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Effect of postmenopausal hormone replacement therapy on cardiovascular mortality rate in Central-Eastern Europe

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ABSTRACT

Objective: To evaluate the possible effects of postmenopausal hormone replacement therapy (HRT) on cardiovascular (CV), stroke, and ischemic heart disease (HD) mortality rates.
Method: Data on CV mortality rates in different countries were taken from World Health Organization (WHO), while rate of HRT use was calculated on data from literature and from pharmaceutical companies providing HRT preparations.
Results: CV mortality rate was significantly higher in Central-Eastern European countries (mean ± SD: 55.5 ± 4.2%) than in Western Europe (39.2 ± 3.1%), the USA (41%), and Canada (36.8%). Mortality rates caused by IHD were slightly higher, while stroke mortality rates were significantly higher in Central-Eastern Europe (14.3 ± 4.2%), than in Western European countries (9.5 ± 1.2%), the USA (6.9%), and Canada (7.4%). The spread of HRT use was 4.9 ± 0.8% in Central-Eastern Europe, significantly differing from that in Western Europe (12.6 ± 5.9%), the USA (34%) and Canada (25%).
Conclusion: CV mortality, especially stroke mortality rates are higher in Central-Eastern Europe than in Western Countries. Moreover, an inverse correlation was found between the spread of HRT use and CV mortality rates. Beside influencing other factors (smoking, fat intake, etc.) known to increase CV mortality, to increase the rate of HRT use might help to improve CV mortality rates in Central-Eastern Europe.

Keywords: hormone replacement therapy, cardiovascular, IHD and stroke mortality

INTRODUCTION

Cardiovascular diseases are the major cause of death in Western industrialized countries, while these diseases are less common in Japan, in the Mediterranean region, and in the developing countries[1,2]. In Western Europe and in North America CV mortality rates have been declining in the last decades, while they have remained the same or even have increased in Central-Eastern Europe[1,2]. Stroke and IHD are the life-threatening abrupt clinical manifestations of an existing CV disease.

After the menopause, women lose their privilege against men of having a lower risk of stroke and myocardial infarction or ischemic heart disease. In menopausal women the risk of coronary heart disease or cerebrovascular incident is almost 50% with a mortality rate of about 30%. The association between CV mortality and the postmenopause is widely accepted: at a given age the relative risk of CV disease is significantly higher for postmenopausal women than for those who are still menstruating[3]. Higher LDL and low HDL serum levels, hypertension, obesity, smoking, alcohol abuse, physical inactivity, as well as premature menopause or any decrease in serum estrogen levels caused by different reasons seem to be the most important risk factors of CV disease.

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The protective effect of estrogen against coronary and cerebrovascular diseases has been widely examined[3,4,5,6], however, some controversy still exists in the literature[7,8]. Most of the data suggest that HRT can reduce the risk of CV diseases in postmenopausal women[3,4,6]. Unfortunately, in Central-Eastern European countries appropriate epidemiologic studies on this topic are not available, probably due to the fact that there are little or no data about the spread of HRT use in these countries.

The aim of the study was to compare the spread of HRT use and the CV mortality data in some Western and Central-Eastern European countries, as well as in the USA and Canada. Preliminary data on this project have been previously published[9].

METHODS

Epidemiologic data, CV, stroke and IHD mortality rates were obtained from national mortality statistics and from annual statistics provided by the World Health Organization. Number of inhabitants in millions, the percentage of women above the age of 40 years, total mortality and mortality rate/1000 inhabitants (male and female), as well as total mortality and mortality rate/1000 women was compared in different countries. CV, IHD and stoke mortality rates are expressed as the percentage of total mortality.

HRT data were obtained either from the literature[10,11] or directly from the shipping records pharmaceutical companies providing HRT products to the countries examined. All of the HRT products contained estrogen with or without progesterone. All drugs were administered either orally or transdermally, women using locally active products (vaginal creams, ovules, etc) were excluded from the study. The number of women treated by different HRT products was then summed up in order to calculate the total number of women currently on HRT. The number of women on HRT between 1997 and 1999 was estimated from these data. Details of this method are described elsewhere[11]. The rate of women on HRT was expressed as the percentage of postmenopausal women and was compared to mortality data in the different countries. Data about the spread of HRT use in Slovakia and in the Ukraine were not available.

Data are expressed as mean ± SD, statistical analysis were performed by student t test. Differences were considered significant when $p<0.05$.

RESULTS

The first column of Table 1. shows the number of inhabitants and the rate of women in different countries. The rate of women is above 50% in each country examined, showing no remarkable differences between Eastern (mean ± SD: 51.8 ± 1.0%) and Western (51. 3 ± 0.8%) European countries. In Hungary the rate of women is among the highest (52.3%). The rate of women above 40 years of age is 46.6 ± 2.8% in Eastern and 47.5 ± 2.3% in Western European countries, showing significant differences from those in North America (43.5 and 43% in the USA and in Canada, $p<0.05$), suggesting that the female population in European societies is somewhat "older" than that in the North American continent. In Hungary the rate of women above 40 is again one of the highest among the countries examined.

The average mortality rate / 1000 inhabitants is somewhat higher in Eastern Europe (11.8 ± 2.1) than in Western Europe (9.9 ± 0.8) and especially than in the USA (8.4) and Canada (7.2). Similarly, the mortality of women (mortality rate / 1000 women) is higher in Eastern Europe (10.8 ± 1.4) than in Western Europe (9.8 ± 1.5) and than in the USA (8.3) and Canada (6.3). These numbers also show that in all of the countries examined total mortality rate / 1000 inhabitants (mortality of the whole male and female population) is somewhat higher than mortality rate of women / 1000 women. In Central-Eastern Europe mortality rates are the highest in Hungary and in the Ukraine, and the lowest in Slovakia. Lower mortality rates were found in the Western European countries, with the highest rates in the United Kingdom and Germany (11.0). Mortality rates are significantly lower both in the USA and in Canada.

Total CV, IHD, and stroke mortality rates are shown in Table 2. CV mortality rates, expressed as the percentage of total mortality are significantly ($p<0.05$) higher in Central-Eastern Europe (55.5 ± 4.2%) than in Western Europe (39.2 ± 3.1%) or in the USA (41.0%) and in Canada (36.8%). It is remarkable that all CV morality rates are above 50% in Central-Eastern, and below 50% in Western countries, as it is shown in the first column of Table 2. The highest rate was found in Romania and in the Ukraine (above 60%), the lowest in France (32.3%) and in the Netherlands (36.6). Comparing the mortality caused by IHD (expressed as the percentage of total mortality) no significant difference was found between the different regions. However, stroke mortality rates were significantly ($p<0.05$) higher in Central-Eastern Europe (14.3 ± 4.2%) than in Western Europe (9.5 ± 1.2%) and in North America (6.9% in the USA and 7.4% in Canada).

Average spread of HRT use was found to be 4.9 ± 0.8% in Central-Eastern Europe, differing significantly ($p<0.01$) from the Western European countries (12.6 ± 5.9%) and strongly different ($p<0.001$) from the USA (34%) and Canada (25%).

TABLE 1
Rate of women and mortality data of Central-Eastern European, Western European and North American countries

Country	No. of inhabitants in millions and Rate of women (%)	Rate of women above 40 yrs (%)	Total mortality and mortality/1000 inhabitants	Total mortatily of women and mort./1000 women
Hungary	10.1 (52.3)	50.7	140.870 (14.2)	66.570 (12.6)
Austria	8.1 (51.5)	47.7	78.339 (9.6)	41.954 (10.1)
Czech Republic	10.3 (51.4)	48.8	109.527 (10.7)	54.388 (10.3)
Poland	38.7 (51.4)	43.3	385.496 (9.9)	182.013 (9.1)
Romania	22.5 (51.0)	44.2	269.166 (11.8)	123.784 (10.8)
The Ukraine	50.7 (53.6)	47.8	719.954 (14.3)	364.945 (13.4)
Slovakia	5.4 (51.3)	43.4	52.686 (9.7)	245.558 (8.8)
Mean ± SD of rate	**51.8 ± 1.0**	**46.6 ± 2.8**	**11.8 ± 2.1**	**10.8 ± 1.4**
The Netherlands	15.8 (50.6)	45.8	135.783 (8.9)	68.541 (8.6)
France	59.1 (52.5)	45.3	535.775 (9.2)	258.984 (8.3)
United kingdom	58.7 (51.0)	47.1	629.746 (10.6)	329.332 (11.0)
Belgium	10.2 (51.1)	48.4	103.778 (10.3)	51.526 (9.9)
Germany	82.1 (51.2)	50.9	860.389 (10.3)	460.072 (11.0)
Mean ± SD of rate	**51.3 ± 0.8**	**47.5 ± 2.3**	**9.9 ± 0.8**	**9.7 ± 1.5**
USA	273.1 (51.1)	43.5	2,314.245 (8.4)	1,154.039 (8.3)
Canada	30.5 (50.5)	43.0	215.668 (7.2)	103.683 (6.3)

TABLE 2
Total cardiovascular, ischemic heart disease, and stroke mortality data, and the spread of HRT use in Central-Eastern European, Western European and North American countries

Country	CV mortality total mortality (%)	IHD/ total mortality (%)	Stroke / total mortality (%)	HRT use (%)
Hungary	51.4	9.3	13.6	4.2
Austria	54.3	11.0	12.3	4.4
Czech Republic	55.1	10.7	15.2	6.0
Poland	50.4	7.3	7.8	5.0
Romania	61.7	8.1	20.6	<1.0
The Ukraine	60.3	11.3	16.0	no data
Slovakia	54.9	10.7	10.2	no data
Mean+SD	**55.5 ± 4.2**	**9.8 ± 1.7**	**14.3 ± 4.2**	**4.9 ± 0.8**
The Netherlands	36.6	10.5	8.9	12.0
France	32.3	5.2	8.1	9.0
United Kingdom	41.4	11.9	10.5	9.0
Belgium	37.4	8.0	9.3	10.0
Germany	48.3	9.6	10.9	23.0
Mean+SD	**39.2 ± 3.1**	**9.0 ± 2.6**	**9.5 ± 1.2**	**12.6 ± 5.9**
USA	41.0	8.9	6.9	34.0
Canada	36.8	10.2	7.4	25.0

DISCUSSION

Our study shows that the spread of HRT use is significantly lower in Central-European countries than in the Western European countries examined, and much lower than in the USA and Canada. No data could be obtained on HRT use in the Ukraine and in Slovakia. On the other hand, CV mortality rates are higher in Central-Europe than in the Western countries and in North America. A significant difference in coronary heart disease incidence and mortality between 7 North and South European countries has been recently shown[12]. According to our data IHD mortality rates were similar in the different regions, while mortality rates due to stroke were higher in the Central-Eastern European countries, suggesting that stroke mortality can be the cause of the higher overall CV mortality rates in that region. It is also important to

note that in Western Europe and in North America CV mortality rates have been declining in the last decades, while they have remained the same or even have increased in Central-Eastern Europe and in Hungary as well[1].

Our data show an inverse correlation between overall CV mortality rates and the spread of HRT use, as well as between stroke mortality and HRT use. In Eastern-European countries CV and stroke mortality rates are significantly higher, and HRT use is significantly lower than in Western Europe, and especially in the USA and Canada. Of course, CV mortality rates of a country or a region might also be influenced by other risk factors, such as obesity, exercise, fat intake and serum lipid levels, smoking, alcohol abuse, etc. These factors can contribute to the differences in CV mortality rates found between Central-Eastern and Western countries. Despite some certain differences in culture Central-Eastern European countries possibly represent a more homogenous population than Western European countries, which again underlines the importance of HRT.

The purported reason behind the fact that the incidence of cardiovascular disease differs significantly between men and women could be in part because of differences in risk factors and hormones[18]. The incidence of atherosclerotic diseases is low in premenopausal women, rises in postmenopausal women, and is reduced to premenopausal levels in postmenopausal women who receive estrogen therapy[18–20]. Until recently, the atheroprotective effects of estrogen were attributed principally to the hormone's effects on serum lipid concentrations. However, estrogen-induced alterations in serum lipid account for only approximately one third of the observed clinical benefits of estrogen[20–22]. Reviews of the data suggested that the direct actions of estrogen on blood vessels contributed substantially to the cardiovascular protective effects of estrogen[21,23]. The vasculature, like the reproductive tissues, bone, liver, and brain, is now recognized as an important target of estrogen's actions. Estrogen increases vasodilatation and inhibits the response of blood vessels to injury and the development of atherosclerosis.

Estrogen also has atheroprotective actions in many normolipidemic or hypercholesterolemic animals[24–29], and it provides protection against vascular injury in mice in which estrogen receptor α[36] or estrogen receptor β has been genetically disrupted. Studies in animals have shown that estrogen increases the regrowth of endothelial cells after denudation, reduces the size of vascular lesions in carotid arteries and the aorta[24–27] and inhibits the proliferation of vascular smooth-muscle cells in carotid arteries[24]. These beneficial effects of estrogen are blocked by high but not by low doses of progesterone[25–27]. Estrogen also appears to be protective in castrated male rats but not in intact male rats[26–27], although it prevents atherosclerosis in intact, apolipoprotein E-deficient male mice[25]. In a study of rabbits with cardiac allografts, estradiol inhibited myointimal proliferation and decreased the vascular expression of major-histocompatibility-complex antigens and the infiltration of immune cells. These protective effects of estrogen treatment had little or no effect on serum lipid concentrations[24,25,30], observations that provide further support for a direct effect of estrogen on blood-vessel walls. Estrogen contributes to long-term vascular protection by inhibiting the proliferation of vascular smooth-muscle cells and accelerating the growth of endothelial cells.

Despite some controversies in the literature most of the authors agree that women on HRT have lower rates of cardiovascular, coronary, and cerebrovascular diseases. It has been recently shown that HRT can reduce blood pressure in postmenopausal women with treated hypertension. Favourable effects of HRT on biomechanics of small arteries and veins[16,17] of rat have been recently published. Estrogens were proved to lower LDL, and increase HDL serum lipid concentrations providing an atheroprotective effect. Moreover, estrogens reduce platelet-aggregation and may influence the activity of different coagulation factors.

In Hungary the number as well as the rate of women above 40 years was found to be one of the highest among the countries examined with a relatively high and with increasing trends in CV mortality rates. This emphasizes the importance of HRT use in Hungary in order to decrease CV mortality and to improve life quality of the peri- and postmenopausal women.

In summary, HRT might be useful to stop unfavorable trends in CV mortality in the Central-Eastern European countries. HRT itself has some cardivascular (thromboembolic events) risks, especially when HRT is used for secondary prevention of coronary heart disease in postmenopausal women[7,8], emphasizing the significance of other efforts with no risks in order to decrease CV mortality. Governmental efforts to decrease smoking, educational programs to let people learn the importance of exercise, low fat intake, etc. can contribute to decrease CV mortality. Central-Eastern Europe seems to be a suitable region for future trials to enhance the spread of HRT use and to detect its impact on CV mortality rates.

A number of questions remain to be addressed in this evolving field. The direct effects of estrogen on the vasculature promote vasodilatation and inhibit the

development and progression of atherosclerosis. However, some of the nonvascular effects of estrogen may offset its beneficial vascular effects. There are currently no identified estrogens with relative selectivity for the vasculature[31,32]. The potential clinical effects of estrogen metabolites, phytoestrogens and local conversion of testosterone to estradiol all need to be explored. Direct myocardial effects of estrogen on cardiac structure and function are likely to be important as well and deserve greater attention. More prospective clinical trials of estrogen therapy for the primary and secondary prevention of cardiovascular disease are needed, including additional prospective studies of estrogen alone or in combination with other compounds (such as progestins and 3-hydroxy-3 methylglutaryl coenzyme a reductase inhibitors). It is likely that the rapid progress in this field day in both basic and clinical sciences will soon lead to the developments of more specific hormonal therapies for cardiovascular disease.

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