Assessing fatal cardiovascular disease risk with the SCORE (Systematic Coronary Risk Evaluation) scale in post-menopausal women 10 years after different hormone treatment regimens

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Abstract
Objective. To assess fatal cardiovascular disease (FCD) risk among women in early post-menopausal years, as evaluated with the Systematic Coronary Risk Evaluation (SCORE) scale. Design. This was a retrospective study of parallel cohorts. Two hundred seventy-three healthy post-menopausal women. Participants received one of the following hormone treatment (HT) regimens: transdermal estradiol (50 μg) (n = 99), sequential cyclic HT with transdermal estradiol (50 μg/day) plus 200 mg/day natural micronised oral progesterone (cycle days 12–25) (n = 63) and combined HT using transdermal estradiol (50 μg) plus 100 mg/day of micronised oral progesterone (n = 61). A group of women who elected not to use HT served as control group (n = 50). SCORE values were assessed before HT or follow up. Results. Only one woman displayed a high-risk SCORE value both before and after 10 years of HT, the remaining had low risk values (<5%) for FCD. After 10 years, SCORE values increased significantly as compared to baseline among HT users (all three regimens) and controls. Although post-treatment SCORE values significantly differed among groups, values were all below the high risk cut-off (5%). There were no FCD events during the 10 year observation period. Conclusion. As assessed with the SCORE scale, FCD risk in young post-menopausal women (HT users and controls) had a slight significant increase after 10 years, being values in the low risk range.

Keywords: Menopause, fatal cardiovascular disease, cardiovascular risk assessment, hormone treatment, SCORE scale, transdermal estradiol, progesterone

Introduction
Cardiovascular disease (CVD) is one of the leading causes of morbid-mortality in developed countries [1–3]. Coronary heart disease is the leading cause of death, and stroke the third among women aged 65 or more. Stroke is more likely to be fatal in women compared to men for reasons that have not been clearly identified. Women aged 45–54 years are twice as likely as men in the same age group to suffer a stroke [4,5]. Comprehensive cardiovascular risk (CVR) assessment models have been constructed using serum lipids, lifestyle and independent risk factors. Currently, several guidelines and CVR tools are available to be used as charts, tables, computed programs and online calculators [6–11]. Equations calculated from the American Framingham cohort are among the most popular [6,7]. In European countries, CVR has been determined using Framingham-derived tables [12,13]. However, their application in Europe presents some differences in terms of definitions, inclusion criteria for non-fatal CVD (stable/unstable angina, myocardial infarction, etc.) and exclusion of other cardiovascular manifestations (stroke, cardiac failure or aortic aneurism). This model somewhat overestimated absolute CVD risk
when used in European countries which are characterised by a lower incidence of cardiovascular events than in the USA [14–18].

The SCORE (Systematic COronary Risk Evaluation) project was developed as a fatal cardiovascular disease (FCD) scoring system used in the European clinical practice [15]. This model estimates the 10-year risk of developing FCD in European countries, and includes the following risk factors: age, sex, smoking habit, systolic blood pressure and either total cholesterol or the total cholesterol/high-density lipoprotein cholesterol (HDL-C) ratio. The European Guide for Cardiovascular Prevention has recommended the SCORE scale that has been used in 12 cohorts from different countries, including Spain, with more than 205,000 studied individuals, 2.7 million year/subject follow up and 7934 cardiovascular deaths [15]. Post-menopausal hormonal therapy (HT) began as, and is still prescribed as, a treatment for moderate to severe menopausal symptoms. It became a potential long-term therapy for the prevention and treatment of the most common causes of female morbidity and mortality, e.g. heart disease, osteoporosis, and dementia – uses that were not approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMEA). But controlled studies found that there was an increased risk in breast cancer and cardiovascular events. Data regarding FCD in post-menopausal women after HT as assessed with the SCORE scale is scarce and/or lacking. Hence, this retrospective study was carried out to assess FCD risk using the SCORE scale among Spanish women in early post-menopausal years before and after 10 years of using different HT regimens.

Material and methods

Population

The present retrospective study of parallel cohorts included a total of 273 post-menopausal women aged 21–64 years at baseline (49.0 ± 6.2 years; 14 women were aged 60–64), attending the Menopause Unit of the University of Granada San Cecilio Clinical Hospital (Granada, Spain) who completed 10 years of HT with one of the following regimens: transdermal estradiol (50 µg) (n = 99), sequential cyclic HT with transdermal estradiol (50 µg/day) plus 200 mg/day natural micronised oral progesterone (cycle days 12–25) (n = 63) and combined HT using transdermal estradiol (50 µg) plus 100 mg/day of micronised oral progesterone (n = 61). A group of 50 non-HT using post-menopausal women by individual election which were also followed up during the same period served as controls. SCORE scale values were calculated for baseline and after 10-years (HT users and control group). All participants were self-described as non-smokers and complained of mild to severe vasomotor symptoms and vaginal discomfort related to atrophy without inflammatory signs. They had ceased menstruation due to natural causes (n = 150; 55.1%), surgery including bilateral ovariectomy (n = 121; 44.1%) for benign conditions (myomatas, endometriosis) or previous malignant disease (one ovarian and one cervical cancer). In addition a radiotherapy (Hodgkin lymphoma, 0.4%) and a chemotherapy-induced menopause (lung osteoblastoma, 0.4%) were also included (Table I). Post-menopausal status was confirmed by a serum estradiol level <20 pg/ml. Each participant was yearly followed up, including physical examination to determine their health status, blood tests, ultrasound and mammography. None were on any chronic medication. This retrospective study was approved by the San Cecilio Hospital Ethics Committee. Data was obtained from individual’s medical records. Women were informed about the study purpose and signed an informed consent for this analysis.

The SCORE scale

The SCORE scale assesses FCD risk using the following variables: sex, smoking habit, age, systolic blood pressure and total cholesterol levels. With this tool, percentage of death due to FCD is calculated for 10 years [15,19]. The individual SCORE is obtained from the non-smoker women’s charts according to the age, cholesterol level and systolic blood pressure. A score higher than 5% indicates a high risk for cardiovascular fatal events.

Statistical analysis

Statistical analysis was performed using SPSS software package (Version 13.0 for Windows, SPSS, Chicago, IL). Data is presented as means ± standard deviations and percentages. Comparison of means among studied groups was performed with one way ANOVA using Bonferroni methodology, whereas differences for means (baseline vs. after 10 years) for each studied group were compared with paired T-student’s test. A p value of <0.05 was considered as statistically significant.

Results

Baseline characteristics, SCORE scale values (FCD risk), total cholesterol (mg/dl), blood pressure values (systolic and diastolic) and body mass index (kg/m²) at baseline and after 10 years of HT according to studied groups are depicted on Table I. Only a 60-year-old woman with 10 years surgical menopause assigned to the transdermal estradiol group presented a high risk SCORE value before and after 10 years HT. At present, this woman is still alive and in
Table I. Baseline characteristics, SCORE scale values (FCD risk), total cholesterol (mg/dl), blood pressure values (systolic and diastolic) and body mass index (kg/m²) at baseline and after 10 years of HT according to studied groups.

<table>
<thead>
<tr>
<th></th>
<th>Non HT use (control) (n = 50)</th>
<th>Transdermal estradiol (n = 99)</th>
<th>Estradiol and cyclic micronised oral progesterone (n = 63)</th>
<th>Combined continuous estradiol + micronised oral progesterone (n = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49.22 ± 5.81*</td>
<td>47.52 ± 6.59</td>
<td>49.88 ± 6.52</td>
<td>50.27 ± 5.45</td>
</tr>
<tr>
<td>Time since menopause (months)</td>
<td>52.16 ± 57.53</td>
<td>47.30 ± 65.12</td>
<td>32.20 ± 35.26</td>
<td>32.59 ± 28.38</td>
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<tr>
<td>Previous malignant neoplasm (n)</td>
<td>0</td>
<td>1 Ovarian cancer,</td>
<td>0</td>
<td>1 Lymphoma,</td>
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<td></td>
<td></td>
<td>1 cervical cancer</td>
<td></td>
<td>1 osteoblastoma</td>
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<tr>
<td>SCORE scale FCD risk (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>0.32 ± 0.65</td>
<td>0.30 ± 0.79</td>
<td>0.34 ± 0.56</td>
<td>0.28 ± 0.54</td>
</tr>
<tr>
<td>10 years</td>
<td>1.66 ± 1.30^†</td>
<td>1.13 ± 1.09^†</td>
<td>1.33 ± 1.04^†</td>
<td>1.26 ± 0.92^‡</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>232.80 ± 33.63</td>
<td>227.13 ± 35.16</td>
<td>225.95 ± 43.91</td>
<td>222.79 ± 46.05</td>
</tr>
<tr>
<td>10 years</td>
<td>239.80 ± 45.43</td>
<td>225.56 ± 45.57</td>
<td>223.95 ± 35.46</td>
<td>224.28 ± 30.38</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>133.80 ± 21.44</td>
<td>137.14 ± 23.31</td>
<td>134.23 ± 32.52</td>
<td>136.41 ± 24.59</td>
</tr>
<tr>
<td>10 years</td>
<td>143.10 ± 20.47^†</td>
<td>139.38 ± 16.52</td>
<td>139.44 ± 15.76</td>
<td>137.62 ± 22.79</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>83.70 ± 12.52</td>
<td>83.14 ± 11.26</td>
<td>79.92 ± 18.69</td>
<td>85.86 ± 17.35</td>
</tr>
<tr>
<td>10 years</td>
<td>90.20 ± 11.47^†</td>
<td>81.08 ± 11.99</td>
<td>83.63 ± 12.36</td>
<td>81.72 ± 15.08</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>28.18 ± 4.18</td>
<td>28.54 ± 4.48</td>
<td>27.61 ± 5.03</td>
<td>26.91 ± 3.92</td>
</tr>
<tr>
<td>10 years</td>
<td>29.57 ± 6.12</td>
<td>29.60 ± 4.45</td>
<td>28.33 ± 4.99</td>
<td>28.69 ± 4.57</td>
</tr>
</tbody>
</table>

*Values are mean ± standard deviations.

^†p < 0.05 as compared to basal using paired Student’s t-test.

§p < 0.05 among groups using ANOVA.


good health. Women of all studied groups were young post-menopausal (<5 years) with no significant differences seen among them.

After 10 years, SCORE values increased significantly as compared to baseline among HT users (all three regimens) and controls. Although post-treatment SCORE values significantly differed among studied groups (higher for controls), values were all below the high risk cut-off (5%). CVD is predominantly an older age disease for women. As such the low frequency of events in women 10 years after menopause transition makes predictive value of any scoring system very difficult to do because of low frequency of events.

A significant increase, in both systolic and diastolic blood pressure, among controls was observed after 10 years as compared to no significant changes found among HT users (all three groups) (Table I). In addition, there were no significant changes in cholesterol levels, BMI and no fatal events after 10 years of HT use. In the 10-year period, there were two non-fatal cardiovascular events. The first was a stroke occurring in a woman 10 years after using continuous combined estrogen plus progesterone treatment. Patient discontinued treatment afterwards. The second was an acute myocardial infarction in a woman who previously had a hysterectomy and was treated with transdermal estrogen alone regimen; she decided to continue HT despite contrary clinical recommendation. Both women were in the low-risk SCORE before and after 10-year HT and are presently alive and in good health status.

Discussion

Variations in cardiovascular mortality rates have been observed both between and within European countries [20–22]. There seems to be a North–East to South–West gradient in CVD mortality (1990–1992; 45–74 years age-adjusted), rates being lowest for both men and women in France, Spain, Switzerland and Italy. In Spain in 2006, the two most relevant components for CVD-related death were heart ischemic disease and stroke that together represent 60% [23]. The identification of individuals at risk may introduce lifestyle changes and interventions aimed to prevent both fatal and non-fatal events. Although exact etiology is still unclear, several CVR factors have been delineated [2,24–26]. Observational data indicates that estrogens protect normal menstrual cycling women from cardiovascular events as compared to post-menopausal ones with estrogenic insufficiency [27]. Therefore, post-menopausal women deserve all preventive measures after proper identification. The SCORE scale has many advantages over other methods to detect CVR: it is intuitive, it considers CVD’s multifactorial nature, it uses fatal events as end-points instead the total CVD, SCORE calibration tables are calculated according to risk factors creating a common clinical
language. In addition, it allows intervention aimed to reduce risk factors and shows how risk increases with age. In contrast, the Framingham index evaluates both non-fatal and fatal events [15]. In young subjects (less than 50 years), the absolute risk SCORE value rarely reaches a 5%, even if risk factors are increased. CVR is not to be necessarily calculated in individuals with established conditions such as diabetes (type 1 and 2), microalbuminuria, or high risk factors which per se are related to high CVR and require treatment and clinical follow up. In remaining individuals, the SCORE scale is very useful for determining CVR. Evaluation with this scale allows determining if several moderate-elevated risks factor may in conjunction render a high-risk SCORE index and it is a strong predictor of CVD-related mortality. To the best of our knowledge, no data are available on the absolute 10-year risk of FCD as assessed with the SCORE scale in post-menopausal women subjected to different HT regimens. In the present series, SCORE values significantly increased compared to baseline for all groups. Although this mild increase may be well age-related, not less important is mentioning that in fact it was significantly higher among control as compared to all HT using groups, reflecting a possible positive effect of HT over blood pressure. In any case, SCORE values among all studied groups remained below 5%, the cut-off SCORE value for high risk and it is likely that HT did not increase risk in this series of young post-menopausal women. CVD is predominantly a disease of older women. Hence, the low frequency of events in women 10 years after the menopausal transition makes predictive value of any scoring system very difficult to perform. However, it seems that HT has no negative influence on FCD risk when used in women in early post-menopausal years. Despite this, prevention with HT is still controversial as the Women’s Health Initiative (WHI) study demonstrated the negative effects of HT in women older than those studied here [28–30]. More research in this regard is warranted.

Low SCORE scale values at initiation of study fit well with previous studies which link lifestyle, leisure, sunlight and diet with CVD prevalence in different European countries and regions [15,20–22,31,32]. Thus, diet is a protective factor against CVD and/or the prevention of major adverse cardiovascular events, as it reduces underlying risk factors. In our series, traditional Mediterranean lifestyle or diet, even with low adherence, could explain low-risk SCORE values found at baseline and after 10-years with and without HT. Unfortunately, we do not have precise information in the present series, regarding diet, vitamin D levels, exercising status and co-morbid risk factors to further speculate.

Research regarding women’s cardiovascular health and disease has become more rigorous, and some treatments and recommendations have changed [33,34]. The greatest shift has been regarding the benefits of certain HT regimens in post-menopausal women; however, current HT formulations can actually increase CVR (heart attacks and strokes) and are not helpful for CVD prevention [28,30]. Although HT may increase stroke risk, we need to make several remarks. Increased risk is associated to oral administration (compared to transdermal) without being influenced by the association or not of a progestagen [35]. Another significant factor that may increase stroke risk is obesity and a history of thrombophilia [36]. HT effects on thrombosis risk, thrombotic variables and inflammatory markers may vary by route of administration. Indeed, transdermal estrogen administration obviates the hepatic ‘first pass’ on protein synthesis [37,38]. In our study, despite women having baseline BMI values in the overweight range, no significant increase occurred after 10 years of HT (all groups). In addition, women of the present series were younger (mean age 49 years) than those included in the WHI cohort (mean age 63 years). Hence, it is arguable that age increases heart attack rates in young women and in those with less than 10 years since the menopause as it is reflected by our results [39]. Our results indicate that during the 10-year study period there were no fatal events, results being below the theoretic risk, in both the control group and for the three different HT regimens. This overall lower risk could be related to general, geographical, ethnic and/or nutritional factors that we cannot presently identify. HT may reduce some risk factors associated to the climacteric syndrome. For instance, women with intense hot flashes, depression or sleep disorders have a higher CVR as compared to women who do not suffer them [40]. It seems quite plausible that co-morbid conditions in the studied population were not prevalent during the 10 years of HT use. Menopausal HT use in women aged 50–59 may reduce fatal cardiovascular events [34]. At least one or two fatal events could have been expected theoretically in our studied population; however, this was not the case.

Estradiol and progesterone, as used in this study, are equal to endogenous hormones. Therefore, replacement with natural compounds would carry the same risk and benefits as the natural menopausal situation. However, in our study malignant disease, endometrial lesions and CVR did not significantly increase over the 10-year period. In this study, women were selected to be treated with HT during 10 years and were non-smokers. The non-fatal events reported in the present series were also below the expected number. In a series from Iceland, the 5% high-risk threshold for fatal CVD corresponded to a 12% coronary heart disease-morbidity risk [41].

This preliminary study has some limitations: it is a retrospective look at parallel cohorts, the number of
cases is low related to the high rate of non-adherent women due to the alarming information from the Spanish mass-media during post-WHI years and the low rate of HT in smoking women. Furthermore, because smoking is an additive risk factor we did not encourage long term HT in those cases. Because of all this, therefore selection bias is a problem. However, as added values of the study one can mention the relatively high dose of estradiol dose for a post-WHI era, and the use of natural micronised oral progesterone as part of the combined HT schemes.

In conclusion, application of the SCORE scale provides an interesting model for FCD risk assessment aimed at promoting a healthy life style based on increasing physical activity, change dietary habits and non-smoking, in the absence of large scale cohort studies.

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