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ORIGINAL RESEARCH

Association of Major Adverse Cardiovascular Events in Patients With Stroke and Cardiac Wall Motion Abnormalities

Saadat Kamran, MD; Naveed Akhtar, MBBS; Rajvir Singh, PhD; Yahya Imam, MBBS; Khawaja H. Haroon, MBBS; Noman Amir, MD; Suhail Hussain, MBBS; Salman Al Jerdi, MD; Laxmi Ojha, MSc; Ahmed Own, MBBS; Ahmad Muhammad, MBBS; Jonathan D. Perkins, PhD

BACKGROUND: The association of cardiac wall motion abnormalities (CWMAs) in patients with stroke who have major adverse cardiovascular events (MACE) remains unclear. The purpose of this study was to estimate the 50-month risk of MACE, including stroke recurrence, acute coronary events, and vascular death in patients with stroke who have CWMAs.

METHODS AND RESULTS: We performed a retrospective analysis of prospectively collected acute stroke data (acute stroke and transient ischemic attack) over 50 months by electronic medical records. Data included demographic and clinical information, vascular imaging, and echocardiography data including CWMAs and MACE. Of a total of 2653 patients with acute stroke/transient ischemic attack, CWMA was observed in 355 (13.4%). In patients with CWMAs, the embolic stroke of undetermined source (50.7%) was the most frequent index stroke subtype and stroke recurrences (P=0.001). In multivariate Cox regression after adjustment for demographics, traditional risk, and confounding factors, CWMA was independently associated with a higher risk of MACE (adjusted hazard ratio [HR], 1.74; 95% CI, 1.37–2.21 [P=0.001]). Similarly, CWMA independently conferred an increased risk for ischemic stroke recurrence (adjusted HR, 1.50; 95% CI, 1.01–2.17 [P=0.04]), risk of acute coronary events (aHR, 2.50; 95% CI, 1.83–3.40 [P=0.001]) and vascular death (adjusted HR, 1.57; 95% CI, 1.04–2.40 [P=0.03]), in comparison to the patients with stroke without CWMA.

CONCLUSIONS: In a multiethnic cohort of ischemic stroke with CWMA, CWMA was associated with 1.7-fold higher risks of MACE independent of established risk factors. Embolic stroke of undetermined source was the most common stroke association with CWMA. Patients with stroke should be screened for CWMA to identify those at higher risk of MACE.

Key Words: cardiac wall motion abnormalities ■ embolic stroke ■ embolic stroke of undetermined source ■ major adverse cardiovascular events

The association between cardiac wall motion abnormalities (CWMAs), a common abnormality found by echocardiography, with stroke and stroke recurrence remains controversial. Whereas some studies have reported CWMA as a high risk source for cardioembolic stroke,[1–6] others consider it a low or uncertain risk source.[7–10] The leading cause of CWMAs is myocardial infarction (MI), of which nearly a third go undetected but may lead to left ventricular (LV) scar and/or CWMAs.[11] LV thrombi can develop months after MI and overlie ventricle wall segments with abnormal motion capable of embolism and resultant ischemic stroke.[12,13]

MESA (Multi-Ethnic Study of Atherosclerosis) reported that regional LV dysfunction predicted cardiovascular events (hard coronary events, nonfatal and

Correspondence to: Saadat Kamran, MD, Neuroscience Institute, Hamad General Hospital, Weill Cornell Medical School, Doha, Qatar 3050. E-mail: skamranmd@hotmail.com

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CLINICAL PERSPECTIVE

What Is New?

- In patients with acute ischemic stroke who have cardiac wall motion abnormalities (CWMAs), CWMA is associated with a 1.7-fold higher risk of major adverse cardiovascular events including stroke recurrence, acute coronary events, and vascular death, independent of established stroke risk factors.
- Embolic stroke of undetermined source is the most common stroke associated with CWMA as well as in stroke recurrence.

What Are the Clinical Implications?

- The association of embolic stroke of undetermined source with CWMAs suggest that CWMAs may be a potential cardioembolic risk factor in embolic stroke of undetermined source.
- Given the adverse prognosis of stroke with CWMAs, screening for CWMAs in patients with stroke can yield important information to refine risk stratification for more intensive treatment of established cardiovascular risk factors.

Nonstandard Abbreviations and Acronyms

aHR	adjusted hazard ratio
CWMA	cardiac wall motion abnormalities
ESUS	embolic stroke of undetermined source
MACE	major adverse cardiovascular events
MESA	Multi-Ethnic Study of Atherosclerosis
mRS	modified Rankin Scale
SHARE	Study of Health Assessment and Risk in Ethnic Groups
SHS	Strong Heart Study
TOAST	Trial of ORG 10172 in Acute Stroke Treatment

fatal stroke).[14] Whereas MESA showed an association between CWMA and stroke, SHS (Strong Heart Study) did not show such an association.[15] Furthermore, the combined echocardiographic findings of the control groups in 3 randomized trials showed that LV systolic dysfunction (characterized as global and focal) was a strong independent predictor of stroke.[16] Many studies have evaluated the major adverse cardiovascular event (MACE) risk in cardiac patients; however, studies evaluating the MACE risk in patients with stroke who have CWMAs are lacking.

The purpose of the current study was to evaluate whether echocardiographic CWMAs in patients with stroke are associated with MACE, particularly ischemic stroke recurrence, in a large multiethnic Asian and North African cohort.

PATIENTS AND METHODS

All acute stroke data including transient ischemic attack (TIA) were prospectively collected at a tertiary referral center with a well-established comprehensive stroke service accredited by Joint Commission International after approval of the institutional review board. All data for patients with acute stroke were collected between January 2015 and February 2019. The data that support the findings of this study are available from the corresponding author upon reasonable request. The study adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board (MRC-01-17-048). The study did not require a consent process because of the study design (retrospective).

We excluded patients with hemorrhagic stroke, malignancy, hypercoagulable state, stroke mimics (eg, migraine, epilepsy, multiple sclerosis), incomplete workup (absence of vascular imaging, echocardiography, and 24-hour Holter monitoring except in small vessel disease), known autoimmune or infiltrative cardiac disease, myocarditis, and any confounding condition such as conduction defects or desynchrony with left bundle branch block. Data collection, including admission, hospital course, follow-up clinic visits, and assessment of events, was performed by reviewing detailed electronic medical records by physicians trained in vascular neurology.

Stroke subtypes were classified according to TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria by stroke neurologists.[4] Embolic stroke of undetermined source (ESUS) was classified according to the Cryptogenic Stroke/ESUS International Working Group.[17] ESUS with intracranial or nonstenotic (<50%) carotid atherosclerotic plaques ipsilateral to the ESUS event were excluded from the ESUS group. TIAs were defined and evaluated according to American Heart Association guidelines.[18]

Data included age, sex, ethnicity, hypertension, diabetes mellitus, dyslipidemia, smoking, coronary artery disease (CAD) (defined by a history of MI or typical angina, a positive diagnostic test [stress test, coronary angiography], or appropriate treatment [coronary stent, coronary artery bypass grafting]). Admission National Institutes of Health Stroke Scale (NIHSS) score, CHA_2DS_2-VASc score, and modified Rankin Scale (mRS) score at 3 months in the stroke clinic were also recorded. Vascular imaging included craniocervical magnetic resonance angiography, computed

tomography angiography, or digital subtraction angiography. Holter monitoring was performed for at least 24 to 48 hours in patients with nonlacunar stroke within 5 days of symptoms (except for patients with known atrial fibrillation).

Transthoracic echocardiography and additional transesophageal echocardiography (at the discretion of the treating physicians) was performed by specialists within 5 days after admission according to American Society of Echocardiography guidelines.[19] The echocardiographic images were reviewed by a cardiologist with expertise in echocardiography. Echocardiographic factors recorded were CWMAs, ejection fraction (EF), atrial fibrillation, LV mass indexed to height$^{2.7}$,[20] left atrial volume index (expressed as mL/m^2), and LV diastolic dysfunction categorized as mild (grade I), moderate (grade II), and severe (grade III).[21]

Follow-Up and End Points

The primary outcome was a MACE, a composite of clinical end points of ischemic stroke recurrence or TIA, acute coronary events, and vascular death during a 50-month follow-up.

Ischemic stroke recurrence was diagnosed by acute neurological symptoms and signs, which correlated with new acute changes on diffusion-weighted magnetic resonance imaging and TIAs were defined and evaluated according to American Heart Association guidelines.[18] Acute coronary events (MI, cardiac revascularization, hospitalization with unstable angina) were diagnosed according to criteria modified from the 2000 Consensus Conference of the European College of Cardiology and American College of Cardiology.[22] Deaths were regarded to be attributable to a cardiovascular cause (fatal MI, fatal stroke [death within 1 month of MI or stroke], sudden death caused by definite CAD, congestive heart failure) unless a noncardiac death could be confirmed.

Statistical Analysis

Frequency distribution with percentages for categorical variables and mean±SD for interval variables were calculated. The association between CWMA and non-CWMA was assessed using chi-square tests for categorical variables. Student *t* tests (equal or unequal variance assumed for significance as appropriate) were used for interval variables to test for mean level difference between the two. The data were right-censored up to the time of the last follow-up. For event-free survival analysis, Kaplan–Meier survival curve and log-rank test were used to look for a significant difference in MACE and individual clinical end points (ischemic stroke recurrence, acute coronary events, and death) between stroke with and without CWMAs. The data were also explored for CWMAs and MACE along with clinical end points (stroke recurrence, acute coronary events, and death) by univariate and multivariate Cox proportional hazards regression analyses after verifying the proportionality test. For multivariable Cox proportional hazards regression, variables were considered as potential risk predictors in the multivariate model when statistically significant in univariate analysis (2-tailed $P<0.05$). Statistical Package for Social Sciences version 26.0 (SPSS Inc) was used for all analyses.

RESULTS

Of a total of 3133 patients, 597 patients did not meet inclusion criteria, meaning the final analysis was performed on 2653 patients. The demographic, clinical, and echocardiographic characteristics of participants with and without CWMAs are summarized in Table 1. Of a total of 2653 patients with acute stroke, 355 (13.4%) had CWMAs. Patients with CWMAs were more likely to be older ($P<0.001$) and men ($P<0.001$), with a higher frequency of hypertension ($P=0.001$), smoking ($P<0.001$), atrial fibrillation ($P=0.05$), left atrial volume index ($P<0.001$), and LV diastolic dysfunction ($P<0.001$); higher NIHSS score at admission ($P=0.002$); higher HbA_{1c} ($P=0.001$), 3-month mRS (0.001), and CHA_2DS_2VASc ($P<0.001$); and lower EF ($P<0.001$). ESUS was the most frequent stroke type associated with CWMAs ($P=0.001$). At discharge, there was no difference in antiplatelet prescription ($P=0.34$) between non-CWMA and CWMA groups, and anticoagulation was more frequently prescribed in patients with CWMA ($P=0.03$), as were statins ($P=0.003$) (Table 1).

Follow-Up and End Points

Overall MACE

During the 50-month follow-up period (median 20 months; interquartile range, 13–31 months [minimum 3 months to maximum 49.5 months]), there were 750 (28.3%) patients with MACE (Table 2). Ischemic stroke recurrence accounted for 309, acute coronary events 386, and vascular deaths 224. The end points of MACE and the composite of all ischemic stroke recurrence, acute coronary events, and death was consistently more frequent in patients with stroke who had CWMAs. In multivariable Cox regression analyses, CWMA was found to be a significant independent predictor of MACE (adjusted hazard ratio [aHR], 1.74; 95% CI, 1.37–2.21 [$P=0.001$]) compared with their counterparts without CWMAs, after adjusting for confounding factors (Table 2).

Table 1. Baseline Characteristics of Patients With and Without CWMAs

Factors	Without CWMA, n=2298 (86.6%)	With CWMA, n=355 (13.4%)	*P* Value
Age, y	55.74±13.4	61.50±12.6	<0.001
Sex			
Women	499 (21.7)	43 (12.1)	<0.001
Men	1798 (78.3)	312 (87.9)	
Race/ethnicity			
South Asia	1379 (60)	191 (53.8)	<0.007
West Asia	625 (27.5)	127 (35.8)	
North Africa	244 (10.6)	33 (9.3)	
White	50 (2.2)	4 (1.1)	
Diabetes mellitus	1358 (59.1)	228 (64.2)	0.07
Hypertension	1827 (79.5)	310 (87.3)	0.001
Smoking	234 (10.3)	108 (31.2)	<0.001
Dyslipidemia	1531 (66.7)	254 (71.5)	0.07
CAD	684 (29.8)	119 (33.5)	0.15
Glycated hemoglobin	6.36±1.4	6.75±1.6	<0.001
Admission NIHSS score	5.00±5.5	6.04±5.9	0.002
Index stroke			
Large artery disease	318 (13.8)	34 (9.6)	0.03
Small vessel disease	843 (36.7)	54 (15.2)	<0.001
ESUS	474 (20.6)	180 (50.7)	<0.001
Cardioembolic	191 (8.3)	42 (11.8)	0.03
Dual pathology	179 (7.8)	14 (3.9)	0.01
Incomplete data	256 (11.1)	16 (4.5)	<0.001
TIA	186 (8.1)	27 (7.6)	0.75
Echocardiography data			
LAVI, mL/m^2	24.85±12.4	29.06±12.4	<0.001
Atrial fibrillation	227 (15.1)	49 (20.1)	0.05
Ejection fraction %	53.61±7.0	41.85±9.6	<0.001
LVMI, g/m$^{2.7}$	37.72±34.1	36.60±31.6	0.56
RWT	0.38±0.5	0.35±0.5	0.24
LVDD, none	835 (44.9)	103 (34.4)	<0.001
Grade I	972 (52.3)	175 (58.5)	
Grade II and III	52 (2.8)	21 (7.0)	
CHA_2DS_2VASc	4.09±1.2	4.69±1.2	<0.001
Discharge medications			
Antiplatelets	1720 (74.8)	274 (77.2)	0.34
Anticoagulation	147 (6.4)	38 (10.7)	0.003
Statins	1524 (68.5)	251 (74.5)	0.03
mRS at 3 mo	1.82±1.7	2.15±1.7	0.001
Stroke recurrence			
Total recurrence	243 (10.6)	66 (18.6)	0.001
Stroke recurrence by type			
Large artery disease	37 (15.2)	12 (18.2)	0.12
Small vessel disease	115 (47.3)	20 (30.3)	0.62
ESUS	59 (24.3)	25 (37.9)	0.001
Cardioembolic	13 (5.3)	3 (4.5)	0.53
TIA	19 (7.8)	6 (9.1)	0.11

Values are expressed as mean±SD or number (percentage). CAD indicates coronary artery disease; CWMA, cardiac wall motion abnormality; ESUS, embolic stroke of undetermined source; LAVI, left atrial volume index; LVDD, left ventricular diastolic dysfunction; LVMI, left ventricular mass indexed to height$^{2.7}$; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; RWT, regional wall thickness; and TIA, transient ischemic attack.

Ischemic Stroke Recurrence

The distribution of ischemic stroke recurrences was 243 of 2298 (10.6%) without CWMA and 66 of 355 (18.6%) with CWMA (*P*=0.001). In non-CWMA, the following type of stroke recurrence was observed: small vessel disease was the highest recurrence (47.3%), followed by ESUS (24.3%), large artery disease (15.2%), cardioembolic stroke (5.3%), and TIA (7.8%). In contrast, ESUS was the most frequent recurrence type in patients with CWMAs (50.7%), followed by small vessel disease (30.3%), large vessel disease (18.2%), cardioembolic stroke (4.5%), and TIA (9.1%). In patients with stroke who had CWMAs, CWMA was independently associated with a 1.5 times higher risk of ischemic stroke recurrence (aHR, 1.50; 95% CI, 1.01–2.17 [*P*=0.04]) (Table 2).

Acute Coronary Events

The occurrence of acute coronary events was more frequent in patients with stroke with CWMA compared with their counterparts without CWMA (32.7% versus 11.7%, respectively; *P*=0.001). Patients with stroke who had CWMAs had a 2.5 times higher risk of acute coronary events (aHR, 2.50; 95% CI, 1.83–3.40 [*P*=0.001]) (Table 2).

Death

Death was more frequent in patients with CWMAs (16.6% versus 7.1%). Similar to stroke recurrence and acute coronary events, CWMA was independently associated with a 1.5 times higher risk of death (aHR, 1.60; 95% CI, 1.04–2.40 [*P*=0.03]) after adjusting for the confounding factors (Table 2).

Kaplan–Meier survival curves showed that patients with stroke who with CWMAs had a significantly lower probability of MACE-free survival compared with patients without CWMA and a higher probability of stroke recurrence and acute coronary events (Figure).

Table 2. Multivariate Cox Regression for the Risk of MACE and MACE Events in Patients With and Without CWMAs

	No. of Events (%)	Log-Rank *P* Value	Unadjusted HR (95% CI)	Adjusted HR (95% CI)*	*P* Value
Overall MACE					
Without CWMA	582 (25.3)		1		
With CWMA	168 (47.3)	0.001	1.70 (1.40–2.01)	1.74 (1.37–2.21)	0.001
Ischemic stroke recurrence					
Without CWMA	243 (10.6)		1		
With CWMA	66 (18.6)	0.006	1.51 (1.12–2.04)	1.50 (1.01–2.17)	0.04
Acute coronary events					
Without CWMA	270 (11.7)		1		
With CWMA	116 (32.7)	0.001	2.44 (1.94–3.08)	2.50 (1.83–3.40)	0.001
Death					
Without CWMA	165 (7.1)		1		
With CWMA	59 (16.6)	0.001	2.34 (1.17–3.20)	1.60 (1.04–2.40)	0.03

CWMA indicates cardiac wall motion abnormality; HR, hazard ratio; and MACE, major adverse cardiovascular events.

*Adjusted for age, sex, ethnicity, glycated hemoglobin, hypertension, smoking, atrial fibrillation, ejection fraction, left atrial volume index, left ventricular diastolic dysfunction, and discharge medications (antiplatelets, anticoagulation, and statins).

DISCUSSION

We found that in a large, multiethnic stroke cohort undergoing echocardiography, CWMA was not a rare condition (13.4%). The current study is the first to our knowledge to report that in patients with stroke with CWMAs, CWMA is independently associated with subsequent MACE, conferring a 1.7-fold increased risk for combined stroke recurrence, acute coronary events, and death compared with patients with stroke without CWMAs over 50 months of follow-up. An interesting finding was that in patients with CWMAs, the most common index, as well as recurrent stroke type, was an ESUS.

Our study shows a positive independent association of CWMA with cardiovascular morbidity and mortality, a trend similar to MESA and SHS.[14,15] MESA showed a significant association of regional myocardial dysfunction with hard cardiovascular events (hard coronary events, nonfatal and fatal stroke) with an aHR of 1.7,[14] and SHS reported a 2.5-fold higher risk of overall cardiovascular events in patients with CWMAs. The risk of coronary events in the present analysis (aHR, 2.5) is comparable to SHS (MI: aHR, 2.2; coronary heart disease: aHR, 2.4) but differed from MESA, which reported a lower risk of all coronary events (excluding MI) (aHR, 1.5). A major difference between the aforementioned studies and our data is ethnicity and the study population. Although MESA was a multiethnic study (Black, White, Chinese, Hispanic participants) and SHS included American Indians, both studies did not include any South Asian patients. The majority of our cohort was of South Asian ethnic origin known to have more extensive, aggressive, diffuse CAD at a younger age; significant LV dysfunction at presentation; and the highest rates of acute MI and stroke.[23–25] Furthermore, in SHARE (Study of Health Assessment and Risk in Ethnic Groups), South Asian ethnic origin was an independent risk factor for cardiovascular disease.[25]

The present study extends previous observations that CWMAs can act as prognostic markers for adverse events by demonstrating that CWMAs independently predict subsequent stroke recurrence. The strength of the association between stroke with CWMA and stroke recurrence in the current (aHR, 1.50) and a previous (aHR, 1.70) study [1] argue against CWMAs being an epiphenomenon. In MESA, stroke was included as part of hard cardiovascular events and not an individual outcome.[14] Similarly, SHS reported a 2.4- to 3.4-fold higher risk of overall cardiovascular events with CWMAs but not stroke independently. This inconsistency between previous and current studies can be explained by differences in study populations of patients without overt cardiovascular disease (inclusion of stroke-free patients), ethnicity (non–South Asians), and a small number of events during follow-up (6 strokes in SHS).[15] Our data support previous publications that suggest a role for CWMAs in stroke,[1,3] highlighting the importance of studying this population as they are already at higher risk.

Notably, half of the first/index stroke and 37.9% of stroke recurrences with CWMAs were classified as ESUS (Table 1), a finding much higher than previously reported.[26,27] Our patients were younger, with a higher frequency of risk factors (diabetes mellitus, hypertension, smoking, dyslipidemia, CAD), and the majority were of South Asian origin. The association between CWMAs and risk of stroke recurrence may be amenable to a combination of anticoagulation and antiplatelet treatment,[28] in addition to aggressive risk reduction using lifestyle and pharmacological interventions. The

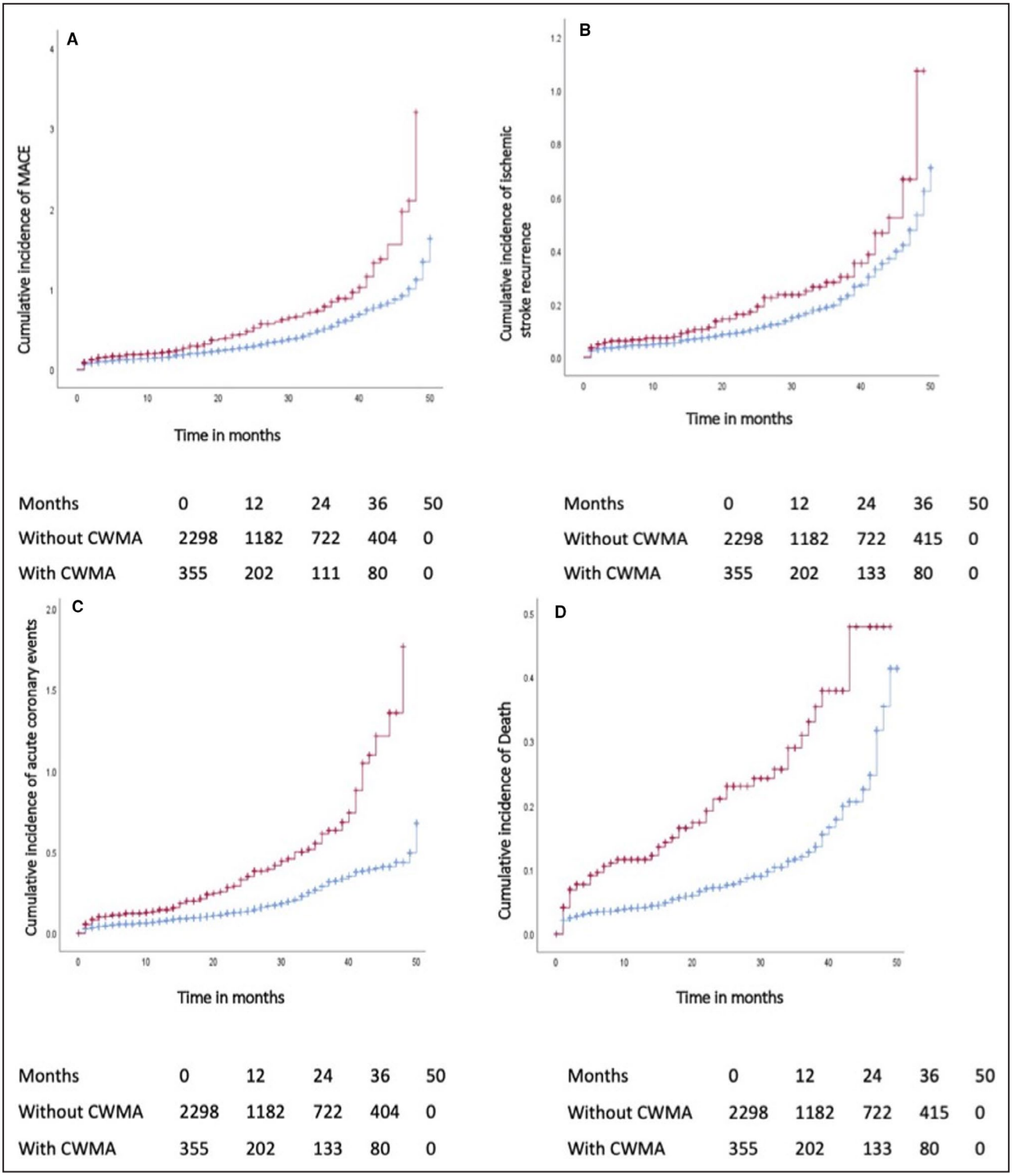

Figure 1. Kaplan–Meier curves showing cumulative incidences by presence (red) and absence (blue) of cardiac wall motion abnormalities (CWMAs) in patients with stroke for (A) overall major adverse cardiovascular events (MACE) (log-rank for difference, *P*=0.001), (B) stroke recurrence (log-rank for difference, *P*=0.006), (C) acute coronary events (log-rank for difference, *P*=0.001), and (D) death (log-rank for difference, *P*=0.001).

benefits of aggressive risk reduction for preventing initial and recurrent cardiovascular events in patients at high risk are well known.[29]

The present findings also suggest that further identification of more homogenous subpopulations of CWMAs with ESUS is required and evaluation of

treatments for these patients in control trials is needed. This is particularly important as many MIs go undetected at the time of occurrence, suggesting that CWMAs may be more widespread than previously assumed.[30] A quarter of stroke cases with CWMAs in our cohort were classified as small or large artery strokes (index/or recurrence), as defined by TOAST criteria.[4] This is likely a result of the systematic use of echocardiography, overlapping stroke causes, and shared risk factors in a larger stroke cohort. Many small or large vessel strokes may have a coexisting potential cardiac source of embolism.[31]

Although patients with stroke and CWMAs had lower EF, EF can be preserved or recover post-MI, particularly small MIs, as the hypercontractile LV segments compensate for the dysfunctional segment.[32] In the present study, CWMAs predicted the outcome independent of the EF, consistent with previous observations.[15,33] Nearly two thirds of the patients with stroke who had CWMAs in our cohort were without clinically evident CAD. The low percentage of reported CAD may be the result of under-reporting, diagnosis, and treatment, particularly in the poor healthcare environment of South Asia. Since the prognosis between recognized and unrecognized MI is similar, with both resulting in a high risk of death, heart failure, or stroke, the screening of CWMAs in patients with stroke assumes significant importance.[34]

Our study has several limitations including its retrospective analysis of prospectively collected, single-center data rather than population-based data, which may have introduced collection bias, registration bias, and unregistered confounding factors. Our stroke recurrence rate may be an underestimation since many expatriates leave the country after stroke rehabilitation. Finally, the number of women was fewer compared with men as a result of the expatriate population being mostly men.

CONCLUSIONS

Our data show that MACE remain a major cause of morbidity and mortality in patients with stroke who have CWMAs. The risk of stroke recurrence, acute coronary events, and death was significantly higher in patients with stroke who had CWMAs after adjusting for established stroke risk factors in a multiethnic population. Furthermore, the high frequency of ESUS in stroke with CWMAs and the high ESUS recurrence risk in these patients suggest that CWMAs may be a potential cardioembolic risk factor in ESUS. Given the adverse prognosis of stroke with CWMAs, screening for CWMAs in patients with stroke can yield important information to refine risk stratification for more intensive treatment of established cardiovascular risk factors.

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Affiliations

Neuroscience Institute, Hamad General Hospital, Doha, Qatar (S.K., N.A., Y.I., K.H.H., N.A., S.H., L.O., A.O., A.M.); Weill Cornell Medical School, Doha, Qatar (S.K., N.A., S.A.J., A.M.); Heart Hospital, Hamad Medical Corporation, Doha, Qatar (R.S.); and Perception Movement Action Research Consortium, University of Edinburgh, United Kingdom (J.D.P.).

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