IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 19, Issue 12 Ser.2 (December. 2020), PP 56-60
www.iosrjournals.org

Lipid Profile of Coronary Heart Disease Patients: A Prospective Observational Study.

Dr. Md. Zulfiker Ali Faruquee[1], Dr. Md. Atiqur Rahman[2], Dr. Md. Ibrahim Khalilullah[3], Dr. Md. Shahnoor Aziz[4], Dr. Md. Rokonuzzaman Selim[5], Dr.MohammodHumayun Kabir[6].

[1]*Consultant, Associate Professor, Department of Cardiac Anesthesiology, Ibrahim Cardiac Hospital & Research Institute, Dhaka, Bangladesh*
[2]*Specialist Cardiac Surgeon, Department of Cardiac Surgery, Ibrahim Cardiac Hospital & Research Institute, Dhaka, Bangladesh*
[3]*Assistant Professor, Department of Cardiac Anesthesiology, Ibrahim Cardiac Hospital & Research Institute, Dhaka, Bangladesh*
[4]*Specialist Cardiac Surgeon, Department of Cardiac Surgery, Ibrahim Cardiac Hospital & Research Institute, Dhaka, Bangladesh*
[5]*Consultant, Associate Professor, Department of Cardiac Surgery, Ibrahim Cardiac Hospital & Research Institute, Dhaka, Bangladesh*
[6]*Specialist, Department of Cardiac Anesthesiology, Ibrahim Cardiac Hospital & Research Institute, Dhaka, Bangladesh*
Corresponding author: *Dr. Md. Zulfiker Ali Faruquee*

Abstract
Background:*Coronary heart disease (CHD) remains the major cause of mortality and morbidity in the entire world population despite therapeutic advances that control many risk factors. Lipid profile is regarded as an important factor in the development of coronary heart disease. There have been numerous studies confirming the association of hyperlipidemias with coronary heart disease in most of the Western as well as Asian countries of the world. We have very few data on the relation between CHD and lipid profile.****Aim of the study:*** *The aim of this study was to determine the prevalence of abnormal lipid levels and its association with coronary heart disease.****Methods:*** *Thiscomparative observational study was conducted in Ibrahim Cardiac Hospital & Research Institute, Dhaka, Bangladesh during the period from January 2018 to December 2019. The study was approved by the ethical committee of the mentioned hospital. Proper written consents were taken from all the participants before starting the main part of intervention. Obeying inclusion and exclusion criteria of this study in total 101 participants were finalized as the study population. Among them with 60 patients with CHD the Case Group was formed and with 41 healthy people the Control Group was formed. All necessary data were collected, analyzed and disseminated by several program of MS-Office and SPSS version 23.****Result:*** *In analyzing the age-wise distribution of serum cholesterol concentration between the groups we found, significant correlations between the Case and Control groups in all age groups (P< 0.0001) in every age group. In analyzing the age-wise distribution of triglyceride concentration between the groups we found, significant correlations between the Case and Control groups in 41-50 and 51-60 years' age groups and in both age groups the P value was found, <0.0001. But in >60 years' age group we did not find any significant correlation (P= 0.478). In analyzing the age-wise distribution of HDL concentration between the groups we found, significant correlations between the Case and Control groups in all age groups (P < 0.0001) in every age group. In analyzing the age-wise distribution of LDL concentration between the groups we found, significant correlations between the Case and Control groups in 41-50 and 51-60 years' age groups where the P values were found, <0.0001 and 0.0002 respectively. But in >60 years' age group we did not find any significant correlation (P = 0.515).* ***Conclusion:*** *In this study, it was found that, the total cholesterol, triglycerides HDL cholesterol and LDL cholesterol concentrations were significantly higher in coronary heart disease (CHD) patients.*

Key words:*Lipid Profile, Coronary heart disease, CHD, Cardiology.*

Date of Submission: 24-11-2020 Date of Acceptance: 08-12-2020

I. Introduction

Lipid profile means the pattern of lipids in the blood. It usually includes the level of total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL) and high density lipoprotein (HDL).In generally the

lipid profile refers a group of tests that are often done together to identify the risk of heart disease. These tests are some potential indicators of whether someone is likely to have a heart attack or stroke caused by the blockage of blood vessels or hardening of the arteries. For a person of about 68 kg typical total blood cholesterol synthesis is about 1g (1000mg) per day.[1]The increased level of TC, TG and LDL is found to be associated with the higher risk of coronary artery disease (CAD) and ischemic stroke.[2] On the other hand, population based studies have consistently demonstrated an inverse association between HDL level with the risk of CAD.[3]Dyslipidemia is one of the primary causes for coronary artery disease (CHD). Elevated total cholesterol (TC), triglycerides (TG), low-density lipoprotein-cholesterol (LDL-C) and lowered high-density lipoprotein-cholesterol (HDL-C) are conventional risk factors in myocardial infarction patients.[4]According to the guidelines of the American Heart Association, the following values are prescribed for the above-mentioned risk factors for cardiovascular disease: total cholesterol: <200 mg/dL; triglycerides: <200 mg/dL; HDL: >40 mg/dL; and LDL: <130 mg/dL.[5] Adak M et al found desirable TC level (<200 mg/dl) in 73.0%, normal TG level (<150 mg/dl) in 59.0%, optimal level of HDL-C (<40 mg/dl) in 82.0% and normal LDL-C (<129 mg/dl) in 32.0%. Nearly 16% male and female had normal (40-60 mg/dl) HDL-C respectively.[4]Adak et al found that higher percentage of female (46.8%) than male (34.9%) had optimal level of LDL-C (<100 mg/dl). About 20.0% male had very high level of LDL-C (>160 mg/dl) while it was noted in 6.7% of female patients.[4]LDL consists of more cholesterol than triglycerides and protein. Because it contains less lipid and more protein in comparison to VLDL, its density is greater. LDL is responsible for carrying cholesterol to cells that need it. The recent genetic analyses of a relatively common single nucleotide polymorphism (SNP) in the endothelial lipase gene and other SNPs associated with HDL cholesterol suggest that genetic mechanisms that raise plasma HDL do not decrease the risk of myocardial infarction[6]. In contrast, an earlier study of SNPs in the cholesteryl ester transfer protein (CETP) that impact HDL levels indicated that SNPs associated with an increase in HDL corresponded with a lower risk of future myocardial infarction[7]. Certain earlier clinical trials with agents that increase HDL showed that elevations in the lipoprotein can decrease the incidence of cardiovascular events[8].On the other hand, VLDL particles mainly carry triglycerides, another type of fat, to your tissues. VLDL is similar to LDL cholesterol, but LDL mainly carries cholesterol to your tissues instead of triglycerides.In human body, cholesterol is an essential component of cell membranes, which are the structures that border every cell[9]. Without cholesterol, T-cells (a type of white blood cell), for example, would not maintain their cell membranes, leading to rupturing of the cells. Cholesterol is also needed for the manufacture of steroid-based hormones, particularly sex hormones like testosterone and progesterone[10]. Other hormones, produced mainly by the adrenal gland, also require cholesterol for production. Aldosterone (the hormone that makes the kidneys retain water) and cortisol (the hormone that is important in suppressing inflammation in the body) are two such examples. Cholesterol must also be present for the skin to manufacture vitamin D, which plays a role in how the body handles calcium and assists in maintaining bone density.[11]Many studies on lipid profile has been conducted in some famous institutions of Bangladesh. Among those institutions or hospitals NICVD[12], Dhaka;ICDDR[13], Dhaka; BSMMU, Dhaka are some noticeable. Although there had been conducted many studies on lipid profile of CHD patients in Bangladesh but there are very dissimilarities among the findings of those studies. Even those variations and dissimilarities are found among several studies of the same institute or hospital. For this reason for acquiring some more specific information we conducted this study.

II. Methodology & Materials

This comparative observational study was conducted in Ibrahim Cardiac Hospital & Research Institute, Dhaka, Bangladesh during the period from January 2018 to December 2019. The study was approved by the ethical committee of the mentioned hospital. Proper written consents were taken from all the participants before starting the main part of intervention. Obeying inclusion and exclusion criteria of this study in total 101 participants were finalized as the study population. Among them with 60 patients with CHD the Case Group was formed and with 41 healthy people the Control Group was formed. The age of the participants was 41 years and above. All the demographic and risk factors related information were collected from the patient's record available in the hospital. A data collection sheet was designed to gather all the necessary information of the patients. The patients of Case Group (n=60) were selected with history of angina or surviving myocardial infarction with or without DM and HTN, admitted and diagnosed in coronary care unit of the mentioned hospital. According to the exclusion criteria of the study, CHD cases with liver impairment, renal disease or thyroid disease were excluded. On the other clinically healthy subjects aged above 41 years who served as population-based controls were selected as the participants of Control Group. Blood sample was collected from the cubital vein of the arm of each patient by a 5cc disposable syringe, which was transferred quickly to a heparinized collecting tube and finally preserved into an ice pot. All these tubes were then transferred to a test tube, were allowed to stand overnight for the serum to separate. Then each serum sample was transferred to a separate Eppendorf tube and stored at -20º C in a refrigerator; lipid profile was performed within one week for each group of samples, after running the controls for confirmation of the accuracy of each test, according to the

procedures provided with Bioconkits. Cholesterol was estimated by enzymatic colorimeter test. Estimation of HDL-C was done through phosphor-tungstic precipitation and LDL-C was also done through the same precipitation method. Estimation of Triglycerides (TG) was done by enzymatic colorimetric test. Serum of VHD patients were used for individual determinations of lipid profile for Cholesterol, HDL-C, LDL-C, and TG by using clinical laboratory kits. All necessary data were collected, analyzed and disseminated by several program of MS-Office and SPSS version 23.

III. Results

In this study, among total participants of Case Group (n=60) in total 47 were male which was 78% and 13 were female which was 22%. Among male participants of Case Group 45%, 36% and the rest 19% were from 51-60, 41-50 and >60 years' age group respectively. On the other hand, Among female participants of Case Group 46%, 31% and the rest 23% were from 51-60, 41-50 and >60 years' age group respectively. In regression analysis between male and female participants of Case Group on the basis of age we found the P value was 0.242. So there had not been any significant correlation. In analyzing the age-wise distribution of serum cholesterol concentration between the groups we found, significant correlations between the Case and Control groups in all age groups and the P value were< 0.0001 in every age groups. On the other hand, in analyzing the age-wise distribution of triglyceride concentration between the groups we found, significant correlations between the Case and Control groups in 41-50 and 51-60 years' age groups and in both age groups the P value was found, <0.0001. But in >60 years' age group we did not find any significant correlation and there the P value was 0.478. In analyzing the age-wise distribution of HDL concentration between the groups we found, significant correlations between the Case and Control groups in all age groups and the P value were < 0.0001 in every age groups. On the other hand, in analyzing the age-wise distribution of LDL concentration between the groups we found, significant correlations between the Case and Control groups in 41-50 and 51-60 years' age groups where the P values were found, <0.0001 and 0.0002 respectively. But in >60 years' age group we did not find any significant correlation and there the P value was 0.515.

Table I: Age distribution among the participants of Case Group (n=60)

Age (Yrs.)	Male (M)		Female (F)		Total		P value
	n	%	n	%	n	%	(M-F)
41-50	17	36.17	4	30.77	21	35.00	0.242
51-60	21	44.68	6	46.15	27	45.00	
>60	9	19.15	3	23.08	12	20.00	
Total	47	100	13	100	60	100	

Table II: Age-wise distribution of serum cholesterol concentration between the groups(n=60)

Age (Yrs.)	Case (n=60)	Control (n=41)	P value
41-50	197.16 ± 28.85	168.92 ± 25.24	< 0.0001
51-60	207.11 ± 18.65	118.75 ± 17.15	< 0.0001
>60	263.91 ± 23.73	193.81 ± 20.88	< 0.0001

Table III: Age-wise distribution of triglyceride concentration between the groups (n=60)

Age (Yrs.)	Case (n=60)	Control (n=41)	P value
41-50	167.13 ± 26.83	109.33 ± 20.44	< 0.0001
51-60	210.71 ± 42.17	125.64 ± 31.71	< 0.0001
>60	152.56 ± 34.64	157.74 ± 37.73	0.4783

Table IV: Age wise distribution of HDL concentration between the groups (n=60)

Age (Yrs.)	Case (n=60)	Control (n=41)	P value
41-50	40.52 ± 5.77	50.71 ± 6.39	< 0.0001
51-60	47.44 ± 5.91	75.32 ± 9.19	< 0.0001
>60	43.73 ± 8.93	86.74 ± 10.48	< 0.0001

Table V: Age wise distribution of LDL concentration between the groups (n=60)

Age (Yrs.)	Case (n=60)	Control (n=41)	P value
41-50	99.88 ± 20.73	75.87 ± 12.56	< 0.0001
51-60	104.71 ± 21.95	90.11 ± 11.84	0.0002
>60	107.66 ± 22.74	97.82 ± 15.77	0.515

IV. Discussion

The aim of this study was to determine the prevalence of abnormal lipid levels and its association with coronary heart disease.Coronary heart disease (CHD) is a leading cause of morbidity and mortality in many countries worldwide (WHO, 2015). CHD refers to a group of a closely related syndrome caused by the imbalance between the myocardial oxygen demand and the blood supply. Depending on the rated severity of coronary artery narrowing and the myocardial response, which is divided into angina pectoris (chest pain), acute myocardial infarction, sudden cardiac death and chronic ischemic heart disease [14].The most common risk factors of CHD are hypertension[15], smoking, obesity [16], diabetes, stress, gender, age and dyslipidemia[17, 18].These are high levels of total cholesterol, Tri acyl glycerols (TAG), low-density lipoprotein cholesterol (LDL-C) and very low-density lipoprotein (VLDL) and with low levels of High density lipoprotein cholesterol (HDL-C) [19] that considered as one of the most common modifiable risk factors for CHD.[20]The key role of cholesterol in CHD have given rise to the universally accepted cholesterol-diet-CHD hypothesis. According to this hypothesis, increased plasma cholesterol concentrations increase the risk of CHD and decreasing plasma cholesterol levels decreases the risk of CHD. The Multiple Risk Factor Intervention Trial (MRFIT) showed that there is an increased risk at levels >200 mg/dL. The Seven Countries Study also demonstrated that elevated plasma cholesterol levels increased the incidence of CHD. The Framingham study clearly demonstrated the association of elevated cholesterol with CHD.[21]In this study among male participants of Case Group 45%, 36% and the rest 19% were from 51-60, 41-50 and >60 years' age group respectively. On the other hand, Among female participants of Case Group 46%, 31% and the rest 23% were from 51-60, 41-50 and >60 years' age group respectively. So middle age may be considered as a potential risk factor. Arteriosclerosis is not clinically evident until middle age or later, when the arterial lesions precipitate the organ injury[22]. The incidence of myocardial infarction increase fivefold between the ages ranging from 40-60[23]. In addition, men are much prone to develop atherosclerosis and its consequences than women [24].Myocardial infarction, CHD and atherosclerosis is uncommon in premenopausal women. It is sad that, the incidence of atherosclerosis-related disease increases, probably owing to a decrease in natural estrogen levels. Generally, the frequency of myocardial infarction in both sexes equalizes by the seventh to eighth decade of life. Dietary and life style are also potential factors for CHD.Epidemiologic studies have linked the intake of high levels of dietary fat rich in cholesterol and saturated fats, with increased plasma cholesterol levels. Therefore, restriction of saturated fat and cholesterol is the cornerstone of dietary therapytolowerdowntheelevatedbloodcholesterollevels.[25]Despitethewideliterature on the relationship between lipid and lipoprotein particles to CHD incidence, there has been controversial evidence on thespecificassociationofTAGwithCHD.TheFramingham study demonstrated that TAGs are independently related in women at all ages but missing statistical significance inthemultivariatestudies inmen.Accordingtotwometa-analyses, TAGs were independent risk factors for CHD, even after adjustment with HDL-C, which is strongly and inversely correlated withTG.[26]In our study, in analyzing the age-wise distribution of triglyceride concentration between the groups we found, significant correlations between the Case and Control groups in 41-50 and 51-60 years' age groups and in both age groups the P value was found, <0.0001. But in >60 years' age group we did not find any significant correlation and there the P value was 0.478. In analyzing the age-wise distribution of HDL concentration between the groups we found, significant correlations between the Case and Control groups in all age groups and the P value were < 0.0001 in every age group. On the other hand, in analyzing the age-wise distribution of LDL concentration between the groups we found, significant correlations between the Case and Control groups in 41-50 and 51-60 years' age groups where the P values were found, <0.0001 and 0.0002 respectively. But in >60 years' age group we did not find any significant correlation and there the P value was 0.515. Clinical studies basedonextensiveliteraturesupportstheinverserelationship between HDL-C levels and atherosclerosis. HDL enhances the reverse cholesterol transport and has anti-oxidative, anti-inflammatory, antithrombotic, and vasoprotective effects[27]. Studies have also consistently demonstrated that HDL-C is inversely associated with the risk of CHD. Thus, an increase in HDL-C is linearly associated with a reduction in cardiovascularrisk.Inlinewiththesefindings,presentstudy demonstrated a significant decrease in the HDL-C levels in patients with CHD when compared tocontrols.[28]The National Cholesterol Education Program (NCEP) recommends an LDL-C goal of<100 mg/dl in patients with established CHD and in those who are CHD risk-equivalent. Aggressive LDL-C reduction is associated with less at hero sclerosis progression, lower rates of revascularization, and fewer ischemic events compared with moderate LDL-C reduction or conventional treatment.[29]

V. Conclusion And Recommendations

In this study, it was found that, the total cholesterol, triglycerides HDL cholesterol and LDL cholesterol concentrations were significantly higher in coronary heart disease (CHD) patients. These findings may be helpful in the treatment arena of CHD and in similar further studies. We had some limitations in this study. This was a single centered study with a small sized sample. So the findings of this study may not reflect the exact

scenario of the whole country. For getting more specific information we would like to recommend for conducting more studies in several places with larger sized sample.

References

[1]. D'Agostino RB, Russell MW, Huse DM, Ellison RC, Silbershatz H, Wilson PW, Hartz SC. Primary and subsequent coronary risk appraisal: New results from the Framingham study. Am Heart J, 2000:139 (2 Pt 1):272-281.

[2]. Nordestgaard BG, Varbo A. Triglyceridesandcardiovascular disease. Lancet. 2014; 384(9943):626-635.

[3]. Natarajan P, Ray KK, Cannon CP. High-density lipoprotein and coronary heart disease: current and future therapies. J Am CollCardiol. 2010; 55(13):1283-1299.

[4]. Adak M, Shivapuri JN. Serum lipid and lipoprotein profile abnormality in predicting the risk of coronary artery disease in non-diabetic patients attending NMCTH, Birgunj. Nepal Med Coll J. 2010;12(3):158-64.

[5]. Bonow RO, Carabello BA, Kanu C. Guidelines for the management of patients with valvular heart disease: a report of the American Heart Association Task Force on Practice Guidelines. Circulation. 2006; 114: 84 – 231.

[6]. Voight BF et al. Plasma HDL cholesterol and risk of myocardial infarction: a mendelianrandomisation study. Lancet. 2012; 380:572–80. [PubMed: 22607825]

[7]. Ridker PM, Pare G, Parker AN, Zee RY, Miletich JP, Chasman DI. Polymorphism in the CETP gene region, HDL cholesterol, and risk of future myocardial infarction: Genomewide analysis among 18 245 initially healthy women from the Women's Genome Health Study. CircCardiovasc Genet. 2009; 2:26–33. [PubMed: 20031564]

[8]. Brown BG, Zhao XQ, Chait A, Fisher LD, Cheung MC, Morse JS, Dowdy AA, Marino EK, Bolson EL, Alaupovic P, Frohlich J, Albers JJ. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. N Engl J Med. 2001; 345:1583–92. [PubMed: 11757504]

[9]. Maxfield FR, Tabas I. Nature. 2005; 438(7068): 612-21

[10]. Underwood JCE, Cross SS. General and Systematic Pathology. 5th edn. Churchill Livingstone. 2009

[11]. Holick MF. N Engl J Med. 2007; 19(3): 266-81

[12]. Akanda, Md& Ali, Zulfikar& Choudhury, Kamrun&Sayami, Lima & Huda, Reaz& Hossain, Shauket&Mohsin, Minhazul& Ali, Md. (2016). Study of Lipid Profile in Adult Population of Bangladesh. Cardiovascular Journal. 8. 128. 10.3329/cardio.v8i2.26815.

[13]. Choudhury, Kamrun&Mainuddin, Akm&Wahiduzzaman, Mohammad &Shariful Islam, Sheikh Mohammed. (2014). Serum lipid profile and its association with hypertension in Bangladesh. Vascular Health and Risk Management. 2014: 10. 327-332. 10.2147/VHRM.S61019.

[14]. Kumar V, Abbas AK, Aster JC.(2015). Robbins &Cotran Pathologic Basis of Disease, 9th Edition, Elsevier Saunders, Philadelphia PA 19103 - 2899, USA.

[15]. JindrichSpinar.(2012). Hypertension and ischemic heart disease. SciverseScienceDirect .54: 433-438.

[16]. Paratz Z, Sonny Palmer, Justin Mariani, Fracp, Fcsanz.(2015).The cardiac complications of obesity. Medicine Today. 16(11):211–232.

[17]. Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, Boekholdt SM, Khaw KT, Gudnason V.(2007).Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies.Circulation. 115(4):450-8.

[18]. Campos Wd, StabeliniNeto A, Bozza R, Ulbrich AZ, Bertin RL, Mascarenhas LP, Silva SG, Sasaki JE.(2010).[Physical activity, lipid consumption and risk factors for atherosclerosis in adolescents].Arq Bras Cardiol. 94(5):601-7.

[19]. Ahmed SM, Clasen ME, Donnelly JE.(1998). Management of dyslipidemia in adults. Am Fam Physician.57:2192.

[20]. Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, et al.(2009). Major lipids, apolipoproteins, and risk of vascular disease. Jama. 302(18):1993–2000.

[21]. Werner M, Garberielson DG, Estman J. Ultramicro determination of serum triacylglycerols by bioluminescent assay. Clin Chem. 1981; 27:268-271.

[22]. Alarabawy RA, El Ahwal HM, Elwagih MM, Ismail A, Khattab MA. Use of multi-detector CT angiography in identification and classification of aorto-iliac diseases; clinical and surgical application. The Egyptian Journal of Radiology and Nuclear Medicine, 2015. http://www.sciencedirect.com/science/article/pii/S0378603X15002041.

[23]. Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. Nature reviews Cardiology, 2011; 8(1):30-41. doi:10.1038/nrcardio.2010.165.

[24]. Institute of Medicine (US) Committee on Preventing the Global Epidemic of Cardiovascular Disease: Meeting the Challenges in Developing Countries; Fuster V, Kelly BB, editors. Promoting Cardiovascular Health in the Developing World: A Critical Challenge to Achieve Global Health. Washington (DC): National Academies Press (US); 2010. 2, Epidemiology of Cardiovascular Disease. Available from: http://www. ncbi. nlm. nih. gov/ books /NBK4 5688/.

[25]. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L et al.,Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004; 364:937-52.

[26]. Wilson PW, Cupples LA, Kannel WB. Is hyperglycemia associated with CVD? The Framingham Study. American Heart Journal. 1991; 121:586-590.

[27]. Castelli WP, Anderson K, Wilson PW, Levy D. Lipids and risk of coronary heart disease. The Framingham Study. Ann Epidemiol. 1992; 2:23-8.

[28]. Gotto AM. Cholesterol intake and serum cholesterol level. N Engl J Med 1991; 324:912-913.

[29]. Panagiotakos DB, Pitsavos C, Skoumas J, Chrysohoou C, Toutouza M, Stefanadis CI, Toutouzas PK. Importance of LDL/HDL cholesterol ratio as a predictor for coronary heart disease events in patients with heterozygous familial hypercholesterolaemia a 15-year follow-up (1987-2002). Curr Med Res Opin. 2003; 19:89-94. pp. 802–809.