients. During follow-up, 238 (21.4%) patients had a MACES. The incidence of MACES was highest in patients with IS and previous CVD. MACES occurred in 36% (76/211) IS with CVD, 24.9% (105/422) IS without CVD patients, 22.0% (35/179) SM with previous CVD and only 6.8% (22/322) SM with no CVD (see figure 1). Most events occurred during the initial year of follow-up. In patients with IS (with or without previous CVD), the most frequent MACES was recurrent stroke. In patients presenting with SMs (with or without CVD), cardiac events, including acute myocardial

Table 1

| Characteristic or investigation | Total (n=1114) | IS with CVD (n=211, 18.9%) | IS without CVD (n=422, 37.9%) | SM with CVD (n=159, 14.3%) | SM without CVD (n=322, 28.9%) | P value |
|---------------------------------|---------------|---------------------------|-------------------------------|---------------------------|-----------------------------|---------|
| Age, mean, years                | 61.7±16.2     | 68.3±12.2                 | 63.3±14.4                    | 67.6±13.1                 | 52.4±17.9                   | 0.0001  |
| Sex                             |               |                           |                               |                           |                             |         |
| Male                            | 610 (54.8)    | 138 (65.4)                | 234 (55.5)                   | 85 (53.5)                 | 153 (47.5)                  | 0.001   |
| Female                          | 504 (45.2)    | 73 (34.6)                 | 188 (44.5)                   | 74 (46.5)                 | 169 (52.5)                  |         |
| Hypertension                    | 803 (72.1)    | 192 (91.0)                | 330 (78.2)                   | 132 (83.0)                | 149 (46.3)                  | 0.0001  |
| Diabetes                        | 757 (68.0)    | 179 (84.8)                | 297 (70.4)                   | 128 (80.5)                | 153 (47.5)                  | 0.0001  |
| Dyslipidaemia                   | 576 (51.7)    | 127 (60.2)                | 232 (55.0)                   | 91 (57.2)                 | 126 (39.1)                  | 0.0001  |
| Atrial fibrillation on admission| 98 (8.8)      | 39 (18.5)                 | 43 (10.2)                    | 13 (8.2)                  | 3 (0.9)                     | 0.0001  |
| Active smoking                  | 220 (19.7)    | 42 (19.9)                 | 87 (20.6)                    | 28 (17.6)                 | 63 (19.6)                   | 0.88    |
| Obesity (BMI ≥30 kg/m²)         | 463 (43.5)    | 82 (42.9)                 | 166 (42.0)                   | 60 (38.0)                 | 155 (48.3)                  | 0.15    |
| NIHSS severity                  |               |                           |                               |                           |                             |         |
| Mild (NIHSS 0–4)                | 821 (73.7)    | 114 (54.0)                | 263 (62.3)                   | 146 (91.8)                | 298 (92.5)                  | 0.0001  |
| Moderate (NIHSS 5–10)           | 178 (16.0)    | 56 (26.5)                 | 97 (23.0)                    | 7 (4.4)                   | 18 (5.6)                    |         |
| Severe (NIHSS >10)              | 115 (10.3)    | 41 (19.4)                 | 62 (14.7)                    | 6 (3.8)                   | 6 (1.9)                     |         |
| Mortality at 90 days            | 51 (4.6)      | 22 (10.4)                 | 24 (5.7)                     | 3 (1.9)                   | 2 (0.6)                     | 0.0001  |

BMI, body mass index; IS, ischaemic stroke; NIHSS, National Institute of Health Stroke Scale; SM, stroke mimic.
infarction were more frequent than ischaemic stroke (see table 2).

Multivariate analysis showed the incidence of MACE was associated with increasing age, sex (male), obesity, presence of atrial fibrillation on admission and National Institute of Health Stroke Scale (NIHSS) on admission as shown in table 3.

Overall, compared with SM patient without CVD, both patients with IS or SM that had CVD had an increased risk of MACE. Although IS patients without CVD were initially found to also have an increased risk of MACE, this lost its statistical significance difference when discharge medications where factored in.

**DISCUSSION**

In this cohort of 1114 patients who had an AS, we made several important observations. Patients who had an IS with a previous history of CVD were most likely to experience severe symptoms at presentation and were significantly more likely to die during hospitalisation and the 90 days following discharge.

### Table 2  Major cardiovascular events (MACEs) during follow-up in the four groups

|                  | Total (n=1114) | IS with CVD (n=211, 18.9%) | IS without CVD (n=422, 37.9%) | SM with CVD (n=159, 14.3%) | SM without CVD (n=322, 28.9%) | P value |
|------------------|----------------|----------------------------|-----------------------------|---------------------------|--------------------------------|---------|
| Total MACE       | 238 (21.4)     | 76 (36.0)                  | 105 (24.9)                  | 35 (22.0)                 | 22 (6.8)                       | 0.0001  |
| MACE at 1 year   | 133 (11.9)     | 44 (20.9)                  | 55 (13.0)                   | 20 (12.6)                 | 14 (4.3)                       | 0.0001  |
| Total MACE per patient over 5 years |          |                            |                            |                           |                                |         |
| No events        | 876 (78.6)     | 135 (64.0)                 | 317 (75.1)                  | 124 (78.0)                | 300 (93.2)                     | 0.0001  |
| One event        | 205 (18.4)     | 61 (28.9)                  | 94 (22.3)                   | 31 (19.5)                 | 19 (5.9)                       |         |
| Two events       | 29 (2.6)       | 13 (6.2)                   | 11 (2.6)                    | 2 (1.3)                   | 3 (0.9)                        |         |
| Three events     | 4 (0.4)        | 2 (0.9)                    | 0                          | 2 (1.3)                   | 0                              |         |
| Poststroke MI (fatal or non-fatal) | 39 (3.5)     | 9 (4.3)                    | 14 (3.3)                    | 11 (6.9)                  | 5 (1.6)                        | 0.02    |
| Recurrent stroke (Ischaemic/haemorrhagic) | 89 (8.0)     | 37 (17.5)                  | 39 (9.2)                    | 8 (5.0)                   | 5 (1.6)                        | 0.0001  |
| Poststroke congestive heart failure | 4 (0.4)        | 2 (0.9)                    | 1 (0.2)                     | 1 (0.6)                   | 0                              | 0.29    |
| Post-stroke cardiac revascularisation (CABG or PCI) | 12 (1.1)     | 4 (1.9)                    | 3 (0.7)                     | 2 (1.3)                   | 3 (0.9)                        | 0.58    |
| Cardiovascular mortality | 105 (9.4)   | 34 (16.1)                  | 44 (10.4)                   | 15 (9.4)                  | 12 (3.7)                       | 0.0001  |
| All-other mortality | 32 (2.9)    | 10 (4.7)                   | 18 (4.3)                    | 4 (2.5)                   | 0                              | 0.002   |
| Cardiovascular mortality – short term | 46 (4.1)   | 20 (9.5)                   | 22 (5.2)                    | 2 (1.3)                   | 2 (0.6)                        | 0.0001  |
| Cardiovascular mortality – long term | 105 (9.4)   | 34 (16.1)                  | 44 (10.4)                   | 15 (9.4)                  | 12 (3.7)                       | 0.0001  |
| All other mortality – short term | 5 (0.4)     | 2 (0.9)                    | 2 (0.5)                     | 1 (0.6)                   | 0                              | 0.43    |
| All other mortality – long term | 32 (2.9)     | 10 (4.7)                   | 18 (4.3)                    | 4 (2.5)                   | 0                              | 0.002   |

The type of MACE events and time of the vascular outcome events are shown in the table. CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous intervention.

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**Figure 1**  Hazard curves showing the 5-year probability of major cardiac adverse events (MACEs) in patients presenting as ischaemic strokes with and without prior cardiovascular disease versus stroke mimics, in Qatar (mean follow-up duration: 24.2±17.1 months) (A) prior to controlling for discharge medications and (B) after controlling for discharge medications.
Table 3  Cox regression analysis of covariates associated with occurrence of major cardiac adverse event (MACE) stratified for diagnosis (stroke mimics vs ischaemic stroke – with or without cardiovascular history) in patients presenting as acute stroke from Qatar

| Characteristic                                      | AHR   | 95.0% CI   | P value |
|-----------------------------------------------------|-------|------------|---------|
| Stroke mimic without prior vascular disease         |       |            |         |
| Ischaemic stroke with prior vascular disease        | 2.183 | 1.145-4.161| 0.018   |
| Ischaemic stroke without prior vascular disease     | 1.268 | 0.657-2.445| 0.479   |
| Stroke mimic with prior vascular disease            | 1.954 | 1.065-3.855| 0.031   |
| Age                                                 | 1.021 | 1.009-1.034| 0.001   |
| Female                                              | 0.495 | 0.351-0.698| 0.0001  |
| AF on admission                                     | 1.830 | 1.150-2.913| 0.011   |
| Obesity (BMI ≥30)                                   | 0.728 | 0.536-0.989| 0.042   |
| NIHSS on admission                                  | 1.065 | 1.041-1.089| 0.000   |

AF, Atrial Fibrillation; AHR, adjusted HR; BMI, body mass index; NIHSS, National Institute of Health Stroke Scale.

More than 20% of patients developed a MACE even during follow-up. Whereas the long-term prognosis was relatively benign in patients with SM with no previous history of CVD, the risk of MACE was high in those with SM with previous CVD. The distribution of functional versus medical mimics in both groups was not statistically significantly different.

Patients who had an IS were more likely to experience recurrent stroke as their MACE event, while patients with SM were more likely to have a cardiac MACE. The incidence of MACE was highest during the initial year following the index event.

Two recent studies followed AS patients for MACE events.2 11 In the study from Oxford, MACE events were documented in 22% of patients and were more frequent in patients over the age of 75 years. Similar to our study, MACE was more frequent in patients with pre-existing CVD versus no history of CVD (22% vs 7%), and recurrent stroke was the most common event. The study from Ontario, Canada, evaluated the risk of cardiac events and compared it with age-matched controls (propensity-matched individuals with no history of stroke). The risk of MACE during follow-up was four times higher in patients who had a stroke and was highest early following the AS.12

The frequency of SM in the Qatari stroke population in our study is around 36% and appears similar to previously published reports.1–3 Similar to reports from Europe and North America, medical mimics account for the majority of patients. In our study, many SM patients had a previous history of stroke (22%, 106/481). Our study is the first report highlighting the importance of MACE during follow-up in SM.

We were able to show that MACE events are high in SM, especially patients with previous history of CVD. The risk of recurrent events is strongly related to the presence or absence of pre-existing CVD. MACE was noted in 22% of SM patients with previous CVD and less than 7% of SM with no history of CVD. Thus, recognising vascular risk factors in SM is therefore important and prevention strategies should be aggressively pursued to reduce the risk of recurrence. An alternate possibility for the high rates of MACE that cannot be excluded is the possibility of a missed diagnosis of an AS (with negative imaging), resulting in a diagnosis of stroke mimic. With the high frequency of small vessel disease in our population, we cannot rule out this possibility.

The strength of our study is the comprehensive nature of our prospective database and the ability to capture all events in a nationwide electronic medical record system. All patients seen in the hospital acutely with stroke-like symptoms were followed, and all MACE events were recorded.

The study has limitations. First, the number of patients is relatively small, and we were not able to verify the cause of death in most patients as autopsy is rarely performed in Qatar. The number is further limited by excluding patients with TIA, potentially influencing the analysis. Second, the study population is from Qatar, thus limiting generalisability. Third, we were unable to verify adherence to prescribed medical therapy as the patients were not seen in the clinic unless they had new events. Fourth, fewer brain, vascular and cardiac imaging studies were performed in women compared with men. We identify this as a concerning trend and cannot provide a clear explanation for this discrepancy. Finally, MACE data were collected from electronic medical records, and individual cases were not verified by the investigators.

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