



By Arthur L Klatsky, MD;
Mary Anne Armstrong, MA

Sex-Based Differences in Causes of Hospitalization for Coronary Heart Disease

To evaluate sex-based difference in clinical manifestations of coronary heart disease (CHD), we prospectively studied sex and other predictors of hospitalization for CHD in 56,926 men (2802 cases) and 72,008 women (1449 cases) for whom baseline data were available from previous examinations. Cox models with ten covariates were used to study first hospital admission for CHD. In age-adjusted (AA) and multivariate (MV) analyses, men had substantially greater relative risk (RR) for acute myocardial infarction (ICD-9 code 410, n = 1757, AA RR = 2.6, MV RR = 2.7) and for chronic ischemic heart disease (ICD-9 codes 412, 414, n = 573, AA RR = 3.3, MV RR = 3.3) than for other acute syndromes (ICD-9 code 411, n = 848, AA RR = 1.6, MV RR = 1.5) or for angina (ICD-9 code 413, n = 753, AA RR = 1.6, MV RR = 1.6); all p values <0.001. Most CHD predictors were more strongly related to risk of coronary artery disease in women, but this relation was similar for the CHD diagnostic subsets. Risk of later death from CHD was similar for the sexes. These data show a major independent sex-based difference in CHD-related diagnoses leading to hospitalization: men are at greater risk for acute myocardial infarction, and women are at greater risk for stable or unstable angina.

Several of these areas of interest may have implications pertinent to various forms of bias ...

Introduction

Possible sex-based disparities with respect to atherosclerotic coronary heart disease (CHD) have become a subject of intense research and debate. Areas of interest include epidemiologic or clinical aspects,¹⁻⁴ differences in risk factors,^{2,3,5,9} problems of diagnostic evaluation,¹⁰⁻¹² disparities in either treatment or prognosis,^{2,3,9,13-19} and prevalence of nonatherosclerotic coronary syndromes or of noncardiac syndromes that mimic CHD problems.^{10,20,21} Several of these areas of interest may have implications pertinent to various forms of bias and raise the possibility of biological, sex-based differences in manifestations of this most prevalent cardiovascular disease.

The Framingham Heart Study² presented prospective population data showing possible sex-based differences in initial clinical manifestation of CHD. These data showed that the initial CHD manifestation in men was more likely to be acute myocardial infarction (MI) or sudden cardiac death, whereas CHD in women was more likely to initially manifest as stable or unstable angina. In the Framingham cohort, clinical CHD developed in women a decade later than in men, and the prognosis for CHD was worse in women than in men. Similar findings have been reported in several clinical studies^{1,3,5} that have speculated that these differences in CHD manifestations and prognosis may be explained by sex differences in risk factors.

We here report prospective Kaiser Permanente (KP) data that show substantial, sex-based differences in clinical CHD hospitalization diagnoses. We also report data about risk-related traits and later mortality among patients hospitalized for CHD.

Methods

Subjects and Data

Baseline data were obtained from results of voluntary health examinations given to 128,934 KP members in San Francisco and Oakland, California from 1978 through 1985. The examination included queries about sociodemographic status, habits, medical history and symptoms, and health measurements.²²

Ascertainment of Hospitalization for CHD

Subjects were monitored until December 31, 1991; until death; until termination of health plan membership; or until first CHD-related hospitalization at a KP facility in Northern California. Duration of patient follow-up totaled 889,611 person-years for the 128,934 persons in the study population. Primary diagnosis for 3931 persons (63% men) hospitalized for CHD included acute MI (ICD-9 code 410), "other acute" CHD syndromes (mainly "unstable angina," ICD-9 code 411), "angina pectoris" (ICD-9 code 413), and "chronic ischemic heart disease" (ICD-9 codes 412 or 414) (Table 1).

Analytic Methods

The Cox proportional hazards model was used for age-adjusted and multivariate analyses. Most multivariate models included age, sex, race, education, marital status, body mass index, cigarette smoking, and a composite "CHD risk" variable consisting of an affirmative response to any of 12 baseline items pertaining to CHD risk or symptoms.^{23,24} Some models also included systolic blood pressure, blood glucose level, and total blood cholesterol level. We also studied subsequent mortality in relation to first CHD hospitalization diag-

In the Framingham cohort, clinical CHD developed in women a decade later than in men, and the prognosis for CHD was worse in women than in men.

ARTHUR L KLATSKY, MD (right), is a retired Senior Consultant in Cardiology for The Permanente Medical Group (TPMG) in Oakland, California, and is an Adjunct Investigator at the Division of Research. E-mail: hartmavn@pacbell.net

MARY ANNE ARMSTRONG, MA (left), is a Biostatistician and Investigator at the Kaiser Permanente Division of Research in Oakland, California. E-mail: maryanne.armstrong@kp.org





Data obtained as late as ten years after hospitalization showed identical mortality rates for men and women ...

nosis by using an automated matching system²⁵ to screen for deaths in California through 1994. This result was validated by manual review conducted by two investigators (MAA, ALK).

Results

Table 2 shows demographic characteristics and selected traits of persons hospitalized for any CHD-related diagnosis. On average, women were older than the men by about three years. There was a substantially greater proportion of black women than black men. In general, women were more likely to have CHD-related risk traits, including smoking, lifelong alcohol abstinence, the CHD risk variable, and history of diabetes (Table 2). This higher prevalence of CHD-related traits among women was generally similar for the four subsets of CHD-related clinical diagnoses. These traits were all included among covariates used in the multivariate analyses.

Among patients who had any CHD-related diagnosis, male/female relative risks for age-adjusted and multivariate analyses were identical (RR = 2.0; 95% CI = 1.9-2.1; $p < 0.001$). Table 3 shows age-adjusted and multivariate relative risk for the four subsets of CHD-related clinical diagnoses. Each subset shows a preponderance of men at $p < 0.001$. However, the data showed a greater male-female disparity ($p < 0.001$) between 1) risk of hospitalization for either acute MI (RR = 2.7) or chronic ischemic heart disease (RR = 3.3) and 2) risk of hospitalization for other acute syndromes (RR = 1.5) or angina (RR = 1.6). Very small differences were observed between age-adjusted and multivariate odds ratios. Independence

of these disparities from race was confirmed by observation that the male-female difference in risk was similar for each racial group represented—white, black, and Asian (data not shown).

Although the established CHD predictors were generally more strongly related to CHD risk in women, the strength of this relation differed little across the subsets of CHD-related clinical diagnoses (Table 4). Age, body mass index, and the composite CHD risk variable were strong predictors in both sexes; for each clinical diagnostic subset, the composite CHD risk variable was a stronger predictor in women than in men. The stronger relation between smoking and CHD diagnoses in women was present in all diagnostic subsets except angina; and for all diagnostic subsets, the inverse relation between alcohol use and CHD diagnoses was slightly stronger in women than in men. Total blood cholesterol level was strongly related to all diagnostic subsets in both sexes. Systolic blood pressure and blood glucose level showed the expected relations to diagnostic subsets in both sexes with no major disparities except that black men were at substantially lower risk than white men for acute MI and chronic ischemic heart disease, whereas black women were at lower risk for acute MI and other acute syndromes. Men were the only group in which the data showed a substantial inverse relation between higher educational attainment and acute MI or angina.

Data obtained as late as ten years after hospitalization showed identical mortality rates for men and women: 29% from all causes and 16% from CHD. Women initially diagnosed with acute MI or chronic ischemic heart disease were 15% more likely than

Table 1. Sex of 3931 persons admitted to hospital for Coronary Heart Disease (CHD)^a

CHD-related diagnosis	Total No. patients	No. (%) men	No. (%) women
Any (ICD-9 codes 410-414)	3931	2482 (63)	1449 (37)
Acute MI (ICD-9 code 410)	1757	1201 (68) ^b	556 (32) ^b
Other acute condition (ICD-9 code 411)	848	456 (54) ^b	392 (46) ^b
Angina (ICD-9 code 413)	753	411 (55) ^b	342 (45) ^b
Chronic CHD (ICD-9 codes 412, 414)	573	414 (72) ^b	159 (28) ^b

^a Among 128,934 patients (including 56,926 [44%] men, 72,008 [56%] women) who received voluntary health examination during the period 1978 through 1985.

^b $P < .0001$ for ICD-9 code 410 or 412/14 vs ICD-9 code 411 or 413.



men to die of any cause or of CHD, whereas women who were initially hospitalized for stable or unstable angina were 20% less likely than men to die of any cause or of CHD. However, after adjustment for age, this sex-based difference in mortality was significant at $p < 0.05$ for comparison of any two diagnostic subsets in any combination. For each diagnostic subset, multiple hospitalizations for CHD occurred slightly more in men (46%) than in women (39%).

Eight women and two men were hospitalized for Prinzmetal's variant angina (ICD-9 code 413.1) or Syndrome X (ICD-9 code 413.9), and 2620 persons (47% of whom were women) were hospitalized for nonspecific chest pain syndromes (ICD-9 code 786.5).

Comments

These prospective hospitalization data are similar to the Framingham Study CHD incidence data² in suggesting that CHD in men is more likely to manifest initially as acute MI, whereas CHD in women is more likely to manifest initially as angina. Relatively high rates of CHD manifesting in women initially as acute MI and nonacute MI syndromes were also reported in several clinical series.^{1,3,5,21} Although this finding has been accepted as a true difference,²⁶ possible selection bias should be examined. Selective gender-related admission would seem unlikely to influence hospitalization for acute MI, but hospitalization for diagnostic evaluation of chest pain could be influenced by sex-related bias about perceived likelihood of CHD. That 53% of patients hospitalized for nonspecific chest pain were men is indirect evidence against the possibility that hospital admissions for stable or unstable angina were substantially biased with respect to sex. The preponderance of men diagnosed with chronic ischemic heart disease is more problematic and difficult to evaluate, because inclusion of some patients in this mixed group represented surgery or other procedures, whereas inclusion of other patients represented sequelae of CHD, such as heart failure and arrhythmia. The relatively high preponderance of men diagnosed with chronic ischemic heart failure is therefore likely to represent a combination of higher male risk for sequelae of acute MI (eg, heart failure) and a greater likelihood that men with any CHD diagnosis will undergo interventional procedures (eg, surgery).

Our finding that standard coronary risk factors were more prevalent in women hospitalized for CHD than in men hospitalized for CHD is generally compatible with other published findings.^{2,3,5-9} However, our findings showed no consistent sex-related disparity for

the subsets of clinical diagnoses we studied. In addition, the small differences between age-adjusted and multivariate data shown in our study (Table 3) suggest independence from the covariates as a group. Thus, our data do not support the hypothesis that risk factor disparities explain sex differences in initial clinical manifestation of CHD.

Table 2. Demographic characteristics of persons admitted to hospital for CHD-related diagnosis

	Acute MI	Other Acute Condition	Angina	Chronic CHD	Any CHD
Mean age at diagnosis (yr)					
Men	63	64	63	62	65
Women	68	65	66	63	68
Age >70 yr at diagnosis (no.)					
Men	16	11	17	7	14
Women	24	14	23	12	18
Race (%)					
White					
Men	66	64	63	70	65
Women	61	54	61	64	59
Black					
Men	22	23	26	16	22
Women	33	36	29	30	32
Asian					
Men	9	8	6	9	8
Women	3	6	5	4	5
Smoker (%) ^a					
Men	29	23	30	22	28
Women	36	30	21	31	39
Nondrinker (%) ^b					
Men	11	10	9	8	10
Women	26	27	25	25	26
At risk for CHD (%) ^c					
Men	65	72	74	74	69
Women	74	76	80	89	78
History of diabetes (%)					
Men	12	10	11	10	11
Women	15	12	11	13	13
CHD = coronary heart disease					
^a At baseline examination					
^b Lifelong alcohol abstainers at baseline examination					
^c Answered "Yes" to any of 12 items about medical history and symptoms					

Table 3. Relative risk (RR)^a for CHD diagnosis in men vs women

Analytic model	Acute myocardial infarction (95% CI)	Other acute condition (95% CI)	Angina (95% CI)	Chronic CHD (95% CI)
Age-adjusted	2.6 (2.3 – 2.9)	1.6 (1.4 – 1.8)	1.6 (1.4 – 1.8)	3.3 (2.7 – 3.9)
Multivariate ^b	2.7 (2.4 – 3.0)	1.5 (1.3 – 1.8)	1.6 (1.4 – 1.9)	3.3 (2.6 – 4.0)

^a P < 0.001 for all RR
^b Controlled for age, race, body mass index, education, marital status, smoking, alcohol intake

Table 4. Relation^a between demographic characteristics and four CHD-related diagnoses in men and women

Characteristic	Relation
Age	Strongly positive for all diagnoses in both sexes; RR's slightly greater in women
Body mass index	Strongly positive for all diagnoses in both sexes; no evident sex disparities
Risk for coronary artery disease ("Yes"/"No") ^b	Strongly positive for all diagnoses in both sexes; RR greater in women
Black race (vs white race)	Inverse for acute MI and chronic ischemic heart disease in men; positive for acute MI and angina in women
Asian race (vs white race)	No relation in either sex
Never married (vs married)	Inverse for acute MI and angina in men; inverse for acute MI in women
College graduate (vs no college)	Slightly inverse for acute MI and angina in men only
≥ 1 pack cigarettes/day (vs none)	Strongly positive for all diagnoses in both sexes; for angina, slightly stronger in women
1-2 alcoholic drinks/day (vs none)	Inverse for acute MI in men; for acute MI and other acute conditions in women; stronger in women
Total blood cholesterol level	Strongly positive for all diagnoses in both sexes; no evident disparities
Systolic blood pressure	Positive for acute myocardial infarction and other acute conditions in men and for acute MI in women; stronger in women
Blood glucose level	Slightly positive for acute MI and other acute conditions in men and for acute MI and chronic ischemic disease in women

^a P < 0.05
^b Answered "Yes" to any of 12 items about medical history and symptoms



Could the explanation be that a larger proportion of women admitted for a non-MI, CHD-related diagnosis have nonatherosclerotic syndromes and that these syndromes are erroneously coded as atherosclerotic CHD? Women are more likely to have Prinzmetal variant angina²⁷ and Syndrome X²⁸; and eight of the ten patients so diagnosed in our study were women. If such dilution of the group of women as acute coronary syndromes and angina were substantial, these diagnoses could reasonably be expected to affect follow-up mortality data, because nonatherosclerotic syndromes have a better prognosis than atherosclerotic disease. As already stated, survival in women was not statistically significantly different than for men in any subset of CHD-related clinical diagnoses.

Our age-adjusted data for mortality rates differ from those in some other studies.^{2,13,19,26} In those studies, women diagnosed with acute MI were substantially older than men compared with our subjects, and a greater proportion of these women than men were diagnosed with Q-wave infarctions, heart failure, and cardiogenic shock. Death among men, in contrast, was more likely to occur outside the hospital setting.

Could this disparity in CHD-related diagnoses for men and women indicate a biological sex difference in coronary atherosclerosis? Data relevant to this speculation are sparse. In one report,²⁹ CHD plaques in eight young women with fatal CHD were compared with CHD plaques in older men and women with fatal CHD. Compared with the older men and women, these young women had a substantially higher percentage of cellular fibrous tissue and lipid-rich foam cells and lesser amounts of dense, fibrous calcified tissue; this result was interpreted as suggesting greater potential reversibility of plaque formation. However, a study using intravascular ultrasound analysis³⁰ failed to show any quantitative or qualitative difference in coronary atherosclerosis between men and women. Other reports^{31,32} suggest different effects of male and female hormones on the interaction of lipid-laden macrophages and endothelial damage. The pertinence of these reports to a sex-based difference in clinical manifestation of CHD is unclear. The possibility of a biological, sex-related difference in atherosclerotic plaque composition remains hypothetical.

Effects of estrogenic hormones are the most obvious explanation for a biological, sex-based difference in CHD manifestations. Although the role of these

hormones in prevention of CHD has become highly controversial, estrogenic substances clearly could affect atherosclerotic mechanisms—not only via lipid effects but also via effects on endothelial function and vascular injury response.^{26,33} In addition, a sex-based difference (possibly hormonally mediated) may also be inherent in thrombophilic or spontaneous antithrombotic tendencies,³⁴⁻³⁷ and this difference might affect the relative likelihood of acute MI vs other CHD syndromes. We did not ascertain which patients in our study were receiving hormone replacement therapy at first hospitalization for CHD.

With respect to first CHD hospitalization, we conclude: 1) among persons hospitalized for CHD-related diagnoses, men are more likely to be diagnosed with acute MI, whereas women hospitalized for CHD-related diagnoses are more likely to have unstable or stable angina, 2) this biological, sex-based disparity is independent of established risk traits for CHD, 3) no explanation for this independence is clear, and 4) a biological, sex-based difference in atherosclerotic plaque composition, endothelial function, or thrombotic tendency is likely. ♦

Previous Presentation: Portions of this material were presented in Abstract form at the 46th Annual Session of the American College of Cardiology in Anaheim, CA, March 1997.

Acknowledgments: This research was supported by grants from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) (1 R01 AA 10830-01); the Alcoholic Beverage Medical Research Foundation; and the Direct Community Investment Benefit Program.

We thank Cynthia Landy for data collection, Harald Kipp for programming assistance, and Sally McBride Allen for technical assistance.

References

- Hochman JS, McCabe CH, Stone PH, et al. Outcome and profile of women and men presenting with acute coronary syndromes: a report from TIMI IIIB. TIMI Investigators. Thrombolysis in myocardial infarction. J Am Coll Cardiol 1997;30(1):141-8.
- Lerner DJ, Kannel WB. 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(2):383-90.
- Robinson K, Conroy RM, Mulcahy R, Hickey N. Risk factors and in-hospital course of first episode of myocardial infarction or acute coronary insufficiency in women. J Am Coll Cardiol 1988;11(5):932-6.
- Milner KA, Funk M, Richards S, Wilmes RM, Vaccarino V, Krumholz HM. Gender differences in symptom presentation associated with coronary heart disease. Am J Cardiol 1999;84(4):396-9.
- Benderly M, Behar S, Reicher-Reiss H, Boyko V, Goldbourt U. Long-term prognosis of women after myocardial infarction. SPRINT Study Group. Secondary Prevention Reinfarction Israeli Nifedipine Trial [see comments]. Am J Epidemiol 1997;146(2):153-60.

Effects of estrogenic hormones are the most obvious explanation for a biological, sex-based difference in CHD manifestations.

... a biological, sex-based difference in atherosclerotic plaque composition, endothelial function, or thrombotic tendency is likely.



6. Wang XL, Tam C, McCredie RM, Wilcken DE. Determinants of severity of coronary artery disease in Australian men and women. *Circulation* 1994;89(5):1974-81.
7. Will JC, Casper M. The contribution of diabetes to early deaths from ischemic heart disease: US gender and racial comparisons. *Am J Public Health* 1996;86(4):576-9.
8. Zuanetti G, Latini R, Maggioni AP, Santoro L, Franzosi MG. Influence of diabetes on mortality in acute myocardial infarction: data from the GISSI-2 Study. *J Am Coll Cardiol* 1993;22(7):1788-94.
9. Frishman WH, Gomberg-Maitland M, Hirsch H, et al. Differences between male and female patients with regard to baseline demographics and clinical outcomes in the Asymptomatic Cardiac Ischemia Pilot (ACIP) Trial. *Clin Cardiol* 1998;21(3):184-90.
10. Sullivan AK, Holdright DR, Wright CA, Sparrow JL, Cunningham D, Fox KM. Chest pain in women: clinical, investigative, and prognostic features. *Br Med J* 1994;308(6933):883-6.
11. Kwok Y, Kim C, Grady D, Segal M, Redberg R. Meta-analysis of exercise testing to detect coronary artery disease in women [see comments]. *Am J Cardiol* 1999;83(5):660-6.
12. Paul SD, Eagle KA, Guidry U, et al. Do gender-based differences in presentation and management influence predictors of hospitalization costs and length of stay after an acute myocardial infarction? *Am J Cardiol* 1995;76(16):1122-5.
13. Kudenchuk PJ, Maynard C, Martin JS, Wirkus M, Weaver WD. Comparison of presentation, treatment, and outcome of acute myocardial infarction in men versus women (The Myocardial Infarction Triage and Intervention Registry). *Am J Cardiol* 1996;78(1):9-14.
14. Woodfield SL, Lundergan CF, Reiner JS, et al. Gender and acute myocardial infarction: is there a different response to thrombolysis? *J Am Coll Cardiol* 1997;29(1):35-42.
15. Schwartz LM, Fisher ES, Tosteson NA, et al. Treatment and health outcomes of women and men in a cohort with coronary artery disease. *Arch Intern Med* 1997;157(14):1545-51.
16. Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM. Sex-based differences in early mortality after myocardial infarction. National Registry of Myocardial Infarction 2 Participants [see comments]. *N Engl J Med* 1999;341(4):217-25.
17. Malacrida R, Genoni M, Maggioni AP, et al. A comparison of the early outcome of acute myocardial infarction in women and men. The Third International Study of Infarct Survival Collaborative Group [see comments]. *N Engl J Med* 1998;338(1):8-14.
18. Chandra NC, Ziegelstein RC, Rogers WJ, et al. Observations of the treatment of women in the United States with myocardial infarction: a report from the National Registry of Myocardial Infarction-I [see comments]. *Arch Intern Med* 1998;158(9):981-8.
19. Tunstall-Pedoe H, Morrison C, Woodward M, Fitzpatrick B, Watt G. Sex differences in myocardial infarction and coronary deaths in the Scottish MONICA population of Glasgow 1985 to 1991. Presentation, diagnosis, treatment, and 28-day case fatality of 3991 events in men and 1551 events in women. *Circulation* 1996;93(11):1981-92.
20. Douglas PS, Ginsburg GS. The evaluation of chest pain in women. *N Engl J Med* 1996;334(20):1311-5.
21. Coronado BE, Griffith JL, Beshansky JR, Selker HP. Hospital mortality in women and men with acute cardiac ischemia: a prospective multicenter study. *J Am Coll Cardiol* 1997;29(7):1490-6.
22. Collen MF, Davis LF. The multitest laboratory in health care. *J Occup Med* 1969;11(7):355-60.
23. Klatsky AL, Armstrong MA, Friedman GD. Relations of alcoholic beverage use to subsequent coronary artery disease hospitalization. *Am J Cardiol* 1986;58(9):710-4.
24. Klatsky AL, Armstrong MA, Friedman GD. Risk of cardiovascular mortality in alcohol drinkers, ex-drinkers and nondrinkers. *Am J Cardiol* 1990;66(17):1237-42.
25. Arellano MG, Peterson GR, Petitti DB, Smith RE. The California Automated Mortality Linkage System (CAMLIS). *Am J Public Health* 1984;74(12):1324-30.
26. Wenger NK. Women, myocardial infarction, and coronary revascularization: concordant and discordant clinical trial and registry data. *Cardiol Rev* 1999;7(2):117-20.
27. Delacretaz E, Kirshenbaum JM, Friedman PL. Prinzmetal's angina. *Circulation* 2000;101(11):E107-8.
28. Cannon RO 3rd. The conundrum of cardiovascular Syndrome X. *Cardiol Rev* 1998;6:213-20.
29. Dollar AL, Kragel AH, Fernicola DJ, Waclawiw MA, Roberts WC. Composition of atherosclerotic plaques in coronary arteries in women less than 40 years of age with fatal coronary artery disease and implications for plaque reversibility. *Am J Cardiol* 1991;67(15):1223-7.
30. Kornowski R, Lansky AJ, Mintz GS, et al. Comparison of men versus women in cross-sectional area luminal narrowing, quantity of plaque, presence of calcium in plaque, and lumen location in coronary arteries by intravascular ultrasound in patients with stable angina pectoris. *Am J Cardiol* 1997;79(12):1601-5.
31. McCrohon JA, Nakhla S, Jessup W, Stanley KK, Celermajer DS. Estrogen and progesterone reduce lipid accumulation in human monocyte-derived macrophages: a sex-specific effect. *Circulation* 1999;100(23):2319-25.
32. McCrohon JA, Jessup W, Handelsman DJ, Celermajer DS. Androgen exposure increases human monocyte adhesion to vascular endothelium and endothelial cell expression of vascular cell adhesion molecule-1. *Circulation* 1999;99(17):2317-22.
33. Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. *N Engl J Med* 1999;340(23):1801-11.
34. Dangas G, Smith DA, Badimon JJ, et al. Gender differences in blood thrombogenicity in hyperlipidemic patients and response to pravastatin. *Am J Cardiol* 1999;84(6):639-43.
35. Ossei-Gerning N, Wilson IJ, Grant PJ. Sex differences in coagulation and fibrinolysis in subjects with coronary artery disease. *Thromb Haemost* 1998;79(4):736-40.
36. MacCallum PK, Cooper JA, Howarth DJ, Meade TW, Miller GJ. Sex differences in the determinants of fibrinolytic activity. *Thromb Haemost* 1998;79(3):587-90.
37. Toft I, Bonna KH, Ingebretsen OC, Nordoy A, Birkeland KI, Jenssen T. Gender differences in the relationships between plasma plasminogen activator inhibitor-1 activity and factors linked to the insulin resistance syndrome in essential hypertension. *Arterioscler Thromb Vasc Biol* 1997;17(3):553-9.