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Effects on cardiovascular morbidity and mortality (additive 1998-2000)

The very first goal of hormone replacement therapy (HRT) was to abolish acute symptoms of menopause. Now, many other aims are expected from more than 30 years of prescription in postmenopausal women living in developed countries. The question of a potential reduction of cardiovascular has been addressed but no clear answer can be given yet. Most studies analysed were observational studies, with all their well-known biases, or small sized randomised trials with, for most of them, surrogate end-points. Some studies had prospective designs, but the lack of randomisation in the delivery of the treatment could not allow a definite conclusion, despite positive results. Moreover, most of these studies were developed in Northern American population whose prescription habits in term of composition and administration route of HRT differed significantly from European populations.

The absolute coronary event risk of women aged 35 to 64 years is significantly lower than the one of men in all countries in the world (table 17.I), as confirmed in 1999 by the international results of the WHO-MONICA project (Tunstall-Pedoe et al., 1999). However, as age increase, women tends to catch up with men in term of cardiovascular risk, and the replacement of what is thought to be the major female protective factor, their endogenous hormones, is a matter of concern. A recent Finnish prospective study (Sourander et al., 1998) involving women participating in a mammography screening program for breast cancer concluded that current hormone replacement therapy (mainly unopposed estrogen) reduced primarily sudden cardiac death and predicted reduced cardiovascular mortality, but did not reduce morbidity. This additional observational study tends to reduce the impact of HRT on cardiovascular morbidity and insists on its effect on mortality. However, the specificity of the population, the fact that most precription were unopposed estrogen limits the generalisation of these results. Conversely in term of cerebrovascular risk, results are more sparse and usually do not conclude at any clear protective effect. Indeed, the effect of HRT on the risk of stroke has been less documented. All studies report consistently no increase or decrease in the risk of ischemic stroke, nor any trends. When analysed by subtype of stroke (subarachnoid hemorrhage, intracerebral hemorrhage, thromboembolic infarction, transient ischemic heart attack), no association could be detected (Pedersen et al., 1997). However the total number

Table 17.I : Coronary event rates (/100 000) in men and women in the world. WHO-MONICA Project 1985-1994 (Tunstall-Pedoe et al., 1999)

Center	Men	Women
China (Beijing)	81	35
Spain (Catalonia)	210	35
Switzerland (Vaud/Fribourg)	231	0
France (Toulouse)	233	36
Italy (Friule)	253	47
Italy (Brianza)	279	42
Germany (Augsburg)	286	63
Switzerland (Ticino)	290	0
France (Strasbourg)	292	64
France (Lille)	298	64
Belgium (Ghent)	346	77
Germany (Bremen)	361	81
Sweden (Göteborg)	363	84
East Germany	370	78
Australia (Perth)	389	92
Yougoslavia (Novi-sad)	422	101
USA (Stanford)	431	134
New-Zealand (Auckland)	434	115
Russia (Moscow I)	453	90
Poland (Tarnobrzeg)	461	110
Russia (Novosibirsk C)	464	111
Russia (Novosibirsk I)	468	130
Russia (Moscow C)	477	92
Australia (Newcastle)	479	153
Iceland	486	99
Belgium (Charleroi)	487	118
Lituania (Kaunas)	498	80
Sweden (North)	509	119
Czech Republic	515	101
Denmark (Glostrup)	517	140
Canada (Halifax)	523	139
Finland (Turku-Loimaa)	549	94
Poland (Warsaw)	586	153
Irland (Belfast)	695	188
Finland (Kuopio)	718	124
Scotland (Glasgow)	777	265
Finland (North Carelia)	835	145

of cases analysed in most studies are small and the difficulty to perform an exhaustive detection of events, particularly concerning transient ischemic heart attacks, do not allow to exclude any deleterious or protective effect. This lack of association with stroke, fatal or non fatal, was recently confirmed in a cohort of Californian women living in Rancho Bernardo (Fung et al., 1999). However, all these results concluding to a potential benefit of HRT on the reduction of cardiovascular risk were obtained from observational studies and one randomised trial. Observational study conclusions are impaired by several major biases (Barret-Connor et al., 1998) : HRT is often not prescribed if cardiovascular diseases, hypertension or diabetes personal histories exist ; low socio-economical status and education level reduce the chance to have HRT prescribed ; the first reason to prescribe HRT is menopause syndrome often affecting thin women ; HRT is often prescribed to women with better metabolic risk factors and healthier way of life ; HRT compliance is impossible to address in these observational studies.

Thus, until now, none of the previous studies were randomised. Such a condition is the only one able to reduce the numerous biases of observational studies whatever their retrospective or prospective design. The only clinical trial on HRT estimating morbidity, mortality and various outcome measures (coronary revascularisation, unstable angina, congestive heart failure, resuscitated cardiac arrest, stroke, transient ischemic attack and peripheral arterial disease), has been published in 1998 (HERS, Hulley et al., 1999). As often observed in cardiovascular disease prevention, more rapid and stronger effect are expected in secondary prevention (i.e. reducing events in patients already affected) than in primary prevention. Thus 2 763 women with coronary disease, younger that 80 (mean age 66.7 years) and postmenopausal, with intact uterus were randomly assigned to either 0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate in 1 tablet daily (n=1 380) or a placebo (n=1 383) and followed-up 4.1 years. Overall no significant difference between groups could be detected whatever the outcome was. This lack of effect occurred despite lower LDL cholesterol levels (–11 %) and higher HDL cholesterol levels (+10 %) in the treated group. When analysing the distribution of event along time, there was a statistically significant time trend, with more coronary events in the HRT group than in the placebo group in year 1 and fewer in years 4 and 5. Concerning adverse effects, there were more venous thromboembolic events and gallbladder disease in treated women, but no significant differences in fracture, cancer and total mortality.

Thus, HERS, with a controlled design, did not report any protective effect. In this trial, risk was increased in the first four months in the HRT group, followed by a decline in the final two years. The same pattern of an early increase in risk followed by a late decrease was reported in the setting of secondary prevention in the Nurses Health Study cohort (Clinical synthesis panel, 1999). This leads to the conclusion that HRT does not bring any protective benefit to women with prior myocardial infarction, but do not

Table 17.II : Effects of postmenopausal HRT on the cardiovascular risk

Authors	Country	Design	Population	Sample Size	Age range	Study period	HRT	Results
Pedersen et al. 1997	Danemark	Case-control	Danish National Patient Register	1 422 cases/ 3 171 controls	45-64	1990-1992	estrogen alone, estrogen with progestagen	No association with any subtypes of stroke
Sourander et al. 1998	Finland	Prospective	Finnish mammography screening program	7 944	57-64	1987-1995	estrogen alone, estrogen with progestagen	Reduced primarily sudden cardiac death and mortality. RR current users 0,21 (0,08-0,59). No association with cardiovascular morbidity
Petitti et al. 1998	USA	Case-control	Northern California Kaiser Permanente medical care program	349 cases/ 349 controls	45-74	1991-1994	estrogen alone, estrogen with progestagen	No association with ischemic stroke
HERS, 1998	USA	Controlled trial with randomisation	Postmenopausal coronary patients	1 380 HRT/ 1 383 placebo	44-79	1993-1994, follow-up 4,1 years	0,625 mg CE + 2,5 mg MPA	No association with cardiovascular morbidity
Fung et al. 1999	USA	Prospective	Rancho Bernardo Community	1 031	over 60	1984-1987, follow-up 8,8 years	estrogen alone, estrogen with progestagen	No association with any subtypes of stroke

exclude possible positive influence in primary prevention or with other routes of administration. As illustrated by the first year of follow-up in HERS and several observational studies, the relative risk of venous thromboembolism seems to be constantly increased but its absolute risk remains small. No clear effect, deleterious of protective could be detected for stroke. Last but not least, this study has been performed in North America with equine conjugated estrogen and MPA. Those drugs are not the most used in other countries as Europe, and large randomised trials prescribing synthesis products or different way of administration are desperately lacking. Concerning the route of administration, one observational study analysed the impact of transdermal estrogen replacement therapy on plasma lipids, an intermediate risk criteria, in women recruited in the population study of the French MONICA project (Bongard et al, 1998). In this study, HRT was associated with lower levels of serum total cholesterol, triglycerides, LDL, VLDL and apolipoprotein B levels. HDL levels did not differ significantly. However, the absence of hard outcomes (mortality, morbidity) do not allows to conclude, all the more because the protective impact on lipid risk does not seem so important as with oral route.

To conclude, at the beginning of year 2000, only one randomised controlled trial analysing the effect of HRT in cardiovascular secondary prevention, is available, HERS (table 17.II). This trial was not able to detect any difference in the cardiovascular outcomes between the HRT group and the placebo group. Moreover, an increased risk of coronary events was observed during the first year of follow-up in the HRT group. To address more definitely potential benefits or deleterious effects, appropriate randomised studies are needed. Such studies in primary prevention are ongoing, as the Women's Health Initiative in the US and the Women's International Study of Long-Duration Estrogen after the Menopause. The results of such trials are not expected until about 2005. However, the composition of treatments used (i.e. natural *vs* synthetic compounds) and the route of administration will need still further investigation whatever the answer of these ongoing trials will be. All this review pleads for multicentre European trials testing these various hypotheses to be able to clearly answer the question of the cardiovascular benefit of HRT.

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