

## **Routes of administration of hormone replacement therapy and cardiovascular effects in postmenopausal women.**

Sharma Manju, Li Xiao-gang, Li Lu-hong, HUANG Rui-xia, YANG Yan, JIANG WEI-hong  
Third Xiangya Hospital of Central South University, China.

### **ABSTRACT**

Earlier results of observational data showed beneficial effects with hormone therapy in women after menopause but the large clinical trials such as the Women's Health Initiative (WHI), Heart and Estrogen/progestin Replacement Study (HERS) failed to demonstrate protective cardiovascular effects. However, re-analysis of WHI results recommended that the adverse outcomes maybe influenced by several factors such as age, time of initiation, dose, route of hormone therapy and pre-existing cardiovascular disease. In recent times, the use of hormone therapy in postmenopausal women is still limited to climacteric symptoms, probably due to insufficient data to support its use in chronic conditions such as cardiovascular disease. However, results from The Kronos Early Estrogen Prevention Study (KEEPS), has been expected to provide a definite answer to reduce cardiovascular disease with hormone therapy in postmenopausal women. Based on the results from recent studies, re-analysis of WHI results, and WHI /HERS reports, this article highlights the cardiovascular effects of hormone replacement therapy with different routes of administration in postmenopausal women.

*Keywords: cardiovascular, hormone replacement therapy, menopaus, therapy routes.*

### **CORRESPONDENCE**

Dr. Jiang Wei hong  
Department of Cardiology  
The Third Xiangya Hospital of Central South University, China  
Email: jwhxy3@126.com

## INTRODUCTION

Cardiovascular disease is the leading cause of death in postmenopausal female compared to age matched male.<sup>1</sup> Cardiovascular disease is a more common cause of death and disability for women in most of the world than osteoporosis and cancer combined.<sup>2</sup> Younger women are protected from cardiovascular disease by the hormones before menopause but this protective mechanism is lost after menopause.<sup>3</sup> Because of loss of this protective mechanism (estrogen) the risk of cardiovascular disease increases with increasing age after menopause.<sup>4</sup> The role of endogenous estrogen in preventing cardiovascular disease diminishes with age and cessation of menstruation.<sup>5</sup> Though the exact role of exogenous hormone therapy in preventing cardiovascular disease in perimenopausal women and postmenopausal women remains controversial, still hormone replacement therapy remains a topic of discussion amongst clinicians as it concerns the health of growing population of menopausal women.

Despite a wealth of observational data to support the use of hormone therapy, large randomized controlled trials such as the Women's Health Initiative (WHI) and the Heart and Estrogen/progestin Replacement Study (HERS), which examined the effects of hormone therapy (conjugated equine estrogen and medroxyprogesterone) via oral routes in older postmenopausal women without evident cardiovascular disease (WHI) or established cardiovascular disease (HERS), failed to demonstrate protective vascular effects of hormone replacement therapy.<sup>6</sup> These large randomized trials made both

the clinicians as well as postmenopausal women reconsider about the protective effects of hormone replacement therapy. At present hormone replacement therapy is only limited to postmenopausal women with vasomotor symptoms. It is not recommended for either primary or secondary prevention of cardiovascular disease in women of any age.<sup>7</sup>

After a subdued period, hormone therapy has again emerged as a topic of discussion, to search for possibilities towards improvement of women's health. The re-examination of the data from the above mentioned large trials (WHI, HERS) indicated the need for further researches based on individual benefits-risks analysis in terms of timing, route of administration, dose, duration and type of hormone. Subgroup analysis of the WHI (WHIMS and WHISCA) showed a statistically nonsignificant reduction in cardiovascular disease risk among women who began hormone therapy within 10 years of menopause, and increased risk if used 10 years after menopause. Therefore initiating hormone therapy early after menopause not only showed beneficial cardiovascular effects also decreased the risk of stroke and venous thromboembolism.<sup>2</sup> Also, The Kronos Early Estrogen Prevention Study (KEEPS), a randomized controlled trial done in healthy women who are within 3 years of menopause, receiving either oral or transdermal estrogen with oral micronized progesterone. This study has been expected to provide a definite answer on whether early hormone therapy reduces cardiovascular disease in menopausal women.<sup>8</sup>

The routes of administration of hormone therapy have been considered as one of

the ways to minimize the adverse events of hormone replacement therapy.<sup>9</sup> The routes of administration of hormones can be broadly divided into oral and non oral routes (transdermal, subcutaneous, vaginal, intranasal routes, etc.).<sup>10</sup> Oral routes have been most widely studied, while transdermal route is rapidly gaining popularity amongst researchers due to its promising effects towards reducing unfavorable events in postmenopausal women. The beneficial cardiovascular effects of transdermal route have been associated with its avoidance of “first-pass hepatic effect” .<sup>11</sup> The beneficial effect of vaginal route has been mostly limited to local application. As far as subcutaneous and intranasal routes are concerned, limited studies have been conducted; therefore cardiovascular effects cannot be established. Also the final cardiovascular effects of estrogens in non-hysterectomized women are influenced by the type, dosage, and route of administration of the progesterone used in association.<sup>6</sup> Thus, in this article cardiovascular effects in postmenopausal women will be limited to oral and transdermal route of administration.

The other concern in postmenopausal women is the presence of risk factors such as hypertension, dyslipidemia, diabetes mellitus, obesity, and smoking leading to adverse cardiovascular events.<sup>12</sup> Therefore it is very crucial to identify and manage the cardiovascular risk factors. The cardiovascular effects of hormone therapy discussed in this article are coronary heart disease, hypertension, venous thromboembolism, stroke, dyslipidemia, and diabetes mellitus. The aim of this article is to focus on the cardiovascular benefits and risks associated with the use

of oral or transdermal hormone replacement therapy in postmenopausal women. Use of hormone replacement therapy to treat menopausal symptoms or other indications is outside the scope of this article.

### Coronary heart disease

The prevention of coronary artery disease is to minimize the mortality in postmenopausal women.<sup>13</sup> The WHI study (Women’s Health Initiative) is the first, large, double blind, placebo-controlled clinical trial of hormone replacement therapy conducted in healthy (without overt disease) postmenopausal women. This clinical trial showed an increased risk of coronary heart disease with oral (estrogen 0.625 mg/day + medroxyprogesterone 2.5 mg/day) hormone therapy in non-hysterectomized women.<sup>14</sup> Three years after stopping hormone replacement therapy cardiovascular risk decreased.<sup>15</sup> Among hysterectomized postmenopausal women, oral estrogen (conjugated equine estrogen) for a median of 5.9 years who were followed up for 10.7 years showed no significant increase or decrease risk for coronary heart disease.<sup>14</sup> Also, in the HERS trial (Heart and Estrogen/ progestin Replacement Study), another randomized clinical trial done with oral hormone therapy (conjugated equine estrogen+ medroxyprogesterone) in postmenopausal women with established coronary heart disease. The primary outcome included nonfatal myocardial infarction or coronary heart disease.<sup>16</sup> Therefore, both the randomized clinical trials showed adverse outcomes with oral hormone therapy in postmenopausal women leading to rapid decrease in use of hormone therapy. In consistent with the HERS trial was the

outcome of ERA trial (The Estrogen Replacement and Atherosclerosis) which showed no beneficial effect with hormone therapy in women with established coronary heart disease.<sup>17</sup> But in another randomized controlled trial done in 1006 healthy women aged 45-58 years who were recently or had perimenopausal symptoms; recruited individuals in this study received 2 mg oral synthetic 17- $\beta$ -estradiol for 12 days, 2 mg 17- $\beta$ -estradiol plus 1 mg norethisterone acetate for 10 days, and 1 mg 17- $\beta$ -estradiol for six days. In hysterectomized women 2 mg oral 17- $\beta$ -estradiol a day was given. The trial was planned for 20 years study, was stopped early (1st august 2002) because of adverse events from other studies (WHI) but follow-up was continued for an additional 5.7 years for a total mean follow-up time of 15.8 years. This was the first randomized trial to study healthy women treated early in postmenopause with 17- $\beta$ -estradiol and norethisterone acetate, and the only study with a 10 year randomized intervention. After 10 years of receiving hormone therapy in women early after menopause showed significant decrease in cardiovascular disease. Additional non-randomized follow-up for a further six years of hormone replacement therapy showed similar outcome. Thus this study showed that hormone therapy when used in recently postmenopausal women and for prolonged period of time does not aggravate adverse cardiovascular events.<sup>18</sup> As far as transdermal route is concerned, researchers have found its beneficial effects more towards venous thromboembolism and stroke. Therefore, transdermal route is preferred if coronary heart disease with risk factors for venous thromboembolism exist in

postmenopausal women with vasomotor symptoms.<sup>19</sup>

### Hypertension

Hypertension is a particularly powerful risk factor in postmenopausal women and lowering of blood pressure is pivotal.<sup>20</sup> Hypertension is an important modifiable risk factor for cardiovascular (CV) morbidity and mortality, and a highly prevalent condition in both men and women.<sup>21</sup> Menopause is commonly characterized by an increase in blood pressure due to aging and loss of endogenous estrogen production.<sup>22</sup> Higher blood pressure may partially explain the elevated risk for cardiovascular events observed in postmenopausal women.<sup>23</sup> The ultimate goal of primary and secondary prevention of hypertension in postmenopausal women is the reduction of morbidity and mortality of adverse clinical events, e.g. stroke, myocardial infarction, and hypertensive nephropathy.<sup>24</sup> Clinical trials suggest that oral estrogen administration may produce either a neutral effect or a small increase in blood pressure in postmenopausal women.<sup>25</sup> Oral high-dose estrogen administration produced a slight increase of the blood pressure in older postmenopausal women with or without an established coronary heart disease. Transdermal estrogen administration has not been studied as extensively but may produce a decrease in blood pressure. Transdermal estrogen had either no effect or produced a slight decrease in blood pressure in postmenopausal women.<sup>26</sup> Micronized progesterone has a neutral or beneficial effect on blood pressure. Drospirenone, a fourth generation progestogen has antiandrogenic properties leading to fall in blood

pressure.<sup>27</sup> In hypertensive women, hormone therapy (Drospirenone/17beta-estradiol) has been found to lower blood pressure when used alone or in combination with hypotensive drugs.<sup>28</sup> A randomized trial done in twenty-two normotensive postmenopausal women receiving transdermal hormone therapy (continuous 17-β estradiol patch at 36 µg/day plus cyclic oral medroxyprogesterone acetate 2.5 mg/day for 12 days/month) for 24 months had a decreased diastolic and mean blood pressure in comparison to control group.<sup>29</sup> Though studies have shown different effects in terms of blood pressure with the use of hormone therapy (oral or transdermal) but the evidence are not sufficient to support the use of hormone therapy in postmenopausal women either for primary or secondary prevention of hypertension.

### **Venous Thromboembolism**

Venous thromboembolism is a serious cardiovascular event whose incidence rises with increasing age due to loss of endogenous hormones.<sup>30</sup> It is also one of the main adverse effects associated with hormone replacement therapy.<sup>30</sup> A personal or family history of venous thromboembolism, especially in individuals with a prothrombotic mutation, is a strong contraindication to oral hormone therapy but transdermal estrogen can be considered after careful individual evaluation of benefits and risks.<sup>31</sup> The risk of venous thromboembolism has a greater tendency to increase with obesity, therefore safer option in obese individuals' maybe transdermal route of hormone administration.<sup>32</sup> Most of the data from the past observational studies and large

clinical trials have shown an increased risk of venous thromboembolism with oral hormone therapy. Metanalysis based on eight observational studies and nine randomized controlled trials showed that oral estrogen increased the risk of venous thromboembolism especially during the first year of life.<sup>33</sup> There is a wealth of evidence to suggest that, unlike oral estrogens, transdermal estrogen does not increase the risk of venous thromboembolism, probably due to its lack of effect on the coagulation cascade.<sup>34</sup> The type of progesterone used has been shown to contribute to the risk of venous thromboembolism.<sup>35</sup> Observational studies suggest that micronized progesterone and dydrogesterone might have a better risk profile than other progestogens with regard to thrombotic risk but randomized control trial should be done to support these findings.<sup>31</sup> Micronized progesterone when used in combination with transdermal estrogen has also been shown not to augment the risk of venous thromboembolism. Thus, clinical and experimental data indicate that transdermal estrogen and micronized progesterone could be the most favorable HRT, particularly in women at risk of adverse events.<sup>36</sup> These findings strongly suggest that the route of estrogen administration as well as type of progesterone may be essential determinants of the overall benefit-risk profile of hormone replacement therapy.<sup>37</sup>

### **Stroke**

The prevention and management of stroke is of paramount importance as it may lead to fatal outcome. Though evidence from clinical trials and observational research indicated that standard-dose hormone therapy increased risk of ischemic stroke in

postmenopausal women; it is likely to be comparatively rare in postmenopausal women of less than 60 years of age.<sup>38</sup> In one of the prospective study, early menopause (before age 42) was associated with increased ischemic stroke risk.<sup>39</sup> Early menopause was also seen to be associated with the presence of a cerebral aneurysm. The cerebral aneurysm formation, growth and rupture are thought to be implicated by estrogen fluctuations, which may also explain the eminent gender discrepancy.<sup>40</sup> The Women's Health Initiative (WHI), a primary prevention study of the impact of hormone therapy on women aged 50 to 79 years, showed an increased risk of stroke, whether the oral hormone given was estrogen alone or estrogen combined with progestin. Therefore, hormone replacement therapy is not recommended for stroke prevention, and it appears to cause harm. The reason for this increased stroke risk is not understood, but some have suggested that the initiation of hormone therapy closest to the time of menopausal transition should decrease the risk.<sup>41</sup> In a population based nested case-control study done in women aged 50-79 years showed increased risk of stroke with high dose transdermal estrogen but risk of stroke did not seem to increase with low dose of transdermal hormone therapy, oral hormone users showed higher rate of stroke with both low dose and high dose HRT.<sup>42</sup> Thus, the inconsistent results either with oral or transdermal routes, hormone replacement therapy in postmenopausal women remain unfavorable for stroke prevention or management.

### Dyslipidemia

High lipid levels are among the important risk factors of cardiovascular disease. It is

also a modifiable risk factor for cardiovascular morbidity and mortality like hypertension. The first-pass hepatic effect seen with oral route can produce benefits including larger reduction in low density lipoprotein (LDL-C), total cholesterol, lipoprotein (a) and insulin resistance and larger increase in high density lipoprotein cholesterol (HDL-C). The adverse effect seen with oral route includes rise in triglycerides levels and in coagulation activation.<sup>43</sup> This adverse effect of long term hormone replacement therapy has been found to be gradual rather than abrupt onset.<sup>44</sup> In contrast, transdermal hormone therapy does not affect lipids and lipoproteins, probably due to the absence of a first-pass hepatic effect.<sup>43</sup> Transdermal route has been found to reduce triglyceride levels. In a retrospective cohort study done in postmenopausal women, who received transdermal estrogen and micronized progesterone for 10 years showed an increase in high density lipoprotein cholesterol (HDL-C) and decrease in triglyceride levels with transdermal estradiol only.<sup>45</sup> The addition of progestogens to estrogen therapy has no adverse effect in terms of lowering LDL but testosterone derived progestogen (levonorgestrel) may show reduction in high density lipoprotein cholesterol (HDL-C) and triglyceride level when given with lower dose of oral estrogen.<sup>46</sup> In recent studies, remnant lipoprotein cholesterol (RLP-C) and high density lipoprotein cholesterol subpopulations have been found to be better predictor of coronary heart disease than high density lipoprotein cholesterol (HDL-C) and plasma triglyceride levels.<sup>47</sup> In postmenopausal women who received oral hormone therapy (unopposed estrogen, estrogen +progesterone) in ERA trial, the data

showed faster progression of adverse cardiovascular event in women with greater reduction in remnant lipoprotein cholesterol (RLP-C) and HDL-cholesterol subpopulations (pre $\beta$ 1 HDL).<sup>48</sup> Though hormone therapy shows beneficial effects in terms of plasma lipid levels in menopausal women, no cardio protective effect has been found.

### Diabetes Mellitus

The number of people with diabetes mellitus, especially type 2 diabetes, is rising due to the increased prevalence of obesity.<sup>49</sup> Menopause is associated with impaired insulin secretion and insulin resistance.<sup>50</sup> Both types of diabetes (Type 1 and Type 2 Diabetes) increased the risks of cardiovascular disease.<sup>51</sup> Type 2 diabetes mellitus has also been found to be associated with dyslipidemia and with an increased risk of coronary heart disease.<sup>52</sup> Both estrogen and progesterone have been found to adversely affect glucose metabolism but low dose of hormone therapy does not affect glucose metabolism.<sup>50</sup> However, high dose hormone therapy (oral hormones) may raise insulin levels and impair glucose tolerance.<sup>53</sup> In postmenopausal women with type 2 diabetes, low dose hormone replacement therapy (continuous oral 17 $\beta$  estradiol 1mg and norethisterone 0.5mg) showed decreased fasting glucose and total cholesterol.<sup>54</sup> The Estrogen Replacement and Atherosclerosis trial, a placebo controlled, randomized trial of HRT (conjugated equine estrogen 0.625 mg/d with or without medroxyprogesterone acetate 2.5 mg/d) in postmenopausal women with established coronary heart disease (mean age, 65  $\pm$  7 years) was associated with faster progression of heart disease in

women with diabetes than in women without diabetes.<sup>52</sup> The incidence of diabetes was reduced for women who received estrogen plus progestin in the WHI and HERS trials.<sup>55</sup> Transdermal estrogen reduced the incidence of new onset diabetes, a risk factor for myocardial infarction. Oral hormone therapy may be preferred in women with evidence of insulin resistance, such as metabolic syndrome or maturity onset diabetes mellitus.<sup>9</sup> Progestogen addition may modify the effects of estrogen on glucose and insulin metabolism, depending on the type of progestogen used. Androgenic progestogen (such as norgestrel) compared to non-androgenic progestogen (such as dydrogesterone) tend to have more negative effects showing increase in insulin resistance.<sup>53</sup> Micronized progesterone has also been shown to reduce the incidence of new onset diabetes when combined with transdermal estrogen.<sup>36</sup> In terms of diabetes management in postmenopausal women, evidence is insufficient to include hormones to lower blood glucose levels.

### CONCLUSION

There appears to exist significant differences between oral and transdermal estrogens in terms of adverse effects, and risks of different types of hormone therapy options. Although transdermal and micronized progesterone could represent the best hormone replacement therapy supported by experimental and clinical data, particularly in women at risk of adverse events, however both transdermal estrogen and micronized progesterone are not free of inconveniences. Transdermal route maybe more favorable if risk for

venous thromboembolism exists, while oral route is preferred in women with high lipid profile. Therefore, choice of an appropriate hormone replacement therapy, dose, route of administration, and estrogen/progestin combination could minimize adverse effects and maximize vascular benefits of hormone therapy, especially if given within a reasonable period to postmenopausal women for the relief of menopausal symptoms. Until a new result from studies such as KEEPS is available, hormone replacement therapy is likely to be limited to climacteric symptoms. In the future individual adjustment of hormone therapy is required and new, well designed clinical trials are further required which will evaluate the beneficial and adverse events of different routes in each individual.

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