Estrogenic Therapy in Men With Ischemic Cerebrovascular Disease: Effect on Recurrent Cerebral Infarction and Survival

FINAL REPORT OF THE VETERANS ADMINISTRATION COOPERATIVE STUDY OF ATHEROSCLEROSIS, NEUROLOGY SECTION

VETERANS ADMINISTRATION COOPERATIVE STUDY GROUP

Abstract:
Estrogenic Therapy in Men With Ischemic Cerebrovascular Disease: Effect on Recurrent Cerebral Infarction and Survival

A cooperative clinical investigation was undertaken in 15 Veterans Administration Hospitals to determine whether long-term therapy with conjugated equine estrogens prevented recurrent cerebral infarction or death due to atherosclerotic vascular disease. Follow-up observations were made for periods up to five years in 572 men with cerebral infarction who were assigned on a random basis to placebo or to treatment with 1.25 to 2.5 mg of Premarin daily.

Estrogen administration failed to reduce the incidence of cerebral infarction, transient cerebral ischemia or death due to vascular disease. Although use of hormones was associated with an overall higher death rate, this excess mortality was due largely to cancer and various other diseases and could not be attributed directly to the medication. Occurrences of and deaths from myocardial infarction were less in treated than control patients, but vascular disorders, such as pulmonary embolism, mesenteric thrombosis and heart failure were more frequent in the former group.

This study failed to demonstrate any beneficial effect in men with cerebral infarction from estrogens given in moderate amounts for as long as five years. There was, on the other hand, no evidence to support current reports that prolonged estrogen use in these dosages produced an increased mortality from thromboembolism.

Additional Key Words: atherosclerosis, myocardial infarction, collagen equine estrogens, stroke morbidity, stroke mortality

Experimental and clinical data have suggested that administration of female sex hormones retards the formation of atherosclerosis and reduces the mortality from coronary and cerebrovascular disease.1-5 Such evidence prompted initiation of a controlled clinical trial by the Veterans Administration to determine the effect of estrogenic hormones on morbidity and mortality resulting from cerebral thrombosis. Preliminary results of this study indicated that the use of conjugated equine estrogens (Premarin) was ineffective in reducing the incidence of recurrent cerebral infarction or mortality from this condition during an average follow-up of 16.7 months.6 The present report describes the outcome in this group of men after five years of observation.

The medications used in this investigation were supplied by Ayerst Laboratories, 685 Third Avenue, New York, New York, 10017.

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Since publication of our initial paper, estrogentic hormones have been implicated as increasing the risk of thromboembolic disease in young women taking oral contraceptives\textsuperscript{7-9} and in elderly men receiving diethylstilbestrol treatment for carcinoma of the prostate.\textsuperscript{10, 11}\ The adverse effects of these substances in men with cerebrovascular disease are also described in this report.

**Case Material and Methods**

A detailed description of the study design appeared in the preliminary report.\textsuperscript{8} From October 1, 1962, to September 30, 1965, 605 male veterans with cerebral infarction were entered into the investigation at 17 Veterans Administration Hospitals. In collecting the data for this report, it was decided to exclude the case material from two of the participating hospitals (28 patients) because of insufficient information as to the nature of the presenting illness. Five additional cases were excluded because of death during the first week of the clinical trial (one in the control and one in the treatment group) or because there was a total lack of follow-up observation. The outcome of the remaining 572 patients constitutes the basis for this report. Premarin therapy was instituted in 289 patients selected randomly, and the remaining 283 patients received capsules identical in appearance but containing lactose. Each patient selected for treatment was given 1.25 mg of Premarin daily for 12 months following which the dose was increased to 2.5 mg daily. Neither the patient nor the investigator was told which medication was being administered. However, side effects from estrogen were common and the alert observer often became aware of the treated cases. In some instances these attempted identifications were incorrect as described subsequently.

Clinical data submitted after a patient was lost to follow-up observation for more than 12 months were not used. This decision was based on the protocol requirement that each patient return for follow-up at six-month intervals. A full five-year period of observation or follow-up until the occurrence of a major end point (e.g., death, myocardial infarction or cerebral infarction) was obtained in 467 cases. Of this group, 239 had been treated with estrogen and 228 were controls. The remaining 105 patients were lost to the study during the five years because of toxic effects from the medication or failure to return for examination. Over half of these losses occurred in the last six months of follow-up and the remainder occurred during the earlier months of observation. These patients were included in the life table analyses for as long as they were under clinical observation.

At each follow-up visit, the patient was questioned and examined for signs of estrogen toxicity (tenderness or enlargement of the breasts, loss of libido, etc.) and for evidence of systemic vascular disease. Clinical findings and appropriate

\begin{table}
\centering
\caption{Clinical Characteristics of Groups of Veterans Randomized to Treatment or Control Groups}
\begin{tabular}{|l|c|c|}
\hline
\textbf{Characteristics} & \textbf{Control} & \textbf{Treated} \\
\hline
\textbf{Number of patients} & 283 & 289 \\
\% & & \\
\hline
\textbf{Race} & & \\
White & 77 & 81 \\
Black & 21 & 18 \\
\hline
\textbf{Age} & & \\
Under 50 & 25 & 25 \\
50 – 59 & 20 & 24 \\
60 and over & 55 & 52 \\
\hline
\textbf{Disability rating} & & \\
1 - 2 & 67 & 69 \\
3 - 4 & 32 & 36 \\
\hline
\textbf{Medical history} & & \\
Hypertension & 53 & 49 \\
Previous myocardial infarction or angina & 27 & 26 \\
Previous cerebro infarction & 15 & 15 \\
Previous transient ischemic attack & 29 & 24 \\
Abnormal EKG & 57 & 49 \\
\hline
\end{tabular}
\end{table}
laboratory studies, including annual electrocardiograms, were recorded. The records on each patient who died or had a vascular episode such as a recurrent stroke, myocardial infarction or transient cerebral ischemia were reviewed by an executive committee. Efforts were also made to obtain precise information about the circumstances of death. Autopsies, including examinations of the brain, were done in approximately 50% of deaths.

Table 1 shows the major clinical characteristics of the treated and control groups. Approximately 79% were white, 53% were older than 60 years and over 50% had hypertension. The two study groups were similar in composition, but the treated patients included somewhat fewer non-whites and men older than 60 years and they also had less hypertension and electrocardiographical abnormalities. There were no differences as to the prevalence of previous myocardial infarction, angina pectoris or cerebral infarction. Approximately 29% of the control patients and 24% of the treated cases had transient ischemic attacks preceding the cerebral infarction that led to their inclusion in this study.

Effects of Treatment on Recurrent Vascular Episodes and Mortality

Table 2 shows the number of patients with new episodes of cerebral or myocardial infarction during follow-up observation. Arbitrarily it was considered that the effect, if any, of the estrogenic hormones in retarding the atherosclerotic process would require at least 18 months of therapy. For this reason, the vascular events observed in our patients are presented according to whether they took place during or after this interval. One or more cerebral infarctions occurred in 71 of the control cases, representing a recurrence rate of 31% during the five years of observation. Among the treated group, 70 patients had an additional cerebral infarction (recurrence rate of 29%). During the five-year period of observation, 73 episodes of transient cerebral ischemia occurred in 46 men on placebo in contrast to 103 events reported for 51 treated patients. Also, during this time 50 of the control group had a myocardial infarction, representing an attack rate of 22%. Among the treated patients there were 43 new myocardial infarctions, an attack rate of 19%. Approximately 80% of these cardiac episodes (84% of controls and 77% of treated cases) were fatal. New occurrences of angina pectoris were also more frequent in the control cases (21 patients), whereas only ten treated patients developed angina. Deaths from other vascular episodes, such as peripheral arterial occlusion, mesenteric thrombosis and pulmonary embolism, were uncommon but occurred in 12 cases receiving estrogen and in seven controls. Comparison of the data from the first 18 months and from 19 to 60 months did not reveal any latent therapeutic benefit from treatment.

Mortality was higher in the estrogen-treated group than in control cases with 114 and 94 deaths, respectively. Therefore, five-year mortality rates were 42% and 36%.

<table>
<thead>
<tr>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occurrence of First Cerebral or Myocardial Infarction During Five Years of Follow-up in Veterans in the Treatment and Control Groups</td>
</tr>
<tr>
<td>Months of follow-up</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>0–18</td>
</tr>
<tr>
<td>19–60</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Cerebral infarctions</td>
</tr>
<tr>
<td>0–18</td>
</tr>
<tr>
<td>19–60</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

*Life table probabilities of occurrence of infarction.
†In parentheses are number of men with cerebral infarction whose death was ascribed to this cause.
§Including sudden and unobserved attacks.
§In parentheses are the number of men with a myocardial infarction whose death was ascribed to this cause.
These overall figures do not adjust for the possibilities that some men assigned to the treatment group may not have taken this medication for several months prior to death or that some of the control cases may have received estrogenic drugs from other sources. As a means of compensating for this factor, mortality rates were calculated by the life table method in which deaths occurring more than 12 months after the patient's last follow-up visit were not included. Cumulative probabilities of death from these life tables are plotted in figure 1. At the end of five years, these rates were 40\% and 34\%, virtually the same as the

**TABLE 3**

<table>
<thead>
<tr>
<th>Causes of death</th>
<th>Within 12 months Control</th>
<th>Treated</th>
<th>19 to 60 months Control</th>
<th>Treated</th>
<th>Total Control</th>
<th>Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral infarction</td>
<td>7</td>
<td>8</td>
<td>13</td>
<td>10</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Complications of stroke*</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>5</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Myocardial infarction†</td>
<td>14</td>
<td>12</td>
<td>28</td>
<td>21</td>
<td>42</td>
<td>33</td>
</tr>
<tr>
<td>Other vascular disease</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>10</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Malignancy</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>9</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Other disease</td>
<td>0</td>
<td>3</td>
<td>7</td>
<td>15</td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td>Trauma</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Unknown cause of death</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Total deaths</td>
<td>35</td>
<td>34</td>
<td>59</td>
<td>80</td>
<td>94</td>
<td>114</td>
</tr>
</tbody>
</table>

*Includes deaths due to immediate and acute complications of cerebral infarction, e.g., aspiration or hypostatic pneumonia, pulmonary embolism, etc.
†Including sudden and unobserved deaths.
ESTROGENIC THERAPY IN MEN

crude rates. At the end of 18 months, 12% of the group treated with estrogen and 13% of the controls had died. Of those who survived the first 18 months, 31% of those receiving treatment and 24% of the controls died during the subsequent 42 months of follow-up. Therefore, there is no evidence that estrogen treatment reduced mortality from all causes during either the full five-year period of follow-up or during the treatment interval after 18 months of medication.

Table 3 shows the causes of death during the first 18 months and in subsequent observation. During the former interval, there were 35 deaths in controls and 34 in the treated group. Cerebral and myocardial infarction were the most common causes of death, with little difference noted between the patients on placebo or Premarin.

During the remaining follow-up period, 59 of the placebo-treated cases died in contrast to 80 of those receiving estrogen. The number of deaths due to cerebral infarction or its complications during this time was approximately the same in both control and treatment groups (14 and 15, respectively). Use of estrogen may have reduced the mortality from myocardial infarction during the final 42 months of study since 28 patients receiving placebo died of this condition as compared to 21 among those receiving estrogen. This possible beneficial effect of estrogen therapy, however, was offset by the fact that during the last 3.5 years of observation, the number of deaths caused by other vascular disorders (pulmonary embolism, mesenteric thrombosis, heart failure and intracranial hemorrhage) was much greater in the treated than in the control group (14 and 4, respectively).

The overall higher mortality observed in the estrogen-treated cases after the first 18 months of the study was due largely to various nonvascular illnesses including cancer, infections, renal disease and gastrointestinal disorders. Nine patients on estrogen developed malignant tumors in contrast to only three of those receiving placebo. Of these, carcinoma of the lung occurred in four treated and two control cases and cancer of the prostate in three treated cases and in none of the controls.

Cumulative probabilities of the first occurrence of a major end point, i.e., cerebral thrombosis, myocardial infarction or death from any cause, as determined from life tables, are plotted in figure 2. At the end of five years, patients in the control group had a slightly lower rate than those receiving estrogenic therapy (49% versus 51%, respectively).

Further analyses were made to determine whether any selected group of patients may have responded favorably to treatment. As may be seen in table 4, the variables investigated in this way were race, age, occurrence of a previous cerebral infarction, site of the vascular lesion and the presence of hypertension or coronary artery disease on entry into the study. As expected, a significantly higher percentage of the major end points was observed, regardless of treatment, among patients over 60 years of age, those with hypertension, those with a history of coronary artery disease or those with electrocardiographical abnormalities. It was surprising to note that nonwhite patients had a better prognosis than whites, but factors responsible for this difference remain to be determined. The patient's degree of disability at the onset of the study failed to influence the mortality or the rate of recurrent cerebral or myocardial infarction. There was no evidence that estrogen therapy was beneficial among any of these selected groups.
TABLE 4

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Probability</th>
<th>Treated</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>283</td>
<td>0.49</td>
<td>289</td>
<td>0.51</td>
</tr>
<tr>
<td>White</td>
<td>219</td>
<td>0.52</td>
<td>235</td>
<td>0.53</td>
</tr>
<tr>
<td>Black</td>
<td>58</td>
<td>0.38</td>
<td>53</td>
<td>0.41</td>
</tr>
<tr>
<td>Under 60 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60+ years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No previous stroke</td>
<td>240</td>
<td>0.47</td>
<td>245</td>
<td>0.51</td>
</tr>
<tr>
<td>Carotid territory</td>
<td>203</td>
<td>0.47</td>
<td>219</td>
<td>0.50</td>
</tr>
<tr>
<td>Disability Class 1</td>
<td>61</td>
<td>0.50</td>
<td>53</td>
<td>0.56</td>
</tr>
<tr>
<td>Disability Class 2</td>
<td>129</td>
<td>0.48</td>
<td>147</td>
<td>0.48</td>
</tr>
<tr>
<td>Disability Class 3 or 4</td>
<td>90</td>
<td>0.50</td>
<td>88</td>
<td>0.53</td>
</tr>
<tr>
<td>With hypertension</td>
<td>151</td>
<td>0.54</td>
<td>143</td>
<td>0.56</td>
</tr>
<tr>
<td>Without hypertension</td>
<td>126</td>
<td>0.40</td>
<td>144</td>
<td>0.46</td>
</tr>
<tr>
<td>With MI or angina</td>
<td>75</td>
<td>0.67</td>
<td>76</td>
<td>0.68</td>
</tr>
<tr>
<td>Without MI or angina</td>
<td>204</td>
<td>0.41</td>
<td>208</td>
<td>0.44</td>
</tr>
<tr>
<td>Abnormal ECG</td>
<td>161</td>
<td>0.57</td>
<td>141</td>
<td>0.58</td>
</tr>
<tr>
<td>Normal ECG</td>
<td>89</td>
<td>0.32</td>
<td>99</td>
<td>0.46</td>
</tr>
</tbody>
</table>

**Toxic Effects of Estrogen Therapy**

Breast tenderness or enlargement was the major side effect of treatment and occurred in 177 patients receiving estrogen. Similar manifestations were thought to have occurred in 55 of the control cases. The risk of these reactions paralleled the duration of Premarin therapy, with a rise from 40% of cases receiving estrogens for one year to approximately 75% of those treated for five years. Since the amount of hormone was doubled after the first 12 months of study, this factor undoubtedly accounted for some increase in side effects. Impotence, skin rashes and other reactions were recorded in less than 5% of the patients. In a few instances, the response to estrogenic hormones necessitated discontinuation of the drug.

**Discussion**

The data presented in this report confirm our preliminary conclusions that the administration of estrogenic hormones to men with cerebral infarction failed to reduce either the recurrence rate of this disorder or the overall mortality rate.6 There is, likewise, no evidence that this form of treatment prevents the occurrence of transient cerebral ischemic episodes. Indeed, the number of such recurrent episodes was greater in the treated group. Deaths from myocardial infarction were somewhat fewer in the treated patients, but this was nullified by an increased mortality from other vascular disorders, such as heart failure, mesenteric thrombosis and pulmonary emboli. The group receiving estrogens had an increase in the number of deaths due to cancer and miscellaneous diseases. Although the greater number of estrogen-treated patients with cancer probably was fortuitous, the fact that prostatic malignancy occurred in three of the treated cases and in none of the controls is noteworthy.

The data obtained in this study do not necessarily negate the possibility that estrogens protect premenopausal women from heart disease or other atherosclerotic vascular complications. The possibility also exists that estrogen may be of some benefit in preventing myocardial infarction in men, since our data indicate that patients receiving this hormone had a decreased incidence of and mortality from this condition. However, the overall occurrence and mortality from other vascular disorders was not influenced by treatment because of a compensating increase in the number of deaths from mesenteric thrombosis, pulmonary embolism and heart failure. The somewhat higher frequency of these acute thrombotic
ESTROGENIC THERAPY IN MEN

According to a recent study, the effect of estrogenic substances on various disorders is consistent with the observations on women using oral contraceptives and might indicate an unfavorable action by the hormone on blood-clotting mechanisms. However, the total number of such cases is too small for definite conclusions.

Most patients in this investigation had severe cerebral atherosclerosis at the onset of therapy and many had extensive coronary disease as well. It seems likely that any clinical effect of estrogenic substances in vascular disease would consist largely in preventing deposition of atheromatous material and not in reducing the degree of atherosclerosis once this process has taken place. It may be that the amount or duration of estrogen treatment was not sufficient. However, use of larger doses or continuation of therapy beyond five years is impractical since approximately 75% of the cases had breast tenderness or enlargement.

This study does not support other current reports indicating that the use of estrogenic hormones produces an increased risk of stroke or heart disease.11 Our cases were comparable in age and other clinical characteristics to those investigated by the VA Cooperative Urologic Research Group which reported that diethylstilbestrol therapy for cancer of the prostate resulted in a mortality from cardiovascular disorders 1.5 times greater than in control patients. However, the amount of estrogenic substance used in the present study was considerably less than that employed by the Urologic Research Group.

Participants

Executive Committee: Robert N. Baker, M.D.; Noble J. David, M.D.; Earl R. Feringa, M.D. (Executive Secretary); Albert Heyman, M.D. (Chairman); and Warren V. Huber, M.D.


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References


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