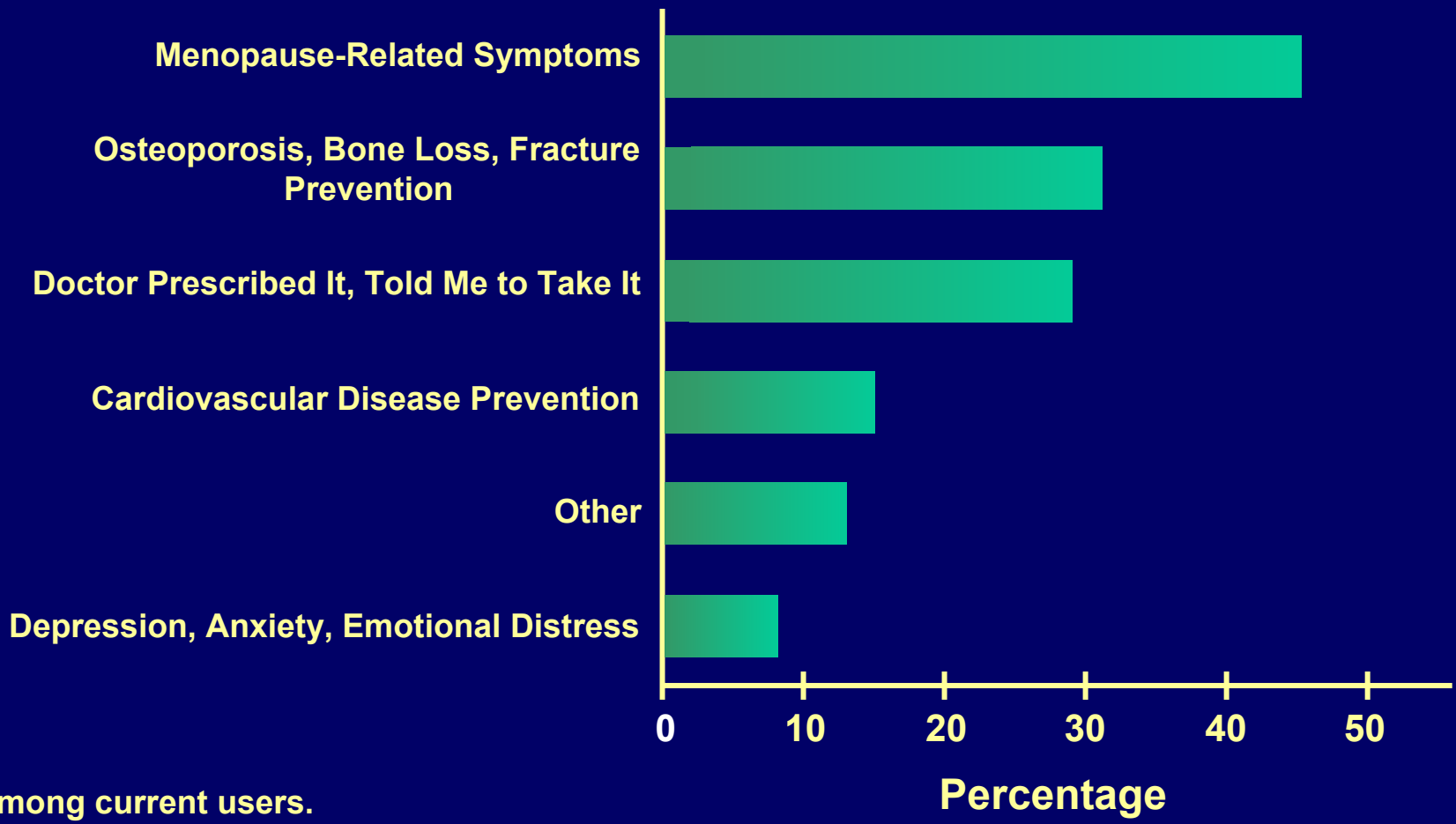
Hormone therapy

Dr. med. Frank Luzuy

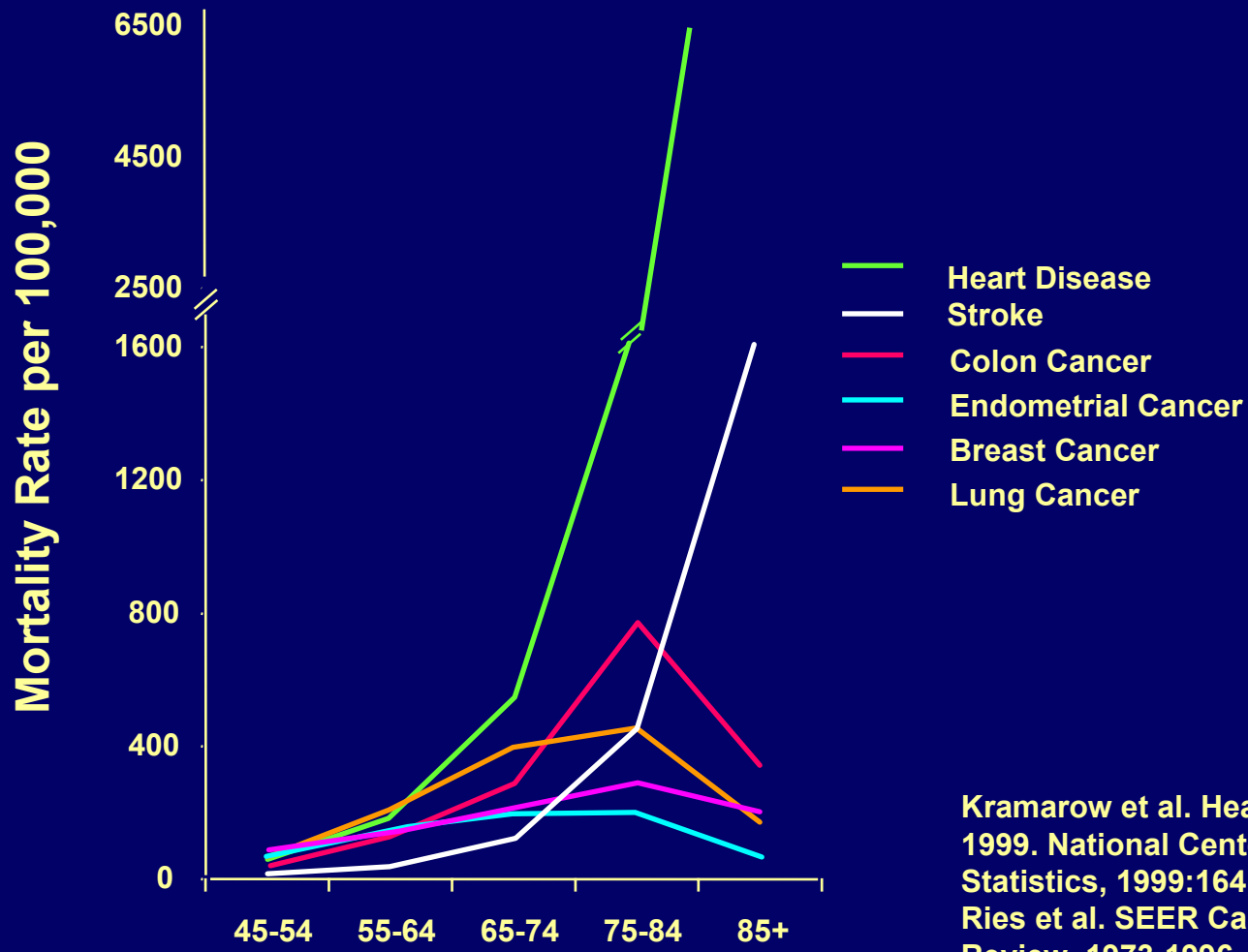
Reasons for Initiating/Continuing HT*



*Among current users.

Newton et al. *J Womens Health* 1997;6:462.

Mortality Rates in Women



Kramarow et al. Health, United States, 1999. National Center for Health Statistics, 1999:164, 167.
Ries et al. SEER Cancer Statistics Review, 1973-1996. National Cancer Institute, 1999.

Benefits and Risks of a HRT

Benefits

- ***improvement of the quality of life during menopause***
  - **vasomotor symptoms**
  - **vaginal atrophy**
  - **dyspareunia**
- ***improvement of the cognitive and mental functions***
- ***prevention of osteoporosis***
- ***prevention of colon cancer***

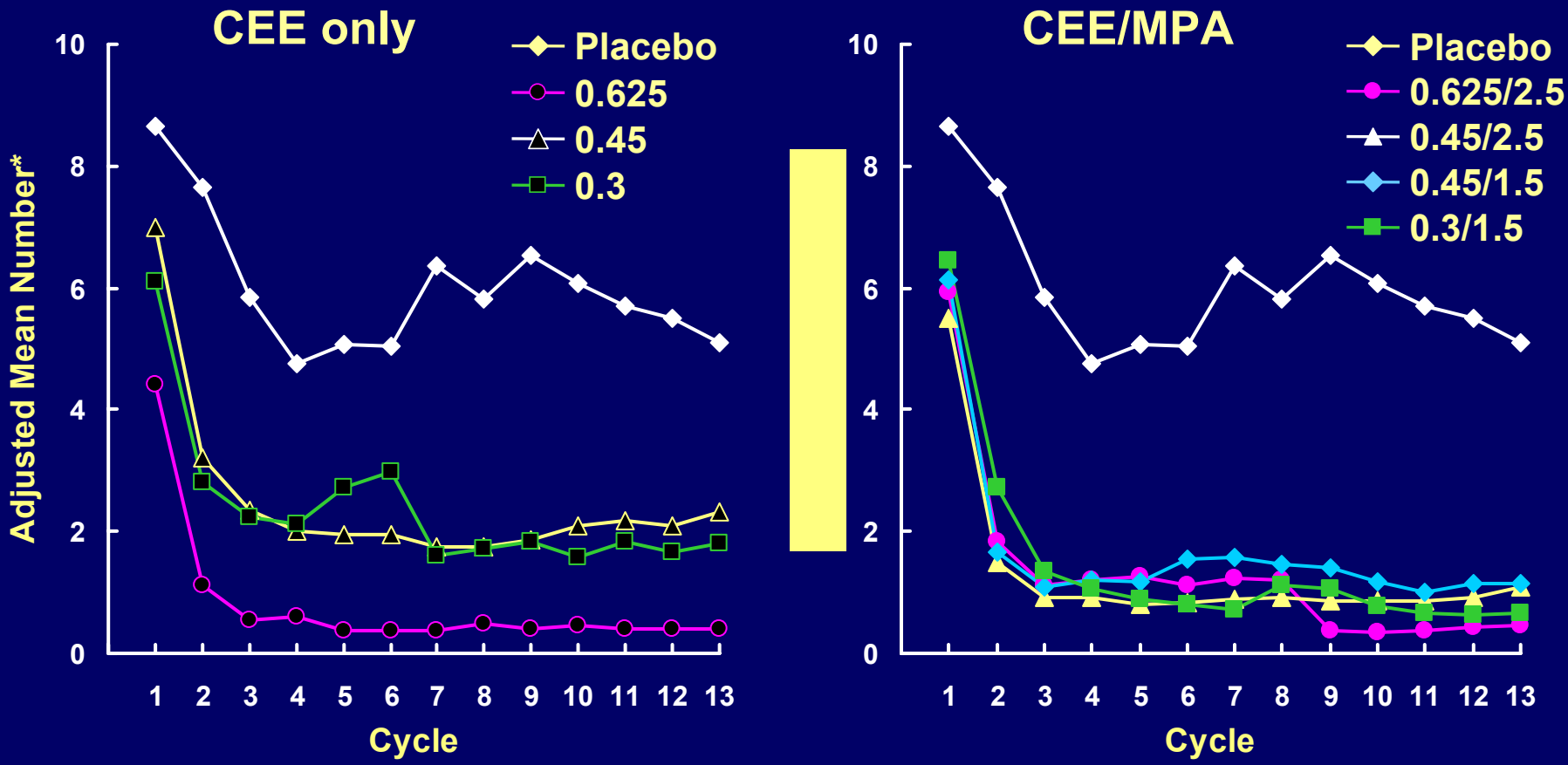
Risks

- ***breast cancer***
- ***thromboembolisms***
- ***cardiovascular risk in elder women***
- ***cerebro-vascular accident (CVA)***

Prevention of Alzheimer ?

Women's HOPE Study

Number of Hot Flushes Over 13 Cycles

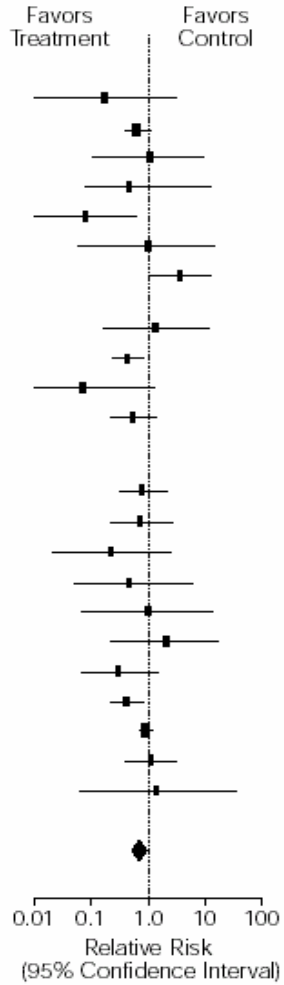


*Adjusted for baseline.
Mean hot flushes at baseline = 12.3 (range 11.3–13.8).

Utian, W, et al. Fertility and Sterility. 2001; 75:1065-1079

HRT: Prevention of non-vertebral fractures meta-analysis (22 studies)

Source, y	No. of Events/ Total No. Treated: Hormone Replacement Therapy	No. of Events/ Total No. Treated: Control	Weight, %	Relative Risk (95% Confidence Interval)*
Aitken et al,[21] 1973	0/68	2/66	0.7	0.19 (0.01-3.97)
Mosekilde et al,[5] 2000	27/502	39/504	14.8	0.70 (0.43-1.12)
Weiss et al,[22] 1999	3/129	1/46	1.3	1.07 (0.11-10.03)
Genant et al,[29] 1997	3/303	2/102	2.0	0.51 (0.09-13.01)
Eiken et al,[23] 1997	1/100	6/51	1.5	0.09 (0.01-0.69)
Cheng et al,[34] 2000	1/40	1/40	0.9	1.00 (0.06-15.44)
Eli Lilly, 2001	12/158	3/152	3.8	3.85 (1.11-13.37)
Bjarnson and Christiansen,[32] 2000	4/112	1/41	1.4	1.46 (0.17-12.72)
Komulainen et al,[9] 1998	13/232	27/232	10.6	0.48 (0.25-0.91)
Nachtigall et al,[18] 1979	0/84	6/84	0.8	0.06 (0-1.34)
Ravn et al,[24] 1999	5/110	39/502	6.4	0.59 (0.24-1.45)
Postmenopausal Estrogen/Progestin Interventions (PEPI),[25] 1996	21/701	6/174	6.5	0.87 (0.36-2.12)
Stevenson and Lees,[35] 2000	10/466	3/110	3.6	0.79 (0.22-2.81)
Delmas et al,[31] 2000	1/90	2/45	1.1	0.25 (0.02-2.68)
Lindsay and Tohme,[33] 1990	1/25	2/25	1.2	0.50 (0.05-5.17)
Wimalawansa,[19] 1998	1/18	1/18	0.9	1.00 (0.07-14.79)
Orr-Walker et al,[27] 2000	2/11	1/12	1.3	2.18 (0.23-20.84)
Alexandersen et al,[20] 1999	2/51	6/49	2.5	0.32 (0.07-1.51)
Herrington et al,[26] 2000	13/204	15/105	9.2	0.45 (0.22-0.90)
Hulley et al,[8] 1998	130/1380	138/1383	24.0	0.94 (0.75-1.19)
Recker et al,[30] 1999	7/64	6/64	5.2	1.17 (0.41-3.28)
Mulnard et al,[28] 2000	1/81	0/39	0.6	1.46 (0.06-35.13)
Total	258/4929	307/3845	100.0	0.73 (0.56-0.94)



significant risk reduction

-27%

Torgerson, D.J, et al. JAMA. 2001; 285:2891-2897

HRT: Prevention of non-vertebral fractures meta-analysis (22 studies)

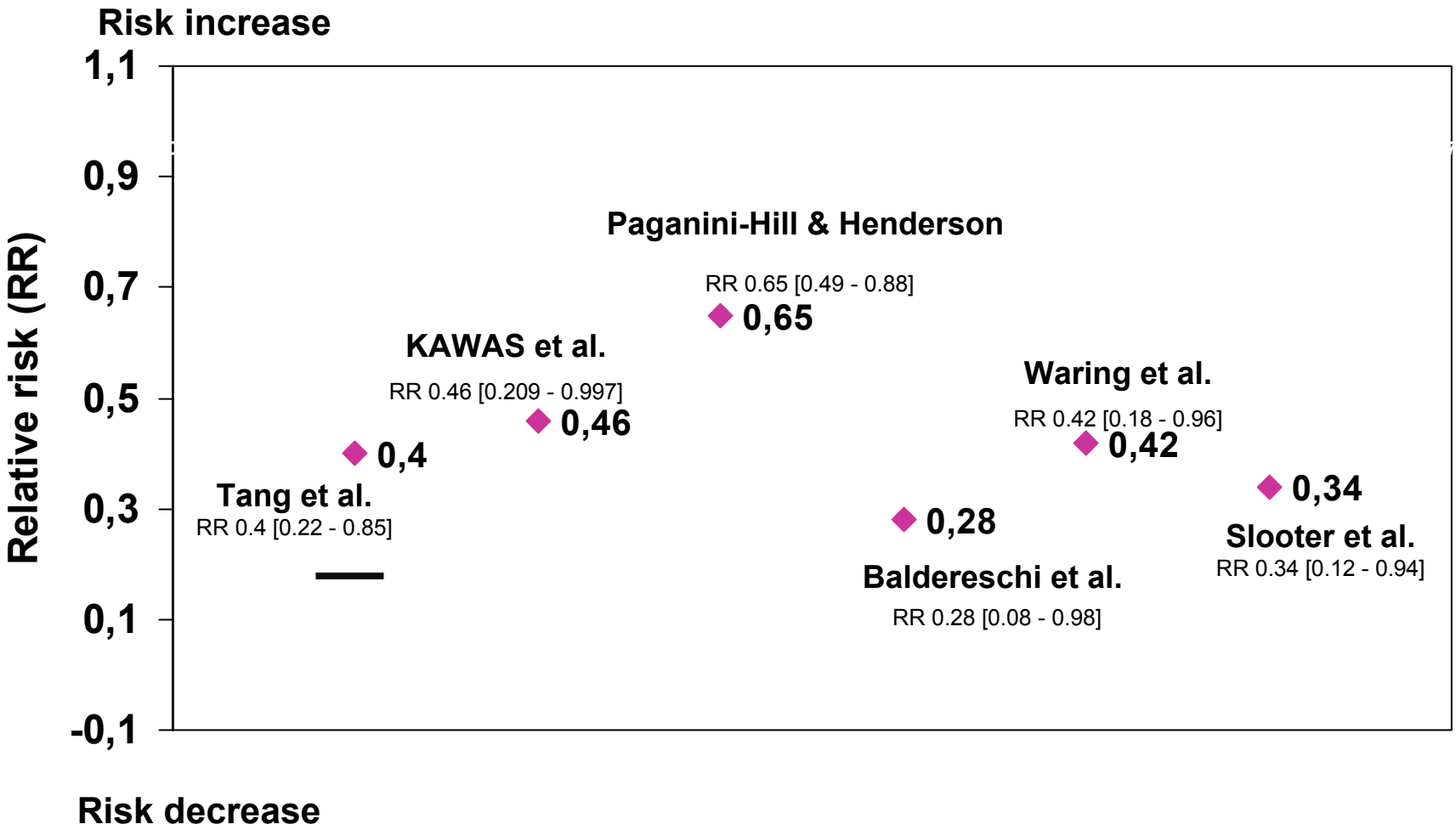
Significant reduction of 27% of non-vertebral hip fractures

- the effect is most striking in women < 60 years, reduction of 35%

Significant reduction of 40% hip and wrist fractures

- the effect is most striking in women < 60 years, reduction of 55%

Prevention Alzheimer's disease by hormone treatment



Römer, T and Langen, L, Menopause-Praxis 2000; 5:3-9

Study of HERS patients:

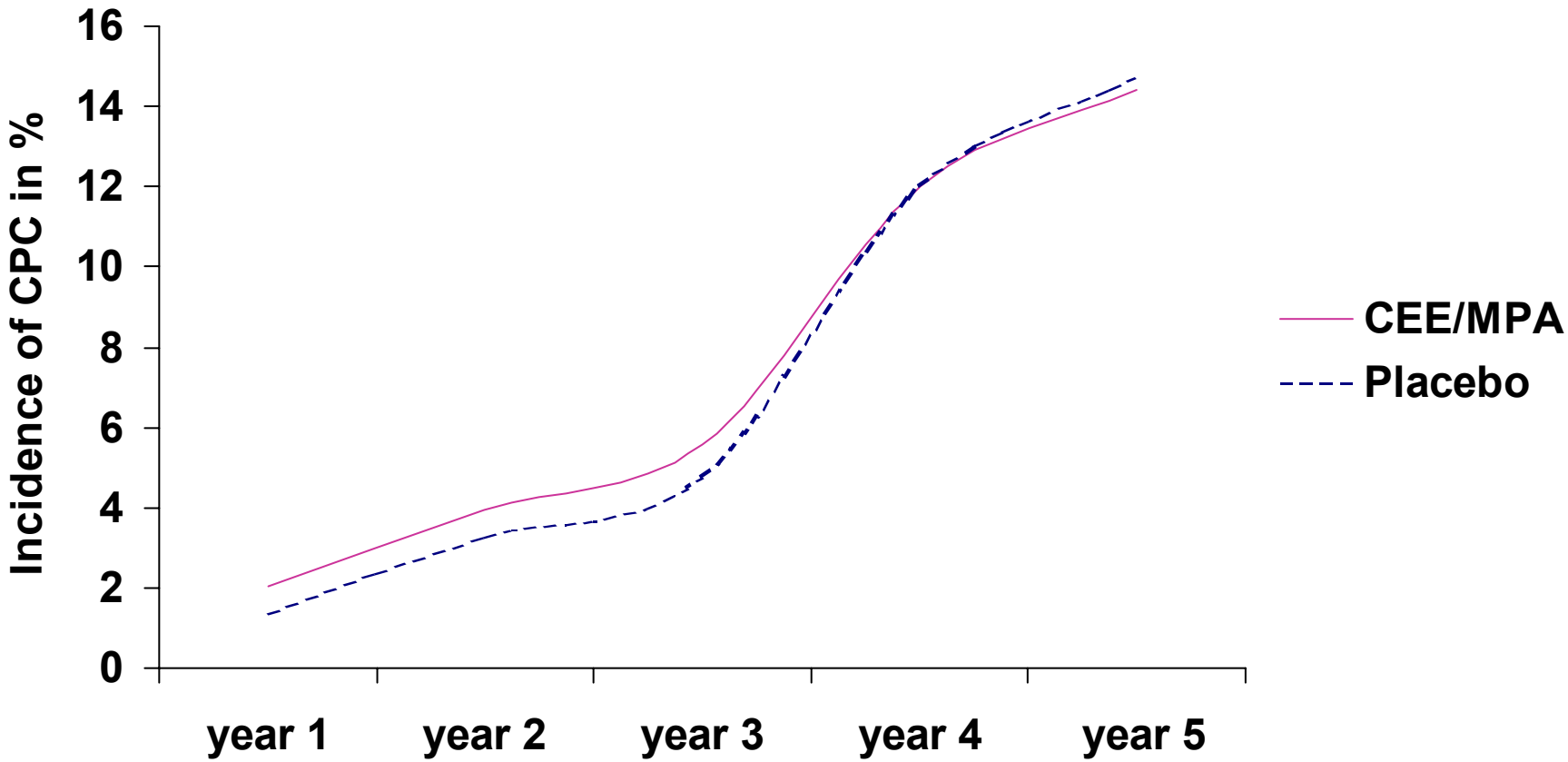
- Age 67 ± 7 years, 89% Caucasian women
- Additional risk factors: diabetes (18%), overweight (55%), smoking (13%)
- Concomitant drugs:

  - Aspirin (78%)
  - beta-blocker (32%)
  - hypolipemiants (45%)
  - diuretics (28%)
  - ECA inhibitors (17%)
  - calcium *a*ntagonists (55%)

- The initial characteristics were comparable

Hulley, S, et al. JAMA. 1998; 280:605-13
Hlatky, M. A, et al. JAMA. 2002; 287:591-597

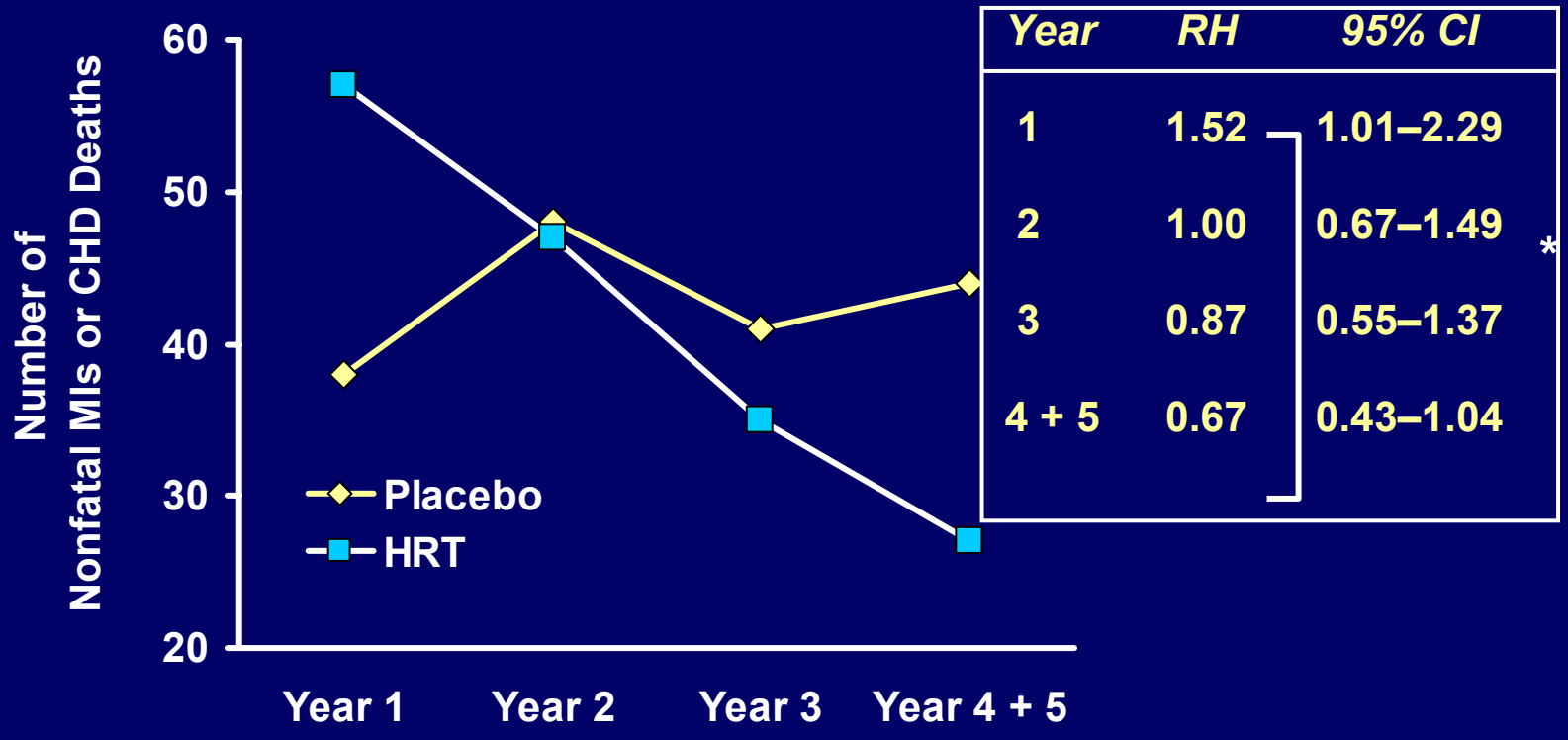
HERS: Additional incidence of CHD under HRT



Adapté selon Hulley, S, et al. *JAMA*. 1998; 280:605-13

Effect of HRT vs Placebo on CHD Events in Women With Established Coronary Disease

HERS

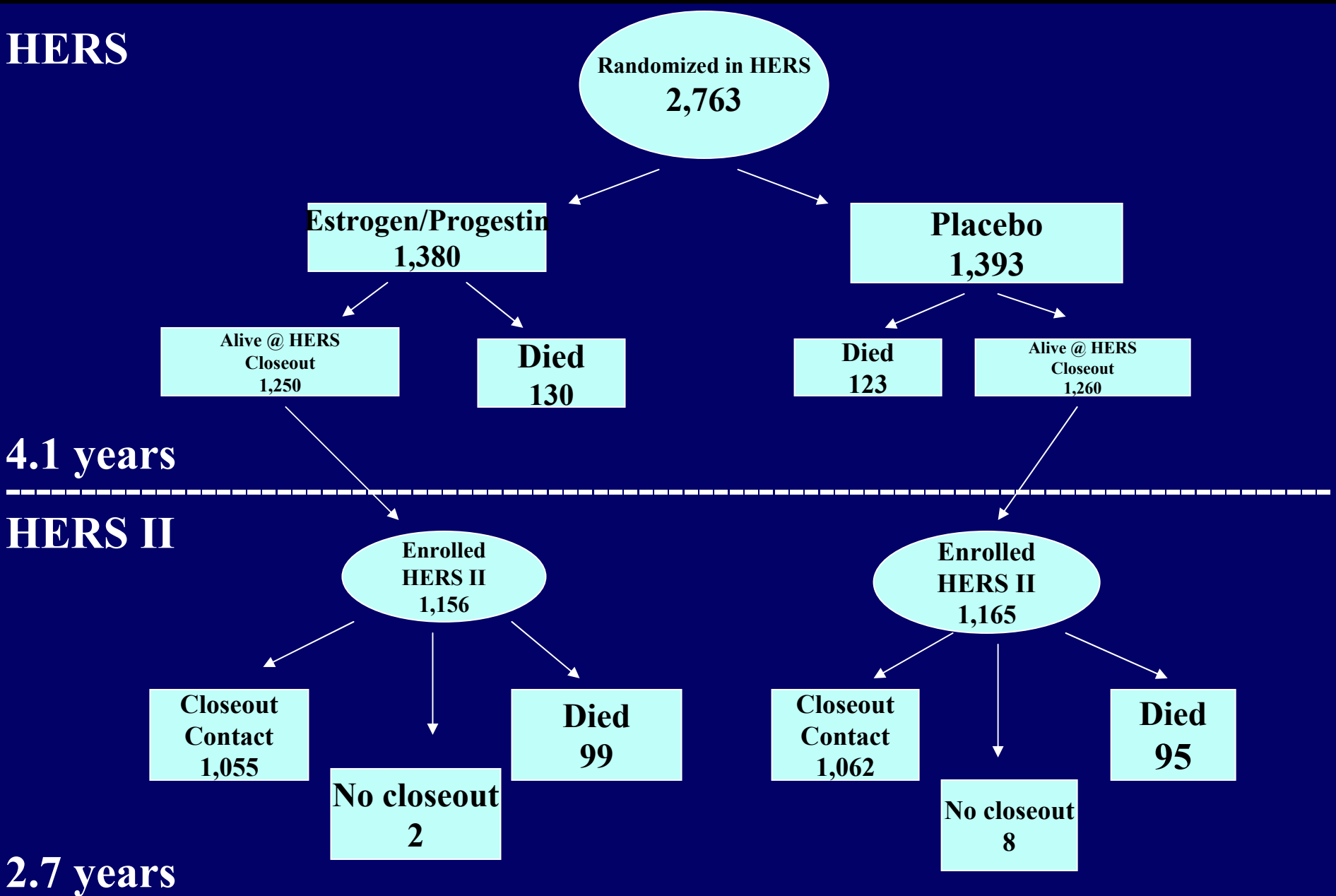


Year	RH	95% CI
1	1.52	1.01–2.29
2	1.00	0.67–1.49
3	0.87	0.55–1.37
4 + 5	0.67	0.43–1.04

*

**P* = .009 for trend in log RH over time.

Hulley S, et al. *JAMA*. 1998;280:605-13.



Grady, D.et al. *JAMA*. 2002

Hulley S, et al. *JAMA*. 2002

In HERS or HERS II, no difference could be established between HRT patients and the placebo group during a CPC event

Results	oestrogen/progestogen	placebo		
primary CPC	**N**	**N**	**RR (95% CI)**	**P**
HERS	179	182	0,99 (0,81-1,22)	0,94
HERS II	111	111	1,00 (0,77-1,29)	0,97
total (HERS + HERS II)	290	293	0,99 (0,84-1,17)	0,93

Relative risk = RR

Grady, D, et al. *JAMA*. 2002; 288:49-57

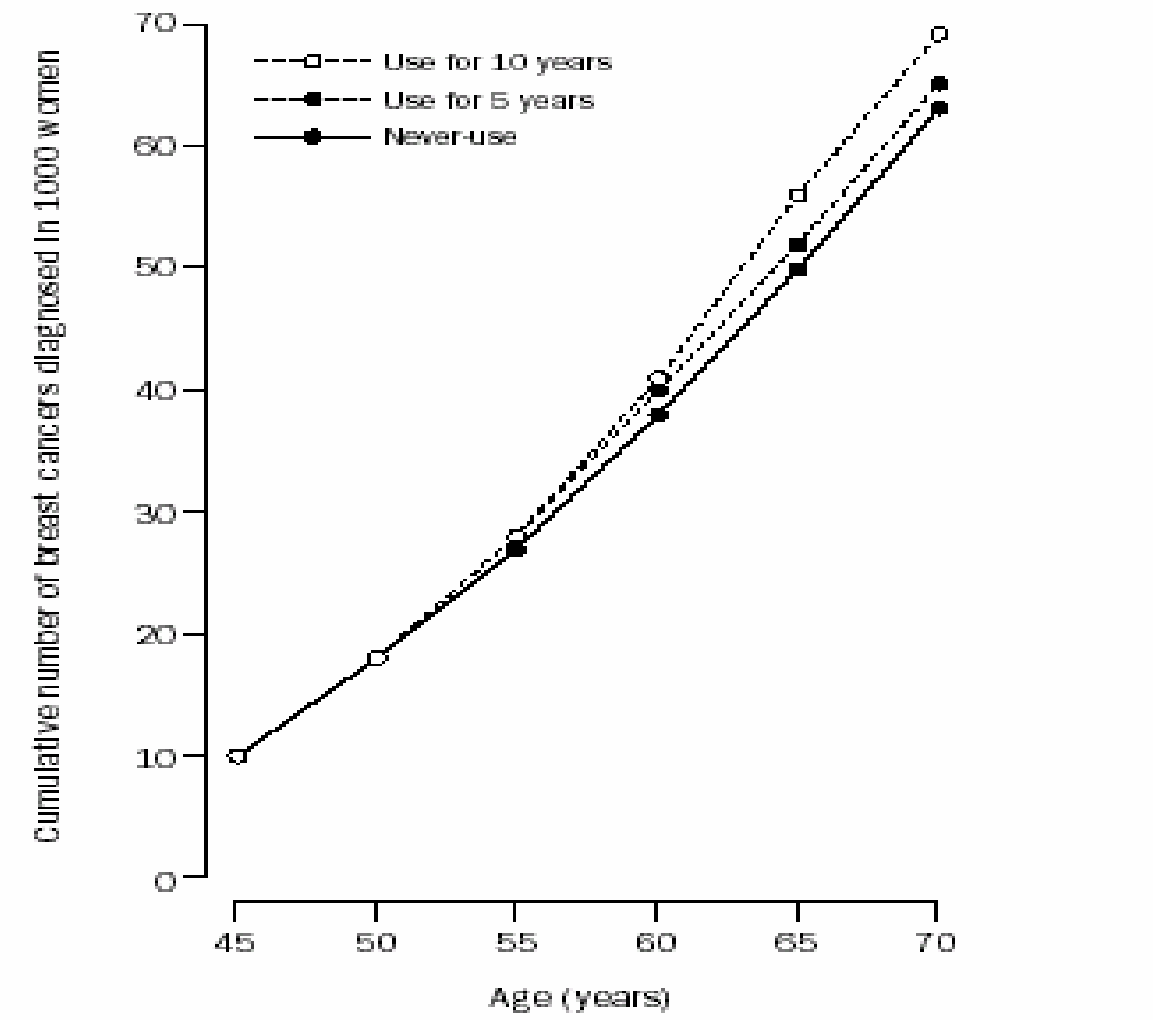
Conclusions - HERS

- **In elder menopausal women with a documented CPC, a HRT is initiated for the sole reason of reducing cardiovascular incidents.**
- ***The patients included in the HERS and HERS II studies were entirely different women who required HRT during early menopause***
  - **most women received concomitant treatment:**

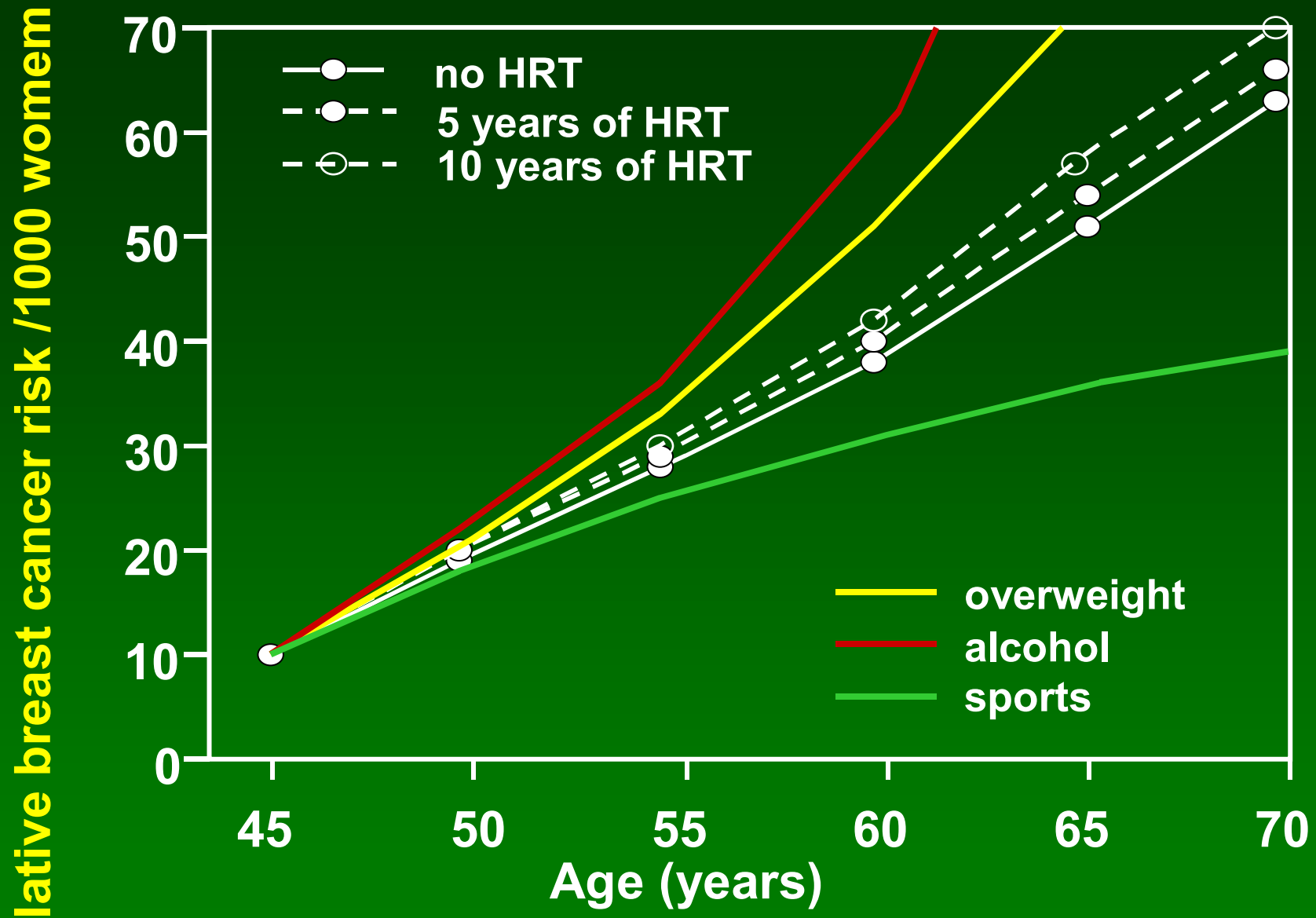
    36% statine, 33% beta-blocker, 80% Aspirin
- ***The HERS II study revealed neither a benefit***

HRT is not indicated for the treatment of CPC!!

HT: Incidence of breast cancer, Beral et al.



Beral et al. Lancet. 1997; 350: 1047-59



Lancet 350, 1997

JAMA, Nov. 5. 1997 Vol 278, No. 17

JAMA, Feb. 18, 1998 Vol 279, No. 7

N. Engl. J.o. Med. 1997 Vol 336, No. 18

Relative Risk for Invasive Breast Cancer in Postmenopausal Women by Alcohol Intake and Postmenopausal Hormone Use 1980-1996

Alcohol intake	*RR*
0.1-4.9 g/d	*1.08*
5.0-9.9 g/d	*1.01*
10-19.9 g/d	*1.24*
>20 g/d	*1.34*

Postmenop. hormone use	*RR*
Past	*0.96*
Current <5 years	*1.39*
Current > 5 years	*1.27*

Ann Intern Med. 2002; 137;798-804

Breast cancer: comparison of HERS, HERSII, WHI study and Beral et al.:

Study	*Breast cancer*		
	Number of additional cases in 1000 women	*Duration of treatment (years)*	*Risk index (IC 95%)*
WHI	*0,8*	*5,2*	*1,26 (0,83-1,92)*
Beral et al.	*2*	*5*	*1,35 (1,21-1,49)*
HERS	*1,7*	*4,1*	*1,38 (0,82-2,31)*
HERS II	*0,4*	*6,8*	*1,08 (0,52-2,24)*
Persson et al.	*NA*	*13,2*	*1,0 (0,8-1,2)*

NA= not studiedé

Writing Group for the Women's Health Initiative Investigators. *JAMA*. 2002;288:321-333.
Hulley, S, et al. JAMA. 2002; 288:58-66
Beral et al. Lancet. 1997; 350: 1047-59
Persson, I, et al. Int.J.Cancer. 1996; 67:327-332

Women's Health Initiative (WHI)

Dr med. Frank Luzuy

WHI
Baseline Characteristics

Characteristic	*HRT n = 8,506*	*Placebo n = 8,102*
Age at screening, yr*	63.2 (7.1)	63.3 (7.1)
Prior hormone use, %	26.1	25.6
Body mass index, kg/m^2*	28.5 (5.8)	28.5 (5.9)
Never smokers, %	49.6	50.0
Diabetes, %	4.4	4.4
Hypertension, %	35.7	36.4
Statin use at baseline, %	6.9	6.8
Family Hx breast cancer, %	16.0	15.3
History of MI†, %	1.6	1.9
History of CABG/PTCA†, %	1.1	1.5‡

*Values are means (SD); †Overall incidence of prior cardiovascular disease = 7.7%; ‡*P* = .04 vs. HRT.

Writing Group for Women's Health Initiative Investigators. *JAMA*. 2002;288:321-333.

WHI Results: CHD
Summary by Year

Year	HRT n (%)	Placebo n (%)	Hazard Ratio*
1	43 (0.51)	23 (0.29)	1.78
2	36 (0.43)	30 (0.38)	1.15
3	20 (0.24)	18 (0.23)	1.06
4	25 (0.32)	24 (0.19)	0.99
5	23 (0.39)	9 (0.16)	2.38
6+	17 (0.33)	18 (0.42)	0.78

n = number of patients; (%) = annualized % calculated from average exposure over ~60 months.
*z score for trend across all years = -1.19; test for trend based on Cox proportional hazard model with time-dependent treatment effects.

Writing Group for Women's Health Initiative Investigators. *JAMA*. 2002;288:321-333.

WHI Results: VTE
Summary by Year

Year	HRT n (%)	Placebo n (%)	Hazard Ratio*
1	49 (0.58)	13 (0.16)	3.60
2	26 (0.31)	11 (0.14)	2.26
3	21 (0.25)	12 (0.15)	1.67
4	27 (0.34)	14 (0.19)	1.84
5	16 (0.27)	6 (0.11)	2.49
6+	12 (0.23)	11 (0.26)	0.90

n = number of patients; (%) = annualized % calculated from average exposure over ~60 months.
*z score for trend across all years = -2.45; test for trend based on Cox proportional hazard model with time-dependent treatment effects. VTE includes DVT and PE.

Writing Group for Women's Health Initiative Investigators. *JAMA*. 2002;288:321-333.

WHI Results: Invasive Breast Cancer

Summary by Year

Year	HRT n (%)	Placebo n (%)	Hazard Ratio*
1	11 (0.13)	17 (0.21)	0.62
2	26 (0.31)	30 (0.38)	0.83
3	28 (0.34)	23 (0.29)	1.16
4	40 (0.50)	22 (0.29)	1.73
5	34 (0.57)	12 (0.22)	2.64
6+	27 (0.53)	20 (0.47)	1.12

n = number of patients; (%) = annualized % calculated from average exposure over ~60 months.
*z score for trend across all years = 2.56; test for trend based on Cox proportional hazard model with time-dependent treatment effects.

Writing Group for Women's Health Initiative Investigators. *JAMA*. 2002;288:321-333.

WHI Results: Cancer Outcomes

Outcome	*HRT n (%)**	*Placebo n (%)**	*Hazard Ratio*	*Nominal 95% CI*	*Adjusted 95% CI*
Cancer					
Invasive breast	**166 (0.38)**	**124 (0.30)**	**1.26**	**1.00-1.59**	**0.83-1.92**
Endometrial	**22 (0.05)**	**25 (0.06)**	**0.83**	**0.47-1.47**	**0.29-2.32**
Colorectal	**45 (0.10)**	**67 (0.16)**	**0.63**	**0.43-0.92**	**0.32-1.24**
Total	**502 (1.14)**	**458 (1.11)**	**1.03**	**0.90-1.17**	**0.86-1.22**

***n = number of patients; (%) = annualized % calculated from average exposure over ~60 months. Nominal = variability based on simple trial for single outcome; Adjusted = corrects variability for multiple analyses over time.**

Writing Group for Women's Health Initiative Investigators. *JAMA*. 2002;288:321-333.

WHI Results

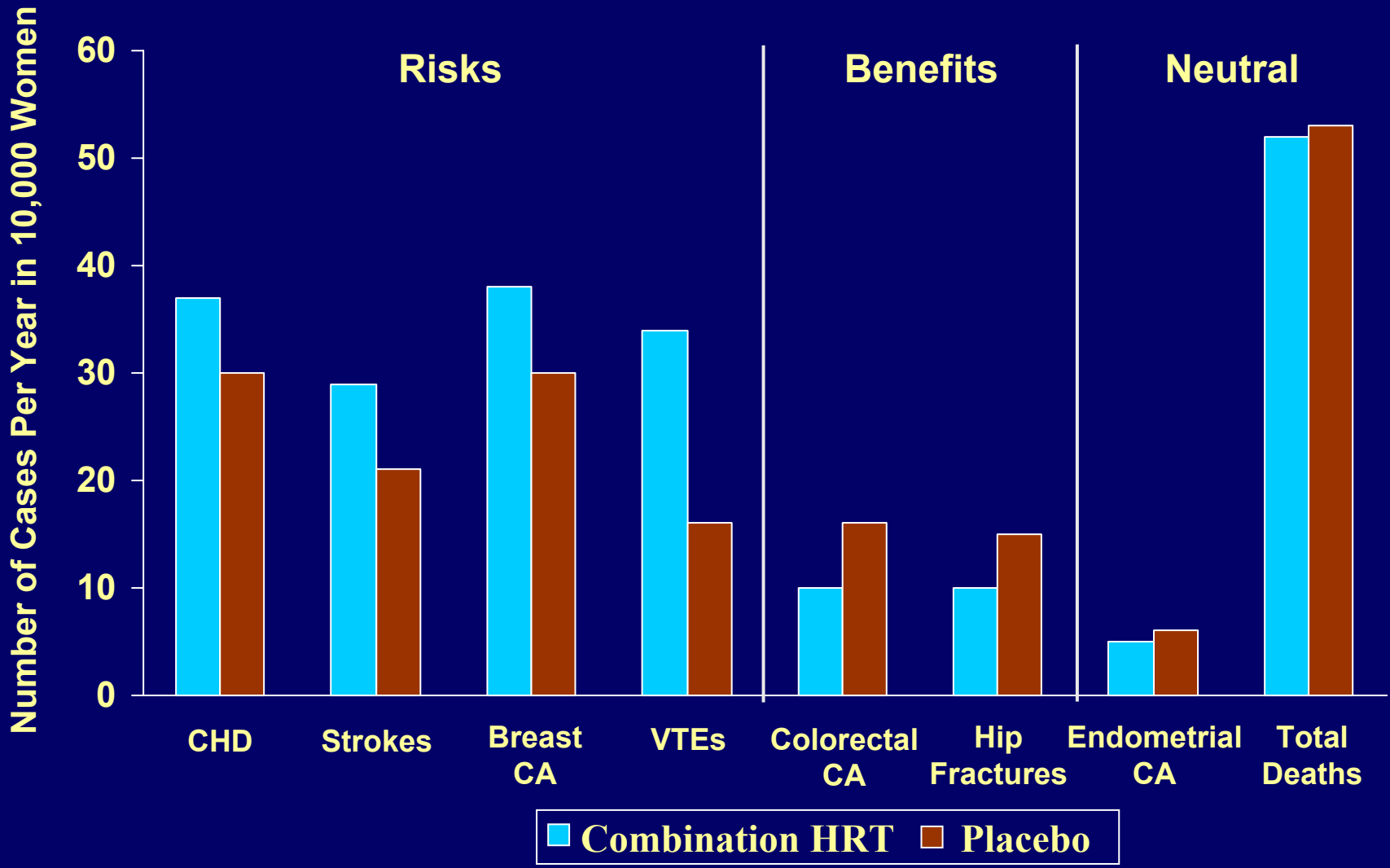
Absolute and Relative Risk or Benefit of HRT

Health Event	*Relative Risk vs. Placebo at 5.2 years*	*Increased Absolute Risk per 10,000 Women/Yr*	*Difference Betweens the groups*
Heart attacks	**1.29**	**7**	***0.40***
Strokes	**1.41**	**8**	***0.45***
Breast cancer	**1.26**	**8**	***0.42***
VTEs	**2.11**	**18**	***2.15***
Colorectal cancer	**0.63**		**0.29**
Hip fractures	**0.66**		**0,25**

Writing Group for Women's Health Initiative Investigators. *JAMA*. 2002;288:321-333.

WHI

Disease Rates for Women on HRT or Placebo



Adapted from *WHI HRT Update*, June 2002.

WHI Results: CVD Outcomes

Outcome	HRT n (%)*	Placebo n (%)*	Hazard Ratio	Nominal 95% CI	Adjusted 95% CI
CHD	164 (0.37)	122 (0.30)	1.29	1.02-1.63	0.85-1.97
CHD death	33 (0.07)	26 (0.06)	1.18	0.70-1.97	0.47-2.98
Nonfatal MI	133 (0.30)	96 (0.23)	1.32	1.02-1.72	0.82-2.13
CABG/PTCA	183 (0.42)	171 (0.41)	1.04	0.84-1.28	0.71-1.51
Stroke	127 (0.29)	85 (0.21)	1.41	1.07-1.85	0.86-2.31
Fatal	16 (0.04)	13 (0.03)	1.20	0.58-2.50	0.32-4.49
Nonfatal	94 (0.21)	59 (0.14)	1.50	1.08-2.08	0.83-2.70
VTE disease	151 (0.34)	67 (0.16)	2.11	1.58-2.82	1.26-3.55
Deep vein thrombosis	115 (0.26)	52 (0.13)	2.07	1.49-2.87	1.14-3.74
Pulmonary embolism	70 (0.16)	31 (0.08)	2.13	1.39-3.25	0.99-4.56
Total CVD	694 (1.57)	546 (1.32)	1.22	1.09-1.36	1.00-1.49

*n = number of patients; % = annualized % calculated from average exposure over ~60 months. Nominal = variability based on simple trial for single outcome; Adjusted = corrects variability for multiple analyses over time.

Writing Group for Women's Health Initiative Investigators. *JAMA*. 2002;288:321-333.

WHI Results: Death and Global Index

Outcome	*HRT n (%)**	*Placebo n (%)**	*Hazard Ratio*	*Nominal 95% CI*	*Adjusted 95% CI*
Death					
Due to other causes	**165 (0.37)**	**166 (0.40)**	**0.92**	**0.74-1.14**	**0.62-1.35**
Total	**231 (0.52)**	**218 (0.53)**	**0.98**	**0.82-1.18**	**0.70-1.37**
Global Index†	**751 (1.70)**	**623 (1.51)**	**1.15**	**1.03-1.28**	**0.95-1.39**

***n = number of patients; (%) = annualized % calculated from average exposure over ~60 months. Nominal = variability based on simple trial for single outcome; Adjusted = corrects variability for multiple analyses over time.**

†Represents the first event for each participant from among the following types: CHD, stroke, PE, breast cancer, endometrial cancer, colorectal cancer, hip fracture, and death due to other causes.

Writing Group for Women's Health Initiative Investigators. *JAMA*. 2002;288:321-333.

WHI Results: Fracture Outcomes

Outcome	*HRT n (%)**	*Placebo n (%)**	*Hazard Ratio*	*Nominal 95% CI*	*Adjusted 95% CI*
Fractures					
Hip	**44 (0.10)**	**62 (0.15)**	**0.66**	**0.45-0.98**	**0.33-1.33**
Vertebral	**41 (0.09)**	**60 (0.15)**	**0.66**	**0.44-0.98**	**0.32-1.34**
Other osteoporotic†	**579 (1.31)**	**701 (1.70)**	**0.77**	**0.69-0.86**	**0.63-0.94**
Total	**650 (1.47)**	**788 (1.91)**	**0.76**	**0.69-0.85**	**0.63-0.92**

***n = number of patients; (%) = annualized % calculated from average exposure over ~60 months. Nominal = variability based on simple trial for single outcome; Adjusted = corrects variability for multiple analyses over time.**

†Includes all fractures other than chest/sternum, skull/face, fingers, toes, and cervical vertebrae, as well as hip and vertebral fractures reported separately.

Writing Group for Women's Health Initiative Investigators. *JAMA*. 2002;288:321-333.

WHI Conclusions I

- **No significant improvement of the breast cancer risk and of CPC was found during a treatment of oestrogen only.**
- **In the combined treatment, the risk of breast cancer did not increase for four years.**
- **The combined treatment need not persued or initiated to prevent secondary cardiopathies.**
- **A purely primary cardiovascular prevention has not been studied.**
- **The average age (63 years) does not correspond to the usual age, at which the treatment is initiated in the female Swiss population.**
-

WHI Conclusions II

- **The profile of the patients chosen for the study was unusual.**
- **In order to prevent osteoporosis, women may consult their doctors to evaluate the benefits against their personal risks of a myocardial infarction, CVA, thrombosis and breast cancer; there are alternative therapies for the prevention of osteoporosis and fractures.**
- **Short-term treatments of menopause-related symptoms have not been studied.**
- **Data are no longer available for other combinations and doses.**

National Institutes of Health: National Heart, Lung, and Blood Institute: *New Facts About: Estrogen/Progestin Hormone Therapy*. July 9, 2002.

Conclusion

Bush T.L., Whiteman M.K.

Hormone replacement therapy and risk of breast cancer.

Jama, 1999; 281 : 2140-2141

« A potential risk improvement, if it exists at all, will be less important or will apply only to a limited population; otherwise it would have been observed more consistently in most epidemiological studies performed with a satisfactory methology. »