

폐경기 여성에서 동맥경화증의 치료 또는 예방을 위한 호르몬 대체요법

가
진 동 규 · 고 광 곤

Hormone Replacement Therapy for Prevention or Treatment of Atherosclerosis in Postmenopausal Women

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서 론

55 1/3

10

2)

1961 57.5 1989 70.8

(老年化指數 : 65

/15 , %) 1970 7.2%

1990 19.4%, 2000 31.9% 가

3)4)

5)

(nitric oxide)

5)

가,⁶⁻⁸⁾

가

Heart and Estrogen/progestin Replacement Study (HERS)

1)

가 4 5 가

1

9)

11%

10%

가

HERS 가 66.7

가

가 : , 405 - 760 1198

가 : (032) 460 - 3683 · : (032) 460 - 3117

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HERS

, 1,091

Sullivan ¹³⁾

92

10

59.3% 999

10

46.3%

본 문

에스트로젠의 항동맥경화 효과의 기전

여성 호르몬 대체요법과 심혈관 질환

LDL

15%

, HDL

15%

가

. Lipid Research Clinics

. ¹⁴⁻¹⁶⁾ LDL

hepatic

Follow - up Study

40 69

(bile acid)

가¹⁷⁾

2,270

LDL

가

LDL

8.5

.¹⁸⁾

HDL

가 apolipoprotein A - I

가 hepatic

가 0.34

lipase

,¹⁵⁾¹⁹⁾

가

.¹⁰⁾

(reverse cholesterol transport)

48,470

가

HDL subparticle

HDL₂

Nurses' Health Study

가

lipoprotein(a)

0.5

,¹⁴⁾²⁰⁾

가

²¹⁾

0.72

lipoprotein(a)

plasminogen

가

, , , , 가

proenzyme . Plasminogen

plasminogen activator

10

fibrin

(clot)

. O' Keefe ¹¹⁾

, lipoprotein(a)가

337

plasminogen

, , ,

plasminogen
rogenic, antithrombolytic

proathe -

, 7

.²²⁾

93%,

75%

LDL

free radical

²³⁾

12%

35%

.²⁴⁾²⁵⁾

LDL

. Coronary Angioplasty Versus Excisional
Atherectomy Trial(CAVEAT)

LDL

(extracellular matrix)

LDL

가

.¹²⁾

LDL

가 proathe -

rogenic 가 , 17 - estradiol
 (foam cell) (pool
 LDL proinflammatory cy - 가
 tokines chemoattractant peptide 가
 (gene expression) , monocyte 가
 (macrophage) , 가
 adhesion molecule adenosine nitroprusside
 (26 - 28)
 LDL lysophosphatidylcholine 가가 estradiol
 oxidized phospholipid component
 (nitric oxide synthase)
 Lieberman 35) 13
 estradiol 9
 Cannon 29)
 17 - estradiol 3 LDL
 가 (antiathe - (reactive hyperemia)
 rogenic) 가 가 가
 (conduit artery)
 가 . Koh 14) conjugated equine
 estrogen 0.625 mg 28 (LDL cholesterol 163 mg/dL)
 가 가 가
 LDL
 30) LDL simvastatin 10 mg
 LDL (Fig. 1).
 lipoprotein(a) Gerhard 36) 17 estradiol micronized progeste -
 rone
 lipoprotein(a) estradiol
 가 HDL LDL estradiol progesterone
 가 가 가
 paraoxonase platelet activating factor
 acetyl hydrolase LDL 32 - 34)
 lipoprotein 가 LDL
 8) Cannon 8) 가 LDL

LDL²⁶⁾

adhesion molecule
(gene transcription and expression)²⁶⁻²⁸⁾

vascular cell adhesion molecule (VCAM) - 1, intercellular adhesion molecule (ICAM) - 1, L - selectin

molecule

cell adhesion molecule

cytokine

(nuclear binding protein gene) (promotor region) NF - B (Nuclear Transcription Factor)

NF - B proinflammatory cytokine

LDL

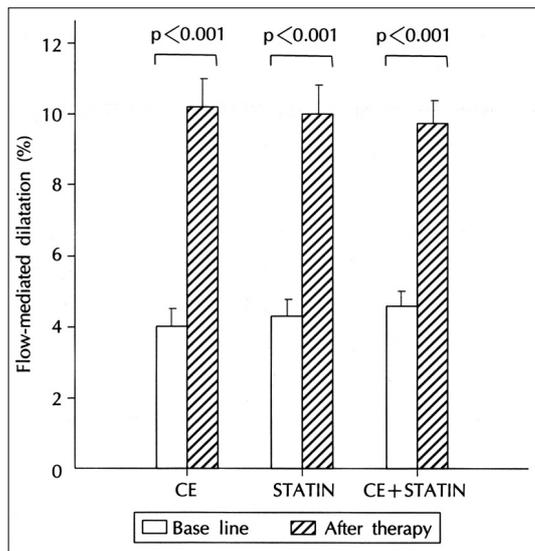


Fig. 1. Flow-mediated dilatation before therapies (open bars) and following (hatched bars) CEE 0.625 mg daily for 6 weeks (left), simvastatin 10 mg daily for 6 weeks (center), and the combination of therapies daily for 6 weeks (right) in 28 hypercholesterolemic postmenopausal women. Standard error of the mean is identified by the error bars. Reproduced from reference 14 with permission from the American Heart Association.

(cytosol) (redox - sensitive mechanism)⁴²⁾

Physicians' Health Study ICAM - 1

가

가

conjugated

equine estrogen simvastatin

E - selectin, ICAM - 1, VCAM - 1 (Fig. 2).

Caulin - Glaser⁴⁴⁾

adhesion molecule 가

Koh⁴⁵⁾

가

cell

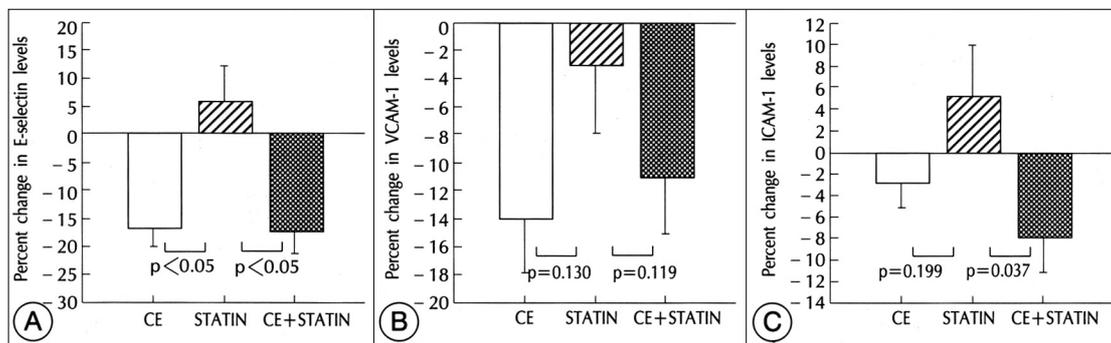


Fig. 2. Percent change in the E-selectin (A), vascular cell adhesion molecule (VCAM-1) (B), and intercellular adhesion molecule (ICAM-1) levels (C) following conjugated estrogen (CE) alone, simvastatin (statin) alone, and combination therapies. Standard error of the mean is identified by the bars. Reproduced from reference 14 with permission from the American Heart Association.

가 가 ,⁴⁶⁻⁴⁹⁾ PAI - 1 가⁵⁵⁾
 가 ,⁵⁰⁻⁵²⁾ PAI - 1 가⁵⁶⁻⁶¹⁾
 가⁶²⁾ plasma PAI - 1 가
 2 4 ,⁴⁶⁻⁴⁹⁾ . Koh⁵⁾
 10,000 1 PAI - 1 가 50%
 . Caine⁵³⁾ (Fig. 3), PAI - 1 plasmin
 thrombin cross - linked fibrin D - dimer
 prothrombin fragment 1+2(F₁₊₂) (Fig. 4). estradiol
 (fibrinopeptide A) , thrombin PAI - 1
 (protein S) , estrogen PAI - 1
 factor F₁₊₂ 가 Koh⁶³⁾
⁵⁴⁾ Plasminogen activator inhibitor(PAI) - 1
 plasminogen activator
 PAI - 1 t - PA : PAI - 1
 6%

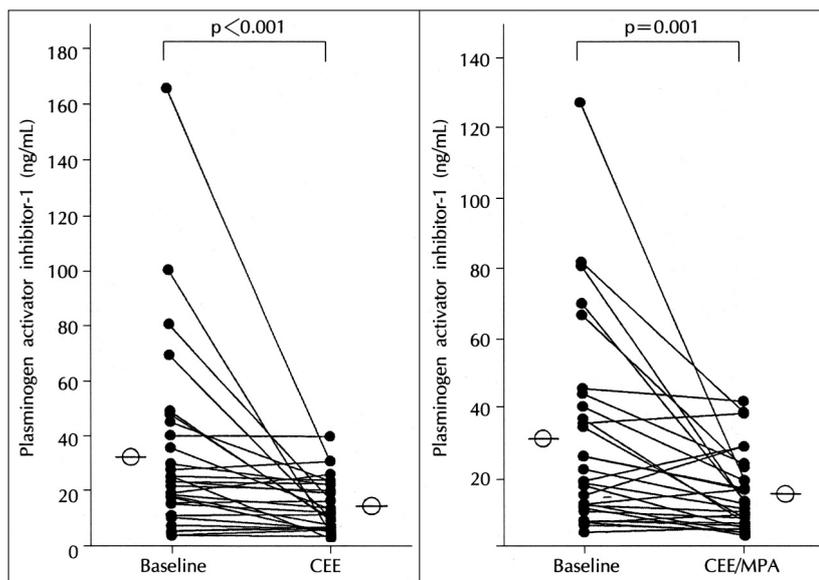


Fig. 3. Changes in plasma levels of plasminogen activator inhibitor (PAI-1) before and after therapy with oral conjugated equine estrogen (CEE) 0.625 mg daily for 1 month, or the combination of CEE 0.625 mg with medroxyprogesterone acetate (MPA) 2.5 mg daily taken for 1 month by 30 healthy postmenopausal women. Mean values are identified by open circles. Used with permission from Koh et al.⁵

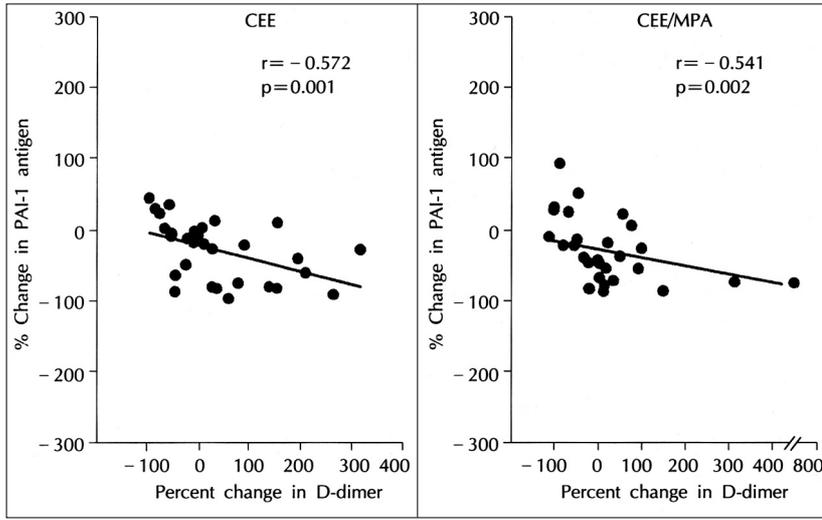


Fig. 4. Scatter plots with the predicted regression line showing the correlation between the percent change in PAI-1 antigen levels and the percent change in D-dimer levels after therapy with CEE alone and after CEE combined with MPA, each for one month in 30 healthy postmenopausal women. Used with permission from Koh et al.⁵

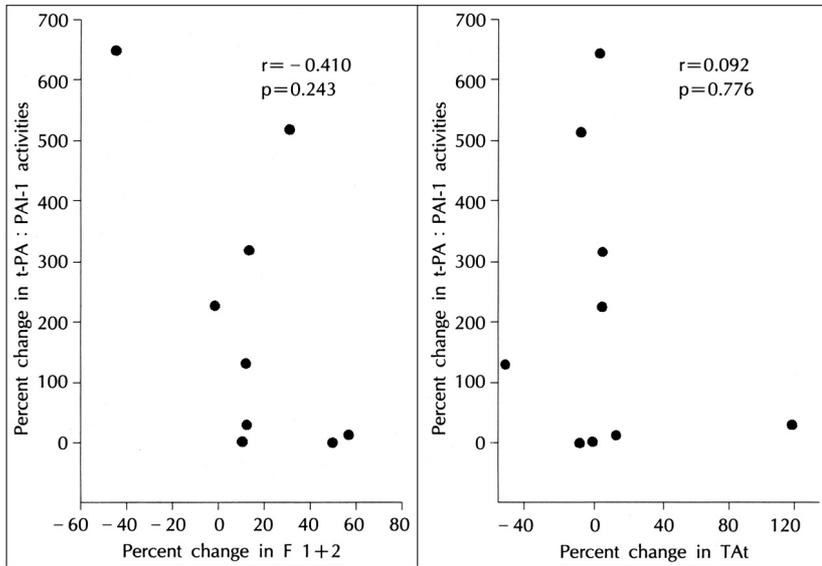


Fig. 5. Scatter plots showing the relations between (left panel) the percent change in prothrombin fragments 1 +2 (F1+2) and (right panel) percent change in thrombin-antithrombin (TAT) complexes to the percent change in the ratio of tissue plasminogen activator (t-PA) to plasminogen activator inhibitor-1 (PAI-1) activities after oral CEE therapy 0.625 mg daily for 1 month by 9 healthy postmenopausal women. Used with permission from Koh et al.⁶³

650% 가 (p=0.008). tPA : 가
 PAI - 1 가 F₁₊₂ thrombin - antithrombin(TAT) 가 PEPI
 (Fig. 5). 6
 16) , (precursor)
 adenomatous atypical 3
 33%

가

호르몬 대체요법과 자궁내막 및 유방암

가

66 - 69)

⁷⁰⁻⁷²⁾ Grodstein ⁷³⁾ Nurses' Health Study 59,337 16

가 호르몬 대체요법의 대안

(multivariate adjusted relative risk)가 0.39(95% 0.19 (Selective estrogen receptor modulators) 0.78),

가 0.60(95% 0.43 0.83)

가

가

가

가가

가

. tamoxifen

Colditz ⁷⁴⁾ Nurses' Health Study

moxifen

LDL

가 1.32,

LDL

⁷⁵⁾

tamoxifen

가 1.41

가

, 5

가

⁷⁶⁾

가 1.46

Raloxifen

가

FDA 가

현재 진행중인 폐경기 여성에서 호르몬 대체요법에 관한 연구들

. 390

HERS 가

Walsh ⁷⁷⁾

raloxifen LDL cho-

lesterol 12%

14%

. lipoprotein(a)

, National Institute of Health (NIH) 가 Women's Angiographic Vitamin and Estrogen(WAVE) , Women's Estrogen/Progestin and Lipid - Lowering Hormone Atherosclerosis Regression Trial(WELL - HART) Estrogen Replacement and Atherosclerosis(ERA)

19% 가

raloxifen

8% 가

HDL cholesterol 11%,

20% 가

PAI - 1 29%

14%

1

fibrinogen 12-

. NIH

Women's Health Initiative

(WHI)

, WHI

27,500

가

HMG - CoA reductase (statin)

Antioxidant Study(CHAOS) vitamin E 400
800 IU 510
77%
86) Vitamin E HDL 가 LDL
가 87) Vitamin E(alpha-toco-
pherol) 가
(oxidative endothelial injury)
, phospholipase A2

thromboxane A2
, LDL cholesterol
, 88)89)
, 90)91)
Conjugated equine estrogen
LDL
5) conjugated equine estrogen
E
(thrombogenic
potential)
가
Koh 92) conjugated
equine estrogen 0.625 mg E 1000 IU 6
E 가
(Fig. 9)

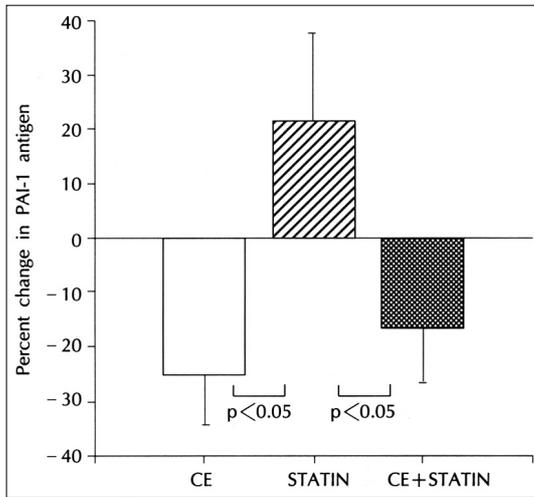
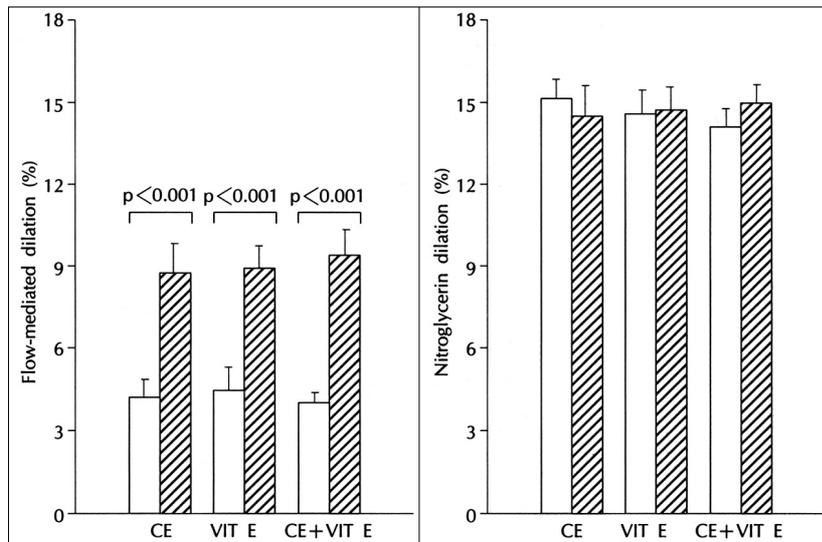


Fig. 8. Percent change in the plasminogen activator inhibitor type-1 (PAI-1) following conjugated estrogen (CE) alone, simvastatin (statin) alone, and combination therapies. Standard error of the mean is identified by the bars. Reproduced from reference 14 with permission from the American Heart Association.

Fig. 9. Flow-mediated (left panel) and nitroglycerin-induced (right panel) dilation before therapies (open bars) and following conjugated estrogen (CE) alone, vitamin E (VIT E) alone, and conjugated estrogen combined with vitamin E (hatched bars). There were no differences in the effect of therapies on flow-mediated dilation ($p = 0.267$ by ANOVA). Standard error of the mean is identified by the error bars. Reproduced from reference 92 with permission from the American Heart Association.



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