Original Articles

Are proton pump inhibitors among the risk factors for acute coronary syndrome?

A multi-centric case-control study between patients attending governmental hospitals in western Saudi Arabia

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ABSTRACT

الأهداف : التعرف على متنبئات متلازمة الشريان التاجي الحادة (ACS) ، وتحديد العلاقة بين استخدام مثبطات مضخة البروتون (PPIs) وحدوث متلازمة الشريان التاجي الحادة غير المميتة بين مرضى المستشفيات الحكومية في جدة ، المملكة العربية السعودية .

المنهجية : تم استخدام دراسة الحالة—والشاهد في مراكز متعددة شملت مستشفيين حكوميين والمستشفى الجامعي الرئيسي في جدة ، وذلك بين شهري يناير وديسمبر من عام 2015. تم اختيار حوالي 118 حالة تتراوح أعمارهم بين 18 سنة وأكبر، والذين تم تشخيصهم مؤخرًا بمتلازمة الشريان التاجي الحادة ، وتم احتجازهم في المستشفى خلال الأشهر الستة السابقة للدراسة . و لكل حالة مختارة ، تم اختيار شاهد واحد يماثله في العمر والجنس. استخدم استبيان موحد لجمع البيانات من خلال مقابلات مع المرضى وكذلك مراجعة السجلات الطبية .

النتائج : وجد أن عدة عوامل تنبأت بمتلازمة الشريان التاجي الحادة وهي : التدخين الحالي (معامل الترجيح = 4.5 ؛ 95% فترة الثقة : 1.92–10.98) ، الوزن الزائد للجسم (معامل الترجيح = 2.99 ؛ 95% فترة الثقة : 1.38–6.45) وارتفاع شحوم الدم معامل الترجيح = 2.51 ؛ 95% فترة الثقة : 1.07–5.84). وارتبط ارتفاع ضغط الدم والسكري والنشاط البدني المعتدل إلى المرتفع مع متلازمة الشريان التاجي الحادة . ومع ذلك ، لم يكن هناك ارتباط إحصائي بين استخدام مثبطات مضخة البروتون وحدوث متلازمة الشريان التاجي الحادة غير القاتلة (0.05<*p*) .

الخلاصة : لم يكن هناك ارتباط بين مثبطات مضخة البروتون وحدوث متلازمة الشريان التاجي الحادة غير المميتة . يعتبر التدخين أول متنبأ لمتلازمة الشريان التاجي الحادة ، يليه زيادة الوزن، وارتفاع شحوم الدم . وعلاوة على ذلك، ارتبطت متلازمة الشريان التاجي الحادة مع مرض السكري المبلغ عنه ذاتياً، وارتفاع ضغط الدم والنشاط البدني المعتدل إلى المرتفع .

Objectives: To identify the predictors of acute coronary syndrome (ACS) and to determine the relationship between usage of proton pump inhibitors (PPIs) and the occurrence of a first non-fatal ACS event among patients that attended governmental hospitals in Jeddah, Saudi Arabia.

Methods: A matched, multi-centric case-control study was performed between January and June of 2015 in Jeddah involving 2 governmental hospitals and the main university hospital. A total of 118 cases aged ≥18 years who were recently diagnosed with ACS were selected. For each case, one control matched by age and gender was selected. Information from an interview questionnaire and from reviewing patients' medical records was recorded on a standardized data collection sheet.

Results: Risk factors for ACS and the relationship between usage of PPIs and the occurrence of a first non-fatal ACS event were measured in 236 cases and matched controls. Current smoking (OR: 4.5; 95% CI: 1.92-10.98), excessive body weight (OR: 2.99; 95% CI: 1.38-6.45), and dyslipidemia (OR: 2.51; 95% CI: 1.07-5.84) were the predictors of ACS. Hypertension, diabetes, and moderate-to-high physical activity were associated with ACS. However, there was no statistical association between use of PPIs and occurrence of the first non-fatal ACS event ($p>0.05$).

Conclusions: There was no association between PPIs and the occurrence of a first non-fatal ACS event. Smoking, increased weight, and dyslipidemia are considered predictors of ACS. Furthermore, ACS is associated with self-reported diabetes, hypertension, and physical activity.

Acute coronary syndrome (ACS) remains one of the chief causes of death worldwide.[1] Hypertension, dyslipidemia, obesity, smoking, and diabetes are considered risk factors for cardiovascular diseases such as ACS.[2] In Saudi Arabia, approximately 50% of people live with 3 or more cardiovascular (CV) risk factors.[3] Moreover, according to the "Saudi Project for Assessment of Coronary Events (SPACE) Registry," 70% of cardiac patients have diabetes and 66% smokers.[4] In addition, hypertension was the biggest risk factor encountered by researchers in the Middle East.[5] Globally, the rise in the amount of deaths is appointed more to hypertension than to other risk factors of CV diseases.[6]

Some studies have reported that proton pump inhibitors (PPIs) could play a role in ACS. Proton pump inhibitors are a group of drugs that are most commonly prescribed in clinical practice. Proton pump inhibitors are preferred when compared to other medications such as histamine H2 receptor antagonists because of their efficacy in suppressing gastric acid secretions.[7] Proton pump inhibitors are used to treat many diseases of the digestive tract, including dyspepsia, gastro-esophageal reflux disease (GERD), peptic ulcers, and Helicobacter pylori (H. pylori) infection.[8] When PPIs are used for a long period, side effects such as bone fractures and low levels of blood magnesium may occur.[9,10] Proton pump inhibitors can reduce the effectiveness of antiplatelet drugs among patients with ACS.[11,12] This effect was attributed to CYP2C19, which is a hepatic enzyme that can be inhibited by PPIs. CYP2C19 is required to activate clopidogrel, an antiplatelet agent.[13] However, in patients with ACS, PPIs also lower the influence of ticagrelor, "an antiplatelet agent that does not require hepatic activation."[14] Several of the latest studies suggest that all members of PPIs raise CV risk for patients who are suffering from ACS in spite of the fact that some of the PPI members do not considerably obstruct CYP2C19.[11,15,16] Accordingly, it is not known if the risk of adverse CV events extends to the general population who ingests PPIs.

A recent study carried out on animals and on *ex-vivo* human tissues revealed the presence of a plausible biological mechanism that might explain the association between PPIs, ACS, and other CV events.[17] Proton pump inhibitors hinder the activity of dimethylarginine dimethylaminohydrolase (DDAH). Dimethylarginine dimethylaminohydrolase is an enzyme that is important for a healthy CV system.[17] Unfortunately, DDAH metabolizes "asymmetrical dimethylarginine (ADMA), an endogenous competitive inhibitor of nitric oxide synthase (NOS)".[17] When endothelial NOS is inhibited, the risk of vascular inflammation and thrombosis is higher. This mechanism could justify the greater risk of unwanted myocardial events in heart patients using PPIs. In fact, plasma ADMA is a risk factor for CV diseases and the death of patients who suffer from ACS, as well as for healthy people.[18-20]

Most of the literature addresses the relationship between PPIs and clopidogrel. However, based on extensive literature review, few studies have addressed the relationship between PPIs alone and ACS.[11,17] Therefore, such a study is necessary. The aims of this study are identifying the predictors of ACS and determining the relationship between the use of PPIs and the first non-fatal ACS event among patients attending general governmental hospitals in Jeddah, Saudi Arabia.

Methods. We used a multi-centric case-control study design. Data was collected between January and June 2015, and the study complied with the Declaration of Helsinki. It was approved by the Institutional Review Board (IRB) of the King Abdulaziz University Hospital (KAUH) (Reference No. 343-14) and by the Directorate of Health Affairs in Jeddah that covers the 2 Ministry of Health (MOH) hospitals (Reference No. A00229). On-line databases such as "PubMed, Clinical Key, Google, Web of Science, and Cochrane Library" were comprehensively searched and reviewed for the period from 2004 to 2018 for studies that explored the relationship between PPIs and ACS.

Three hospitals were selected from Jeddah, Saudi Arabia. A simple random sampling technique, using a table of random digits, was used to select the hospitals. Two of the selected hospitals belonged to MOH and one was the main university hospital, the KAUH.

The sample size was calculated through EpiTools statistical calculation,[21] with a suggested power of 80 and a 2-sided confidence level of 95%. The ratio of cases to controls was 1:1, with the percentage of control group exposed to PPIs as 44%.[22] The odds ratio was suggested to be 2, based on a similar study.[23] The calculated total sample size was 260 (130 cases and 130 controls). Twelve controls had no old files and/or had a previous history of ACS, stroke, or heart disease. In addition, we excluded 12 cases of patients who had died during the hospital stay. Therefore, a total of 118 cases and 118 controls were included.

All eligible consecutively admitted cases of ACS who agreed to participate were selected from the cardiac care unit (CCU), cardiac and medical wards, and emergency department (ED). Cases of ACS were defined as "any patients with unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI) or ST-segment elevation myocardial infarction (STEMI)." A cardiologist diagnosed this admission according to electrocardiography (ECG) changes with a rise in cardiac biomarkers of necrosis (serum creatine phosphokinase, troponins, and myoglobin).

For each selected case, one control was selected, matched by ±5 years in age and gender from the same hospital. The controls included any hospitalized patients admitted without any clinical symptoms or suspicion of cardiovascular diseases (CVDs) or any heart disease in their present and past medical history (they were selected through purposive sampling). The controls were selected from the ED and inpatient medical wards.

Data was collected through a validated data collection sheet. Validity was assessed by 2 experts. The sheet was completed through an interview questionnaire that was answered by both case and control participants and by a review of medical record. It contained sections about personal and socio-economic data and family history of CVDs. Medical history was also determined by assessing hypertension, diabetes mellitus (DM), and hyperlipidemia. Patients were also asked about their use of aspirin or clopidogrel and about their lifestyle habits, such as smoking. Physical activity level was established through "the short form of the International Physical Activity Questionnaire (IPAQ)".[24]

Statistical analysis. Hypertension was defined as "systolic blood pressure (SBP) ≥140 mm Hg and/or diastolic blood pressure (DBP) ≥90 mm Hg."[25] The glycemic profile was classified according to the American Diabetes Association. Patients were determined to be diabetic if their fasting blood glucose (FBG) level was ≥7 mmol/L, their glycated hemoglobin (HbA1c) was ≥6.5%, or their random plasma glucose was ≥11.1 mmol/L.[26] Body mass index (BMI) was estimated by dividing weight in kilograms by the square of height in meters. Body mass index was categorized into 3 categories: normal (<25), overweight (25-29.9), and obese (≥30).[27] Dyslipidemia was defined as follows: high total cholesterol if ≥5.2 mmol/L, high triglyceride levels if ≥1.7 mmol/L, high low-density lipoprotein (LDL) if ≥4.12 mmol/L, and low levels of high-density lipoprotein (HDL) if ≤1.03 mmol/L[28] Current smokers were defined as "those who smoked at least one cigarette per day", and former smokers were defined as "those who had stopped smoking more than one

year". Participants who do not belong to the previous categories were classified as non-current smokers. Regarding physical activity, participants were classified according to the scoring system provided by IPAQ as having low, moderate, or high physical activity.[24]

Statistical analysis. We evaluated the data with IBM SPSS Statistics for Windows, Version 20 (IBM Corp., Armonk, N.Y., USA). Normally distributed continuous variables were displayed as means and standard deviations (SDs), and categorical variables were displayed as frequency tables. Associations between categorical variables were assessed by a chi-squared test and between continuous variables by a Student's t-test. Estimations for logistic regression analysis were used to determine the predictors of ACS according to PPI use and other covariates. We displayed the outcome results as crude and adjusted odds ratios (aORs) and confidence intervals (95% CI).

Results. We included a total of 118 cases aged ≥18 years with ACS (first attack) and an equal number of controls matched by age and gender. The age varied between 18 and 84 with a mean±SD of 54±11.7 years for cases and 54±12 years for controls. Males accounted for 76% and females accounted for 24% of the total number of cases and controls (with no statistically significant difference for age and gender between cases and controls). Saudis represented 38.6% of the sample. The results showed that approximately 50.8% of the cases of ACS were considered STEMI and 28.8% were NSTEMI and only 20% of them had unstable angina. The most frequently used type of PPI was omeprazole (66%), followed by pantoprazole (23%).

Table 1 reveals that participants with cases of ACS used the PPIs less frequently than the controls (19% versus 29%,) with no statistically significant differences (*p*=0.07). The table also shows that cases of ACS were associated with increased BMI (*p*<0.001). Participants with cases of ACS were about 3 times more overweight and obese compared to the controls. Similarly, smokers were about 3.5 times more likely to have ACS than non-smokers. Moreover, almost half of the cases (42%) had dyslipidemia compared to one-fifth of the controls (18%), with statistically significant differences. Regarding physical activity, the relationship between moderate to high physical activity and ACS was statistically significant. Table 1 also shows that more than half (56.8%) of the cases were hypertensive compared to 42% of the controls. In addition, diabetes was more apparent among cases than controls.

Table 1 - Comparison between cases and controls regarding the possible associated factors of acute coronary syndrome (ACS) in Jeddah hospitals, Saudi Arabia.

Variable	Cases (n=118)		Controls (n=118)		x^2	P-value
PPI use[*]					3.26	0.07
Yes	22	(19.1)	34	(29.3)		
No	93	(80.9)	82	(70.7)		
Hypertension					4.90	0.03
Yes	67	(56.8)	50	(42.4)		
No	51	(43.2)	68	(57.6)		
Diabetes					15.41	<0.001
Yes	68	(57.6)	38	(32.2)		
No	50	(42.4)	80	(67.8)		
Dyslipidemia[‡]					15.38	<0.001
Yes	45	(42.1)	19	(17.6)		
No	62	(57.9)	89	(82.4)		
Overweight & obesity					13.87	0.001
Yes	74	(76.3)	40	(49.4)		
No	23	(23.7)	41	(50.6)		
Use of anticoagulant					0.70	0.40
Yes	41	(34.7)	35	(29.7)		
No	77	(65.3)	83	(70.3)		
Current smoking					17.99	0.001
Yes	51	(43.2)	21	(17.8)		
No	67	(56.8)	97	(82.2)		
Ex-smoking[‡]					0.77	0.38
Yes	22	(32.8)	26	(26.5)		
No	45	(67.2)	72	(73.5)		
Physical activity[‡]					10.72	0.001
Moderate & high	64	(55.0)	40	(33.9)		
Low	52	(44.8)	78	(66.1)		

[*]The responses of 5 cases and controls were "I don't know" and dealt with as missing data, [‡] Some patients didn't answer this question

Discussion. Regarding the risk factors for ACS, the current study revealed significant associations between hypertension, diabetes, dyslipidemia, current smoking, and excessive body weight (BMI >25 kg/m^2) and increased risk of ACS. Similarly, Kastorini et al[29] reported significant associations between hypertension, diabetes, dyslipidemia, and smoking and CVDs in Greece.

Regarding family history, our study showed an absence of a significant association between family history of premature heart disease and ACS, which disagrees with the results of Kastorini et al.[29] The cause of such a discrepancy might be because we asked specifically about family history of premature heart disease. Results from Oman in 2010 also found an association between family history and coronary heart disease.[30] This difference between our study and their study could be because they made comparisons between the young (<40 years of age) and the old (>40 years of age), but our study addressed the relation of family history without differentiating the age of the study sample.

Our results found that moderate-to-high physical activity increased the risk of ACS. Most of our ACS patients recalled that they were physically exerting themselves just before the ACS event. Our study showed that 30.5% of the sample were smokers, which correlates with the results of Alsuwaidi et al study.[31] Additionally, 43.2% of our ACS cases were current smokers compared to 54% of ACS patients in Alsuwaidi et al study.[31]

The current study revealed an absence of statistical association between the use of PPIs and the first attack

Table 2 - Calculated odds ratios regarding the possible associated factors of acute coronary syndrome (ACS) in Jeddah hospitals, Saudi Arabia.

Variable	Crude OR	95% CI	aOR	95% CI of aOR
Current smoking	3.52	1.94-6.38	4.60	1.93-10.98
Overweight & obesity	3.29	1.74-6.25	2.99	1.39-6.45
Dyslipidemia	3.40	1.82-6.36	2.51	1.08-5.84
Hypertension	1.78	1.07-2.99	0.67	0.30-1.47
Diabetes	2.86	1.68-4.87	0.59	0.26-1.32
Moderate to high physical activity	2.4	1.42-4.07	0.54	0.26-1.14
Use of anticoagulant	1.26	0.73-2.18	NA	NA
Use of PPI	0.57	0.31-1.05	NA	NA
Ex-smoking	1.35	0.69-2.67	NA	NA

aOR - adjusted odds ratio and 95% confidence interval for nationality, and the significant variables from table 1, NA - not applicable (not significant in the bivariate analysis, therefore not entered in the regression model).

of non-fatal ACS. Similarly, Simon et al[32] conducted a large nationwide cohort study in France and inferred that PPI use was not associated with increased risk of CVDs. However, a Taiwanese study concluded that PPIs might be independently associated with increased risk of myocardial infarction (MI).[33] Researchers performed a propensity score matched analysis with an adjusted hazard ratio (aHR) =1.58; 95% CI: 1.11-2.25. Furthermore, the aOR was 4.61 (95% CI:1.76-12.07) for the 7-day window and 3.47 (95% CI: 1.76-6.83) for the 14-day window from the case-crossover part of their study. The differences between our study and the Taiwanese study could be due to the ample sizes, study duration, and the source of information. Moreover, Shah et al[34] published a study in 2015 that utilized a data mining approach to examine the association between use of PPI for GERD and MI incidence among the U.S. population. They discovered that patients who used PPIs had a slightly increased risk for MI (aOR: 1.16; 95% CI: 1.09-1.24).[34] Other studies showed associations between ACS and other CVDs among patients known to use PPI concomitantly with the antiplatelet drug clopidogrel.[12,16,23,35-39]

Our data obtained from the medical records (such as lipid profile and HbA1c) did not show any significance between cases and controls. This result agrees with results from an older international standardized case-control study.[40] It is possible that the actual blood pressure and lipid profile usually measured after the ACS event might have fallen in some patients due to the drugs used in the acute phase or due to the infarction itself. Similarly, the blood glucose level could be high because of the stress of having the disease.[40]

The interpretations of our conclusions could be used to distribute important messages to public health officials, which could lead to healthier lifestyles and CVD prevention policies.

The power for the comparison of PPI use in cases of ACS and controls was lower than expected. This could be due to the calculation of a sample size with a relatively high OR, in addition to the exclusions and dropouts previously mentioned in the methodology. Moreover, there is recall bias in the case-control study especially with the doses, duration, and the frequency of PPI use. However, to minimize recall bias, the interviewer exhibited pictures of all the brands of PPIs available in the pharmacies in KSA. Additionally, we used the show cards that are associated with the global physical activity questionnaire by the World Health Organization,[41] which could have confused the patients during the interview and did not help in physical activity recall, especially for the controls. No data was collected on medications and herbals that could influence ACS and cardiotoxicity other than PPI and anticoagulants. Moreover, we cannot exclude selection bias; the study included only the patients who survived the first non-fatal event of ACS. Controls were hospitalized and selected by purposive sampling based on their age, gender, and the ability to cooperate with the study team.

In conclusion, there was no relationship between the use of PPIs and the development of the first attack of non-fatal ACS. Regarding the risk factors of ACS, smoking is considered the first predictor, followed by excessive body weight and dyslipidemia. Furthermore, ACS is associated with self-reported DM, hypertension, and moderate-to-high physical activity.

It is necessary to conduct more studies, especially cohort studies, and to assess the effect of PPIs alone on the occurrence of ACS. Proton pump inhibitors can yet be used in patients who suffer from gastro-esophageal disorders to alleviate symptoms and enhance their quality of life; however, further investigations regarding drug safety of the PPIs for acute and chronic use should continue. Finally, we should encourage the continuation of health education and promotion to modify the current known risk factors that influence the occurrences of ACS.

References

1. Khaled S, Matahen R. Cardiovascular risk factors profile in patients with acute coronary syndrome with particular reference to left ventricular ejection fraction. *Indian Heart J* 2018; 70: 45-49.
2. Ibrahim NK, Mahnashi M, Al-Dhaheri A, Al-Zahrani B, Al-Wadie E, Aljabri M, et al. Risk factors of coronary heart disease among medical students in King Abdulaziz University, Jeddah, Saudi Arabia. *BMC Public Health* 2014; 14: 411.
3. Ahmed AM, Hersi A, Mashhoud W, Arafah MR, Abreu PC, Al Rowaily MA, et al. Cardiovascular risk factors burden in Saudi Arabia: The Africa Middle East Cardiovascular Epidemiological (ACE) study. *J Saudi Heart Assoc* 2017; 29: 235-243.
4. Al-Saif SM, Alhabib KF, Ullah A, Hersi A, Alfaleh H, Alnemer K, et al. Age and its relationship to acute coronary syndromes in the Saudi Project for Assessment of Coronary Events (SPACE) registry: The SPACE age study. *J Saudi Heart Assoc* 2012; 24: 9-16.
5. El-Menyar A, Zubaid M, Shehab A, Bulbanat B, Albustani N, Alenezi F, et al. Prevalence and impact of cardiovascular risk factors among patients presenting with acute coronary syndrome in the middle East. *Clin Cardiol* 2011; 34: 51-58.

6. Tzoulaki I, Elliott P, Kontis V, Ezzati M. Worldwide exposures to cardiovascular risk factors and associated health effects: current knowledge and data gaps. *Circulation* 2016; 133: 2314-2333.

7. Pello Lázaro AM, Cristóbal C, Franco-Peláez JA, Tarín N, Aceña Á, Carda R, et al. Use of proton-pump inhibitors predicts heart failure and death in patients with coronary artery disease. *PloS One* 2017; 12: e0169826.

8. Savarino V, Dulbecco P, de Bortoli N, Ottonello A, Savarino E. The appropriate use of proton pump inhibitors (PPIs): need for a reappraisal. *European Journal of Internal Medicine* 2017; 37: 19-24.

9. Gray SL, LaCroix AZ, Larson J, Robbins J, Cauley JA, Manson JE, et al. Proton pump inhibitor use, hip fracture, and change in bone mineral density in postmenopausal women: results from the Women's Health Initiative. *Arch Intern Med* 2010; 170: 765-771.

10. Hoorn EJ, van der Hoek J, de Man RA, Kuipers EJ, Bolwerk C, Zietse R. A case series of proton pump inhibitor-induced hypomagnesemia. *Am J Kidney Dis* 2010; 56: 112-116.

11. Charlot M, Ahlehoff O, Norgaard ML, Jorgensen CH, Sorensen R, Abildstrom SZ, et al. Proton-pump inhibitors are associated with increased cardiovascular risk independent of clopidogrel use: a nationwide cohort study. *Ann Intern Med* 2010; 153: 378-386.

12. Ho PM, Maddox TM, Wang L, Fihn SD, Jesse RL, Peterson ED, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA* 2009; 301: 937-944.

13. Gerson LB. Proton pump inhibitors and potential interactions with clopidogrel: an update. *Curr Gastroenterol Rep* 2013; 15: 329.

14. Goodman SG, Clare R, Pieper KS, Nicolau JC, Storey RF, Cantor WJ, et al. Association of proton pump inhibitor use on cardiovascular outcomes with clopidogrel and ticagrelor: insights from the platelet inhibition and patient outcomes trial. *Circulation* 2012; 125: 978-986.

15. Charlot M, Grove EL, Hansen PR, Olesen JB, Ahlehoff O, Selmer C, et al. Proton pump inhibitor use and risk of adverse cardiovascular events in aspirin treated patients with first time myocardial infarction: nationwide propensity score matched study. *BMJ* 2011; 342: d2690.

16. Juurlink DN, Gomes T, Ko DT, Szmitko PE, Austin PC, Tu JV, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. *CMAJ* 2009; 180: 713-718.

17. Ghebremariam YT, LePendu P, Lee JC, Erlanson DA, Slaviero A, Shah NH, et al. Unexpected effect of proton pump inhibitors: elevation of the cardiovascular risk factor asymmetric dimethylarginine. *Circulation* 2013; 128: 845-853.

18. Ari H, Ari S, Erdogan E, Tiryakioglu O, Ustundag Y, Huysal K, et al. A novel predictor of restenosis and adverse cardiac events: asymmetric dimethylarginine. *Heart Vessels* 2010; 25: 19-26.

19. Boger RH, Sullivan LM, Schwedhelm E, Wang TJ, Maas R, Benjamin EJ, et al. Plasma asymmetric dimethylarginine and incidence of cardiovascular disease and death in the community. *Circulation* 2009; 119: 1592-1600.

20. Lu TM, Chung MY, Lin MW, Hsu CP, Lin SJ. Plasma asymmetric dimethylarginine predicts death and major adverse cardiovascular events in individuals referred for coronary angiography. *Int J Cardiol* 2011; 153: 135-140.

21. Dean AG, Sullivan KM, Soe MM. OpenEpi: Open source epidemiologic statistics for public health. [cited 2015]. Available from: www.OpenEpi.com

22. Mayet A. Improper use of antisecretory drugs in a tertiary care teaching hospital: an observational study. *Saudi Journal of Gastroenterology* 2007; 13: 124-128.

23. Gupta E, Bansal D, Sotos J, Olden K. Risk of adverse clinical outcomes with concomitant use of clopidogrel and proton pump inhibitors following percutaneous coronary intervention. *Dig Dis Sci* 2010; 55: 1964-1968.

24. Bauman A, Ainsworth BE, Sallis JF, Hagströmer M, Craig CL, Bull FC, et al. The descriptive epidemiology of sitting: a 20-country comparison using the International Physical Activity Questionnaire (IPAQ). *American Journal of Preventive Medicine* 2011; 41: 228-235.

25. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the eighth joint national committee (JNC 8). *JAMA* 2014; 311: 507-520.

26. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2010; 33 (Supplement 1): S62-S69.

27. Wang Y, Lim Hn Caballero B. Use and interpretation of anthropometry. Modern nutrition in health and disease. 11th ed. South Holland (Netherlands): Wolters Kluwer Health Adis (ESP); 2012. p. 649-659.

28. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; 63 (25 Pt B): 2889-2934.

29. Kastorini CM, Georgousopoulou E, Vemmos KN, Nikolaou V, Kantas D, Milionis HJ, et al. Comparative analysis of cardiovascular disease risk factors influencing nonfatal acute coronary syndrome and ischemic stroke. *Am J Cardiol* 2013; 112: 349-354.

30. Panduranga P, Sulaiman K, Al-Zakwani I, Abdelrahman S. Acute coronary syndrome in young adults from Oman: results from the gulf registry of acute coronary events. *Heart Views* 2010; 11: 93-98.

31. Al Suwaidi J, Zubaid M, El-Menyar AA, Singh R, Asaad N, Sulaiman K, et al. Prevalence and outcome of cigarette and waterpipe smoking among patients with acute coronary syndrome in six Middle-Eastern countries. *Eur J Prev Cardiol* 2012; 19: 118-125.

32. Simon T, Steg PG, Gilard M, Blanchard D, Bonello L, Hanssen M, et al. Clinical events as a function of proton pump inhibitor use, clopidogrel use, and cytochrome P450 2C19 genotype in a large nationwide cohort of acute myocardial infarction: results from the French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) registry. *Circulation* 2011; 123: 474-482.

33. Shih CJ, Chen YT, Ou SM, Li SY, Chen TJ, Wang SJ. Proton pump inhibitor use represents an independent risk factor for myocardial infarction. *International Journal of Cardiology* 2014; 177: 292-27.

34. Shah NH, LePendu P, Bauer-Mehren A, Ghebremariam YT, Iyer SV, Marcus J, et al. Proton pump inhibitor usage and the risk of myocardial infarction in the general population. *PloS One* 2015; 10: e0124653.

35. Bhurke SM, Martin BC, Li C, Franks AM, Bursac Z, Said Q. Effect of the clopidogrel-proton pump inhibitor drug interaction on adverse cardiovascular events in patients with acute coronary syndrome. *Pharmacotherapy* 2012; 32: 809-818.

36. Huang B, Huang Y, Li Y, Yao H, Jing X, Huang H, et al. Adverse cardiovascular effects of concomitant use of proton pump inhibitors and clopidogrel in patients with coronary artery disease: a systematic review and meta-analysis. *Arch Med Res* 2012; 43: 212-224.

37. Kimura T, Morimoto T, Furukawa Y, Nakagawa Y, Kadota K, Iwabuchi M, et al. Association of the use of proton pump inhibitors with adverse cardiovascular and bleeding outcomes after percutaneous coronary intervention in the Japanese real world clinical practice. *Cardiovasc Interv Ther* 2011; 26: 222-233.

38. Ortolani P, Marino M, Marzocchi A, De Palma R, Branzi A. One-year clinical outcome in patients with acute coronary syndrome treated with concomitant use of clopidogrel and proton pump inhibitors: results from a regional cohort study. *J Cardiovasc Med (Hagerstown)* 2012; 13: 783-789.

39. Tsai YW, Wen YW, Huang WF, Chen PF, Kuo KN, Hsiao FY. Cardiovascular and gastrointestinal events of three antiplatelet therapies: clopidogrel, clopidogrel plus proton-pump inhibitors, and aspirin plus proton-pump inhibitors in patients with previous gastrointestinal bleeding. *J Gastroenterol* 2011; 46: 39-45.

40. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the Interheart study): case-control study. *Lancet* 2004; 364: 937-952.

41. World Health Organization. Global Physical Activity Surveillance, GPAQ show cards 2015. Available from: http://www.who.int/chp/steps/GPAQ/en/.