Association between Peripheral Artery Disease and Major Adverse Cardiovascular Events in Patients with Acute Coronary Syndrome: Findings from the Gulf COAST Registry

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Significance of the Study

- This study is among the first few studies in the Arabian Gulf region to have evaluated the association of peripheral artery disease (PAD) and 12-month cardiovascular outcomes in acute coronary syndrome. The study demonstrated that PAD was associated with major adverse cardiovascular outcomes. Aggressive management of these patients is essential to alleviate the adverse outcomes.

Abstract

Objective: To evaluate the association between peripheral artery disease (PAD) and major adverse cardiovascular events (MACE) in patients with acute coronary syndrome (ACS) in the Arabian Gulf. *Methods:* Data from 4,044 consecutive patients diagnosed with ACS admitted to 29 hospitals in four Arabian Gulf countries from January 2012 to January 2013 were analyzed. PAD was defined as any of the following: claudication, amputation for arterial vascular insufficiency, vascular reconstruction, bypass surgery, or percutaneous intervention in the extremities, documented aortic aneurysm or an ankle brachial index of <0.8 in any of the legs. MACE included stroke/transient ischemic attack (TIA), myocardial infarction (MI), all-cause mortality, and re-admissions for cardiac reasons diagnosed between hospital admission and at 1-year post discharge. Analyses were performed using univariate and multivariate statistical techniques. *Results:* The overall mean age of the cohort was 60 ± 13 years and 66% (*n* = 2,686) were males. A total of 3.3% (*n* = 132) of the patients had PAD. Patients with PAD were more likely to be associated with smoking, prior MI, hypertension, diabetes mellitus, and stroke/TIA. At the 1-year follow-up, patients with PAD were significantly more likely to have MACE (adjusted OR [aOR], 2.07; 95% confidence inter-

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val [CI]: 1.41–3.06; $p < 0.001$). The higher rates of events were also observed across all MACE components; stroke/TIA (aOR, 3.22; 95% CI: 1.80–5.75; $p < 0.001$), MI (aOR, 2.15; 95% CI: 1.29–3.59; $p = 0.003$), all-cause mortality (aOR, 2.21; 95% CI: 1.33–3.69; $p = 0.002$), and readmissions for cardiac reasons (aOR, 1.83; 95% CI: 1.24–2.70; $p = 0.003$). **Conclusions:** PAD was significantly associated with MACE in ACS patients in the Arabian Gulf.

Introduction

Peripheral artery disease (PAD) is a circulatory problem in which atherosclerosis affects the peripheral vessels, restricting the blood supply to the leg muscles and lower extremities. It is quite prevalent, affecting between 3 and 20% of patients worldwide, especially the elderly [1, 2]. The number of PAD cases has been increasing globally from 13% in high-income regions of the world to as high as 29% in low-/middle-income regions of the world [3]. PAD is associated with increased risk of atherosclerosis with its different manifestations of myocardial infarction (MI), acute coronary syndrome (ACS), ischemic stroke, and death [4, 5]. PAD is also associated with increased rehospitalizations and healthcare costs [6, 7].

Studies on PAD in ACS and non-ACS patients in the Arabian Gulf are limited. The Gulf region and the Arab Middle East lack reports of long-term outcomes of ACS patients with preexisting PAD [8, 9]. Here, we report on the influence of PAD on long-term major adverse cardiovascular events (MACE) in patients with ACS in the Arabian Gulf. This was achieved by analyzing data from the Gulf locals with acute coronary syndrome events (Gulf COAST) registry.

Methods

Details of the methods of the Gulf COAST registry have been previously reported [10]. Briefly, the Gulf COAST registry was a prospective, multicenter, multinational, longitudinal, cohort study of consecutive citizens, from the Gulf region of the Middle East (Bahrain, Kuwait, Oman, and United Arab Emirates). Patients were admitted to 29 hospitals between January 2012 and January 2013 with a discharge diagnosis of ACS. The registry enrolled a total of 4,044 patients who were 18 years of age or older with ACS diagnosed according to the clinical data standards of the American College of Cardiology (ACC) [11]. Apart from excluding noncitizens and those who were not willing/able to provide consent to be included in the study, there were no other exclusion criteria. This study was approved by the local institutional ethics committees of the participating centers.

PAD was defined as any of the following: claudication, either with exertion or at rest, amputation for arterial vascular insufficiency, vascular reconstruction, bypass surgery, or percutaneous intervention to the extremities, documented aortic aneurysm, or an ankle brachial index (ABI) of <0.8 in any of the legs [12]. MACE included all events of stroke/transient ischemic attack (TIA), MI, all-cause mortality, and readmissions for cardiac reasons from hospital admission through to 1-year follow-up. In order to verify data accuracy, a clinical research associate visited at least once all participating hospitals and selected, at random, 10% of paper and electronic case report forms for data verification.

Data collected included patient demographics, prior history and risk factors, 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 1, 6, and 12 months from the date of enrolment and was carried out by clinic visits or telephone interviews. For this study, only the 12-month cumulative outcome data are reported.

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 cells <5). For continuous variables, mean and standard deviation were used to summarize the data while analyses were performed using Student's t test. The association between PAD and 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 [13]. Apart from GRACE risk score variables, the logistic models were also adjusted for gender, smoking status, diabetes mellitus, 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 [14] as well as the C-index [15]. An a priori two-tailed level of significance was set at the 0.05 level. Statistical analyses were conducted using STATA version 13.1 (StataCorp, 2013, Stata Statistical Software, College Station, TX, USA).

Results

The Gulf COAST registry consisted of 4,044 patients. The overall mean age of the cohort was 60 ± 13 years of which 66% ($n = 2,686$) were males. At the 1-year follow-up, 3.7% ($n = 151$) of the patients were lost to follow-up. A total of 39% of the patients ($n = 1,590$) were current or prior smokers and 3.1% ($n = 126$) were alcohol consumers. Comorbid conditions were common in this cohort particularly hypertension ($n = 2,617$; 65%), dyslipidemia ($n = 2,284$; 56%), and diabetes mellitus ($n = 2,166$; 54%). At total of 40% ($n = 1,613$) of the patients had cardiac catheterization, of which 66% ($n = 1,063$) had percutane-

Table 1. Demographic and clinical characteristics of ACS patients in the Arabian Gulf stratified by PAD status: findings from the Gulf COAST registry

Characteristics	All (n = 4,044)	PAD absent (n = 3,912)	present (n = 132)	p value
Demographic				
Age, years	60±13	60±13	67±12	<0.001
Male gender	2,686 (66)	2,590 (66)	96 (73)	0.119
BMI, kg/m^2	29.0±8.9	29.0±9.0	28.2±5.6	0.264
Smoking (current or prior)	1,590 (39)	1,523 (39)	67 (51)	0.006
Alcohol use	126 (3.1)	121 (3.1)	5 (3.8)	0.651
Past medical history				
Prior MI	1,052 (26)	977 (25)	75 (57)	<0.001
Dyslipidemia	2,284 (56)	2,181 (56)	103 (78)	<0.001
Premature CAD	606 (15)	578 (15)	28 (21)	0.042
Hypertension	2,617 (65)	2,497 (64)	120 (91)	<0.001
Diabetes mellitus	2,166 (54)	2,061 (53)	105 (80)	<0.001
Stroke/TIA	290 (7.2)	252 (6.4)	38 (29)	<0.001
Clinical parameters at presentation				
HR, bpm	85±21	85±21	88±22	0.149
SBP, mm Hg	141±28	141±27	147±37	0.025
DBP, mm Hg	81±16	81±16	79±18	0.367
Crea, p50 (IQR), µmol/L	83 (67–106)	82 (67–104)	112 (75–166)	<0.001
LDL, mmol/L	4.3±18	4.3±18	4.0±2.6	0.051
LVEF, %	48±13	49±13	40±13	<0.001
GRACE risk	128±42	128±42	152±42	<0.001
Killip class				
I – no heart failure	3,170 (78)	3,101 (79)	69 (52)	
II – rales	536 (13)	503 (13)	33 (25)	<0.001
III – pulmonary edema	298 (7.4)	271 (6.9)	27 (20)	
IV – cardiogenic shock	40 (1.0)	37 (1.0)	3 (2.3)	
Diagnosis at discharge				
LBBB MI	36 (0.9)	35 (0.9)	1 (0.8)	
NSTEMI	1,906 (47)	1,821 (47)	85 (64)	
STEMI	997 (25)	980 (25)	17 (13)	<0.001
Unstable angina	1,103 (27)	1,074 (27)	29 (22)	

Values are given as n (%) or mean ± SD, unless specified otherwise. BMI was missing in 54 subjects, HR in 5 subjects, SBP and DBP in 6 subjects, creatinine in 20 subjects, LDL in 831 subjects, LVEF in 1,398 subjects, and GRACE risk in 25 subjects and in 2 subjects at the discharge diagnosis. Percentages might not add up to 100% due to rounding off. 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; p50, median; IQR, interquartile range; LDL, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; LBBB MI, left bundle branch block myocardial infarction; NSTEMI, non-ST myocardial infarction; STEMI, ST myocardial infarction.

ous coronary intervention, while only 5.3% (n = 85) had coronary artery bypass graft (CABG). A total of 3.3% (n = 132) of the patients had PAD on admission.

As shown in Table 1, those with PAD were more likely to be older (67 vs. 60 years; p < 0.001), current or prior smokers (51 vs. 39%; p = 0.006), to have prior MI (57 vs. 25%; p < 0.001), dyslipidemia (78 vs. 56%; p < 0.001), premature coronary artery disease (CAD) (21 vs. 15%; p =

0.042), hypertension (91 vs. 64%; p < 0.001), diabetes mellitus (80 vs. 53%; p < 0.001), and prior stroke/TIA (29 vs. 6.4%; p < 0.001). PAD patients were also more likely to present with higher systolic blood pressure (147 vs. 141 mm Hg; p = 0.025), serum creatinine (112 vs. 82 µmol/L; p < 0.001), GRACE risk score (152 vs. 128; p < 0.001), and lower left ventricular ejection fraction (40 vs. 49%; p < 0.001).

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Table 2. Medication utilization of ACS patients in the Arabian Gulf stratified by PAD status: findings from the Gulf COAST registry

Characteristics	All (n = 4,044)	PAD		p value
		absent (n = 3,912)	present (n = 132)	
Prior medications (n = 3,007)[a]				
Aspirin	2,397 (80)	2,284 (79)	113 (88)	0.023
Clopidogrel	863 (29)	808 (28)	55 (43)	<0.001
ACEIs	1,562 (52)	1,500 (52)	62 (48)	0.367
ARBs	573 (19)	536 (19)	37 (29)	0.004
Beta-blockers	1,828 (61)	1,741 (60)	67 (67)	0.114
Statins	2,428 (81)	2,314 (80)	114 (88)	0.025
Other LLDs	60 (2.0)	56 (2.0)	4 (3.1)	0.359
Oral nitrates	1,049 (35)	992 (34)	57 (44)	0.023
CCBs	599 (20)	547 (19)	52 (40)	<0.001
Medications at discharge (n = 3,681)[b]				
Aspirin	3,559 (97)	3,452 (97)	107 (93)	0.027
Clopidogrel	2,698 (73)	2,600 (73)	98 (85)	0.003
ACEIs	2,475 (67)	2,412 (68)	63 (55)	0.004
ARBs	558 (15)	534 (15)	24 (21)	0.075
Beta-blockers	3,123 (85)	3,025 (85)	98 (85)	0.909
Statins	3,568 (97)	3,458 (97)	110 (96)	0.769
Other LLDs	87 (2.4)	82 (2.3)	5 (4.4)	0.149
Oral nitrates	2,212 (60)	2,134 (60)	78 (68)	0.066
CCBs	570 (15)	539 (15)	31 (27)	<0.001
5-drug regimen[c]	1,922 (52)	1,861 (52)	61 (53)	0.856

Values are given as n (%), unless otherwise specified. Percentages might not add up to 100% due to rounding off. ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; LLDs, lipid-lowering drugs; CCBs, calcium channel blockers. [a] In the prior history, 1,037 patients had missing medications [b] At hospital discharge, 193 patients had missing information on medications. [c] The 5-drug regimen is defined as concurrent prescribing of aspirin, clopidogrel, ACEI/ARB, statin, and beta-blocker.

Table 2 shows prior-to-admission and postdischarge medication utilization stratified by PAD status. Prior to admission, patients with PAD were more likely to be on aspirin (88 vs. 79%; $p = 0.023$), clopidogrel (43 vs. 28%; $p < 0.001$), ARBs (29 vs. 19%; $p = 0.004$), statins (88 vs. 80%; $p = 0.025$), and calcium channel blockers (CCBs) (40 vs. 19%; $p < 0.001$). At discharge, those with PAD were still more likely to be prescribed clopidogrel (85 vs. 73%; $p = 0.003$) and CCBs (27 vs. 15%; $p < 0.001$), but they were less likely to be prescribed aspirin (93 vs. 97%; $p = 0.027$) and ACEIs (55 vs. 68%; $p = 0.004$). Only 52% ($n = 1,922$) of the patients were prescribed the 5-drug regimen (aspirin, clopidogrel, ACEI/ARB, statin, beta-blocker) concurrently.

As shown in Table 3, the overall cumulative stroke/TIA, MI, all-cause mortality, readmissions for cardiac reasons and MACE at the 1-year follow-up were 4.4% ($n = 176$), 7.1% ($n = 287$), 12.0% ($n = 487$), 24.5% ($n = 990$), and 36.2% ($n = 1,462$), respectively. Adjusting for

demographic and clinical characteristics, at the 1-year follow-up, patients with PAD were significantly more likely to be associated with MACE events (adjusted OR [aOR], 2.07; 95% confidence interval [CI]: 1.41–3.06; $p < 0.001$). The higher rates of events were also observed across all MACE components, stroke/TIA (aOR, 3.22; 95% CI: 1.80–5.75; $p < 0.001$), MI (aOR, 2.15; 95% CI: 1.29–3.59; $p = 0.003$), all-cause mortality (aOR, 2.21; 95% CI: 1.33–3.69; $p = 0.002$), and readmissions for cardiac reasons (aOR, 1.83; 95% CI: 1.24–2.70; $p = 0.003$).

Discussion

This large, prospective, multinational, multicenter study from the Arabian Gulf demonstrated that at the 1-year follow-up, patients presenting with ACS and suffering from preexisting PAD had significantly worse cardiovascular outcomes compared to those who did not

Table 3. Association between PAD and MACE in ACS patients in the Arabian Gulf: findings from the Gulf COAST registry

Outcome	Univariate statistics				Multivariate logistic regression			
	all (n = 4,044)	no PAD (n = 3,912)	PAD (n = 132)	p value	aOR (95% CI)	adj. p value	HL	ROC
Stroke/TIA								
12-month	176 (4.4)	159 (4.1)	17 (12.9)	<0.001	3.22 (1.80–5.75)	<0.001	0.099	0.70
MI								
12-month	287 (7.1)	266 (6.8)	21 (15.9)	<0.001	2.15 (1.29–3.59)	0.003	0.161	0.70
All-cause mortality								
12-month	487 (12.0)	453 (11.6)	34 (25.8)	<0.001	2.21 (1.33–3.69)	0.002	0.117	0.76
Readmissions for cardiac reasons								
12-month	990 (24.5)	939 (24.0)	51 (38.6)	<0.001	1.83 (1.24–2.70)	0.003	0.215	0.58
MACE								
12-month	1,462 (36.2)	1,384 (35.4)	78 (59.1)	<0.001	2.07 (1.41–3.06)	<0.001	0.286	0.63

Values are given as n (%), unless otherwise specified. MACE included cumulative events of stroke/TIA, MI, mortality, and readmissions for cardiac reasons up to 1-year of follow-up. 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, diabetes mellitus, 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 was a total of 3.7% ($n = 151$) of the patients lost to follow-up. aOR, 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.

suffer preexisting PAD. Specifically, after multivariate adjustment, those with PAD were more likely to have stroke/TIA, MI, all-cause mortality, and readmissions for cardiac reasons.

These findings corroborate with similar studies that also found an association between comorbid PAD (mortality, MI, and stroke) [4, 5, 9, 16–20] and readmission for cardiac reasons [6, 7]. The only report on PAD in ACS patients from the Arabian Gulf region was published by Al-Thani et al. [9]; however, their study evaluated only the short-term in-hospital outcomes. The current study is one of only few studies worldwide evaluating not only the association between PAD and mortality, but also exploring various other cardiovascular outcomes including readmissions for cardiologic reasons in the same setting.

Various hypotheses have been postulated to explain the relationship between PAD and MACE. Impairment of endothelial function, as indicated by brachial-artery flow-mediated vasodilation has been suggested, leading to arterial stiffness and increased stress on the heart [21]. The relationship between PAD and adverse cardiac events has also been reported to be due to more extensive and calcified coronary atherosclerosis, constrictive arterial remodeling, and greater disease progression [22]. Grenon et al. [20] demonstrated that inflammatory markers (IL-6,

TNF-α, fibrinogen) explained nearly 20% of the association of PAD with cardiovascular morbidity and mortality. The increased propensity to develop MACE events could be partly explained by the comorbidities associated with PAD. However, these adverse cardiac events persisted despite multivariate adjustments.

The recent guidelines of the American Heart Association/American College of Cardiology (AHA/ACC) (2016) and the European Society of Cardiology (ESC) (2017) [1, 2] on the diagnosis and treatment of PAD recommend smoking cessation, a healthy diet, physical activity, statin use, glycemic control, antiplatelet use, and blood pressure control with the use of renin-angiotensin system (RAS) blockers (ACEI/ARB) considered as first-line therapy to reduce morbidity and mortality. In the current study, 73% (93/128) of the PAD patients had a BMI of >25 kg/m², 51% (67/132) of the patients were current or prior smokers, only 38% (30/80) of the diabetics with nonmissing values had their HbA1c controlled (<7%) and 45% (58/130) of those with hypertension had their blood pressure controlled (<120/80 mmHg). In order to reduce morbidity and mortality in patients with PAD, better control of lifestyle changes and clinical parameters as well as optimal medication use are warranted.

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Table 4. Demographic, clinical, and presentation characteristics between the Gulf COAST group remaining at the end of the year and the cohort that was lost to follow-up

Characteristics	LTF (n = 151) 3.7%	Remaining (n = 3,893) 96.3%	p value
Demographic			
Age, years	60±13	60±13	0.714
Male gender	103 (68)	2,583 (66)	0.635
BMI, kg/m²	29.0±5.6	29.0±9.0	0.998
Clinical			
Prior MI	35 (23)	1,017 (26)	0.418
Hypertension	90 (60)	2,527 (65)	0.180
Diabetes mellitus	85 (56)	2,081 (53)	0.493
Presentation			
SBP, mm Hg	141±29	141±27	0.980
DBP, mm Hg	81±16	81±16	0.566
Killip ≥2	31 (21)	843 (22)	0.742
GRACE risk score	130±41	128±42	0.710

Values are given as n (%) or mean ± SD, unless specified otherwise. LTF, lost to follow-up; BMI was missing in 54 subjects, SBP and DBP in 6 subjects, and GRACE in 25 subjects. Percentages may not add up to 100% due to rounding off. SD, standard deviation; BMI, body mass index; MI, myocardial infarction; SBP, systolic blood pressure; DBP, diastolic blood pressure; GRACE, global registry of acute coronary events.

Only 52% of the PAD patients were on the 5-drug combination regimen concurrently. Prior regional and international studies have assessed the 4-drug, rather than the 5-drug, evidence-based cardiac combinations, and the use ranged from 46 to 65% [23–26] which is similar to the current study. Access to healthcare, a concern raised in the West, is unlikely to have contributed to these low numbers in the Arabian Gulf where healthcare, including medications, is free for all citizens. Patients could have had side effects or contraindications to any of the components of the 5-drug combination and these could have biased the prescribing negatively. However, the Gulf COAST registry did not capture any of this information. Physicians themselves might also have contributed to these sub-optimal findings by not being aware of current updated guidelines on the management of ACS.

A prior study [27] has raised concerns about access to healthcare affecting adherence to evidence-based cardiac medications. However, the unexpected low adherence rate (of 52%) is quite surprising and difficult to explain, given the fact that this was a homogenous Arabian Gulf population with free universal health coverage. Lower adherence rates have been attributable to patient characteristics, hospital type, and lack of familiarity with the evidence-based ACC/AHA/ESC guidelines that recommend the concurrent use of an evidence-based cardiac medication combination of an anti-platelet drug, an ACEI or ARB, a beta-blocker, and a statin, to optimize clinical outcomes in ACS patients [28, 29].

Our study has limitations. First, due to the inherent nature of the uncontrolled observational study design, its ability to assess causal relationships is limited. Second, the analysis relies only on patients admitted to the hospital with a diagnosis of ACS and hence cannot be generalized to the entire population of patients with PAD. Third, the study could not establish the extent and severity of PAD given the limitations of the registry design. A more strict ABI threshold for PAD (of <0.8) was used rather than the usual cutoff threshold of <0.9 and this could have potentially missed those with milder forms of PAD and consequently biasing the outcomes. Fourth, a high prevalence of diabetes mellitus (80%) in PAD patients could have led to the false negative of ankle pressure [30]. Fifth, we reported all-cause mortality where, if data were available, cardiovascular mortality would have been more appropriate. Sixth, a total of 3.7% (n = 151) of the patients were lost to follow-up at 1 year. However, this number was relatively small, and importantly, there were no significant differences in the demographic, clinical, and presentation characteristics of the Gulf COAST group lost to follow-up at 1 year against the cohort that remained at the end of the 1-year follow-up (Table 4).

Conclusion

This is one of only a few studies in the Arabian Gulf region to demonstrate the relationship between PAD and various MACE components in ACS patients in the same setting. Specifically, PAD was significantly associated with increased 12-month rates of stroke/TIA, MI, all-cause mortality, and readmissions for cardiac reasons. There is a considerable opportunity to improve outcomes in these high-risk patients.

Acknowledgement

Statement of Ethics

This study was approved by the local institutional ethics committees of the participating centers.

Disclosure Statement

Appendix

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References

1 Aboyans V, Ricco JB, Bartelink ME, Björck M, Brodmann M, Cohnert T, et al.; ESC Scientific Document Group. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J. 2018 Mar;39(9):763–816.

2 Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. J Am Coll Cardiol. 2017 Mar;69(11):1465–508.

3 Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. Lancet. 2013 Oct;382(9901):1329–40.

4 Patel MR, Becker RC, Wojdyla DM, Emanuelsson H, Hiatt WR, Horrow J, et al. Cardiovascular events in acute coronary syndrome patients with peripheral arterial disease treated with ticagrelor compared with clopidogrel: data from the PLATO Trial. Eur J Prev Cardiol. 2015 Jun;22(6):734–42.

5 Inohara T, Pieper K, Wojdyla DM, Patel MR, Jones WS, Tricoci P, et al. Incidence, timing, and type of first and recurrent ischemic events in patients with and without peripheral artery disease after an acute coronary syndrome. Am Heart J. 2018 Jul;201:25–32.

6 Mahoney EM, Wang K, Keo HH, Duval S, Smolderen KG, Cohen DJ, et al.; Reduction of Atherothrombosis for Continued Health (REACH) Registry Investigators. Vascular hospitalization rates and costs in patients with peripheral artery disease in the United States. Circ Cardiovasc Qual Outcomes. 2010 Nov; 3(6):642–51.

7 Hasvold P, Nordanstig J, Kragsterman B, Kristensen T, Falkenberg M, Johansson S, et al. Long-term cardiovascular outcome, use of resources, and healthcare costs in patients with peripheral artery disease: results from a nationwide Swedish study. Eur Heart J Qual Care Clin Outcomes. 2018 Jan;4(1):10–7.

8 Kumar A, Al-Bader M, Al-Thani H, El-Menyar A, Al Suwaidi J, Al-Zakwani I, et al. Multicenter cross-sectional study of asymptomatic peripheral arterial disease among patients with a single previous coronary or cerebrovascular event in the Arabian Gulf. Curr Med Res Opin. 2014 Sep;30(9):1725–32.

9 Al-Thani HA, El-Menyar A, Zubaid M, Rashed WA, Ridha M, Almahmeed W, et al. Peripheral arterial disease in patients presenting with acute coronary syndrome in six middle eastern countries. Int J Vasc Med. 2011; 2011:815902.

10 Zubaid M, Thani KB, Rashed W, Alsheikh-Ali A, Alrawahi N, Ridha M, et al.; Gulf COAST investigators. Design and Rationale of Gulf locals with Acute Coronary Syndrome Events (Gulf Coast) Registry. Open Cardiovasc Med J. 2014 Sep;8(1):88–93.

11 Weintraub WS, Karlsberg RP, Tcheng JE, Boris JR, Buxton AE, Dove JT, et al. ACCF/AHA 2011 key data elements and definitions of a base cardiovascular vocabulary for electronic health records: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Data Standards. J Am Coll Cardiol. 2011 Jul; 58(2):202–22.

12 Bhatt DL, Peterson ED, Harrington RA, Ou FS, Cannon CP, Gibson CM, et al.; CRUSADE Investigators. Prior polyvascular disease: risk factor for adverse ischaemic outcomes in acute coronary syndromes. Eur Heart J. 2009 May;30(10):1195–202.

13 Panduranga P, Sulaiman K, Al-Zakwani I, Zubaid M, Rashed W, Al-Mahmeed W, et al. Utilization and determinants of in-hospital cardiac catheterization in patients with acute coronary syndrome from the Middle East. Angiology. 2010 Nov;61(8):744–50.

14 Lemeshow S, Hosmer DW Jr. A review of goodness of fit statistics for use in the development of logistic regression models. Am J Epidemiol. 1982 Jan;115(1):92–106.

15 Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology. 1982 Apr; 143(1):29–36.

16 Monreal M, Alvarez L, Vilaseca B, Coll R, Suárez C, Toril J, et al.; FRENA Investigators. Clinical outcome in patients with peripheral artery disease. Results from a prospective registry (FRENA). Eur J Intern Med. 2008 May; 19(3):192–7.

17 Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med. 1992 Feb;326(6):381–6.

18 Newman AB, Shemanski L, Manolio TA, Cushman M, Mittelmark M, Polak JF, et al.; The Cardiovascular Health Study Group. Ankle-arm index as a predictor of cardiovascular disease and mortality in the Cardiovascular Health Study. Arterioscler Thromb Vasc Biol. 1999 Mar;19(3):538–45.

19 Froehlich JB, Mukherjee D, Avezum A, Budaj A, Kline-Rogers EM, López-Sendón J, et al.; GRACE Investigators. Association of peripheral artery disease with treatment and outcomes in acute coronary syndromes. The Global Registry of Acute Coronary Events (GRACE). Am Heart J. 2006 May;151(5): 1123–8.

20 Grenon SM, Vittinghoff E, Owens CD, Conte MS, Whooley M, Cohen BE. Peripheral artery disease and risk of cardiovascular events in patients with coronary artery disease: insights from the Heart and Soul Study. Vasc Med. 2013 Aug;18(4):176–84.

21 Pasqualini L, Marchesi S, Vaudo G, Siepi D, Angeli F, Paris L, et al. Association between endothelial dysfunction and major cardiovascular events in peripheral arterial disease. Vasa. 2003 Aug;32(3):139–43.

22 Hussein AA, Uno K, Wolski K, Kapadia S, Schoenhagen P, Tuzcu EM, et al. Peripheral arterial disease and progression of coronary atherosclerosis. J Am Coll Cardiol. 2011 Mar; 57(10):1220–5.

23 Bi Y, Gao R, Patel A, et al. Evidence-based medication use among Chinese patients with acute coronary syndromes at the time of hospital discharge and 1 year after hospitalization: results from the Clinical Pathways for Acute Coronary Syndromes in China (CPACS) study. Am Heart J 2009 Mar;157(3): 509–16e1.

24 Al-Zakwani I, Zubaid M, Panduranga P, Rashed W, Sulaiman K, Almahmeed W, et al. Medication use pattern and predictors of optimal therapy at discharge in 8176 patients with acute coronary syndrome from 6 Middle Eastern countries: data from the gulf registry of acute coronary events. Angiology. 2011 Aug;62(6):447–54.

25 Yan AT, Yan RT, Tan M, Huynh T, Soghrati K, Brunner LJ, et al.; Canadian ACS Registries Investigators. Optimal medical therapy at discharge in patients with acute coronary syndromes: temporal changes, characteristics, and 1-year outcome. Am Heart J. 2007 Dec; 154(6):1108–15.

26 Al-Zakwani I, Sulaiman K, Al Za'abi M, Panduranga P, Al-Habib K, Asaad N, et al. Impact of evidence-based cardiac medication on short- and long-term mortality in 7,567 acute coronary syndrome patients in the Gulf RACE-II registry. Int J Clin Pharmacol Ther. 2012 Jun;50(6):418–25.

27 Vathesatogkit P, Batty GD, Woodward M. Socioeconomic disadvantage and disease-specific mortality in Asia: systematic review with meta-analysis of population-based cohort studies. J Epidemiol Community Health. 2014 Apr;68(4):375–83.

28 Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, et al.; American College of Cardiology; American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction); American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons; American Association of Cardiovascular and Pulmonary Rehabilitation; Society for Academic Emergency Medicine. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. J Am Coll Cardiol. 2007 Aug;50(7):e1–157.

29 Wright RS, Anderson JL, Adams CD, Bridges CR, Casey DE Jr, Ettinger SM, et al.; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2011 ACCF/AHA focused update incorporated into the ACC/AHA 2007 Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in collaboration with the American Academy of Family Physicians, Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons. J Am Coll Cardiol. 2011 May; 57(19):e215–367.

30 Nam SC, Han SH, Lim SH, Hong YS, Won JH, Bae JI, et al. Factors affecting the validity of ankle-brachial index in the diagnosis of peripheral arterial obstructive disease. Angiology. 2010 May;61(4):392–6.