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Article

Association Between Non-Steroidal Anti-Inflammatory Drug Use and Major Cardiovascular Outcomes in Patients with Acute Coronary Syndrome in the Arabian Gulf

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Running Title: Association between NSAID use and MACE in ACS patients

Abstract: Objectives Studies on the association between non-steroidal anti-inflammatory drugs (NSAIDs) and major adverse cardiovascular events (MACE) in the Arabian Gulf are scarce. The aim of this study was to evaluate the association between NSAIDs use and MACE in acute coronary syndrome (ACS) patients in the Arabian Gulf region. ***Methods:*** Data was analyzed from 3,007 consecutive patients diagnosed with ACS admitted to 29 hospitals in four Arabian Gulf countries from January 2012 to January 2013 as well as being on *prior* NSAIDs use during the *index* admission. MACE included stroke/transient ischemic attacks (TIAs), myocardial infarction (MI), all-cause mortality and readmissions for cardiac reasons. ***Results***: The overall mean age of the cohort was 62 ± 12 years and 9.6% (n = 290) of the patients were on *prior* NSAID use during the *index* admission. At 12-months follow-up, after adjusting for confounding factors, those on NSAIDs were significantly more likely to have had MACE (adjusted OR (aOR), 1.89; 95% confidence interval (CI): 1.44-2.48; $p < 0.001$). Specifically, the higher event rates observed were stroke/TIA (aOR, 2.50; 95% CI: 1.51-4.14; $p < 0.001$) and readmissions for cardiac reasons (aOR, 2.09; 95% CI: 1.59-2.74; $p < 0.001$) but not MI (aOR, 1.26; 95% CI: 0.80-1.99; $p = 0.320$) and all-cause mortality (aOR, 0.79; 95% CI: 0.46-1.34; $p = 0.383$). ***Conclusions***: NSAIDs use was associated with significant stroke/TIA events as well as readmissions for cardiac reasons. However, NSAIDs were not associated with increased MI or all-cause mortality rates in ACS patients in the Arabian Gulf.

Keywords*:* non-steroidal anti-inflammatory drug; stroke; acute coronary syndrome; myocardial infarction; mortality; readmission

1. Introduction

Acute coronary syndrome (ACS) is one of the leading causes of morbidity and mortality in Asia as well as globally [1,2] accounting for approximately seven million deaths and 129 million disability-adjusted life years (DALYs) annually worldwide [3,4]. ACS is also associated with significant economic burden on both direct and indirect healthcare costs with economic analyses suggesting that hospitalizations and readmissions for ACS accounts for 60-90% of total annual health care costs [5–7].

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of a group of medications that is widely used and easily available over the counter (OTC). More than 70 million prescriptions for NSAIDs are

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written annually, and taking into account OTC medications, 30 billion doses of NSAIDs are consumed annually in the United States alone [8]. They are used, in the short- and long-term, for a variety of indications including pain and rheumatoid arthritis, amongst many others. Besides gastrointestinal bleeding, which is partially alleviated by the use of proton pump inhibitors (PPIs), NSAIDs have also been associated with major adverse cardiovascular events (MACE) including stroke [9,10]. The cardiovascular risk may not only be limited to non-selective NSAIDS but also to selective cyclooxygenase 2 (COX-2) inhibitors [11].

There is currently limited research on the use of NSAIDs in ACS population in the Arabian Gulf. Hence, the aim of this study was to evaluate the association between NSAIDs use and MACE events including readmissions for cardiac reasons in ACS patients in the Arabian Gulf.

2. Methods

The Gulf COAST registry methods have already been previously reported [12]. In summary, the Gulf COAST registry was a prospective, multicenter, multinational, longitudinal, cohort study of consecutive citizens, from the Arabian Gulf (Bahrain, Kuwait, Oman and United Arab Emirates), admitted to 29 hospitals with a diagnosis of ACS from January 2012 to January 2013. The registry enrolled a total of 4,044 patients who were ≥18 years of age with ACS diagnosed according to American College of Cardiology (ACC) clinical data standards [13]. Apart from excluding non-citizens as well as those who were not willing/able to provide consent, there were no other exclusion criteria. The study was approved by the local institutional ethics committees of participating centers in the four Arabian Gulf countries.

Data collected included patient demographics (age, gender, employment status, marital status, education status, health insurance, body mass index (BMI), tobacco and alcohol use), medical history and risk factors related to MACE, prior medication use, laboratory data, clinical presentation and management during hospital stay including medications, reperfusion therapy and procedures and discharge medications. Follow up was performed at 12-months from the date of enrolment and was carried out by clinic visits or telephone interviews.

The main predictor variable was NSAID use while the outcomes collected included 12-months cumulative stroke/transient ischemic attack (TIA), myocardial infarction (MI), all-cause mortality and readmissions for cardiac reasons as well as overall MACE.

2.1. Statistical Analysis

For categorical variables, frequencies and percentages were reported. Differences among groups were analyzed using Pearson's χ^2 tests (or Fisher's exact tests for expected cells of <5). For continuous variables, mean and standard deviation were used to present the data while analyses were performed using Student's t-test. Continuous variables that were not normally distributed were summarized as median and interquartile range and analyses conducted using Wilcoxon-Mann-Whitney tests. The association between NSAID use and MACE (stroke/TIA, MI, all-cause mortality, readmissions for cardiac reasons and overall MACE) was evaluated by multivariate logistic regression utilizing the simultaneous method and adjusting for GRACE risk score for in-hospital mortality, which has been validated in an Arabian Gulf ACS Registry [14]. Apart from GRACE risk score variables (which is derived from age, heart rate, systolic blood pressure (BP), serum creatinine, cardiac arrest at admission, ST segment deviation on EKG, abnormal cardiac enzymes and *Killip* class), the logistic models were also adjusted for gender, smoking status, marital status, employment status, education status, BMI, diabetes mellitus, peripheral artery disease, percutaneous coronary intervention (PCI)/coronary artery bypass graft (CABG), prior event and use of evidence-based cardiac medications at hospital discharge (aspirin, clopidogrel, beta blocker, statin, angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB)).

The goodness-of-fit of the multivariable logistic models was examined using the Hosmer & Lemeshow goodness-of-fit statistic [15] as well as the *C*-index [16]. An a *priori* two-tailed level of

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significance was set at the 0.05 level. Statistical analyses were conducted using STATA version 16.1 (StataCorp, 2013, Stata Statistical Software, College Station, TX, USA).

3. Results

Out of the 4,044 subjects enrolled by the Gulf COAST registry, the present analysis only included patients with non-missing NSAID information (N = 3,007). A total of 9.6% (n = 290) of the patients were on *prior* NSAID use during the *index* admission. The overall mean age of the cohort was 62 ± 12 years of which 62% (n = 1,851) were males. A total of 22% (n = 647) of the patients were employed and 83% (n = 2,495) were married. Thirty four percent of the patients (n = 1,037) were current or prior smokers and 2.9% (n = 87) were alcohol consumers. Comorbid conditions were common, particularly hypertension (81%; n = 2,433), dyslipidaemia (70%; n = 2,101) and diabetes mellitus (63%; n = 1,903).

As shown in ***Table 1***, those on NSAIDs (compared to those that were not on NSAIDs) were more likely to be female (44% *vs* 38%; p = 0.049), educated (54% *vs* 46%; p = 0.013), associated with dyslipidaemia (77% *vs* 69%; p = 0.009), hypertension (86% *vs* 80%; p = 0.016) and heart failure (20% *vs* 14%; p = 0.012). However, those on NSAIDs were less likely to be associated with diabetes mellitus (57% *vs* 64%; p = 0.018) and non ST-elevation MI (41% *vs* 52%; p < 0.001).

Table 2 shows medication utilization prior to admission and post-discharge stratified by NSAIDs use. Prior to the *index* admission, those on NSAIDs were also more likely to have been on aspirin (85% *vs* 79%; p = 0.023) and clopidogrel (35% *vs* 28%; p = 0.015). While 98% (n = 2,705) of the cohort was treated optimally with the dual antiplatelet combination (aspirin and clopidogrel concurrently), only 52% (n = 1427) of the patients were prescribed the 5-drug regimen (aspirin, clopidogrel, ACEI/ARB, statin, beta blocker) concurrently which was significantly higher among those on NSAIDs than those not on NSAIDs (62% *vs* 51%; p = 0.001).

The overall MACE rate was 41.1% (n = 1,195) with significant differences among the groups as shown in ***Table 3.*** Adjusting for demographic and clinical characteristics as well as socioeconomic measures (insurance type, employment, education and marital status), at 12-months follow-up, those on NSAIDs were significantly more likely to have had MACE (adjusted OR (aOR), 1.89; 95% confidence interval (CI): 1.44-2.48; p < 0.001). The higher event rates were specifically observed in stroke/TIA (aOR, 2.50; 95% CI: 1.51-4.14; p < 0.001) and in readmissions for cardiac reasons (aOR, 2.09; 95% CI: 1.59-2.74; p < 0.001) but not in MI (aOR, 1.26; 95% CI: 0.80-1.99; p = 0.320) and 12-months all-cause mortality (aOR, 0.79; 95% CI: 0.46-1.34; p = 0.383).

Table 1. Demographic and clinical characteristics of the acute coronary syndrome cohort stratified by non-steroidal anti-inflammatory drug (NSAID) use.

Characteristic, *n (%) unless specified otherwise*	**All** (N = 3,007)	**NSAID use**		***p*-value**
		No (n = 2,717)	**Yes** (n = 290)	
Demographic				
Age, mean±SD, years	62±12	62±12	63±12	0.124
Female gender	1,156 (38%)	1,029 (38%)	127 (44%)	0.049
Educated	1,410 (47%)	1,254 (46%)	156 (54%)	0.013
Employed	647 (22%)	592 (22%)	55 (19%)	0.266
Married	2,495 (83%)	2,252 (83%)	243 (84%)	0.696
BMI, mean±SD, kg/m^2	29.1±7.0	29.1±7.1	28.7±6.3	0.305
Smoking (current or prior)	1,037 (34%)	939 (35%)	98 (34%)	0.794
Alcohol	87 (2.9%)	75 (2.8%)	12 (4.1%)	0.183

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Past medical history				
Prior MI	1,026 (34%)	933 (34%)	93 (32%)	0.438
Dyslipidemia	2,101 (70%)	1,879 (69%)	222 (77%)	0.009
Premature CAD	446 (15%)	405 (15%)	41 (14%)	0.726
Hypertension	2,433 (81%)	2,183 (80%)	250 (86%)	0.016
Heart failure	441 (15%)	384 (14%)	57 (20%)	0.012
Diabetes mellitus	1,903 (63%)	1,738 (64%)	165 (57%)	0.018
Stroke/TIA	274 (9.1%)	254 (9.0%)	29 (10%)	0.580
Clinical (parameters) at presentation				
HR, mean±SD, bpm	86±21	86±21	85±22	0.229
SBP, mean±SD, mmHg	142±28	142±28	143±29	0.519
DBP, mean±SD, mmHg	80±16	80±16	80±17	0.800
Crea, *p*50 (IQR), µmol/L	86 (68-113)	86 (68-113)	85 (68-104)	0.772
LVEF, mean±SD, %	49±13	48±13	50±13	<0.001
GRACE risk, mean±SD	130±42	130±42	130±43	0.789
CRUSADE risk score	38±15	38±15	38±15	0.735
Major bleed	62 (2.1%)	54 (2.0%)	8 (2.8%)	0.380
Killip class				
I – no heart failure	2270 (75%)	2063 (76%)	207 (71%)	0.320
II – rales	457 (15%)	403 (15%)	54 (19%)	
III – pulmonary edema	250 (8.3%)	224 (8.2%)	26 (9.0%)	
IV – cardiogenic shock	30 (1.0%)	27 (1.0%)	3 (1.0%)	
*Discharged diagnosis**				
LBBB MI	19 (0.7%)	16 (0.6%)	3 (1.1%)	<0.001
NSTEMI	1474 (51%)	1358 (52%)	116 (41%)	
STEMI	476 (17%)	433 (17%)	43 (15%)	
Unstable angina	908 (32%)	789 (30%)	119 (42%)	

SD, standard deviation; BMI, body mass index; MI, myocardial infarction; CAD, coronary artery disease; TIA, transient ischemic attack; HR, heart rate; bpm, beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; Crea, first serum creatinine; *p*50, median; IQR, interquartile range; LVEF, left ventricular ejection fraction; GRACE, global registry of acute coronary events; LBBB, left bundle branch block; NSTEMI, non-ST myocardial infarction; STEMI, ST-elevation myocardial infarction. BMI was missing in 47 subjects, HR in 4 subjects, SBP and DBP in 5 subjects, creatinine in 10 subjects, LVEF was missing in 468 subjects, GRACE in 14 subjects, 64 subjects in CRUSADE risk score. *The 'discharged diagnosis' excluded 129 patients that died in-hospital during the index admission while 1 patient had 'discharged diagnosis' missing. Percentages might not add up to 100% due to rounding off.

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Table 2. Medication utilization of the acute coronary syndrome cohort stratified by non-steroidal anti-inflammatory drug (NSAID) use.

Characteristic, *n (%) unless specified otherwise*	**All** (N = 3,007)	**NSAID use**		***p*-value**
		No (n = 2,717)	**Yes** (n = 290)	
Prior medications				
Aspirin	2,397 (80%)	2,151 (79%)	246 (85%)	0.023
Clopidogrel	863 (29%)	762 (28%)	101 (35%)	0.015
ACEIs	1,562 (52%)	1,437 (53%)	125 (43%)	0.002
ARBs	573 (19%)	485 (18%)	88 (30%)	<0.001
Beta blockers	1,828 (61%)	1,639 (60%)	189 (65%)	0.108
Statins	2,428 (81%)	2,186 (80%)	242 (83%)	0.219
Other LLDs	60 (2.0%)	57 (2.1%)	3 (1.0%)	0.273
Oral nitrates	1,049 (35%)	670 (42%)	379 (27%)	<0.001
CCBs	599 (20%)	523 (19%)	76 (26%)	0.005
H2-receptor antagonists	410 (14%)	331 (12%)	79 (27%)	<0.001
Proton pump inhibitors	617 (21%)	527 (19%)	90 (31%)	<0.001
*Discharged medications (N=2,747)**				
Aspirin	2,645 (96%)	2,388 (96%)	257 (98%)	0.197
Clopidogrel	2,009 (73%)	1,792 (72%)	217 (83%)	<0.001
ACEIs	1,795 (65%)	1624 (65%)	171 (65%)	0.907
ARBs	499 (18%)	443 (18%)	56 (21%)	0.168
Beta blockers	2,324 (85%)	2,089 (84%)	235 (89%)	0.025
Statins	2,675 (97%)	2,414 (97%)	261 (99%)	0.050
Other LLDs	75 (2.7%)	67 (2.7%)	8 (3.0%)	0.745
Oral nitrates	1,722 (63%)	1,562 (63%)	160 (61%)	0.509
CCBs	509 (19%)	462 (19%)	47 (18%)	0.770
Dual antiplatelets	2,705 (98%)	2,445 (98%)	260 (99%)	0.589
5-drug regimen	1,427 (52%)	1,265 (51%)	162 (62%)	0.001
H2-receptor antagonists	582 (21%)	517 (21%)	65 (25%)	0.142
Proton pump inhibitors	356 (13%)	315 (13%)	41 (16%)	0.183

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; LLD, lipid lowering drug; CCBs, calcium channel blockers; Dual antiplatelets, aspirin and clopidogrel concurrently; 5 drug regimen, concurrent prescribing of aspirin, clopidogrel, ACEI/ARB, statin, beta blocker. The discharged medications excluded those that died in-hospital (n=129) during the *index* admission as well as those that had missing drug information (n=131), while those on discharged ARB, statins, other LLTs, oral nitrates, CCBs, proton pump inhibitors and H2 receptor blockers had one further patient excluded due to missing drug information. Percentages might not add up to 100% due to rounding off.

Table 3. Association between non-steroidal anti-inflammatory drug (NSAID) use and 12-month cumulative major adverse cardiovascular events (MACE) in acute coronary syndrome patients in the Arabian Gulf.

Outcome	Univariate statistics (NSAID use)				Multivariate logistic regression			
	All (N = 2910)	**No** (n = 2627)	**Yes** (n = 283)	***p*-value**	**Adj. OR [95% CI]**	**Adj. *p*-value**	**HL**	**ROC**
Stroke/TIA	143 (4.9%)	115 (4.4%)	28 (9.9%)	<0.001	2.50 [1.51-4.14]	<0.001	0.917	0.75
Myocardial infarction	249 (8.6%)	223 (8.5%)	26 (9.2%)	0.690	1.26 [0.80-1.99]	0.320	0.102	0.71
All-cause Mortality	395 (13.6%)	366 (14.0%)	29 (10.3%)	0.086	0.79 [0.46-1.34]	0.383	0.075	0.78
Re-admissions	823 (28.3%)	705 (26.8%)	118 (41.7%)	<0.001	2.09 [1.59-2.74]	<0.001	0.665	0.61
Total MACE	1195 (41.1%)	1052 (40.1%)	143 (50.5%)	0.001	1.89 [1.44-2.48]	<0.001	0.391	0.67

Adj. OR, adjusted odds ratio; CI, confidence interval; HL, Hosmer & Lemeshow *p*-value; ROC, area under the receiver operating curve (also known as *c*-statistic); TIA, transient ischemic attack; re-admissions, re-admissions for cardiac reasons. MACE included stroke/TIA, myocardial infarction, mortality and re-admissions for cardiac reasons. For 6-month and 12-month follow-up, the events were cumulative. Multivariate analyses were conducted using logistic regression models utilizing the simultaneous method. The covariates in the models included GRACE risk score (derived from age, heart rate, systolic blood pressure, serum creatinine, cardiac arrest at admission, ST segment deviation on EKG, abnormal cardiac enzymes and Killip class) as well as gender, smoking status, marital status, employment status, education status, body mass index, diabetes mellitus, peripheral artery disease, percutaneous coronary intervention/coronary artery bypass graft, prior event and use of evidence-based cardiac medications at hospital discharge (aspirin, clopidogrel, beta blocker, statin, angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB)). Over the 1-year follow-up period, there were losses to follow-up of 97 (3.2%) patients.

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4. Discussion

To the best of our knowledge, this is the only study in the Arabian Gulf, to have evaluated the association between NSAIDs use and the development of MACE in ACS patients. At 12-months follow-up, those on prior use of NSAIDs were associated with increased risk of stroke/TIA events and readmissions for cardiac reasons when compared to those that were not on NSAIDs. However, NSAIDs use was not associated with increased MI or all-cause mortality rates in ACS patients in the Arabian Gulf.

Similar to the current findings, a number of other meta-analyses and review articles have also reported that the use of various types of NSAIDs (both non-selective as well as COX-2 inhibitors) are associated with the development of stroke/TIA events compered to patients not using NSAIDs.[17–22] The potential mechanisms for NSAID-associated increase in stroke risk is hypothesized to be due to vasoconstriction secondary to inhibition of prostacyclin-induced vasodilation, hypertension induced by direct renal effects on sodium excretion leading to volume expansion and thrombosis due to prostaglandin-mediated platelet aggregation.[23] This study did not document the actual types of NSAIDs used and this shortcoming may pose a significant limitation as some have been more associated with stroke/TIA events than others.[**Error! Bookmark not defined.**] Furthermore, this study also did not report the duration of use of NSAIDs. However, no safe window on concomitant use of NSAIDs has been reported, with even a short-term (0-3 days) use has been associated with increased risk of bleeding compared with no NSAIDs use.[24]

Our findings showed a significant association between the use of NSAIDs in patients with ACS and readmissions due to cardiac reasons which can be partly explained by the type, dose and duration of use of NSAIDs which were not documented in our study. Furthermore, the risk of cardiac complication is higher in the first week of NSAIDs use, but not for all type of NSAIDs as reported in some studies.[25] A population-based matched case–control study in Finland[26] showed that hospitalizations due to myocardial infarction in patients using NSAIDs accounted for 17,000 hospitalizations annually. The current study did not show any differences in myocardial infarction rates between the groups not only at baseline (Table 1) but also at 1-year follow-up (Table 3), however, the NSAIDs group was associated with higher prevalence of hypertension and heart failure (Table 1) which has been reported as the main reason behind readmissions in ACS patients.[27]

In conclusion, NSAIDs use was associated with significant increase in stroke/TIA events as well as readmissions for cardiac reasons. However, NSAIDs were not associated with increased MI or all-cause mortality rates in ACS patients in the Arabian Gulf.

5. Limitations

As this was a retrospective study and the fact that the analyses were also adjusted for various confounding factors, bias could still have existed between the groups as we were not able to control for unmeasured confounding variables. Instead of all-cause mortality, it would have been more pertinent to have reported cardiovascular mortality. Even though all types of NSAIDs are implicated in cardiovascular events, it would have been more informative to have reported the different types of NSAIDs. Furthermore, NSAIDs use was only reported during the *index* hospital admission, they could have been stopped or changed during the 1-year follow-up. However, as reported earlier, there is no safe window on concomitant use of NSAIDs with even a short-term period of a few days use has been associated with increased risk of bleeding.[**Error! Bookmark not defined.**] A total of 3.2% (n = 97) of the subjects were lost to follow-up at 12-months and this could have biased the outcomes; however, there were no significant differences in the demographic and clinical characteristics between the patients that were lost to follow-up against the group that remained during the 12-months follow-up period (***Table 4***).

Table 4. Demographic and clinical characteristics between the non-steroidal anti-inflammatory drug group remaining at the end of the year and the cohort that was lost to follow-up (LTF).

Characteristic, *mean±SD unless specified otherwise*	LTF (n = 97) 3.2%	Remaining (n = 2910) 96.8%	*p*-value
Demographic			
Age, years	62±11	62±12	0.940
Female gender, n (%)	38 (39%)	1,118 (38%)	0.880
BMI, kg/m^2	29.4±5.5	29.1±7.1	0.646
Clinical, n (%)			
Prior MI	32 (33%)	994 (34%)	0.811
Hypertension	81 (84%)	2,352 (81%)	0.509
Diabetes mellitus	69 (71%)	1,834 (63%)	0.103
Stroke/TIA	8 (8.3%)	266 (9.1%)	0.764
Presentation, n (%)			
SBP, mmHg	143±29	142±28	0.960
DBP, mmHg	80±17	80±16	0.832
Killip ≥2, n (%)	23 (24%)	714 (25%)	0.853
GRACE risk score	132±41	130±42	0.668
CRUSADE risk score	39±15	38±15	0.603
Major bleeding	3 (3.1%)	59 (2.0%)	0.451
Prior PCI	30 (31%)	793 (27%)	0.424

SD standard deviation, *BMI* body mass index, *MI* myocardial infarction, TIA, transient ischemic attack, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *GRACE* global registry of acute coronary events, *PCI* percutaneous coronary intervention (includes any prior PCI). BMI was missing in 47 subjects, SBP and DBP in 5 subjects, GRACE risk score in 14 subjects and 64 subjects in the CRUSADE risk score. Percentages may not add up too 100% due to rounding off.

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Conflicts of interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data Availability Statement: Data was anonymized for this study. All data are available upon request to the corresponding author.

Institutional Board approval: The study was approved by the local institutional ethics committees of participating centers in the four Arabian Gulf countries (Kuwait, Joint Committee for the Protection of Human Subjects in Research, VDR/JC/89, 13/10/2011; Oman, Ethical Review & Approve Committee, Ministry of Health Research, MH/DGP/R&S/PROPOSAL_APPROVED/1/2012, 9/1/2012; Bahrain, Secondary Care Medical Research Subcommittee, Ministry of Health, 23/12/2011; Abu Dhabi UAE, Institutional Review Board/Research Ethics Committee, Sheikh Khalifa Medical City, REC-24.11.2011 [RS 189], 24/11/2011; Abu Dhabi UAE, Institutional Review Board, Medical Services Corps, General Head Quarters Armed Forces, 18/11/2011; Al Ain UAE, Al Ain Medical District Human Research Ethics Committee, Faculty of Medicine & Health Sciences, United Arab

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