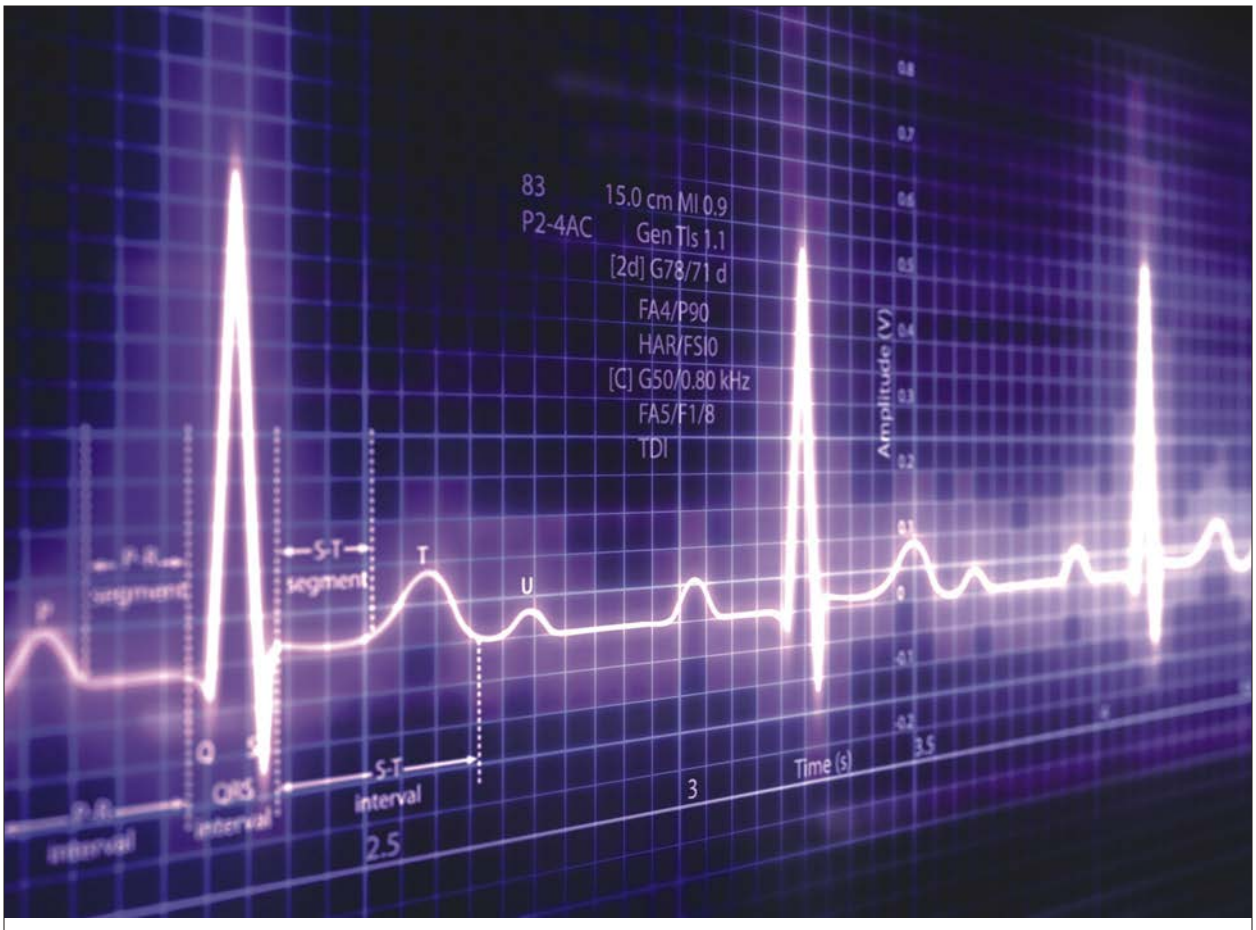

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Correlation Between Homocysteinemia and Coronary Heart Diseases in African Patients

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ABSTRACT

Many studies are related to high prevalence of hyperhomocysteinemia in Western Africa, suggesting the necessity to evaluate the consequence of this risk factor on diseases in this area. Some studies showed a strong association between hyperhomocysteinemia and stroke in these populations but studies on the relationship between hyperhomocysteinemia and coronary heart diseases are rare. The purpose of present study was to determine the correlation between hyperhomocysteinemia and coronary heart diseases in African patients. In this cross sectional study, we analyzed the relationship between hyperhomocysteinemia and coronary heart diseases just as other conventional risk factors in 207 admitted African patients divided into case and control groups based on the diagnosis of coronary heart disease, from January 2008 to June, 2011. There was no correlation between homocysteine level and conventional risk factors. The prevalence of hyperhomocysteinemia was 56.5% in patients with coronary heart diseases vs. 50% in patients without coronary heart disease, p = 0.37; OR = 1.30 (95% CI:0.72-2.33). However, 66.7% of patients with acute coronary syndrome vs., 48.4% of patients without acute coronary syndrome had hyperhomocysteinemia, p = 0.03; OR = 2.12 (1.04-4.32); in the same way, 75% of patients with myocardial infarction vs. 49.7% of patients without myocardial infarction had hyperhomocysteinemia, p = 0.03; OR = 3.03 (95% CI:1.06-8.7). The prevalence of hyperhomocysteinemia was 66.7% in patients with acute coronary syndrome vs. 40.7% in patients with stable angina pectoris, p = 0.03. These differences persisted after adjusting for age, gender and LDL cholesterol. There was a strong correlation between hyperhomocysteinemia and acute coronary syndromes in black African patients. Further prospective studies must be performed on this novel risk factor in this area.

Key words: Hyperhomocysteinemia, coronary heart diseases, acute coronary syndrome, novel risk factor, African patients

INTRODUCTION

Although, the incidence of cardiovascular diseases has been decreasing over the last quarter century in many high-income populations, its incidence in low-and middle-income populations, such as Togo, has been rising steadily, so that most of global deaths from cardiovascular diseases now occur in those populations (Murray and Lopez, 1994; Mahajan *et al*., 2009). A significant proportion of these deaths related to the cardiovascular diseases are due to stroke and coronary heart diseases (WHO, 2003) which management is still very difficult in our areas because of the

absence of adequate revascularization structures, thus the importance of the prevention which must be based on the fighting against the risk factors. According to the Braunwald's heart disease, 50% of all myocardial infarctions occur in individuals without overt hyperlipidemia, despite the importance of blood lipids (Ridker and Libby, 2011). Some studies experienced no high difference in the distribution of the conventional risk factors among patients with and without CHD (Khot *et al*., 2003; Greenland *et al*., 2003), suggesting the identification and evaluation of novel atherosclerotic risk factors such as C Reactive Protein, lipoprotein (a) and hyperhomocysteinemia (Balakumar *et al*., 2007; Ridker and Libby, 2011; Salari and Abdollahi, 2011).

If several epidemiologic studies have linked hyperhomocysteinemia with an increased risk for coronary artery disease (Lopez-Jimenez *et al*., 2007; Homocysteine Studies Collaboration, 2002; Balakumar *et al*., 2007), other studies find no effects of folic acid, B6, B12 substitution on the occlusive diseases (Ray *et al*., 2007; Ebbing *et al*., 2008; Imasa *et al*., 2009). However, individuals who have hyperhomocysteinemia are usually prescribed a vitamin regimen that includes vitamins B6, B9 and B12 (Eichholzer *et al*., 2006; Wang *et al*., 2007) in order to reduce homocysteine levels, but this treatment does not show a reduction of cardiovascular events in patients with a high cardiovascular risk (Ray *et al*., 2007; Spence *et al*., 2005).

In sub-Saharan Africa, if some clinical studies (Damorou *et al*., 2010) and population ones (Amouzou *et al*., 2004) revealed significant prevalence rates of hyperhomocysteinemia, few studies were carried out on the role of hyperhomocysteinemia in the occurring of ischemic heart diseases, thus the interest of present study. The purpose of this study was then to determine the relationship between hyperhomocysteinemia and CHD in West-African patients.

MATERIALS AND METHODS

Study population: This study was performed at the Department of Cardiology in the Campus University Teaching Hospital in Lome. This cross sectional study has included 207 cardiovascular patients of African descent with 69 (33.3%) patients of coronary heart diseases and 138 patients with no evidence of CHD, who were admitted between January 2008 and June 2011 and who were tested for the level of homocysteine. The CHD group was comprised of 27 stable angina pectoris, 22 unstable angina, 13 non ST-segment elevation myocardial infarction (NSTEMI) and 7 ST-segment elevation myocardial infarction (STEMI). Acute coronary syndrome (ACS) gathers unstable angina and Myocardial Infarction (MI) (Fox *et al*., 2006; Kushner *et al*., 2009; Wright *et al*., 2011). The diagnosis of CHD was based on non-invasive cardiac investigations and the measurement of cardiac biomarkers which were Troponin I and the MB isoenzyme of creatine phosphokinase (CK-MB); a Troponin I value >0.05 UI L^{-1} and that of CK-MB>25 UI L^{-1} were consider to be elevated. None of the patients benefited from coronary angiography. Then, the following criteria was used according to the ESC 2006 guidelines for the management of stable angina (Fox *et al*., 2006), the ACC 2011 guidelines for the management of patients with Unstable Angina/NSTEMI (Wright *et al*., 2011) and the ACC (2009) guidelines for the management of patients with STEMI (Kushner *et al*., 2009):

- **Stable angina pectoris:** Chest pain started by exercise and improved by rest or trinitrin (associated sometimes with a positive exercise ECG test)
- **Unstable angina:** Chest discomfort or anginal equivalent associated with ECG changes of ischemia (ST-segment depression or prominent T-wave inversion but no ST elevation and no Q wave) and normal cardiac biomarkers of necrosis

- **NSTEMI:** Chest discomfort or anginal equivalent associated with ECG changes of ischemia (but no ST-segment elevation and no Q wave) and elevated cardiac biomarkers of necrosis
- **STEMI:** Rest angina presenting with persistent ST-segment elevation and elevated cardiac biomarkers

The control group comprised 138 patients with chronic mitral valve prolapse matched for age and sex to the cases. There was neither stroke nor vascular diseases in these patients.

All the patients included in this study benefited from a Doppler-echocardiography. Patients with severe renal insufficiency were not included (creatinine clearance <30 mL min^{-1}) and all patients were free of drugs which would influence the plasma homocysteine levels, including folate or multivitamins.

The Body Mass Index (BMI) was calculated for each patient. The patients were classified into three groups: obese patients, with BMI≥30 kg m^{-2}; overweight patients, with 25 kg m^{-2} ≤BMI<30 kg m^{-2} and normal weight patients, with BMI are <25 kg m^{-2}. A patient was considered to be hypertensive if the systolic blood pressure≥140 mmHg or the diastolic blood pressure ≥90 mmHg. The supine blood pressure in both two arms was measured by a nurse using a manual sphygmomanometer (Mancia *et al.*, 2007).

Measurement of blood homocysteine levels: Blood samples were taking during fasting. Plasma homocysteine concentrations were measured by use of the Abbott's fluorescence polarization immunoassay. Normal values ranged between 5 and 15 μmol L^{-1}. Hyperhomocysteinemia was defined as homocysteine levels that were greater than 15 μmol L^{-1} (Akbari *et al.*, 2010) and patients with hyperhomocysteinemia were further classified into three groups: moderate hyperhomocysteinemia, with homocysteine levels between 16 and 30 μmol L^{-1}; intermediate hyperhomocysteinemia, with homocysteine levels between 31 and 100 μmol L^{-1} and severe hyperhomocysteinemia, with homocysteine levels greater than 100 μmol L^{-1} (Akbari *et al.*, 2010).

Measurement of other biochemical parameters: Serum total cholesterol, triglycerides, HDL and uric acid concentrations were determined enzymatically. Fasting glucose and creatinine levels were also measured in all the patients included in this study. Dyslipidemia was defined for a total serum cholesterol >200 mg dL^{-1}, or LDL-cholesterol >130 mg dL^{-1}, or triglycerides level >150 mg dL^{-1}, or HDL-cholesterol <40 mg dL^{-1}. Diabetes was defined for a fasting glucose >126 mg dL^{-1} twice and hyperuricemia was considered if uric acid level >70 m L^{-1}. Creatinine clearance was calculated with Cockcroft-Gault formula (Cockcroft and Gault, 1976).

Data analysis: Quantitative variables are presented as the mean±standard deviation and categorical variables are presented as the number and its corresponding percentage. The χ^2 test was used for categorical variables and the t test or the analysis of variance (ANOVA) for continuous variables.

Odds ratios (OR) and 95% confidence intervals (95%CI) were calculated using a logistic regression analysis. In multiple logistic regressions, all CHD, ACS and MI were consecutively considered as dependent variables, with appropriate adjustment for covariates. Pearson's Correlation coefficient (r) was determined by linear regression to evaluate the relationship between the homocysteine level and Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), total cholesterol, LDL, HDL, triglycerides, fasting glucose, uric acid and creatinine clearance. p-values <0.05 were considered to be statistically significant. All statistical analyses were performed using the CDC Epi-Info v. 3.5.3 software.

RESULTS

Characteristics of the study population: Table 1 summarized the characteristics of the study population. In the two groups (patients with CHD and patients without CHD) there was no significant difference in age or sex and there was no significant difference in conventional risk factors if taken individually such as arterial hypertension, diabetes, tobacco addiction, hyperuricemia and obesity. Only LDL cholesterol was significantly present in patients with CHD, p = 0.007, OR = 2.6 (95%CI = 1.24-5.52).

Mean age in this sample was 57.8±9.9 years (range: 24-90). There were 99 men vs. 108 female (sex ratio: 0.91). In the 207 patients included, 108 had hyperhomocysteinemia (52.2%) with 13% of moderate hyperhomocysteinemia and 87% of intermediary hyperhomocysteinemia. None of patients had severe hyperhomocysteinemia.

Table 1: Characteristics of the study group (n = 207)

Characteristics	CHD (+)	CHD (-)	p-value	OR (95% CI)
No.	69	138	-	
Age	57.9±10.8	57.8±10	0.94	
Male (n%)	29 (42)	58 (42)	-	-
BMI (kg m^{-2})	27.8±5.1	28.2±5.4	0.60	-
Systolic blood pressure (mmHg)	146.1±27.3	147.9±29.2	0.66	-
Diastolic blood pressure (mmHg)	91.0±14.5	93.9±15.8	0.20	-
BMI (kg m^{-2}) (%)				-
≥25 to <30	23 (33.3%)	53 (38.4%)	0.47	-
≥30	23 (33.3%)	47 (34.0%)	0.91	-
Hypertension n (%)	54 (78.3)	110 (79.7)	0.80	-
Fasting glucose (g L^{-1})	1.17±0.35	1.06±0.42	0.06	-
Serum lipids (mg dL^{-1})				-
Total cholesterol	220±50	210±40	0.12	-
Total triglycerides	130±45	128±58	0.80	-
HDL cholesterol	42±13	42±11	-	-
LDL cholesterol	165±47	150±45	0.02	-
Serum uric acid (mg L^{-1})	62.2±20.4	65.3±22.9	0.36	-
Creatinine clearance (mL min^{-1})	88.9±39.5	87.8±41.4	0.85	-
Diabetes No. (%)	8 (11.6)	11 (8)	0.39	-
Tobacco addiction No. (%)	2 (2.9)	6 (4.3)	0.89	-
Hypercholestrolemia No. (%)	47 (68.1)	75 (54.3)	0.057	1.7(0.94-3.33)
Low HDL n (%)	27 (39.1)	47 (34.0)	0.47	-
Hyper LDL n (%)	57 (82.6)	89 (64.5)	0.007	2.6(1.24-5.52)
Hypertriglyceridemia No. (%)	20 (29)	33 (23.9%)	0.43	-
Hyper uricemia n (%)	23 (33.3)	53 (38.4)	0.47	-

CHD: Coronary heart disease, *Data are Mean±SD, unless otherwise indicated, p-values are for comparison between patients with CHD and those without any CHD

Table 2: Association of conventional risk factors in two groups

Number of associated risk factor	CHD+ (n = 69)	CHD- (n = 138)	p-value
≤ 1	16 (23.2)	37 (28)	0.43
2	37 (53.6)	72 (54.5)	0.92
3	15 (21.7)	18 (13.6)	0.14
≥4	1 (1.4)	5 (3.8)	

CHD: Coronary heart disease, * Data are in No. (%)

Table 3: Correlation coefficients of plasma homocysteine level and metabolic components

	Homocysteine level (μmol L^{-1})		
Variables	r	SE	p-value
SBP (mmHg)	0.032	0.023	0.16
DBP (mmHg)	0.005	0.043	0.89
Total cholesterol (mg dL^{-1})	- 0.006	0.014	0.66
Triglycerides (mg dL^{-1})	0.0001	0.012	0.99
LDL (mg dL^{-1})	- 0.007	0.014	0.64
HDL (mg dL^{-1})	- 0.030	0.057	0.59
Fasting glucose (mg dL^{-1})	- 0.010	0.016	0.54
Uric acid (mg L^{-1})	0.044	0.032	0.16
Creatinine level (mg L^{-1})	0.473†	0.155	0.002†
Creatinine clearance (mL min^{-1})	- 0.023	0.024	0.33

DBP: Diastolic blood pressure, SBP: Systolic blood pressure, SE: Standard error, *Correlation between selected paired variables was analysis with Pearson's correlation, †Statistics for variables significantly associated with Homocysteinemia at $p<0.05$

Mean homocysteine level in this sample was 18.0±9.3 μmol L^{-1} (range: 6.2-76.2); it was 19.1±9.4 in men vs. 17.1±9.2 in female, p = 0.12. The prevalence of hyperhomocysteinemia was 64.6% in men vs. 41% in women, p<0.01, OR = 2.6 (1.48-4.65).

Mean creatinine clearance was 88.9±39.5 mL min^{-1} (range: 41.1-200) in the entire sample.

Association of conventional risk factors: The association of six conventional risk factors was checked in two groups: obesity, tobacco addiction, arterial hypertension, dyslipidemia, diabetes and hyperuricemia. There was no significant difference between two groups (Table 2).

Relationship between plasma homocysteine level and metabolic components: Pearson's correlation coefficients showed no correlation between plasma homocysteine level and metabolic components. Only creatinine was positively correlated with homocysteinemia (r = 0.473, p = 0.002). But this positive correlation was not found with creatinine clearance (Table 3).

Relationship between CHD and homocysteine level: Mean homocysteine level was 18.8±11.4 μmol L^{-1} in patients with CHD vs. 17.7±8.1 μmol L^{-1} in patients without CHD, p = 0.42. In the CHD's group, mean homocysteine level was 16.4±10.9 μmol L^{-1} in patients with stable angina pectoris vs. 20.3±11.6 μmol L^{-1} in patients with acute coronary syndrome, p = 0.10. The prevalence of hyperhomocysteinemia was 11 (66.7%) in patients with acute coronary syndrome vs. 28 (40.7%) in patients with stable angina pectoris, p = 0.03.

The association between hyperhomocysteinemia and all types CHD was not strong, OR= 1.30 (95% CI: 0.72-2.33). However, there was a strong association between hyperhomocysteinemia and ACS, OR = 2.12 (95% CI: 1.04-4.35), p = 0.03. There was also a strong association between hyperhomocysteinemia and MI, OR = 3.03, 95% CI: 1.06-8.7, p = 0.03. These differences persisted after adjusting for age, gender, arterial hypertension, LDL cholesterol and diabetes (Table 4).

Table 4: Relationship between hyperhomocysteinemia and different types of coronary heart diseases

	High Hcy (n%)	Normal Hcy No. (%)	OR* (95%CI)	p-value	OR†(95%CI)	p-value
CHD(+) n = 69	39 (56.5)	30 (43.5)	1.30 (0.72-2.32)	0.37	1.43 (0.75-2.72)	0.26
CHD(-) n = 138	69 (50.0)	69 (50.0)				
ACS(+) n = 42	28 (66.7)	14 (33.3)	2.12 (1.04-4.32)	0.03	2.36 (1.07-5.16)	0.03
ACS(-) n = 165	80 (48.5)	85 (51.5)				
MI(+) n = 20	15 (75.0)	5 (25.0)	3.03 (1.06-8.68)	0.03	4.12 (1.07-15.8)	0.03
MI(-) n = 187	93 (49.7)	94 (50.3)				

ACS: Acute coronary syndrome, CHD: Coronary heart disease, Hcy: Homocysteine level, MI: Myocardial infarction, *Unadjusted Odd ratios with 95%CI in brackets, †Odds Ratios adjusted for age, gender, LDL: Cholesterol

DISCUSSION

In a population of cardiovascular patients of African descent, we analyzed the relationship between hyperhomocysteinemia and CHD. The diagnosis of CHD was not based on angiographic findings; because this practice does not exist in Togo hospitals. Then the definitions of CHD were done according to non invasive investigations and the measurement of cardiac biomarkers (Fox *et al*., 2006; Kushner *et al*., 2009; Wright *et al*., 2011).

There is nowadays no consensus on the definition of hyperhomocysteinemia; then, this value varies among studies: Xiao *et al*. (2011) in China considered homocysteine level >12 μmol L^{-1} as hyperhomocysteinemia; however, Souissi *et al*. (2006) in Tunisia defined hyperhomocysteinemia for a plasma homocysteine concentration >17 μmol L^{-1} while Nevado and Imsa (2008) in Philippines chose a value >16 μmol L^{-1}. In this study, hyperhomocysteinemia has been defined for a plasma homocysteine level >15 μmol L^{-1} (Akbari *et al*., 2010) according to previous studies in Western African and Asian populations which mentioned a high prevalence of moderate hyperhomocysteinemia mainly due to folate deficiency (Amouzou *et al*., 2004; Akpalu and Nyame, 2009; Owusu *et al*., 2010).

In this study, there was no significant difference in age or sex and there was no significant difference in conventional risk factors if taken individually among CHD and control group. Only LDL cholesterol was significantly present in patients with CHD, OR = 2.6, $p<0.01$. The study of the association of conventional risk factors showed no significant difference in two groups. Previous large surveys related this fact and confirmed then the interest for checking novel risk factors in CHD patients (Ridker and Libby, 2011; Khot *et al*., 2003; Greenland *et al*., 2003).

We did not notice any correlation between homocysteine level and conventional coronary risk factors. Laraqui *et al*. (2002) also did not determine any correlation between homocysteinemia and conventional coronary risk factors among angiographically proven coronary patients. Xiao *et al*. (2011) reported a positive correlation between HDL and homocysteinemia but no correlation with other metabolic components. Like Xiao *et al*. (2011) a positive correlation between homocysteinemia and creatinine level has been shown in this study, but there was no correlation with creatinine clearance. The correlation of serum creatinine shown in this study is a well-documented finding in the literature and has been attributed to the direct association of creatinine production with homocysteine formation and the role of the kidney in the homocysteine metabolism hence, the mild-moderate elevations of homocysteine commonly observed in end-stage renal disease (Akpalu and Nyame, 2009).

In present study performed in African patients, there was no significant difference between mean homocysteine level and hyperhomocysteinemia between all coronary patients and control

group. But after having individualized acute coronary syndrome, this difference became significant. Mean plasma homocysteine concentration and hyperhomocysteinemia prevalence were significantly higher in CHD patients than controls in many other studies (Laraqui *et al.*, 2002; Xiao *et al.*, 2011) in which coronary patients were selected after coronary angiography contrary to this study; this difference can be explained by a possible bias in the selection of the coronary patients in present study; thus, several other non atherothrombotic causes can lead to a stable angina pectoris such as angina with "normal" coronary arteries, syndrome X and vasospastic angina (Fox *et al.*, 2006). This stresses the importance of the angiography in the diagnosis of coronary patients especially in those with stable angina. But such investigation is not available in our country. Control subjects in present study are patients; this may be a selective bias of no association between homocysteine level and all CHD. This difference can also be linked to the variability of blood sampling for homocysteine level; so El-Khayat *et al.* (2004) recommended the methylene-tetrahydrofolate reductase (MTHFR) mutation analysis for patients with variable or ambiguous homocysteine levels, as plasma levels are dependent on other factors as sample handling, which is not the case with DNA results.

The correlation between hyperhomocysteinemia and all CHD was weak in this study, OR = 1.30 (0.72-2.33). This correlation was stronger with ACS (OR = 2.12) and myocardial infarction (OR = 3.03) and these associations between hyperhomocysteinemia and ACS persisted after adjusting for main cardiovascular risk factors. Helfenstein *et al.* (2005) and Speidl *et al.* (2007) in Australia found similar result (OR = 4) for MI diagnosed in non invasive investigations. In the same way, Laghari *et al.* (2009) related that hyperhomocysteinemia increases the risk of MI in patients with type 2 diabetes. In china, Xiao *et al.* (2011) reported a positive correlation between hyperhomocysteinemia and angiographically proven coronary artery disease (OR: 1.61; 95%CI: 1.26 to 2.05) and Souissi *et al.* (2006) in Tunisia showed an OR of 2.99.

In Black Africa, studies on the relationship between plasma homocysteine level and cardiovascular diseases give controversial findings. Then, El-Mabchour *et al.* (2010) in Benin related that increased plasma homocysteine levels are associated with alcohol intake, hypertension and LDL cholesterol among 541 subjects in the same way, Akpalu and Nyame (2009) in Ghana found a positive correlation between plasma homocysteine and stroke and Abdel *et al.* (2009) in Sudan reported that mean total plasma homocysteine levels ($\mu mol\ L^{-1}$) were significantly higher in patients with CHD (17.64±11.68), recurrent venous thrombosis (5.06±10.55) than in healthy adult controls (7.85±3.39). However, many other studies related no association between increased homocysteine levels and stroke in these African populations (Okubadejo *et al.*, 2008; Glew *et al.*, 2004; Ebesunun *et al.*, 2008).

Other studies related that increased homocysteine level is associated with mortality and serious nonfatal outcomes in patients with unstable angina and NSTEMI (Nevado and Imasa, 2008).

Despite this strong correlation between hyperhomocysteinemia and CHD noted in several studies (Homocysteine Studies Collaboration, 2002), it is still unclear whether decreasing plasma homocysteine levels through diet or drugs may be paralleled by a reduction in cardiovascular risk (Ciaccio and Bellia, 2010). As a result, the clinical implications of this study may be misleading, as what is associated with increased levels of homocysteine is a previous ACS, not an increased overall cardiovascular risk. This has also been discussed in many other studies from high income countries, which suggested that increased homocysteine levels can be responsible for arterial ischemic events, such as MI, stroke or peripheral vascular disease (Ray *et al.*, 2007; Ebbing *et al.*, 2008; Imasa *et al.*, 2009; Spence *et al.*, 2005; Ciaccio and Bellia, 2010).

In fact, recent reports supported that increased homocysteine levels are not directly responsible for cardiovascular disease, but were merely present in individuals suffering for acute and/or chronic cardiovascular events, as a collateral finding (Clarke *et al*., 2010; U.S. Preventive Services Task Force, 2009); then, Pezshkeyan *et al*. (2005) showed that hyperhomocysteinemia has no important role in progress of atherosclerotic lesions. In addition, some recent trials did not find an effect of treatment with folic acid/vitamin B12 or vitamin B6 on total mortality or cardiovascular events and did not support the use of B vitamins as secondary prevention in patients with coronary artery disease (Ebbing *et al*., 2008; Imasa *et al*., 2009). Accordingly, the US Preventive Services found no evidence that treating people who have elevated homocysteine levels decreases their risk of subsequent cardiovascular events (U.S. Preventive Services Task Force, 2009). However to date, there is no large consensus on this question. Thus, further studies on the safety of such supplements are suggested. The carrying SUFOLOM 3 study is expected to give a consistent response to these questions (Blacher *et al*., 2005).

CONCLUSION

There was a strong correlation between hyperhomocysteinemia and acute coronary syndrome in Western African patients. It seems important to initiate prospective studies in these African populations where the prevalence of hyperhomocysteinemia is very high because of an increased in folic acid deficiency.

Conflict of interest: The authors have not transmitted any conflicts of interest.

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