

Impact of Anemia on In-Hospital, One-Month and One-Year Mortality in Patients with Acute Coronary Syndrome from the Middle East

Kadhim Sulaiman; Panduranga Prashanth; Ibrahim Al-Zakwani; Wael Al-Mahmeed; Ahmed Al-Motarreb; Jassim Al Suwaidi; Haitham Amin; Nidal Asaad; Ahmad Hersi; Hussam Al Faleh; Shukri Al Saif; Alawi A. Alsheikh-Ali; Jawad Al Lawati; and Khalid Al-Habib

Aim: The aim of this study was to evaluate the impact of admission anemia on in-hospital, one-month, and one-year mortality in patients from the Middle East with acute coronary syndrome (ACS).

Methods: Data were analyzed from 7922 consecutive patients admitted to hospitals throughout six Middle-Eastern countries with the final diagnosis of ACS, as part of Gulf RACE II (Registry of Acute Coronary Events II). Anemia at admission was defined according to the World Health Organization definition (<13 g/dL in men and <12 g/dL in women). Analyses were conducted using univariate and multivariate statistical techniques.

Results: The median age of the cohort was 56 (48–65) years, with the majority being male (79%). Anemia at admission was present in 2241 patients (28%). Patients with anemia were more likely to have in-hospital complications including heart failure, recurrent ischemia, re-infarction, cardiogenic shock, stroke, and major bleed. Even after adjustment, anemia was still associated with mortality at in-hospital (odds ratio [OR]=1.71, 95% confidence interval [CI], 1.34-2.17; $P<0.001$), at one-month (OR=1.34, 95% CI, 1.06-1.71; $P=0.016$), and at one-year (OR=1.22, 95% CI, 1.01-1.49; $P=0.049$) post-admission with ACS.

Conclusions: Admission anemia in patients with ACS from six Middle-Eastern countries was strongly associated with mortality at in-hospital, one-month, and at one-year. Hence, admission anemia must be considered in the initial risk assessment of ACS patients along with other risk scores.

Keywords: Acute coronary syndrome; Anemia; Hemoglobin; Mortality; Middle East

Anemia at admission and during hospitalization is common in acute coronary syndrome (ACS) patients, and these patients are reported to have poor in-hospital, short-term, and long-term prognosis.¹⁻⁹ In addition, the need for blood transfusion due to anemia in the setting of ACS is associated with higher short-term mortality.¹⁰ Furthermore, a low baseline hemoglobin level in ACS patients has been found to be an independent predictor of the risk of in-hospital major bleeding and risk of death and myocardial infarction at 30 days.¹¹

Low hemoglobin levels are common among the Middle-Eastern adult population when compared to the Western population, mainly due to a high prevalence of hemoglobinopathies in the Arab population as well as nutritional deficiencies.¹² There are currently no studies in the Middle East evaluating the influence of anemia in ACS patients. Hence, we undertook this study to evaluate the impact of admission anemia on in-hospital, 1-month, and 1-year mortality in patients with ACS from the Middle East.

Corresponding Author: Dr. Kadhim Sulaiman; Department of Cardiology; Royal Hospital; PO Box 1331; Muscat PC-111; Sultanate of Oman; Phone: +968-99360025; Fax: +968-24697727; Email: kjsulaiman@hotmail.com

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Table 1. Demographic and clinical characteristics of the study cohort stratified by anemia (N=7922).

Characteristic	All (N=7,922)	Anemia		P
		No (n=5681; 72%)	Yes (n=2241; 28%)	
Demographic				
Age, median years (IQR)	56 (48-65)	54 (46-63)	60 (53-70)	<0.001
Female gender, n (%)	1,685 (21%)	989 (17%)	696 (31%)	<0.001
Medical history, n (%)				
Diabetes mellitus	3,132 (40%)	2,045 (36%)	1,087 (49%)	<0.001
Hyperlipidemia	2,596 (33%)	1,740 (31%)	856 (38%)	<0.001
Hypertension	3,744 (47%)	2,456 (43%)	1,288 (57%)	<0.001
Chronic renal failure	318 (4.0%)	86 (1.5%)	232 (10.5%)	<0.001
Khat chew	1,406 (18%)	997 (18%)	409 (18%)	0.326
Smoking status (includes hasheesh)				
Never	3,736 (47%)	2,417 (43%)	1,319 (59%)	
Former	1,360 (17%)	953 (17%)	407 (18%)	<0.001
Current	2,826 (36%)	2,311 (41%)	515 (23%)	
Myocardial infarction				
PCI	726 (9.2%)	481 (8.5%)	241 (10.8%)	0.001
CABG	335 (4.2%)	192 (3.4%)	143 (6.4%)	<0.001
Stroke	340 (4.3%)	179 (3.2%)	161 (7.2%)	<0.001
Presentation, n (%)				
Systolic blood pressure ≤90 mmHg	394 (5.0%)	223 (3.9%)	171 (7.6%)	<0.001
Heart rate >100 bpm	1,410 (18%)	920 (16%)	490 (22%)	<0.001
Killip score >2	666 (8.4%)	405 (7.1%)	261 (11.6%)	<0.001
STEMI	3,428 (43%)	2,634 (46%)	794 (35%)	<0.001
GRACE risk score				
Low	3,067 (39%)	2,534 (45%)	533 (24%)	<0.001
Medium	3,053 (39%)	2,154 (38%)	899 (40%)	0.067
High	1,701 (21%)	921 (16%)	780 (35%)	<0.001

Anemia was defined according to the WHO definition (<13 g/dL in men and <12 g/dL in women).

IQR, Interquartile range; PCI, Percutaneous coronary intervention; CABG, Coronary artery bypass surgery; STEMI, ST elevation myocardial infarction; GRACE, Global Registry of Acute Coronary Events.

Analyses were conducted using Wilcoxon-Mann-Whitney test and Pearson's χ^2 tests, whenever appropriate

Methods

This study was a retrospective analysis of ACS patients enrolled in a prospective registry, Gulf Registry of Acute Coronary Events – II (Gulf RACE-II), from six Middle-Eastern countries. Gulf RACE-II design and methods are similar to Gulf RACE-I that has been previously reported.¹³ The Gulf RACE-II is a large prospective, multinational, multicenter registry of acute coronary events in the Middle East, focusing on the epidemiology, management practices, and outcomes of patients with ACS. Gulf RACE-II registry included consecutive patients above 18 years of age hospitalized with the final diagnosis of ACS (including unstable angina, ST-elevation myocardial infarction [STEMI], and non-STEMI) from 65 hospitals in six Middle-Eastern countries. Data were collected prospectively during the period between October 2008 and June 2009. The study

recruited 7881 consecutive ACS patients from six adjacent Middle-Eastern Gulf countries: Bahrain, Saudi Arabia, Qatar, Oman, United Arab Emirates, and Yemen. There were no exclusion criteria. All hospitals included were either secondary or tertiary care hospitals and each hospital had coronary care units on-site, managed by either general physicians or cardiologists. On-site cardiac catheterization laboratories were available in 43% of hospitals.

A case report form for each patient with suspected ACS was completed upon hospital admission by assigned physicians and/or research assistants working in each hospital using standard definitions and completed throughout the patient's hospital stay. All case report forms were verified by a cardiologist then sent online (www.gulf-ac.com) to the principal coordinating center, where the forms were further

Table 2. In-hospital outcome/procedure, medications, and mortality characteristics of the study cohort stratified by anemia (N=7922).

Characteristic	All (N=7922)	Anemia		P
		No (n=5681; 72%)	Yes (n=2241; 28%)	
In-hospital outcome/procedure, n (%)				
Congestive heart failure	1,040 (13%)	584 (10%)	456 (20%)	<0.001
Recurrent ischemia	1,231 (16%)	785 (14%)	446 (20%)	<0.001
Reinfarction	172 (2.2%)	92 (1.6%)	80 (3.6%)	<0.001
Cardiogenic shock	457 (5.8%)	247 (4.4%)	210 (9.4%)	<0.001
Stroke	56 (0.7%)	28 (0.5%)	28 (1.3%)	<0.001
Major bleed	48 (0.6%)	20 (0.4%)	28 (1.3%)	<0.001
PCI	1,224 (15%)	992 (17%)	232 (10%)	<0.001
CABG	607 (7.7%)	428 (7.5%)	179 (8.0%)	0.498
Medications during 24h of admission, n (%)				
Aspirin	7,794 (98%)	5,601 (99%)	2,193 (98%)	0.020
Clopidogrel	6,036 (76%)	4,502 (79%)	1,534 (68%)	<0.001
Beta blocker	5,890 (74%)	4,313 (76%)	1,577 (70%)	<0.001
Statin	7,507 (95%)	5,437 (96%)	2,070 (92%)	<0.001
ACEI	5,599 (71%)	4,113 (72%)	1,486 (66%)	<0.001
ARB	394 (5.0%)	250 (4.4%)	144 (6.4%)	<0.001
Medications at discharge, n (%)				
Aspirin	7,350 (93%)	5,347 (94%)	2,003 (89%)	<0.001
Clopidogrel	5,359 (68%)	4,055 (71%)	1,304 (58%)	<0.001
Beta blocker	6,261 (79%)	4,624 (81%)	1,637 (73%)	<0.001
Statin	7,210 (91%)	5,261 (93%)	1,949 (87%)	<0.001
ACEI	5,635 (71%)	4,159 (73%)	1,476 (66%)	<0.001
ARB	536 (6.8%)	366 (6.4%)	170 (7.6%)	0.067
Mortality, n (%)*				
In-hospital	361 (4.56%)	178 (3.13%)	183 (8.17%)	<0.001
1-month	572 (8.2%)	307 (6.1%)	265 (13.3%)	<0.001
1-year	771 (12.6%)	431 (9.9%)	340 (19.3%)	<0.001

Anemia was defined according to the WHO definition (<13 g/dL in men and <12 g/dL in women).

PCI, Percutaneous coronary intervention; CABG, Coronary artery bypass surgery; ACEI, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker.

*Percentages for 1-month and 1-year mortalities include only those who were alive at discharge and at 1 month and not lost to follow-up.

Analyses were conducted using Pearson's χ^2 tests.

checked for potentially incorrect data before submission for final analysis. All the patients were evaluated for in-hospital clinical outcomes including mortality and were followed-up for mortality at 1-month and 1-year using telephone interviews. The diagnosis of the different types of ACS and definitions of data variables were based on the American College of Cardiology (ACC) clinical data standards.¹⁴ In addition, patients were stratified into low-, medium-, and high-risk groups based on tertiles of the calculated baseline Global Registry of Acute Coronary Events (GRACE) risk score (variables: age, Killip class, systolic blood pressure, ST segment deviation, cardiac arrest on admission, serum creatinine, raised cardiac markers, heart rate).¹⁵ The study cohort is categorized (n = 7922) on the basis of presence or

absence of anemia at admission. Hemoglobin levels were measured within 60 minutes of admission. Anemia was defined according to the criteria of the World Health Organization (hemoglobin <13 g/dL in men and <12 g/dL in women).¹⁶ Accordingly, data were analyzed and compared for clinical characteristics, management, and in-hospital, 1-month and 1-year mortality. The study received ethical approval from the institutional ethical bodies in all participating countries.

Statistical Analyses

Descriptive statistics were used to summarize the data. For categorical variables, frequencies and percentages were reported. Differences between groups were analyzed using

Table 3. In-hospital, 1-month, and 1-year mortalities stratified by admission anemia in patients with acute coronary syndrome (ACS).

	In-hospital		1-month		1-year
ACS (N)	7922		7011		6123
No anemia (n)	5681		5024		4359
Anemia (n)	2241		1987		1764
Died, n (%)	361 (4.56%)		572 (8.16%)		771 (12.6%)
No anemia, n (%)	178 (3.13%)	<i>P</i> <0.001	307 (6.11%)	<i>P</i> <0.001	431 (9.9%)
Anemia, n (%)	183 (8.17%)		265 (13.3%)		340 (19.3%)
Lost-to-follow-up, n (%)	n/a		550 (7.27%)		316 (4.91%)

Anemia was defined according to the WHO definition (<13 g/dL in men and <12 g/dL in women).

Pearson's χ^2 tests. For continuous variables, median and interquartile range were used to present the data while analysis was performed using Wilcoxon-Mann-Whitney test. The association of anemia on mortality (in-hospital, 1-month, and at 1-year) controlling for medication use, GRACE risk score, smoking status, diabetes mellitus, in-hospital percutaneous coronary intervention (PCI), and coronary artery bypass graft (CABG), were evaluated using multivariable logistic regression. To assess the incremental value of adding anemia, changes in the appropriateness of these models when anemia was added were compared. As recommended,¹⁷ the different approaches used were (1) changes in the Bayes information criterion (BIC) and Akaike information criterion (AIC), lower values for the BIC and AIC indicated better fit; and (2) changes in indexes of calibration (Pearson's χ^2 and Hosmer-Lemeshow statistics) and discrimination (C-statistics). An *a priori* two-tailed level of significance was set at the 0.05 level. Statistical analyses were conducted using STATA version 11.1 (STATA Corporation, College Station, TX).

Results

Of 7930 patients with ACS enrolled in Gulf RACE-II, eight patients (0.1%) were excluded from the present analysis due to missing admission hemoglobin values. The remaining 7922 patients represent the sample size for this study. Demographic and clinical characteristics of the cohort are

shown in table 1. The median age of the cohort was 56 (48–65) years with the majority being male (79%). The median hemoglobin level at admission was 13.8 g/dL (range, 12.2 g/dL–15.0 g/dL). Anemia was present in 2241 patients (28%).

Those ACS patients with anemia were more likely to be older and female and less likely to be current smokers. Patients with anemia were more likely to have significant comorbidities including diabetes, hyperlipidemia, hypertension, chronic renal failure, and stroke. They were also more likely to have had prior myocardial infarction and revascularization procedures (PCI and CABG). They were more likely to present with lower systolic blood pressure, higher heart rates, higher Killip class, and higher GRACE risk scores. Moreover, ACS patients with anemia were more likely to present with non-STEMI than STEMI.

As demonstrated in table 2, ACS patients with anemia were also more likely to experience in-hospital complications including congestive heart failure (CHF), recurrent ischemia, reinfarction, cardiogenic shock, stroke, and major bleed. However, they were less likely to have primary PCIs performed. Moreover, ACS patients with anemia were also less likely to receive recommended evidence-based medications than their counterparts without anemia, whether during hospital admission (within 24 hours) or at discharge. They were less likely to receive aspirin, clopidogrel, beta-blocker, statin, and angiotension converting enzyme inhibitors (ACEI) during discharge than those ACS patients without anemia. However, ACS patients with anemia were more likely to have used either aspirin or clopidogrel before admission than those who did not have anemia (53% vs 36%; *P*<0.001). The overall in-hospital mortality rate was 4.56% (361 of 7922), while 1-month and 1-year mortalities were 8.2% (572 of 7011) and 12.6% (771 of 6123), respectively. Anemia was associated with higher in-hospital (8.17% vs 3.13%; *P*<0.001), 1-month (13.3% vs 6.11%; *P*<0.001), and 1-year (19.3% vs 9.9%; *P*<0.001) mortalities compared to those patients without anemia (table 3). Figure 1 represents graded response of anemia on mortality. Survival decreased significantly in a graded manner correlating with decreasing admission hemoglobin level. Higher levels of hemoglobin were associated with lower mortality (3.11% vs 11.27% in

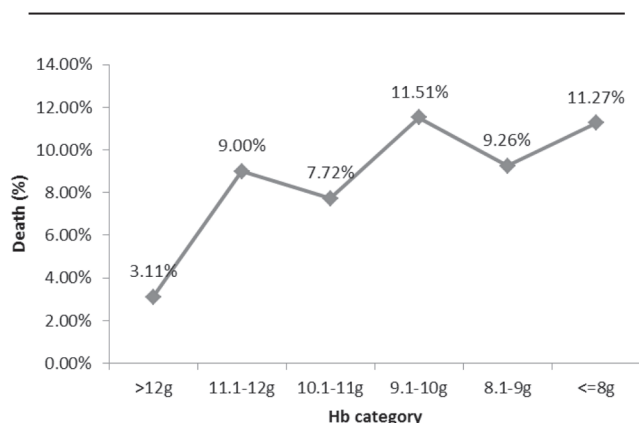


Figure 1. Graded response of hemoglobin (Hb) on mortality.

Table 4. Impact of anemia on in-hospital, 1-month, and 1-year mortalities of the study cohort using multiple logistic regressions.

	Mortality					
	In-hospital		1-month		1-year	
Anemia						
OR (95% CI)	1.71 (1.34-2.17)		1.34 (1.06-1.71)		1.22 (1.01-1.49)	
P value	<0.001		0.016		0.046	
	Anemia					
Measures of fit	No	Yes	No	Yes	No	Yes
LR χ^2 test	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Pseudo R^2	0.164	0.171	0.360	0.362	0.264	0.265
BIC	-346	-356	-1,203	-1,120	-1,038	-1,033
AIC	2,291	2,273	2,332	2,328	3,178	3,176
C statistic	0.81	0.82	0.84	0.84	0.80	0.80
P value						
Pearson's GOF	<0.001	<0.001	0.338	0.848	0.474	0.366
HL GOF	0.860	0.418	0.017	0.032	0.259	0.031

Anemia was defined according to the WHO definition (<13 g/dL in men and <12 g/dL in women).

OR, Odds ratio; CI, Confidence interval; LR, Likelihood ratio; BIC, Bayesian information criterion; AIC, Akaike information criterion; HL, Hosmer & Lemeshow; GOF, Goodness of fit.

The covariates in the models included medication (aspirin/clopidogrel, beta-blocker, statin, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker) as well as GRACE risk score (derived from the following variables: age, systolic blood pressure, serum creatinine, heart rate, cardiac enzyme, Killip class, and cardiac arrest on admission), smoking status, diabetes mellitus, in-hospital percutaneous coronary intervention and coronary artery bypass graft.

patients with hemoglobin >12 g/dL compared to patients with hemoglobin <8 g/dL, respectively).

Anemia was an independent predictor of mortality in-hospital, at 1-month, and at 1-year. The multiple regression models demonstrated that this relationship persisted even after adjustment. The adjusted odds ratio associated with anemia ranged from 1.01 to 2.17 for in-hospital, 1-month, and 1-year mortality (table 4). The addition of anemia improved both the discriminatory capacity and calibration of the models, with increased C statistics as well as decreased BIC and AIC statistics. However, the impact of anemia on mortality was highest during hospital admission, but lessened after discharge as denoted by smaller changes in the goodness of fit statistics (table 4).

Discussion

In this study from Middle-Eastern countries, admission anemia in ACS patients proved to be independently associated with increased in-hospital, 1-month and 1-year mortality. Anemia was present in 28% of the ACS patients studied confirming that anemia is frequently found in patients with ACS, although the prevalence varies widely between 10% to 30% depending on the definition used in various studies.¹⁻⁹

In accordance with the findings linking anemia and poor clinical outcomes in ACS patients, this study demonstrated that ACS patients with anemia were more likely to be older, female, and associated with comorbidities like diabetes, hypertension, chronic renal failure, and stroke,^{1-9,18,19} thus

identifying a high-risk population with poor hematopoietic reserve. They were more likely to present with lower systolic blood pressure, higher heart rates, and higher Killip class and GRACE risk scores.^{3,9,18,19} Sabatine et al³ reported hypotension, higher heart rate, and Killip class in STEMI patients with anemia. This was similar in our study, but was noted in all types of ACS patients, indicating that anemia in ACS as a poor prognostic factor is not confined to STEMI, but is universal among all types of ACS patients from the Middle East. In this study, ACS patients with anemia were more likely to present with non-STEMI than STEMI. The lower rate of anemia in STEMI patients may reflect younger age and less co-morbidities, including heart failure, when compared to non-STEMI patients. In the present study, anemic patients with ACS were more likely to experience in-hospital complications including CHF,^{4,5,9} recurrent ischemia,^{2,3,19} reinfarction,^{3,8,11} cardiogenic shock,¹⁸ major bleed,¹¹ and stroke.^{8,20} Furthermore, the presence of anemia in ACS patients doubled the risk of CHF and cardiogenic shock.^{4,5,8,9,18} However, these findings should be interpreted in the context of the study's limitations. It is possible that anemia may be a marker for poor outcomes rather than a mediator, and that residual confounding factors (in the relationship between anemia and mortality) cannot be excluded.

There are multiple possible reasons for this worse clinical outcome and mortality in anemic patients with ACS. Reduction of myocardial oxygen supply along with increased myocardial oxygen demand (due to a compensatory higher stroke volume,

tachycardia and decrease in blood viscosity required to maintain adequate systemic oxygenation) are the two most important causes by which anemia exerts its harmful effects on the myocardium.²¹ The compensatory mechanisms are mediated by sympathetic nervous system activation, which is deleterious in ACS.⁶ Anemia in the presence of a fixed coronary artery stenosis decreases myocardial ability to increase cardiac output and thereby results in left ventricle dysfunction. This, along with exacerbation of ischemia by anemia in the post-ACS patient, may be responsible for the excess long-term mortality in this population.⁶ Anemia also leads to volume expansion, contributing to the development of CHF. Tissue hypoxemia results in lowering of systemic vascular resistance, leading to activation of the renin-angiotensin-aldosterone and sympathetic nervous systems and subsequent volume expansion. Over time, fluid retention increases the cardiac workload, leading to ventricular remodeling including hypertrophy and dilation.¹⁹ Furthermore, these adaptive hemodynamic changes (ventricular dilatation and eccentric remodeling) causes higher oxygen consumption, increased diastolic wall stress, interstitial fibrosis, accelerated myocyte loss, and contribute to the development of CHF,^{7,21,22} which in turn causes hemodilution and precipitates further anemia.

Furthermore, in the present study, ACS patients with anemia were less likely to receive recommended evidenced-based medications as well as primary PCI.^{5,18,19} This may reflect the reluctance of physicians to initiate necessary medications or perform invasive procedures to avoid complications, especially bleeding complications and renal dysfunction.¹⁸ This could contribute to the poor prognosis in the anemic group. However, in the multivariable analyses, which included these treatments, anemia was independently associated with excess mortality.

One of the main findings of the present study is that admission anemia during ACS was not only related to statistically significant higher in-hospital mortality,^{2,8,18} but also predicted 1-month^{1,3,11,18} and 1-year mortality.^{5-7,9,23-26} The multiple regression models showed that this relationship persisted even after adjustment with GRACE risk score.¹⁸ Sabatine et al³ did not find an increase in cardiovascular mortality, myocardial infarction, or recurrent ischemia in non-STEMI patients until hemoglobin values dropped below 10 g/dL. In this study, anemia <13 g/dL in men and <12 g/dL in women in a graded manner demonstrated increasing mortality, indicating that admission anemia *per se* (whether mild or severe) has a pronounced impact on survival in this Middle-Eastern population. All the previous studies on this subject included a very defined subpopulation of patients with ACS and anemia¹⁻⁹ or included varying durations of follow-up, either 30-days or 1-year or more. This study demonstrated that admission anemia (WHO-defined) in all types of ACS at three levels of follow-up (in-hospital, 1-month and 1-year) was independently associated with increasing mortality.

There are a few limitations of this study. The methods used in collecting data for the Gulf RACE are subject to limitations seen in a registry-type database. The causes of chronic anemia were not known, and the prognosis may vary according to the cause. There was no information regarding post-discharge hemoglobin level, which may also influence the long-term prognosis. Transfusions and additional bleeding events may account for some of the poor short- and long-term mortality. Furthermore, lack of predictor variables, as well as losses to follow-up at 1-month and 1-year could have affected the study's findings. Lastly, the GRACE risk score was proposed to estimate the risk of in-hospital mortality, not 1-month or 1-year mortality. Additionally, a second GRACE risk score was not performed as it indicated 6-month mortality, not 1-month or 1-year mortality.

In conclusion, admission anemia in patients with ACS from six Middle-Eastern countries is strongly associated with adverse in-hospital clinical outcomes, as well as poor 1-month and 1-year mortality. Hence, admission anemia should be considered in the initial risk assessment of ACS patients along with other risk scores.

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Author Affiliations

*Kadhim Sulaiman**; *Panduranga Prashanth**;
Ibrahim Al-Zakwani†; *Wael Al-Mahmeed‡*;
Ahmed Al-Motarreb§; *Jassim Al Suwaidi¶*; *Haitham Amin||*;
Nidal Asaad¶; *Ahmad Hersi***; *Hussam Al Faleh***;
Shukri Al Saif ††; *Alawi A. Alsheikh-Ali‡,§§*;
Jawad Al Lawati¶¶; *Khalid Al-Habib***

**Department of Cardiology, Royal Hospital, Muscat, Oman*

†*Department of Pharmacology and Clinical Pharmacy, College of Medicine and Health Sciences, Sultan Qaboos University, Muscat, Oman and Gulf Health Research, Muscat, Oman*

‡*Division of Cardiology, Sheikh Khalifa Medical City, Abu Dhabi, United Arab Emirates*

§*Faculty of Medicine, Sana's University, Sana'a, Yemen*

¶*Hamad Medical Corporation, Doha, Qatar*

||*Mohammed Bin Khalifa Cardiac Center, Manama, Bahrain*

***King Fahad Cardiac Centre, King Saud University, Riyadh, Kingdom of Saudi Arabia*

††*Saud Al-Babtain Cardiac Centre, Dammam, Saudi Arabia*

§§*Tufts Clinical and Translational Science Institute, Tufts University School of Medicine, Boston, Massachusetts, USA*

¶¶*Department of Non-Communicable Diseases Surveillance and Control, Ministry of Health, Muscat, Oman*