www.jmscr.igmpublication.org

Impact Factor 3.79
ISSN (e)-2347-176x

IGM Publication

Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

A Review Based Study on Risk factors for Coronary Heart Disease

Authors

Keesari. Rohali[1], G. Likitha[2], A. Alekhya[3], Venkata Sravani Polamraju[4], Dr.P.Srinivas[5]

[1,2,3]Department of Pharm.D (Doctor of Pharmacy),
Malla Reddy Institute of Pharmaceutical Sciences, Hyderabad, Telangana.
[4]Assistant Professor, Department of Pharm.D and Pharmacy Practice,
Malla Reddy Institute of Pharmaceutical Sciences, Hyderabad, Telangana.
[5]Duty Medical Officer, Narayana Hrudayalaya Hospitals, Hyderabad, Telangana.

Corresponding Author
Keesari. Rohali
Department of Pharm.D (Doctor of Pharmacy),
Malla Reddy Institute of Pharmaceutical Sciences, Hyderabad, Telangana

Abstract

Coronary heart disease (CHD) is a major cause of morbidity and mortality and has various risk factors. CHD has a multi-factorial etiology with many of the risk factors being influenced by the lifestyle. The cost of management of CHD is a significant economic burden and so prevention of coronary heart disease is very important step in the management. In recent years, attempts to combat this disease have extended beyond treatment and have centered mainly on prevention. The risk factors for CHD are classified into: Modifiable, Non Modifiable and Emerging risk factors. The modifiable risk factors are hypertension, diabetes mellitus(DM), dyslipidaemia, tobacco smoking, obesity, sedentary life style. The non-modifiable risk factors include advancing age, sex, family history of cardiovascular events. The emerging risk factors include elevated homocysteine, small dense lipoprotein (Lpa), plasminogen activator inhibitor, inflammatory markers such as C-reactive protein, infectious agents like chlamydia. The risk factors of CHD, if identified at an early stage can play a significant role in planning primary and secondary preventive strategies for CHD and its complications. *This review focuses on the modifiable and non modifiable risk factors and also sheds light upon the emerging risk factors contributing to the development of coronary heart disease.*

Keywords: *Coronary Heart Disease, Modifiable risk factors, Non modifiable risk factors, Emerging risk factors, Prevention.*

CHD is the major threat to modern society and, according to estimate, it will remain so at least by 2020. CHD or ischemic heart disease occurs because of reduced coronary blood flow or complete circulatory obstruction in a part of the myocardium. This leads to myocardial lesions, which determine the symptomatology, clinical course and outcome of the disease. According to symptomatology and clinical course, ischemic heart disease is categorized into acute coronary syndrome, non-Q wave ST-segment elevation myocardial infarction (STEMI), non-Q wave non-ST-segment elevation myocardial infarction (NSTEMI), unstable angina, and stable angina. In almost 99% of cases, CHD is caused by atherosclerosis, and less frequently by spasm that is usually idiopathic, or by a drug such as cocaine. Atherosclerosis is characterized by subintimal plaques that can reduce or obstruct blood flow through the vessel.[1]The risk factors for CHD are classified into; Modifiable, Non Modifiable and Emerging risk factors.The modifiable risk factors are Hypertension, Diabetes Mellitus(DM), Dyslipidaemia, Tobacco Smoking, Obesity, Sedentary life style. The non-modifiable factors include Advancing age, Sex, Family history of premature cardiovascular events. The emerging risk factors include elevated Homocysteine, small dense Lipoprotein (Lpa), Plasma fibrinogen, inflammatory markers such as C-reactive protein, infectious agents like Chlamydia.[2]

1. Modifiable Risk Factors

a. Hypertension :

Hypertension is a well-established risk factor for CHD. [3] Hypertension, whether labile or fixed, borderline or definite, casual or basal, systolic or diastolic, at any age regardless of gender, is the most common and a powerful contributor to atherosclerotic coronary heart disease.[4] Hypertension is classified as either primary (essential) hypertension or secondary hypertension; about 90–95% of cases are categorized as primary hypertension which means high blood pressure with no obvious underlying medical cause.[5] The remaining 5–10% of cases categorized as secondary hypertension is caused by other conditions that affect the kidneys, arteries, heart or endocrine system. A number of factors increase Hypertension, including obesity, insulin resistance, high alcohol intake, high salt intake (in salt-sensitive patients), aging and perhaps sedentary lifestyle, stress, low potassium intake, and low calcium intake.[6][7]Furthermore, many of these factors are additive, such as obesity and alcohol intake. Higher levels of blood pressure are typically associated with abnormal cholesterol levels, greater body mass index, and an increased prevalence of diabetes. The main mechanism of action through which hypertension leads to the development of atherosclerosis is mechanical damage to endothelial cells due to altered hemodynamics, i.e.enhanced force of the blood flow,or to the formation of whirls at vascular bifurcations.[1] Dietary and lifestyle changes can improve blood pressure control and decrease the risk of health complications, although drug treatment is still often necessary in people for whom lifestyle changes are not enough or not effective. The treatment of moderately high

arterial blood pressure (defined as >160/100mmHg) with medications is associated with an improved life expectancy.[8][9]

b. Diabetes Mellitus :

Diabetes mellitus is an established risk factor for coronary heart disease.[10] Hyperlipoproteinemia, hypertriglyceridemia in particular, i.e. elevated levels of very - low density lipoprotein (VLDL) particles and atherogenic LDL deriving from VLDL, with concurrent decrease in the level of protective HDL particles, are quite common in diabetic patients. LDL particles that undergo non enzymatic glucosylation due to elevated blood glucose are fast and intensively phagocytosed by macrophages, thus stimulating atherogenesis. Hyperinsulinemia causes damage to vascular endothelium. [1] Hyperglycemia results in multiple biochemical changes, a few of which we will list: The glycosylation of proteins in the arterial wall is thought to contribute to diabetic atherosclerosis. The nonenzymatic reaction between glucose and arterial wall proteins results in the formation of advanced glycation end products (AGE), process that is enhanced in hyperglycemia. AGEs are thought to directly interfere with endothelial cell function and accelerate atherosclerosis. Additionally, hyperglycemia increases the formation of reactive oxygen species (ROS); these ROS inhibit endothelial production of nitric oxide, a potent vasodilator and regulator of platelet activation.[11] Furthermore, those ROS prevent the migration of vascular smooth muscle cells into the intimal plaques, a step necessary to the stabilization of coronary plaques. Such plaques then carry an increased risk of rupture, as is known of diabetic coronary plaques.[12] Shechter et al. were able to demonstrate the role of glucose as an independent predictor of platelet dependent thrombosis.[13] Furthermore, insulin has been found to increase serum concentrations of Plasminogen Activator Inhibitor type I (PAI-1) [14] which has been shown to correlate with impaired fibrinolysis.[15] A regular program of physical activity and weight control should be prescribed to improve insulin sensitivity. Use of thiazolidinediones may be considered early in the course of hypoglycemic therapy.[16]

c. Dyslipidemia:

Dyslipidemia is a primary, widely established as an independent major risk factor for coronary artery disease (CAD) and may even be a prerequisite for CAD, occurring before other major risk factors come into play.[17] Dyslipidemia is defined as an abnormal plasma lipid status. Common lipid abnormalities include elevated levels of total cholesterol, LDL-cholesterol, lipoprotein (a), triglyceride, HDL-cholesterol and a preponderance of small dense LDL particles. These abnormalities can be found alone or in combination.[1] A recent study of Gupta et al[19] indicated that elevated TC and LDL cholesterol, low HDL cholesterol and triglycerides was associated with CAD. Most international studies e.g. the MRFIT Study Group;[20] Seven Countries Study [21] and Framingham Study [22][23] emphasized the importance of elevated LDL and TC in the

development of CAD. A study that considered CHD prediction using TC, LDL-C, TC/HDL-C ratio, and LDL-C/HDL-C ratio[24] concluded that "total cholesterol/HDL is a superior measure of risk for CHD compared with either total cholesterol or LDL cholesterol, and that current practice guidelines could be more efficient if risk stratification was based on this ratio rather than primarily on the LDL cholesterol level." Primary and secondary prevention studies including the Coronary Primary Prevention Trial, Helsinki Heart Study, and the Coronary Drug Project have shown that lowering the atherogenic low density lipoproteins (LDL) and very low density lipoproteins (VLDL) whilst raising the high density lipoproteins (HDL) significantly decreases the risk for coronary disease.[25]

d. Tobacco Smoking:

Tobacco smoking is a well established major preventable risk factor for coronary heart disease (CHD).[26] Research has shown conclusively that smoking accelerates arteriosclerosis (hardening of the arteries) and atherosclerosis (a type of arteriosclerosis characterized by fatty deposits in the artery walls), increasing the risk of heart disease, stroke, and peripheral vascular disease.[27] Consequently, smokers have a higher risk of cardiovascular disease in general, and heart attacks in particular, than non-smokers.[27] Smoking also affects serum cholesterol. Smokers tend to have decreased levels of high-density lipoproteins (HDL - the "good cholesterol) and increased levels of low-density lipoproteins (LDL- the "bad' cholesterol) and triglycerides (a blood fat), thereby raising the risk and severity of atherosclerosis.[28] Cigarettes may promote atherosclerosis by a variety of mechanisms. Several ingredients of tobacco lead to the narrowing of blood vessels, increasing the likelihood of a blockage, and thus a heart attack . According to a study by an international team of researchers, people under 40 are five times more likely to have a heart attack if they smoke.[29] Smoking also increases the levels of carbon monoxide, a poisonous gas that is inhaled in smoke. Over the long time, this increased level of carbon monoxide from the inhaled smoke itself contributes to damaging the lining of the blood vessels and accelerates the process of atherosclerosis.[28] Cigarette smoking can also enhance platelet activity, which in turn may lead to the formation of thrombi, and an increase in plasma fibrin and hematocrit, thus contributing to blood viscosity.[1] Education and counselling by physicians been found to be effective in decreasing the risk of tobacco use.[30]

e. Obesity:

Obesity increases the risk of developing CHD. Many studies have found that obesity is an independent risk factor for CHD. Obesity increases the risk of developing diabetes, impaired glucose tolerance, raised cholesterol and high blood pressure. Obesity is well known to cause the elevation of LDL and triglycerides with a decrease in HDL; and it promotes atherosclerosis.[31][32] In extremely obese persons, low level of protective HDL-cholesterol is an independent risk factor for the hyperinsulinemia combined with

hyperglycaemia. Adipose tissue in obese people is the biggest endocrine organ in the body. Secretion of various hormones (the most important leptin), leads to insulin resistance and the occurrence of type 2 diabetes. Weight gain increases proportionately with blood pressure and all its harmful effects on the walls of blood vessels. Excessive calories intakes, which are, not spend but stored in our body as fat. It is believed that cholesterol and fatty acids in the blood have a crucial effect on the development of atherosclerotic plaques in blood vessels.[1] Weight reduction was associated with an improvement in risk factors and favorable changes in triglycerides, high and low-density lipoprotein levels and blood pressure.[33][34] These observations suggest a beneficial effect of weight reduction, but direct evidence that weight loss reduces the risk of CHD is currently not available . Because of the difficulty of achieving and maintaining weight loss, the prevention of obesity is of utmost importance.

f. Sedentary Lifestyle:

Sedentary life style- with resultant poor cardiopulmonary fitness-has also implicated as a coronary risk factor.[35]Inadequate physical activity decreases the concentration of HDL .[1] Sedentary lifestyle, and inactivity may contribute to higher blood pressure, elevated blood lipid levels, and insulin resistance associated with glucose intolerance in diabetics (insulin resistance or metabolic syndrome). Exercise to the level of about 300 kcal three times a week is useful in improving maximal oxygen uptake, improving cardiorespiratory efficiency, promoting collateral artery formation, and promoting potential alterations in the risk of ventricular fibrillation, coronary thrombosis, and improved tolerance to stress. Epidemiologic studies have found that mortality is directly related to resting heart rate and a low heart rate difference between resting and maximal exercise heart rate, and inversely related to exercise heart rate.[36] A regular exercise program has been shown to reduce all-cause and cardiac mortality. Light to moderate exercise, of the type enhancing cardiopul- monary fitness (vigorous walking, jogging, bicycling, swimming) may be protective if approached properly to avoid potential hazards especially when combined with reasonable alterations in diet and smoking habits.[35]

2. Non-Modifiable Risk Factors

a. Advancing Age:

The absolute risk of CHD and other atherosclerotic diseases is higher in the elderly compared with any other age group.[37] Among CV diseases, more than 75-80% of the population aged 65 and over die from vascular diseases, in particular coronary heart disease. The most important pathologic cause is atherosclerosis, which results in coronary and cerebrovascular events and other major health problems.[38] Elderly individuals have different properties of lipid metabolism compared with younger individuals, as physiological changes can be seen in the lipid profile of the elderly. In general, atherogenic particles increase with age. Age-related changes in the total serum cholesterol

concentration primarily result from an increase in LDL cholesterol levels. Apolipoprotein B and LDL cholesterol show a progressive increase with age.[39] The mechanisms responsible for the progressive age-related elevation in LDL cholesterol have not been fully explained; however, various data suggest a decrease in the fractional catabolic rate of LDL cholesterol as playing a primary role. This reduction in LDL cholesterol catabolism is believed to result from diminished activity of hepatic LDL cholesterol receptors.[40] Triglycerides (TG) increase with age, and reaches maximum values in men at age 50-59 and in women at 60-69. In contrast, HDL cholesterol levels do not vary much with age, being approximately 10 mg/dL higher in women than men throughout their lifetime.[39] Aging is also associated with changes in the mechanical and structural properties of the vascular wall, which leads to the loss of arterial elasticity and reduced arterial compliance and may subsequently lead to coronary artery disease.[41]

b. Sex:

There is a marked difference in coronary heart disease (CHD) risk between sexes.[42] CHD is 2 to 5 times more common in middle -aged men than in women, and this sex ratio varies between populations.[43] In both sexes, the risk of CHD increases markedly with age. At younger ages, blood pressure and LDL cholesterol are lower among women than men and throughout life women smokeless and have higher HDL cholesterol levels. One further large difference between men and women is that levels of central obesity, as measured by waist hip ratios, are very much smaller among women.[37] The absolute risk of CHD is lower in women at all ages up to the very elderly when disease rates almost converge. Over the age of 55 years, the decrease in estrogen production after menopause changes the female lipid metabolism toward a more atherogenic form by decreasing the HDL cholesterol level and by increasing LDL and total cholesterol, triglyceride, and lipoprotein(a) levels.[40][44] In addition to the lipid effect, estrogen may have cardioprotective effects through glucose metabolism and the hemostatic system, and it may also have a direct effect on endothelial cell function.[46][47] Women have more obesity, higher total cholesterol and more diabetes than men, and over the age of 65 years have more hypertension than men. The major clinical and public health challenges are how to reduce the risk of CHD among middle-aged men closer to that in women and how to prevent the marked increase in CHD risk with aging, particularly in women. The HDL/total cholesterol ratio was the major determinant of the sex difference in CHD risk, and the increase in risk factor levels, particularly in serum cholesterol and blood pressure, explained a substantial part of the age-related increase in CHD incidence and mortality. Both HDL and total cholesterol levels can be modified by dietary and lifestyle changes.[48][49] The increase in serum cholesterol and blood pressure with age is not an inevitable physical phenomenon, it can be prevented.[50] Reduction in smoking would also reduce CHD incidence and mortality markedly, particularly in men. In addition to lifestyle

changes, cardiovascular risk can be controlled by pharmacological means, such as antihypertensive and cholesterol-lowering drug treatments. [51][52][53][54]

c. Family History of Cardiovacular events:

A family history of coronary heart disease (FHCHD) has been conclusively shown to be an independent risk factor for coronary heart disease.[55][56] Evidence exists indicating an increased risk of CHD in close relatives of persons who experience a heart attack early in life, e.g., prior to age 50.[57][58] There are numerous examples of multiple premature attacks within families. In contrast, there is little evidence for familial aggregation when the disease first occurs late in life. It is likely that much of this predisposition is mediated by familial resemblances in key risk factors, e.g., hypercholesterolemia, hypertension, cigarette smoking.[59] Obviously, most of these predisposing influences are under both environmental and genetic control. Families share not only genes, but also living habits, e.g., "rich" diet, cigarette smoking, sedentary living habit . Hence the preventive approach, through early detection and control of risk factors, must be a family affair.[35]

3. Emerging Risk Factors

a. Homocysteine:

Over the past 10 years many studies have demonstrated a relationshi between elevated levels of total plasma homocysteine and increased risk of CHD. [60] Observations in large clinical and epidemiological studies have suggested that elevated homocysteine levels are a risk factor for atherosclerosis. Moreover, moderate and intermediate hyperhomocysteinemia is present in 12% to 47% of patients with coronary, cerebral, or peripheral arterial occlusive disease. Elevated plasma homocysteine may be an important cause for atherosclerosis formation.[61] Homocysteine a sulphur containing amino acid, which is derived from the dietary methionine, has been associated with cardiovascular events. Several studies show that the sites of adverse effect of homocysteine include endothelial surface, vascular smooth muscle cells, connective tissue, interaction with plasma lipoprotein, clotting factor and platelets.[62] Homocysteine is said to have a direct toxic effect on endothelial cells. It is also proposed that homo ysteine induced endothelial injury exposes the subendothelial matrix, which in turn leads to platelet activation.[63] The association between raised homocysteine and thrombosis was reported by McCully[64], who demonstrated thrombovascular abnormality in homocystinuria patients. In the last three decades several studies [65][66] showed an association between homocysteine and CAD. In a recent study Nair et al reported that methylenetetra hydrofolate reductase (MTHFR) gene mutation causing hyper homocysteinemia is a risk factor for CAD.[67] Boushy et al[68] showed homocysteine as an independent graded risk predictor for atherosclerotic disease in coronary, cerebral and peripheral vessels. Homocysteine is the best predictor of CHD risk amongst other conventional risk factor in CAD patients.[69]

b. Small dense Lipoprotein (Lpa):

The role of lipoprotein(a) [Lp(a)] as a risk factor for Coronary Heart Disease (CHD) has received considerable attention in recent years.Lipoprotein (a) [Lp(a)] is a cholesterol-rich lipoprotein that is distinguished by its content of a glycoprotein called apolipoprotein(a) [apo(a)] . Apolipoprotein B is the major apolipoprotein associated with LDL;The structure of lipoprotein (a) is similar to plasminogen and tPA (tissue plasminogen activator) and it competes with plasminogen for its binding site, leading to reduced fibrinolysis . Lp(a) stimulates secretion of PAI-1, it leads to thrombogenesis. Lp(a) also carries cholesterol and thus contributes to atherosclerosis.[70][71] In addition, Lp(a) transports the more atherogenic proinflammatory oxidized phospholipids, which attract inflammatory cells to vessel walls,[72][73] and leads to smooth muscle cell proliferation.[74] In a study conducted by Martyn et al. Lipoprotein (a) concentration was found to be almost twice as high in subjects with severe CAD compared with normal subjects which concluded that CAD is associated with increased lipoprotein(a) concentrations independently of the size of circulating apolipoprotein(a) isoforms.[75]

Although Lp[a] levels appear to be unaffected by lifestyle attributes such as diet and physical activity,[76] some classes of antihypercholesterolemic agents may have an effect on Lp[a] concentrations.[77][78] Reports that these medications can produce regression of atherosclerotic plaque in hypercholesterolemic populations[79][80] suggest the possibility that medication usage can alter the effect of Lp[a] on plaque development. Of these medications, niacin and neomycin alone or in combination appear to be the only commonly used antihypercholesterolemic agents that do lower Lp[a] levels.[81][82]

c. Plasma fibrinogen:

Plasma fibrinogen is an independent risk factor for coronary heart disease(CHD).[83] Increased plasma fibrinogen is a risk factor of CHD because it increases blood viscosity and platelet aggregation and promotes thrombogenesis. Plasma fibrinogen influences platelet aggregations and blood viscosity, interacts with plasminogen binding and in combination with thrombin, mediates the final step in clot formation and the response to vascular injury. In addition, fibrinogen associates positively with age, obesity, smoking cigarettes, diabetes and LDL-cholesterol level and inversely with HDL-cholesterol level, alcohol use physical activity and exercise level.[84] Seven prospective studies have each observed an increase in incident coronary heart disease risk with increasing plasma fibrinogen level. [85][86] It would appear necessary to decrease fibrinogen levels therapeutically in order to alleviate ischaemic symptoms. Unfortunately, fibrinogen levels cannot be lowered drastically by means of oral drugs. However, intravenous Ancrod or fibrinolytic agents break down fibrinogen enzymatically and have been reported to be clinically effective in coronary heart disease and claudication. [87] Clearly there is a demand for fibrinogen-lowering oral drugs. [88] Drugs such as , n-3 fatty acids, lipid lowering drugs or beta-blockers are all associated with relatively small but significant decreases in

fibrinogen levels and plasma viscosity . Measure-ments of fibrinogen (or plasma viscosity) should probably be included in the cardiovascular risk profile. A better understanding of the mechanisms involved could lead to more effective methods of prevention and treatment of arteriosclerotic disease.[89]

d. Inflammatory markers like C-reactive protein: Elevated baseline concentrations of C-reactive protein (CRP), the classical acute phase protein, are associated with the long-term risk of coronary heart disease in general populations, whilst the major acute phase response of CRP following myocardial infarction is associated with death and cardiac complications. The pathogenic and clinical significance of these associations is controversial.[90] C-reactive protein (CRP), a plasma protein synthesised by the liver, is a sensitive and dynamic systemic marker of inflammation.[91] Its concentration in the circulation can increase by up to 10 000-fold during acute responses to serious infection or major tissue damage.[92] Rather, systemic inflammation also plays a pivotal role in atherothrombotic inception and progression [91][92][93]. Mononuclear cells, macrophages, and T lymphocytes are prominent in atheromatous plaques in the arterial wall [94][95][96][97]. Furthermore, the shoulder region of a plaque, the most vulnerable site for rupture in acute coronary syndromes, is heavily infiltrated with inflammatory cells [98][99][100]. Cytokines, which cause the de novo hepatic production of acute phase reactants such as C-reactive protein (CRP) [101],binds to LDL[102][103] and is present in atherosclerotic plaques,[104] so it has been proposed that CRP may have a causal role in coronary heart disease. A recent statement from the Centers for Disease Control and Prevention and the American Heart Association concluded that it is reasonable to measure C-reactive protein, a sensitive circulating marker of inflammation, as an adjunct to the measurement of established risk factors in order to assess the risk of coronary heart disease.[105]More than being a marker of inflammation, CRP may influence directly vascular vulnerability through several mechanisms, including enhanced expression of local adhesion molecules, increased expression of endothelial PAI-1 (plasminogen activator inhibitor), reduced endothelial nitric oxide bioactivity, altered LDL uptake by macrophages and co localization with complement within atherosclerotic lesions.[84] Several reports have suggested that plasma C reactive protein and other possible markers of low grade inflammation can predict increased risks of coronary heart disease, but it is not known whether the associations are causal.[92][96]

e. Infections such as Chylamadia:

The possible role of chronic infections and CHD has been investigated in a number of studies. A great number of studies found evidence for an association between C .pneumoniae antibodies and CHD. [106] Atherogenic processes resemble many aspects of chronic inflammation[107], a response that may be promoted by microorganisms.[108][110] Accordingly, reviews

have revisited the venerable hypothesis of an infectious etiology.[108][109][111] Experimental animal studies have shown that bacterial and viral agents could contribute to atherogenesis. Chlamydia pneumoniae widely distributed, can infect blood vessel wall cells, and exhibit persistence, latency, and recurrence of infection. However, the potential mechanisms of infection-induced atherosclerosis remain speculative.The earliest lesions of atherogenesis consist of arterial intimal accumulations of foam cells (primarily lipid-laden macrophages) and T lymphocytes intermixed with smooth muscle cells.[107] Infection could indirectly influence this process without infiltrating the artery wall . Host defenses to extravascular infections usually elicit proinflammatory cytokines and stimulate increased expression of cellular adhesion molecules, enhancing leukocyte adhesion.

These cytokines could elicit a second wave or "echo" from inflammatory cells already at sites of atherogenesis, such as arterial wall cells or macrophages.[112] Circulating microbial products such as endotoxin can also produce an echo. Similarly, cytokines induced by extravascular infection (specifically interleukin-6) characteristically elicit hepatic synthesis of acute-phase reactants, some of which might promote atheromata complicated by thrombosis. Accordingly, levels of the acute-phase reactant fibrinogen correlate prospectively with risk for coronary events, and plasminogen activator inhibitor can promote clot stability by interfering with fibrinolysis. [107][110] Still, direct infection of the arterial wall could promote evolution of atherosclerotic lesions or precipitate acute cardiovascular events. Over 30 peer reviewed publications from investigators worldwide, using different diagnostic methods, have localized C. pneumoniae antigen, DNA, or both in atheromata; three reports did not find such components. [108,113,114] Although detection rates have varied depending on the diagnostic methods used, the cumulative evidence supports existence of the organism in many lesions.[108][113] If evidence substantiates a link between infection and atherosclerotic CVD, targeted antimicrobial therapy might mitigate atherosclerosis in persons at risk; controlling infections might decrease the impact of disease. Inappropriate antimicrobial therapy, however, could accelerate development of resistance in both associated and nontargeted organisms, without changing disease outcomes. Studies linking level of antibiotic use and prevalence of resistant bacteria in hospitals and communities justify these concerns; trends toward more frequent erythromycin and penicillin-resistant pneumococci with higher antibiotic consumption reversed when macrolide use was reduced. [115][116]

CONCLUSION

Coronary Heart disease is affected by number of modifiable and non-modifiable predisposing risk factors. A very little is known about the emerging risk factors such as such elevated homocysteine, small dense lipoprotein (Lpa), plasminogen activator inhibitor, inflammatory markers such as C-reactive protein, infectious agents like chlamydia. In this review an update is provided

about the role of various modifiable and non-modifiable risk factors with much focus on the emerging risk factors contributing to the development of Coronary Heart Disease (CHD). Focusing on timely identification and early prevention of risk factors can greatly help in reducing the prevalence of Coronary Heart Disease.

REFERENCES

1. K. Pesek et al.: The Prevalence of CHD Risk Factors in Zagorje County, Coll. Antropol. 31 (2007) 3: 709–715.
2. Libby P. Prevention and treatment of atherosclerosis. In: Braunwald E, Fauci AS, Kasper DL Hauser AL, Longo DL, Jameson JL (eds). Harrison's Principles of thInternal Medicine. 16 edition. Mac Graw Hill, U.S.A., 2005: 1430 -1433.
3. Marty.S.Player Dana.E.King, Arch.D. Mainous, Mark.E.Geesey. Psychosocial Factors and Progression From Prehyper tension to Hypertension or Coronary Heart Disease . Ann Fam Med 2007;5:403-411
4. Kannel WB. Blood pressure as a cardiovascular risk factor: Prevention and treatment. JAMA 1996;275:1571–1576.
5. Carretero OA, Oparil S; Oparil (January 2000). "Essential hypertension. Part I: definition and etiology". Circulation 101 (3): 329–35.
6. INTERSALT Co-operative Research Group. Sodium, potassium, body mass, alcohol and blood pressure: the INTERSALT study. J Hypertens. 1988;6 (suppl. 4):S584–S586.
7. Sever PS, Poulter NR. A hypothesis for the pathogenesis of essential hypertension: the initiating factors. J Hypertens. 1989;7(suppl 1):S9–S12.
8. Diao, D; Wright, JM; Cundiff, DK; Gueyffier, F (Aug 15, 2012). "Pharmacotherapy for mild hyperten-sion.". The Cochrane database of systematic reviews 8:CD006742.
9. Arguedas, JA; Leiva, V; Wright, JM (Oct 30, 2013). "Blood pressure targets for hypertension in people with diabetes mellitus.". The Cochrane database of systematic reviews 10: CD008277.
10. Spencer EA, Pirie KL, Stevens RJ. Diabetes and modifiable risk factors for cardiovascular disease: the prospective Million Women Study. Eur J Epidemiol. 2008;23:793–799.
11. A. D'Souza, M. Hussain, F. C. Howarth, N. M. Woods, K. Bidasee, and J. Singh, “Pathogenesis and pathophysiology of accelerated atherosclerosis in the diabetic heart,” Molecular and Cellular Bio chem.-istry, vol. 331, no. 1-2, pp. 89–116, 2009.
12. P. R. Moreno, K. R. Purushothaman, V. Fuster et al., “Plaque neovascularization is increased in ruptured atherosclerotic lesions of human aorta: implications for plaque vulnerability,”Circulation, vol. 110, no. 14, pp. 2032–2038, 2004.
13. M. Shechter, C. N. Bairey Merz, M. J. Paul-Labrador, and S. Kaul, “Blood glucose and platelet-dependent thrombosis

in patients with coronary artery disease," Journal of the American College of Cardiology, vol. 35, no. 2, pp. 300–307, 2000.

14. D. J. Schneider and B. E. Sobel, "Augmentation of synthesis of plasminogen activator inhibitor type 1 by insulin and insulin-like growth factor type I: implications for vascular disease in hyperinsulinemic states," Proceedings of the National Academy of Sciences of the United States of America, vol. 88, no. 22, pp. 9959–9963, 1991.
15. J. B. McGill, D. J. Schneider, C. L. Arfken, C. L. Lucore, and B. E. Sobel, "Factors responsible for impaired fibrinolysis in obese subjects and NIDDM patients," Diabetes, vol. 43, no. 1, pp. 104–109, 1994.
16. Meigs JB.Prevention of coronary heart disease in diabetes.Curr Treat Options Cardiovasc Med. 2005 Aug;7(4):259-71.
17. MK Garg , Mohan V Kulkarni, Namita Mahalle, Sadanand S Naik.Study of pattern of dyslipidemia and its correlation with cardiovascular risk factors in patients with proven coronary artery disease.Indian Journal of Endocrinology and Metabolism, Vol. 18, No. 1, January-February, 2014, pp. 48-55
18. Ballantyne, C.M.; Keefe, O. Jr. & Gotto, A.M. (2007). Dyslipidemia essentials, Physician, s Press, ISBN 1-890114-65-0, Michigan, USA .
19. Gupta R, Vashisht S, Bahl VK, Wasir HS, Correlation of lipoprotein (A) to angiograpically defined coronary artery disease in Indians. Int J Cardiol 1996;57:265-70
20. Neaton JD, Wentworth D. Serum cholesterol, blood pressure, cigarette smoking and death from coronary heart disease : Overall findings and differences by age for 316, 099 white men. Multiple risk factor intervention trial Research Group. Arch Int Med 1992:56.
21. Keys A, Menotti A, Karvonen MJT AL. The Diet and 15 year death rate in the seven countries study. Am J Epidemiology 1986;124:903-91.
22. Levy D, Kannel WB. Cardiovascular risks. New insights from framingham. Am Heart J 1988;116: 266-27.
23. Castelli WP. Epidemiology of caronary heart disease. The Framingham Study. Am J Med 1984;76(Supll.2A): 4-12.
24. Kinosian B, Glick H, Garland G. Cholesterol and coronary heart disease: predicting risks by levels and ratios. Ann Intern Med. 1994;121:641–647.
25. Kashyap ML.Cholesterol and atherosclerosis: a contemporary perspective. Ann Acad Med Singapore. 1997 Jul;26(4):517-23
26. Parish S, Collins R, Peto R, Youngman L, Barton J, Jayne K, et al.Cigarette smoking,tar yields, and non-fatal myocardial infarction: 14 000 cases and 32 000 controls in the United Kingdom. The international studies of infarct survival (ISIS) collaborators.BMJ1995; 311:471.
27. Ambrose JA, Barua RS (2004) The

pathophysiology of cigarette smoking and Cardiovascular disease: an update. J Am Coll Cardiol 43: 1731-1737.

28. Raphael B, Herman H, Saxena S, Moodie R, Schmoike M, et al. (2005) Links between mental and physical health and illness. In: Herman H. Saxen S., Moodie R. editors, promoting mental health: concept, emerging evidence, practice. A report of the World Health Organisation, Department of Mental Health and Substance Abuse in Collaboration with the Victorian Health Promotion Foundation and University of Melbourne. Geneva.
29. "Health : Young smokers' heart attack risk". BBC. 2004-08-24. Retrieved 2005-12-18.
30. Summaries for patients. Primary care interventions to prevent tobacco use in children and adolescents: U.S. Preventive Services Task Force recommendation statement". Annals of Internal Medicine 159 (8): I–36. Oct 2013.
31. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. Circulation 1983 May;67(5):968977.
32. Zalesin KC, Franklin BA, Miller WM, Peterson ED, McCullough PA. Impact of obesity on cardiovascular disease. Endocrinol Metab Clin North Am 2008 Sep; 37(3):663-684, ix.
33. Gaal LF, Wauters MA, De Leeuw IH. The beneficial effects omodest weight loss on cardiovascular risk factors. Int J Obes Relat Metab Disord 1997;21 (Suppl 1):S5–S9.
34. Wood PD, Stefanick ML,Williams PT, Haskell WL. The effects on plasma lipoproteins of a prudent weight-reducing diet, with or without exercise, in over weight men and women. New Engl J Med 1991;325:461–466
35. Jeremiah stamler, Frederick H. Epstein. Risk Factors as Guides to Preventive Action.PREVENTIVE MEDICINE 1,27-48 (1972).
36. Taylor RS, Brown A, Ebrahim S, et al. Exercise-based rehabilitation for patients with coronary heart disease: Systematic review and metaanalysis of randomized controlled trials [see comment]. Am J Med 2004;116:682–692.
37. David Wood . Asymptomatic individuals – risk stratification in the prevention of coronary heart dis-ease. Br Med Bull (2001) 59 (1): 3-16.
38. Ozturk, S., & Kutlu M. (2010). Hyperlipidemia in older patients and methods of treatment. Turkish Journal of Geriatrics Supp 2, pp. 41 -46.
39. Aslam, F., Haque, A., Lee, V.L., & Foody, J. A. (2009). Hyperlipidemia in older adults. Clin Geriatr Med, Vol. 25, pp. 591-606.
40. Ericsson, S., Eriksson, M., Vitols, S.,Einarsson, K., Berglund, L., Angelin, B.(1991). Influence of age on the

metabolism of plasma low density lipoproteins in healthy males. J Clin Invest; Vol. 87, No. 2, pp. 591-596.

41. Jani B, Rajkumar C (2006). "Ageing and vascular ageing". Postgrad Med J 82: 357–362.
42. Castelli WP. Epidemiology of coronary heart disease: the Framingham Study. Am J Med. 1984;76:4–12.
43. Pekka Jousilahti, Erkki Vartiainen, Jaakko Tuomilehto, Pekka Puska,.Sex, Age, Cardiovascular Risk Factors, and Coronary Heart Disease A Prospective Follow-Up Study of 14 786 Middle-Aged Men and Women in Finland.Circulation. 1999; 99: 1165-1172.
44. Matthews KA, Meilahn E, Kuller LH, Kelsey SF, Caggiula AW, Wing RR. Menopause and risk factors for coronary heart disease. N Engl J Med. 1989; 321:641–646.
45. Bonithon-Kopp C, Scarabin P-Y, Darne B, Malmejak A, Guize L. Menopause-related changes in lipoproteins and some other cardiovascular risk factors. Int J Epidemiol. 1990;19:42–48.
46. Grady D, Rubin SM, Petitti DB, Fox CS, Black D, Ettinger B, Ernster VL, Cummings SR. Hormone therapy to prevent disease and prolong life in post menopausal women. Ann Intern Med. 1992;117:1016–1037.
47. Shahar E, Folsom AR, Salomaa VV, Stinson VL, McGovern PG, Shimakawa T, Chambless LE, Wu KK, for the Atherosclerosis Risk in Communities (ARIC) Study Investigators. Relation of hormone-replacement therapy to measures of plasma fibrinolytic activity. Circulation. 1996;93:1970–1975.
48. Wood PD, Stefanick ML, Dreon DM, Frey-Hewitt B, Garay SC, Williams PT, Superko HR, Fortmann SP, Albers JJ, Vranizan KM, Albers JJ, Vranizan KM, Ellsworth NM, Terry RB, Haskell WL. Changes in plasma lipids and lipoproteins in overweight men during weight loss through dieting as compared withexercise. N Engl J Med. 1988;319:1173–1179.
49. Jousilahti P, Vartiainen E, Pekkanen J, Tuomilehto J, Sundval J, Puska P. Serum cholesterol distribution and coronary heart disease risk: observations and predictions among the middle-aged population in eastern Finland. Circulation. 1998;97: 1087–1094.
50. Law MR, Frost CD, Wald NJ. By how much does dietary salt reduction lower blood pressure? III: analysis of data from trials of salt reduction. BMJ. 1991; 302:819–824.
51. Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, Goldwin J, Qizilbash N, Taylor JO, Hennekens CH. Blood pressure, stroke, and coronary heart disease, II: short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. Lancet. 1990;335:827–838.
52. Staessen JA, Fagard R, Lutgarde T, Celis

H, Arabidze GG, Birkenhäger WH, Bulpitt CJ, de Leeuw PW, Dollery CT, Fletcher AE, Forette F, Leonetti G, Nachev C, O'Brien ET, Rosenfeld J, Rodicio JL, Tuomilehto J, Zanchetti A, for the Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Randomised double-blind compareson of placebo and active treat-ment for older patients with isolated systolic hypertension. Lancet. 1997;350: 757–764.

53. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344:1383–1389.
54. Johannesson M, Jönsson B, Kjekshus J, Olsson AG, Pedersen TR, Wedel H. Cost effectiveness of simvastatin treatment to lower cholesterol levels in patients with coronary heart disease. N Engl J Med. 1997;336:332–336.
55. Boer JM, Feskens EJ, Verschuren WM, Seidell JC, Kromhout D. The joint impact of family history of myocardial infarction and other risk factors on 12 year coronary heart disease mortality. Epidemiology 1999 Nov;10(6):767-770.
56. Hawe E, Talmud PJ, Miller GJ, Humphries SE; Second Northwick Park Heart Study. Family history is a coronary heart disease risk factor in the Second Northwick Park Heart Study. Ann Hum Genet 2003 Mar;67(Pt 2):97-106.
57. EPSTEIN, F. H. Risk factors in coronary heart disease-Environmental and hereditary influ-ences. Zsrael]. Med. Sci. 3, 594 (1967).
58. STAMLER, J. "Lectures on Preventive Cardiology." Crone and Stratton, New York, N. Y., 1967.
59. EPSTEIN, F. H. AND OSTRANDER, L. D., JR. Detection of individual suscep-tibility toward coronary disease. Prog. Cardiouasc. Dis. 13, 324 (1971).
60. Jacobsen DW. Homocysteine and vitamins in cardiovascular disease. Clin Chem 1998;44:1833–1843.
61. JC Fruchart, MC Nierman, ESG Stroes, JJP Kastelein, P Duriez. New risk factors for atherosclerosis and patient risk assessment. Circulation. 2004; 109 (suppl III): III 15-9.
62. Sheshadri N, Robinson K. Homocysteine B Vitamin and Coronary artery disease. Med.Clin. North America 2000; 84: 215-37.
63. Yeolekar ME, Bichile SK, Shete MM. Hyperhomocysteinemia and vascular disease: Role and implications. J Assoc Physicians India 2002;50(suppl):5-8.
64. McCully KS. Vascular pathology of Homocysteine implications for the pathogenesis of arteriosclerosis. Am J Pathol 1969; 56: 111-28
65. McCully KS, Wilson RB. Homocysteine theory of arteriosclerosis. Arteriosclerosis 1975; 22: 215-27.
66. Mayer EL, Jacobsen DW, Robinson K.

Homocysteine and coronary atherosclerosis. J. Am. Coll. Cardiol 1996; 27:51727.

67. Nair KG, Nair SR, Ashavaid TF, Dalal JJ, Eghlim FF. Methylenetetrahydrofolate reductase gene mutation and hyper homocysteinemia as a risk factor for coronary heart disease in Indian population. JAPI 2002; May, 50 (suppl): 915.
68. Nair KG, Nair SR, Ashavaid TF, Dalal JJ, Eghlim FF. Methylenetetra hydrofolate reductase gene mutation and hyperhomocysteinemia as a risk factor for coronary heart disease in Indian population. JAPI 2002; May, 50 (suppl): 915.
69. Harish Rao B, V. Govindaraju and C.N. Manjunath. RISK PREDICTION – HOMOCYSTEINE IN CORONARY HEART DISEASE.Indian Journal of Clinical Biochemistry, 2007 / 22 (1) 18-21.
70. Schreiner PJ, Morrisett JD, Sharrett AR, Patsch W, Tyroler HA, Wu K et al. (1993). "Lipoprotein[a] as a risk factor for preclinical atherosclerosis". Arterioscler. Thromb. 13 (6): 826–33.
71. Sotiriou SN, Orlova VV, Al-Fakhri N, Ihanus E, Economopoulou M, Isermann B et al. (2006). "Lipoprotein (a) in atherosclerotic plaques recruits inflammatory cells through interaction with Mac-1 integrin". FASEB J. 20 (3): 559–61.
72. Gouni-Berthold I, Berthold HK (November 2011). "Lipoprotein(a): current perspectives". Curr Vasc Pharmacol 9 (6): 682–92.
73. Tsimikas S, Witztum JL (August 2008). "The role of oxidized phospholipids in mediating lipoprotein (a) atherogenicity". Curr. Opin. Lipidol. 19 (4): 369–77.
74. Ichikawa T, Unoki H, Sun H, Shimoyamada H, Marcovina S, Shikama H et al. (January 2002). "Lipoprotein(a) promotes smooth muscle cell proliferation and dedifferentiation in atherosclerotic lesions of human apo(a) transgenic rabbits". Am. J. Pathol. 160 (1): 227–36 .
75. Martyn Farrer, Frances L. Game, Catherine J. AJbers, H. Andrew W. Neil, Peter H. Winocour, Mike F. Laker, Philip C. Adams, K. George M.M. Alberti Coronary Artery Disease Is Associated With Increased Lipoprotein(a) Concentrations Independent of the Size of Circulating Apolipoprotein (a) Isoforms 1994;Vol 14, No 8 August 1994.
76. Scanu AM: Lipoprotein[a]: A potential bridge between the fields of atherosclerosis and thrombosis. Arch Pathol Lab Med 1988; 112: 1045-1047.
77. JQrgens G, Ashy A, Zenker G: Raised serum Iipoprotein during treatment with lovastatin. Lancet 1989;1:911—912.
78. Vessby B, Kostner G, Lithell H, Thomis J: Diverging effects of cholestyramine on apolipoprotein B and Iipoprotein Lp[a]. Atherosclerosis 1982;44:61-71.
79. Brown G, Albers JA, Fisher LD, Schaefer SM, Lin J-T, Kaplan C, Zhao X-Q, Bisson BD, Fitzpatrick VF, Dodge HT: Regression of coronary artery disease as a result of intensive lipid-lowering therapy

in men with high levels of apolipo protein B. N Engl J Med 1990;323:1289-1298.

80. Cashin-Hemphill L, Sanmarco ME, Blankenhorn DH and the CLAS coronary film panelists and staff: Augmented beneficial effects of colestipal-niacin therapy at four years in the CLAS trial, (abstract) Circulation 1989;8O(suppl I1):II-381.
81. Carlson LA, Hamsten A, Asplund A: Pronounced lowering of serum levels of Iipoprotein Lp[a] in hyperlipidaemic subjects treated with nicotinic acid. / Int Med 1989;226:271-276 .
82. Gurakar A, Hoeg JM, Kostner G, Papadopoulos NM, Brewer HB Jr: Levels of Iipoprotein Lp[a] decline with neomycin and niacin treatment. Atherosclerosis 1985^57:293-301.
83. Margita Eriksson, Nils Egberg, Sarah Wamala,Kristina Orth-Gomér,Murray A. Mittleman, Karin Schenck-Gustaf-sson.Relationship Between Plasma Fibrinogen and Coronary Heart Disease in Women.Arteriosclerosis, Thrombosis, and Vascular Biology. 1999; 19: 67-72.
84. Ksenija Pešek, Tomislav Pešek and Siniša Roginić (2011). The Importance of Risk Factors Analysis in the Prevention of Cardiovascular Disease (CVD), Atherosclerotic Cardiovascular Disease, Dr. Ksenija Pesek (Ed.), ISBN: 978-953-307-695-9.
85. Meade TW, North WRS, Chakrabarti R et al. Haemostatic function and cardiovascular death: early results of a prospective study. Lancet 1980; i: 1050–4.
86. Cremer P, Nagel D, Labrot B et al. Lipoprotein Lp(a) as predictor of myocardial infarction in comparison to fibrinogen, LDL cholesterol and other risk factors: results from the prospective Gottingen Risk Incidence and Prevalence Study (GRIPS). Eur J Clin Invest 1994; 24: 444–53.
87. Lowe GDO. Defibrination. blood flow and blood rheology. Clin Hemorheol 1984: 4: 15-28.
88. Pickart L. Fat metabolism, the fibrinogen/ fibrinolytic system and blood flow: new potentials for the pharma-cological treatment of coronary heart disease. Pharmacology 1981 ; 23: 271-80.
89. E. Ernst .Review article Plasma fibrinogen - an independent cardiovascular risk factor. Journal of lnternal Medicine 1990; 227: 365-372
90. J. P. Casas ,T. Shah , A. D. Hingorani, J. Danesh and M. B. Pepys .C-reactive protein and coronary heart disease: a critical review.Journal of Internal Medi-cine.Volume 264, Issue 4, pages 295–314.
91. Libby P, Ridker PM. Novel inflammatory markers of coronary risk: theory versus practice Circulation 1999;100:1148-1150.
92. Ross R. Atherosclerosis—an inflammatory disease. N Engl J Med 1999;340:115-126.
93. Libby P. Molecular bases of the acute coronary syndromes. Circulation 1995;91:2844-2850.

94. Cybulsky MI, Gimbrone MA, Jr. Endothelial expression of a mononuclear leukocyte adhesion molecule during atherogenesis. Science 1991;251:788-791.
95. Navab M, Hama SY, Nguyen TB, Fogelman AM. Monocyte adhesion and transmigration in atherosclerosis. Coron Artery Dis 1994;5:198-204.
96. Nagel T, Resnick N, Atkinson WJ, Dewey CF, Jr, Gimbrone MA, Jr. Shear stress selectively upregulates intercellular adhesion molecule-1 expression in cultured human vascular endothelial cells. J Clin Invest 1994;94:885-891.
97. Nakashima Y, Raines EW, Plump AS, Breslow JL, Ross R. Upregulation of VCAM-1 and ICAM-1 at atherosclerosis-prone sites on the endothelium in the ApoE-deficient mouse. Arterioscler Thromb Vasc Biol 1998;18:842-851.
98. Moreno PR, Falk E, Palacios IF, Newell JB, Fuster V, Fallon JT. Macrophage infiltration in acute coronary syndromes. Implications for plaque rupture. Circulation 1994;90:775-778.
99. van der Wal AC, Becker AE, van der Loos CM, Das PK. Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology. Circulation 1994;89:36-44.
100. Richardson PD, Davies MJ, Born GV. Influence of plaque configuration and stress distribution on fissuring of coronary atherosclerotic plaques. Lancet 1989; 2:941-944.
101. Pepys MB, Baltz ML. Acute phase proteins with special reference to C-reactive protein and related proteins (pentaxins) and serum amyloid A protein. Adv Immunol 1983;34:141-212.
102. FC de Beer, AK Soutar, ML Baltz, IM Trayner, A Feinstein, MB Pepys .Low density lipoprotein and very low density lipoprotein are selectively bound by aggregated C reactive protein. J Exp Med, 156 (1982), pp. 230–242.
103. MB Pepys, IF Rowe, ML Baltz.C-reactive protein: binding to lipids and lipoproteins. Int Rev Exp Pathol, 27 (1985), pp. 83–111.
104. YX Zhang, WJ Cliff, GI Schoefl, G Higgins. Coronary C-reactive protein distribution: its relation to development of atherosclerosis. Atherosclerosis, 145(1999), pp. 375–379.
105. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003;107:499-511
106. Danesh J, Collins R, Peto R. Chronic infections and coronary heart: is there any link.The Lancet Volume 350, Issue 9075, 9 August 1997, Pages 430–436.

107. Ross R. Atherosclerosis–an inflammatory disease. N Engl J Med 1999; 340:115-26.

108. Gaydos CA, Quinn TC. The role of Chlamydia pneumoniae in cardiovascular disease. Adv Intern Med 2000;45:139-73.

109. Muhlestein JB. Chronic infection and coronary artery disease. Med Clin North Am 2000;84:123-48.

110. Kol A, Libby P. Molecular mediators of arterial inflammation: A role for microbial products? Am Heart J 1999; 138(5 Pt 2):450-2.

111. Nieto FJ. Infections and atherosclerosis: new clues from an old hypothesis? Am J Epidemiol 1998;148:937-58.

112. Clinton SK, Fleet JC, Loppnow H, Salomon RN, Clark BD, Cannon JG, et al. Interleukin-1 gene expression in rabbit vascular tissue in vivo. Am J Pathol 1991; 138:1005-14.

113. Kuo C-C, Campbell LA. Detection of Chlamydia pneumoniae in arterial tissues. J Infect Dis 2000;181 Suppl 3:432-4.

114. Taylor-Robinson D, Thomas BJ. Chlamydia pneumoniae in atherosclerotic tissue. J Infect Dis 2000;181 Suppl 3:437-40.

115. Stamm WE. Potential for antimicrobial resistance in Chlamydia pneumoniae. J Infect Dis 2000;181 Suppl 3:456-9.

116. Arason VA, Kristinsson KG, Sigurdsson JA, Stefansdottir G, Molstad S, Gudmundsson S. Do antimicrobials increase the carriage rate of penicillin resistant pneumococci in children? Cross-sectional prevalence study. BMJ 1996;313:387-91.