

내피세포기능에 대한 Statin 약물의 효과 : 혈관운동기능, 염증반응, 그리고 섬유소용해기능

가
손 지 원 · 고 광 곤

Effects of Statins on Endothelium : Vasomotor Function, Inflammation, and Hemostasis

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서 론

3 - hydroxy - 3 - methylglutaryl coenzyme A(HMG - CoA) reductase inhibitor statin end points (2-8) 3 3 3 statins(lovastatin, pravastatin, simvastatin) LDL - cholesterol 가 (10)(11) 50% LDL - cholesterol 가 (12)(13) Lipid Research Clinics Prevalence Study 10 LDL - cholesterol 47% (14) Finnish cohort of the Seven Countries Study 30 (13) National Cholesterol Education Program(NCEPII) guidelines (11) LDL - cholesterol

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¹⁴⁾ LDL - cho -
 lesterol HDL - cholesterol,¹⁵⁾ fibrinogen,¹⁶⁾
 plasma viscosity,¹⁷⁾ C - reactive protein¹⁸⁾

. Nitric oxide
 LDL - cholesterol end points
 가 ²⁾⁴⁾⁸⁾
 가 LDL - choles -
 rol 가 가 , hyperhomocysteinemia,
 Scandinavian Simvastatin Survival Study endothelium
 LDL - cholesterol ,
 major coronary events가 ,
²⁾ West of Scotland Coronary Prevention Study lipidrich ,
 (WOSCOPS) , LDL -
 cholesterol 가
 LDL - cholesterol endothelium 가
 Framingham

가 ⁴⁾ Pravastatin
 LDL - cholesterol 가 19% 50%
 54% LDL - cho - ²⁴⁾²⁵⁾
 leterol 가 ⁴⁾ 70%
 Framingham 가
 , pravastatin minor plaque 가
 35% ²⁶⁾ 가
 가 nonlipid ¹⁹⁾²⁰⁾
 WOSCOPS ,
 가
⁴⁾⁵⁾⁸⁾²¹⁾²²⁾
 Endothelial 가 가
 . 1980 Furchgott Zawadzki²³⁾ ²⁴⁾²⁵⁾
 endothelium

가 endothelium endothe -
 lium , lium
 Endothelium
 가
 Endothelium endothelium statin
¹⁾
²⁾ ,

본 문

내피세포기능 장애의 기전과 결과들(Mechanisms and consequences of endothelial dysfunction)

산화질소와 고콜레스테롤혈증(Nitric oxide and hypercholesterolemia) .³⁵⁾ endothelial superoxide anion 가 가

arginine(L - NMMA) N^G - monomethyl - L - .³⁵⁾ 가 endothelium nitric oxide (forearm) 가 , ace - . Nitric oxide 가 가

tylcholine L - NMMA 가 nitrogen oxide 가 가 .³⁶⁾ nitric oxide endothelium LDL 가 ni - endothelium nitric oxide trogen oxide 가 (peroxynit - .²⁷⁾ , LDL nitric oxide synthase tran - bradykinin .²⁸⁾ bradykinin scription .³⁸⁾ nitric oxide constitutive , nitric oxide in - G - protein - dependent pertussis toxin - sen - ducible form 가 .³⁹⁾ sitive signal transduction pathway , nitric oxide , nitric oxide superoxide anion free radical nitrogen oxide

산화 질소와 동맥경화증(Nitric oxide and atherosclerosis) 가 . Koh .⁴⁰⁾ 가 9 endothelial nitric

tylcholine .^{30 - 32)} ace - oxide bioassay 가

acetylcholine 가 2 april angiotensin quin - . nitrate 3

acetylcholine nitro - endothelial nitric oxide quina - glycerin(nitric oxide donor) nitrogen oxide pril 20 40 mg 8 .

가 nitric oxide quinapril flow - mediated dilation 가 가 , quinapril 19% (Fig. 1). , quinapril (Fig. 2). quinapril angiotensin - induced oxidant str - ess nitric oxide endothelium nitric oxide . 가

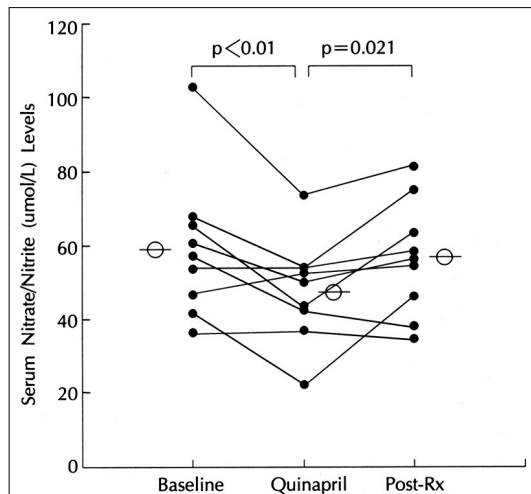
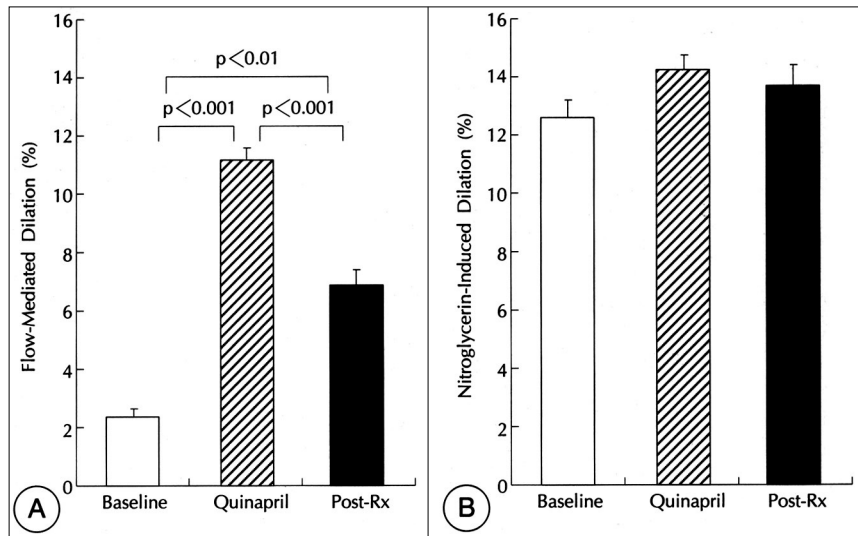


Fig. 2. Serum levels of nitrate/nitrite at respective pretreatment baseline, after quinapril for 8 weeks, and 1 week after stopping therapy (Post-Rx). Open circles represent mean values. Used with permission from Koh et al.⁴⁰⁾

, proinflammatory cytokines
 . nitric oxide
 growth factor
 nitric oxide
 thase nitric oxide
 nitric oxide , L - arginine
 가 가
⁴³⁾⁴⁴⁾ Endothelium
 nitric oxide

감염, 염증과 내피세포기능 장애(Infection, inflammation and endothelial dysfunction)

가 ⁴¹⁾ stress⁴²⁾ ⁴⁵⁾⁴⁶⁾
 , nitric oxide 가
 nitric oxide nore - ⁴⁷⁾
 pinephrine 가 ⁴²⁾ 가
 endothelium 가
 . Nitric oxide endothelin
 , growth factors
 intima 가 가

interleukin - 1, 6, TNF -
 thromycin 6 4가 가
 , 가
 ,
 (cytokines, C - reactive pro -
 tein, and white cell count)
 가 48 - 50)
 ,
 vascular beds
 ,
 51)
 atheroma
 가? endotoxin,
 proinflammatory cytokines(TNF) endo -
 thelium nitric oxide vasodila -
 tor anti - aggregatory prostanoids
 52 - 54) 54) 52)53)
 .
 endotoxin cytokines
 endothelium
 52)53)
 ,
 endothelial "stunning"
 53)
 endothelium
 ,
 ,
 55)56)
 Chlamydia pneumoniae⁵⁷⁾ Herpes simplex
 cytomegalovirus IgG seropo - sivity⁵⁸⁾
 .
 seropositivity
 C - reactive protein
 . Anderson 59)
 Chlamydia pneumoniae
 azithro -
 mycin
 . 47) C - reactive protein, in -

interleukin - 1, 6, TNF -
 thromycin 6 4가 가
 , 가
 ,
 약물 스타틴(지질 저하제)의 생물학적 효과들(Biologi -
 cal effects of statins)
 (Effects of statins
 on vasomotor function)
 mediated vasodilation endothelial -
 60)61)
 pravastatin lovastatin
 acetylcholine
 endothelium
 61)62) Simvastatin
 63)64) Statin
 65)66)
 67) Statin endothelium
 .
 Goode Heagerty⁶⁸⁾ 18
 line
 16 age, sex - matched
 10
 , LDL 56%
 ,
 55)56)
 Chlamydia pneumoniae⁵⁷⁾ Herpes simplex
 cytomegalovirus IgG seropo - sivity⁵⁸⁾
 .
 seropositivity
 C - reactive protein
 . Anderson 59)
 Chlamydia pneumoniae
 azithro -
 mycin
 . 47) C - reactive protein, in -
 tylocholone nitroprusside
 28 conjugated equine estro -
 gen 0.625 mg, simvastatin 10 mg, 가
 6 . Hyperemia nit -
 roglycerin
 . simvastatin
 LDL - cholesterol 25%
 simvastatin flow - mediated 4.3% 10%
 (Fig. 3).
 fluvastatin⁷⁰⁾ LDL - apheresis⁷¹⁾

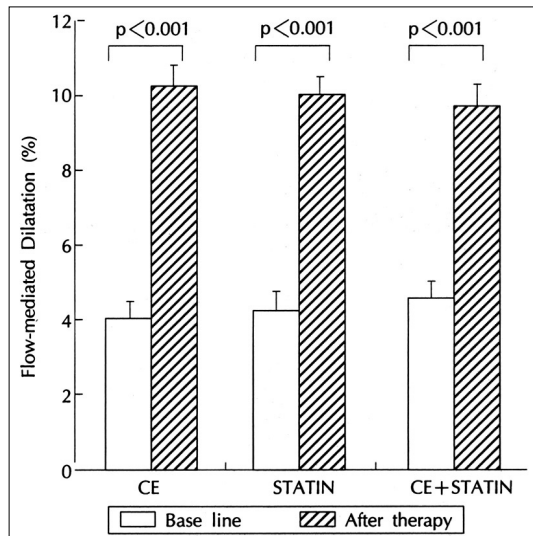


Fig. 3. Flow-mediated dilatation before therapies (open bars) and following (hatched bars) CEE 0.625mg daily for 6 weeks (left), simvastatin 10mg daily for 6 weeks (center), and the combination of therapies daily for 6 weeks (right) in 28 hypercholesterolemic postmenopausal women. Standard error of the mean is identified by the error bars. Used with permission from Koh et al.⁶⁹⁾

endothelium

nitric oxide

17 - estradiol

nitric oxide ()

nitrogen oxides(nitrites, nitrates) 가

72)

chemiluminescence ELISA

nitric oxide 가 가

73)74)

nitrate -

30 nitrate - 가 nitrogen

oxide 66.2 ± 46.1 46.4 ± 26.2 μmol/L(p

0.001) Koh 69)75)

nitrogen oxide nitrate (

75 100 mg)가

3 nitrate - (15 mg)

76)

Koh conjugated equine estro -

gen simvastatin 가 “

nitric oxide

가

nitrate/nitrite⁷⁷⁾

가

nitric oxide 가

flow - mediated dilation

, CEE

simvastatin

nitrate/

Statin

nitric oxide

endothelium

radical

nitic oxide 가

endothelium

oxide

40)

가

78) Koh

(Fig. 2).

Statin

LDL

nitric oxide

nitric oxide

endothelium

endothelium

statin

79) Statin

free radical

nitric oxide

Kleinveld 80) 23

18 pravastatin simvastatin

LDL - 36 %

, copper - catalyzed LDL oxidation

Statin LDL

가

81)

LDL LDL

HMG - CoA reductase inhibitor

82) simvastatin

superoxide anion LDL

, Girona 83)

simvastatin

simvastatin

1 NF - kB
atorvastatin
Pasterkamp⁹²⁾ (local vs general)
45% 41%
(fibrous cap) 2
3
가 CD68 acid phos -
phatase
84% 71%
cap shoulder 가
Abe⁹³⁾
HDL - cholesterol 가 가 IC -
AM - 1 VCAM - 1 가 가
Rohde⁹⁴⁾ 92
intima - media cell adhesion mo -
lecule 가
intimamedia 3
가 ICAM - 1
가 가 VCAM - 1
cell adhesion mo -
lecule intima - media
가 가 가
pravastatin
cyclosporin natural
killer cell⁹⁵⁾
Ridker⁹⁶⁾ Womens Health Study
3
122
C - reactive protein
C - reactive protein 가
C - reactive protein 가 가
5 , 7
Strandberg⁹⁷⁾ simvastatin atorvasta -

Palomaki⁸⁴⁾ lovastatin metal ion -
independent oxidation - toco - pherol
depletion time 44% , metal ion -
dependent oxidation conjugated - diene (local vs general)
lag time 7% statin
LDL
nitric oxide 가 , end -
othelium , , end -
othelium .
(Effects of statins on in -
flammation)
endothelium cap shoulder 가
, subendothelial . Oxidized
LDL
foam cell .
T cytokine end -
othelium , , collagen
,^{85 - 87)} Scalia⁸⁸⁾
endothelium P - selectin, ICAM -
1, VCAM - 1
intestinal micro -
vascular endothelium end -
othelial adhesion molecules가
가⁸⁹⁾⁹⁰⁾
in vitro
endothelium
가 , lovastatin simvastatin
Fluvastatin⁹⁰⁾
platelet activation fa -
ctor leukotrien B4
Bustos⁹¹⁾ atorva -
statin
monocyte chemoattractant protein - 1
가 atorvastatin
tumor necrosis factor alpha (TNF -
) monocyte chemoattractant protein -

tin C - reactive protein ester가 cholesterol crystal 가

Koh ⁶⁹⁾ 28
 conjugated equine estrogen 0.625 mg, simvastatin 10 mg, 가 6
 simvastatin 가 E - selectin, ICAM - 1, VCAM - 1
 .(Fig. 4) simvastatin
 28 interleukin - 6 level
 2.20 ± 1.30 1.88 ± 0.97 ng/ml
 , Rosenson ⁹⁸⁾
 simvastatin nitric oxide
 endothelium -

(Effect of statins
 on plaque stability)

stress
 가
 가
 (matrix degradation cascade)
 가

Statin phospholipid - containing pools free
 cholesterol trapping acyl - coenzyme A
 cholesterol acyltransferase free cholesterol
 , cholesterol
 mevalonate mevalonate
 LDL (endocytosis)
 cholesterol -
 rol ester ⁹⁹⁾ Kempen ¹⁰⁰⁾ pra -
 vastatin lovastatin simvastatin
 cholesterol 가

LDL - cholesterol ¹⁰¹⁾
¹⁰²⁾ (lipid core)
 cholesterol

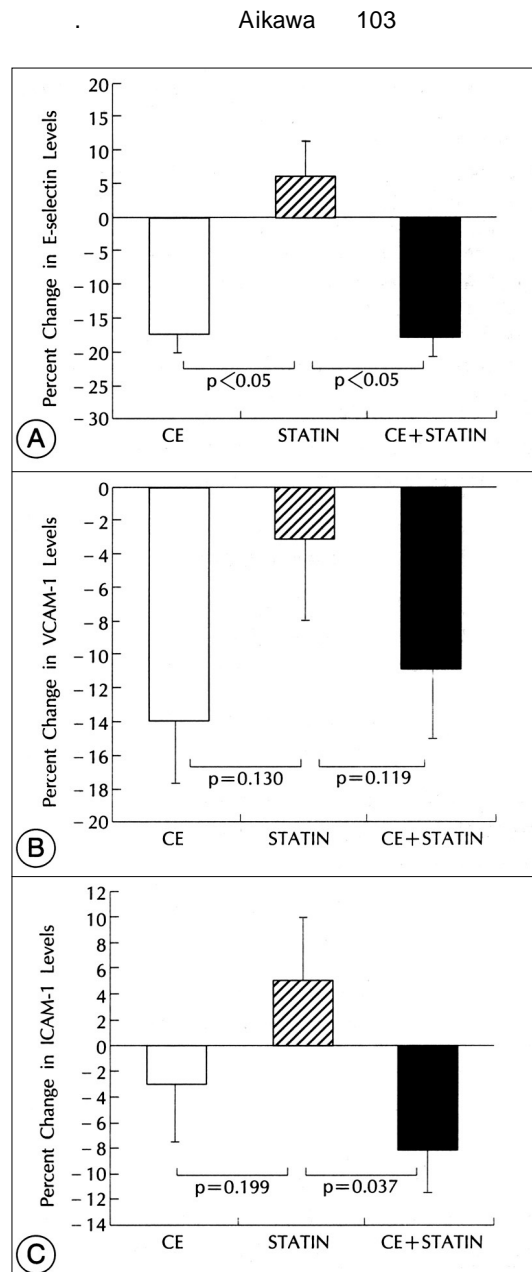


Fig. 4. Percent change in the E-selectin (A), vascular cell adhesion molecule (VCAM-1) (B), and intercellular adhesion molecule (ICAM-1) levels (C) following CEE 0.625mg daily for 6 weeks (left), simvastatin 10mg daily for 6 weeks (center), and the combination of therapies daily for 6 weeks (right) in 28 hypercholesterolemic postmenopausal women. Standard error of the mean is identified by the error bars. Used with permission from Koh et al.⁶⁹⁾

platelet-derived growth factor - B

(가)

(가

) matrix metalloproteinase - 3

- 9 Ai -

kawa ¹⁰⁴⁾ 33

4

matrix metalloproteinase - 1 가

. Sirius red

(interstitial collagen)

가 ,

Xu ¹⁰⁵⁾

LDL matrix metalloproteinase - 9

, matrix me -

talloproteinase - 1

. Bellosta ¹⁰⁶⁾ 가

(fibrous cap)

matrix metalloproteinase - 9

fluvastatin simvastatin

가 . Fluvastatin

matrix metalloproteinase - 9

matrix metalloproteinase - 9

. Simvastatin

지혈 표식자에 대한 스타틴의 효과(Effects of statins on vascular hemostasis markers)

pool proteog -

lycans ,

Koh ¹⁰⁷⁾

statin 가 proth -

rombotic tissue factor ,

1. (Coagulation system)
- 1 - 1) Tissue factor
 - Tissue factor messenger RNA
 - ¹⁰⁸⁾ Tiss -
 - ue factor plasma factor VII cofactor factor
 - a ,
 - (extrinsic coagulation pathway)
 - ¹⁰⁹⁾ Brand ¹¹⁰⁾ oxidized LDL
 - lipopolysaccharide - induced tis -
 - sue factor
 - statin fluvastatin simvastatin tissue factor
 - geranylgeranylated protein
 - tissue factor
 - ¹¹¹⁾ Tissue factor
 - pravastatin . Ferro ¹¹²⁾ si -
 - mvasatin a 24 mo -
 - nocyte - tissue factor
 - TFPI(tissue factor pathway
 - inhibitor) serine protease inhibitor
 - . TFPI 가
 - ¹¹³⁾ a b ¹¹⁴⁾
 - 가 . Simvastatin factor c
 - LDL TFPI ¹¹⁵⁾
- 1 - 2) (Platelet aggregation)
 - LDL 가
 - ¹¹⁶⁾ Simva -
 - statin 2 ,
 - thromboxane 4 24
 - ¹¹⁷⁾ Lovastatin pravastatin
 - cytosolic ¹¹⁸⁾ Statin
- 1 - 3) (Fibrinogen and viscosity)

Eriksson¹¹⁹⁾ inogen - regulating cytokine , fibr -
65 inogen gene locus 가
nity - based, casecontrol study ,¹³⁴⁾
가 .¹³⁵⁾
가 .¹³⁶⁾
가
4 가 4 2. (Fibrinolytic system)
odds ratio 6.0 , Statin lipoprotein(a)
odds ratio 3.0 . 가 plasminogen
shear stress , endothelium activator inhibitor(PAI) - 1 .
othelium , end - 2 - 1) Plasminogen activator inhibitor - 1
가 , PAI - 1¹³⁷⁾ ^{137 - 139)}
st - . Koh¹⁴⁰⁾
atin 가 PAI - 1
. Lovastatin 26¹²¹⁾ 49¹²²⁾ 가 D - dimer 가
6 가 19 %
24% 가 , 260¹²³⁾ 가
12 5% 가 . 가 .
15 35

¹²⁴⁾¹²⁵⁾ Mayer¹²⁶⁾ . Brown¹⁴¹⁾ gemfibr -
16 lovastatin 20 ozil niacin transforming grow -
가 10% th factor - 1 mitogen
, 12 . Lovastatin PAI - 1
가 ,¹²⁷⁾ PAI - 1
¹²⁴⁾ ,¹²⁵⁾¹²⁷⁾ Pravast - niacin , gemfibrozil
atin 16 24 10 HMG - CoA reductase inhibitor pravastatin
24 3가 PAI - 1¹⁴²⁾¹⁴³⁾
7% 9% .¹²⁹⁾¹³⁰⁾ Simvastatin 12 PAI - 1
111 10 2 4가 PAI - 1 endothelium
¹²⁸⁾¹³⁰⁾¹³¹⁾
simvastatin , ,
¹³¹⁾ Atorvastatin(80 mg) Pravastatin PAI - 1 26% 56%
22 가 6¹³²⁾ . Lovastatin PAI - 1 22%
가 46% 가 ,¹²²⁾ 260 34%
95 10 mg 가 가 .¹²³⁾ Atorvastatin
80 mg 12 PAI - 1 36% 가 .¹²³⁾ Si -
가 19% 24% 가 .¹³³⁾ mvastatin 111 2
statin fibr - PAI - 1 18% 가 .¹⁴⁴⁾ Fluvastatin

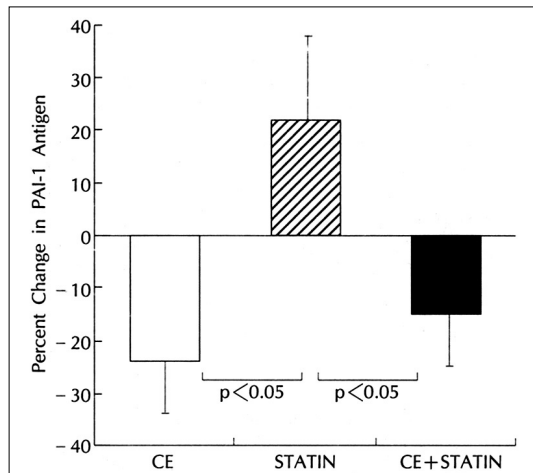


Fig. 5. Percent change in the plasminogen activator inhibitor type-1 (PAI-1) following conjugated estrogen (CE) alone, simvastatin (statin) alone, and combination therapies. Standard error of the mean is identified by the bars. Used with permission from Koh et al.⁶⁹⁾

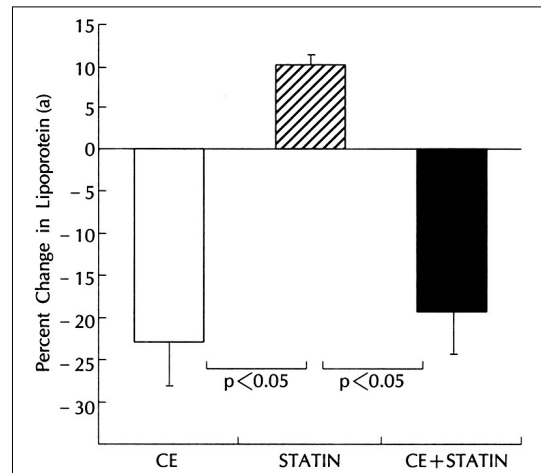


Fig. 6. Percent change in lipoprotein (a) from respective pre-treatment values after CEE alone, simvastatin alone, and the combination of therapies daily for 6 weeks in 28 hyper-cholesterolemic postmenopausal women ($p < 0.001$ by AN-OVA). SEM is identified by the bars. Used with permission from Koh et al.⁶⁹⁾

PAI - 1¹⁴⁵⁾ Koh
⁶⁹⁾ 28 con -
 conjugated equine estrogen 0.625 mg, simvastatin 10
 mg, 27가 6
 simvastatin PAI - 1
 19.2 ng/ml 18.6 ng/ml
 (Fig. 5). simvastatin
 D -
 dimer

2 - 2) Lipoprotein(a)
 Lipoprotein(a) plasminogen , ,
 plasminogen plasminogen
¹⁴⁶⁾ Lipoprotein(a)
 statin 34% 가 ,¹⁴⁷⁾¹⁴⁸⁾
 Koh ⁶⁹⁾ 28
 conjugated equine estrogen 0.625 mg, simva -
 statin 10 mg, 27가 6
 simvastatin
 lipoprotein(a) 28.8 mg/ml
 31.8 mg/ml
 (Fig. 6). lipopro -

tein(a) 가
 , statin
 가
 결론
 Endothelium
 . Statin
 endothelium ,
 가
 ,
 statin
 endothelium
 .
 Statin endothelium
 , , extra -

cellular matrix protein 가
 가 . Statin
 (deposition) (aggregation),
 (reology),
 . statin
 .
 중심 단어 : . . HMG - CoA

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