

# **SERMS (Raloxifene) and Tibolone**

**Professor Steven R. Cummings, MD**  
**San Francisco Coordinating Center**

**Consultations, honoraria: Lilly, Pfizer, Organon**

# Raloxifene

SF<sub>6</sub> coordinating center

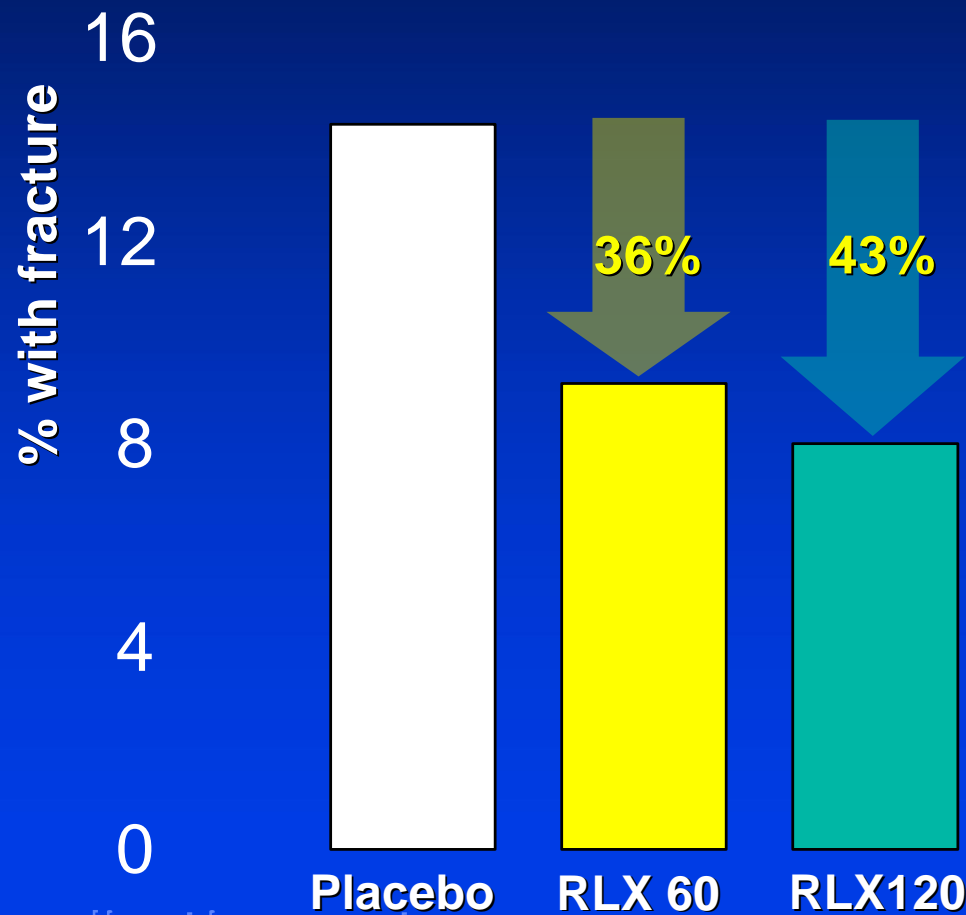
## MORE

- 7,705 women with osteoporosis
- Placebo vs. 60 or 120mg raloxifene for 4 years

## RUTH

- 10,101 women at high risk of CVD
- Placebo vs. 60 mg raloxifene for 5 years

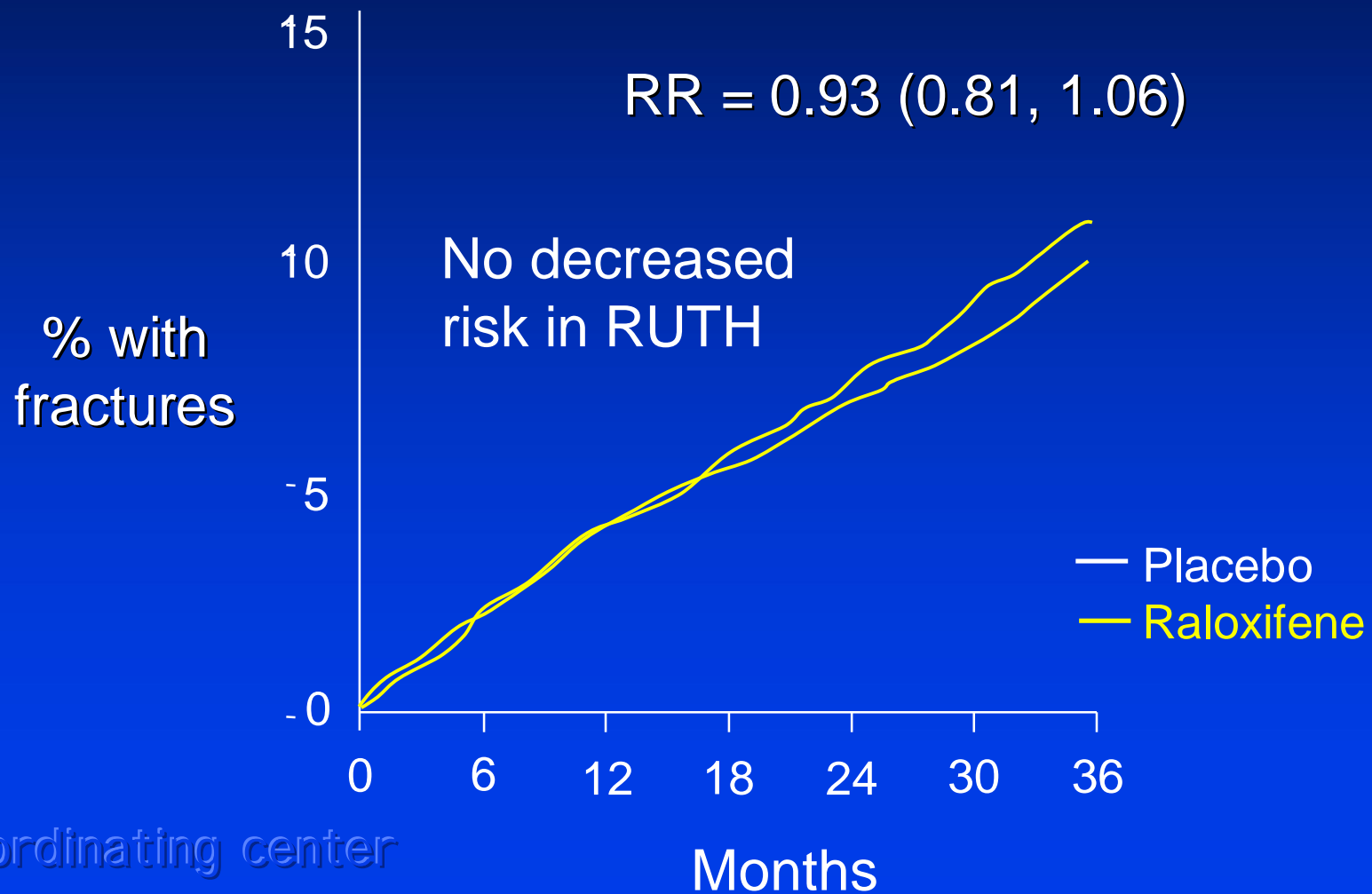
# MORE: 4 years of Raloxifene decreased the risk of vertebral fracture\*



RUTH trial

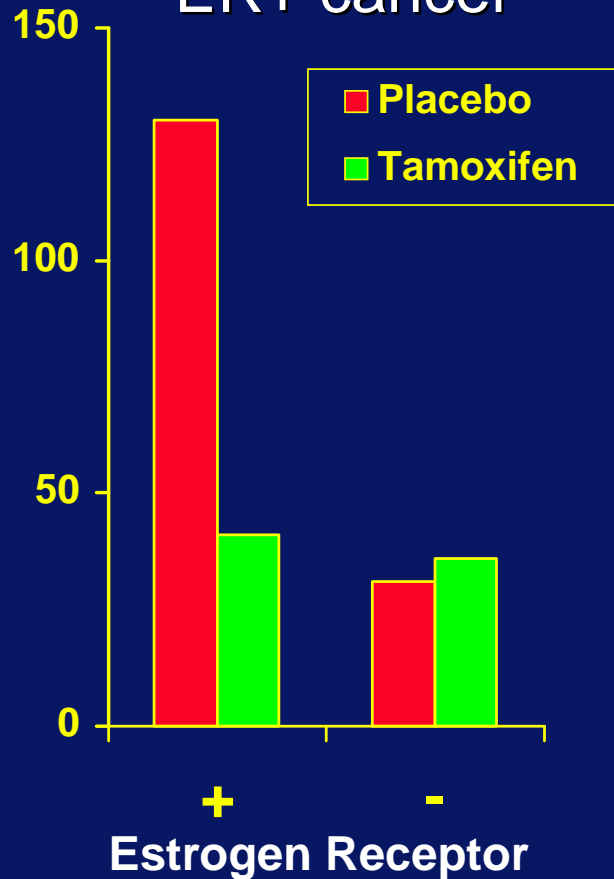
- 35% decreased risk of clinical vertebral fracture

# 4 years of raloxifene did not decrease the risk of non-spine fractures

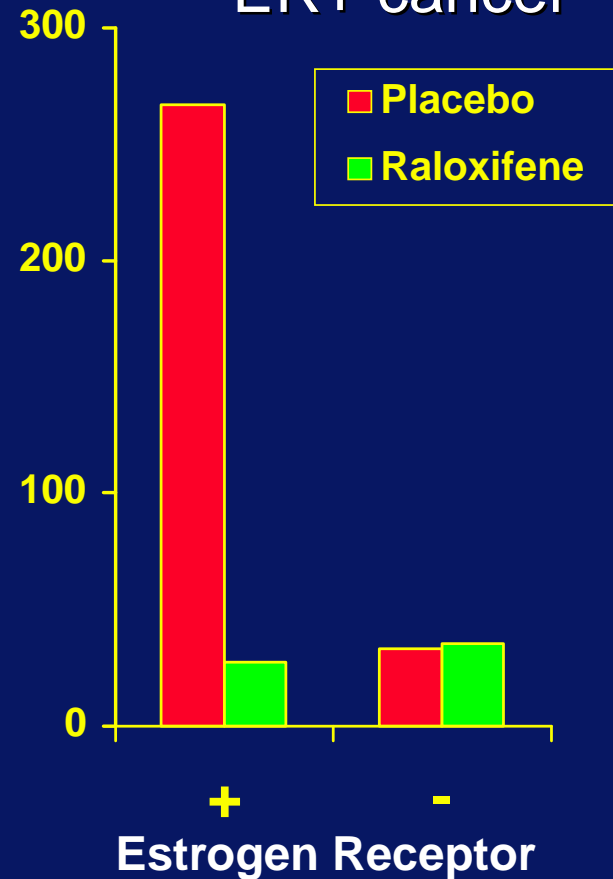


# Tamoxifen and raloxifene reduce the risk of ER+ breast cancer

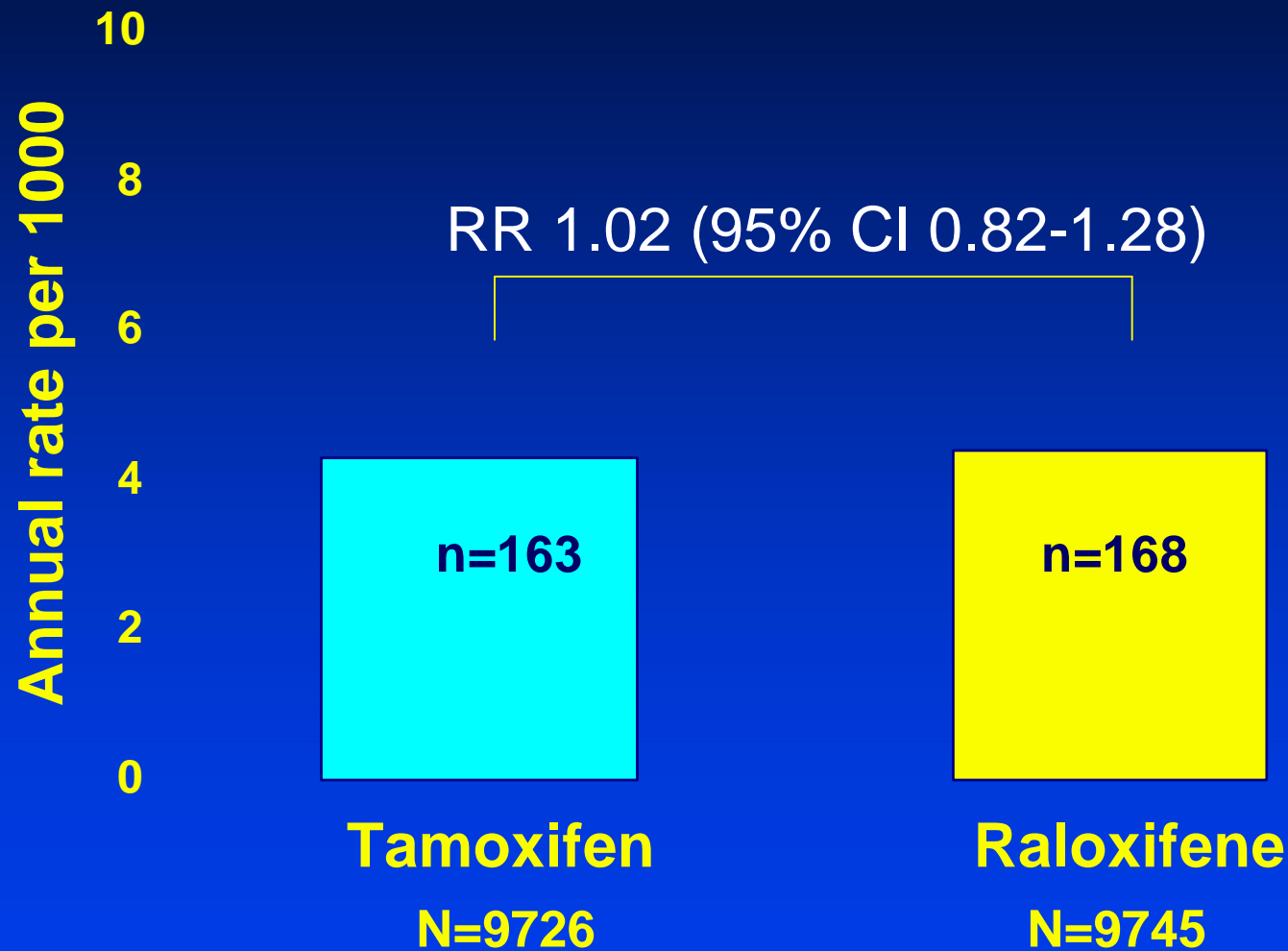
Tamoxifen:  
76% decreased  
ER+ cancer



Raloxifene  
84% decreased  
ER+ cancer

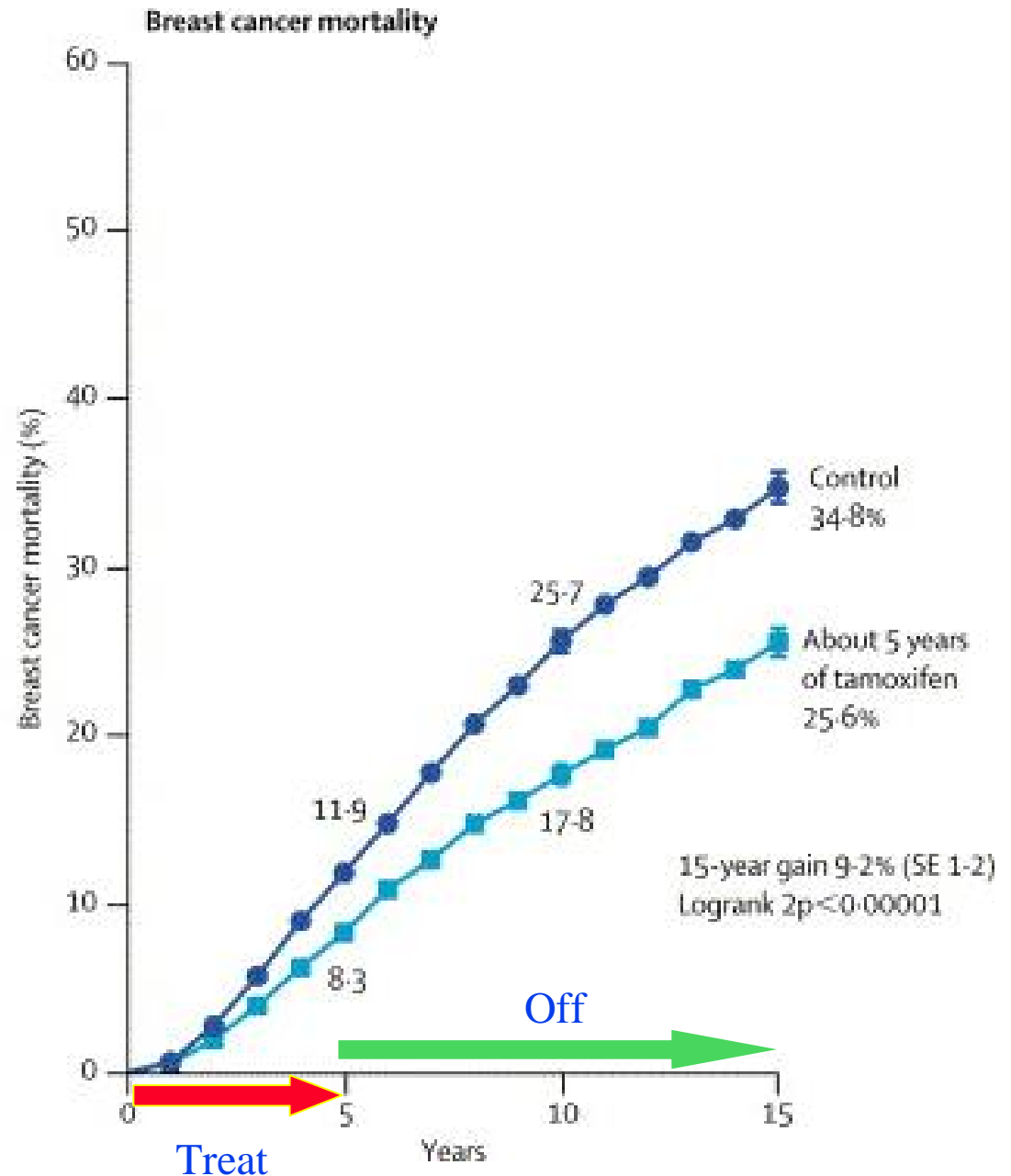


# Tamoxifen and raloxifene reduce breast cancer to a similar degree: the STAR Trial



## Benefits Persist

- 5 years of tamoxifen continues to reduce breast cancer risk and mortality for at least 10 years after stopping treatment
- Adverse effects (and costs) last only 5 years

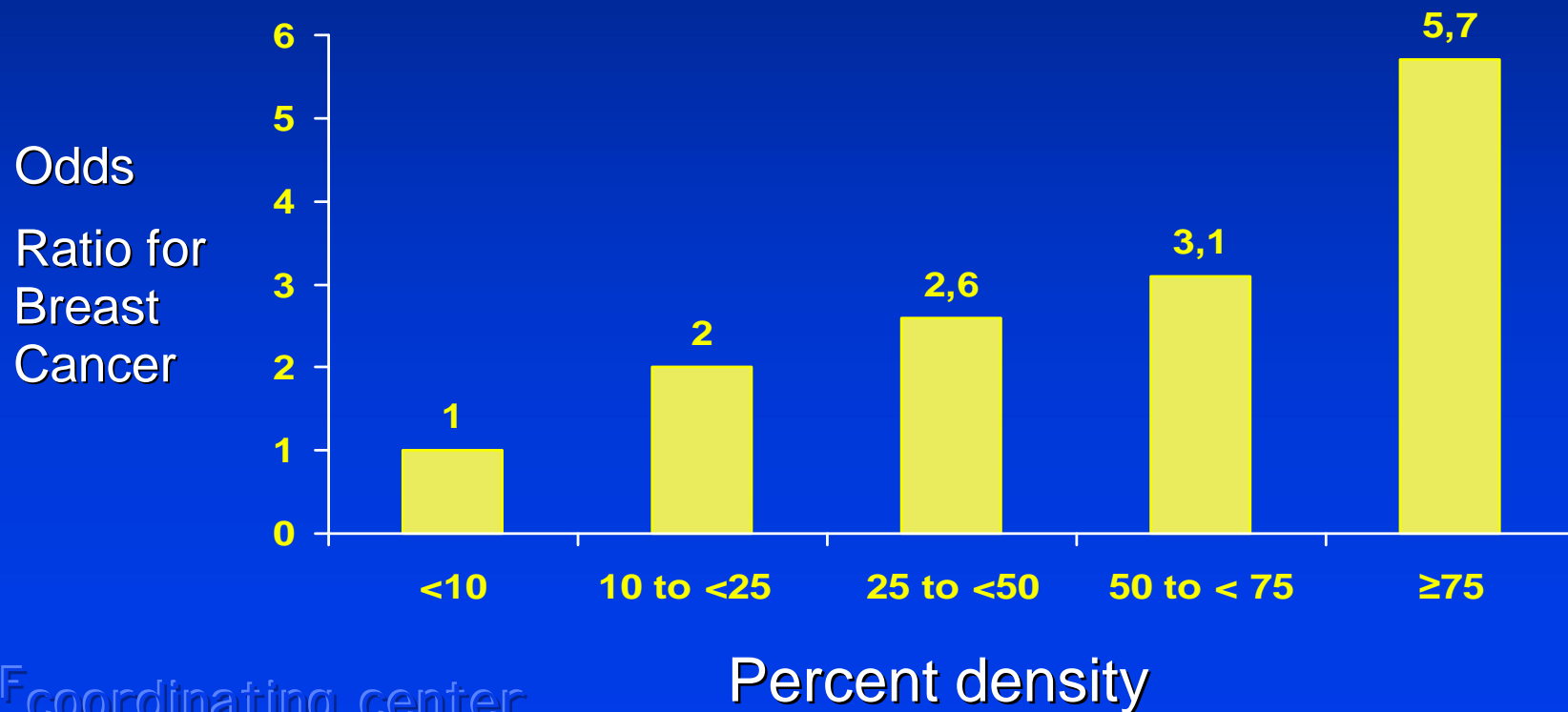
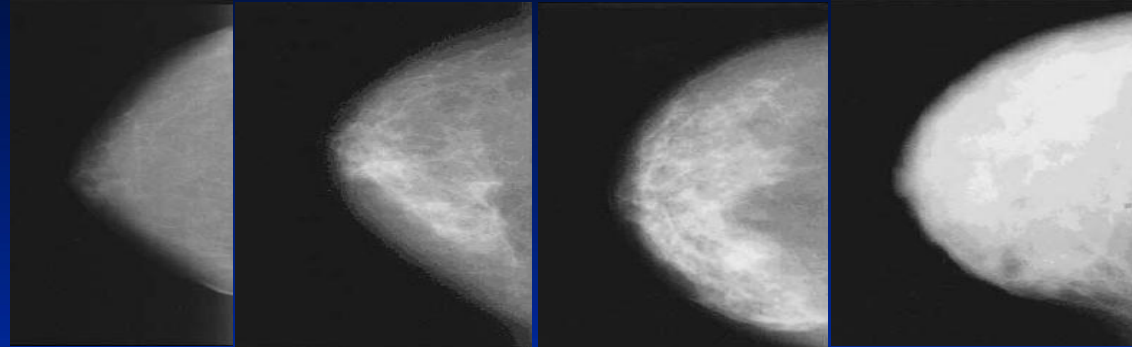


# Who should take raloxifene or tamoxifen to prevent breast cancer?

# 5- year risk of invasive breast cancer simple approach

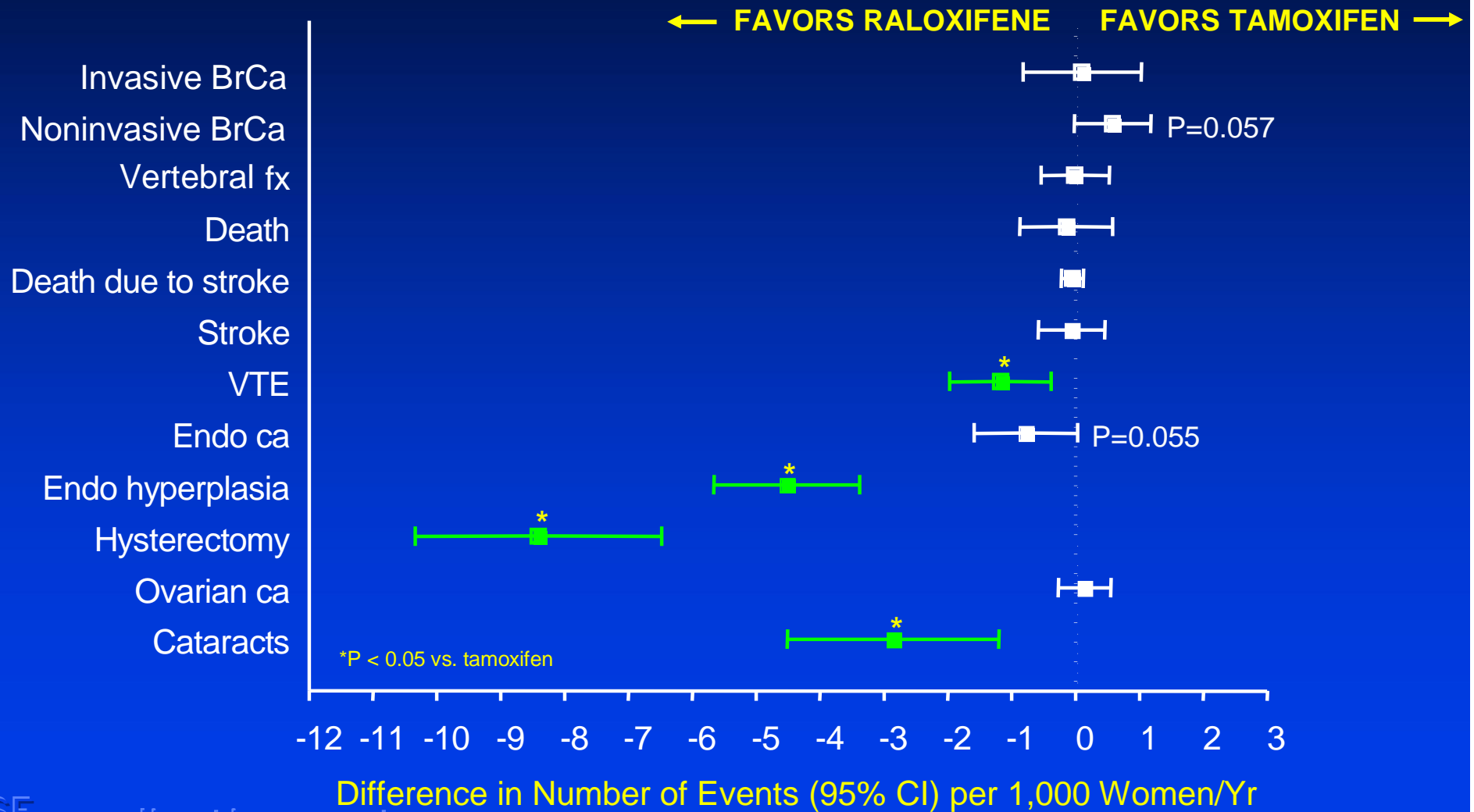
	<i>Age</i>			
	<b>45</b>	<b>55</b>	<b>65</b>	<b>75</b>
<b>Family history</b>	1.6	<b>2.4</b>	<b>3.2</b>	<b>3.4</b>
No family history	0.7	1.1	1.5	1.6

# Increasing breast density and increasing and risk of breast cancer



# STAR Trial

## Comparison of efficacy and safety outcomes



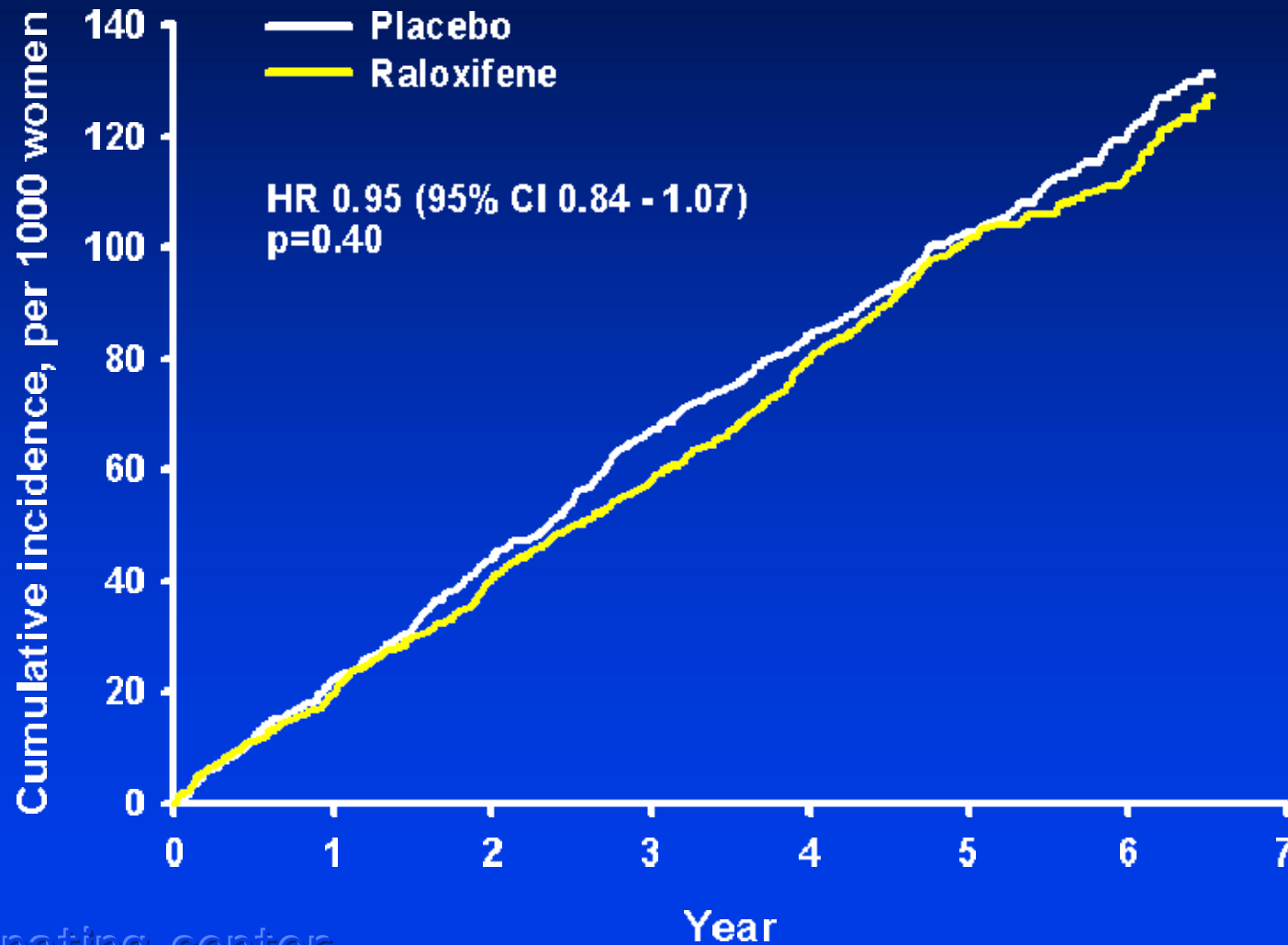
# The Future of Breast Cancer Prevention

- Women will routinely get an estimate of their risk of breast cancer when they have a mammogram
- Those at high risk ( $>3\%$  / 5 years?) should consider a SERM
- Those at low risk with low density may not need mammograms

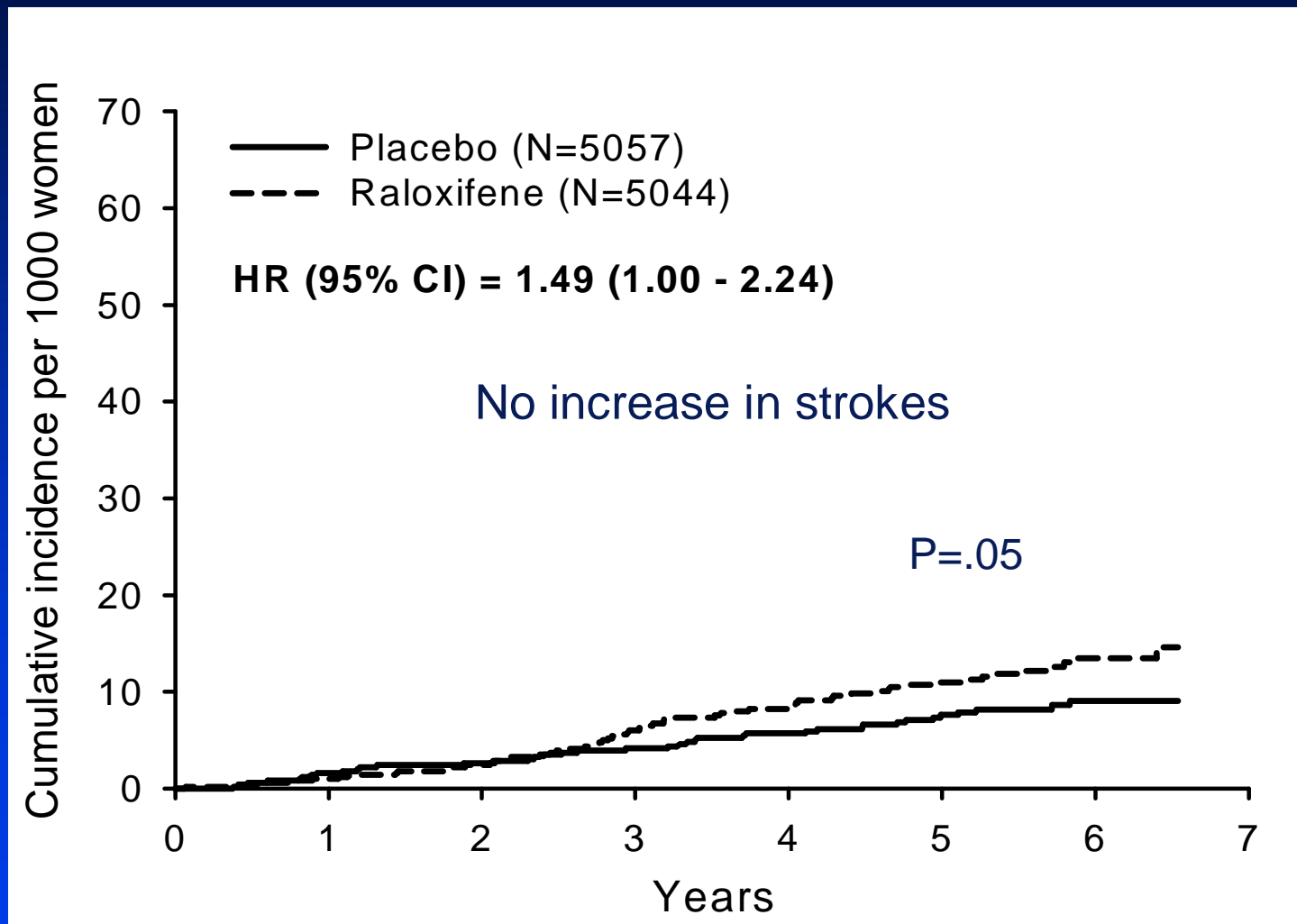
# Raloxifene safety and symptoms

- Hot flushes - about 5%
- “Flu syndrome” (~3-5%)
- Leg cramps (raloxifene) (<5%)
- VTE: 2-5 per 1,000

# RUTH Trial: Raloxifene does not decrease the risk of CHD



# RUTH: Raloxifene and fatal stroke



# New more potent SERMs

- Lasofoxifene (Pfizer)
- Basodoxifene (Wyeth)
- Arzoxifene (Lilly)
  
- Do they reduce the risk of nonvertebral fracture?
- What other effects?

# Raloxifene

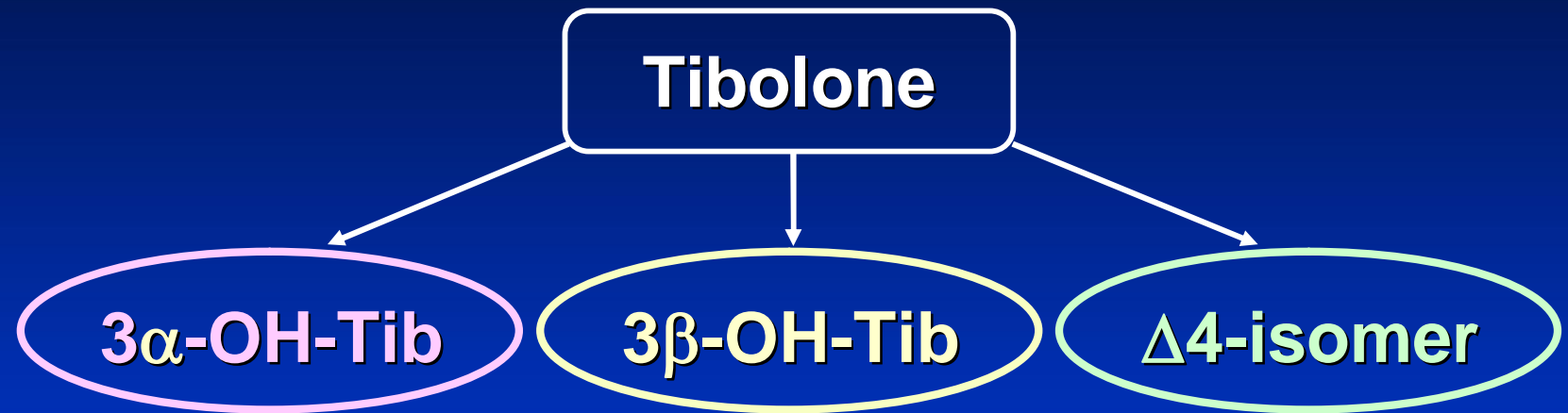
- Approved for prevention of breast cancer
  - Safer than tamoxifen
- Bisphosphonates are the 1st choice for women with osteoporosis
- Do not use raloxifene in women at high risk of CVD
- New SERMs are coming

# Tibolone

SF<sub>6</sub> coordinating center

# Tibolone

## 3 active metabolites



- Estrogenic

- Estrogenic

- Androgenic

- Progestogenic

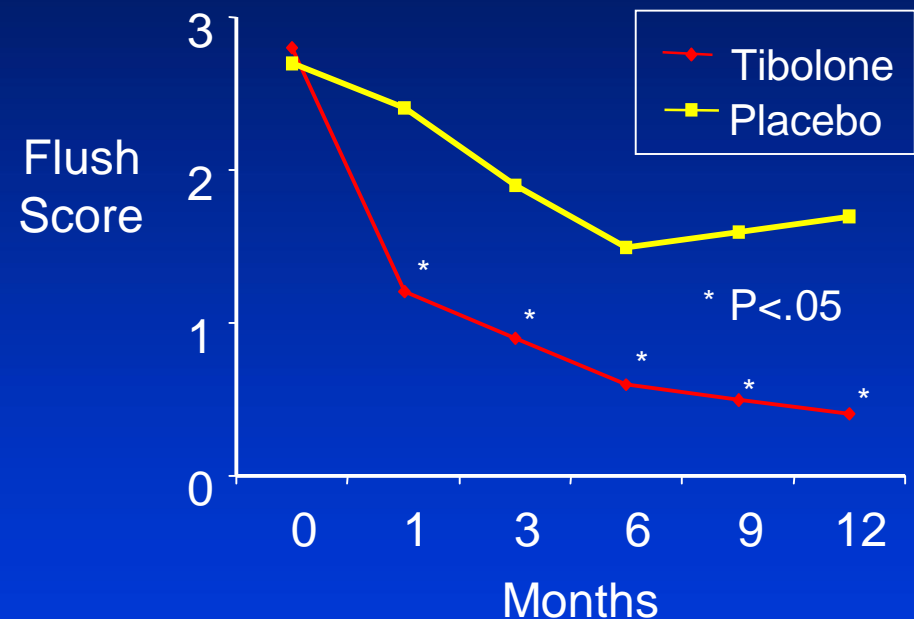
## Two uses

- Treatment of postmenopausal symptoms
- Prevention of diseases
  - Fractures
  - Cancer
  - Heart disease?

# Menopausal symptoms

# Hot flushes

- Placebo-controlled trials: decreases hot flushes
- Trials vs. estrogens: similar efficacy



Benedek-Jaszmann, 1987

# Trials of Tibolone and Sexuality

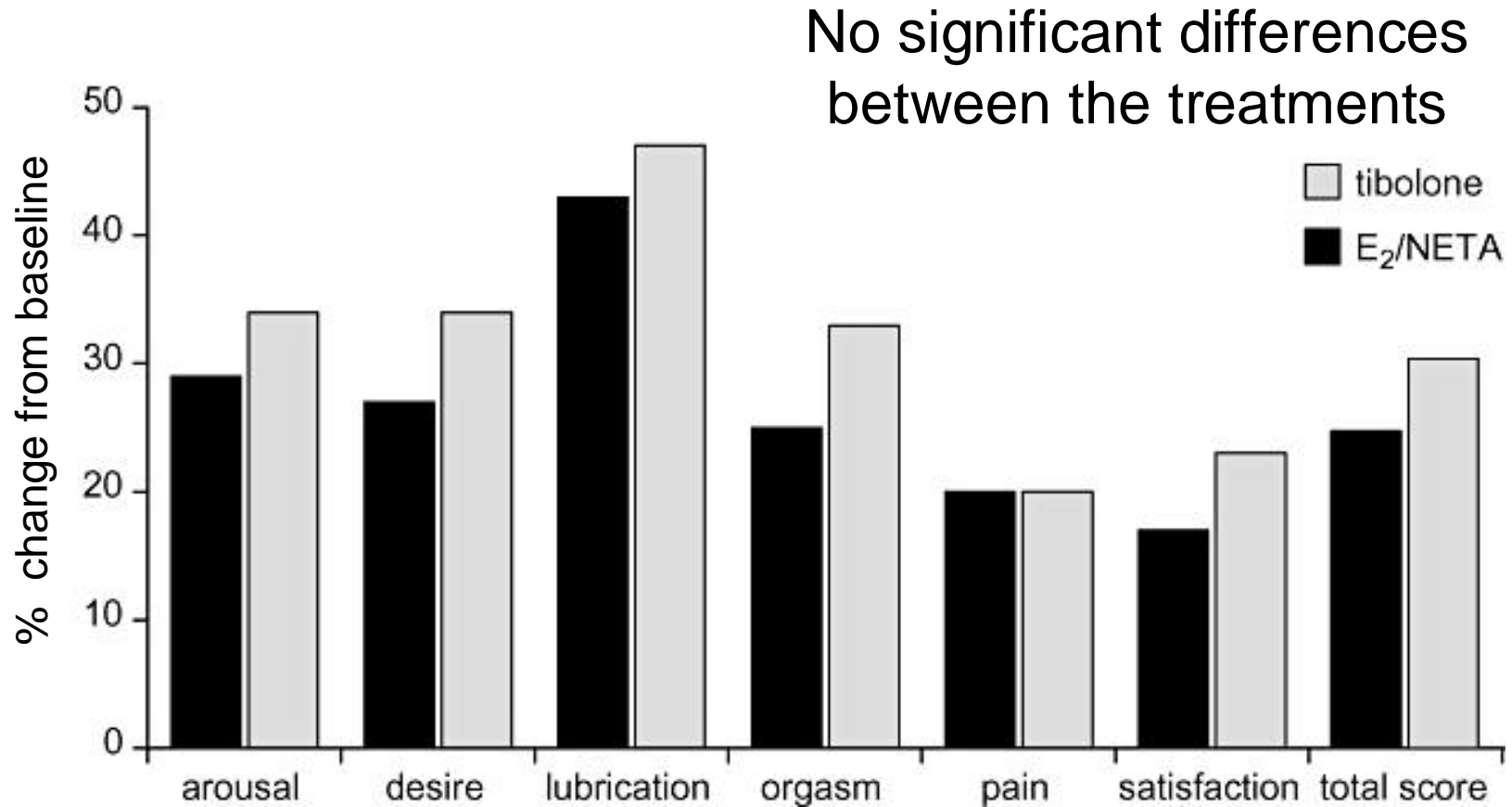
- 2 small randomized, blinded placebo-controlled trials
  - Lan (2002): More fantasies, desire, arousability and vaginal lubrication. No greater frequency of sex.

# LISA Trial

- 40 - 68 year old with satisfying premenopausal sex life but low satisfaction and high 'sexual distress' after menopause.
- 403 randomized to tibolone or E2(50 $\mu$ g) + NETA(140 $\mu$ g) patch (twice weekly)

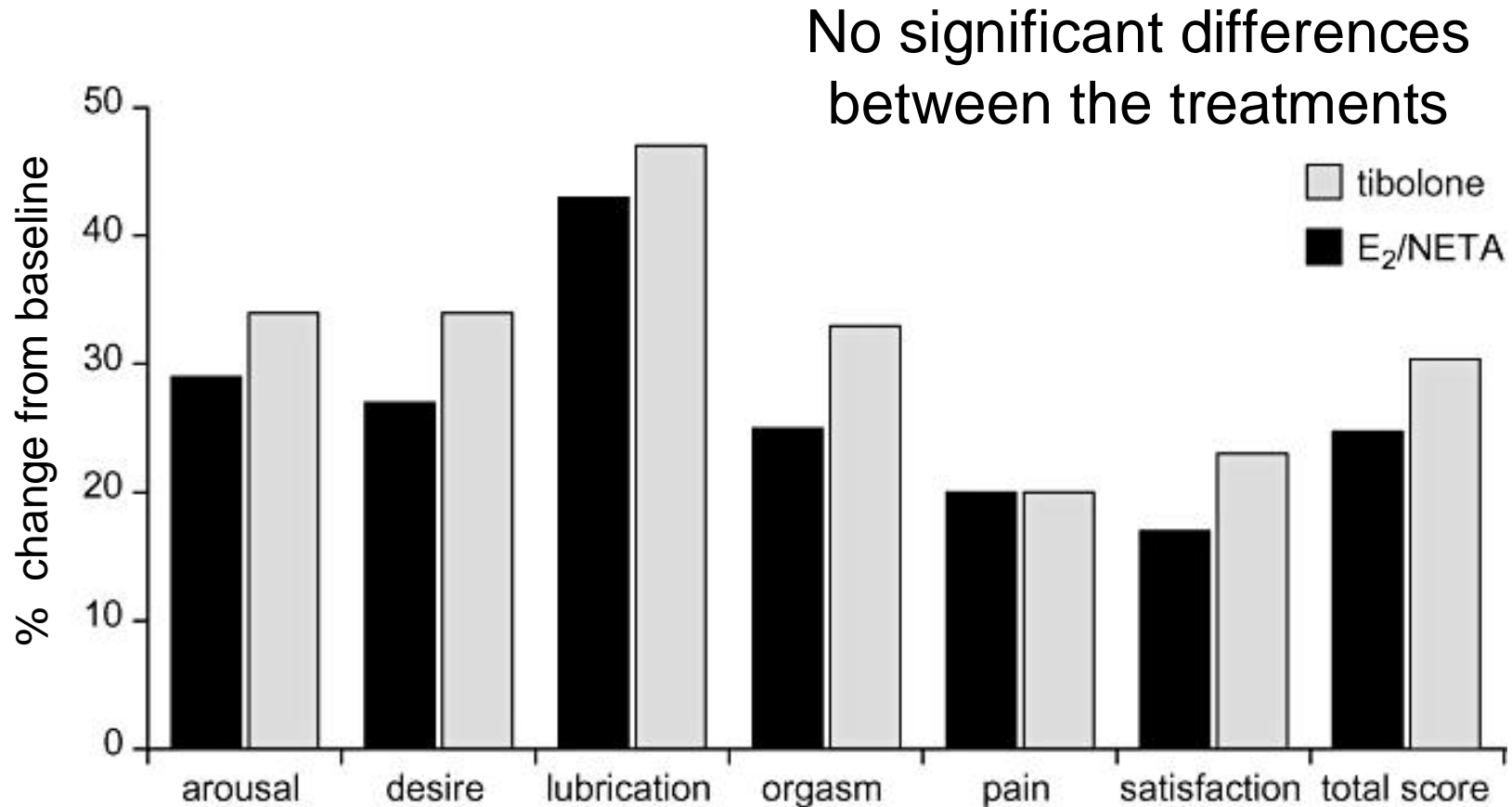
# LISA Trial

## Changes from baseline



# LISA Trial

## Changes from baseline



Partner less likely to refuse the woman's initiative (P<0.001)

# Menopausal symptoms

## Tibolone vs. $17\beta$ E2

- 40 after surgical menopause randomly given tibolone 2.5 or  $17\beta$  E2 2mg/d
- No differences in hot flushes
- Tibolone: greater interest in sex; less depressed mood.

## Tibolone vs. raloxifene

- 308 women age 60 to 79 with 'osteopenia'
- Raloxifene 60 mg vs. Tibolone 1.25 mg
- Women's Health Questionnaire:
  - Tibolone: fewer hot flushes; somewhat less depressed mood, higher 'sexual behavior' score.
- Greater vaginal lubrication and vaginal maturation

# Tibolone might increase lean body mass and muscle strength

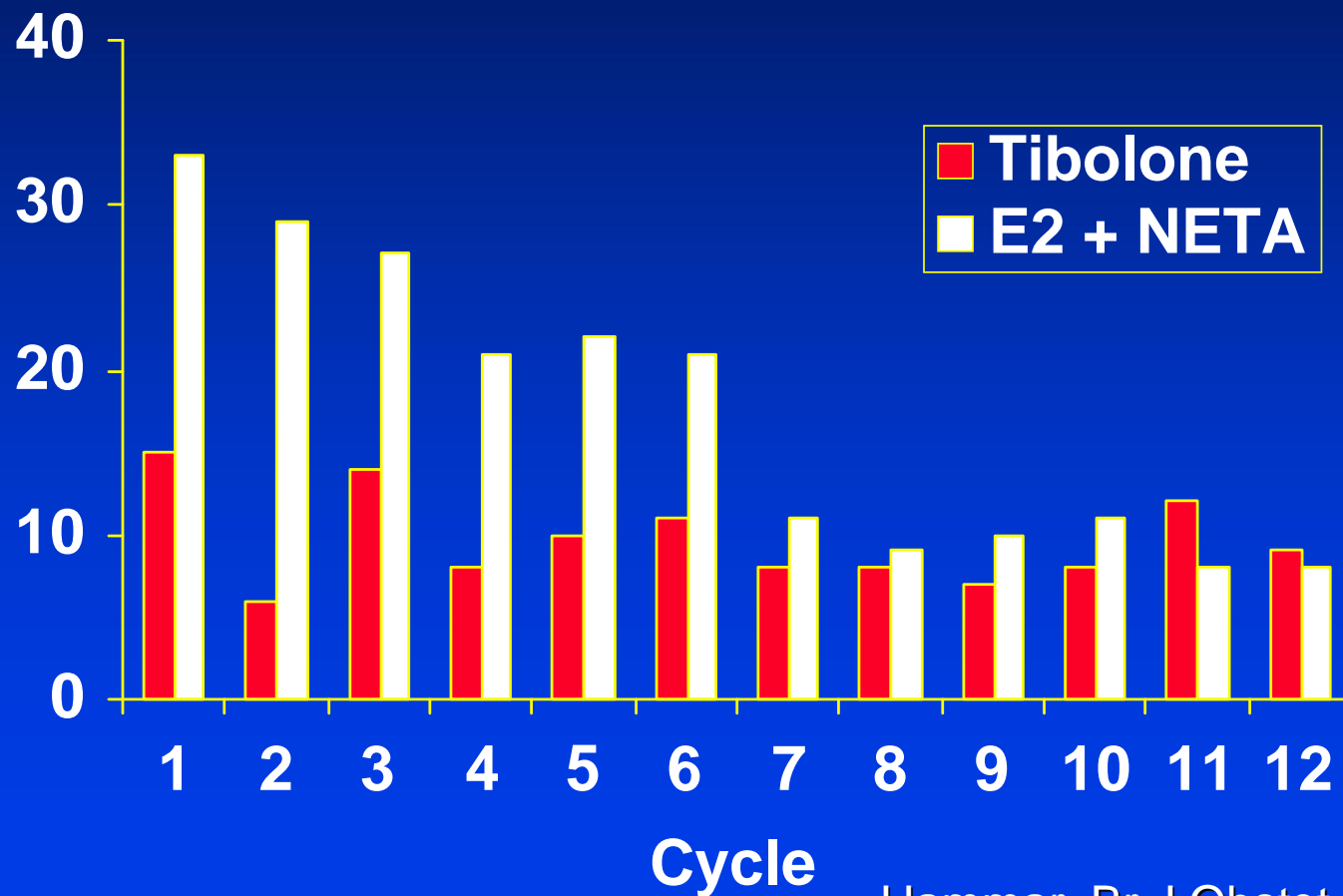
## Systematic review

- 4/5 placebo-controlled randomized trials found tibolone increased weight.
  - 1 trial: +0.85kg lean body mass (P=0.003)
- 1 small trial: 3-6% increased grip and isokinetic knee extensor strength

# Endometrial effects

# Bleeding or spotting trials of tibolone vs. E2/NETA

1st 6 months: tibolone < bleeding than HT



# THEBES

- 3,240 women age 45 to 65 years
- Randomized to tibolone 1.25 or 2.5 mg or CEE 0.625 / MPA 2.5 mg daily for 2 years
- No endometrial hyperplasia or cancer in tibolone groups; 2 with HT
- No difference in endometrial thickness
- Vaginal bleeding / 2 years
  - Tibolone 1.25 mg: 13%, 2.5 mg: 20%
  - CEE/MPA: 43%

# LIFT Trial

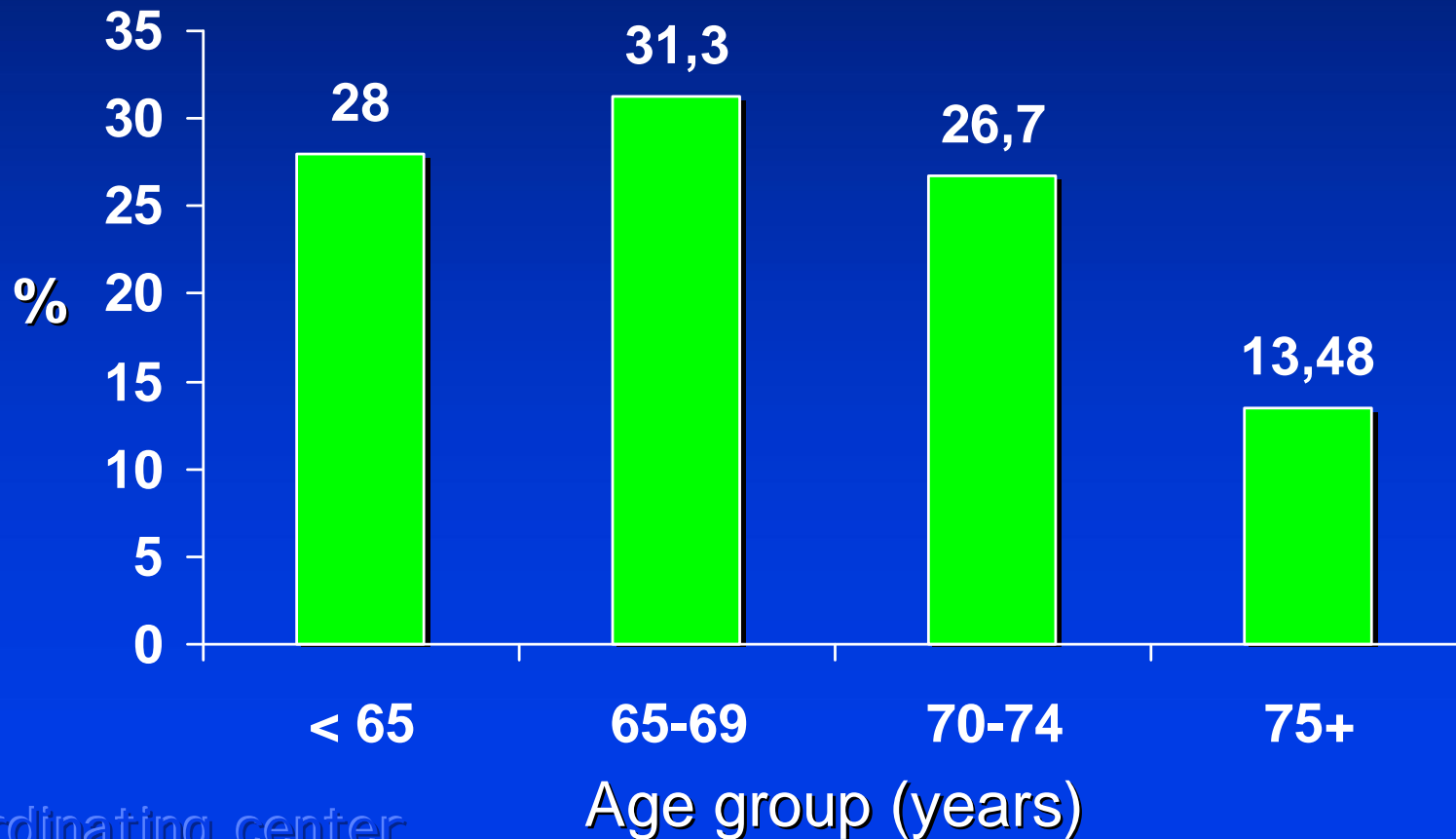
- 4538 postmenopausal women
  - Age  $\geq$  60 years with osteoporosis
- 1.25 mg of tibolone or placebo

# Characteristics

	Tibolone	Placebo
Vertebral fracture (%)	27	26
Mean total hip T-score	-1.8	-1.8
Mean spine T-score	-2.9	-2.9
BMI	25.7	25.7

# Age distribution in LIFT

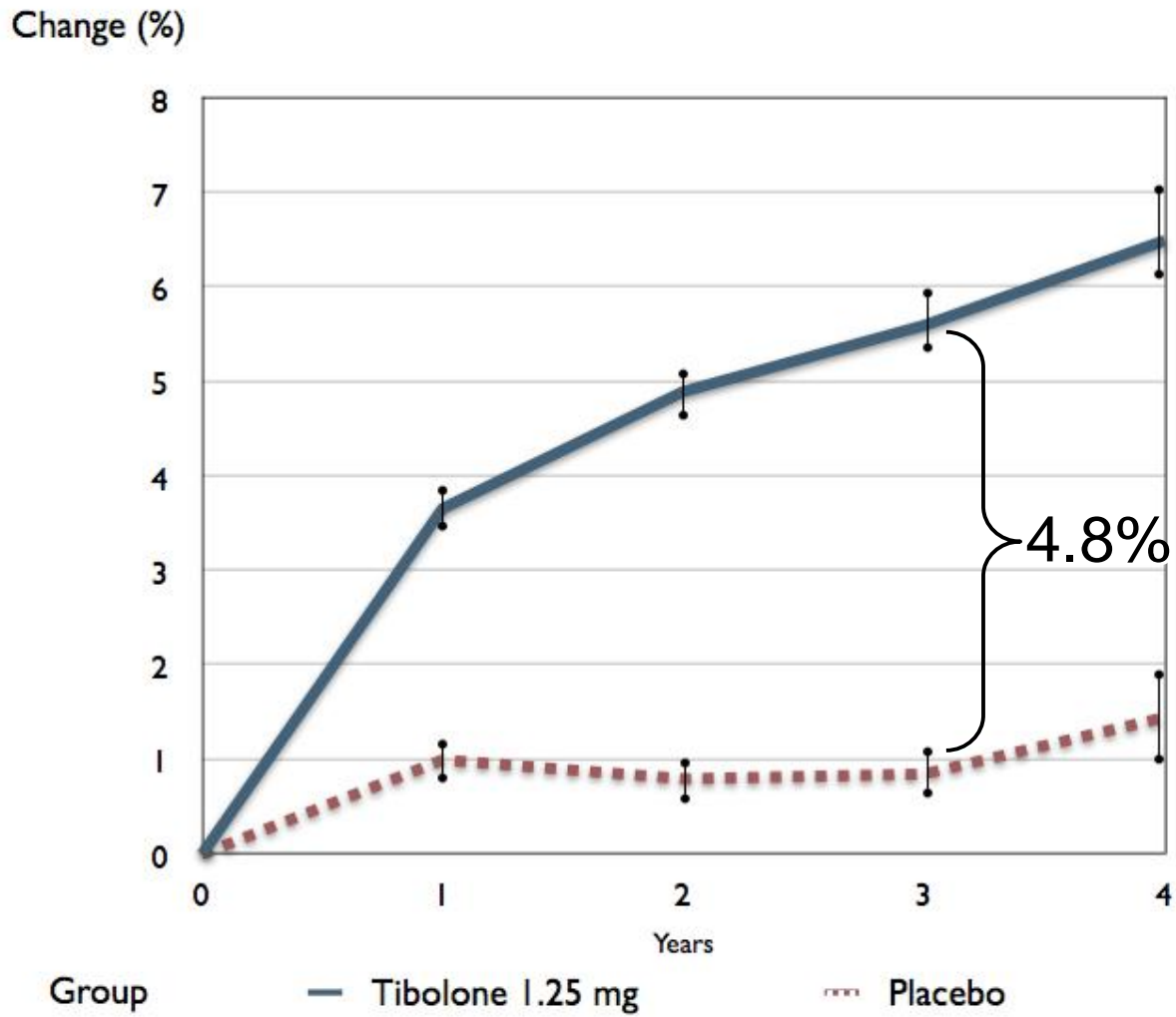
Mean: 68 years



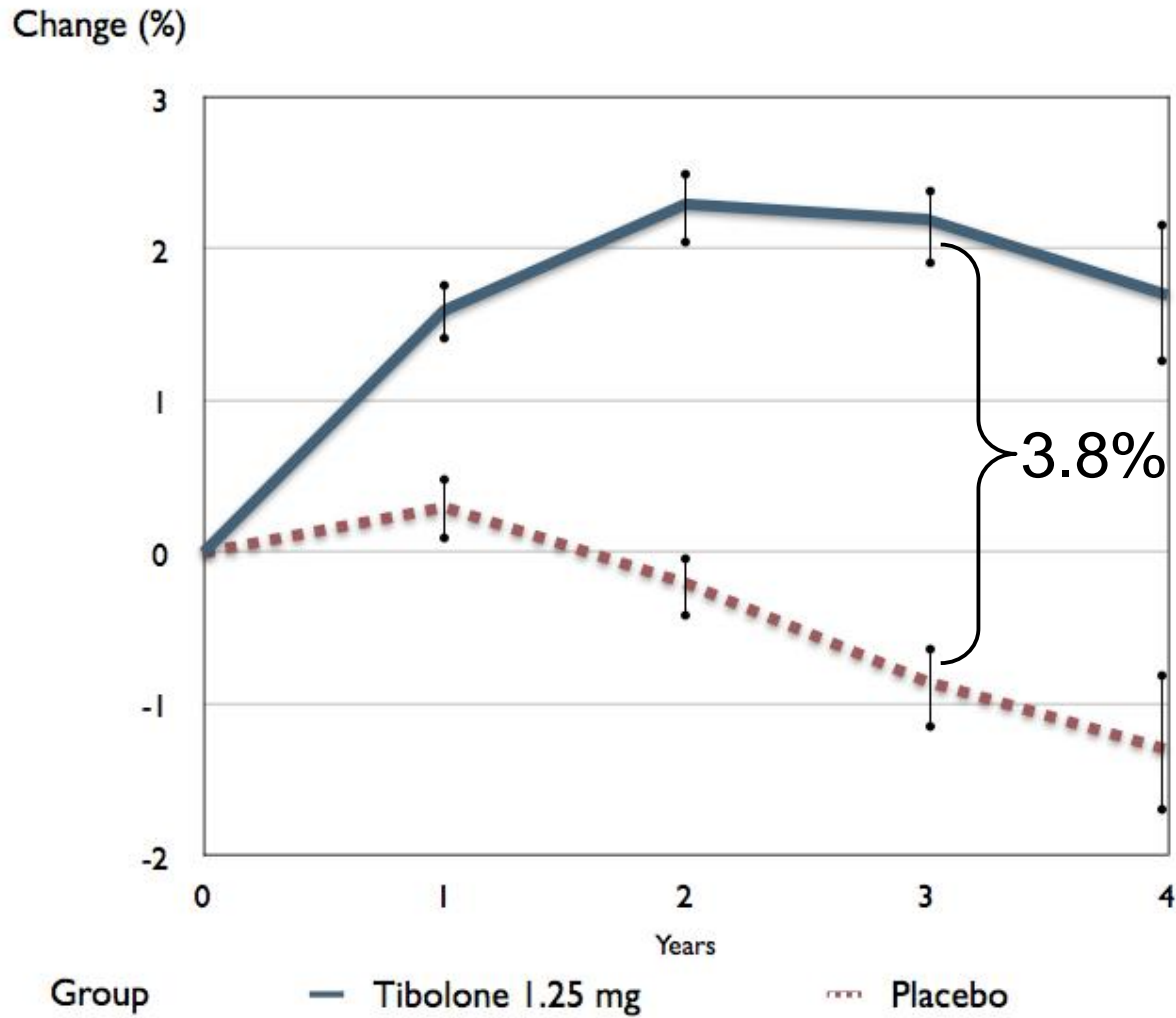
# LIFT discontinued, February, 2006

- LIFT DSMB and Steering Committee recommended discontinuation
- Increased risk of stroke
- Achieved the primary endpoint of reduction in vertebral fractures
- Median 3 years follow-up
- About 60% follow-up; 91% took  $\geq 80\%$  of study tablets

# Spine BMD



# Femoral neck BMD

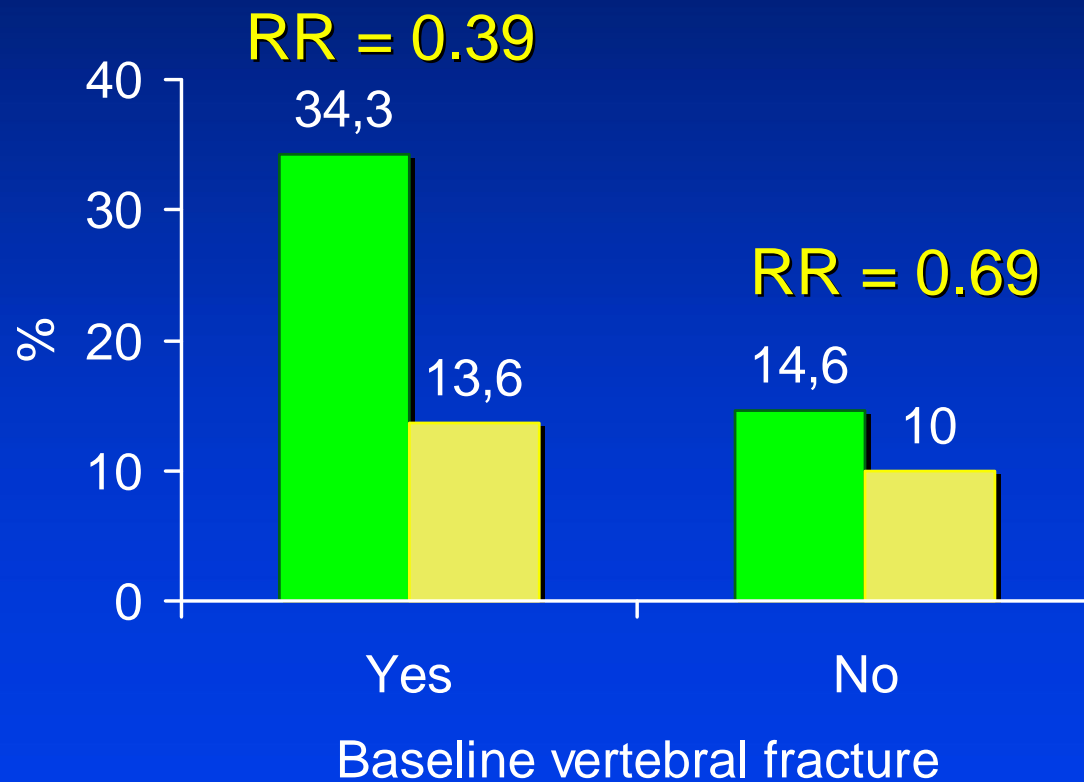


# Decreased risk of vertebral fracture

Overall: RH = 0.55 (95% C.I. = 0.40, 0.74)

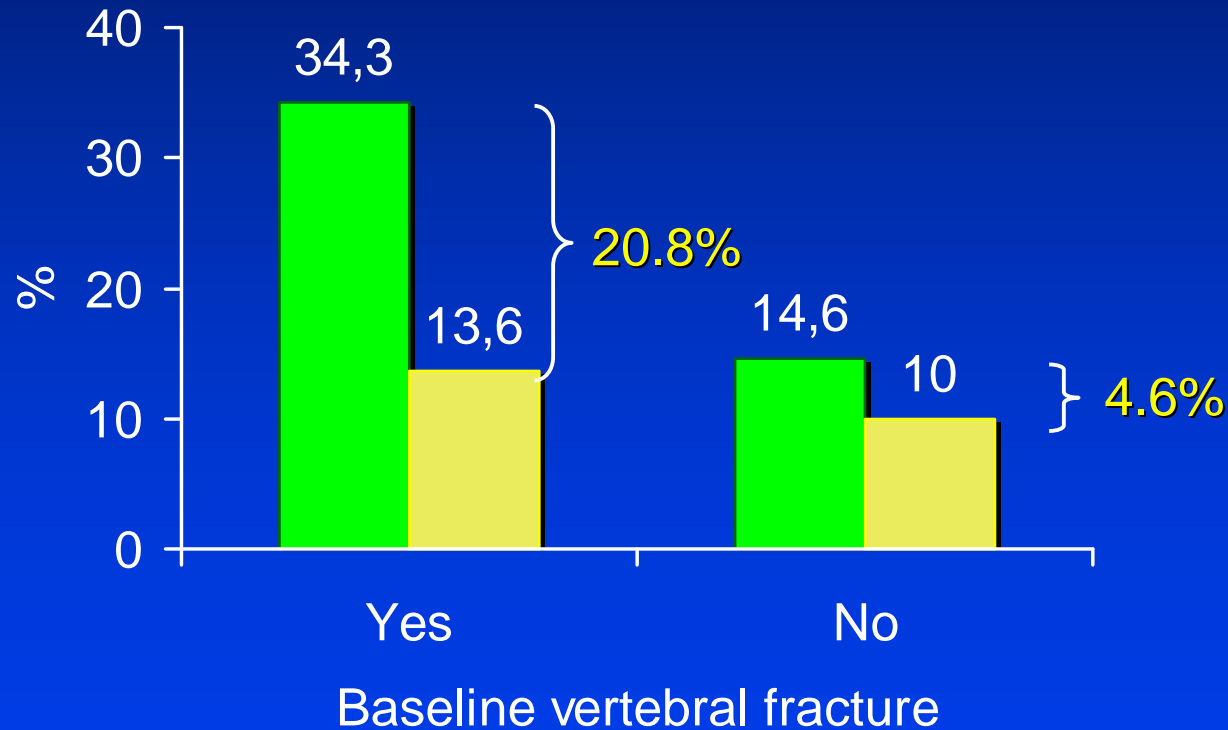
# Decreased risk of vertebral fracture

Overall: RR = 0.55 (95% C.I. = 0.40, 0.74)



# Decreased risk of vertebral fracture

Overall: RH = 0.55 (95% C.I. = 0.40, 0.74)

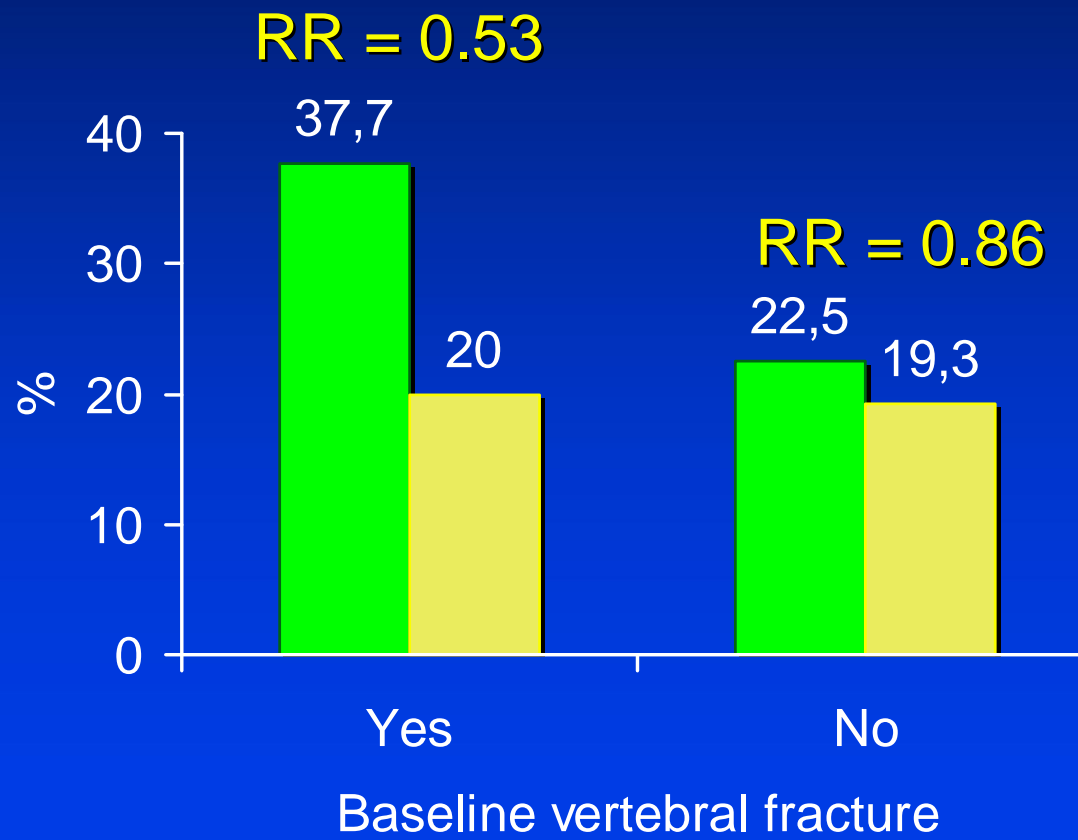


# Decreased risk of nonvertebral fracture

Overall: RH = 0.74 (95% C.I. = 0.58, 0.93)

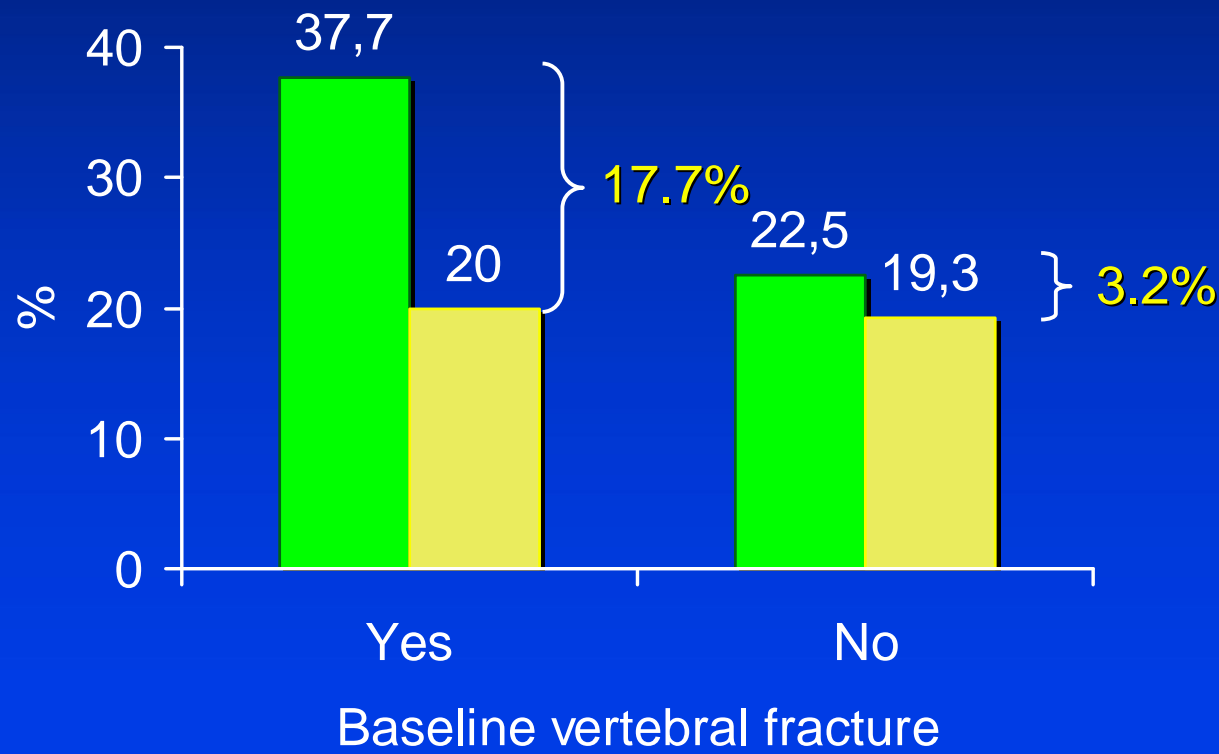
# Decreased risk of nonvertebral fracture

Overall: RR = 0.74 (95% C.I. = 0.58, 0.93)



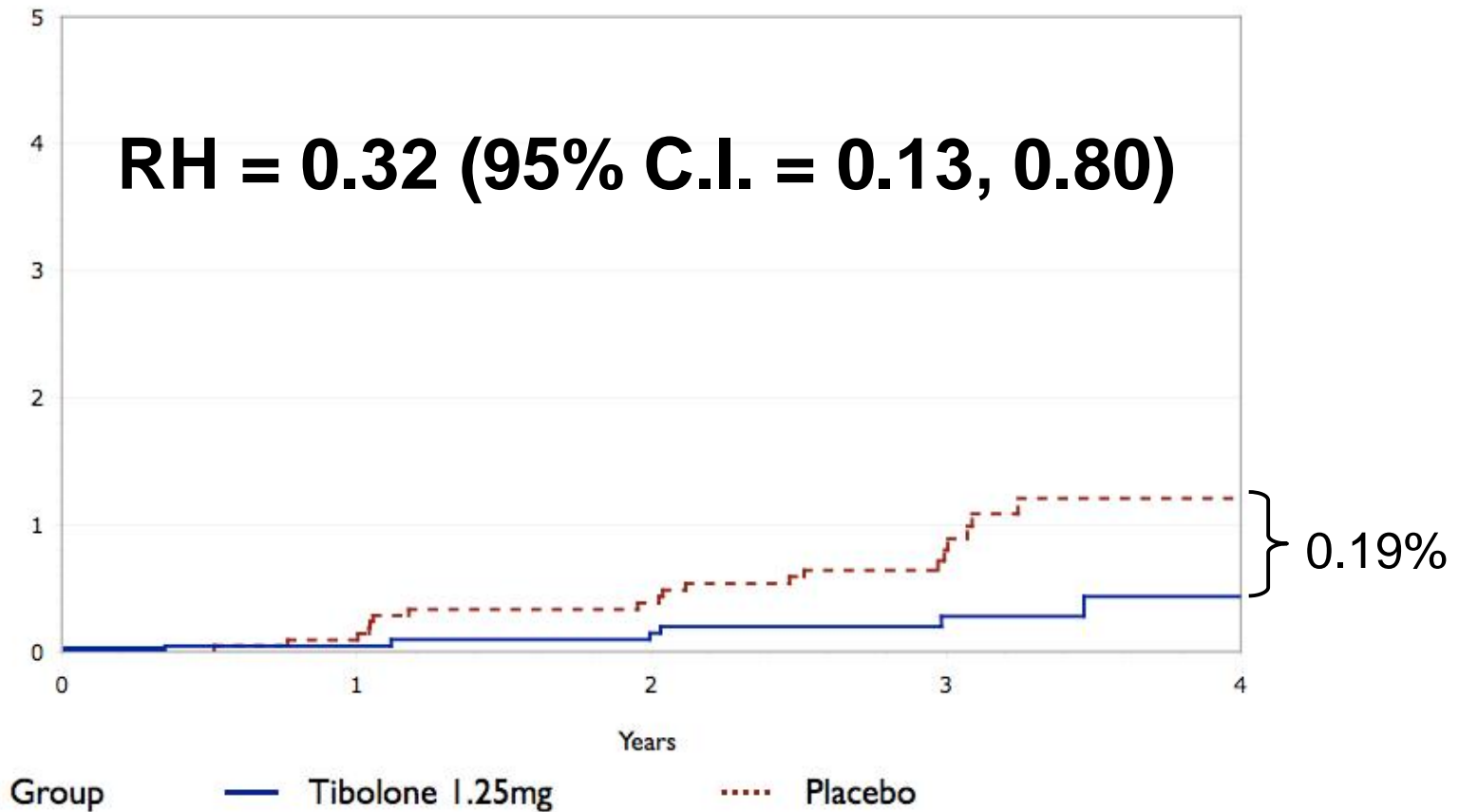
# Decreased risk of nonvertebral fracture

Overall: RH = 0.55 (95% C.I. = 0.40, 0.74)



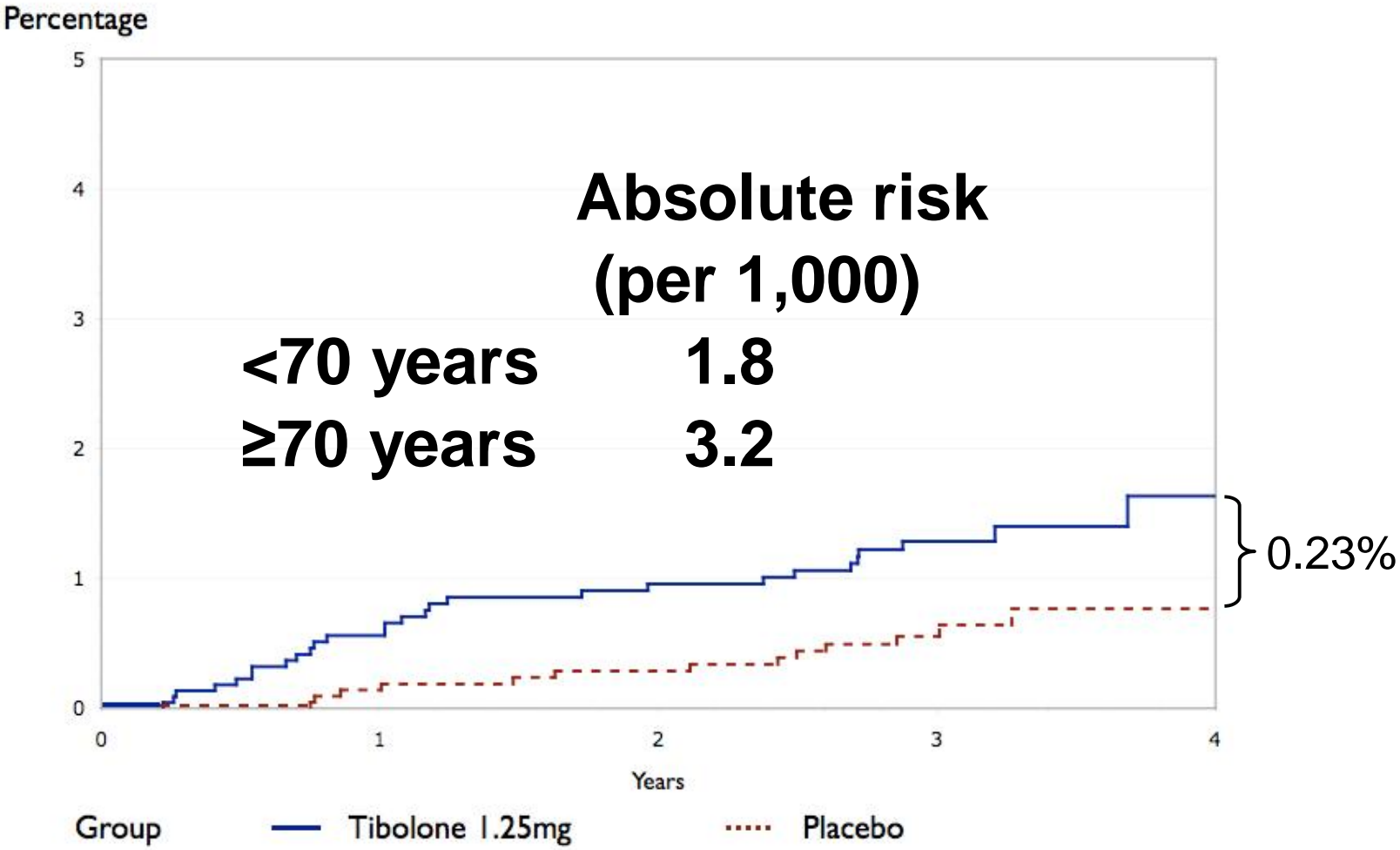
# Decreased risk of breast cancer

Percentage



Cummings, et al. NEJM 2008 (accepted)

# Increased risk of stroke



## Other outcomes

	<u>RR (95% CI)</u>	
Colon cancer	0.31 (0.10, 0.96)	P=0.04
VTE	0.57 (0.19, 1.69)	
Endometrial cancer	Pbo: 0, Tibolone: 4	P=0.06

## Other effects

	<u>% excess</u>
• Vaginal discharge	8%
• Vaginal bleeding	6%
• Vaginal infection	6%
• Breast discomfort	6%
• Steatohepatitis (high GGT)	3%
• Weight gain average	+0.6 kg
• Fewer falls	2%

P<0.05 for all

# Limitations

- Elderly women
- 1.25 mg (half the usual dose)
- 3 years

# Role of tibolone

If you treat menopausal symptoms with a drug

- *Compared with estrogen therapies, tibolone has*
  - Similar decrease in hot flushes
  - Probably increases libido and improves mood
  - Less vaginal bleeding
- Tibolone reduces fractures risk (so does ET)
  - In women with vertebral fractures
- Tibolone reduces breast cancer risk
  - Raloxifene is better proven
- Not for women  $\geq$  age 65 or risk factors for stroke

