ISSN: 0975-833X

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

Vol.6, Issue 09, September - 2014

Impact Factor: SJIF : 3.845
Indexing: Thomson Reuters: ENDNOTE

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 6, Issue, 09, pp.8621-8625, September, 2014

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

ANTI-INFLAMMATORY AND ANTI-LIPEMIC EFFECT OF STATIN THERAPY IN CORONARY ARTERY DISEASE PATIENTS WITH CALCIUM CALCIFICATION

[1]Noor N Nafie, [2]Basil O Saleh and [3]Sabah M Fadhil

[1]Clinical Biochemistry, College of Al-Rasheed Pharmacy, Baghdad, Iraq
[2]Clinical Biochemistry, Biochemistry Department, College of Medicine, Baghdad University, Iraq
[3]Ibn-Al-Bitar Hospital, Baghdad, Iraq

ARTICLE INFO

Article History:
Received 08th June, 2014
Received in revised form
16th July, 2014
Accepted 25th August, 2014
Published online 30th September, 2014

Key words:

Statin therapy,
3-Hydroxy-3-Methylglutaryl,
High Sensitive C-reactive Protein,
Lipid Profile Parameters,
HbA1c%.

ABSTRACT

Background: Inflammation plays a central role in atherosclerosis. In multiple epidemiologic studies, inflammatory biomarkers such as high sensitive C-reactive protein (hs-CRP), has been associated with increased risk of coronary heart disease (CHD) and it has been directly implicated in the pathogenesis of atherosclerosis The present study was designed to show the anti-inflammatory and anti-lipemic effect of 6-8 months of statin treatment via the measurement of serum hs-CRP and lipid profile parameters.

Subjects and Methods: This study was carried out at Biochemistry Department, College of Medicine, Baghdad University and at Ibn-Al-Bitar Hospital, Bagdad, Iraq, during the period from February 2013 to November 2013. It included 25 patients with coronary artery disease and who have had a mild to moderate coronary artery Ca score of < 400 agatston unit (AU) and not on statin treatment (GI). Twenty of these patients were putted on atrovastatin treatment for 6-8 months and regarded as GII. Investigations included serum measurement of high sensitive-(hs-) CRP, lipid profile parameters, fasting serum glucose and HbA1c in both groups.

Results: After the complete course of treatment with statin, the mean value of hs-CRP concentration of GI (2.77±2.83 mg/l) was decreased in comparison to those before treatment of the same patients group (GII, 3.04±3.45 mg/l), but did not reach the significant level. The mean value of HDL-cholesterol and VLDL-cholesterol concentrations were significantly increased in GII when compared to GI (P=0.001, P= 0.019, respectively). The glycemic index measured by HbA1c and fasting glucose did not differ significantly between both groups.

Conclusion: This study concluded the anti-inflammatory and anti-lipemic role of statin in coronary artery disease patients as reflected by significant increase of serum HDL-cholesterol. However, the insignificant effect of statin on serum hs-CRP concentration may need for longer period of its treatment.

INTRODUCTION

In the general population, vascular calcification is invariably localized to intimal atherosclerotic plaques, and the coronary artery calcification (CAC) score, as ascertained by electron-beam computed tomography (EBCT), reliably predicts plaque burden (Roche, 2005, Paumelle and Staels, 2007). The intimal calcification associated with atherosclerosis is an active, cell-mediated process, and is promoted by a variety of stimuli, such as oxidized low-density lipoprotein (Chopra and Flanders, 2009 and Thompson *et al*., 1999). Coronary calcium deposition, expressed as the coronary calcium score (CCS), is a precisely quantifiable and reproducible measure of underlying coronary artery disease which has been shown in large prospective studies to be strongly associated with the risk of future cardiovascular events (Roche, 2005). Despite the strong predictive value of CCS, radiation exposure and financial costs remain significant concerns. Therefore, discovery of biomarkers as surrogates for CCS would be highly beneficial. Classical biomarkers for cardiovascular disease such as high sensitivity C-reactive protein (hs-CRP), FVIIIc, fibrinogen and soluble intercellular adhesion molecule (sICAM) were found to be associated with CCS (Rodriguez-Moran and Guerrero-Romero, 2003). Other inflammatory markers like interleukin-6 and tumor necrosis factor-α often failed to show a correlation, suggesting that the inflammatory markers used to predict coronary heart disease fail to predict coronary artery calcification. Statins is the divertive of 3-hydroxy-3-methylglutaryl, HMG-CoA reductase inhibitors (Roche, 2005). These classes of drug are among the most widely prescribed classes of medicines in the world. Clinical trials over more than 2 decades have shown that statins are safe and prevent

Corresponding author: Basil O Saleh,
Clinical Biochemistry, Biochemistry Department, College of Medicine, Baghdad University, Iraq.

cardiovascular (CV) deaths, major CV events (stroke, myocardial infarction), and total mortality (Rodriguez-Moran and Guerrero-Romero, 2003). Statins are widely used in clinics for the treatment of atherosclerosis and other cardiovascular diseases (CVD). Statins attenuate the intracellular levels of cholesterol by inhibiting the rate-limiting enzyme 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase, either by competing with the normal substrate in the enzyme's active site, or by altering the conformation of the enzyme by binding to its active site (Dhawan and Sidhu, 2014). One of the mechanism of its action is through lipid-mediated effects. Statins exert their lipid-mediated action by decreasing the production of cholesterol and low-density lipoproteins (LDL), by up-regulation of LDL-receptors and uptake of circulatory LDL. Reduction in intracellular cholesterol induces activation of a protease, causing release of sterol regulatory element binding proteins (SREBPs) from the endoplasmic reticulum. SREBPs are then translocated to the nucleus, where they increase the expression of the LDL-receptor gene that controls the cholesterol homeostasis (Paumelle and Staels, 2007). The other mechanism of action is non-lipid-mediated pleiotropic effects. Statins empower multiple pleiotropic modes of action independent of lipid-mediated effects, mediated by their ability to block the generation of isoprenoid intermediates like farensyl pyrophosphate (FPP) and geranyl-geranylphosphate (GGPP) in vascular cells, which serve as lipid attachments for a variety of intracellular signaling molecules, like Rab and Rho (Dhawan and Sidhu, 2014, Chopra and Flanders, 2009). C-reactive protein (CRP) is an acute-phase protein (Thompson *et al.*, 1999) it synthesized by the liver in response to factors released by macrophages and fat cells (adipocytes). It is a member of the Pentraxin family of proteins and is not related to C-peptide or protein C. C-reactive protein was the first pattern recognition receptor (PRR) to be identified (Mantovani *et al.*, 2008).

High-sensitivity C-reactive protein (hs-CRP), the first acute phase protein detected by highly sensitive methods, is a sensitive marker of inflammation. The modest changes in serum hs-RP levels can be extremely useful in predicting cardiovascular and cerebrovascular hazardous events in essential hypertensive patients. This protein, hs-CRP, has been a novel risk factor for ischemic stroke, coronary ischemic disease, and overall mortality. In short hs-CRP is not only an important inflammatory marker but also a direct pathogenic factor of cardiovascular and cerebrovascular diseases (Wu *et al.*, 2013). Inflammatory mechanisms play a central role in all phases of atherosclerosis, from the initial recruitment of circulating leukocytes to the arterial wall to the rupture of unstable plaques, which results in the clinical manifestations of the disease. CRP may be involved in each of these stages by direct influencing processes like complement activation, apoptosis, vascular cell activation, monocyte recruitment, lipid accumulation and thrombosis. Each of these processes offers several mechanisms by which CRP may influence its progress (Paffen and DeMaat, 2006). Several studies have suggested CRP as biomarker for cardiovascular and cerebrovascular diseases. However, this protein also seems to be a mediator of atherosclerosis. Angiogenesis is a recognized mechanism involved in the development of complicated atherosclerotic plaques and previous studies have provided controversial data regarding the possible angiogenic or antiangiogenic effect of CRP. The hypothesis of CRP role in modulating angiogenesis was studied thoroughly, and as such, its presence in vascular regions of developing arterial plaques may be implicated in their progression to unstable, hemorrhagic lesions prone to rupture. While other studies show that CRP, at concentrations commonly found in the circulation of patients with active carotid disease, is highly pro-angiogenic both in vitro, and in vivo. Furthermore, CRP activates cell signaling and increases expression of key genes associated with angiogenesis (Turu *et al.*, 2008).

MATERIALS AND MATHODS

This study was conducted at the Department of Biochemistry, College of Medicine, University of Baghdad and at the Cardiologic Clinics of Ibn-Al-Bitar Hospital, Baghdad, Iraq, during the period from February 2013 to November 2013. A total of 45 subjects with suspected ischemic heart diseases (IHDs) were encountered, 25 of them who were not on statin derivatives treatment were included in this study and referred to as GI. These patients were investigated firstly for coronary artery calcium score and the percent of coronary artery stenosis (atherosclerotic lesion; less and more than 50 % as well as 70 % lesion) using Multi-Slice Computed Tomography Scanner (Brilliance 64, Philips Medical Systems). Twenty patients of this group (GI) were followed after starting them with atrovostatin therapy (10-40 mg/day) for 6-8 months and these patients represented by GII. Computed Tomography Scan for measurement of coronary artery Ca score was performed at Ibn-Al-Bitar Hospital, using a multi detector 64, CT scanner (Brilliance 64, Philips Medical Systems, The Netherlands).

Coronary Artery Calcification Scoring (CACS)

It has as its primary goal of the early detection of Coronary Artery Disease (CAD). CAD is the most common cause of death. Calcification within the coronary artery wall can be an indicator of the presence of coronary artery disease. CACS can detect calcium in many people with CAD at an early stage, before the symptoms of heart disease – such as angina, heart attack or sudden death occur. The first symptom of CAD in up to 25% of people is sudden death. A high calcium score increases the probability that a person may have a clinically significant coronary narrowing in a least one vessel. In some people, additional investigations such as stress testing may be warranted.

CT Imaging

1 ECG: is monitored before and through the scan
2 Contrast: Uniform distribution of contrast media throughout study.
3 Beta-Blockers: Sometimes required to lower heart rate (< 60 beat per minute).

CT techniques

The protocol for coronary (CTA) includes 0.067 mm slice thickness cuts obtained at 0.64 – millimeter mm interval with a tracing marker placed upon the ascending thoracic aorta. Usually, 100 ml of nonionic contrast media is injected at 6ml/s

through a large –bore intravenous access in the antecubital fossa. Reconstruction of the raw data was performed using the Philips work stations. Serial axial images, as well as the reconstructed multi planar and maximum intensity projections, were used primarily for diagnostic purposes. Three-dimensional volume rendering was also used to help diagnose patients. The calculator of radiation dose (3-12) megahertz (Msir) (Shaw *et al.,* 2003). Three-five millilitre (ml) of blood was aspirated from peripheral vein of each subject before and after statin treatment course (GI and GII) after an overnight fasting state (10 -12 hour).

The blood was divided into two parts, 2.5 ml was transferred into EDTA anti-coagulant tube with immediate mixing for HbA1c measurement, the second part was left to clot for 30 minute, and then the serum was obtained by centrifugation at 2500 X g for 15 minutes and stored at -20º C till the time of estimation of the hs-CRP concentration, fasting serum glucose and lipid profile parameters. hs-CRP (Latex) High Sensitive Assay was measured using the kits Cat. No. 04628918 190; Roch/Hitachi Cobas System. (Roach diagnostic GmbH, D-68298Mannheium for USA distribution, indianpolis, IN, English) according to method reported by (Roberts *et al.,* 2001). Calculation: Roach het/Hitachi systems automatically calculate the analyte concentration of each sample. Glycated Hemoglobin (HbA1c) was measured by spectrophotometric method by using the kit provided from (Human Gesellschaft fùr Biochemical and Diagnostica mbH Max-Planck-Ring 21.62505 Wiesbaden. Germany). Measurements of fasting serum glucose, total cholesterol, TG, HDL-cholesterol concentrations and the estimated levels of LDL-cholesterol, non-HDL-cholesterol and atherogenic index (AI) were performed using the methods reported by (Onat *et al.*, 2010).

Statistical Analysis of data was carried out using the available statistical package of SPSS-22 (Statistical Packages for Social Sciences- version 22). Data were presented in simple measures of mean and standard deviation (SD) values. The significance of difference of different means (quantitative data) were tested using Paired-t-test for difference of paired observations. Pearson correlation was calculated for the correlation between two quantitative variables with its t-test for testing the significance of correlation. Statistical significance was considered whenever the P-value was less than 0.05.

RESULTS

The mean (±SD) value of age of patients was 57.70±5.70 year. The mean value of coronary artery calcium score of patients before treatment was 100.3 AU. The mean (±SD) of body mass index (BMI) value of patients of GI was (31.2±5.0 Kg/m ^{2}) compared to the same patients after 4-6 months of statin treatment, GII (30.9±5.2 Kg/m^2), without significant difference. Table 1 shows the mean (±SD) values of the measured serum hs-CRP, HbA1c, fasting glucose and lipid profile parameters. The results of this study showed that the course of statin treatment (6-8 months) had a reduction effect on the serum levels of hs-CRP (GII; 2.77±2.83 mg/l) in comparison to that before treatment of the same patients group (GI; 3.04±3.45 mg/l), but did not reach the significant level. In addition, there was no significant effect of statin treatment on the measured glycemic index parameters, with the mean values of the fasting serum glucose and HbA1c of GII (6.66±1.98 mmol/l, 6.55±1.74 %, respectively) compared to those before treatment of the same patients group (GII; 7.02±1.42 mmol/l, 6.70±1.80 %, respectively). However, the results showed significant increased of serum concentrations of both HDL-cholesterol and VLDL-cholesterol in patients after complete course of treatment (GII, 1.39±0.34 mmol/l, 0.56±0.32 mmol/l, respectively) compared to their concentration before starting treatment (GI, 0.99±0.30 mmol/l, 0.34±0.18 mmol/l, P= 0.001, 0.019; respectively). The results also revealed that the mean values of serum non-HDL cholesterol and atherogenic index of patients of GII (2.78±2.23 mmol/l, 0.44±0.24, respectively) did not differ significantly from that of GI (2.77±2.30 mmol/l, 0.52±0.23, respectively).

DISCUSSION

The present study showed a non significant reduction in the concentration of hs-CRP after complete course of statin treatment in ischemic heart patients who had mild to moderate coronary artery calcification (Fig.1). Statin has a reduction effect on serum level of (hs-CRP) through various pleiotropic effects that include improvement in endothelial dysfunction, increased expression of endothelial nitric oxide synthase (eNOS), enhanced bioavailability of nitric oxide (NO), potent antioxidant potential and anti-inflammatory properties. Therefore pleiotropic effects of the statins improve vascular

Table 1. Statin treatment and Biochemical Parameters

Studied Parameter	Group I-before statin Treatment (n=20)	Group II-after statin Treatment (n=20)	P-value
hs-CRP (mg/l)	3.04±3.45	2.77±2.83	0.716^{NS}
HbA1c%	6.70±1.80	6.55±1.74	0.789^{NS}
Fasting serum glucose (mmol/l)	7.02±2.41	6.61±1.98	0.411^{NS}
Total cholesterol (mmol/l)	4.64±0.89	4.43±1.29	0.409^{NS}
TG (mmol/l)	1.65±1.01	1.75±0.71	0.718^{NS}
HDL-C (mmol/l)	0.99±0.30	1.39±0.34	0.001$^{\bullet}$
LDL-C (mmol/l)	3.13±1.07	2.80±1.27	0.353^{NS}
VLDL-C (mmol/l)	0.34±0.18	0.56±0.32	0.019$^{\bullet}$
Non-HDL (mmol/l)	2.77±2.30	2.78±2.23	0.988^{NS}
Atherogenic index	0.52±0.23	0.44±0.24	0.231^{NS}

Paired t-test showed significant difference in serum level of HDL-C and VLDL-C between the two groups P=0.001, P= 0.019, respectively, NS non significant differences.

relaxation, promote new vessel formation, and inhibit platelet aggregation and reducing vascular inflammation. It is noteworthy that the pleiotropic properties of the statins have r relaxation, promote new vessel formation, and inhibit platelet aggregation and reducing vascular inflammation. It is noteworthy that the pleiotropic properties of the statins have been beneficial in a variety of diseases that involve a number of organs and organ systems. By enhancing eNOS expression and thereby increasing NO bioavailability, reducing oxidative stress and proinflammatory cytokine production (Gabbasov *et al.,* 2007). Other study indicated that maximal doses of atorvastatin lower serum hs-CRP levels by substantially decreasing the median hs- CRP serum with no significant effect on the median hs-CRP production rate (Thongtang *et al.,* 2013)

Careful review reported by Yousuf et al. explained that statins are likely to mutually benefit individuals with or without elevated hs-CRP levels. Further, the use of achieved h-CRP level to guide the intensity of lipid-modifying therapy is a hypothesis that is as yet unproven as a strategy. At this time, the existing evidence remains insufficient to justify widespread use of hs-CRP in clinical practice. It may be time to remove h-CRP from the list of potential bandits of atherosclerosis. Further investigation with anti-inflammatory therapies may help bring vascular inflammation closer to the bedside and refine the role of hs-CRP as a therapeutic target in preventing CVD (Yousuf, 2013). Data in (Table 1) revealed the effect of course of statin treatment (6-8 months) on the levels of the measured glycemic index and lipid profile parameters with no significant changes in the mean values of the serum fasting glucose and HbA1c after treatment compared to those before treatment of the same patients group. Some studies found the median HbA1c values were minimally, but significantly higher in the rosuvastatin than the placebo group (5.9% versus 5.8%, respectively), and the incidence of physician-reported diabetes was significantly higher in the rosuvaStatin arm (Ridker *et al.,* 2008). The data also showed significant increased of serum of HDL-cholesterol and VLDL-cholesterol concentration in patients after complete course of treatment compared to their concentration before starting treatment, these finding may explain the response of IHD patients to statin treatment through main mechanism of action through elevation of HDL value after follow up and this improved important role of HDL as anti-atherogenic from progression of CVD.

There are many studies suggested the important of statin treatment in CAD through the following hypothesis: Francis and Pierce, 2011 suggested the role of HDL in Plaque regression through using statin treatment, it is now known that plaques are able to regress. Plaque reversal occurs by removal of lipids and necrotic material, endothelial repair, or halt of vascular smooth muscle cell proliferation. Several mechanisms explain this reversal, such as high-density lipoprotein cholesterol (HDL-C) action, destruction of foam cells and macrophages in lymph nodes and restoration of endothelium by neighboring cells or circulating progenitors (Francis and Pierce, 2011). There is little information about the effect of statin on VLDL-cholesterol concentration and its relation to atherosclerosis. However, literature documented that some studies have hypothesized that atorvastatin could increase TG-rich VLDL uptake by the liver. Accordingly, some authors have shown that atorvastatin increases the VLDL-apolipoprotein (apo) B fractional catabolic rate (FCR) but has no effect on its production (Watts *et al.,* 2003). Another study suggested that VLDL-cholesterol is associated with CAC independent of established CVD risk factors, particularly in women, and has value even beyond apoB levels and when TGs are elevated. Further study is warranted of serum VLDL-C and other markers of TG-rich lipoproteins in predicting CVD in high-risk patients and as markers in genomic and therapeutic trials (Prenner *et al.,* 2014). Future investigation regarding their pharmacodynamic properties is warranted in light of the recent observation that these treatments can influence VLDL and HDL structure and function in a potentially beneficial manner after statin treatment. In conclusion The present study conclude that 6-8 months of statin treatment is not adequate for significant reduction in serum level of culprit inflammatory factor, the CRP. Statin emphasized its anti-lipiemic therapy and anti-inflammatory effect through significant increasing of serum levels of HDL-cholesterol and VLDL-cholesterol in IHD patients with mild to moderate vascular calcification. Limitation of the study are the difficulties in follow up of statin treatment for 10-12 months and in coronary artery calcium calcification score measurement after statin treatment because of safety consideration.

Acknowledgment

The authors would like to introduce their thanks and gratitude to all members of Laboratory Teaching of Ibn-Al-Bitar Hospital for their assistance in blood separation, collection and storage. We also would like to express high gratitude to all consultant cardiologists in this hospital for their help in patients selection and Ca CT-scan scoring.

REFERENCES

Chopra V, and Flanders, SA. Does statin use improve pneumonia outcomes? Chest, 2009; 136(5): p. 1381-8.

C-reactive protein exerts angiogenic effects on vascular endothelial cells and modulates associated signalling pathways and gene expression. BMC Cell Biology 2008, 9:47.

Dhawan V, Sidhu H. Statins: are they wonder drugs? *The British Journal of Cardiology*, 2014; 21(40): p. doi: 10.5837.

Francis AA and Pierce GN. An integrated approach for the mechanisms responsible for atherosclerotic plaqueregression. *Exp Clin Cardiol*, 2011; 16(3): p. 77-86.

Gabbasov ZA, *Agapov AA, Saburova OS, Komlev AE, Soboleva EL, Akchurin RS.* Circulating stromal osteonectin- positive progenitor cells and stenotic coronary atherosclerosis. Can *J Physiol Pharmacol*, 2007; 85(3-4): p. 295-300.

Mantovani A, Garlanda C, Doni A, Bottazzi B. Pentraxins in Innate Immunity: From C-Reactive Protein to the Long Pentraxin PTX3 J Clin Immunol (2008) 28:1–13 DOI 10.1007/s10875-007-9126-7.

Onat A, Can G, Kaya H, HergenÃ§ G. Atherogenic index of plasma" (log10 triglyceride/high-density lipoprotein-

cholesterol) predicts high blood pressure, diabetes, and vascular events. J Clin Lipidol. 2010;4(2):89-98.

Paumelle R and Staels B. Peroxisome proliferator-activated receptors mediate pleiotropic actions of statins. *Circ Res*, 2007; 100(10): p. 1394-5.

Prenner SB, Mulvey CK, Ferguson JF, Rickels MR, Bhatt AB, Reilly MP. Very low density lipoprotein cholesterol associates with coronary artery calcification in type 2 diabetes beyond circulating levels of triglycerides. Atherosclerosis, 2014; 236 (2):244–250.

Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ, JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008 Nov 20;359(21):2195-207. doi: 10.1056/NEJMoa0807646.

Roberts WL, Moulton L, Law TC, Farrow G, Cooper-Anderson M, Savory J, *et al.* Evaluation of nine automated high-sensitivity C-reactive protein methods: Implications for clinical and epidemiological applications. Part 2. Clin Chem. 2001;47:418–25.

Roche VF. Antihyperlipidemic Statins: A Self-Contained, Clinically Relevant Medicinal Chemistry Lesson. *American Journal of Pharmaceutical Education*, 2005; 69(4): p. 546-560.

Rodriguez-Moran M and Guerrero-Romero F. Elevated concentrations of C-reactive protein in subjects with type 2 diabetes mellitus are moderately influenced by glycemic control. *J Endocrinol Invest*, 2003; 26(3): p. 216-21.

Shaw LJ, Raggi P, Schisterman E, Berman DS, Callister TQ. Prognostic value of cardiac risk factors and coronary artery calcium screening for all-cause mortality. Radiology. 2003 Sep;228(3):826-33. Epub 2003 Jul 17.

Thompson D, Pepys MB, Wood SP. The physiological structure of human C-reactive protein and its complex with phosphocholine. Structure. 1999 Feb 15;7(2):169-77.

Thongtang N, Diffenderfer MR, Ooi EM, Asztalos BF, et al. Effects of atorvastatin on human C-reactive protein metabolism. Atherosclerosis. 2013;226:466-70.

Turu MM, Slevin M, Matou S, West D, Rodríguez C, Luque A, Grau-Olivares M, Badimon L, Martinez-Gonzalez J, Krupinski J.

Watts GF, Barrett PH, Ji J, Serone AP, Chan DC, Croft KD, Loehrer F, Johnson AG. Differential regulation of lipoprotein kinetics by atorvastatin and fenofibrate in subjects with the metabolic syndrome. Diabetes 2003;52:803–811.

Wu A, Zhang D, Gao Y, Lou L, Zhu H, Chai L, Lv X, Sun Y, Zhu L, Wang S .The Correlation between High-Sensitivity C-Reactive Protein, Matrix Metallopeptidase 9, and Traditional Chinese Medicine Syndrome in Patients with Hypertension.Evid Based Complement Alternat Med 2013; 28: P 780937. Epub 2013 Mar 28.

Yousuf O, Mohanty BD, Martin SS, Joshi PH, Blaha MJ, Nasir K, Blumenthal RS, Budoff MJ. High-Sensitivity C-Reactive Protein and Cardiovascular Disease J Am Coll Cardiol. 2013;62(5):397-408.

****

OPEN ACCESS

ISSN-0975-833X

Directory of Research Journals Indexing

Google scholar

YAHOO! INDIA www.yahoo.in

OCLC WorldCat

Scribd

A division of the American Chemical Society

New Jour Electronic Journals & Newsletters

DRJI

INDEX COPERNICUS INTERNATIONAL

Journal Seek

HINARI Research in Health

DOAJ DIRECTORY OF OPEN ACCESS JOURNALS

ULRICHS GLOBAL SERIALS DIRECTORY