UDC: 616.132.2:616.153.915]-055.2
Professional paper

IMPACT OF DYSLIPIDEMIA ON CORONARY HEART DISEASE IN WOMEN (REVIEW)

Klara HYSENAJ[1], Rezarta STENA[2], Shpetim QYRA[3], Blerina BANI[2]

[1*]*Clinical Department, Faculty of Medical and Technical Sciences, AL*
[2] *Pre-Clinical Department, Faculty of Medical and Technical Sciences, AL*
[3] *Institute of Public Health*
[*]*Corresponding author e-mail: Klara.hysenaj@uniel.edu.al*

Abstract

Introduction: The increase in the level of lipids in the blood is one of the risk factors for cardiovascular diseases (due to atherosclerosis and thrombosis) increasing premature morbidity, disability, financial cost and mortality, not only in the EU and the USA, but also in countries developing worldwide. It has been proven that lipid disorders promote the development of atherosclerosis and its clinical consequences such as CVD including (coronary heart disease, acute myocardial infarction, peripheral artery disease, heart failure and sudden death). Combinations of lipoprotein levels and lipid fractions play a major risk role in terms of coronary heart diseases.
Purpose: Evidence of dyslipidemia as a risk factor for CVD, especially in obese women who suffer from metabolic syndrome or diabetes and have lipid profiles that negatively affect the risk of coronary heart disease. Methodology: International literature review in PubMed, CINAHL, Am J Cardiology, Int J Public Health; in accordance with the purpose and objectives of the study.
Result: Coronary heart diseases are the leading cause of death among women and men although they are less common and appear later in women than in men. Each year 345,000 women suffer from an initial or recurrent myocardial infarction, and 261,000 women die from MI. Compared to men, women, and especially women in the postmenopausal period, remain at high risk for coronary disease. In women, calcification occurs 10 to 15 years later. Multiple angiographic studies of coronary arteries have shown a lower rate of epicardial coronary artery disease in women than in age-matched men. Elevated levels of Lp (a) appear to be more associated with the occurrence of coronary heart disease than with the severity of coronary artery disease in both sexes. Outcome data in women using lipid-lowering medications other than statins are extremely limited.
Conclusion: The importance of a healthy lifestyle should begin in childhood and continue throughout life. Although the benefits of lipid-lowering therapy in women with cardiovascular disease are clear, more data are needed in those without cardiovascular disease. Clinical trials for lipid-lowering women with cardiovascular disease to date have used a strategy focused on lowering LDL-cholesterol, which may not be optimal for women who have low HDL-cholesterol or triglyceride levels. which are very important factors affecting coronary heart disease. It remains to be determined whether outcomes among women will improve if treatment strategies are directed toward more aggressive and comprehensive modification of lipoprotein profiles.

Keywords: dyslipidemia, MI, lipids, cardiovascular disease, statins.

Introduction

Coronary heart disease is the leading cause of death for American women and beyond. There is a large difference between young and old women as well as between women and men regarding coronary heart pathologies, their incidence, and their prevalence throughout the life cycle. Combinations of lipoprotein levels and lipid fractions play a major risk role in terms of coronary heart disease. Likewise, the effects of hormones on the level of lipoproteins are complex, change throughout life, and are influenced by taking hormonal contraceptives and hormone replacement therapy. Obese women who suffer from metabolic syndrome or diabetes have lipid profiles that negatively affect the risk of coronary heart disease. Various evidences suggest that lipid-lowering statin therapy provides benefits in reducing the risk of coronary heart disease for women; however, they remain incompletely treated, and more data

are needed to determine the prevention and treatment of cardiovascular pathologies in this population.
In 2002, 3 million women were affected by myocardial infarction (MI), while 3.3 million were found to have a medical history of angina pectoris (American Heart Association. Statistical Fact Sheet Populations et al., January 26, 2005). Each year, 345,000 women suffer from an initial or recurrent myocardial infarction, and 261,000 women die from MI. From 1970 to 2001, discharges from the hospital of female patients related to coronary heart pathologies increased by 47% (American Heart Association. Statistical Fact Sheet Populations et al., January 26, 2005). Compared to men, women, and especially postmenopausal women, remain at high risk for coronary heart disease.

Purpose

Evidence of dyslipidemia as a risk factor for CVD, especially in obese women who suffer from metabolic syndrome or diabetes and have lipid profiles that negatively affect the risk of coronary heart disease.

Methodology

International literature review.

The data search for this study was carried out in PUBMEDCINAHL, Am J Cardiology, Int J Public Health based on the selection of the key words of the study, which are women, cardiovascular disease, dyslipidemia, and statins. Initially, 140 articles focusing on dyslipidemia and cardiovascular diseases, mainly in women, were selected. After filtering the articles according to the inclusion and exclusion criteria, 94 complete, accessible English-language articles were selected. After applying these criteria, 15 articles were selected that were included in the study and review of the literature on the selected topic.
The extraction of the results was done in a descriptive way after the construction of the table where the data obtained from the selected studies were thrown.

Results

Gender differences in the presentation of coronary arteriosclerosis

Coronary arteriosclerosis begins in early childhood, and the risk of being affected by it increases with age. There is a close relationship between traditional risk factors for the cardiovascular system and the extent of arteriosclerotic diseases in children and adolescents, men and women, that is analogous to what is seen in adults. Arteriosclerosis is usually more pronounced in individuals with multiple coexisting risk factors (Berenson GS et al., Srinivasan SR et al., Bao W et al., Newman WP III et al., Tracy RE et al., & Wattigney WA et al., 1998). In older individuals, women have lower rates of coronary artery calcification than men, although calcification increases with age in both sexes (calcification occurs 10 to 15 years later in women) (Hoff JA et al., Chomka EV et al., Krainik AJ et al., Daviglus M et al., Rich S et al., &Kondos GT., et al., 2001). Numerous coronary artery angiographic studies have shown a lower rate of epicardial coronary artery disease in women than in age-matched men.
This gender discrepancy is proven even after the classification of different symptoms (typical angina pectoris, atypical angina pectoris, chest pain manifested not in the form of angina pectoris) (Chaitman BR et al., Bourassa MG at al.,& Davis K et al., 1981). It is also proven in

populations without clinical manifestations of coronary heart diseases that undergo coronary angiography for a surgical intervention at the level of heart valves (Enriquez-Sarano M et al., Klodas E et al., Garratt KN et al., Bailey KR et al., Tajik AJ et al., &Holmes DR Jr et al.,). An intravascular ultrasound study by Rasheed et al.(Rasheed Q et al., Nair R et al., Sheehan H et al., & Hodgson JM et al., 1994)., showed that arteriosclerotic plaques were more present in men than in women (47% vs. 33%, p = 0.06). In a study of individuals over 40 years of age who died 1 year after coronary artery bypass grafting, women were found to have a greater amount of fibrous tissue, although there was no difference in gender related to the severity of the obstruction or the amount of intracellular lipids (Mautner SL et al., Lin F et al., Mautner GC et al.,& Roberts WC et al., 1993). From a series of autopsies, it was noted that women were twice as likely as men to have narrowing of the atherosclerotic plaques (37% vs. 18%), while plaque rupture was more common in men than men. among women (respectively, 82% and 63%) (Arbustini E et al., Dal Bello B et al., & Morbini P et al., 1999).
Among victims who experienced sudden death, (Burke AP et al., Farb A et al., Malcom GT et al., Liang Y et al., Smialek J et al., &Virmani R et al., 1998) found that acute coronary thrombosis was associated with the narrowing of atherosclerotic plaques in young and premenopausal women, whereas plaque rupture with superimposed thrombi or healed infarction without thrombosis was more typical in older women, who may have been postmenopausal. The risk for these women was also related to several other factors, such as smoking, increased glycated hemoglobin, high cholesterol, and hypertension (Burke AP et al., Farb A et al., Malcom GT et al., Liang Y et al., Smialek J et al., & Virmani R et al., 1998).

Lipoproteins during life stages

Lipoprotein levels in girls and boys before puberty are similar. The level of low-density lipoproteins (LDL) in childhood and adulthood is higher compared to high-density lipoproteins and triglycerides (Bao W et al., Srinivasan SR et al., Wattigney WA et al., Bao W et al., & Berenson GS et al., 1996).The change in high-density lipoprotein level and HDL particle size in both sexes appears as early as puberty, with women having higher high-density lipoprotein levels throughout their lives compared to men (National Heart, Lung, and Blood Institute., et al., July 1980). (Freedman DS et al., Bowman BA et al., Srinivasan SR et al., Berenson GS et al., & Otvos JD et al., 2001). (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults., et al .,September 6, 2005). (Gardner CD et al., Tribble DLet al., Young DR et al., Ahn D et al., & Fortmann SP et al., 2000). This gender difference in HDL-cholesterol levels is preserved even in men or women with coronary heart disease, who usually tend to have lower HDL-cholesterol levels than people without coronary heart disease (The Bezafibrate Infarction Prevention (BIP) Study Group, Israel., et al.,1992). A significant proportion of women suffering from coronary heart disease have HDL-cholesterol levels ≥ 60 mg/dl, which has been considered a protective value against coronary heart disease (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults., et al .,September 6, 2005) (Gardner CD et al., Tribble DLet al., Young DR et al., Ahn D et al.,& Fortmann SP et al., 2000) (The Bezafibrate Infarction Prevention (BIP) Study Group, Israel., et al.,1992) (Bittner V et al., Simon JA et al., Fong J et al., Blumenthal RS et al., Newby K et al.,& Stefanick ML., et al., 2000) . In contrast to HDL cholesterol, low-density lipoprotein (LDL) and total cholesterol levels are lower in young and middle- aged women than in age-matched men, but after menopause, the opposite happens (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults., et al .,September 6, 2005) (Gardner CD et al., Tribble DLet al., Young DR et al., Ahn D et al.,& Fortmann SP et al., 2000) (The Bezafibrate Infarction Prevention (BIP) Study Group, Israel., et al.,1992) (Bittner V et al., Simon JA et al., Fong J et al., Blumenthal RS et al.,

Newby K et al.,& Stefanick ML., et al., 2000) (Gardner CD et al., Winkleby MA et al., & Fortmann SP., et al .,2000).

Premenopause

Hormonal influences on the level of lipoproteins are complex (Sacks FM et al., & Walsh BW et al., 1994). In premenopausal women, lipoprotein levels vary throughout the menstrual cycle, with considerable heterogeneity between individuals (Gosland IF et al., Wynn V et al., Crook D et al., &Miller NE., et al.,1997). Women who have given birth tend to have lower LDL-cholesterol levels than women who have not given birth (van Stiphout WA et al., Hofman A et al.,& de Bruijn AM.et al.,1987). The effects of contraceptive preparations vary based on the dose of estrogen, the dose of progestin, the androgenicity of the progestin, and the route of administration. The increase in the level of triglycerides up to 57%, accompanied by a decrease in LDL, occurs in the case of the use of oral contraceptives, while the changes in the levels of LDL-cholesterol and HDL tend to be at smaller levels (Greenlund KJ et al., Webber LS et al., Srinivasan S et al., Wattigney W et al., Johnson C et al.,& Berenson GS., et al .,1997) (Gosland IF et al., Wynn V et al., Crook D et al., &Miller NE., et al.,1997) (Foulon T et al., Payen N et al., Laporte F et al .,2001).

Postmenopause

Total cholesterol levels are known to increase in menopause (Akahoshi M et al ., Soda M et al., Nakashima E et al., Shimaoka K et al, Seto S et al., & Yano K ., et al. 2007) (Hjortland MC et al., McNamara PM et al., & Kannel WB., et al ., 1976) (van Beresteijn EC et al., Korevaar JC et al., Huijbregts PC et al., Schouten EG et al., Burema J et al.,& Kok FJ., et al., 1993).

Regarding LDL-cholesterol levels in menopause, they increase, although such an increase is not evident in all studies (Campos H et al., McNamara JR et al., Wilson PWF et al., Ordovas JM et al., &Schaefer EJ et al.,1988)(Carr MC et al., Kim KH et al.,& Zambon A et al.,2000) (Do KA et al., Green A et al., Guthrie JR et al., Dudley EC et al., Burger HG et al.,& Denerstein L et al., 2000) (Matthews KA et al., Meilahn E et al., Kuller LH et al., Kelsey SF et al., Caggiula AW et al.,& Wing RR.et al., 1989) (Matthews KA et al., Wing RR et al.., Kuller LH et al., Meilahn EN et al.,& Plantinga P et al .,1994). In some cases, a decrease in the level of HDL2 particles has been reported, while HDL-cholesterol levels tend to remain constant. Postmenopausal women tend to have greater increases in lipoprotein levels after consuming a high-fat meal than premenopausal women (van Beek AP et al., de Ruijter-Heijstek FC et al., Erkelens DW et al., &de Bruin TWA et al., 1999).

Lipoproteins in obesity and diabetes

Many studies document adverse changes in the lipid profile between obese women and women with metabolic syndrome or diabetes mellitus (Barrett-Connor E et al., Giardina E-GV et al., Gitt AK et al., Gudat U et al., Steinberg HO et al., &Tschoepe D et al., 2004) . These lipid changes are characterized by a greater prevalence of the B phenotype of LDLs, lower levels of HDL-cholesterol, and higher levels of triglycerides (Austin MA et al., Selby JV et al .,1995). Adverse lipoprotein changes associated with diabetes tend to be more pronounced in women than in men and may have a greater adverse prognostic impact of diabetes among women, which has been consistently demonstrated (Foulon T et al., Payen N et al., & Laporte F et al .,2001) (Walden CE et al., Knopp RH et al., Wahl PW et al., Beach KW et al.,

&Strandness E Jr et al., 1984)(Lerner DJ et al., & Kannel WB. et al .,1986) (Natarajan S et al., Liao Y et al., Cao G et al., Lipsitz SR et al.,& McGee DL et al ., 2003).

Impact of dyslipidemia on women

This literature review will focus only on the impact of dyslipidemia. Many studies show that the risk of coronary heart disease increases with increasing levels of LDL cholesterol and total cholesterol and decreases with increasing levels of HDL cholesterol in both sexes, but the relative importance of these lipoprotein fractions may vary by gender (Anderson KM et al., Castelli WP et al., & Levy D et al. 2006) (Castelli WP et al., Garrison RJ et al., Wilson PWF et al., Abbott RD et al., Kalousdian S et al., & Kannel WB et al .,1986) (Sharrett AR et al., Ballantyne CM et al.,& Coady SA et al .,2001)(Brunner D et al., Weisbort J et al., & Meshulam N et al .,1987) (Bass KM et al, Newschaffer CJ et al., Klag MJ et al.,& Bush TL et al .,1993) (Bass KM et al, Newschaffer CJ et al., Klag MJ et al., & Bush TL et al .,1993). HDL-cholesterol, total cholesterol, and triglycerides are more closely related to the risk of coronary heart disease in women, while LDL- cholesterol appears to be a stronger predictor for men (Brunner D et al., Weisbort J et al., & Meshulam N et al .,1987) (Bass KM et al, Newschaffer CJ et al., Klag MJ et al.,& Bush TL et al .,1993) . Lipoproteins at abnormal levels can often cause coronary heart disease in healthy women, but they can re-emerge in women who may have had these episodes before (Kannel WB., et al .,1995) (Shlipak MG et al., Chaput LA et al., Vittinghoff E et al., 2003).
Levels of residual cholesterol and triglycerides are higher in postmenopausal women than in premenopausal women and higher in those with coronary heart disease than in healthy women (Sanada M et al., Nakagawa H et al., Kodama I et al., Sakasita T et al., &Ohama K et al 2000) (Fukushima H et al., Kugiyama K et al., &Sugiyama S et al., 2001). RLP cholesterol in the Framingham Heart Study 50 was an independent risk factor for cardiovascular disease among enrolled women. Although the levels in this group were on average very high, it was observed that they were not directly related to the progression of coronary heart disease or other clinical events (Bittner V et al., Tripputi M et al., Hsia J et al., Gupta H et al., & Steffes M., et al., 2004). Elevated levels of Lp (a) appear to be more associated with the occurrence of coronary heart disease than with the severity of coronary artery disease in both sexes. In the Framingham study, increased levels of Lp(a) in women strongly predicted MI but also showed an association with the development of cerebrovascular diseases (Bostom AG et al., Gagnon DR et al., &Cupples LA et al ., 1994). Elevated Lp (a) also predicted recurrent coronary heart disease events among women.

Impact of lipid-lowering therapy in women

A strong lifestyle modification directly affects the stabilization or regression of coronary lesions (Ornish D et al., Scherwitz LW et al.,& Billings JH et al., 1998) (Hambrecht R et al., Niebauer J et al., &Marburger C et al.,1993). Although this modification is more visible in men than in women with coronary disease, the latter should necessarily deal with the regulation of some factors such as weight management, adherence to a healthy diet, and regular physical activity, which will then have beneficial effects on the lipid profile (and other risk factors) in both women and men. Therefore, lifestyle modification should be recommended to all women with dyslipidemia, as described in current prevention guidelines (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults., et al ., September 6, 2005). After taking statins, which affect the reduction of lipids, changes in lipoprotein levels are similar in both men and women (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults., et al ., September 6, 2005)

(Goldberg AC., et al) . The cardiovascular benefits of lipid-lowering therapy in women are usually less clear than in men because women are underrepresented in most clinical trials, and gender-specific subgroup results are often not reported. Outcome data for women using lipid-lowering medications other than statins is extremely limited (Walsh JME et al., &Pignone M et al .,2004).

Angiographic benefit in women and men with familial hypercholesterolemia treated with lovastatin was shown by Kane et al. (Kane JP et al., Malloy MJ et al., Ports TA et al., Phillips NR. et al, Diehl JC et al., &Havel RJ et al., e.,1990).in 1990. In a meta-analysis by LaRosa et al. (LaRosa JC et al., He J et al., & Vupputuri S et al .,1999). of clinical outcome data after statin use showed that women and men achieved similar reductions in coronary disease prevention, so the number needed to treat was calculated to be 31 for women and 27 for men. Another meta-analysis of statins updated by Walsh and Pignone (Walsh JME et al.,& Pignone M et al .,2004) included newer trials, such as antihypertensive treatment and lipid-lowering treatment to prevent heart attack (ALLHAT), the Anglo-Scandinavian lipid-lowering trial of Cardiac Results, or the Heart Protection Study. The Heart Protection Study is particularly important because it enrolled over 5,000 women, more than all other previous trials combined, and showed that major vascular events were significantly reduced by statin use from 17.7% to 14.4%. After the studies, the authors concluded that women with coronary heart disease who are treated with statins achieve a 20% to 30% reduction in coronary heart disease, MI, and revascularization mortality but do not have a total reduction in mortality.

Acute coronary syndrome

Trials of statins in patients with acute coronary syndrome were not included in the updated meta-analysis. In the study evaluating atorvastatin and infection therapy, after combining the two elements, a reduction of up to 16% was achieved, which included a reduction in deaths from unknown causes, a reduction in MI, a reduction in unstable angina requiring rehospitalization, a reduction in revascularization, and a reduction in cerebrovascular strokes. 61 In an aggressive lipid-lowering therapy that lowered LDL-cholesterol to a level of 62 mg/dl, women comprised only 22% of study subjects, which showed that the benefit of lowering the lipid profile was stable in all gender age groups (Cannon CP et al., Braunwald E et al., &McCabe CH et al .,2004)

Primary prevention

After analyzing women without coronary heart disease, authors Wlsch and Pignone concluded that there was insufficient evidence to determine whether lipid-lowering therapy was effective in reducing coronary heart disease episodes in women without cardiovascular disease. Previous (Walsh JME et al., &Pignone M et al .,2004).

The Third Report of the Adolescent Treatment Panel (ATP III) of the National Cholesterol Education Program does not recommend different treatment guidelines for men and women. They recommend considering drug therapy for middle-aged women with a 10-year risk of less than 10% for cardiovascular heart disease. This treatment is somewhat more protective for these women than it is for middle-aged men in the same risk category (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults., et al ., 2002).

Statin therapy

According to clinical evidence, the most commonly used lipid-lowering drugs are statins. The efficacy of statins is currently shown in Tables 1 (Vaughan CJ et al., &Gotto AM Jr et al. (Update on statins: 2003.
Circulation 2004) (DeAngelis G., et al .,2004) (Grundy SM et al., Cleeman JI et al.,& Bairey Merz CN et al ,.2004).. Statins are generally readily accepted by the body and may cause mild liver abnormalities or muscle toxicities at a low incidence. The most important interactions between other drugs and statins have been reported, especially with statins metabolized by the CYP 3A4 system (Tables 2 Vaughan CJ et al., &Gotto AM Jr et al. (Update on statins: 2003. Circulation 2004) (DeAngelis G., et al .,2004) (Grundy SM et al., Cleeman JI et al., &Bairey Merz CN et al ,.2004) . Statins should not be used in some categories, such as pregnant women, women who are trying to conceive, or those who are breastfeeding. The reader can refer to the ATP III guidelines for more detailed information on non-statin drugs currently available in pharmacies (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults., et al ., 2002).

Table 1. Comparative efficacy and pharmacological data of currently available statins Changes in % Dosage of Standard Protein

Changes % Proteins **Dosage form** **Standards**

Medication	2TC	2LDL-C	1HDL-C	2TG	Tablets, mg	Dose, mg *	Metabolism	Connection %	T1/2, h	Hydrophilic
Atorvastatin	25–45	26–60	5–13	17–53	10,20,40,80	10	CYP3A4	98	13–30	No
Fluvastatin	16–27	22–36	3–11	12–25	20,40, 80	40–80	CYP2C9	98	0.5–3.0	No
Lovastatin	16–34	21–42	2–10	6–27	10,20, 40	40	CYP3A4	>95	2–4	No
Pravastatin	16–25	22–34	2–12	15–24	10,20,40,80	40	Sulfation	43–67	2–3	Yes
Rosuvastatin	33–46	45–63	8–14	10–35	5,10,20,40	5–10	CYP2C9,CYP2C19	88	19	Yes
Simvastatin	19–	26–47	8–16	12–34	5,10,20,40, 80	20–40	CYP3A4	95–98	1–3	No

	36									

Table 1 is based on data compiled from references 63–65. The standard dose is a dose that will achieve a 30% to 40% reduction in LDL-C, as recommended by Grundy et al. (64). CYP = cytochrome P; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides; T1/2 = halflife.

Table 2. Important drug interactions with selected statins

Lipid-lowering agents are: Fenofibrates (especially gemfibrozil), niacin
Cardiovascular agents Warfarin, digoxin, verapamil, and amiodaone
Immunosuppressive agents Tacrolimus, cyclosporine
Agents for treating infections Fluconazole, itraconazole, and keyoconazole Erythromycin, clarithromycin HIV protease inhibitor
Psychoactive agents Nefazodone, venlafaxine, fluoxetine, sertraline, and benzodiazepine
Others Antihistamines, citrus juice

Table 2 is based on the data in References 63–65: HIV = human immunodeficiency virus.

Undertreatment and treatment changes

The HERS (Schrott HG et al., Bittner V et al., Vittinghoff E et al., Herrington DM et al., &Hulley S et al .1997)., study, which enrolled postmenopausal women suffering from coronary heart disease from 1993 to 1994, concluded that of those 47% receiving lipid-lowering therapy, only 37% met their LDL target. of <130 mg/dl as recommended by the 1988 ATP guidelines, and only 9% of them met the LDL-cholesterol goal of ≤100 mg/dl as recommended by the 1993 guidelines. During 1994 and 1997, Miller et al. reported the treatment rates of enrolled patients who participated in the Randomized Prospective Evaluation of Vascular Effects of the Norvasc Trial. During that period, the proportion of women who achieved an LDL-cholesterol goal of <100 mg/dl increased from 6% to 12%, while the proportion of men increased from 17% to 31%[67]. Data compiled from 1998 to 1999 from the National Myocardial Infarction Registry showed that women were less likely than men to receive lipid-lowering therapy after hospital discharge, although less than a third of patients of both sexes discontinued treatment. The 1996 and1997 Women's Ischemia Syndrome Evaluation Study showed that only 24% of women had a history of coronary heart disease, 56% of them were at high risk for coronary heart disease, and 88% of them were at lower risk, having met the respective LDL- cholesterol targets. All women underwent diagnostic coronary angiography, but the angiographic results did not influence

their therapy, neither in women with newly diagnosed coronary artery disease nor in those with a previously confirmed diagnosis (Bittner V et al., Olson M et al., & Kelsey SF et al ., 2000)

Usually, the reasons for undertreatment of lipoproteins are complex and related to the preferences of the doctor and the patient, as well as to environmental factors such as personal care or the cost of medication. Current guidelines for the prevention of cardiovascular risk in women repeatedly emphasize the importance of maintaining normal lipoproteins. A recent report from the Cardiac Rehabilitation Center shows that treatment rates among women with coronary heart disease have improved, as 49% of them who completed cardiac rehabilitation between 1996 and 2003 achieved their LDL-cholesterol goal of less than 100 mg/dl (Sanderson BK et al., & Bittner V et al.,2005) . It is not yet known whether this situation is improved in less developed settings or in women without known cardiovascular disease who are at high risk for subsequent cardiovascular events.

Conclusion on future directions for lipids in cardiovascular disease

Coronary heart diseases are the most important cause of death in women and are one of the main factors affecting disability and poor quality of life for many of them. Dyslipidemia is also an important risk factor for the onset and progression of atherosclerosis and is closely related to cardiovascular events. The importance of a healthy lifestyle should begin in childhood and continue throughout life. Although the benefits of lipid-lowering therapy in women with cardiovascular disease are clear, more data is needed in those without cardiovascular disease. Clinical trials for lipid-lowering women with cardiovascular disease to date have used a strategy focused on lowering LDL-cholesterol, which may not be optimal for women who have low HDL-cholesterol or triglyceride levels. which are very important factors affecting coronary heart disease. It remains to be determined whether outcomes among women will improve if treatment strategies are directed toward more aggressive and comprehensive modification of lipoprotein profiles.

References

[1] Akahoshi M., Soda M, Nakashima E., Shimaoka K, Seto S., Yano K., et al. (2007).Effects of menopause on trends of serum cholesterol, blood pressure, and body mass index. Circulation 1996;94:61– 6.

[2] American Heart Association. Statistical Fact Sheet Populations et al.(January 26, 2005).Women and Cardiovascular Diseases: Statistics. Available at:http:/americanheart.org/downloadable/heart/1104938287787FS10WM05rev.

[3] Anderson KM., Castelli WP., Levy D., et al. (2006). Cholesterol and mortality: 30 years of follow-up from the Framingham Study. JAMA 1987;257: 2176 – 80.

[4] Arbustini E., Dal Bello B., Morbini P., et al. (2008). Plaque erosion is a major substrate for coronary thrombosis in acute myocardial infarction. Heart 1999;82:269 –72.

[5] Austin MA., Selby JV.,et al. (1995). LDL subclass phenotypes and the risk factors of the insulin resistance syndrome. Int J Obes Relat Metab Disord 19 Suppl 1:S22– 6.

[6] Bao W., Srinivasan SR., Wattigney WA., Bao W., Berenson GS., et al.(1996). Usefulness of childhood low-density lipoprotein cholesterol level in predicting adult dyslipidemia and other cardiovascular risks: the Bogalusa Heart Study. Arch Intern Med 1996;156:1315–20.

[7] Barrett-Connor E., Giardina E-GV., Gitt AK., Gudat U., Steinberg HO., Tschoepe D., et al.(2004). Women and heart disease: the role of diabetes and hyperglycemia. Arch Intern Med 2004;164:934 – 42.

[8] Bass KM, Newschaffer CJ., Klag MJ., Bush TL., et al.(1993). Plasma lipoprotein levels as predictors of cardiovascular death in women. Arch Intern Med 1993;153:2209 –16.

[9] Berenson GS., Srinivasan SR., Bao W., Newman WP III., Tracy RE., Wattigney WA., et al.(1998). for the Bogalusa Heart Study. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. N Engl J Med 1998;338:1650 – 6.

[7] Bittner V., Olson M., Kelsey SF., et al.(2000) ., for the WISE Investigators. Effect of coronary

angiography on use of lipid-lowering agents in women: a report from the Women's Ischemia Syndrome Evaluation (WISE) study. Am J Cardiol 2000;85:1083– 8.

[8] Bittner V., Simon JA., Fong J., Blumenthal RS., Newby K., Stefanick ML., et al.(2000). Correlates of high HDL cholesterol among women with coronary heart disease. Am Heart J 2000;139:288 – 96.

[12] Bittner V., Tripputi M., Hsia J., Gupta H., Steffes M., et al.(2004). for the WAVE Investigators. Remnant-like lipoproteins, hormone therapy, and angiographic and clinical outcomes: the Women's Angiographic Vita- min & Estrogen trial. Am Heart J 2004;148:293–9.

[9] Bostom AG., Gagnon DR., Cupples LA., et al. (1994).A prospective investigation of elevated lipoprotein (a) detected by electrophoresis and cardiovascular disease in women: the Framingham Heart Study. Circulation 1994;90:1688 – 95.

[10] Brunner D., Weisbort J., Meshulam N., et al.(1987). Relation of serum total cholesterol and high-density lipoprotein cholesterol percentage to the incidence of definite coronary events: twenty-year follow-up of the Donolo-Tel Aviv Prospective Coronary Artery Disease Study. Am J Cardiol 1987;59:1271– 6.

[11] Burke AP., Farb A., Malcom GT., Liang Y., Smialek J., Virmani R.., et al.(1998). Effect of risk factors on the mechanism of acute thrombosis and sudden coronary death in women. Circulation 1998;97:2110 – 6.

[12] Campos H., McNamara JR., Wilson PWF., Ordovas JM., Schaefer EJ., et al.(1988). Differences in low density lipoprotein subfractions and apolipoproteins in premenopausal and postmenopausal women. J Clin Endocrinol Metab 1988;67:30 –5.

[13] Cannon CP., Braunwald E., McCabe CH., et al.(2004) for the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350:1495–504.

[14] Carr MC., Kim KH., Zambon A., et al.(2000). Changes in LDL density across the menopausal transition. J Invest Med 2000;48:245–50.

[15] Castelli WP., Garrison RJ., Wilson PWF., Abbott RD., Kalousdian S., Kannel WB., et al.(1986). Incidence of coronary heart disease and lipoprotein cholesterol levels: the Framingham Study. JAMA 1986;256:2835– 8.

[16] Chaitman BR., Bourassa MG., Davis K., et al.(1981). Angiographic prevalence of high-risk coronary artery disease in patient subsets (CASS). Circulation 1981;64:360 –7.

[17] Colhoun HM., Betteridge DJ., Durrington PN., et al.(2004). on behalf of the CARDS Investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004;364:685–96.

[18] DeAngelis G., et al.(2004). The influence of statin characteristics on their safety and tolerability. Int J Clin Pract 2004;58:945–55.

[19] Do KA., Green A., Guthrie JR., Dudley EC., Burger HG., Denerstein L., et al.(2000). Longitudinal study of risk factors for coronary heart disease across the menopausal transition. Am J Epidemiol 2000;151:584 –93.

[20] Enriquez-Sarano M., Klodas E., Garratt KN, Bailey KR., Tajik AJ., Holmes DR Jr., et al. Secular trends in coronary atherosclerosis: analysis in patients with valvular regurgitation. N Engl J Med

[21] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults., et al .(September 6, 2005). Second report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Available at: http://www.nhlbi.nih.gov/guidelines/ cholesterol/atp3_rpt.htm. Accessed September 6, 2005.

[22] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults., et al .(2002). Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): final report. Circulation 2002;106: 3143– 421.

[23] Fonarow GC., French WJ., Parsons LS., Sun H., Malmgren JA., et al.(2001). for the National Registry of Myocardial Infarction 3 Participants. Use of lipid-lowering medications at discharge in patients with acute myocardial infarction: data from the National Registry of Myocardial Infarction 3. Circulation 2001;103:38 – 44.

[24] Foulon T., Payen N., Laporte F., et al.(2001). Effects of two low-dose oral contraceptives containing ethinylestradiol and either desogestrel or levonorgestrel on serum lipids and lipoproteins with particular regard to LDL size.

[25] Contraception 2001;64:11– 6.

[26] Freedman DS., Bowman BA., Srinivasan SR., Berenson GS., Otvos JD., et al.(2001). Distribution

and correlates of high-density lipoprotein subclasses among children and adolescents. Metabolism 2001;50:370 – 6.

[27] Fukushima H., Kugiyama K., Sugiyama S., et al.(2001). Comparison of remnant-like lipoprotein particles in postmenopausal women with and without coronary artery disease and in men with coronary artery disease. Am J Cardiol 2001;88:1370 –3.

[28] Gardner CD., Tribble DL., Young DR., Ahn D., Fortmann SP., (2000). Population frequency distributions of HDL, HDL(2), and HDL(3) cholesterol and apolipoproteins A-I and B in healthy men and women and associations with age, gender, hormonal status, and sex hormone use: the Stanford Five City Project. Prev Med 2000;31: 335– 45.

[29] Gardner CD., Winkleby MA., Fortmann SP., et al .(2000). Population frequency distribution of non– high-density lipoprotein cholesterol (Third Na- tional Health and Nutrition Examination Survey [NHANES III], 1988 –1994). Am J Cardiol 2000;86:299 –304.

[30] Godsland IF., Crook D., Simpson R., et al.(1990). The effects of different formulations of oral contraceptive agents on lipid and carbohydrate metabolism. N Engl J Med 1990;323:1375– 81.

[31] Goldberg AC., et al. A meta-analysis of randomized controlled studies on the effects of extended-release niacin in women. Am J Cardiol 2004;94:121– 4.

[32] Bass KM, Newschaffer CJ., Klag MJ., Bush TL., et al.(1993). High density lipoprotein: the clinical implications of recent studies. N Engl J Med 1989;321:1311– 6.

[33] Gosland IF., Wynn V., Crook D., Miller NE., et al. (1997). Sex, plasma lipoproteins and atherosclerosis: prevailing assumptions and outstanding questions. Am Heart J 1997;114:1467–503.

[34] Greenlund KJ., Webber LS., Srinivasan S., Wattigney W., Johnson C., Berenson GS., et al.(1997). Associations of oral contraceptive use with serum lipids and lipoproteins in young women: the Bogalusa Heart Study. Ann Epidemiol 1997;7:561–7.

[35] Grundy SM., Cleeman JI., Bairey Merz CN., et al.(2004)., for the Coordinating Committee of the National Cholesterol Education Program. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation 2004;110:227–39.

[36] Hambrecht R., Niebauer J., Marburger C., et al. (1993).Various intensities of leisure time physical activity in patients with coronary artery disease: effects on cardiorespiratory fitness and progression of coronary atherosclerotic lesions. J Am Coll Cardiol 1993;22:468 –77.

[37] Heart Protection Study Collaborative Group. Et al.(2002).MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7–22.

[38] Hjortland MC., McNamara PM., Kannel WB., et al.(1976).Some atherogenic concomitants of menopause: the Framingham Study. Am J Epide- miol 1976;103;304 –11.

[39] Hoff JA., Chomka EV., Krainik AJ., Daviglus M., Rich S., Kondos GT., et al.(2001). Age and gender distribution of coronary artery calcium detected by electron beam tomography in 35,246 adults. Am J Cardiol 2001;87: 1335–9.

[40] J Am Coll Cardiol., et al.(2005) by the American College of Cardiology Foundation46:1628–35)© 2005

[41] Kane JP., Malloy MJ., Ports TA., Phillips NR., Diehl JC., Havel RJ., et al.(1990). Regression of coronary atherosclerosis during treatment of familial hypercholesterolemia with combined drug regimens. JAMA 1990; 264:3007–12.

[42] Kannel WB., et al.(1995). Range of serum cholesterol values in the population developing coronary artery disease. Am J Cardiol 1995;76:69C–77C.

[43] LaRosa JC., He J., Vupputuri S., et al.(1999). Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. JAMA 1999;282:2340 – 6.

[44] Lerner DJ., Kannel WB., et al.(1986). Patterns of coronary heart disease morbidity and mortality in the sexes: a 26- year follow-up of the Framingham population. Am Heart J 1986;111:383–90.

[45] Mahoney LT., Burns TL., Stanford W., et al.(1996).Coronary risk factors measured in childhood and young adult life are associated with coronary artery calcification in young adults: the Muscatine Study. J Am Coll Cardiol 1996;27:277– 84.

[46] Matthews KA., Meilahn E., Kuller LH., Kelsey SF., Caggiula AW., Wing RR., et al.(1989). Menopause and risk factors for coronary heart disease. N Engl J Med 1989;321:641– 6.

[47] Matthews KA., Wing RR.., Kuller LH., Meilahn EN., Plantinga P., et al. (1994). Influence of the perimenopause on cardiovascular risk factors and symptoms of middle-aged healthy women. Arch Intern Med 1994; 154:2349 –55.

[48] Mautner SL., Lin F., Mautner GC., Roberts WC., et al.(1993). Comparison in women versus men of composition of atherosclerotic plaques in native coronary arteries and in saphenous veins used

as aortocoronary conduits. J Am Coll Cardiol 1993;21:1312– 8.
[49] McNamara JR., Shah PK., Nakajima K., et al.(2001). Remnant-like particle (RLP) cholesterol is an independent cardiovascular disease risk factor in women: results from the Framingham Heart Study. Atherosclerosis 2001;154:229 –36.
[50] Miller M., Byington R., Hunninghake D., Pitt B., Furberg CD. Et al.(2000)., for the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT) Investigators. Sex bias and underutilization of lipid-lowering therapy in patients with coronary artery disease at academic medical centers in the United States and Canada. Arch Intern Med 2000;160:343–7.
[51] Natarajan S., Liao Y., Cao G., Lipsitz SR., McGee DL., et al.(2003). Sex differences in risk for coronary heart disease mortality associated with diabetes and established coronary heart disease. Arch Intern Med 2003;163: 1735– 40.
[52] National Heart, Lung, and Blood Institute., et al.(July 1980). The Lipid Research Clinics Population Studies Data Book: Volume 1—The Prevalence Study. Bethesda, MD: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, NIH Publication No. 80-1527, July 1980.
[53] Ornish D., Scherwitz LW., Billings JH., et al.(1998). Intensive lifestyle changes for reversal of coronary heart disease. JAMA 1998;280: 2001–7.
[54] Rasheed Q., Nair R., Sheehan H., Hodgson JM., et al.(1994). Correlation of intracoronary ultrasound plaque characteristics in atherosclerotic coronary artery disease patients with clinical variables. Am J Cardiol 1994;73:753– 8.
[55] Sacks FM., Walsh BW., et al.(1994). Sex hormones and lipoprotein metabolism. Curr Opin Lipidol 1994;5:236 – 40.
[56] Sanada M., Nakagawa H., Kodama I., Sakasita T., Ohama K., (2000). The effect of hormone replacement therapy on metabolism of lipoprotein remnants in postmenopausal women. Maturitas 2000;34:75– 82.
[57] Sanderson BK., Bittner V., et al.(2005).Women in cardiac rehabilitation: out- comes and identifying risk for drop-out. Am Heart J 2005. In press
[58] Schrott HG., Bittner V., Vittinghoff E., Herrington DM., Hulley S., et al .(1997)., for the HERS Research Group. Adherence to National Cholesterol Education Program treatment goals in postmenopausal women with heart disease: the Heart and Estrogen/progestin Replacement Study (HERS). JAMA 1997;277:1281– 6.
[59] Sharrett AR., Ballantyne CM., Coady SA., et al. (2001).Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein (a), apolipoproteins A-I and B, and HDL density subfractions: the Atherosclerosis Risk in Communities (ARIC) study. Circulation 2001;104:1108 –13.
[60] Shlipak MG., Chaput LA., Vittinghoff E., et al. (2003).,for the Heart and Estrogen/progestin Replacement Study (HERS) Investigators. Lipid changes on hormone therapy and coronary heart disease events in the Heart and Estrogen/progestin Replacement Study (HERS). Am Heart J 2003;146:870 –5.
[61] The Bezafibrate Infarction Prevention (BIP) Study Group, Israel., et al. (1992).Lipids and lipoproteins in symptomatic coronary heart disease: distribution, intercorrelations, and significance for risk classification in 6,700 men and 2,500 women. Circulation 1992;86:839 – 46.
[62] van Beek AP., de Ruijter-Heijstek FC., Erkelens DW., de Bruin TWA., et al.(1999).Menopause is associated with reduced protection from post- prandial lipemia. Arterioscler Thromb Vasc Biol 1999;19:2737– 41.
[63] van Beresteijn EC., Korevaar JC., Huijbregts PC., Schouten EG., Burema J., Kok FJ., et al.(1993). Perimenopausal increase in serum cholesterol: a 10-year longitudinal study. Am J Epidemiol 1993;137:383–92.
[64] van Stiphout WA., Hofman A., de Bruijn AM.et al.(1987). Serum lipids in young women before, during, and after pregnancy. Am J Epidemiol 1987; 126:922– 8.
[65] Vaughan CJ., Gotto AM Jr., et al. (Update on statins: 2003. Circulation 2004). Update on statins: 2003. Circulation 2004;110:886 –92.
[66] Walden CE., Knopp RH., Wahl PW., Beach KW., Strandness E Jr., et al. (1984). Sex differences in the effect of diabetes mellitus on lipoprotein triglyceride and cholesterol concentrations. N Engl J Med 1984;311: 953–9.
[67] Walsh JME., Pignone M., et al.(2004). Drug treatment of hyperlipidemia in women. JAMA 2004;291:2243–52.