CARDIOVASCULAR DISEASES IN OLD WOMEN

[1]SITAR-TĂUT ADELA-VIVIANA, [2]D. ZDRENGHEA, [3]DANA POP

[1,2,3]„Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca

Abstract: *Cardiovascular diseases represent the first mortality cause, in both sexes, but the most studies have been focused on the presence of cardiovascular pathology in men, women being "ignored" (especially those ones over 65 years old). The purpose of the present study is to determine the prevalence of cardiovascular diseases in women from Zorilor neighborhood, Cluj-Napoca, Romania.*

Keywords: *cardiovascular disease, women*

Rezumat: *Bolile cardiovasculare reprezintă prima cauză de mortalitate la ambele sexe. Cu toate acestea, majoritatea studiilor s-au focalizat pe prezenţa patologiei cardiovasculare la sexul masculin, femeile fiind „ignorate" , în special cele peste 65 de ani. Studiul de faţă şi-a propus determinarea prevalenţei bolilor cardiovasculare la femeile de această etate, din Cartierul Zorilor, Cluj-Napoca, România.*

Cuvinte cheie: *boli cardiovasculare, femei*

INTRODUCTION

Cardiovascular diseases represent the first mortality cause in women (1,2,3,4,5), killing more women than men.(1) There are studies with opposite results regarding the annual cardiovascular mortality rates registered in women. Thereby, Wenger (4) sustains the idea that a reduction in cardiovascular mortality (due to progresses made in cardiovascular diseases' therapy, but not in reducing incidence of cardiovascular disease) had been notices. In opposite, others sustained the idea that, starting with '80, even if cardiac mortality had progressively decreased in male (with 30% - 50%), in women it had progressively increased.(6,7,9).

Regarding the ischemic heart disease mortality and morbidity, both of them had decreased in both sexes, but much faster in men.(10) If coronary heart disease incidence is substantially lower in women before the age of 50, after this age, the increases reached to the same level as the one registered in men.(11)

Thereby, Stramba-Badiale – in a European consent published by European Society of Cardiology, based on a World Health Organization (WHO) report from 2008 – showed that the most important mortality causes in women are represented by ischemic heart disease-23%, stroke-18%, and other cardiovascular diseases -15%.(3) In the same time, the data published in 2009 by American Heart Association showed that cardiovascular disease's prevalence is greater that 70 percentages, in both sexes, in people older that 60 years.(12) Therefore, European society is focusing not only on cardiovascular diseases' diagnose, but also on elaborating preventive measures applied in women.

The aim of present study was to determine the prevalence of cardiovascular diseases in women from Zorilor neighborhood, Cluj-Napoca, Romania, but also to analyze the differences between the two sexes regarding cardiovascular pathology in older people (more than 65 years).

MATERIAL AND METHODS

The study was made on a representative sample (515 people over 65 years old, 264 females and 251 males) from an urban population from Zorilor neighborhood, Cluj-Napoca. The study was carried out using general practitioner's files, between February 2007 and April 2007. Data about blood pressure, weight, height, plasma lipids values, glycaemia and ECG were collected. Uncomplicated hypertension was not registered as a cardiovascular disease, being considered a cardiovascular risk factor.

The data was analyzed using SPSS 16.0 for Windows (Demo Version). We calculated mean and standard deviation for normal distributed quantitative variables. Differences between quantitative variables were examined using Student test (independent-sample T test), and for qualitative variables we performed χ^2 test. A p value less than 0.05 was considered significant from statistical point of view.

RESULTS

The mean age of women was 73.73±6.13 years, in comparison with the mean age of men which was 73.08±6.74 years ($p>0.05$). 264 women (51.3%) and 251 (48.7%) males were included in the present research. No significant differences between sexes were registered regarding the prevalence of diabetes mellitus (21.2% vs. 16.7%, $p>0.05$), but a significant higher percentage of women were dislipidemic (48.5% vs. 32.3 %, $p<0.001$), obese (29.5% vs. 20.3%, $p=0.02$), hypertensive (91.3% vs. 84.9%, $p=0.02$). Smoking prevalence was significantly higher in men (7.4% in women vs. 18.1% in men,

p=0.008).

As we noticed, the ischemic heart disease prevalence is higher in women in comparison with men (55.7% vs. 47.4%, p>0.05), the difference being present for some ischemic heart disease forms such as silent ischemia (4.51% vs. 3.2%, p>0.05) or stable angina (21.2% vs. 12.7%, p=0.011). On the other side, myocardial infarction prevalence was higher in men (12%) in comparison with values registered in women (5.7%), p=0.012. Regarding the prevalence of other forms of ischemic heart disease (arrhythmias or heart failure), those were more prevalent in women (24.24% in women vs. 19.52% in men, p=NS). We have to emphasis the fact that in studied files we did not met acute coronary syndromes, these patients being admitted in emergency care units. Surprisingly, heart failure was met in just 9.8% of the women, respectively in 11.2% of the men sample (p=NS).No significant difference between sexes regarding arrhythmias or atrioventricular conduction disturbances prevalence were registered (23.5% in women vs. 22.7% in men, p>0.05). Ischemic etiology was present in 87.09% of women and in 84.21% of the cases in men. We are mentioning the fact that in this sample were included patients with arrhythmias and various cardiovascular diseases (such as ischemic heart disease, heart failure, or stroke)

Stroke prevalence was slightly greater in men (19.9%) in comparison with women (16.3%), difference not being statistical significantly different (p>0.05). In turn, an approximate double number of men - 25 (10.01%) had presented peripheral artery disease, in comparison with 12 (4.8%) women, the difference being statistically significant. Synthesizing, the groups' characteristics are presented in Table no. **1.**

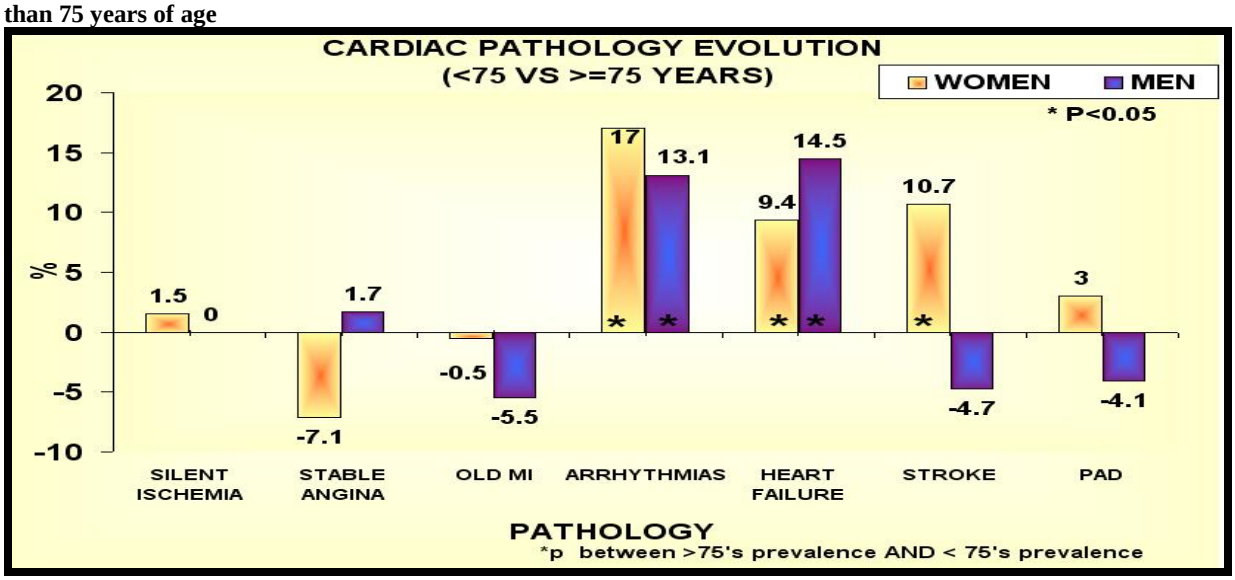
On our sample, no significant differences between two sexes were found regarding the distribution of subjects under vs. over 75 years old. Thereby, 153 (58%) of the women were under 75 years, 111 (42%) over 75 years, while the corresponding values and percentages for men were 167 (62.5%), 94 (37.5%) respectively. Further analyses depending on patients' age (under vs. over 75 years old) showed that if in those under 75 years, women presented a greater prevalence of stable angina (24.2% in women vs. 12.1% in men, p=0.008), while the men were more frequently affected by myocardial infarction (5.9% in women vs. 14% in men, p=0.02), stroke (11.8% in women vs. 21.7% in men, p=0.023), or peripheral artery disease (3.3% in women vs. 11.5% in men, p=0.008).

On the other hand, in older people (over 75 years) no more differences between sexes were present. Growing older, women become – in comparison with the younger ones – more frequently affected by ischemic heart disease (62% vs. 51%, p=0.07), heart failure (15.3% vs. 5.9%, p=0.011), arrhythmias (33.3% vs. 16.3%, p=0.001), strokes (6.3% vs. 3.3%, p=0.019). No differences were found in women, depending on age (>75 vs. <75 years), regarding the prevalence of silent ischemia (5.4% vs. 3.9%, p>0.05), old myocardial infarction (5.4 % vs. 5.9%, p>0.05), stable angina (17.1% vs. 24.2%, p=0.16), peripheral artery disease (6.3% vs. 3.3%, p=0.242). Similar results were revealed in men, the recorded cardiovascular diseases' percentages in those over 75 years vs. those less than 75 years being as follows: ischemic heart disease 56.45 vs. 42% (p=0.02), heart failure 20.2% vs. 5.7% (p<0.001), arrhythmias 30.9% vs. 21.7% (p=0.017), silent ischemia (3.2 % vs. 3.3%, p>0.05), old myocardial infarction (8.5% vs. 14%, p=0.19), stable angina (13.8% vs. 12.1%, p>0.05), stroke (17% vs. 21.7%, p>0.05), and peripheral artery disease (7.4 % vs. 11.5%, p>0.05). The differences between cardiovascular diseases' prevalence in both sexes between patients under 75 years and those over 75 years old are presented in Picture no. 1. These differences were calculated as disease's prevalence in those over 75 years old minus the one encountered in those less than 75 years**.**

Table no. 1: Characteristics of patients

	General No (%)	**Women No (%)**	**Men No (%)**	**P**
Total number	515p	51.3%(264)	48.7%(251)	p>0.05
Mean age ± SD	73±6.43	73.73±6.13	73.08±6.74	p>0.05
RISK FACTORS				
HBP	454(88.15)	241(91.3)	213(84.9)	p=0.02
DM	98(19.02)	56(21.2)	42(16.7)	p>0.05
Smoking	37(12.3)	12(7.4)	25(18.1)	p=0.004
ISCHEMIC HEART DISEASE				
Ischemic cardiopathy	266(51.65)	147(55.71)	119(47.4)	p=0.06
Silent ischemia	20(3.9)	12(4.51)	8(3.2)	p>0.05
Stable angina	88(17.08)	56(21.2)	32(12.7)	p=0.011
Old mi	45(6.67)	15(5.7)	30(12.0)	p=0.012
Other form of ischemic disease	113(21.94)	64(24.24)	4919.52)	p=0.203
ARRHYTHMIAS AND CONDUCTION DISTURBANCE	119(23.10)	62(23.5)	57(22.7)	p>0.05
HEART FAILURE	54(10.48)	26(9.8)	28(11.2)	p>0.05
STROKE	93(18.05)	43(16.3)	50(19.9)	p>0.05
PERIPHERAL ARTERY DISEASE	37(7.18)	12(4.5)	25(10.01)	p=0.017

Picture no. 1 Cardiovascular disease prevalence' s differences between people over 75 years of age and those less than 75 years of age



DISCUSSIONS

According to statistics made in 2002, Romania places the third position in women mortality due to ischemic heart disease, and the fourth one respectively, in male the same top (13). Generally, among ischemic patients, men presented more severe complication, represented by acute coronary syndromes or sudden death.(14)

The ischemic heart disease's incidence and prevalence are growing in parallel with aging, being greater in men.(15) After the age of 75, the number of cardiovascular disease diagnosed women is greater that in men, (16) probably due to the fact that the number of women with this age is greater (13). Unlike the literature, even if the ischemic heart disease's prevalence was higher in older patients, on our sample the prevalence was higher in women, no matter of age groups: under 75 years old (in women 51% vs. 42% in men, $p>0.05$) and over 75 years (in women 62.2% vs. 56.4% in men, $p>0.05$).

Women present – in comparison with men – angina 10 years later (16,17), and first myocardial infarction 20 years later.(18) Even if, generally, the ischemic heart disease's first manifestation is represented by angina in women, (19) in men either myocardial infarction, either sudden death was recorded as first "symptom".(17,20) Comparing with literature (which describes a lower stable angina's prevalence in women, in comparison with men, (21,22) on our sample, its prevalence was higher in women - for the whole sample (21.2% vs. 12.7%, $p<0.05$), but also for subgroups determined by subject's age, in those less than 75 years old (in women 24.2% vs. 12.1% in men, $p=0.008$), and in those over the age of 75 (in women 17,1% vs. 13,8% in men $p>0.05$).

As we recorded, there are many evidences showing the fact that differences regarding first symptoms between sexes are present.(23) Diagnosed coronary acute syndrome's prevalence is lower in women.(23) Unlike the male gender (myocardial infarction being more prevalent in men), in women unstable angina is responsible for the coronary acute syndrome majority,(24) this relationship being true especially before the age of 65, after this women presenting in the same proportion ST elevation acute coronary syndromes.(27)

If women present more frequently non Q myocardial infarction, men present Q-wave myocardial infarction.(25,26) Pain incidence is similar in both sexes, but in women are frequently present atypical localization (back, neck, or maxillary) being accompanied by nausea, fatigability, dyspnoea, or anxiety.(28,29)

Myocardial infarction diagnosed hospitalized women are older, presenting more frequently hypertension, diabetes mellitus.(14,23) Thus, the mean age of myocardial infarction in Central and East Europe is 68 years old in women, in comparison with 59 in men.(30) Prevalence of "normal coronary" or without significant obstruction is two times fold greater in women, especially in non ST elevation acute coronary syndromes.(31)

Regarding the post myocardial infarction complications, women present a worse Killip class.(32) No matters the age, the most frequent complications in women are represented by heart failure and reinfarction, even if (when the patient is admitted in hospital) the ventricular function is similar in both sexes.(33)

Mitral regurgitation, rupture of interventricular septum, rupture of ventricular wall, ventricular aneurysm, high degree AV block, and asistola are more frequent in men.(13,34,35) Among acute coronary syndrome in admitted patients, on discharge, the unstable angina is more frequent registered in women's files.(23,24,36,37)

In according with other studies, (17) in the present one, old myocardial infarction prevalence was 5.7% in women vs. 12% in men, the difference being

statistical significant (p=0.012). As Stramba-Badiale sustained in his study (27), ageing is responsible for attenuating sexes' differences regarding the old myocardial infarction prevalence. On our sample, silent ischemia was present in a significant greater percentage in women (4.51%) in comparison with men (3.2%). Other studies also demonstrated that women over the age of 55 present more frequently silent ischemia, sometimes being the first "symptom" of myocardial infarction. A possible explanation enunciated by other previous studies, (38,39) is represented by a greater diabetes mellitus prevalence in women, the values registered in our study being 21.2% in women and 16.7% in men.

As we already know, the two sexes differ regarding the electrophysiological arrhythmias' substrate.(40) Whereas these differences, it is no surprisingly the fact that they are also present in arrhythmias recorded in two sexes.(40) Framingham study has shown that men are 1.5 times fold more frequently affected by atrial fibrillation, (41) but because the number of older (>75 years) women is almost double in comparison with men, no significant difference was found regarding the absolute number of those ones affected by atrial fibrillation.(42) In opposite, ventricular fibrillation or ventricular tachycardia is rarely met in women.(13) On our sample, no significant differences between women and men regarding arrhythmias' prevalence was found (23.5% vs. 22.7%, p>0.05), but the differences appeared when we went further with the analyses (arrhythmias were more frequent in older patients – over 75 years old – in comparison with the younger ones – under 75 years – 33.3% vs. 16.3%, p=0.001 in women, 30.9% vs. 17.8%, p=0.01 in men).

Heart failure has a similar prevalence in both sexes, prevalence growing with ageing. Men are diagnosed earlier, the diagnosis being delayed in women after the age of 75. Our data are in according with literature, no significant differences between women and men regarding heart failure's prevalence being found. But differences were present in term of subject's age (over and under 75 years old): in women 15.3% vs. 5.9% (p=0.011) and in men 20.2% vs. 5.7% (p<0.001).

Heart failure etiology was represented by ischemic heart disease in all women and in 96.42% of the men. In literature, diastolic heart failure with preserved systolic function is more frequent in women.(43) The most important causes of heart failure are represented in both sexes by hypertension and ischemic heart disease, but hypertensive women have a greater risk to develop heart failure.(27) In the present study, ischemic etiology was predominant. In USA, mortality due to the heart failure in women is 61% of all mortality causes, 46% of all cases representing the myocardial infarction complication.(30)

Mortality in ischemic women are due, in a small measure, to the cardiac arrhythmias, (17) the rhythm's and frequency's control being different in men and in women. Women have a greater rest cardiac frequency, a lower sinus node recovery time and greater heart rate variability due probably to a parasympathetic dominance (44).

Women with long QT interval are more susceptible to develop torsade de pointes (45). On the other side, women with QT long syndrome (LQT1, but also LQT2 stage) have a greater risk in developing cardiac events (46)(47). It seems that sexual hormones can play an important role in potassium channel modulation, the testosterone being responsible for QT interval shortening (47). In the same time, in women QT prolongation is due to a variety of medication, this being in relationship with menstrual cycle's phases and being under the influence of progesterone and estrogen levels.

The stroke prevalence was greater in men (19.9% vs. 16.3%), the only exception being registered in the older group (over 75 years). Older women, in comparison with the younger ones had presented, in a greater proportion, stroke (22.5 % vs. 11.8%, p=0.01).

According to some statistical data published in 2002 (13), Romania is the third in the top regarding stroke mortality in women and fourth in men, being "exceeded" only by Russia, Bulgaria, respective China.(13) In another European study, the authors reported that investigations such as computer tomography, echocardiography, or coronary angiography are far less performed in women.(27) In the same time, surgery on carotid arteries is in a significantly lower number met in women. The recovery after stroke takes time, with a negative prognostic in women, probably due to the older age of women.(27) Transient ischemic attack is more frequent in women with atrial fibrillation.(27) ATRIA trial showed that even if number of women with atrial fibrillation was greater in comparison with that in men, a smaller number of women are submitted to anticoagulant therapy.(48).

Previous studies had shown that peripheral artery disease's prevalence is greater in men (49)(50). Only approximately 10 percentages of the patients has typical complaints (intermittent claudication), (51) 40% from our sample does not present any kind of symptoms and 50% presenting atypical accusations. Especially in older women, up to 60 percentages of them did not report any symptom. The prevalence of peripheral artery disease on our sample was significantly greater in men, no matter the age group. A possible explanation, is representing by the fact that also the smoking prevalence was greater in men (18% vs. 7.4% in women), in according with literature.

CONCLUSIONS

In Romania, cardiovascular disease's prevalence is in accordance with that one registered in the entire world, but it is increasing in women, which present in a greater proportion than men, silent ischemia, stable angina, and arrhythmias. If in younger ages, men are known to be affected in a greater measure by myocardial infarction, stroke, or peripheral artery disease, the discrepancies disappear when people is growing older (no significant differences being registered in those over 75 years old). A possible explanation is represented by the greater prevalence of cardiovascular risk in women, they

being frequently diabetics, dyslipidaemic, obese, or hypertensive. That's why, on national level, concerted health programs are imperiously necessary to be developed in order to accomplish not only a good control of risk factors, but also an adequate cardiovascular diseases' therapy.

Funding: CEEX Grant no 98/2006, "Optimization of degenerative cardiovascular diseases' treatment in postmenopausal women" (MENOCARD). Project manager Prof. Dr. Zdrenghea D.

REFERENCES

1. Mosca L, Banka , Benjamin E, Berra K, Bushnell C, Dolor R, Ganiats T, Gomes A, Gornik H, Gracia C, Gulati M, Haan C, Judelson D, Keenan N, Kelepouris E, Michos E, Newby L, Oparil S, Ouyang P, Oz M, Petitti D, Pinn V, Redberg R, Scott R, Sherif K, Smith S, Sopko G,. Steinhorn R, Stone N, Taubert K, Todd B, Urbina E, Wenger N for the Expert Panel/Writing Group. Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women, 2007 Update. JACC 2007(49):1230–50.
2. Alfonso F, Bermejo J, Segovia J. Cardiovascular disease in women. Why now? Rev Esp Cardiol 2006 Mar;59(3):259-63.
3. Stramba-Badiale M, Fox K, Priori S, Collins P, Daly C, Graham I, Jonsson B, Schenck- Gustafsson, Tendera M. Cardiovascular diseases in women: a statement from the policy conference of the European Society of Cardiology . Eur Heart J 2006(27);994-1005.
4. Wenger N, Shaw L, Vaccarino V. Coronary heart disease in women: update 2008.Clin Pharmacol Ther. 2008;83 (1):37-51.
5. Pilote L, Dasgupta K, Guru V, Humphries K, McGrath J et al. A comprehensive view of sexspecific issues related to cardiovascular disease. CMAJ 2007; 176(6) S1-41
6. BRAUNWALD-Heart Disease. A textbook of cardiovascular medicine – Eighth Edition. Ed Saunders, 2008:1955-1983.
7. Collins P, Rosano G, Casey C, Daly C, Gambacciani M,Hadji P, Kaaja R, Mikkola T, Palacios S, Preston R,Simon T, Stevenson J, Stramba-Badiale M. Management of cardiovascular risk in the peri-menopausal woman: a consensus statement of European cardiologists and gynaecologists. Euro Heart J 2007;28:2028–2040.
8. Stangl V, Baumann G, Stangl K Coronary atherogenic risk factors in women. Eur Heart J 2002;23:1738–1752.
9. O'Flaherty M, Ford E, Allender S, Scarborough, Capwell S. coronary heart disease trends in England and Wales from 1984 to 2004: concealed leveling of mortality rates among young adults. Heart 2008;94:178-81.
10. Anand S, Islam S, Rosengren A, Franzosi M, Steyn K, Yusufali A, Keltai M, Diaz R, Rangarajan S, Yusuf S. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. Eur Heart J 2008; 29:932-40.
11. Llotd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson B, Flegal K, Ford E, Furie K, Go A, Greenlund K, Haase N, Hailpern S, Ho M, Howard V,. Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott M, Meigs J, Mozaffarian D, Nichol G, O'Donnell, Roger V, Rosamond W, Sacco R, Sorlie P, Stafford R, Steinberg J, Thom T, Wasserthiel-Smoller S, Wong N, Wylie-Rosett J, Hong Y and for the American Heart Association Statuistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics 2009 Update: A Report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulating 2009;119:e21-e181.
12. Marrugat J, Sala J, Aboal J. Epidemiology of Cardiovascular Disease in Women. Rev Esp Cardiol. 2006;59(3):264-74.
13. Heer T, Gitt AK, Juenger C, et al. Gender differences in acute non-ST-segment elevation myocardial infarction. Am J Cardiol 2006;98:160–6.
14. National Center for Health Statistics. Health, United States. 2004 with chartbook on trends in the health of Americans. Hyattsville, Maryland: National Centre for Health Statistics, 2004.
15. Heart Disease and Stroke Statistics — 2009 Update, American Heart Association http://www.americanheart.org/downloadable/heart/12378344126 7009Heart%20and%20Stroke%20Update.pdf
16. Andreotti F, Marchese N. Women and coronary heart disease. Heart 2008;94:108-116.
17. Welty F. Cardiovascular Disease and Dyslipidemia in Women. Arch Intern Med.2001;161:514-522.
18. Wenger N, Shaw L, Vaccarino V. Coronary heart disease in women: update 2008.Clin Pharmacol Ther. 2008;83(1):37-51.
19. Lawlor D, Whincup P, Emberson J, Rees K, Walker M, Ebrahim S. The challenge of secondary prevention for coronary heart disease in older patients: A finding from the British Women's Heart and Health Study and the British Regional Heart Study. Family Practice 2004;21:582-6.
20. Hemingway H, McCallum A, Shipley M, Manderbacka K, Martikainen P, Keskimäki I. Incidence and Prognostic Implications of Stable Angina Pectoris Among Women and Men. JAMA. 2006;295:1404-11.
21. Kuller L, Arnold A, Psaty B, Robbins J. O'Leary DH, Tracy RP,. Burke GL, Manolio TA, Chaves PHM. 10-Year Follow-up of Subclinical Cardiovascular Disease and Risk of Coronary Heart Disease in the Cardiovascular Health Study. Arch Intern Med. 2006;166:71-78.
22. Pilote L, Dasgupta K, Guru V, Humphries K, McGrath J et al. A comprehensive view of sex-specific issues related to cardiovascular disease. CMAJ 2007;176(6) S1-41.

23. SONG Xian-tao, CHEN Yun-dai, PAN Wei-qi, LÜ Shu-zheng, For the CRACE investigators Gender based differences in patients with acute coronary syndrome: findings from Chinese Registry of Acute Coronary Events (CRACE). Chin Med J 2007;120(12):1063-1067.
24. National Heart, Lung, and Blood Institute. Incidence and prevalence: 2006 chart book on cardiovascular and lung diseases. Bethesda, Maryland: National Institutes of Health, 2006.
25. Hemingway H, McCallum A, Shipley M, et al. Incidence and prognostic implications of stable angina pectoris among women and men. JAMA 2006;295:1404–11.
26. Stramba-Badiale M, Fox KM, Priori SG, Collins P, Daly C, Graham I, Jonsson B, Schenck-Gustafsson, Tendera M. Cardiovascular diseases in women: a statement from the policy conference of the European Society of Cardiology . Eur Heart J 2006(27);994-1005.
27. Patel H, Rosengren A, Ekman I. Symptoms in acute coronary syndromes: does sex make a difference? Am Heart J. 2004;148:27–33.
28. Pope J, Aufderheide T, Ruthazer R et al. Missed diagnoses of acute cardiac ischemia in the emergency department. N Engl J Med 2000;342:1163–7.
29. Libby: Braunwald's Heart Disease, 8th ed. - 2007 - Saunders, An Imprint of Elsevier.
30. Bugiardini R, Bairey Merz CN. Angina with ‘‘normal’’ coronary arteries: a changing philosophy. JAMA 2005;293:477–84.
31. Coronado BE, Griffith JL, Beshansky JR, Selker JT. Hospital mortality in women and men with acute cardiac ischemia: a prospective multicenter study. J Am Coll Cardiol. 1997;29:1490-6.
32. Weaver WD, White HD, Wilcox RG, Aylward PE, Morris D, Guerci A, et al for the GUSTO-I Investigators. Comparisons of characteristics and outcomes among women and men with acute myocardial infarction treated with thrombolytic therapy. JAMA.1996;275:777-82.
33. Goldberg RJ, Gorak EJ, Yarzebski J, Hosmer DW, Dalen P, Gore JM, et al. A community wide perspective of sex differences and temporal trends in the incidence and survival rates after acute myocardial infarction and out-of-hospital deaths caused by coronary heart disease. Circulation. 1993;87:1947-53.
34. Gottlieb S, Harpaz D, Shotan A. Sex differences in management and outcome after acute myocardial infarction in the 1990s. Circulation. 2000;102:2484-98.
35. Kannel WB, Feinleib M. Natural history of angina in the Framingham study. Prognosis and survival. Am J Card. 1972;29:154–63.
36. Hochman JS, Tamis JE, Thompson TD, et al. Sex, clinical presentation, and outcome in patients with acute coronary syndromes. Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes IIb Investigators. N Engl J Med 1999;341:226–32.
37. 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 1985-91: presentation, diagnosis, treatment, and 28-day case fatality of 3,991 events in men and women. Circulation. 1996;93:1981-92.
38. Killip T, Kimball JT. Treatment of myocardial infarction in a coronary care unit; a two-year experience with 250 patients. Am J M Cardiol. 1967;20:457-64.
39. Bernal O, Moro C. Cardiac Arrhythmias in Women. Rev Esp Cardiol. 2006;59(6):609-18.
40. Kannel WB, Benjamin EJ. Final Draft Status of the Epidemiology of Atrial Fibrillation . Med Clin North Am. 2008;92(1):17–ix.
41. Feinberg W, Blackshear J, Laupacis A. et al: Prevalence,age distributon and gender of patients with atrialfibrillation. Analysis and implications. Arch InternMed 1995;155:469-473.
42. Pilote L, Dasgupta K, Guru V, Humphries K, McGrath J et al. A comprehensive view of sex-specific issues related to cardiovascular disease. CMAJ 2007;176(6) S1-41.
43. Levy D et al. Long-term trends in the incidence of and survival with heart failure. N. Engl. J. Med. 2002;347:1397–1402.
44. Abi-Gerges N et al. Sex differences in ventricular repolarization: from cardiac electrophysiology to Torsades de Pointes. Fundam. Clin. Pharmacol. 2004;18:139–151.
45. Regitz-Zagrosek V. Therapeutic implications of the gender-specific aspects of cardiovascular disease. Nature Reviews Drug Discovery.2006;5:425-239.
46. Locati E et al. Age- and sex-related differences in clinical manifestations in patients with congenital long-QT syndrome: findings from the International LQTS Registry. Circulation. 1998;97:2237–2244.
47. Zareba W. et al. Modulating effects of age and gender on the clinical course of long QT syndrome by genotype. J Am Coll Cardiol.2003;42:103–109.
48. Fang M, Singer D, Chang Y, Hylek E, Henault L, Jensvold N, Go AS. Gender differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation: the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study. Circulation. 2005;112:1687–1691.
49. Criqui M. Peripheral arterial disease- epidemiological aspects. Vasc Med 6 (Suppl) 2001;3.
50. Hirsch A, Haskal Z, Hertzer N et al: ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): A collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients with Peripheral Arterial Disease), 2005. http://www.acc.org/clinical/guidelines/pad/index.pdf
51. Thom T, Hasse N, Rosamond W et al. Heart disease and stroke statistics—2006 update: A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2006;113:e85.