

Menopause, HRT & CV Disease

박 형 무

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stages of reproductive aging in women

FMP

Reproductive	Menopausal transition		Postmenopause	
	early	late	early	late
	4 – 5 yrs		1	4 yrs
	Perimenopause			

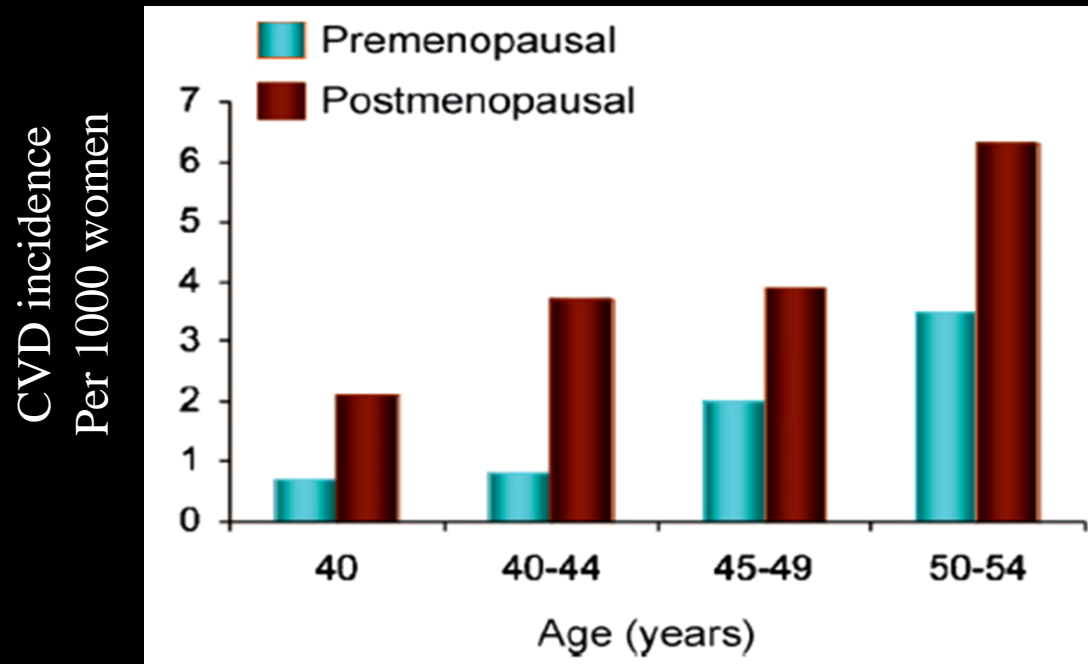
NIH, NAMS, ASRM 2001

Menopause increases risk of CVD

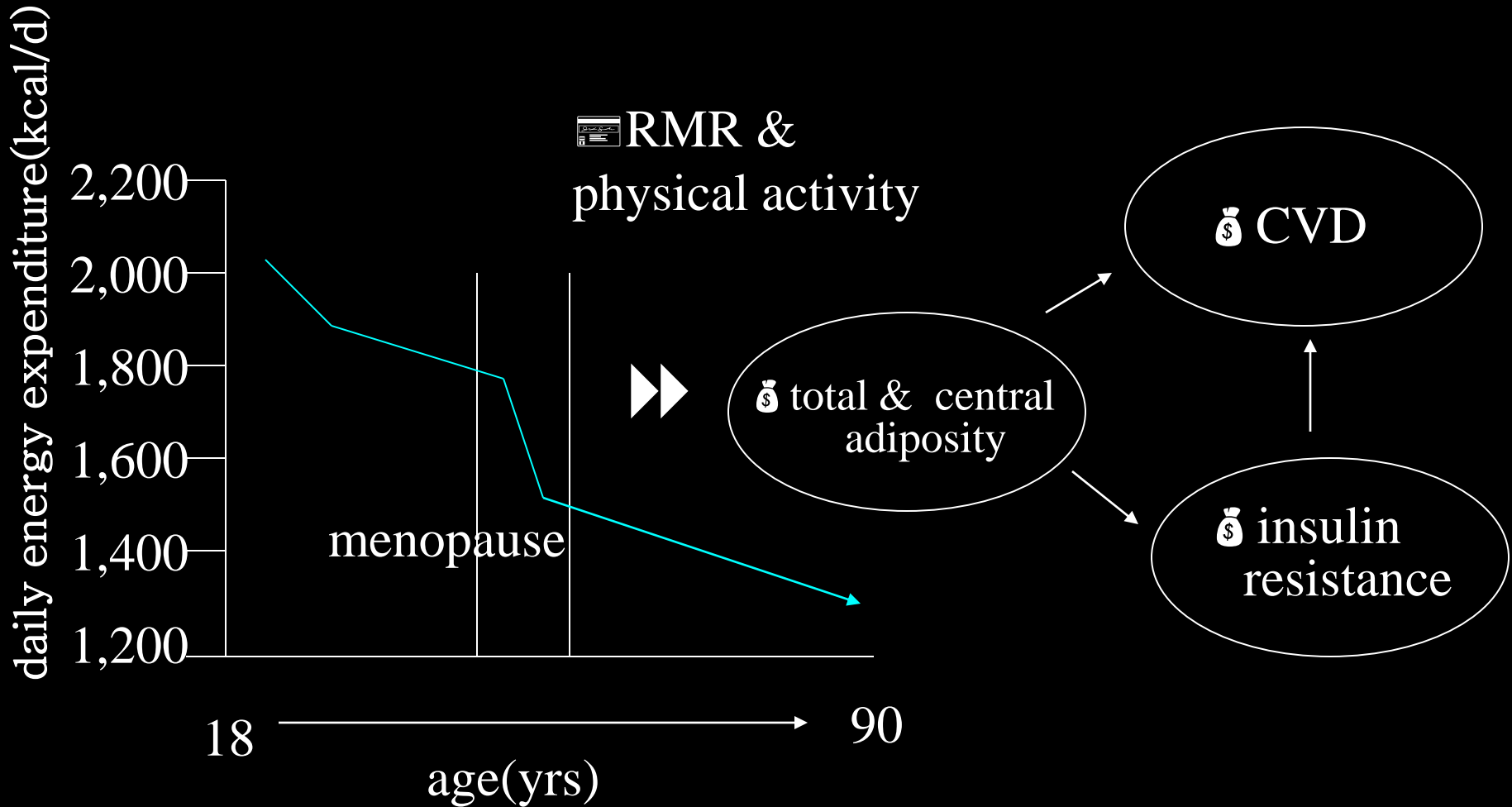
CVD incidence

marked increase after time of menopause

higher in PMW at same age



menopause-induced changes in energy expenditure



Postmenopausal hypertension

activation of RAS

activation of sympathetic nervous system

increase in endothelin and oxidative stress

obesity type II DM

HRT & CHD

findings of observational study

30-50% lower risk of CHD in estrogen users

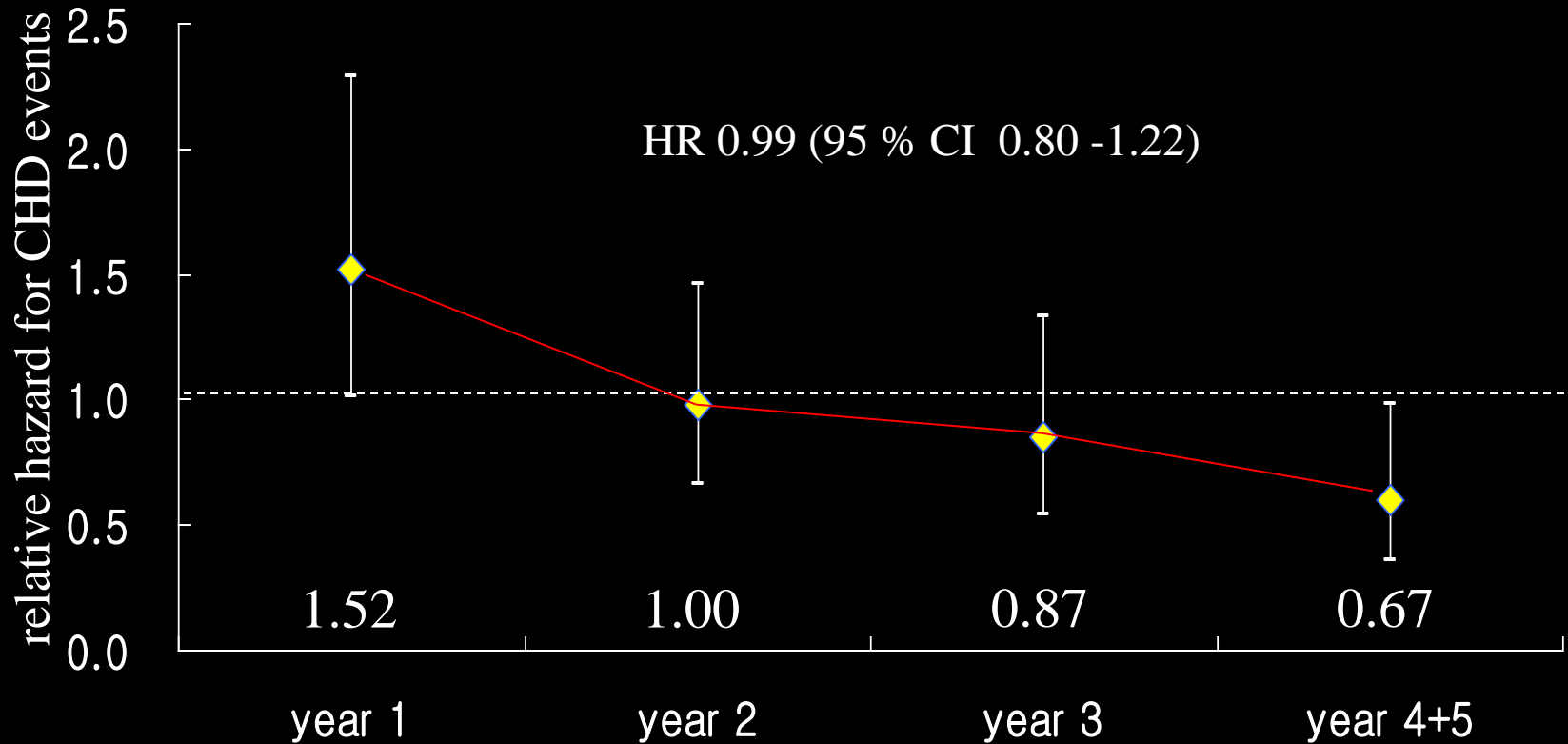
stronger protection in women with CHD

similar benefit in E/P users

Heart & Estrogen / Progestin Replacement Study (HERS)

2763 PMW with established CHD

CEE 0.625 mg + MPA 2.5 mg for 4.1 yrs



HRT for secondary prevention of CHD

Clinical outcome studies		Tx	기간 (yr)	RR
HERS	1998	CEE + MPA	4.1	0.99 (0.80-1.22)
PHASE	2002	TD 17 β E2	2.6	1.29 (0.84-1.95)
ESPRIT	2002	E2 valerate	2.0	0.99 (0.70-1.41)
Surrogate studies		Coronary angiographic trials		Carotid artery IMT trials
		ERA	2000	PHOREA 2001
		WAVE	2002	
		WELL-HART	2003	

Progression of coronary atherosclerosis : no effect

WHI

EPT 16,608 (55 %) CEE 0.625 mg + MPA 2.5 mg/d F/U : 5.2 yrs

ET 10,739 (45 %) CEE 0.625 mg/d F/U : 6.8 yrs

	EPT		ET	
	HR	/만인년	HR	/만인년
CHD	1.29	+7 (30)		
Breast Ca.	1.26	+8 (30)		
Stroke	1.41	+8 (21)	1.39	+12 (32)
VTE	2.11	+18 (16)		
Hip Fx	0.66	- 5 (15)	0.61	- 6 (17)
Colorectal Ca.	0.63	- 6 (16)		
Dementia *	2.05	+23 (22)		

() absolute risk in control

US FDA : boxed warning

WHI study

2003 Jan 8

ET / EPT should not be used for Px of CVD
increased risks of MI, stroke, VTE, breast ca in PMW

WHI 연구의 문제점

- 대상군 : 평균 나이 63.2세 고령의 무증상 여성

YSM	< 5	5 to 10	10 to < 15	≥ 15
Enrollees %	17	19	21	43

women assigned to HRT

hypertension 36 % / obesity 34 % / smoker 49 %
 prior CVD 7.6 %

- 높은 탈락율 (42%) / unblinding (41%)

- **HRT** 단일형태/용량/투여경로와 방법

type

dose

route

regimen

CEE 0.625mg + MPA 2.5mg

oral

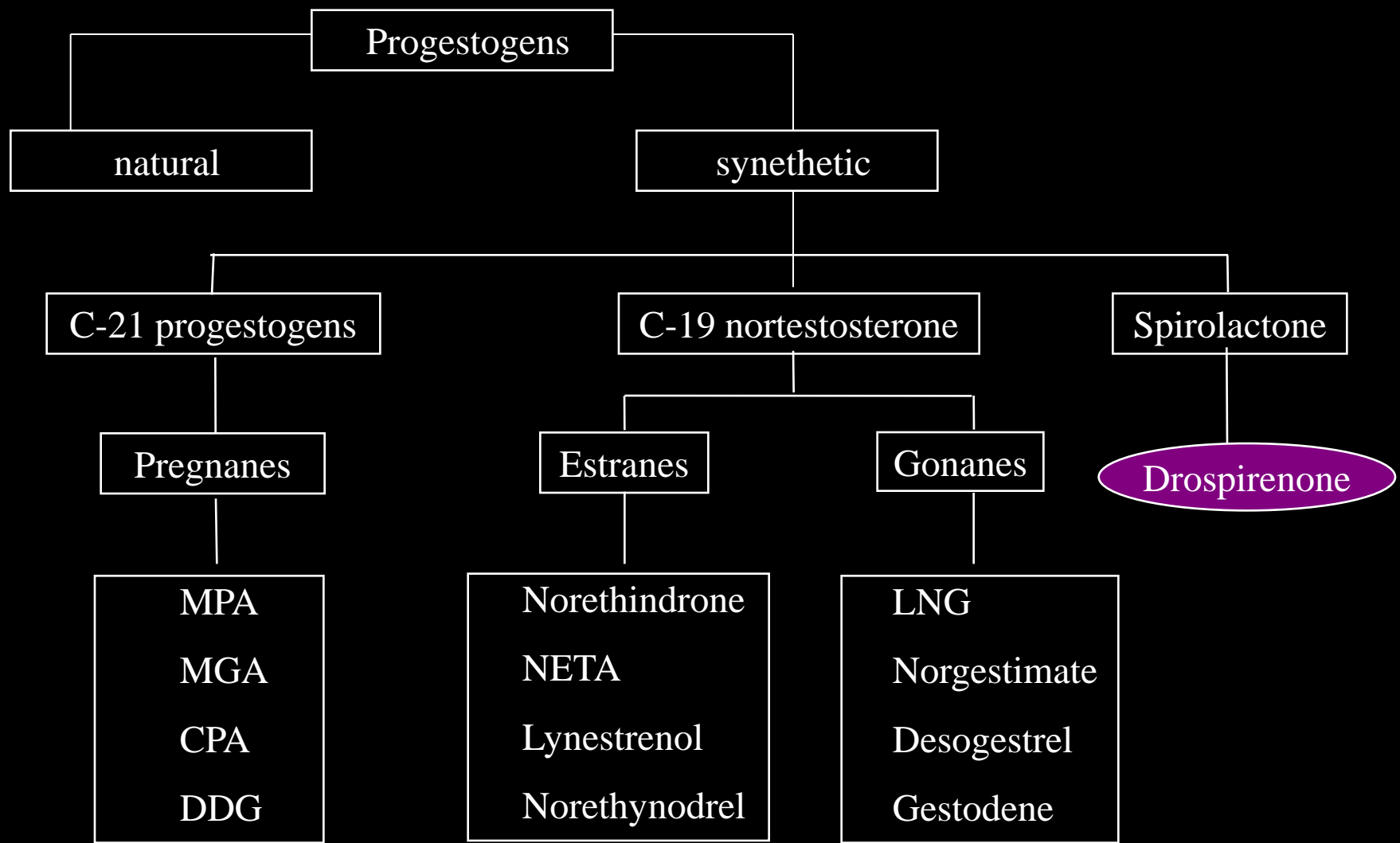
continuous combined

치료 용량

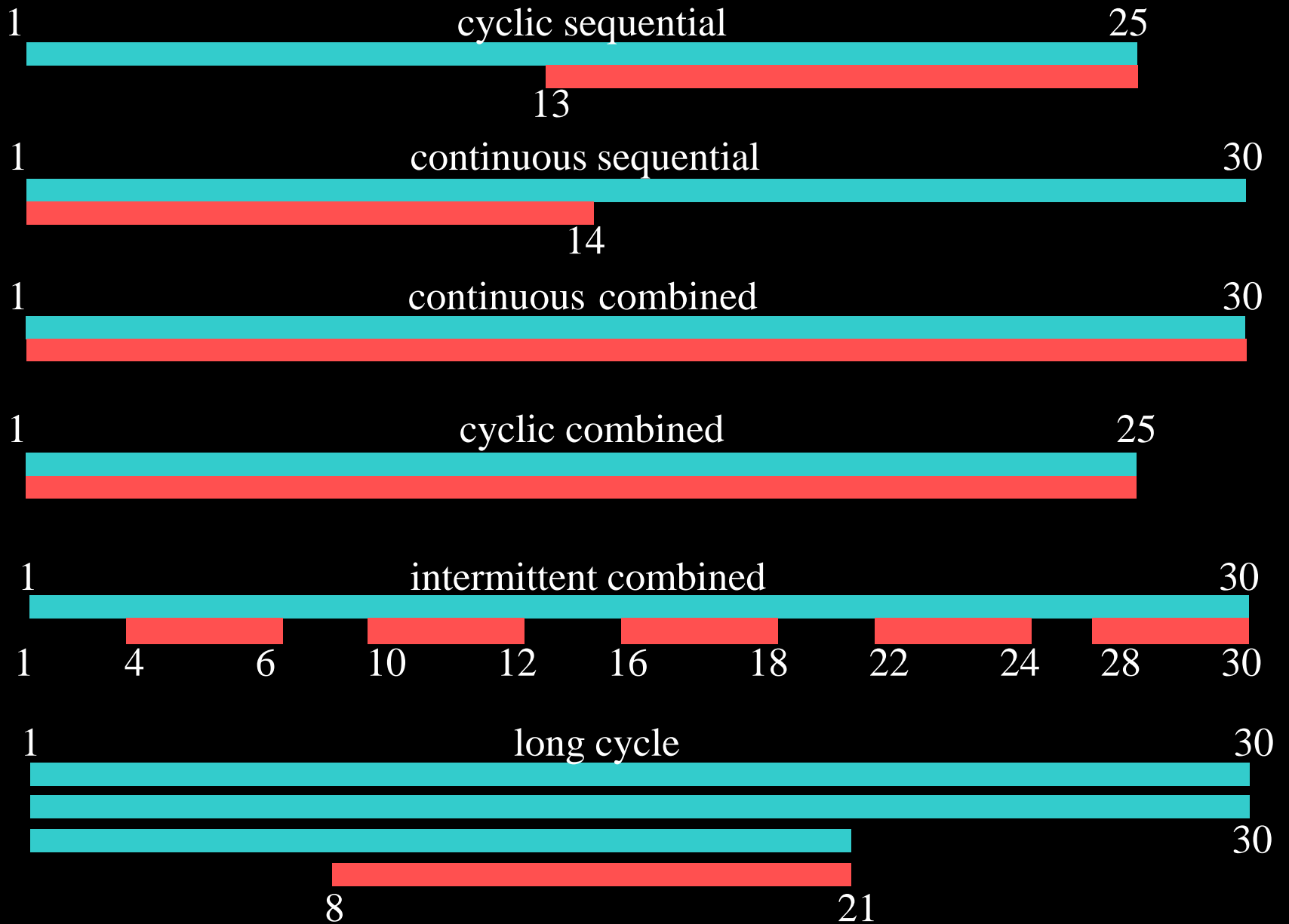
		high	standard	low	ultra-low
CEE	mg	1.25	0.625	0.3 /0.45	
17 β -E ₂	mg	4.0	2.0	1.0	0.5
E ₂ valerate	mg		2.0	1.0	
Transdermal 17 β -E ₂	μ g	100	50	25	14

super ultra-low dose

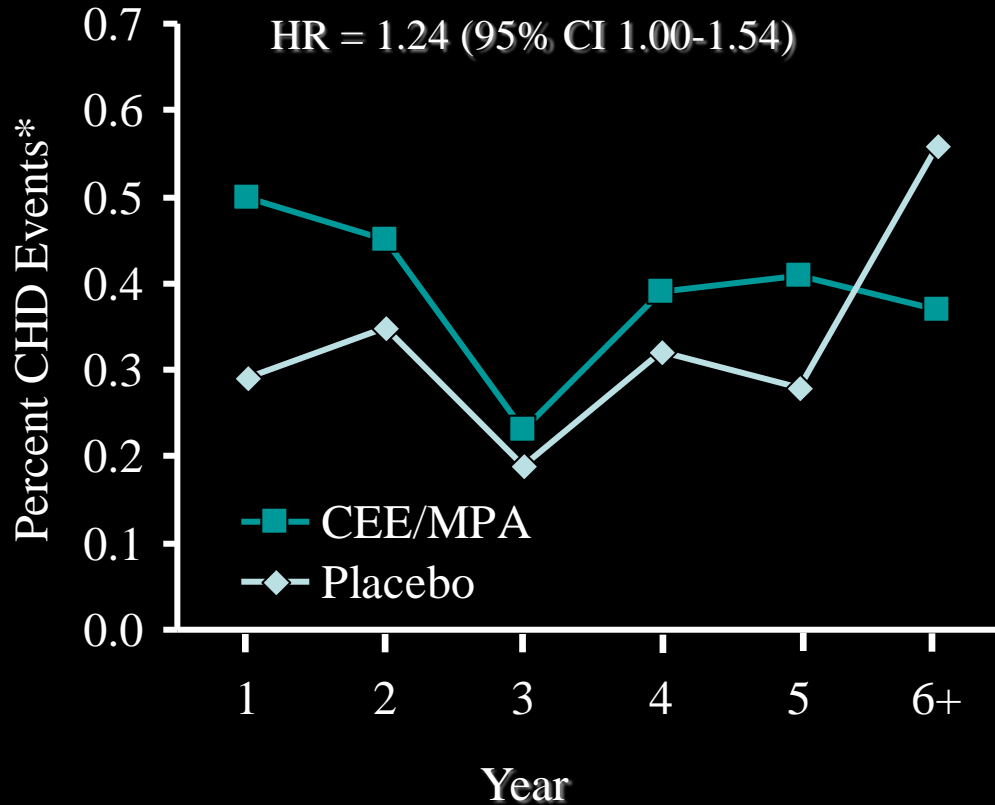
classification of progestogens



HRT



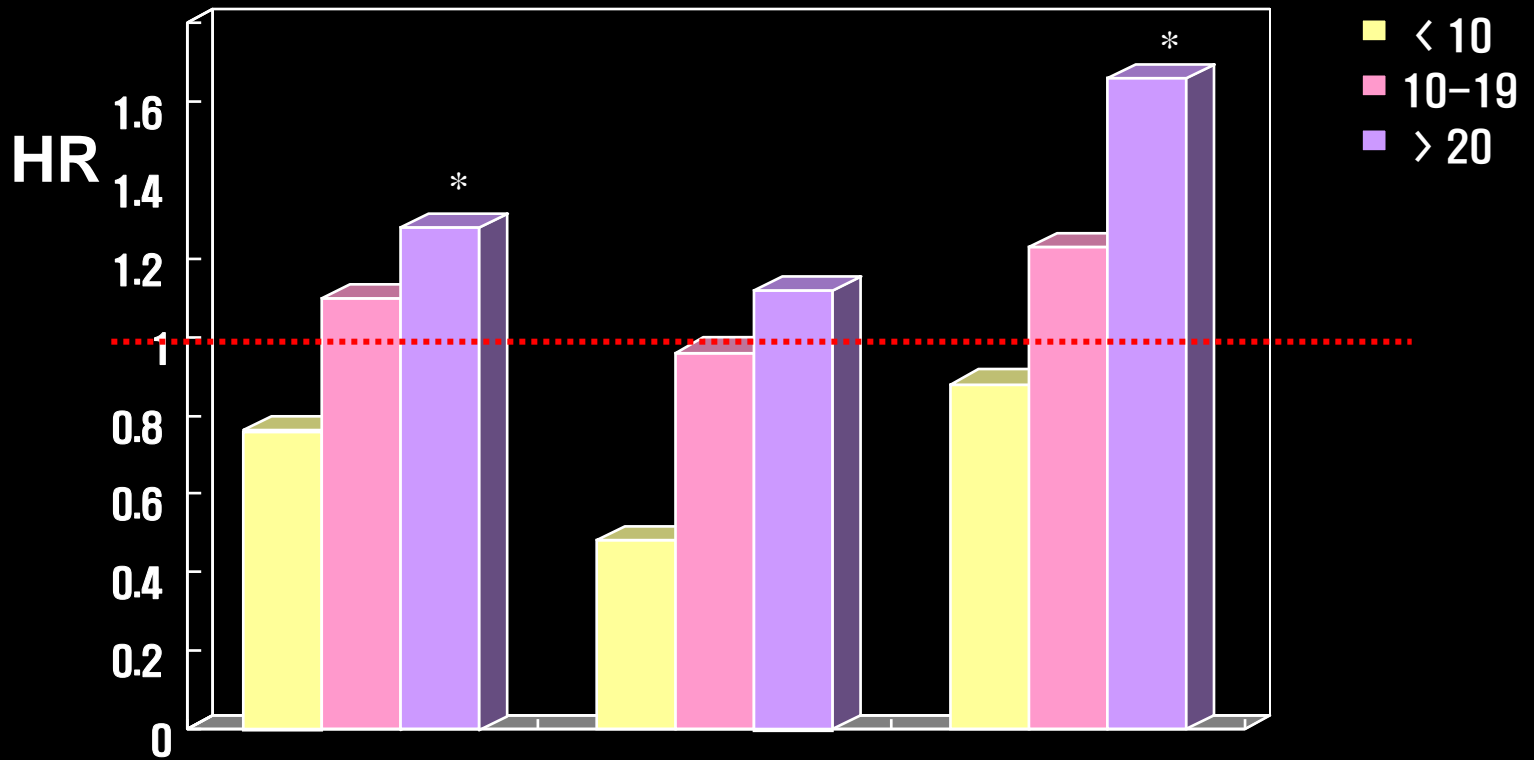
Annualized Percent CHD Events by Year



Year	Hazard Ratio	95% CI
1	1.81	(1.09-3.01)
2	1.34	(0.82-2.18)
3	1.27	(0.64-2.50)
4	1.25	(0.74-2.12)
5	1.45	(0.81-2.59)
6+	0.70	(0.42-1.14)

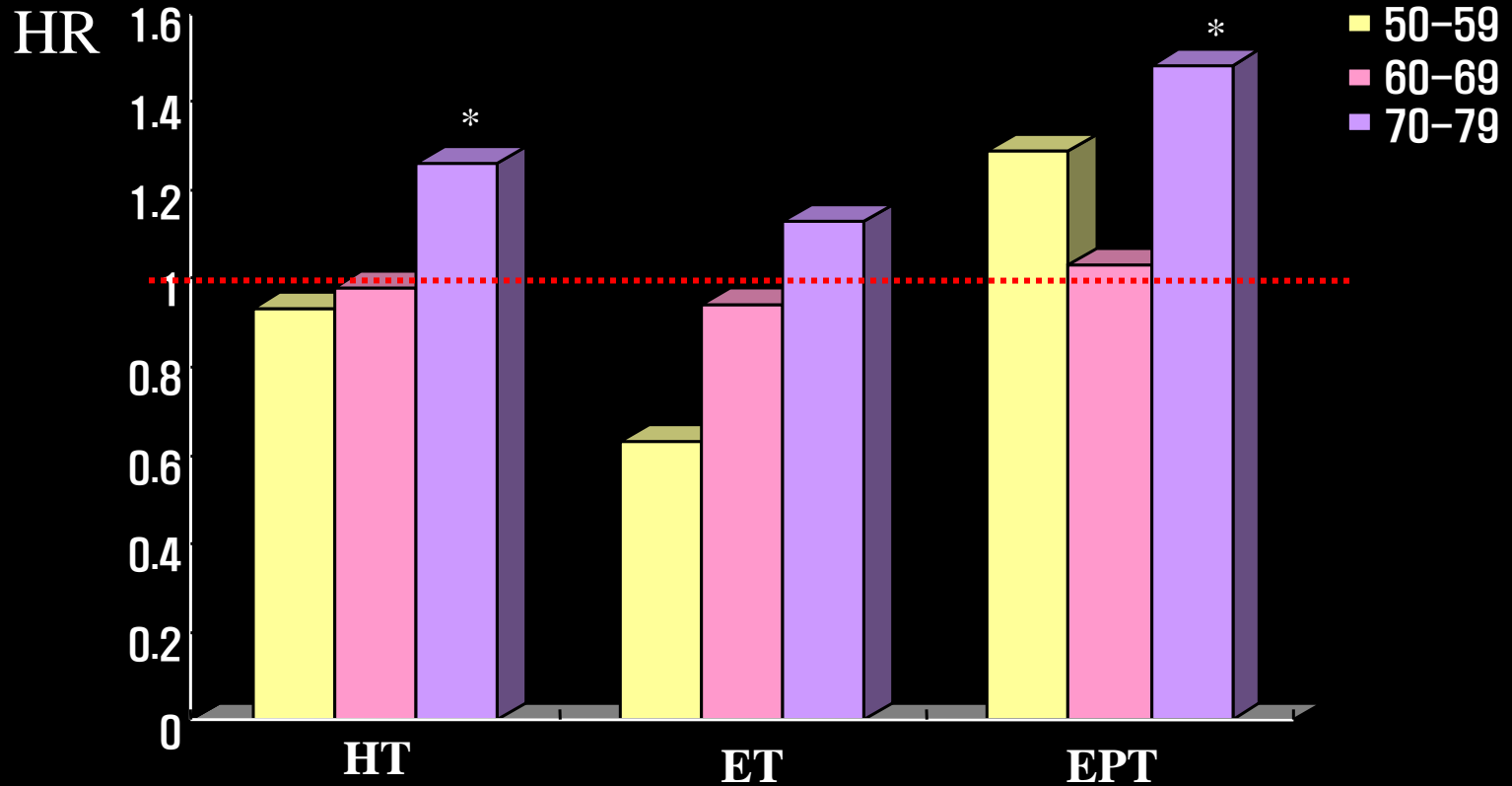
$P = .02$ for trend over time
(z score = -2.36)

WHI : Risk of CHD by YSM



	<10	10~19	≥20	P for trend
total	0.76 (0.50-1.16)	1.10 (0.84-1.45)	1.28 (1.03-1.58)	.02
만명당	-6	+4	+17	

WHI : Risk of CHD by age



	50-59	60-69	70-79	P for trend
total	0.93 (0.65-1.33)	0.98 (0.79-1.21)	1.26 (1.00-1.59)	.16
만명당	-2	-1	+19	

“Timing hypothesis” concept

HRT initiation

age / time since menopause

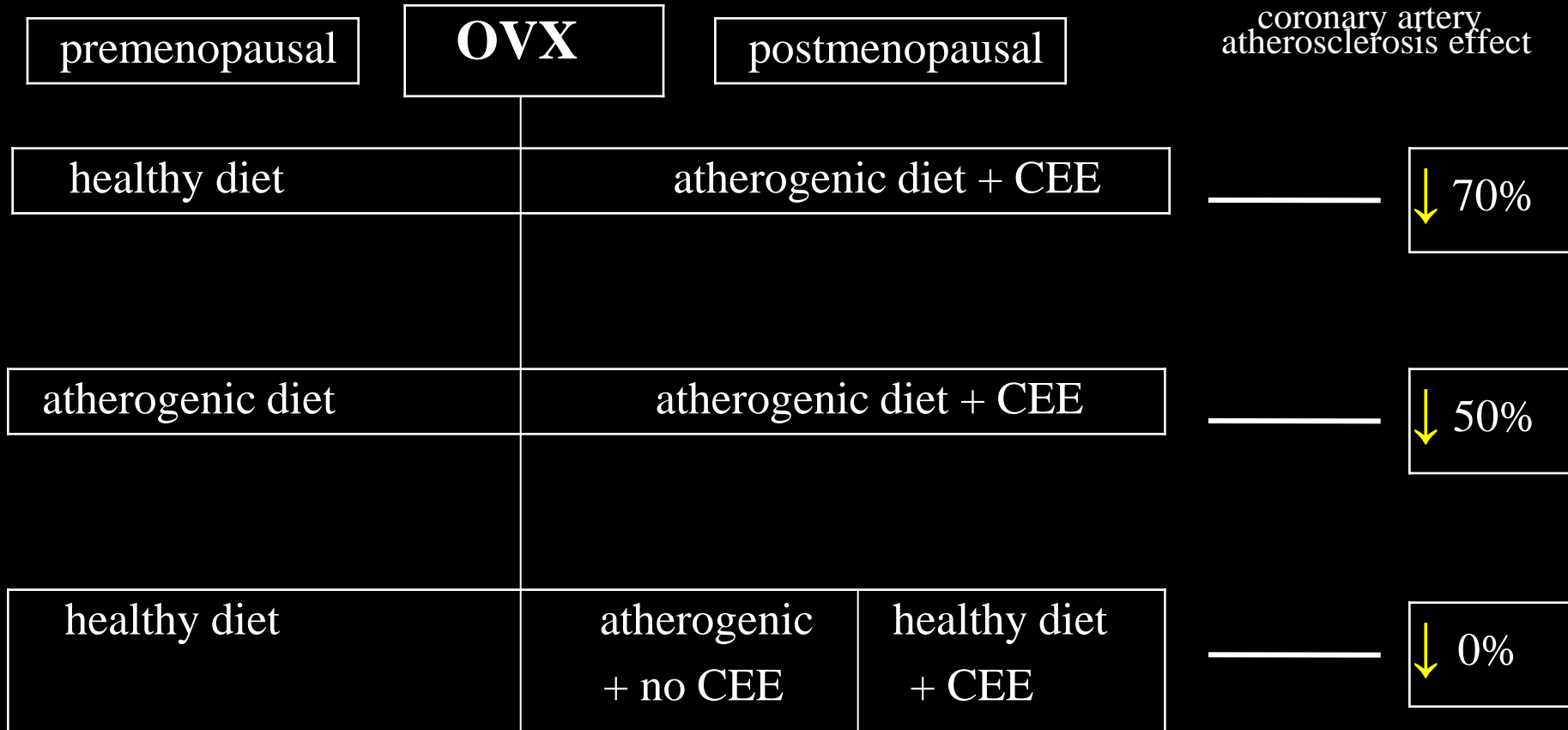
Initiation of HRT in PMW < 60 yrs of age

within 10 yrs of menopause

reduces CHD & total mortality

Rossuw JE JAMA 2007;297:1465

animal study : estrogen-induced inhibition of atherosclerosis



Estrogen in Prevention of Atherosclerosis (EPAT)

healthy PMW

17 β -E₂ 1 mg /d for 2 yrs

CA – IMT : slower progression

reduction in progression of subclinical atherosclerosis

Lipid lowering medication : no effect

Hodis Ann Intern Med 2001;135:939

Nurses' Health Study

HRT & CHD

1976- 2000 follow up

timing of initiation with respect to time since menopause

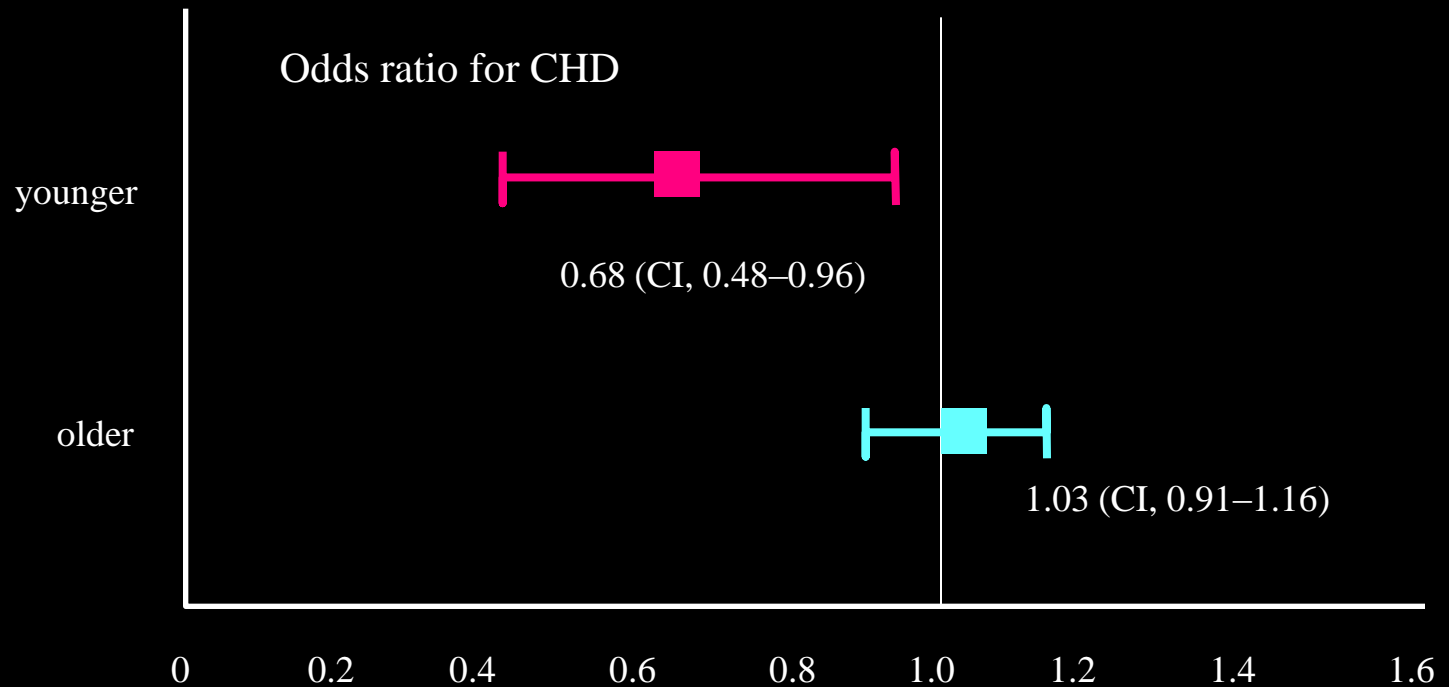
after Menopause	< 4 yrs		> 10 yrs	
	RR	95% CI	RR	95% CI
E	0.66	0.54-0.88	0.87	0.69-1.10
E + P	0.72	0.56-0.92	0.90	0.62-1.29

Grodstein J Women Health 2006:15:35

Meta-analysis

23 RCTs

younger : 폐경 후 10년 이하 / 60세 이하

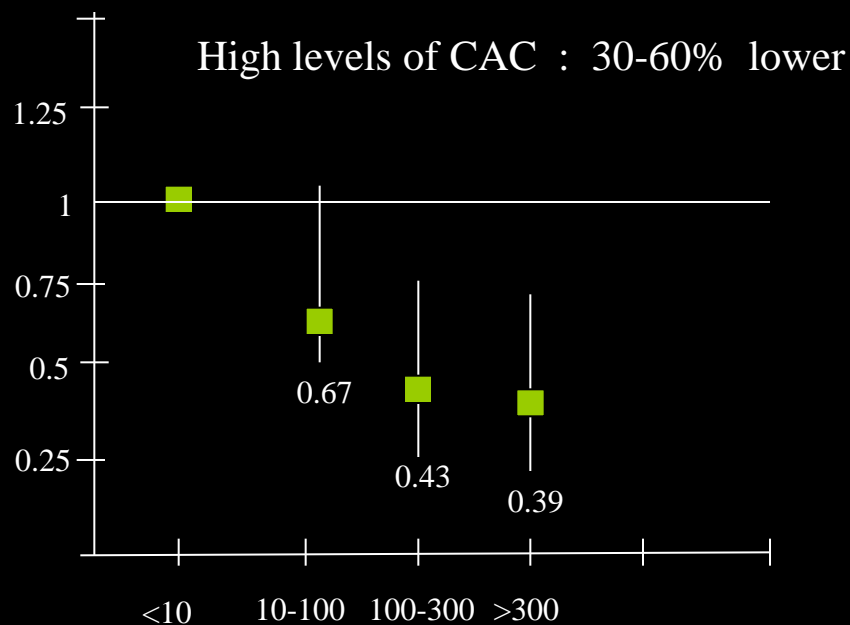


WHI - Coronary Artery Calcium Study (CACS)

ET PMW 50-59 yrs 7.4yrs of TX

Lower mean CAC score

ET	PBO	P value
83.1	123.1	0.02



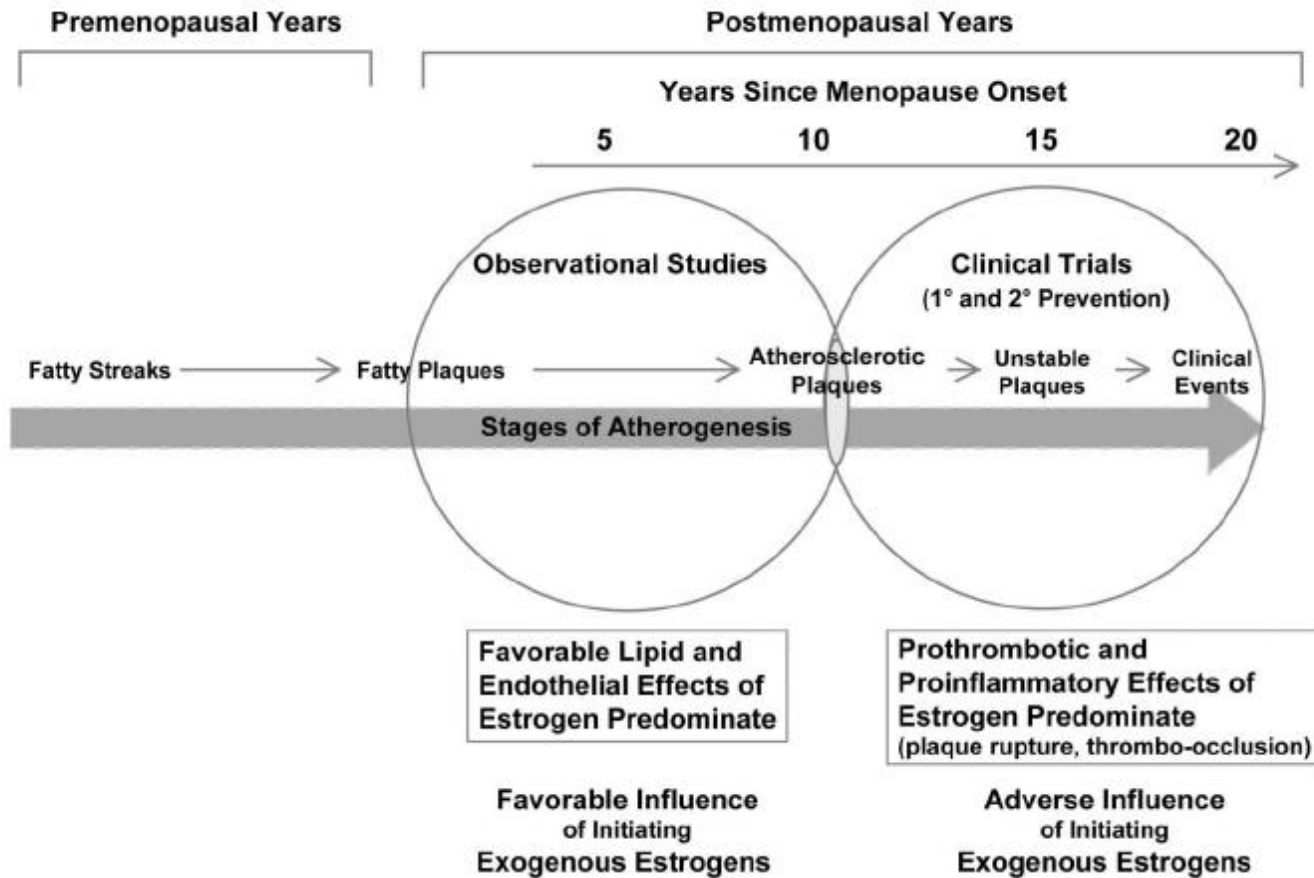
PMW 50-59 yrs on ET

less CAC

lower atheromatous plaque burden

less atherosclerosis

timing of HT initiation



HRT & CHD

HRT is not recommended for primary or secondary prevention of CVD

“ Windows of opportunity concept ”

cardioprotective if started around time of menopause &
continued long-term

PMW < 60 yrs within 10 yrs of menopause

HRT dose not cause early harm &
may reduce CHD risk

Critical window hypothesis

Kronos Early Estrogen Prevention Study(KEEPS)

8 center 720 PMW 42-58yrs, < 3yrs PM
CEE 0.45mg or TD E2 50 μ g + cyclic oral micronized P4
effect on coronary calcium & carotid IMT

Early versus Late Interventional Trial with Estradiol (ELITE)

504 PMW < 6 yrs vs. >10yrs
oral E2 1mg/d + vaginal P. gel
carotid IMT & cognition

WHI : risk of Stroke

	all	Ischemic	Hemorrhagic
EPT	1.31 (1.02-1.68)	1.44 (1.09-1.90)	0.82 (0.43-1.56)
ET	1.37 (1.09-1.73)	1.55 (1.19-2.01)	0.64 (0.35-1.18)

Ischemic stroke : EPT 79.8 %
ET 80.3 %

Wassertheil-Smoller JAMA 2003;289:2673
Hendrix Circulation 2006;113:2425

risk of stroke

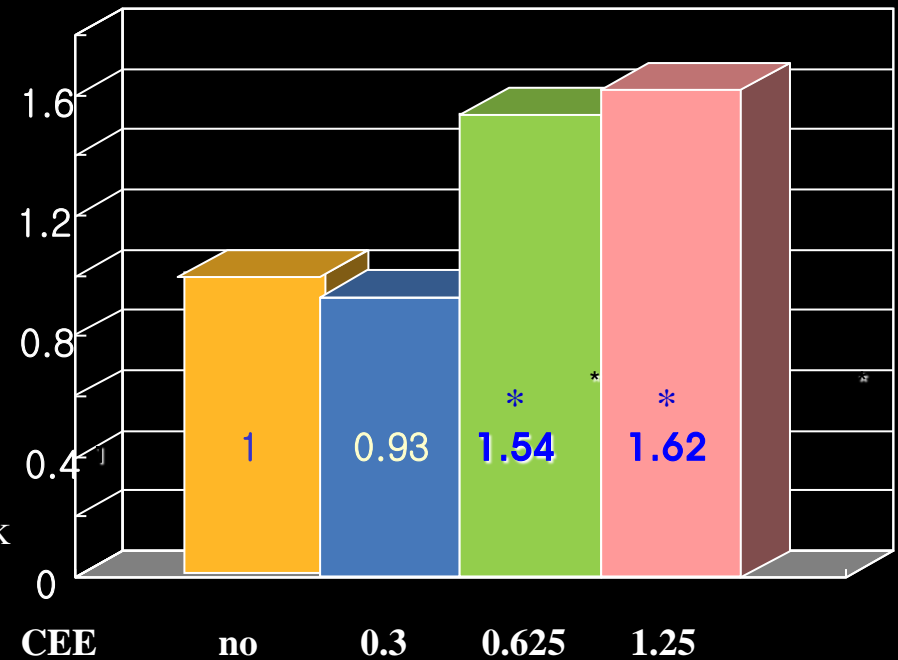
NHS 1976 - 2004

485987 person-yrs (never user) / 409629 (current user)

currents users	RR	95% CI
ET	1.39	1.18-1.63
EPT	1.27	1.04-1.56

initiation	RR	95% CI
Near menopause	1.20	1.06-1.58
≥ 10yrs after menopause	1.31	1.06-1.63

short-term use (< 5y) at young age : no increase risk



P for trend < 0.001

Risk of VTE in EPT trial

	HT	PBO	HR (95% CI)
	absolute risk *		
VTE	+18 (35)	17	2.06 (1.57-2.70)
DVT	+13 (26)	13	1.95 (1.45-2.67)
PE	+10 (18)	8	2.13 (1.45-3.11)

Risk of VTE by age & BMI

age	HR			BMI	HR		
	PBO	EPT	absolute risk		PBO	EPT	absolute risk *
50-59	1.00	2.27	+ 11	< 25	1.0	1.78	+7
60-69	2.31	4.28	+ 16	25-30	1.63	3.80	+20
70-79	3.37	7.46	+ 35	≥ 30	2.87	5.61	+26

*: 10000 person-years

Greater risk with increasing age & weight

VTE

low dose : lower risk than standard dose

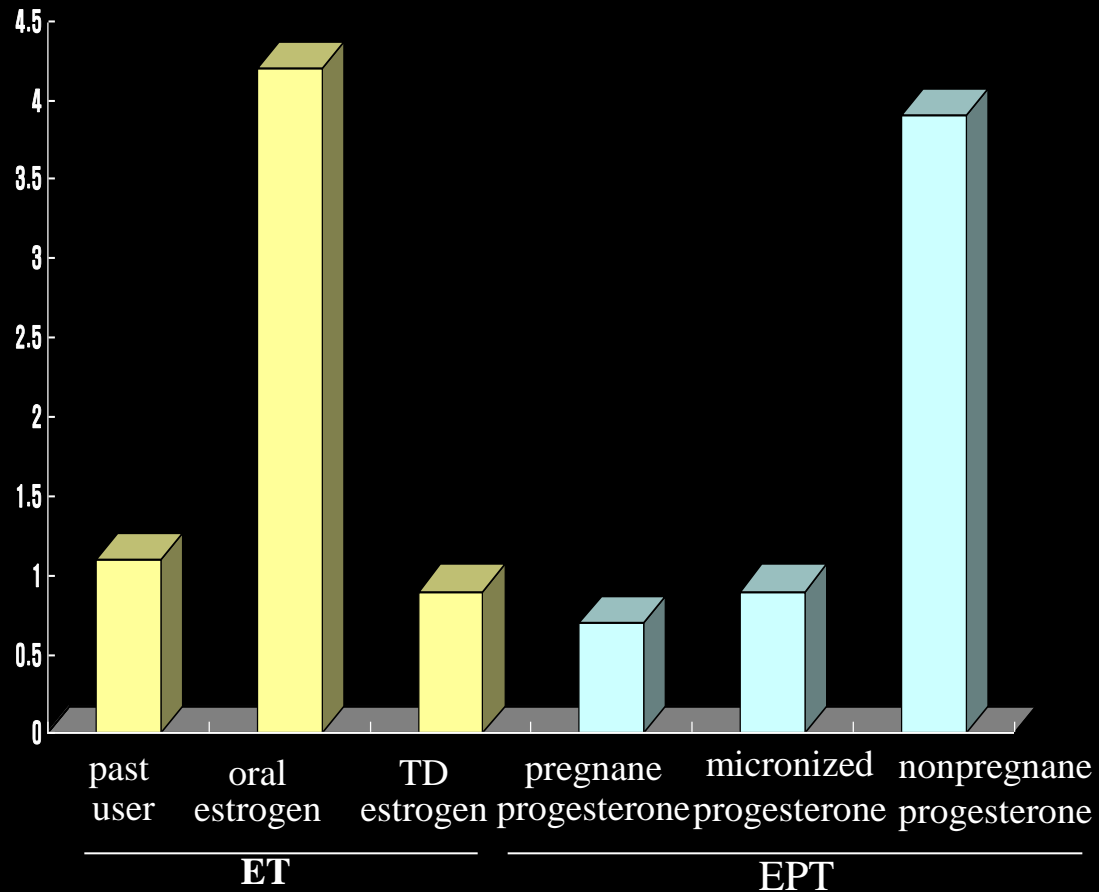
CEE	용량 mg	RR
	1.25	6.9
	0.625	3.3
	0.3	2.1

Jick Lancet 1996

HT & VTE risk

ESTHER study

	OR	95% CI
estrogen use		
Past use	1.1	0.6 – 1.7
Current use		
Oral	4.2	1.5 – 11.6
TD	0.9	0.4 – 2.1
estrogen + progestgen use		
micronized progesterone	0.7	0.3 – 1.9
pregnane derivatives	0.9	0.4 – 2.3
norpregnane derivatives	3.9	1.5 – 10.0



HT & VTE risk

meta-analysis of 9RC trial

	OR	95% CI
oral E	2.1	1.4 – 3.1
high BMI	2.6	2.1 – 3.3
+ oral E	5.4	2.9 – 10.6
+ TD E	no additional risk	
prothrombotic mutation *	3.3	2.6 – 4.1
+ oral E	8.0	5.4 – 11.9
+ TD E	no additional risk	

*factor V Leiden mutation
prothrombin G20210A mutation

TD E may be safer than oral E

Menopause, HRT & CVD

요약

1. 일차 or 이차 예방 : 권유되지 않음
2. 개별화 된 맞춤 치료
 - 1) 치료의 개시 시기
 - 2) 종류 / 용량 / 투여 경로 / 방법

stroke

The risk of stroke is correlated with age

HRT

increased risk of ischemic stroke

“ early initiation effect “ lack of consistent data

younger PMW 50-59yrs : no increase in risk

low-dose / transdermal : no increase

VET

Risk increases with age & obesity

HRT

2-3x increase

occurred within first 2yrs following Tx initiation

lower dose : less risk

TD HRT : no increase