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Combined hormone replacement therapy and risk of breast cancer in a French cohort study of 3175 women

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ABSTRACT

The largest-to-date randomized trial (Women's Health Initiative) comparing the effects of hormone replacement therapy (HRT) and a placebo concluded that the continuous use of an oral combination of conjugated equine estrogens (CEE) and medroxyprogesterone acetate (MPA) increases the risk of breast cancer. This conclusion may not apply to women taking other estrogen and progestin formulations, as suggested by discrepancies in the findings of *in vitro* studies, epidemiological surveys and, mostly, *in vivo* studies of human breast epithelial cell proliferation showing opposite effects of HRT combining CEE plus MPA or estradiol plus progesterone. To evaluate the risk of breast cancer associated with the use of the latter combination, commonly prescribed in France, a cohort including 3175 postmenopausal women was followed for a mean of 8.9 years (28 367 woman-years). In total, 1739 (55%) of these women were users of one type of estrogen replacement with systemic effect during at least 12 months, any time after the menopause, and were classified as HRT users. Among them, 83% were receiving exclusively or mostly a combination of a transdermal estradiol gel and a progestin other than MPA. Some 105 cases of breast cancer occurred during the follow-up period, corresponding to a mean of 37 new cases per 10 000 women/year. Using multivariate analysis adjusted for the calendar period of treatment, date of birth and age at menopause, we were unable to detect an increase in the relative risk (RR) of breast cancer (RR 0.98, 95% confidence interval (CI): 0.65–1.5) in the HRT users. The RR of breast cancer per year of use of HRT was 1.005 (95% CI 0.97–1.05). These results do not justify early interruption of such a type of HRT, which is beneficial for quality of life, prevention of bone loss and cardiovascular risk profile, without the activation of coagulation and inflammatory protein synthesis measured in users of oral estrogens.

INTRODUCTION

Despite the large number of epidemiological studies analyzing the risk of breast cancer during hormone replacement therapy (HRT), the specific influence of combined estrogen plus progestin treatments is still the subject of debate[1–9]. In most of these studies, the combined HRT users account for a small minority, selected according to unspecified and probably variable criteria, among a majority of unopposed estrogen users, thus weakening the power of statistical analysis and

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introducing potential biases. Following two recent randomized trials, the Heart and Estrogen/progestin Replacement Study (HERS)[10] and the Women's Health Initiative (WHI)[11], the larger concluded that the continuous use, with a duration of 5 or more years, of an oral combination of conjugated equine estrogens (CEE) and medroxyprogesterone acetate (MPA) increased the risk of breast cancer. This conclusion may not apply to women taking other estrogen and progestogen formulations because differences in routes of administration, doses and sequences of HRT may variously alter the risk. For example, the daily urinary excretion of 16-hydroxyestrone, a potentially genotoxic metabolite[12], is quite different in users of oral and transdermal estrogens[13], and the assumption of a difference in risk level depending on the route of estrogen administration is not unrealistic. Moreover, the consequence of stimulation of 17β-hydroxysteroid dehydrogenase activity by the progestin may be reversed if the main estrogen accumulated in breast tissue is estrone instead of estradiol[14,15]. Oral CEE increase estrone and estrone sulfate far more than estradiol plasma and breast tissue levels[16], and MPA is a synthetic progestin that may be different from progesterone or other progestins in its effects on breast tissues[2]. According to surgical breast biopsies performed in postmenopausal women, the breast epithelial cell mitotic activity increases during treatment with oral CEE, and even more so during HRT combining oral CEE and MPA[17]. Some of the epidemiological surveys and the largest randomized trial suggest that this HRT regimen is not optimal for breast tissues and should be stopped as soon as possible[5–7,11].

In France, the most widely prescribed HRT for the unselected majority of postmenopausal women combines transdermal estradiol with oral progesterone or closely related progestins[18,19]. The use of transdermal estradiol leads to a plasma and breast tissue estradiol/estrone ratio close to one[20,21]. According to surgical breast biopsies, this HRT regimen induces better control of mitogenic activity, and should be more favorable for the breast epithelium[22].

The present cohort study aimed to evaluate the long-term influence of such combined HRT on breast cancer incidence in a French population.

SUBJECTS AND METHODS

Study population

All women who had consulted at least once between January 1975 and December 1987 at the department of Endocrinology and Reproductive Medicine, Necker Hospital, Paris (ERN), and who were postmenopausal or had reached the age of 50 years between these two dates, were eligible for inclusion in the cohort. Their main reasons for consulting were climacteric symptoms, benign breast symptoms, uterine symptoms, non-gynecological symptoms or routine check-up.

To eliminate non-informative cases, women with less than 1 year of follow-up were excluded. Women who had developed breast cancer or a cancer at another site, before the beginning of the follow-up, were also excluded. Using these criteria, a total of 3175 women were included in the study.

Data collection

The main sources of data were ERN medical records. In the case of missing information, patients were questioned by mail, and, if they did not respond, they were contacted by telephone. Demographic data, menopausal status, HRT use, type and duration of use, and breast cancer occurrence were collected.

Additionally, a more detailed questionnaire was sent by post to a subcohort of 2069 women who attended ERN for the first time between 1979 and 1984, the mid-period of recruitment. The additional information concerned socio-economic status, reproductive factors and family history of breast cancer. The questionnaire also included the main reason for the first visit to ERN.

HRT use analysis

Users of any type of estrogen replacement with systemic effect for at least 12 months, any time after the menopause, were classified as HRT users. To eliminate non-causal exposure, women who had used estrogens for less than 12 months, or who used only vaginal formulations, were classified as HRT non-users. Many of the HRT users had received several different types of HRT. Treatments had been changed because of either side-effects or the development of new formulations. To analyze the specific effect of one type of HRT, we selected the women who had used this type of HRT for the longest time.

Statistical methods

Both internal and external analyses were performed. Women were analyzed for their risk of

breast cancer over the period starting on the date of their first visit to ERN for menopausal women, or at the time of the menopause for women still premenopausal at the date of their first visit. The end of follow-up was defined as the first of the following four events:

(1) Data collection cut-off on 1 December 1995;

(2) The last information, obtained from ERN medical record, telephone interview or mail questionnaire;

(3) Occurrence of breast cancer;

(4) The date of death.

For external comparison, the expected number of breast cancers during the follow-up period was estimated using the rates by 5-year calendar period, and 5-year age class, estimated by the FRANCIM (Reseau des Registres des Cancers, France) Group for France for the period from 1975 to 1995. This estimation was performed using data from all local cancer registries in France and national mortality data[23]. The standardized incidence ratio (SIR) was defined as the ratio of observed to expected number of breast cancers. The SIR of breast cancer was modelled assuming that the number of breast cancers followed a Poisson distribution. Statistical tests were carried out using the deviance of nested models[24]. These analyses were done using AMFIT software[25] and Statistical Analysis System (SAS) software. As the confidence interval of an SIR ratio cannot be calculated analytically, we performed simulations. For each SIR ratio (study population/general French population), 100 000 pairs of values were simulated and their ratios were calculated. The 2500th and the 97 500th of these ratios, classified in ascending order, were retained as the lower and upper limits of the 95% confidence interval of the SIR ratio.

Internal statistical analysis was performed using (time) Cox's proportional hazards regression[26]. Because breast cancer incidence increased in France between 1975 and 1995[23,27], and was also strongly related to age at menopause, all analyses were adjusted for calendar period, date of birth and age at menopause. In the subcohort of 1918 women with more complete information, the analysis was additionally adjusted on the main risk factors for breast cancer. Analysis of the role of 'duration of HRT use' and of 'time since last use of HRT' was performed using these variables as time-dependent variables in a Cox's proportional hazards model.

RESULTS

The median year of inclusion of the 3175 women was 1982, and their mean age at inclusion was 50 years (range 20–59 years). Among these 3175 women, 1739 (55%) were defined as users of HRT. The median date of the first visit to ERN was 1980 for both HRT users and non-users, and the median date of start of follow-up was 1982 for HRT users and 1981 for non-users. During the follow-up period, a mean 3% of patients were lost each year. The mean follow-up was 8.9 years (ranging from 1 to 24 years), collecting a total of 28 367 woman-years.

The main characteristics of HRT users and non-users are given in Table 1. In the whole cohort, age at menopause was similar between the two groups of women. The duration of follow-up was slightly longer (9.3 years) in HRT users than in non-users (8.6 years). As expected, the main reason for the first consultation was significantly related to the use of HRT: among the HRT users, 74% of women gave climacteric symptoms as the main reason for the first visit, while this percentage fell to 26% in non-users. Women with a surgical menopause were also more frequently HRT users than those with a natural menopause. HRT users had fewer children than non-users. Last, among HRT users, fewer were retired at the time of inclusion than among HRT non-users ($p < 0.0001$).

Use of HRT and breast cancer risk

In the total cohort, 105 women developed breast cancer during the follow-up period. Among the 105 women with breast cancer, 43 were classified as HRT non-users and 62 as HRT users (Table 2).

From external comparison, the expected number of breast cancers from the general French population of the same age during the same calendar period was 65.6. Thus, our total cohort had an excess of risk of 60%. This excess of risk was similar among the HRT users (62 observed vs. 37.1 expected) and among the HRT non-users (43 observed vs. 28.5 expected) (Table 2). The ratio of the SIRs was 1.11 (95% confidence interval (CI) 0.75–1.66).

From internal comparison, the unadjusted relative risk of breast cancer associated with HRT use was 1.12 (CI 0.73–1.75, $p = 0.6$), compared with the non-users. When adjusting for calendar period of treatment, date of birth and age at menopause (Table 2), the risk of breast cancer was 0.98 (CI 0.65–1.5).

Table 1 Characteristics of cohort according to hormone replacement therapy (HRT) use. Values are expressed as mean (SD) unless otherwise specified

	Use of HRT		
Characteristics	*No (n = 1436)*	*Yes (n = 1739)*	*p Value**
Whole cohort			
Age at menopause in years	50 (4.6)	50 (4.7)	NS
Follow-up in years	8.6 (5.7)	9.3 (5.2)	< 0.001
Additional questionnaire (1979–84)			
Menopausal symptoms as reason for first visit	26%	74%	< 0.0001
Surgical menopause	16%	22%	< 0.005
Age at natural menopause (years)	52 (3.8)	51 (3.5)	NS
Age at surgical menopause (years)	46 (6.7)	47 (6.1)	NS
Number of children	2.2 (2.0)	1.9 (1.5)	0.02
Age at first full-term pregnancy (years)	26 (5.0)	26 (4.8)	NS
Breast cancer in first- and second-degree relatives	11%	12%	NS
History of benign breast symptoms	35%	40%	NS
Professional status			
executive	21%	26%	NS
retired	12%	6%	0.0001

*Wilcoxon rank test for continuous variable and Fisher exact test for proportion; NS, not significant

Table 2 Standardized incidence ratio (SIR) and relative risk (RR) of breast cancer (BC) according to hormone replacement therapy (HRT) use

HRT use	*Number of women*	*Observed number of BC (O)*	*Expected number of BC (E)*†	*Ratio of SIRs*‡	*RR of BC (95% CI)*††
Non-users	1436	43	28.5	1*	1**
Any HRT	1739	62	37.1	1.11 (0.75–1.66)	0.98 (0.65–1.48)
Estrogen + progestin‡‡	1545	59	32.8	1.19 (0.81–1.79)	1.10 (0.73–1.66)

*External reference category; **internal reference category; †expected number of breast cancers from general French population rates; ‡ratio between standardized incidence ratio (SIR = O/E) in category and that among patients who did not receive any HRT; ††adjusted to period of treatment, date of birth and age at menopause; ‡‡type of HRT used for longest time; CI, confidence interval

In the subcohort of the 1918 women who responded to the additional questionnaire (92.7% response rate), 64 breast cancers occurred during follow-up, and a similar relative risk of breast cancer in HRT users was observed (RR = 0.92, CI 0.55–1.5) as compared with the risk in the total cohort of HRT users, when adjusting for date of birth and age at menopause. Further adjustments on the number of children, age at birth of first child, family history of breast cancer and professional status did not significantly modify this risk.

Hormonal constituents and breast cancer risk

Among the 1739 HRT users in the total cohort, 1545 women (89% of HRT users) used mostly or exclusively combined HRT, and 59 developed breast cancer during the follow-up. The number of expected breast cancer was 32.8. From external comparison, the risk of breast cancers was 1.19 (CI 0.81–1.79). From internal comparison, the relative risk adjusted for the calendar period of treatment, date of birth and age at menopause was 1.10 (CI 0.73–1.66), compared with the risk among HRT non-users (Table 2).

In combined HRT users, estrogens were mainly transdermal estradiol gel formulation (83%), and, less often, transdermal estradiol patches, oral estradiol or oral CEE; progestins were mainly oral micronized progesterone (58%) or dydrogesterone (10%). Other progestins used were promegestone, lynestrenol, chlormadinone acetate and nomegestrol acetate. Fewer than 3% used MPA. All progestins were prescribed for at least 10 days per month, but inter- and intraindividual variations were too great (10, 12, 14, 25 or 30 days) to allow reliable estimation of the potential influence of these criteria.

Subgroup analyses

Among the women who had no family history of breast cancer, the risk associated with HRT use was 0.72 (CI 0.38–1.4), whereas it was 2.6 (CI 0.54–13) among those who reported a family history of breast cancer. These results were based on only ten breast cancers, and the interaction test was not statistically significant. Of the other factors registered in the questionnaire (number of children, age at birth of first child, professional status, main reason for the first consultation, surgical menopause), none appeared to modify the risk of breast cancer associated with the use of HRT. Body mass index (BMI) was recorded only for women with breast cancer: among these women, BMI was not significantly different in HRT users (23 kg/m^2) and non-users (24 kg/m^2).

Duration and timing of exposure

No significant increase in the risk of breast cancer was associated with the duration of HRT use (Table 3). The relative risk per year of HRT use was estimated to be 1.005 (CI 0.97–1.05, $p = 0.8$). Similarly, the risks among current, former and past HRT users were shown to be entirely comparable (Table 4). When both duration of use and the last period of use were analyzed together, no significant increase in breast cancer incidence was observed in any of the four subgroups considered (Table 5).

DISCUSSION

The present cohort study, based on 28 367 woman-years, analyzed the risk of breast cancer in 3175 women who consulted at ERN for the first time between 1975 and 1987. This risk was assessed in 1739 (55%) women who had used

Table 3 Relative risk (RR) of breast cancer (BC) according to duration of hormone replacement therapy (HRT) use

Duration of HRT use (years)	*Number of women*	*Average follow-up* (years)	*Number of BC*	*RR*† *(95% CI)*	*p Value*
None or < 1	1436	9	43	1*	
1–4	600	8	20	0.86 (0.49–1.49)	0.6
5–9	437	9	24	1.03 (0.61–1.75)	0.9
≥ 10	702	12	18	1.15 (0.64–2.05)	0.6
Per year				1.005 (0.97–1.05)	0.8

*Reference category; †Cox's proportional hazards risk model, using duration of HRT use as time-dependent variable, stratified on period of treatment, date of birth and age at menopause; CI, confidence interval

Table 4 Relative risk (RR) of breast cancer (BC) according to last period of hormone replacement therapy (HRT) use

Last use of HRT†	*Number of women*	*Number of BC*	*RR*‡ *(95% CI)*	*p Value*
Non-users	1436	43	1*	
Current users	845	30	0.83 (0.51–1.34)	0.4
Former users††	215	11	1.42 (0.76–2.64)	0.3
Past users‡‡	674	21	1.12 (0.63–1.98)	0.7

*Reference category; †information missing for five women; ‡Cox's proportional hazards risk model, with time since last use of HRT as time-dependent variable, stratified on period of treatment, date of birth and age at menopause; ††stopped during past 4 years; ‡‡stopped 5 years ago or more; CI, confidence interval

Table 5 Relative risk (RR) of breast cancer (BC) associated with hormone replacement therapy (HRT) use according to both last period of use and duration of use

	Duration of use (years)			
	≤ 5		5 or more	
Last period of use† (years)	*BC/n*‡	*RR*†† *(95% CI)*	*BC/n*‡	*RR*†† *(95% CI)*
< 5	7/268	0.59 (0.26–1.34)	34/792	1.08 (0.68–1.72)
5 or more	13/331	1.13 (0.58–2.19)	8/343	1.23 (0.51–2.97)

†Information missing for five women; ‡total number of patients; ††relative risk of BC estimated by Cox's proportional hazards model, using duration of HRT use and time since last use of HRT as time-dependent variables, and adjusted on period of treatment, date of birth and age at menopause (reference category is subgroup of non-users of HRT); CI, confidence interval

HRT compared with 1436 (45%) women who had not. During a mean follow-up of 8.9 years (ranging from 1 to 24 years), 105 women developed invasive breast cancer, 62 of them being HRT users. Both external and internal comparisons of risk associated with the use of HRT were performed. The incidence of breast cancer measured in both HRT users and non-users consulting at ERN was higher than the incidence estimated for the general French population of the same age during the same historical period. This first suggests that breast cancer cases were not underdiagnosed in the study cohort, but also that the study population consulting at ERN may have been at higher risk than the general population. Within the French population, large variations in the incidence of breast cancer, related to geographical area and urban versus country residency, have already been reported[23]. This relative excess may be due in part to the urban and socioeconomic status of women consulting for any reason at ERN, and also to their general acceptance of regular mammograms. The 105 cases of breast cancer occurring during the follow-up period correspond to a mean of 37 new cases per 10 000 women/year, and is quite similar to the incidence (35 new cases per 10 000 women/year) measured in the US multicentric randomized trial requiring annual mammograms and clinical breast examinations[11].

HRT users and non-users were slightly different with respect to some of the potential risk factors analyzed (professional activity, incidence of surgical menopause, duration of follow-up, number of children). The greatest difference between groups was found for the main reason for the first visit to ERN: 74% of those consulting mainly for menopausal symptoms received a HRT prescription, while only 26% of women of the same age consulting for another main reason were given the same prescription (Table 1). A personal history of benign breast symptoms, such as diagnosis of 'fibrocystic breast disease', or cyclic breast tenderness with or without dense mammograms, had no apparent influence on prescription. Family history of breast cancer was not different in users (12%) and non-users (11%), and apparently was not a reason to discourage women from using HRT.

From internal analysis, there was no significant increase in the risk of breast cancer related to use of the specific type of HRT most prescribed in France. In a univariate analysis, the relative risk of breast cancer was 1.12 (CI 0.73–1.75, $p = 0.6$). After adjustment for the calendar period of treatment, date of birth and age at menopause, the relative risk was 0.98 (CI 0.65–1.5). This relative risk was similar in the women whose follow-up was based on their medical file at ERN, completed by mail or telephone interview, and in the women having replied to an additional questionnaire. As in the WHI trial[11], the relative risk of breast cancer in HRT users was not significantly affected by their family history or other risk factors.

In an analysis limited to the 59 breast cancer patients who received mostly or exclusively estrogen combined with a progestin, 10–30 days each month, the adjusted relative risk was 1.10 (CI 0.73–1.66). This relative risk was similar in the women whose follow-up was based on their medical file at ERN, completed by mail or telephone interview, and in the women having replied to an additional questionnaire. Based on a mean follow-up of 8.9 years and a duration of HRT > 5 years for 47% of the treated population, the relative risk of breast cancer per year of exposure to HRT was 1.005 (CI 0.97–1.05). Therefore, in contrast with some recent US cohort studies and

one randomized trial, no increase in breast cancer risk was detected in combined HRT users, neither in the mid- nor in the long-term.

The first specificity of the French cohort is that the standard prescription for unselected average postmenopausal women was combined HRT, actually used by 89% of the treated group. By contrast, only 4–12% of the treated populations included in cohorts in the 1970s, 1980s and 1990s used a progestin combined with estrogens, while the majority received unopposed estrogens[1,5–9]. The various criteria for selecting this minority are largely unknown, and may have introduced unidentified biases[4]. For example, among 2082 postmenopausal breast cancer patients analyzed in a recent US cohort study[5], only 101 (4.8%) used MPA added for ± 10 days per month to CEE. A harmful effect associated with duration of estrogen–progestin use was reported (RR 1.08 per year of treatment, CI 1.02–1.16), based on only 18 cases (0.8% of the total) of invasive breast cancer diagnosed in recent users of combined HRT for > 4 years with a BMI index < 24.4 kg/m^2 (RR 1.9, CI 1.1–3.3). Multiplying small selected subgroups increases the risk of results being simply due to chance distribution of collected or uncollected subject characteristics, and, hence, is misleading[4]. In one study, only the sequential use of a progesterone-derived progestin (5.3% of cases) appeared to be associated with a significantly increased risk[5]. Another study showed that only the continuous combined use of testosterone-derived progestins (1.9% of cases) was associated with an increased risk[8], and, in a third, the risk was similar for use of oral estrogens alone and for sequential or continuous combined HRT (11.2% of cases)[9]. The present French cohort study, in which combined HRT is prescribed to an unselected majority of the treated population, avoids this major methodological bias.

The WHI randomized trial concluded that the continuous use of an oral combination of CEE and MPA increases the risk of breast cancer. Thirty-eight new cases per 10 000 women/year, as a mean, were diagnosed in this HRT group, while 30 new cases per 10 000 women/year were diagnosed in the placebo group. The power of our study to detect an excess of eight cases per 10 000 women/year, corresponding to a relative risk of 1.23, is 62%. Therefore, we may have missed such a relatively small increase. However, in the WHI trial, even if the previous use of HRT by 30% of the study population is quite confusing, the most impressive result is the rapid increase during the follow-up period in breast cancer incidence ratio between HRT and placebo groups. This ratio rose from 0.62 after the first year to 2.64 by the fifth year. Based on an analysis of the effect of HRT duration, a trend of this magnitude is highly improbable in our study, which has a power higher than 95% to detect such a time-related change between the 1–4-year use group and the 5–9-year group.

Then, the main specificity of the French cohort is that 83% of the combined HRT users were receiving mostly or exclusively a transdermal estradiol gel formulation, and the progestin was oral micronized progesterone in 58%, while MPA users were less than 3%. It is plausible that various combinations of estrogens and progestins may differently influence the relative risk of breast cancer. The serum and breast tissue levels of estrone and estrone sulfate and the estrone/estradiol ratio are far higher following oral estrogens than following transdermal estradiol[16,20,21]. The first consequence may be a difference in progestin-stimulated 17β-hydroxysteroid dehydrogenase activities[14]. The balance between 17β-hydroxysteroid dehydrogenase activities of the first reducing estrone to estradiol and second, oxidizing estradiol to estrone may favor the synthesis of estradiol if the estrone/estradiol ratio is high in the epithelial cell environment. For estrogen-dependent breast cancer cells, almost exclusively equipped with the first isoform of the enzyme, estrone will become almost as active as estradiol[15]. Furthermore, MPA has been described to stimulate the reducing rather than the oxidizing activity in human breast cells[14]. Accordingly, the addition of MPA to oral CEE, which provides predominantly estrone, has been shown to increase the mitogenic activity of breast epithelial cells *in vivo*[17]. Conversely, in one *in vitro* study, MPA reduced the mitogenic effect of estradiol on MCF-7 cells, supporting the concept of a pivotal influence of the baseline estrone/estradiol ratio on the results[28]. When this ratio is close to or lower than 1, the main effect of progesterone in normal human breast cells *in vitro* is to down-regulate the estradiol receptor and to decrease proliferation[29]. Additionally, the endogenous surge of progesterone during the luteal phase stimulates more the oxidation of estradiol into estrone than the reduction of estrone into estradiol[30,31]. *In vivo*, the addition of progesterone to transdermal estradiol has been shown to decrease the mitogenic activity of breast epithelial cells[20,22,32].

Another consequence of high levels of estrone is that the daily urinary excretion of 16OH-estrone, a metabolite expected to be genotoxic[12],

has been shown to be four-fold higher in users of oral estradiol than in users of transdermal estradiol[13].

The potential increase in the risk of breast cancer linked to the use of oral estrogens combined with synthetic progestins is one of the reasons for discouraging postmenopausal women from using any type of HRT for more than a few years[11,33]. The results of the present study, in long-term users of a combination of transdermal estradiol and a progestin closer to progesterone than MPA, do not show any increase in breast cancer risk. The power required to detect a time-related change in the relative risk of breast cancer similar to that measured in the WHI is higher than 95%. Also, analysis of the clinical and biological characteristics of breast tumors diagnosed in French HRT users does not suggest that prognosis is worse than in untreated postmenopausal women[34]. We conclude that, at present, there is no evidence to recommend early interruption of this type of HRT, which is beneficial for quality of life and prevention of bone loss, and is associated with an improved cardiovascular risk profile without the activation of coagulation measured in oral estrogen users[18,19,35,36].

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