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Original article

# Effects of Raloxifene on Endothelial Function and Hemostasis in Women With Ischemic Heart Disease

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ABSTRACT

*Introduction and objectives:* Modulation of vascular tone is one of the most relevant estrogen effects. A beneficial effect on endothelial function in postmenopausal women has also been proposed for the selective estrogen receptor modulator raloxifene. However, its effects in women with established cardiovascular disease have not been fully elucidated. In addition, recent trials have generated controversy regarding thromboembolic risk with raloxifene use. The aim of the study was to assess the effect of raloxifene on: *a)* endothelial function and *b)* coagulation and fibrinolysis pathways.

*Methods:* The MERCED trial was a prospective, randomized clinical trial. Thirty-three postmenopausal women with ischemic heart disease were enrolled in the study. Raloxifene treatment was administered for a 3-month period, according to a double-blind crossover design. Assessment of vascular function and biologic parameters related to coagulation pathways were conducted at various pre-established time-points.

*Results:* Flow-mediated dilatation was severely impaired in the study population, and raloxifene had no effect on endothelial function. Treatment with raloxifene was associated to decreased levels of fibrinogen (3.41 [3.11-3.74] vs. 3.69 [3.40-4.00], $P < .05$); prothrombin fragments $F_{1+2}$ (0.93 [0.77-1.12] vs. 0.94 [0.78-1.15], $P < .05$); and plasmin/antiplasmin complexes (211 [166-267] vs. 242 [199-295], $P < .01$).

*Conclusions:* The present study provides evidence that in postmenopausal women with demonstrated endothelial dysfunction and ischemic heart disease, mid-term treatment with raloxifene does not affect endothelial function. In the MERCED trial, no increased thrombotic risk was observed, but a decreased thrombotic and fibrinolytic activity was observed with raloxifene. Further studies are required to determine whether thrombotic risk is associated with specific clinical characteristics or subgroups of postmenopausal women with cardiovascular disease.



## Efecto del raloxifeno en la función endotelial y la hemostasia en mujeres con enfermedad coronaria

*Palabras clave:*
Endotelio
Enfermedad coronaria
Raloxifeno
Fibrinolisis
Trombosis
Mujer

RESUMEN

*Introducción y objetivos:* La modulación del tono vascular es uno de los efectos estrogénicos más relevantes. En mujeres posmenopáusicas, se ha propuesto un efecto beneficioso en la función endotelial del modulador selectivo del receptor estrogénico raloxifeno, aunque sus efectos en mujeres con cardiopatía isquémica establecida no han sido estudiados plenamente. Estudios recientes han generado controversia respecto al riesgo tromboembólico del raloxifeno. El objetivo del estudio es determinar el efecto del raloxifeno en: *a)* la función endotelial, y *b)* las vías de la coagulación y la fibrinolisis en mujeres posmenopáusicas con enfermedad coronaria.

*Métodos:* El estudio MERCED es un ensayo prospectivo y aleatorizado que incluye a 33 mujeres posmenopáusicas con enfermedad coronaria. Se administra raloxifeno durante 3 meses, comparado con placebo, en un diseño cruzado y a doble ciego, y se analiza de forma seriada la función vascular y los parámetros biológicos relacionados con las vías de la coagulación.

*Resultados:* Se ha observado una grave alteración de la vasodilatación mediada por flujo a nivel basal y el tratamiento con raloxifeno no ha modificado significativamente la función endotelial. El raloxifeno ha inducido un descenso de los valores de fibrinógeno (3,41 [3,11-3,74] frente a 3,69 [3,4-4]; $p < 0,05$), los

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fragmentos $F_{1+2}$ de la protrombina (0,93 [0,77-1,12] frente a 0,94 [0,78-1,15]; $p < 0,05$) y los complejos plasmina/antiplasmina (211 [166-267] frente a 242 [199-295]; $p < 0,01$).
*Conclusiones:* El tratamiento a medio plazo con raloxifeno en mujeres con enfermedad coronaria no afecta a la función endotelial. Además, se ha documentado menor actividad trombótica y fibrinolítica con raloxifeno. Será necesario determinar si el riesgo trombótico adscrito al raloxifeno en estudios previos se asocia únicamente a subgrupos específicos de mujeres posmenopáusicas con enfermedad cardiovascular.


**Abbreviations**

FMD: Flow-mediated dilatation
PAI-1: Plasminogen activator inhibitor type-1
PAP: Plasmin/antiplasmin
SERM: Selective estrogen receptor modulator
TAFI: Thrombin-activatable fibrinolysis inhibitor

## INTRODUCTION

Modulation of vascular tone is one of the most relevant effects of estrogens.[1] Intracoronary or percutaneous estrogen administration has been shown to restore the vasodilator response to acetylcholine, both in patients with atherosclerotic coronary artery disease and those with angiographically normal coronary arteries but with proven endothelial dysfunction.[2–4]

Since the publication of the HERS study,[5] demonstrating an increased risk in thromboembolic complications and breast cancer in postmenopausal women treated with a combination of estrogen plus progesterone, there has been growing interest in evaluating the effects of the selective estrogen receptor modulators in the cardiovascular system.

A beneficial effect on endothelial function has also been proposed for the selective estrogen receptor modulator (SERM) raloxifene.[6,7] More specifically, a previous clinical study in postmenopausal women receiving raloxifene for 12 months demonstrated an increased brachial artery endothelial function as compared with control patients. From a thrombosis point-of-view, raloxifene has been reported to modify coagulation parameters. On one hand, a favorable decrease in fibrinogen levels has been reported in postmenopausal women[8]; on the hand, an increase in procoagulant parameters has been documented with raloxifene mid-term treatment.[9] No previous studies analyzing coagulation and fibrinolysis pathways in women with established cardiovascular disease have been conducted.

The MORE study[10] had shown a decreased risk of cardiovascular events in a subgroup of postmenopausal women at increased cardiovascular risk. The RUTH study sought to analyze the effect of raloxifene on women with demonstrated ischemic heart disease or at increased risk, but failed to demonstrate any reduction of the risk of coronary heart disease. In addition, an excess of fatal stroke and thromboembolic events was observed. No assessment of coagulation and fibrinolysis parameters was done in the RUTH study.[11]

We undertook the MERCED trial with the aim to study the effects of raloxifene on endothelial function in postmenopausal women with coronary heart disease. In addition, to assess thrombosis risk, a thorough analysis of coagulation and fibrinolysis pathways has been conducted.

## METHODS

### Study Design

The MERCED study was a 2-center, national, randomized, double-blind, cross-over trial. Treatment sequence allocation (raloxifene-placebo; placebo-raloxifene) was randomly assigned by blocks of 4 patients for both participating centers. Patients, their treating physicians, and the investigators performing endothelial function analysis in each center were blinded to treatment sequence allocation. Study design follows the CONSORT statement for reporting randomized trials.

Study duration was 28 weeks, divided in 3 phases: a 12-week period during which patients were randomly assigned with the use of a computer-generated table to receive either raloxifene 60 mg/day or placebo, followed by a 4-week wash-out period, and a final 12-week period in which the patients switched to the corresponding placebo or raloxifene. A balanced permuted-block approach (in blocks of 4 patients) was used to prepare the randomization tables for each participating center. Randomization tables were provided by the *Unidad de Ensayos Clínicos* of the *Hospital Clínic*, and study medications were provided by the pharmacy department at our institution. Figure 1 illustrates the study flowchart.

The protocol was approved by the local ethics committee of each participating center and the Agencia Española del Medicamento..

Analysis of blood samples for biochemistry and coagulation was conducted in a centralized manner. Endothelial function analysis was performed at each participating center using the same study protocol and sonographic equipment and software. Measurements of endothelial function parameters were also centrally evaluated.

### Study Population

Consecutive postmenopausal women (plasma estradiol levels < 30 pg/mL and FSH > 40 UI/L), aged ≤70 years, admitted to the cardiology department of the participating centers, with documented coronary artery disease (at least 1 vessel with a stenosis >70% or history of a previous myocardial infarction) were assessed for eligibility. Exclusion criteria were contraindications to raloxifene (previous venous thrombotic disorders, hepatic disease, breast or endometrial cancer), chronic renal failure (creatinine >2 mg/dL), participation in a clinical trial < 30 days prior to randomization or having received hormone replacement therapy in the previous 6 months. All patients gave written informed consent. Before enrollment, patients underwent a thorough gynecological evaluation consisting of a pelvic exam, pap smear and mammography in all patients, and pelvic sonography when indicated.

### Endothelial Function Assessment

Endothelial function was studied using high-resolution ultrasound of the brachial artery, according to a previously validated