2

Cardiovascular morbidity and mortality in postmenopausal women on HRT

Because the increased cardiovascular risk (CVR) observed in postmenopausal women is at least partially attributed to the loss of female hormone following the onset of menopause, it is reasonable to assume that hormone replacement therapy (HRT) administered to menopausal women to counteract some of the symptoms linked to their deficit in estrogen could also diminish the risk of cardiovascular morbidity or mortality. This was strongly suggested in a meta-analysis published in 1991 by Stampfer and Colditz. They concluded that women exposed to estrogen after menopause had a relative risk of cardiovascular disease of 0.56 (95 % confidence interval [0.50-0.61].

A number of publications, studying the potential influence of HRT on CVD and all-cause mortality, or on thromboembolism or stroke have been submitted to analysis. The studies are either observational studies involving large cohorts, such as the Framingham or the Nurses' Health studies, or case control studies. Studies about hormone replacement therapy (HRT) and all-causes mortality have also been considered. Only one is a case-control randomized trial (Nachtigall, 1979).

Prospective studies

The main lines of the protocols used and the results of nine prospective studies analyzed below are described in tables 2.I and 2.II.

In the Framingham Heart Study, Wilson et al. (1985) studied the effect of estrogen use on mortality from cardiovascular disease in 1 234 postmenopausal women aged 50 to 83 years. No benefits from estrogen use were observed in the study group ; in particular, mortality from cardiovascular disease did not differ between estrogen users and nonusers.

Criqui et al. (1988), in this same prospective cohort, studied the association between postmenopausal estrogen use and mortality from cardiovascular disease, coronary heart disease, cancer and all causes in a cohort of

Table 2.I : Postmenopausal estrogen replacement therapy and cardiovascular morbidity

Authors	Population	N	Age range	Study period	HRT	Morbidity
Colditz et al. (1987)	US women prospective (Nurses'Health Study : NHS) CHD : non fatal MI, death due to CHD	121 700	30-55 in 1976	1976 to 1982	CE	RR users vs preMp: 0.9 (0.6-1.6)
Grodstein et Stampfer (1996)	NHS MI or death from coronary disease	59 337	30 to 55 at baseline	1976-1992	estrogen alone estrogen with progestin(EP)	EP adjusted RR current users vs never : 0.39 (0.19-0.78) E alone : 0.60 (0.43-0.83)
Falkeborn et al. (1992)	Sweden prospective cohort study with prescriptio-based and record linkage system first acute MI	23 174	35 and older	1977-1983	E2, CE, Other E E+PG	observed number of first MI compared with that expected for women<60 at the entry, with E2 or CE , RR: 0.69 (0.54-0.86) with E2-levonorgestrel, RR: 0.53 (0.30-0.87)
Stampfer et al. (1985, 1991)	NHS stokes, nonfatal MI, deaths from coronary causes	48 470	30 to 63	10 years 1976-86	conjugated E	adjusted RR major coronary disease current vs never : 0.56 (0.40-0.80) fatal CV diseases : 0.61 (0.37-1.00)-
Wilson et al. (1985)	Framingham Heart Study CHD=angina pectoris, MI, coronary death, sudden death CVD= CHD +cerebrovascular disease etc...	1 234	50 to 83	8 yearsfrom 1970-1972	CE	favorable CV risk profile for E users RR CHD users vs nonusers: 1.9 ($p<0.01$) RR total CVD: 1.76 ($p<0.01$)
Hunt et al. (1990)	England and Wales longitudinal cohort comparison with expected rates	4 544 long-term users of HRT	45 to 54 years at fisrt use of HRT	1966?-1988	combined or alone	mortality ration for ischaemic heart disease(RR: 0.41; 0.20-0.59) and all circulatory diseases (RR: 0.44; 0.28-0.59) significantly lower than expected
Nachtigall et al. (1979)	postmenop double-blind randomised	84	control: 54.9	10-year	premarin 2.5 daily medroxyprog 10mg daily for 7 days in each month	no difference in the incidence of thrombophlebitis, MI

Table 2.I : Postmenopausal estrogen replacement therapy and cardiovascular morbidity *(continued)*

Authors	Population	N	Age range	Study period	HRT	Morbidity
Bain et al. (1981)	US nurses MI case-control	123	30-55 in 1976	1976	CE ?	RR adjusted for age ever vs never: 0.9 (0.6-1.2) RR current vs never: 0.7 (0.5-1.1) bilateral oophorectomy RR current vs never: 0.4 (0.2-0.8)
Hernandez Avila et al. (1990)	Group Health Cooperative nested case-control MI	103	50 to 64	1978-1984	CE	adjusted RR current vs never: 0.7 (0.4-1.4) RR past vs never: 0.6 (0.1-2.1)
Rosenberg et al. (1993)	Massachusetts case-control fisrt MI	858	45-69	1986-1990	CE	RR ever use alone E: 0.9 (0.7-1.2) RR E+P: 1.2(0.6-2.4) decreased risk with duration of use (p=0.08)
Pfeffer et al. (1978)	retirement community case-control MI	2 203	57 to 98	11-year interval	CE ?	no association between E use and MI : adjusted RR current use : 0.68 (0.32-1.42)
Ross et al. (1981)	medical recors of Los Angeles death from ischaemic disease compared with living and deceased control groups case-control	133	?	1971-1976	CE	RR users vs living controls or vs deceased controls : 0.43 (0.24-0.75)
Thompson et al. (1989)	women in general practices case-control stroke or MI	603	45-69	1982	different preparations progestogens	RR more than one prescription vs no prescription: 1.36 (1.01-1.81) RR more than one precription progestogens alone vs no prescription: 1.9 (1.11-3.25)

Table 2.II : Postmenopausal estrogen replacement therapy and mortality

Authors	Population	N	Age range	Study period	HRT	Mortality
Bush et al. (1987)	white US women cohort of the Lipid Research Clinics Program	2 270	40-69	enrolment 1972 and 76 8.5 years follow-up	oral E: premarin	age adjusted RR of cardiovascular disease deaths users vs nonusers: 0.34 (0.12-0.81)
Criqui et al. (1988)	US planned community cohort study	1 868	50-79	12 years since 1972	E : CE ?	age adjusted all cause RR users vs nonusers: 0.69 (0.55-0.87) after adjustment for other factors rr: 0.79 (0.62-1.01) never and current smokers RR:0.67 (0.45-0.99) past smokers RR: 1.32 (0.84-2.08)
Henderson et al. (1991, 1992)	retirement community California prospective study	8 881	median age at enrolment:73	1981-1988 7.5 years	estrogen CE	age adjusted RR all cause mortality users vs nonusers: 0.8 (0.70-0.87) RR currents users vs lifetime nonusers (0.52-0.78) current long term users : RR=0.64 ($p<0.001$)

1 868 women aged 50-79 years. The study indicated a protective effect of postmenopausal estrogen use on cardiovascular disease mortality in current smokers, and a weaker, non significant effect in « never-smokers ». Overall, postmenopausal estrogen appeared protective for total mortality.

In a prospective study of 8 881 postmenopausal female residents of Leisure World (Laguna Hills), Henderson et al. (1991) evaluated the relationship between estrogen use and overall mortality. Mortality decreased with increasing duration of use and was lower among current users than among women who used estrogens only in the distant past. Women who had used estrogen replacement therapy had a reduced mortality from all categories of acute and chronic arteriosclerotic disease and cerebrovascular disease.

Folsom et al. in 1995 assessed the association of hormone replacement therapy with mortality and the incidence of multiple diseases in over 40 000 postmenopausal women followed for 6 years as part of the Iowa Womens' Health Study. The study indicated a negative association of HRT with total mortality and coronary heart disease (relative risk -RR - total mortality = 0.78, 95 % CI 0.65, 0.94 and coronary heart disease mortality = 0.74 ; 95 % CI 0.48, 1.12) when women who had never used HRT were compared with current users.

Kunt et al. in 1990 examined all causes of mortality and cardiovascular mortality in a cohort of 4544 long-term users of HRT in comparison with expected rates in the female population of England and Wales. Overall mortality remained significantly lower than expected on the basis of national rates (relative risk 0.56, 95 % CI 0.47-0.66). The mortality rates for ischemic heart disease (RR 0.41, 95 % CI 0.20-0.61) and all circulatory diseases (RR 0.44, 95 % CI 0.28-0.59) were also significantly lower than expected.

Fakelson et al. (1992) determined the risk of a first acute myocardial infarction after treatment with estrogen alone or estrogen-progestogen combinations in 23 174 women aged 35 years and older in Uppsala Health Care Region. Women prescribed any type of non-contraceptive estrogen had evidence of a reduced risk of a first acute myocardial infarction as compared with women in the general population. The protective effect was about 30 % for women prescribed potent estrogens such as estradiol compounds or conjugated estrogens at perimenopausal ages. The protective effect persisted during the seven-year follow-up period.

A cohort of 2 270 white women, aged 40-69 years at baseline, was followed for an average of 8.5 years in the Lipid Research Clinics Program Follow-up Study (Bush et al., 1987). The age-adjusted relative risk of cardiovascular disease deaths in users compared with nonusers was 0.34 (95 % CI 0.16-0.88).

In a first study from the Nurses' Health Study based on four years of follow-up, Stampfer et al. in 1985 reported that estrogen therapy reduced the risk of coronary heart disease. The age-adjusted risk of coronary disease in women who had used hormones was 0.5 (95 % CI 0.3-0.8 p=0.007). In a second

study in 1991, Stampfer et al. on 10 years of follow-up confirmed that current estrogen use was associated with a reduction in the incidence of coronary heart disease as well as in mortality from cardiovascular disease, but not with any change in the risk of stroke.

More recently, Grodstein and Stampfer (1996) reported an analysis based on 16 years of follow-up data in 59 337 postmenopausal women participating in the Nurses' Health Study. A marked decrease was observed in the risk of major coronary heart disease among women who took estrogen with progestin, as compared with the risk among women who did not use hormones. However, there was no significant association between stroke and the use of combined hormones. The addition of progestin does not appear to attenuate the cardioprotective effects of post menopausal estrogen therapy.

Case-control studies

Results from six main case-control studies are presented in tables 2.I and 2.II. Rosenberg et al. (1993) conducted a case-control study of myocardial infarction among Massachusetts women aged 45-69 years during 1986-90, in which each case was age-matched with a control from the same geographic area. The results suggest that estrogen alone use may reduce the risk of first myocardial infarction. The risk decreased as the duration of use increased, but only in recent users (versus past users).

Bain et al. in 1981 (Nurses' Health Study) compared the relative risk of non users with the relative risk of women who had taken female hormones (0.9 ; 95 % CI : 0.6-1.2) and current users (0.7 ; 0.5-1.0). For women with bilateral oophorectomy, the RR for current users was 0.4 (0.2-0.8). For each case of MI, 20 control women were selected randomly.

Thompson et al. (1989) investigated the association between the use of HRT both overall and separately according to progestogen and estrogen content, and the incidence of stroke and myocardial infarction (MI) in women aged 45-69 years in the UK. There was no evidence that the use of HRT was a major cardiovascular risk or benefit. The women who had used HRT had used it on average for only 15 months, some 9 years before.

Ross et al. (1981) studied a Los Angeles retirement community to identify an association between estrogen therapy and death from ischemic heart disease. Women dying from this disease over a five-year period were compared with living and deceased control groups. Compared with living controls, cases using conjugated estrogens had a relative risk of death from ischemic heart disease of 0.43 (0.24-0.75). The comparison with deceased controls gave a similar relative risk.

Hernandez Avila et al. in 1990 evaluated the relation between postmenopausal estrogen use and the risk of first myocardial infarction using both cohort

and nested case-control analyses derived from the Group Health Cooperative of Puget Sound (aged to 50 to 64 years). The relative incidence of myocardial infarction among current users compared with nonusers, adjusted for age and calendar year, was 0.7 (0.4-1.3).

Recently Grodstein et al. (1997) reported a case control analysis from the Nurses' Health Study. The authors documented 3 637 deaths from 1976 to 1994. Each participant who died was matched with 10 controls alive at the time of her death. After adjustement for confounding variables, current hormone users had a relative risk of death of 0.63 (0.56-0.70). The apparent benefit decreased with long term use (RR=0.80 ; 0.67-0.96 after 10 or more years) because of an increase in mortality from breast cancer among long term hormone users. Current users with coronary risk factors (69 % of the women) had the largest reduction in mortality, with substantially less benefit for those at low risk.

Critical analysis

The first studies suggesting that HRT could protect postmenopausal women against the cardiovascular risk were published in the early eighties. Since then, the effect of these treatments has been analyzed in a number of cohort studies and several meta-analysis have been published (Barrett-Connor and Bush, 1990 ; Stampfer and Colditz, 1991 ; Grady et al., 1992 ; Scarabin and Plu-Bureau, 1993). All these reports suggest that a decrease in the cardiovascular risk (up to 30 to 45 %) can be obtained in postmenopausal women who have been treated or are still treated with estrogens. Overall, the risk of cardiovascular mortality is estimated to be 0.80 (confidence interval at 95 % : 0.65-0.97) (Scarabin and Plu-Bureau, 1993). In this last review, estrogens did not protect against the risk of cerebrovascular events. More recently, Grodstein et al. (1997) suggested that with additional years of estrogen use, expected mortality advantages were in part offset by the risk of breast cancer.

It must be pointed out that the different studies do not consider the same cardiovascular diseases. They may be myocardial infarctions, fatal or not, and sometimes it is not specified if the event is stroke or infarction. The above-mentioned effects have been observed with oral estrogens. There are no reports describing the activity of estrogens administered by other routes, except when these treatments have been applied to women presenting additional cardiovascular risks.

To prevent the adverse effect of estrogens on the endometrium, a progestogen is now co-prescribed. It remains to be determined if this combination interferes with the action of estrogens on the cardiovascular risk. Out of the five studies reporting the activity of an estroprogestogen combination, the most reliable is from Grodstein et al. (1996). This prospective study has

been conducted in the framework of the Nurses' Health Study and gives a relative risk (RR) of 0.39 (95 % CI : 0.19-0.78) when treated women are compared with untreated women.

Overall, the results of epidemiological studies argue strongly for a protective role of estrogens administered after the menopause, but a number of reservations have to be addressed. Most of them concern oral estrogens given alone (no combined progestogen) and of equine origin. Currently in Europe the treatment consists of administering natural estrogens combined with a progestogen in non hysterectomized women. So far, the effects of percutaneous or transdermal estrogens have never been submitted to any large scale clinical trial reported in the literature.

In addition, no reliable information is available indicating to what extent the effects of a given treatment are influenced by dosages and duration. It seems that women currently on HRT are better protected than those who have been treated in the past, but this observation needs to be confirmed (Henderson et al., 1988, Stampfer et al., 1985).

Another problem is that these results on the protective effects of HRT have been obtained in observational studies. Biases linked to this type of study imply that the differences observed in cardiovascular morbidity can be explained, partially, by existing differences between treated and untreated women. The evaluation of the relative risk has been only slightly modified when adjustments taking into account the main risk factors have been performed. Nevertheless, other parameters which have not been considered in these studies can differentiate treated from untreated women. In the USA, HRT is preferentially prescribed to healthy women (Hemminki and Sihvo, 1993).

This observation has been confirmed by an investigation showing that in most of the prospective studies performed to evaluate the effects of HRT on the cardiovascular risk, the relative incidence of all-type cancers was below 1 in the treated women (Posthuma et al., 1994). It was noted that the protection against cancer increased with the decrease in the cardiovascular risk. A diminution in the cancer risk can hardly be attributed to HRT ; indeed it is known to increase the risk of endometrial cancer, suspected to have the same effect on breast cancer and as far as the other types of neoplasms are concerned it has never been reported to be beneficial. Thus, it is likely that HRT treated women developed less tumors because they were healthier than their untreated counterparts from the outset. In the Nurses' Health study, women taking hormones appear to be at a greater risk of breast cancer than of death from cardiovascular disease (Grodstein et al., 1997).

In non-experimental studies, it is important to consider compliance as an other potential bias (Petitti, 1994). Two randomized trials have evaluated the efficacy of secondary prevention in patients who previously had a myocardial infarction. It was observed that, in the placebo group, good compliance was

associated with a decrease in all-cause mortality (Coronary Drug Project Research Group, 1980 ; Gallagher et al., 1993). In one of these reports, the placebo group women showed a compliance of 75 % (corresponding to ingestion of 75 % of the prescribed drugs). These subjects presented a mortality risk 64 % lower than women with worse compliance (RR : 0.36 ; CI 95 % : 0.13-1.0) after adjustment for the severity of the initial ischemic event and various socio-economic factors. Users of HRT are, by definition, women who should have good compliance.

Within a cohort of more than 49 000 postmenopausal American women (Sturgeon et al., 1995), a lower all-cause mortality rate was observed in the estrogen-treated group (minimum one treatment) as compared with never-users (RR : 0.7 ; CI 95 % : 0.7-0.8). This difference was even more obvious among current users (RR : 0.3 ; CI 95 % : 0.2-0.4). In contrast, an increase in all-cause mortality was observed in users who had discontinued the treatment for 2 to 3 years as compared with never-users (RR : 1.4 ; CI : 1.2-1.7). A plausible explanation for this observation could be that only healthy women stick to their treatment, which is discontinued as soon as a subject experiences any pathological symptom. This phenomenon, known as the « healthy estrogen user survivor effect » (Sturgeon, 1995) suggest a bias linked to the selection of the healthiest women for HRT prescription. In a recent report, a Dutch group estimated that when a decrease of 35 to 45 % in the cardiovascular risk is observed in HRT-treated women, 20 % should be subtracted because of the health selection bias (Vandenbroucke, 1995).

In a recent review (Paganini-Hill, 1995), the data of nineteen studies considering the potential relationships between HRT and cerebrovascular disease were evaluated. In seven studies the risk of death by stroke was reported to be 20 % to 60 % lower among estrogen users than among nonusers, but the results are not always statistically significant. In contrast, two cohort studies (the Nurses' Health Study reported by Grodstein et al., 1996, and the Framingham heart study in 1985) report an increased risk for estrogen users. In studying the influence of HRT on stroke, potential biases (selection bias, recall bias and confounding bias) have to be considered for their impact on the estimate of cardiovascular risk. There are no studies investigating the effects of transdermal estrogens and very few concerning those of combined treatments. From the published literature, it is not possible to draw any conclusions concerning a duration effect, a dose effect or a modification in the risk following discontinuation of exposure.

Four studies (two cohort studies and two case-control studies) indicate that the thromboembolitic risk is increased in treated women, particularly at the beginning of treatment, as reported in two of the four studies. Similar results are obtained for transdermal administration. In one study, a dose-effect was observed. Observational studies can present indication biases, but these results cannot be explained only by a bias because they are all in agreement and of importance (RR multiplied by 2 to 4).

To conclude, a number of studies show that hormone replacement therapy (HRT) administered to menopausal women diminish (up to 30 to 45 %) the risk of cardiovascular morbidity or mortality. Most of them concern oral estrogen given alone (no combined with progestogen) and of equine origin. This protection is also mentioned with the administration of estroprogestogen, but the effects percutaneous or transdermal estrogens (currently used in Europe) have never been submitted to any large scale clinical trial. No reliable information is available indicating to what extend the effects of a given treatment are influenced by dosage and duration. It seem that women currently on HRT are better protected than those who have been treated in the past.

The results on the protective effects of HRT have been obtained in observational studies. Biases are linked to this types of study : in the USA, HRT is preferentially prescribed to healthy women ; users of HRT are women who should have good compliance. Only controlled trials will allow to conclude whether or not HRT, especially as prescribed in Europe, can lower the risk of coronary heart disease. Such studies are currently ongoing (Eaker et Hahn 1994).

BIBLIOGRAPHY

BAIN C, WILLETT W, HENNEKENS CH, ROSNER B et al. Use of postmenopausal hormones and risk of myocardial infarction. *Circulation* 1981, **64** : 42-46

BARRETT-CONNOR E. Estrogen and cardiovascular disease. Epidemiologic studies from the USA. *Gynecologie* 1991, **42** : 23-25

BARRETT-CONNOR E, BROWN WV, TURNER J, AUSTIN M, CRIQUI MH. Heart disease risk factors and hormone use in postmenopausal women. *JAMA* 1979, **241** : 2167-2169

BARRETT-CONNOR E, BUSH TL. Estrogen and coronary heart disease in women. *JAMA* 1991, **265** : 1861-1867

BARRETT-CONNOR E. Epidemiology and the menopause : A global overview. *Int J Fertil* 1993, **38** : 6-14

BARRETT-CONNOR E. Postmenopausal estrogen and prevention bias. *Ann Intern Med* 1991, **115** : 455-456

BARRETT-CONNOR E. The menopause, hormone replacement, and cardiovascular disease : the epidemiologic evidence. *Maturitas* 1996, **23** : 227-234

BUSH TL, BARRETT-CONNOR E, COWAN LD, CRIQUI MH et al. Cardiovascular mortality and noncontraceptive use of estrogen in women : results from the Lipid Research Clinics Program Follow-up Study. *Circulation* 1987, **75** : 1102-1109

COLDITZ GA, WILLETT WC, STAMPFER MJ, ROSNER B et al. Menopause and the risk of coronary heart disease in women. *N Engl J Med* 1987, **316** : 1105-1110

CRIQUI MH, SUAREZ L, BARRETT-CONNOR E, MCPHILLIPS J et al. Postmenopausal estrogen use and mortality. Results from a prospective study in a defined, homogeneous community. *Am J Epidemiol* 1988, **128** : 606-614

EGELAND GM, KULLER LH, MATTHEWS KA, KELSEY SF et al. Premenopausal determinants of menopausal estrogen use. *Prev Med* 1991, **20** : 343-349

ETTINGER B, FRIEDMAN GD, BUSH T, QUESENBERNG CP JR. Reduced mortality associated with long-term postmenopausal oestrogen therapy. *Obstet Gynecol* 1996, **87** : 6-12

FALKEBORN M, PERSSON I, ADAMI HO, BERGSTROM R et al. The risk of acute myocardial infarction after oestrogen and oestrogen-progestogen replacement. *Br J Obstet Gynaecol* 1992, **99** : 821-828

FALKEBORN M, PERSSON I, TERENT A, ADAMI HO et al. Hormone replacement therapy and the risk of stroke. Follow-up of a population-based cohort in Sweden. *Arch Intern Med* 1993, **153** : 1201-1209

FOLSOM AR, MINK PJ, SELLERS TA, HONG CP et al. Hormonal replacement therapy and morbidity and mortality in a prospective study of postmenopausal women. *Am J Publ Health* 1995, **85** : 1128-1132

GRODSTEIN F, STAMPFER M. The epidemiology of coronary heart disease and estrogen replacement in postmenopausal women. *Prog Cardiovasc Dis* 1995, **38** : 199-210

GRODSTEIN F, STAMPFER MJ, MANSON JE, COLDITZ GA et al. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med* 1996, **335** : 453-461

GRODSTEIN F. Invited commentary : can selection bias explain the cardiovascular benefits of estrogen replacement therapy ? *Am J Epidemiol* 1996, **143** : 979-982

GRODSTEIN F, STAMPFER MJ, COLDITZ GA, WILLETT WC et al. Postmenopausal hormone therapy and mortality. *N Engl J Med* 1997, **336** : 1769-1775

HENDERSON BE, PAGANINI-HILL A, ROSS RK. Decreased mortality in users of estrogen replacement therapy. *Arch Int Med* 1991, **151** : 75-78

HENDERSON BE, PAGANINI-HILL A, ROSS RK. The effect of estrogen replacement therapy on mortality. *Prim Cardiol* 1992, **18** : 56-57+61-

HERNANDEZ AVILA M, WALKER AM, JICK H. Use of replacement estrogens and the risk of myocardial infarction. *Epidemiology* 1990, **1** : 128-133

HUNT K, VESSEY M, MCPHERSON K. Mortality in a cohort of long-term users of hormone replacement therapy : An updated analysis. *Br J Obstet Gynaecol* 1990, **97** : 1080-1086

MATTHEWS KA, KULLER LH, WING RR, MEILAHN EN, PLANTINGA P. Prior to use of estrogen replacement therapy, are users healthier than non users ? *Am J Epidemiol* 1996, **143** : 971-978

MEADE TW, BERRA A. Hormone replacement therapy and cardiovascular disease. *Br Med Bull* 1992, **48** : 276-308

NACHTIGALL LE, NACHTIGALL RH, NACHTIGALL RD, BECKMAN EM. Estrogen replacement therapy II : a prospective study in the relationship to carcinoma and cardiovascular and metabolic problems. *Obstet Gynecol* 1979, **54** : 74-79

PAGANINI-HILL A, ROSS RK, HENDERSON BE. Postmenopausal oestrogen treatment and stroke : a prospective study. *Br Med J* 1988, **297** : 519-522

PAGANINI-HILL A. Estrogen replacement therapy and stroke. *Prog Cardiovasc Dis* 1995, **38** : 223-242

PETITTI DB. Coronary heart disease and estrogen replacement therapy. Can compliance bias explain the results of observational studies? *Ann Epidemiol* 1994, **4** : 115-118

PFEFFER RI, WHIPPLE GH, KUROSAKI TT, CHAPMAN JM. Coronary risk and estrogen use in postmenopausal women. *Am J Epidemiol* 1978, **107** : 479-497

POSTHUMA WF, WESTENDORP RG, VANDENBROUCKE JP. Cardioprotective effect of hormone replacement therapy in postmenopausal women : is the evidence biased ? *Br Med J* 1994, **308** : 1268-1269

ROSENBERG L, PALMER JR, SHAPIRO S. A case-control study of myocardial infarction in relation to use of estrogen supplements. *Am J Epidemiol* 1993, **137** : 54-63

ROSS RK, PAGANINI-HILL A, MACK TM, ARTHUR M, HENDERSON BE. Menopausal oestrogen therapy and protection from death from ischaemic heart disease. *Lancet* 1981, **1** : 858-860

ROSS RK, PIKE MC, HENDERSON BE, MACK TM, LOBO RA. Stroke prevention and oestrogen replacement therapy. *Lancet* 1989, **1** : 505

SAMSIOE G. Hormone replacement therapy and cardiovascular disease. *Int J Fertil* 1993, **38** : 23-29

SCARABIN PY, PLU-BUREAU G. Quantitative evaluation of the cardiovascular risk associated with hormone substitution therapy during menopause. *Arch Mal Coeur Vaiss Prat* 1993, **86** : 243-248

SCHAIRER C, ADAMI HO, HOOVER R, PERSSON I. Cause specific mortality in women receiving hormone replacement therapy. *Epidemiology* 1997, **8** : 59-65

SHAPIRO S. Postmenopausal estrogen use and heart disease. *N Engl J Med* 1987, **316 :** 164-165

STAMPFER MJ, COLDITZ GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. *Prev Med* 1991, **20** : 47-63

STAMPFER MJ, COLDITZ GA, WILLETT WC, MANSON JAE et al. Postmenopausal estrogen therapy and cardiovascular disease - Ten-year follow-up from the Nurses' Health Study. *New Engl J Med* 1991, **325** : 756-762

STAMPFER MJ, WILLETT WC, COLDITZ GA, ROSNER B et al. A prospective study of postmenopausal estrogen therapy and coronary heart disease. *N Engl J Med* 1985, **313** : 1044-1049

STURGEON SR, SCHAIRER C, BRINTON LA, PEARSON T, HOOVER RN. Evidence of a healthy estrogen user survivor effect. *Epidemiology* 1995, **6** : 227-231

THOMPSON SG, MEADE TW, GREENBERG G. The use of hormonal replacement therapy and the risk of stroke and myocardial infarction in women. *J Epidemiol Comm Health* 1989, **43** : 173-178

VANDENBROUCKE JP. How much of the cardioprotective effect of postmenopausal estrogens is real ? *Epidemiology* 1995, **6** : 207-208

VANDENBROUCKE JP. Postmenopausal oestrogen and cardioprotection. *Lancet* 1991, **337** : 833-834

VANDENBROUCKE JP. Postmenopausal oestrogen and cardioprotection. *Lancet* 1991, **337** : 1482-1483

WILSON PW, GARRISON RJ, CASTELLI WP. Postmenopausal estrogen use, cigarette smoking, and cardiovascular morbidity in women over 50. The Framingham Study. *N Engl J Med* 1985, **313** : 1038-1043

WOLF PH, MADANS JH, FINUCANE FF, HIGGINS M, KLEINMAN JC. Reduction of cardiovascular disease-related mortality among postmenopausal women who use hormones : evidence from a national cohort. *Am J Obstet Gynecol* 1991, **164** : 489-494