CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 11/20/97

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SLIDES

FDA Advisory Committee Meeting
Bethesda, Maryland
November 20, 1997

Compound: Raloxifene HCl
Proposed Indication:
Prevention of Postmenopausal Osteoporosis

Jennifer L. Stotka, M.D.
Director, U.S. Regulatory Affairs
Eli Lilly and Company

Raloxifene

- Selective Estrogen Receptor Modulators (SERMs)
  - Selective ability to act like estrogen in the skeleton and cardiovascular system
  - No estrogen-like activity in the breast and uterus
- NDA submitted in June, 1997
  - Clinical trials involved ~ 13,000 women
  - Application comprised 878 volumes

FDA Guidelines
Osteoporosis

- Development of raloxifene commenced prior to completion of the 1994 FDA Osteoporosis Guidelines

- Raloxifene works through the estrogen receptor
  - FDA agreed to treat raloxifene as an estrogen in clinical development

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The recommended primary efficacy endpoint for prevention and treatment studies for estrogens is Bone Mineral Density

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Efficacy

- Preclinical data show the relationship between BMD and bone strength is normal and is similar to estrogen

- Raloxifene is estrogen-like
  - Acts through the estrogen receptor
  - Effects on bone and calcium metabolism similar to estrogen

Efficacy and Safety

- Raloxifene 60 mg prevents bone loss at the spine and hip and conserves total body bone mineral
- Raloxifene has beneficial effects on bone and cardiovascular intermediate endpoints without stimulatory effects on the endometrium or breast
- No oncogenic risks associated with raloxifene therapy for postmenopausal women

Safety

- Events probably causally related to raloxifene therapy:
  - Idiopathic leg cramps
  - Hot flashes
  - Venous thromboembolic events

Raloxifene Data

- Skeleton
- Cardiovascular System
- Uterus
- Breast

Lilly Advisory Committee Presentation
Raloxifene

Introduction	Jennifer L. Stotka, MD
Unmet Medical Needs	Ethel S. Siris, MD (Columbia University)
Preclinical Overview and Clinical Efficacy	John D. Termine, PhD Willard H. Dere, MD
Clinical Safety	Fredric J. Cohen, MD
Benefit / Risk and Conclusions	Willard H. Dere, MD

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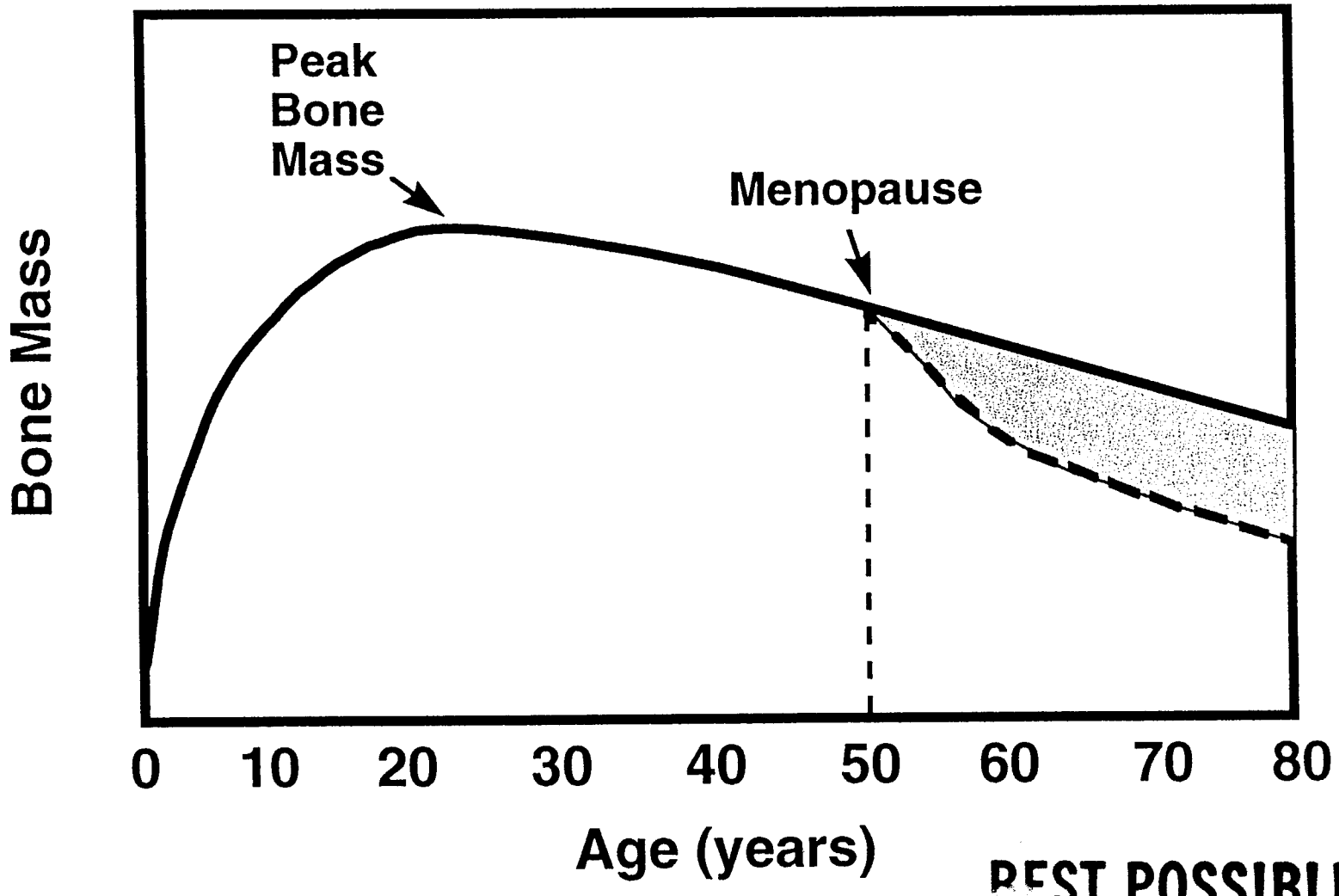
Cornell University

Ethel Siris, MD
Columbia University

Introduction and Unmet Medical Needs

Ethel Siris, MD

The Natural History of Osteoporosis



Osteoporosis
The Burden of Illness

- Number of fractures per year
  - Spine 700,000
  - Wrist 200,000
  - Hip 300,000
- Direct medical cost: $13.8 billion (1995)

National Osteoporosis Foundation

Hormone Replacement Therapy (HRT)

- Treatment of choice for menopausal symptoms and genitourinary atrophy
- Potential benefits in decreasing cardiovascular disease
- Proven benefits in preventing osteoporosis

Postmenopausal Women's Concerns about HRT

- Resumption of menses
- Breast symptoms
- Fear of breast cancer

APPEARS THIS WAY
ON ORIGINAL

Poor Long-Term Adherence to HRT

	After	Adherence
In general population:	3 months	73%
	1 year	60%
	5 years	5-34%
In low BMD patients:	8 months	60%

Speroff et al. 1991, Ryan et al. 1992, Marwick 1994

Other Therapeutic Choices for Prevention of Osteoporosis

- Calcium supplementation
- Alendronate 5 mg/day

APPEARS THIS WAY
ON ORIGINAL

Raloxifene
A Selective Estrogen Receptor Modulator

- Prevention of bone loss
- Favorable effects on cardiovascular intermediate endpoints
- No endometrial stimulation or uterine bleeding
- No increased risk of breast cancer
- Favorable benefit / risk profile

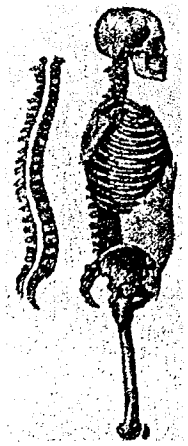
Preclinical Overview and Clinical Efficacy

John D. Termine, PhD
Willard H. Dere, MD

Selective Estrogen Receptor Modulator

Agonist

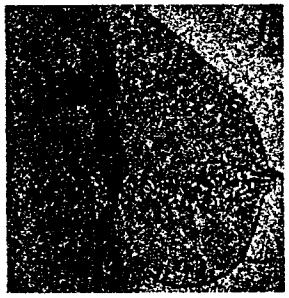
Bone



CVS

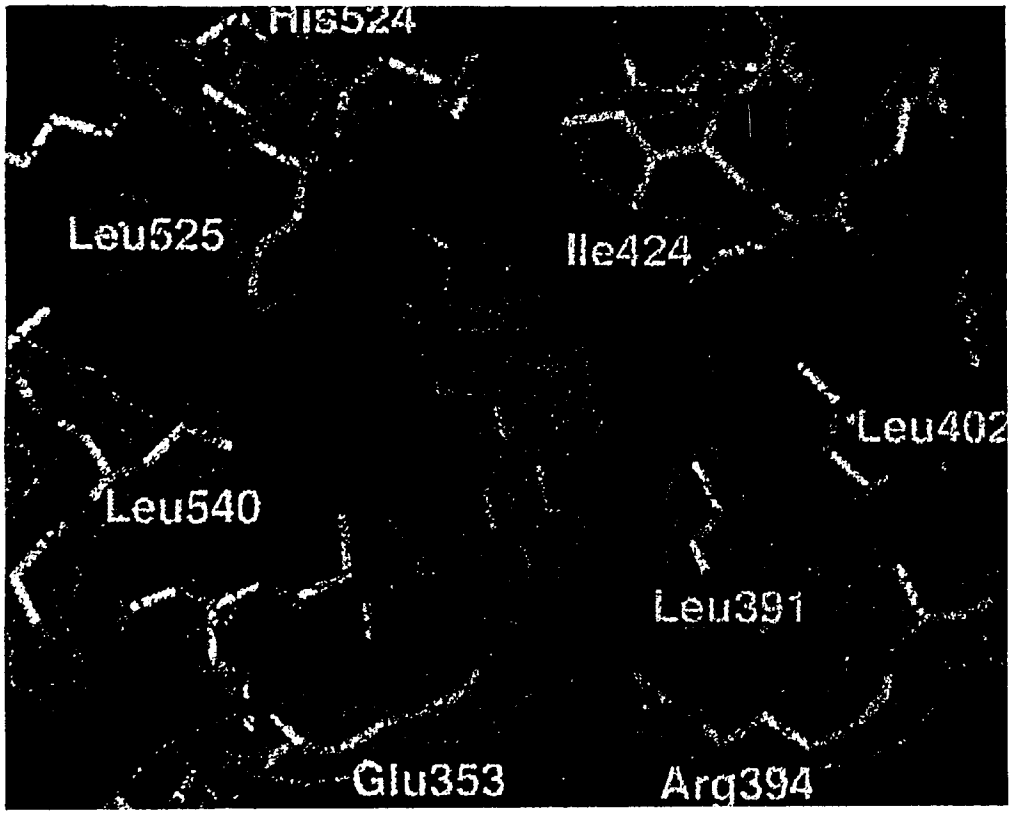
Antagonist

Breast



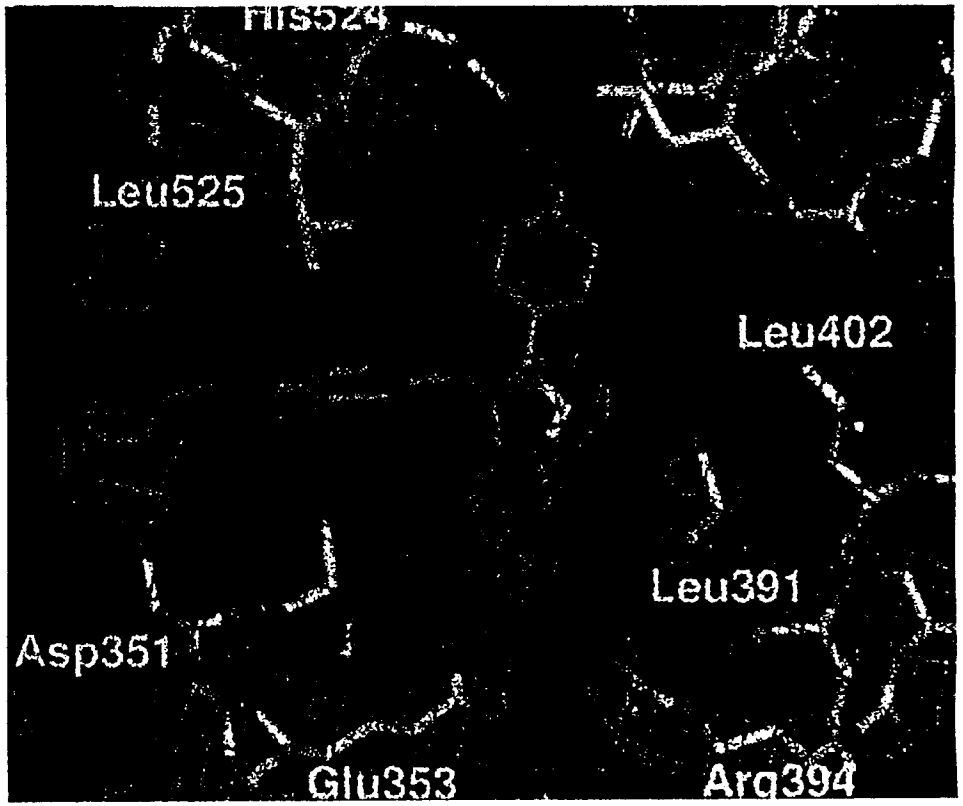
Uterus

Three Dimensional Structure of ERα / E_2 and ERα / RLX Complexes



Estradiol

Kd=86 pM



Raloxifene

Kd=54 pM

Brzozowski et al. 1997

Estrogen Agonist Effects of Raloxifene in Bone and Other Tissues In Vitro

Osteoclastic bone resorption cultures	Estrogen	Raloxifene
• non-stimulated	no effect	no effect
• IL-6 induced	inhibition	inhibition

Non-osseous cells/organ culture

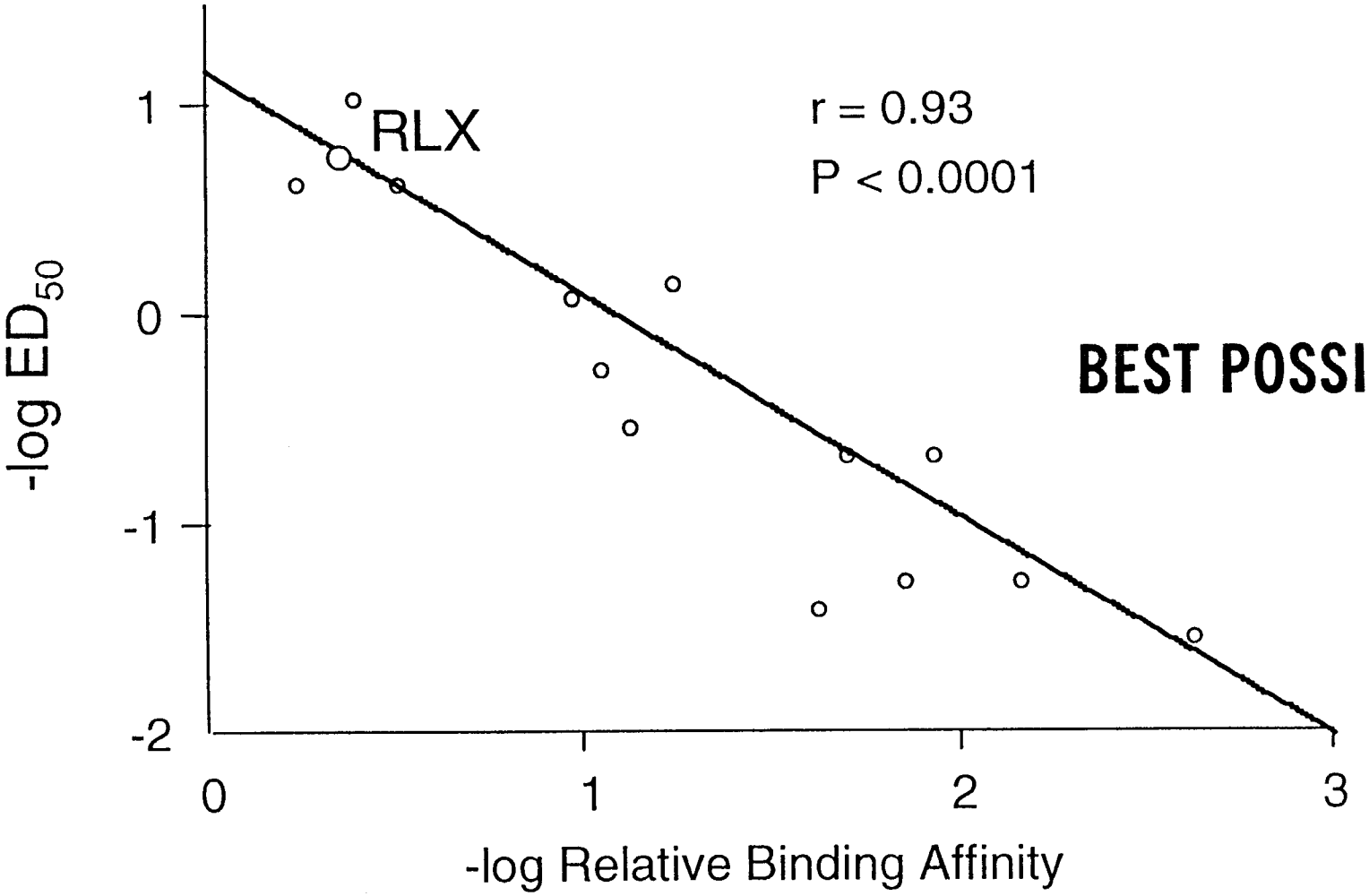
- endothelial cells
- smooth muscle cells
- aortic strips
- dermal fibroblasts
- vaginal epithelial cells

Effects are similar in direction, dose response and magnitude

Raloxifene Acts Like Estrogen in Rat Bone

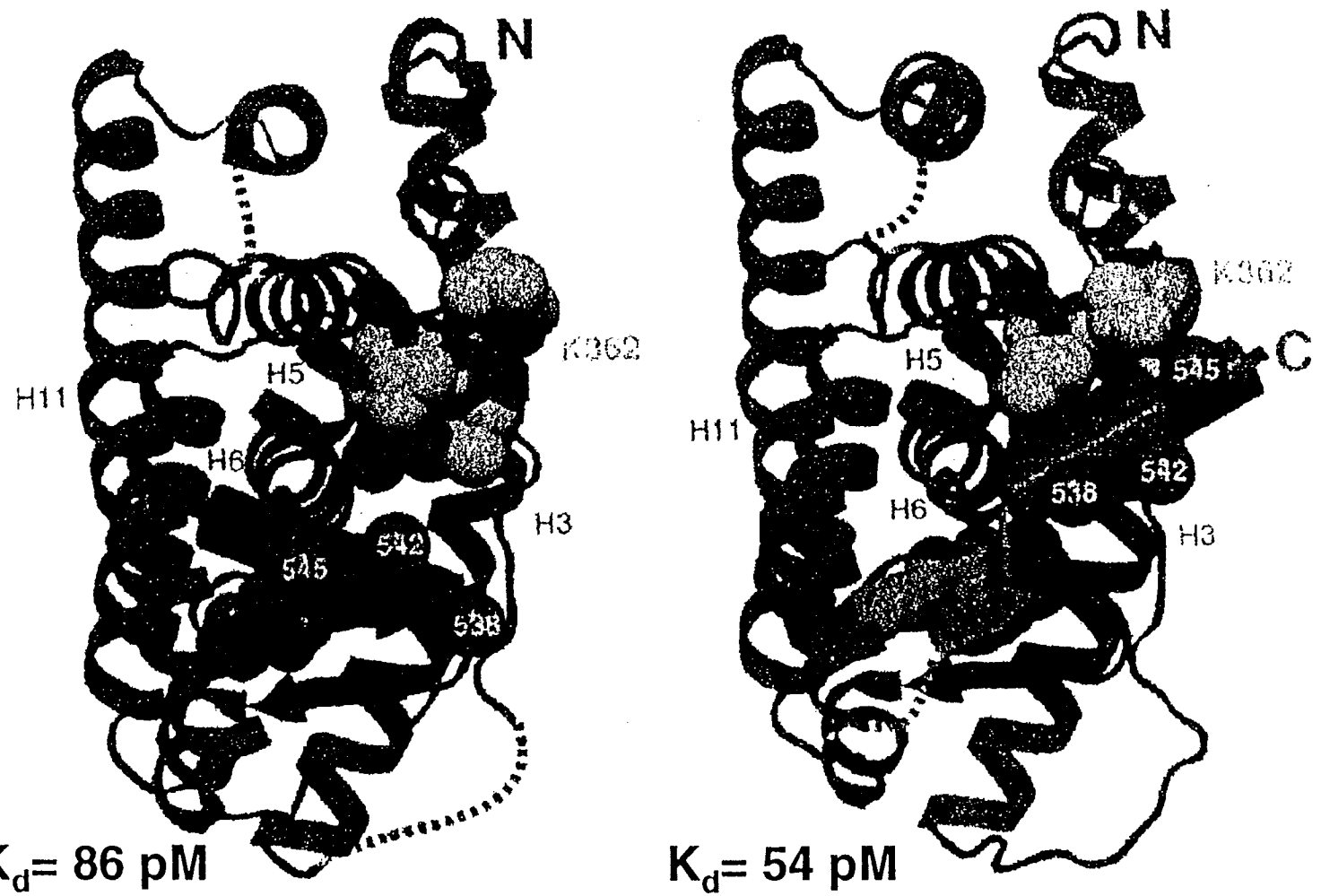
	Estrogen	Raloxifene
• Longitudinal growth	↓↓↓	↓↓↓
• Bone mineral density		
– prevention models	+++	+++
– estrogen replete animals	N/A	no Δ
– treatment models	+	+
• Biomechanical effect		
– whole tissue properties	++	++
– material properties	normal	normal
• Histomorphometry		
– resorption	↓↓↓	↓↓↓
– formation	↓↓↓	↓↓ or no Δ
• Bone turnover markers	↓↓	↓↓
• Bone cytokine pathways		
– IL-6	↓↓↓	↓↓↓
– TGF- ß3	↑↑↑	↑↑↑

Correlation Between Cholesterol-Lowering ED50 and Relative Binding Affinity to ER for a Series of Raloxifene Analogs



Kauffman et al. 1997

Estradiol and Raloxifene Occupy the Same Ligand Binding Site

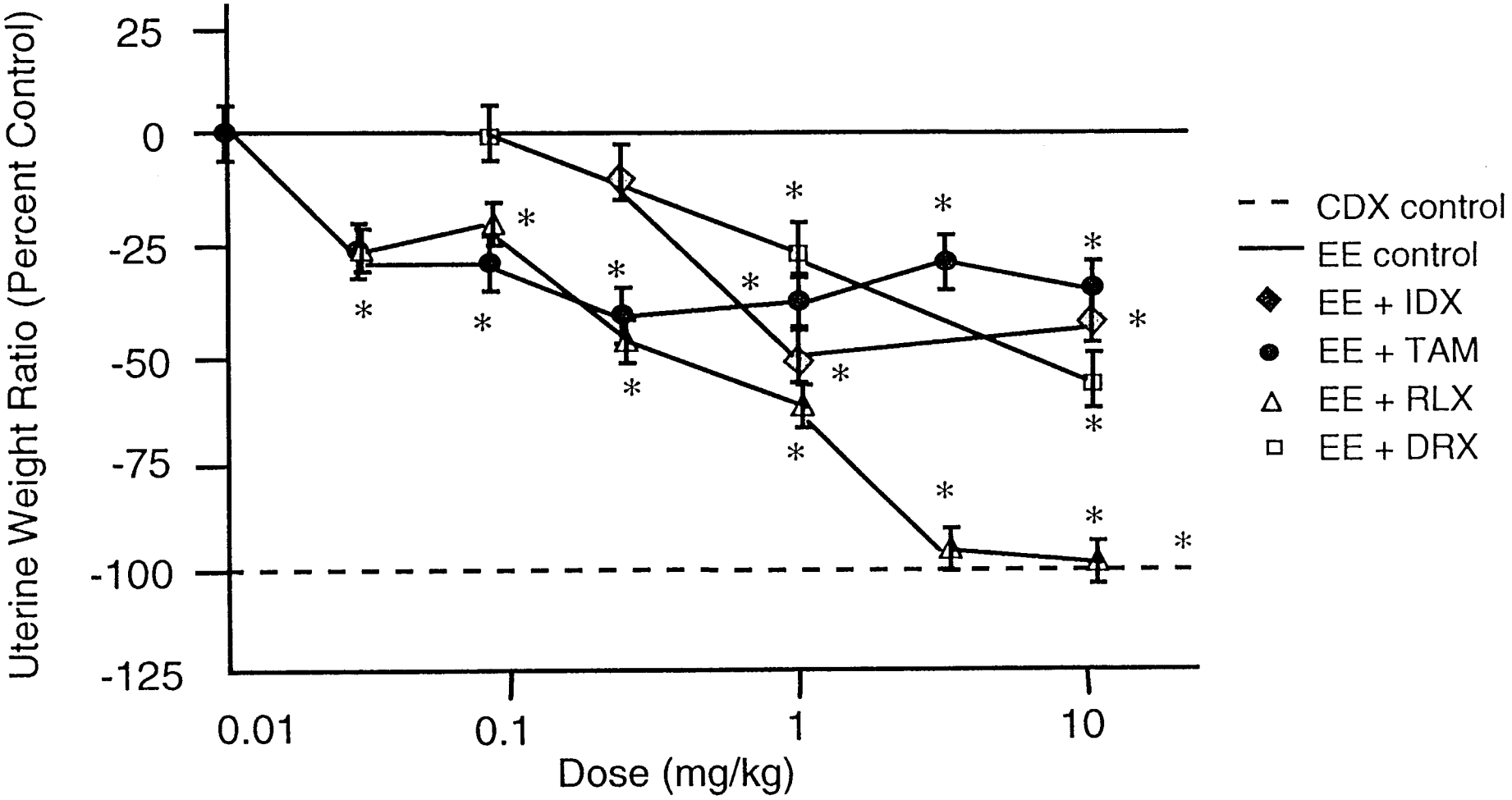


K_d= 86 pM

K_d= 54 pM

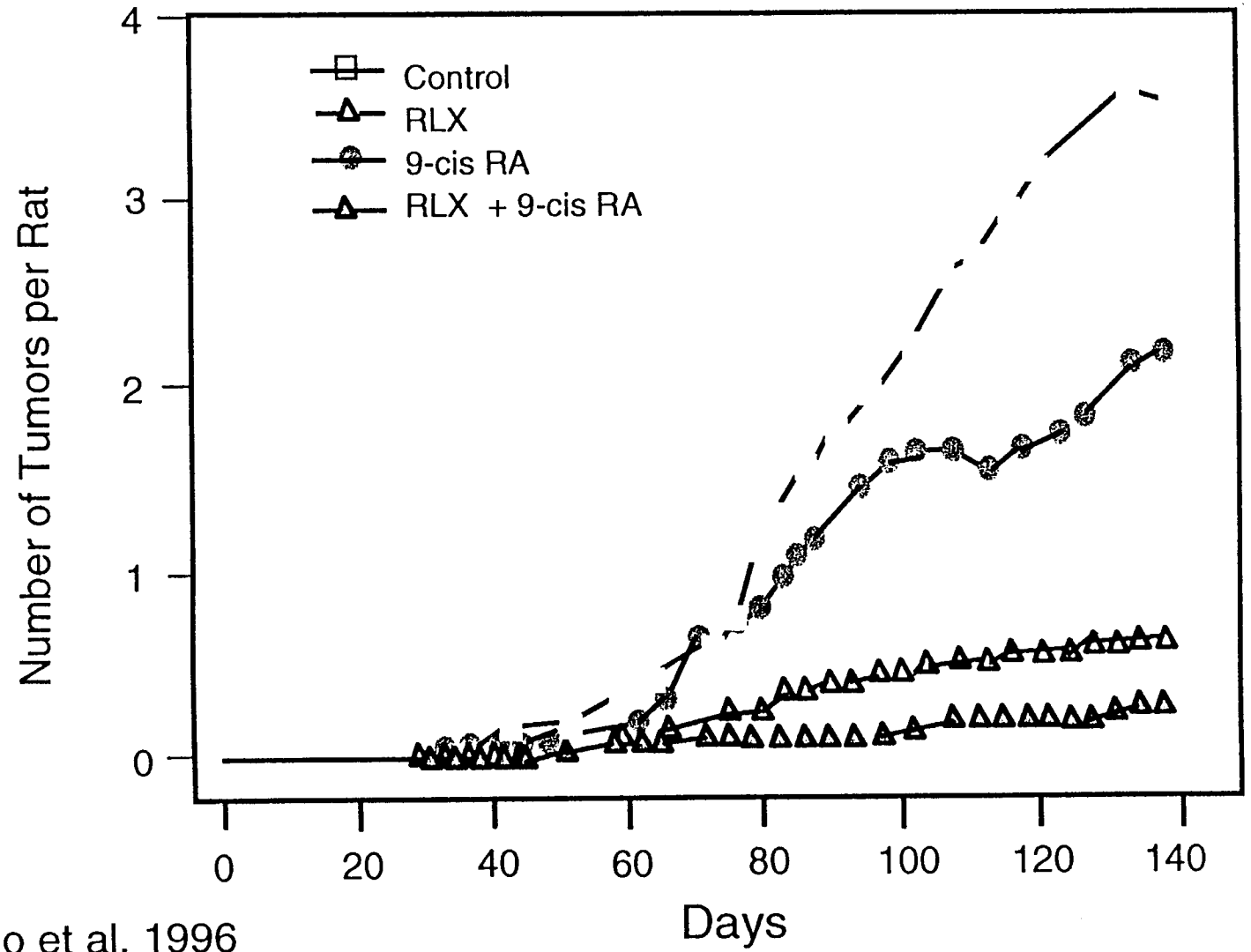
Figure adapted from Brzozowski et al. 1997

Raloxifene Acts as a Complete Anti-Estrogen in the Rat Uterus



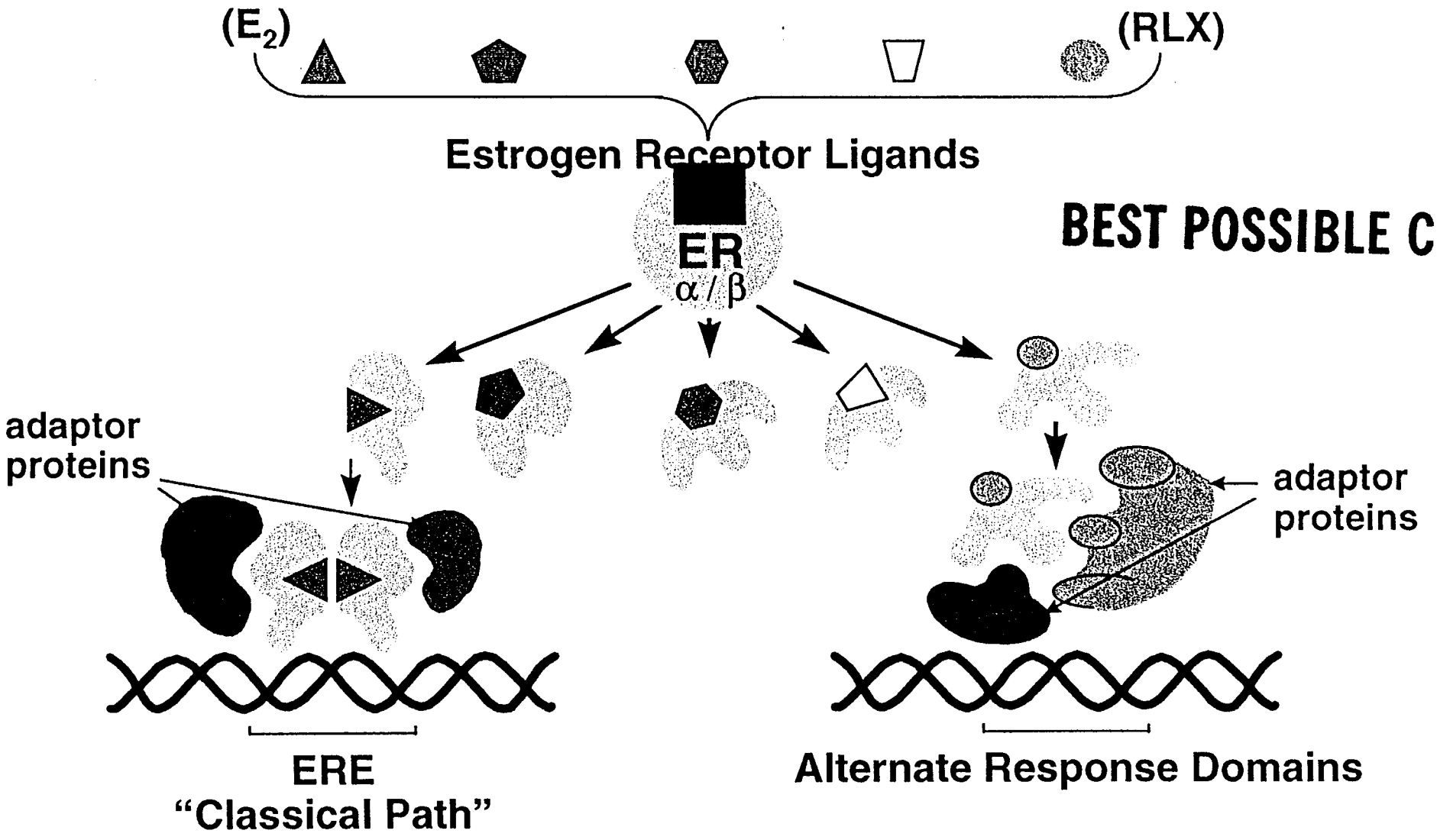
Bryant et al. 1996

Raloxifene Prevents Carcinogen Induced Tumors in Rats



Anzano et al. 1996

Estrogen Receptor Transcription Pathways



Adapted from McDonnell et al. (1995), Yang et al. (1996), Paech et al. (1997)

Role of ERα and ERβ in Body Organ Systems

Central nervous system: beta and alpha

Ovary: beta and alpha

Blood vessels: beta

Bone: beta

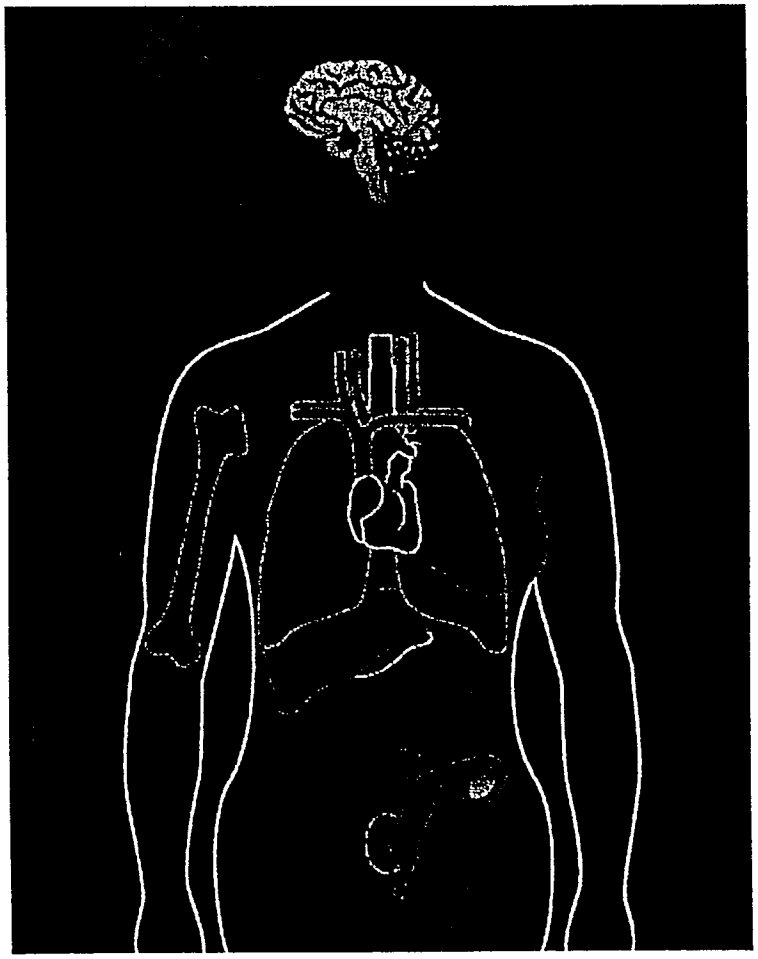
Lungs: beta

Urogenital tract: beta

Breast: alpha

Liver: alpha

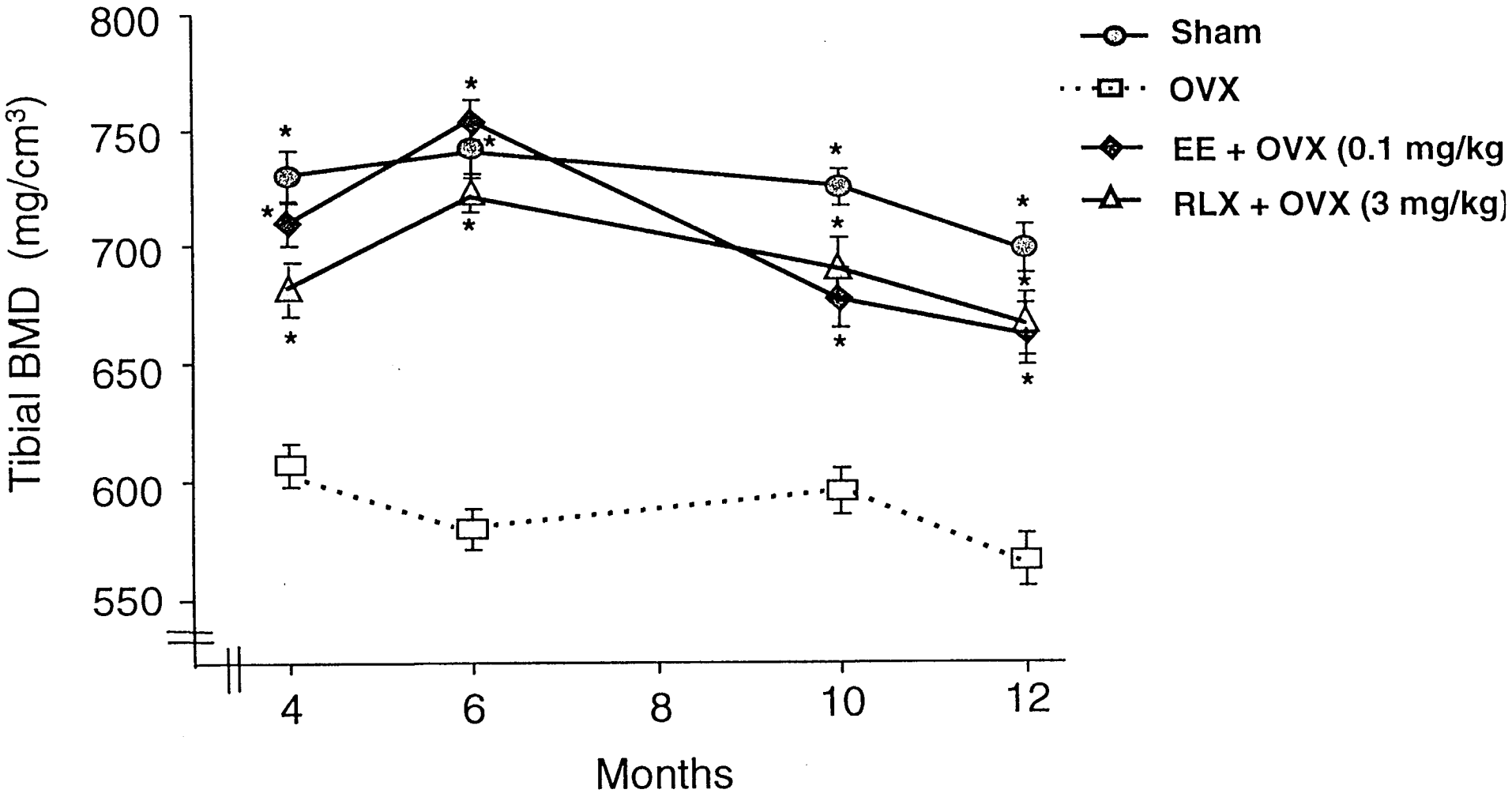
Uterus: alpha



alpha beta

Couse et al. 1997, Shughrue et al. 1996, Arts et al. 1997

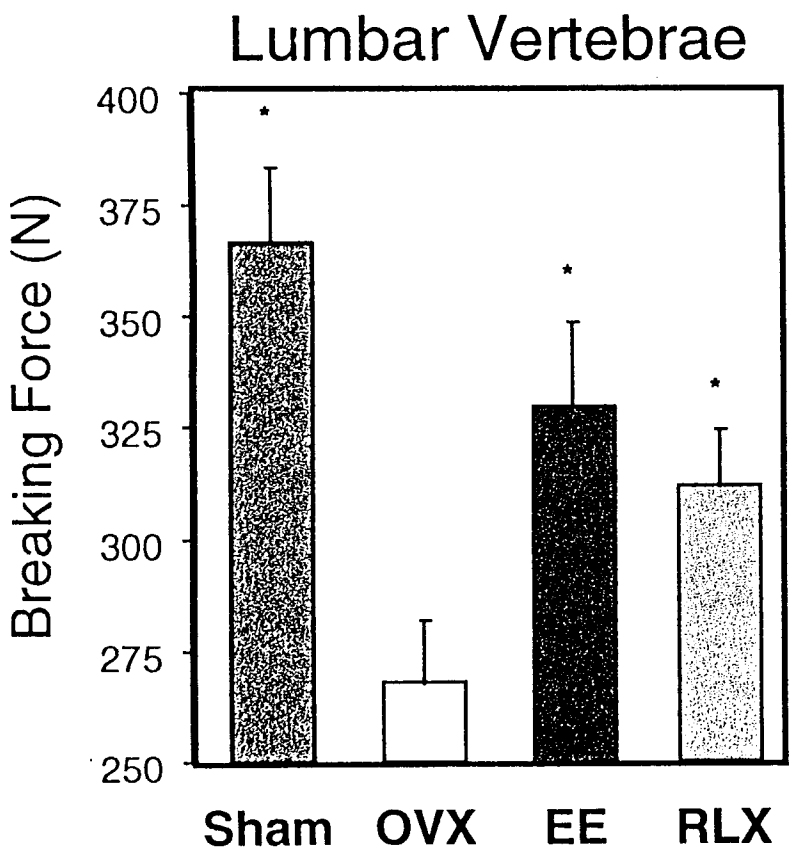
Raloxifene Prevents Bone Loss in the OVX Rat

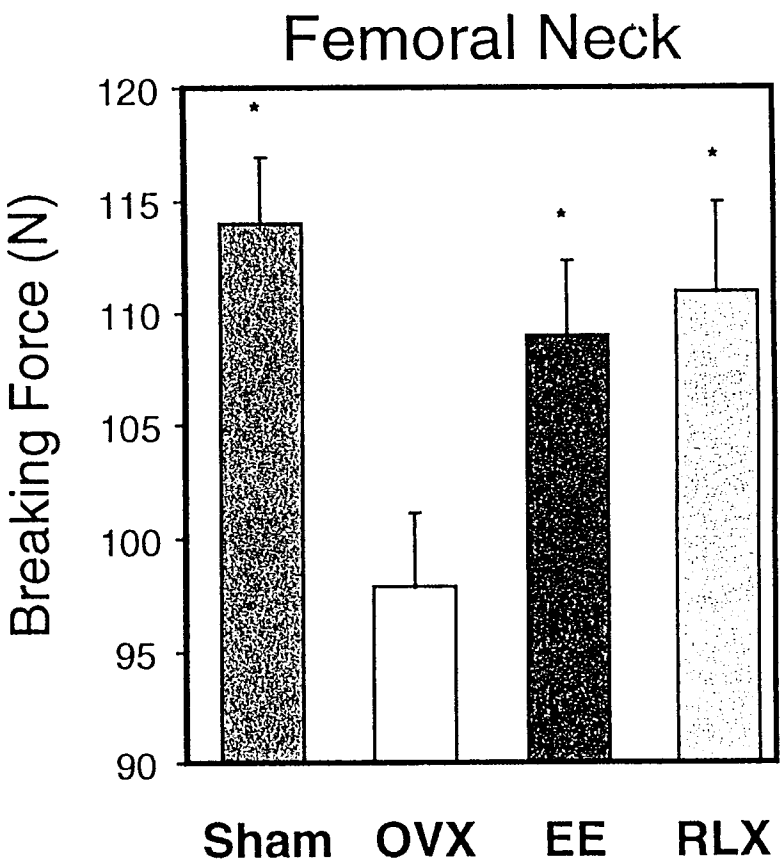


Bryant et al. 1995

*$p \leq 0.05$

Raloxifene Preserves Bone Strength in the OVX Rat

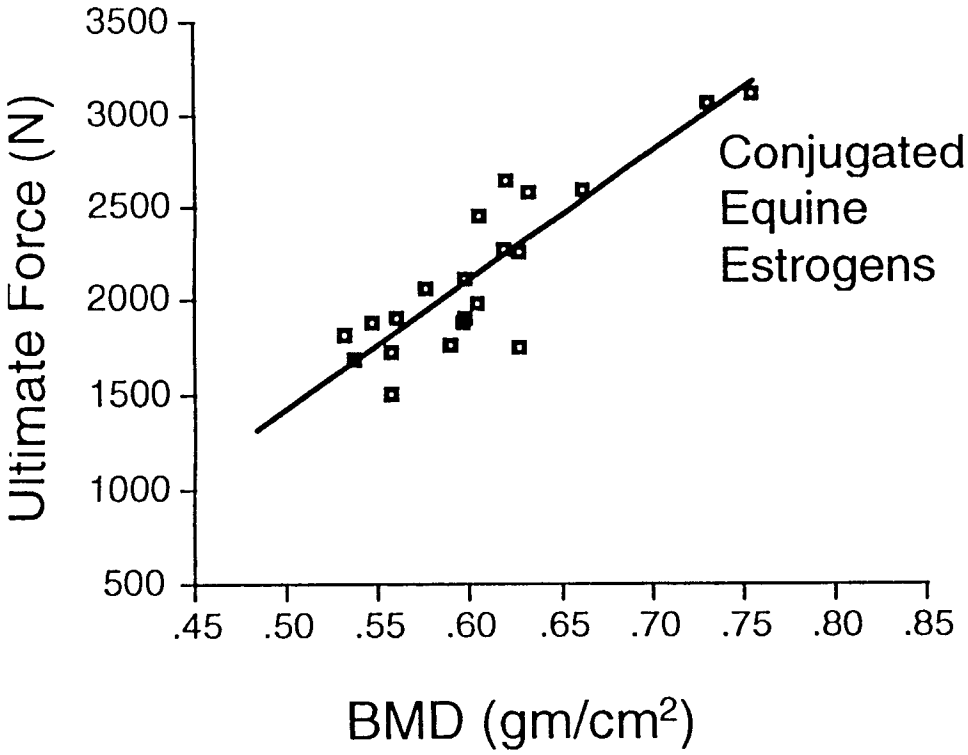




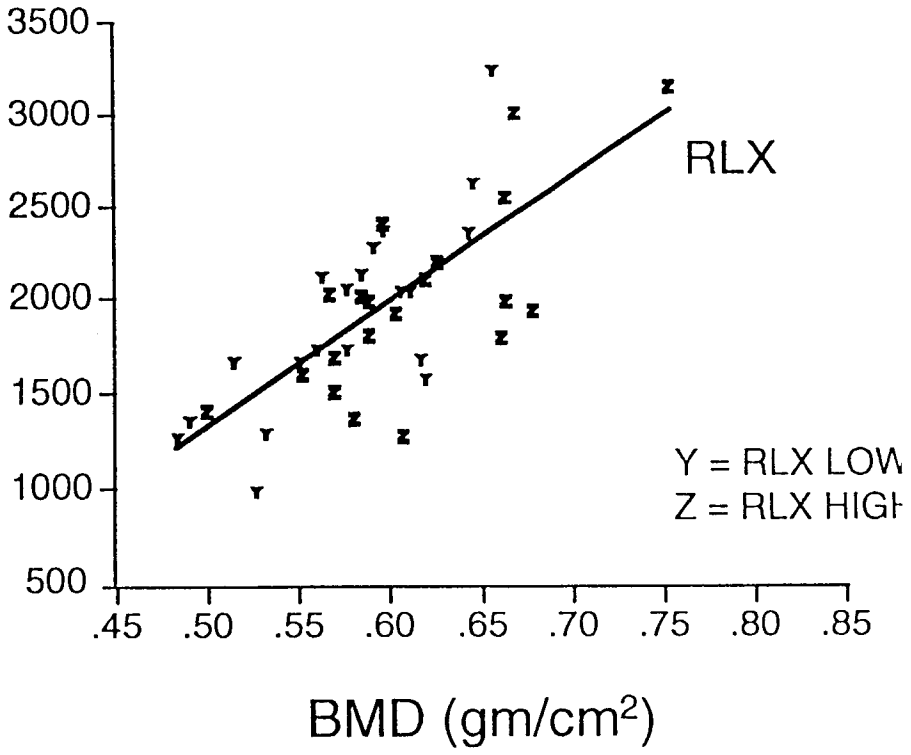
Turner et al. 1994

* = $p < 0.05$ vs OVX control

Relationship Between Vertebral BMD and Ultimate Force in Cynomolgus Monkeys



r = 0.78, p < 0.0001



r = 0.73, p < 0.0001

Histological Criteria for Normal Bone Quality

- No woven bone
- No marrow fibrosis
- No mineralization defect
- No cellular toxicity (light microscopy)
- Histologically normal appearance

Raloxifene maintains normal bone quality

Clinical Efficacy

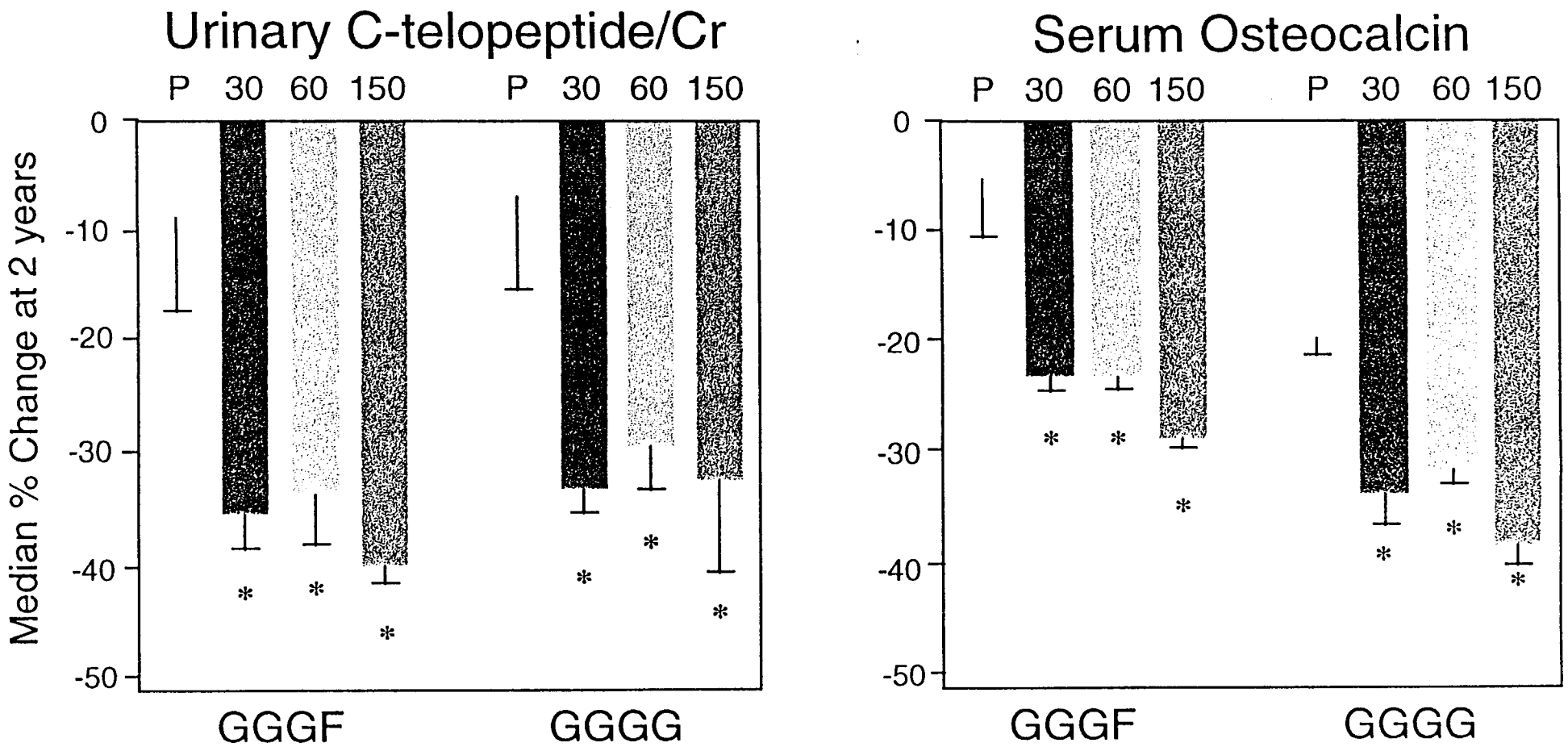
Willard H. Dere, MD

Osteoporosis Prevention Studies
Study Characteristics

	GGGF	GGGG	GGGH
Number of Subjects	601	544	619
Years Postmenopausal*	4.9	4.6	6.1
Percent Hysterectomy	12	19	100
Spine BMD (T-Score)*	-1.01	-0.92	-0.74
Therapy Arms	RLX 30 RLX 60 RLX 150 Placebo	RLX 30 RLX60 RLX150 Placebo	RLX 60 RLX150 Premarin® Placebo

* mean

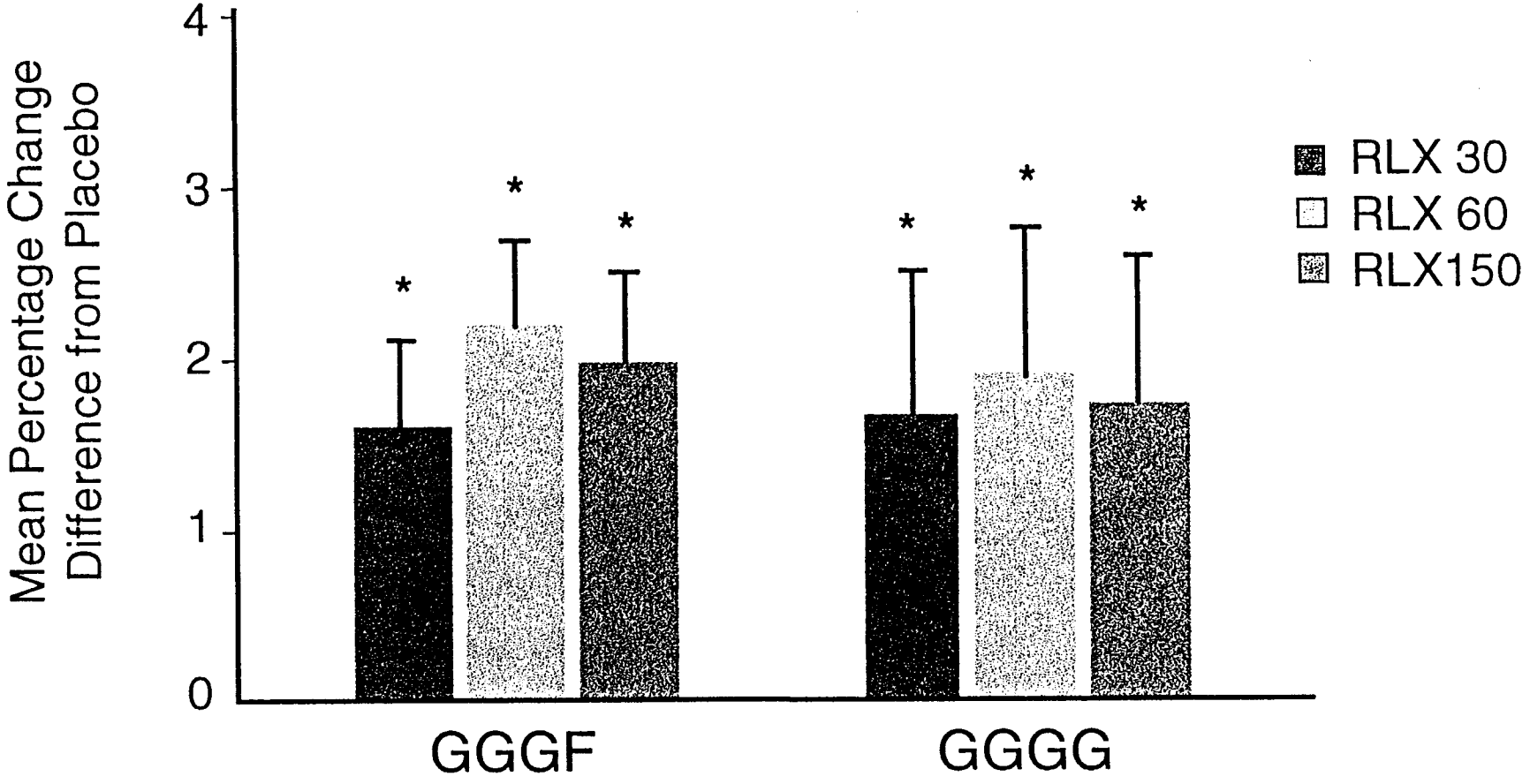
Raloxifene Effects on Bone Turnover



Raloxifene decreases biochemical markers of bone metabolism to the range seen in premenopausal women

* p<0.05 compared to placeb

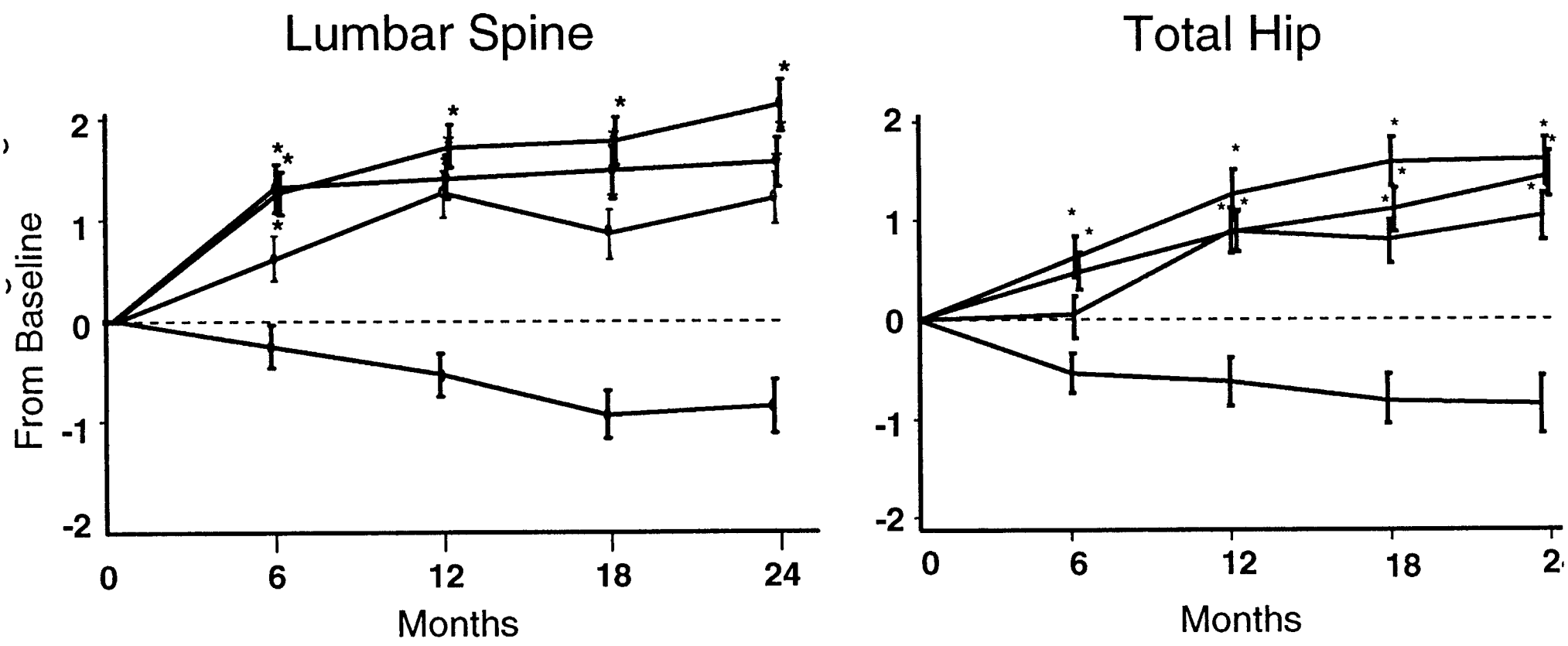
Raloxifene Effect on Total Body BMC



Raloxifene increases total body BMC compared with placebo through 2 years

* $p \leq 0.029$ compared to placebo

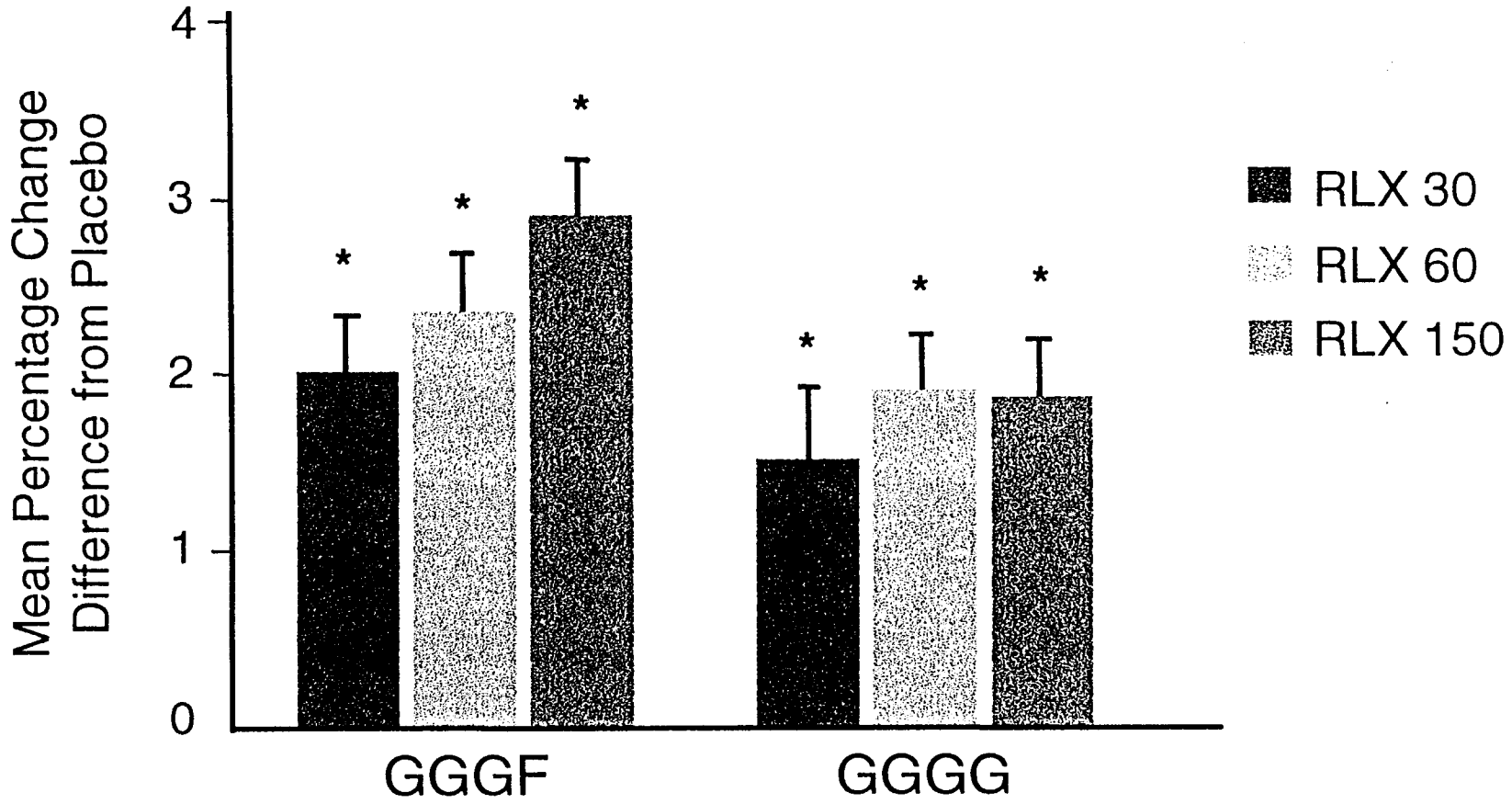
Raloxifene Effects on BMD



Study GGGF

* p<0.029 compared to placeb

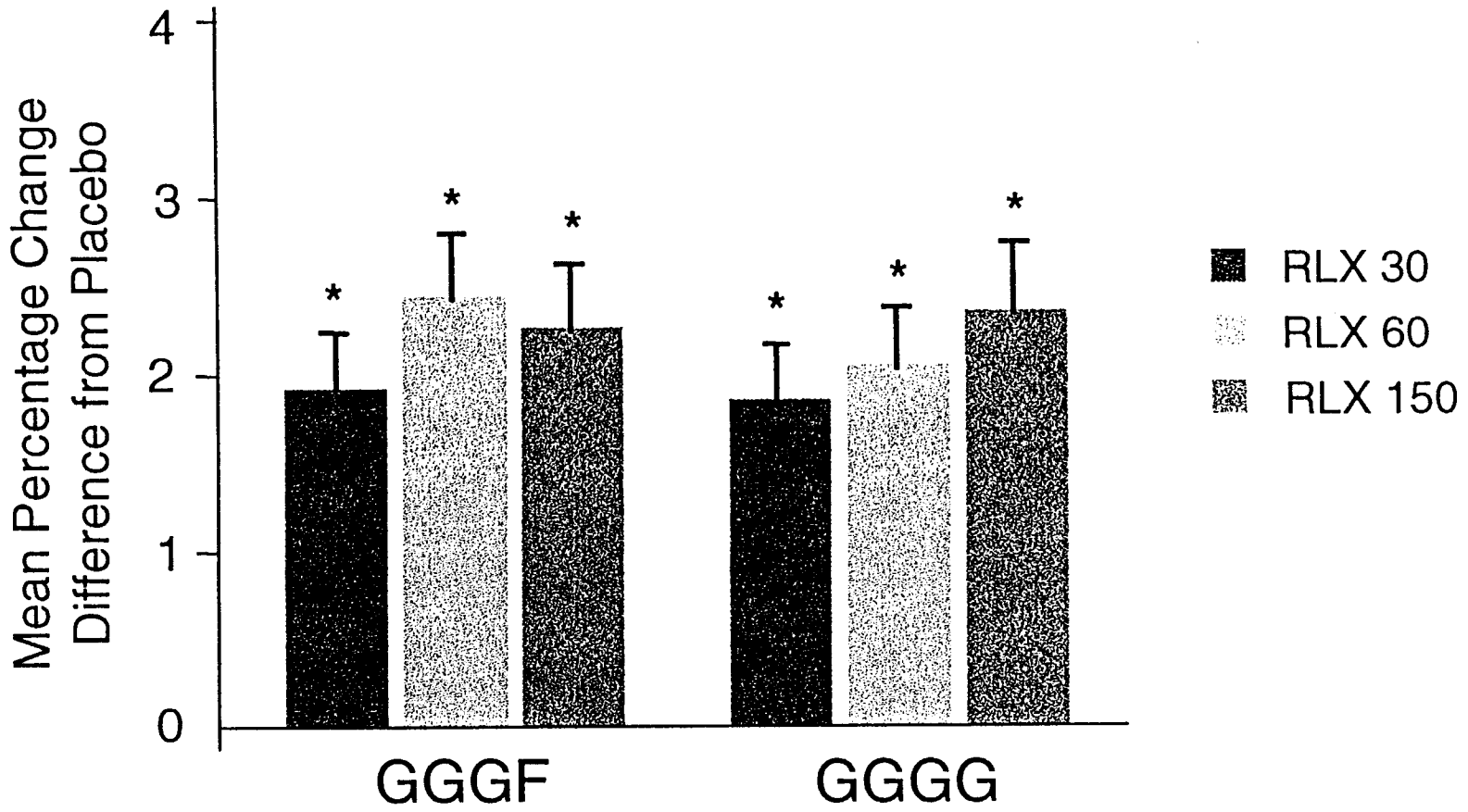
Raloxifene Effect on Lumbar Spine BMD



Raloxifene increases lumbar spine BMD through 2 years

* $p \leq 0.029$ compared to placebo

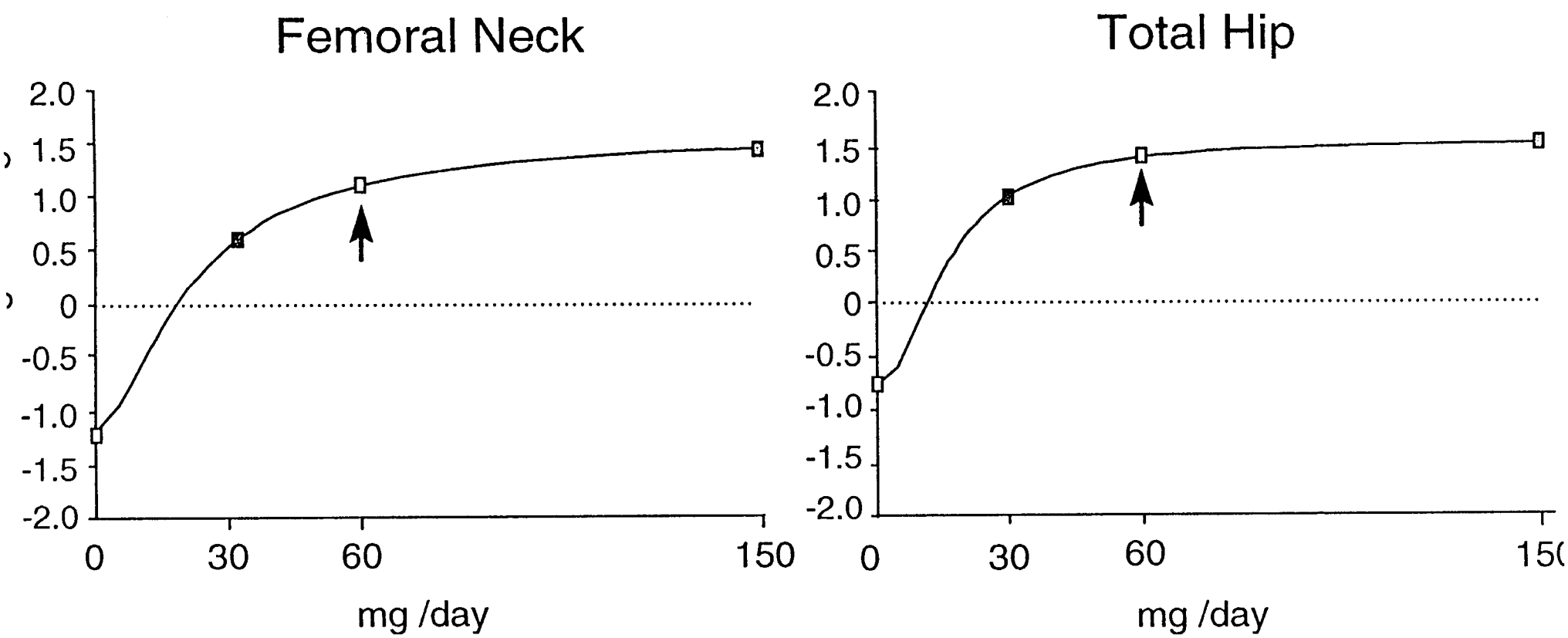
Raloxifene Effect on Total Hip BMD



Raloxifene increases total hip BMD through 2 years

* $p \leq 0.029$ compared to placebo

Percentage Change in BMD Comparison Using Non-linear Models



Raloxifene 60 mg/day is the lowest maximally effective dose

Studies GGGF and GGGG

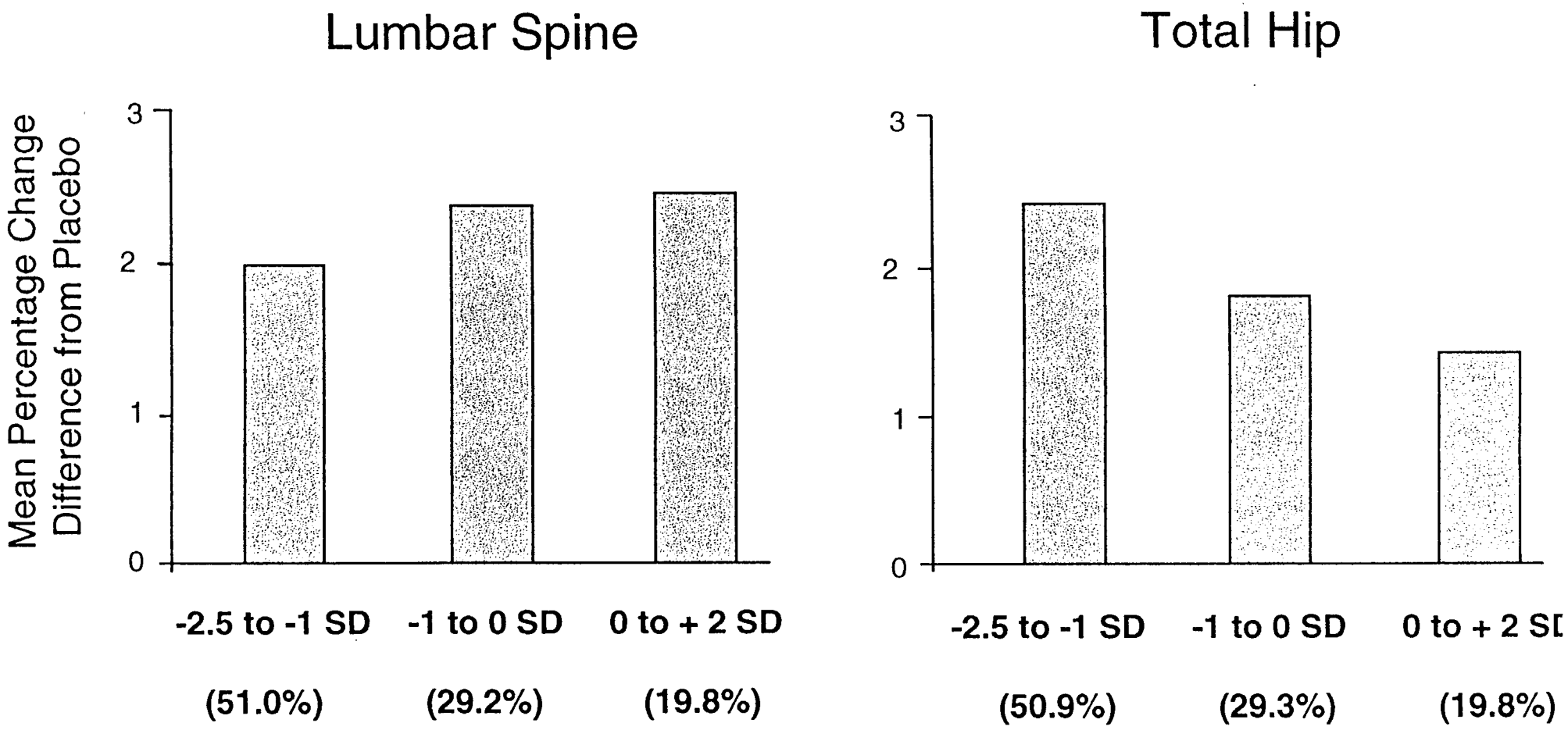
Actual (observed) BMD percentage change

Subgroup Analyses

- Initial BMD
- Initial bone turnover
- Age

Subjects respond regardless of subgroup category

Raloxifene 60 mg Effects Stratified By Initial BMD



Studies GGGF and GGGG

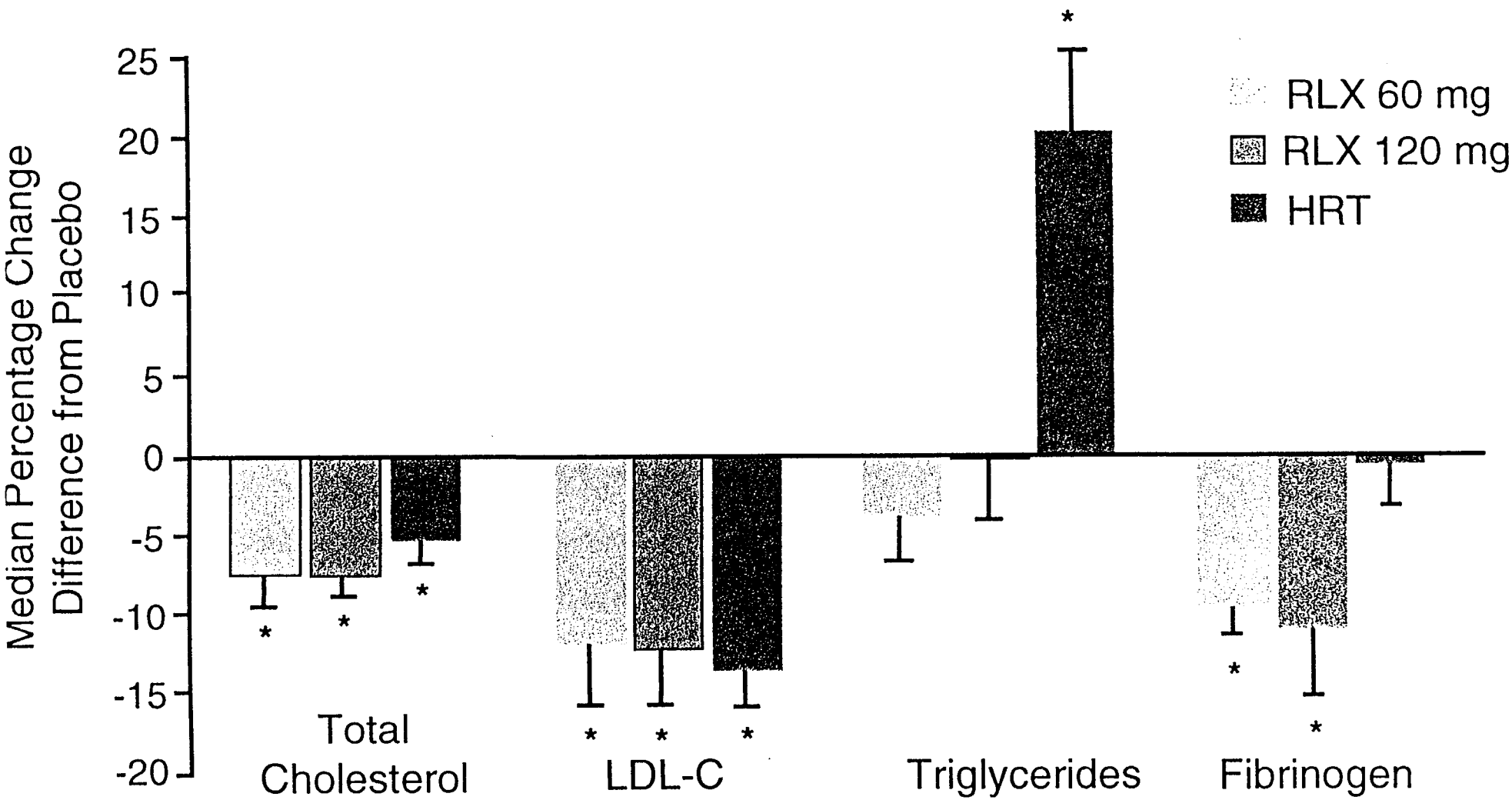
Intermediate Cardiovascular Endpoints

Summary of Cardiovascular Effects of Raloxifene 60 mg

- Lowers total cholesterol
- Lowers LDL-C
- Lowers fibrinogen
- Lowers Lp(a)
- Does not raise triglycerides
- Is neutral on FPA, F_{1+2}, and PAI-1
- Is neutral on total HDL-C

Raloxifene may reduce cardiovascular risk

Raloxifene Effects on Intermediate Cardiovascular Endpoints



Study GGGY

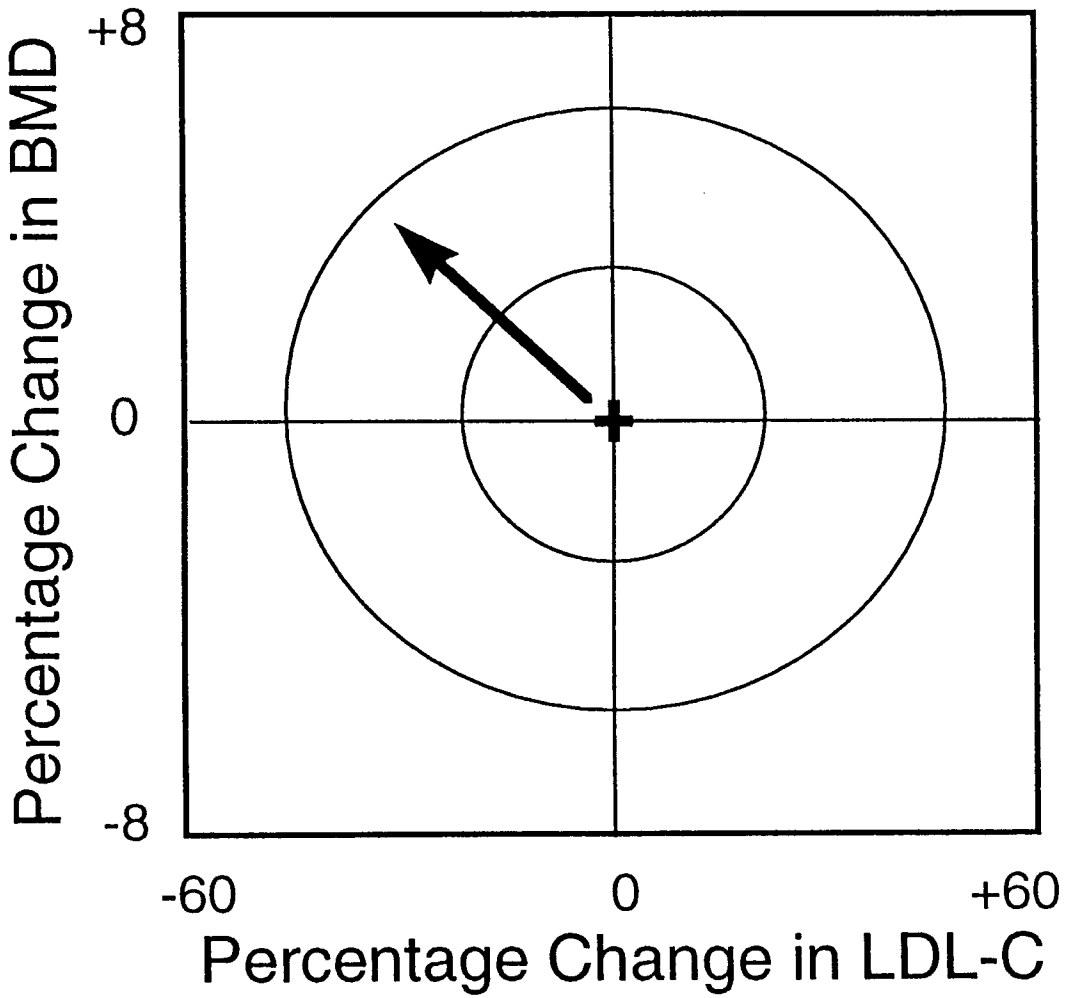
* $p<0.05$ compared to placebo

Summary

Raloxifene 60 mg

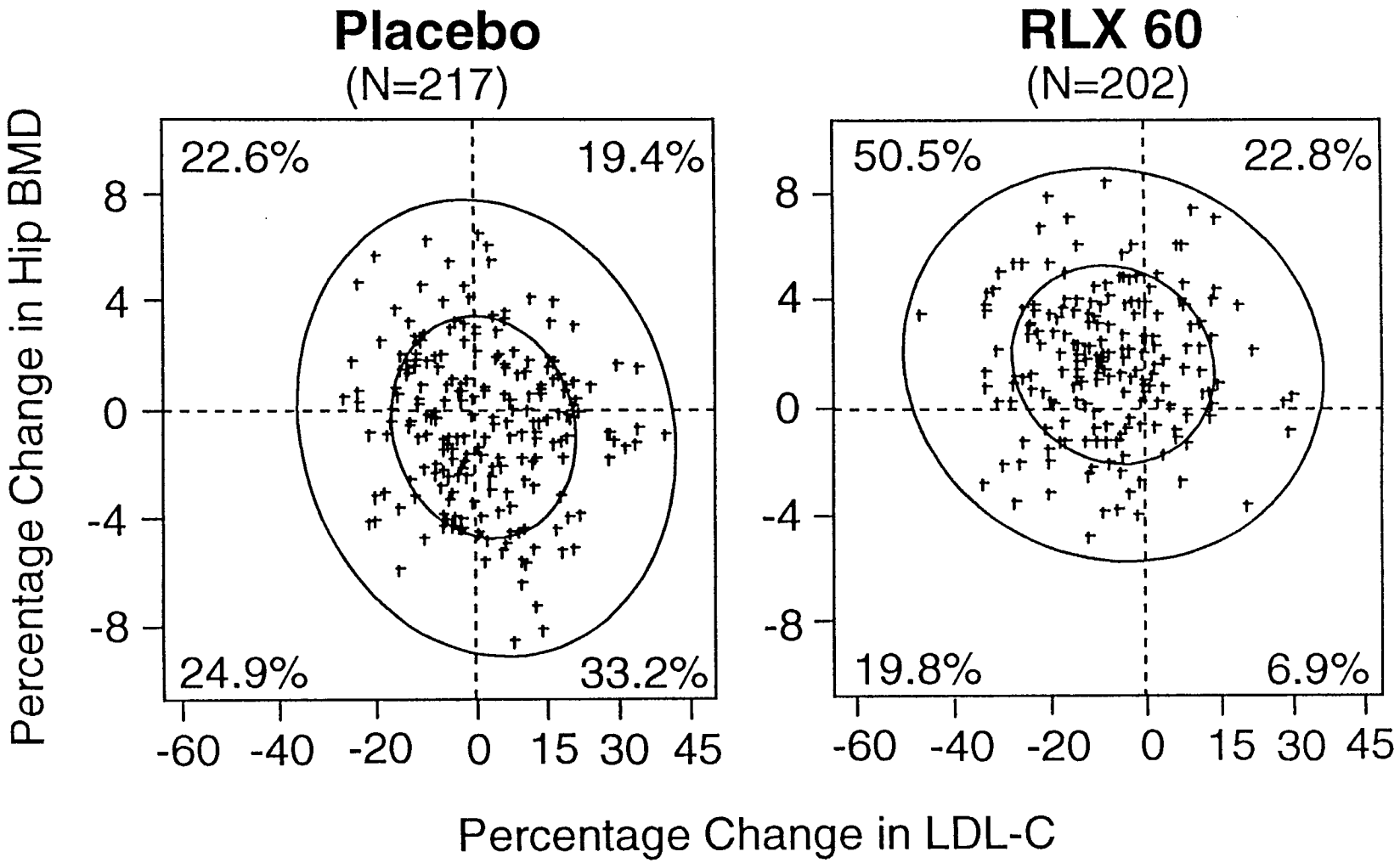
- Decreases bone turnover as assessed by biochemical markers of bone metabolism
- Increases spine and hip BMD and total body BMC
- Decreases fibrinogen, total and LDL-cholesterol without increasing triglycerides

Total Hip BMD and Serum LDL-C
Bivariate Analysis



Circles contain 50 and 95 percent of subjects, respectively

Raloxifene Exerts Global Population Benefit on Hip BMD and LDL-C



Studies GGGG and GGGF

Conclusions

- Working through estrogenic mechanisms, raloxifene prevents osteoporosis and maintains normal bone quality

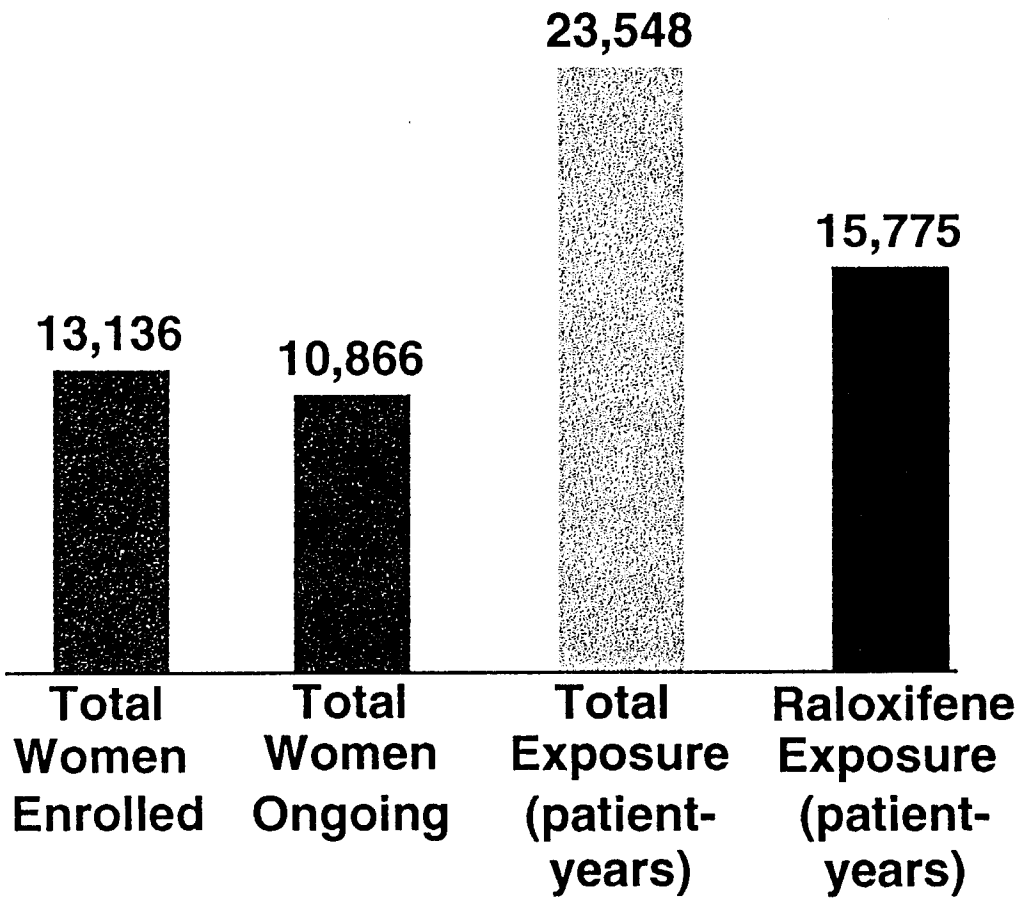
- Raloxifene 60 mg per day is the lowest maximally effective dose

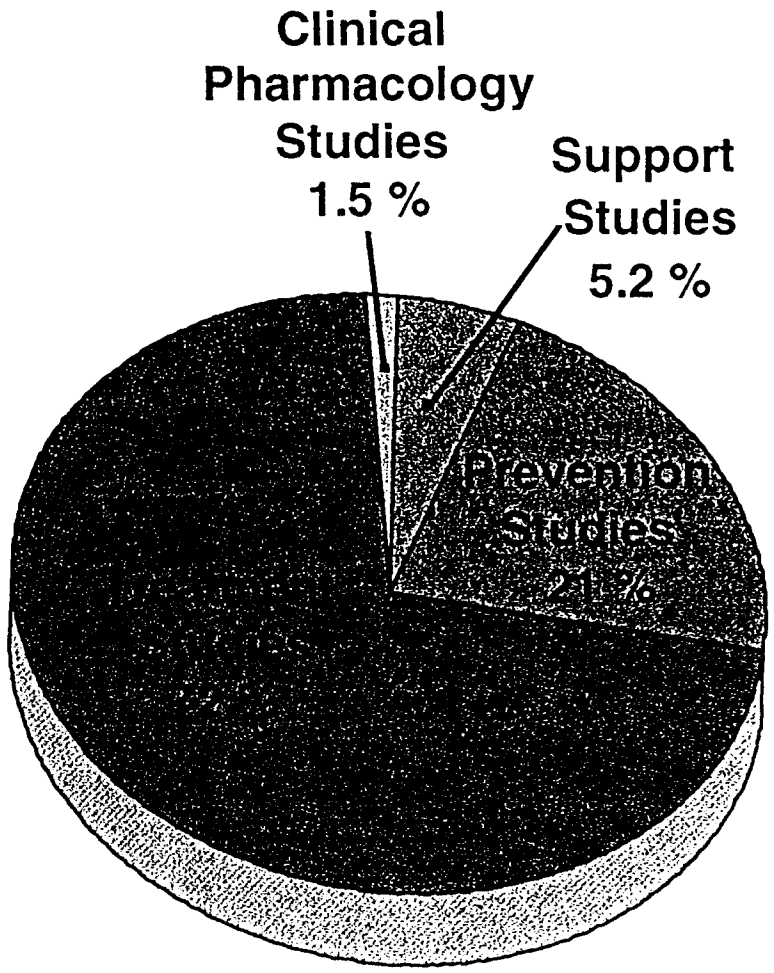
- Effects of raloxifene on intermediate markers of cardiovascular risk may provide added benefit

Raloxifene Clinical Safety

Fredric J. Cohen, MD

Scope of Safety Assessments





Total Exposure (patient-years)
23,548

Data from all fully enrolled studies as of 22 Sept 1997

Safety Data Integration

Primary Placebo-Controlled Studies

- GGGF
- GGGG
- GGGH
- GGGN
- GGGY

N = 2043

ERT-Controlled Studies

- GGGH
- GGGM

N = 670

HRT-Controlled Studies

- GGGR
- GGGX
- GGGY
- GGGZ

N = 974

Other clinical studies used for safety analyses include:
GGGK, GGGP, GGHD, GGHG, GGHI, JOAA (**N = 8374**)

Agenda

General Safety

- Toxicology/Phase 1
- Phase 2 and 3
  - Mortality
  - Serious Adverse Events
  - Discontinuations
  - General Adverse Events

Specific Safety

- Menopause-Related Adverse Events
- Circulatory System
- Reproductive System

Conclusions

Phase 1 Clinical Testing

- Preceded by toxicology testing: no findings of clinical relevance to postmenopausal women
- 20 Phase 1 Studies, 376 volunteers
- Oral dosing up to 600 mg/day
- No acute toxicity or physiological changes
- May be given once daily without regard to food
- Not metabolized via P450

General Safety

Mortality

- No significant change in mortality at any dose

Serious Adverse Events

- No therapy difference in incidence of serious adverse events, overall or individually

Discontinuations

- No therapy difference overall or for discontinuations due to adverse event

Vital Signs and Laboratory Findings

- No effect on vital signs; no clinically important effects on laboratory parameters

Adverse Events

	Placebo N = 584 (%)	RLX 30 N = 288 (%)	RLX 60 N = 581 (%)	RLX HI N = 590 (%)	TOTAL N = 2043 (%)
Any Event	87	85	87	87	87
Vasodilatation*	18	17	25	28	23
Leg cramps*	2	3	6	5	4

$p<0.05$ for overall therapy difference and linear dose trend

RLX HI refers to RLX120/150

Leg Cramps

	Placebo N = 584 (%)	RLX 30 N = 288 (%)	RLX 60 N = 581 (%)	RLX HI N = 590 (%)	TOTAL N = 2043 (%)
Incidence*	1.9	3.1	5.9	5.3	4.2
Severe	0.2	0.3	0.3	0.2	0.2
Discontinued	0.0	0.0	0.0	0.3	0.1

$p<0.05$ for overall therapy difference and linear dose trend

Hot Flashes

	Placebo N = 584 (%)	RLX 30 N = 288 (%)	RLX 60 N = 581 (%)	RLX HI N = 590 (%)	TOTAL N = 2043 (%)
Incidence*	18	17	25	28	23
Severe	1.9	1.7	2.1	3.2	2.3
Discontinued	2.2	1.7	1.7	3.1	2.3

Incidence differences limited to 1st 6 months of therapy

$p<0.05$ for overall therapy difference and linear dose trend

Lack of Effect on Other Reported Menopause-Related Adverse Events

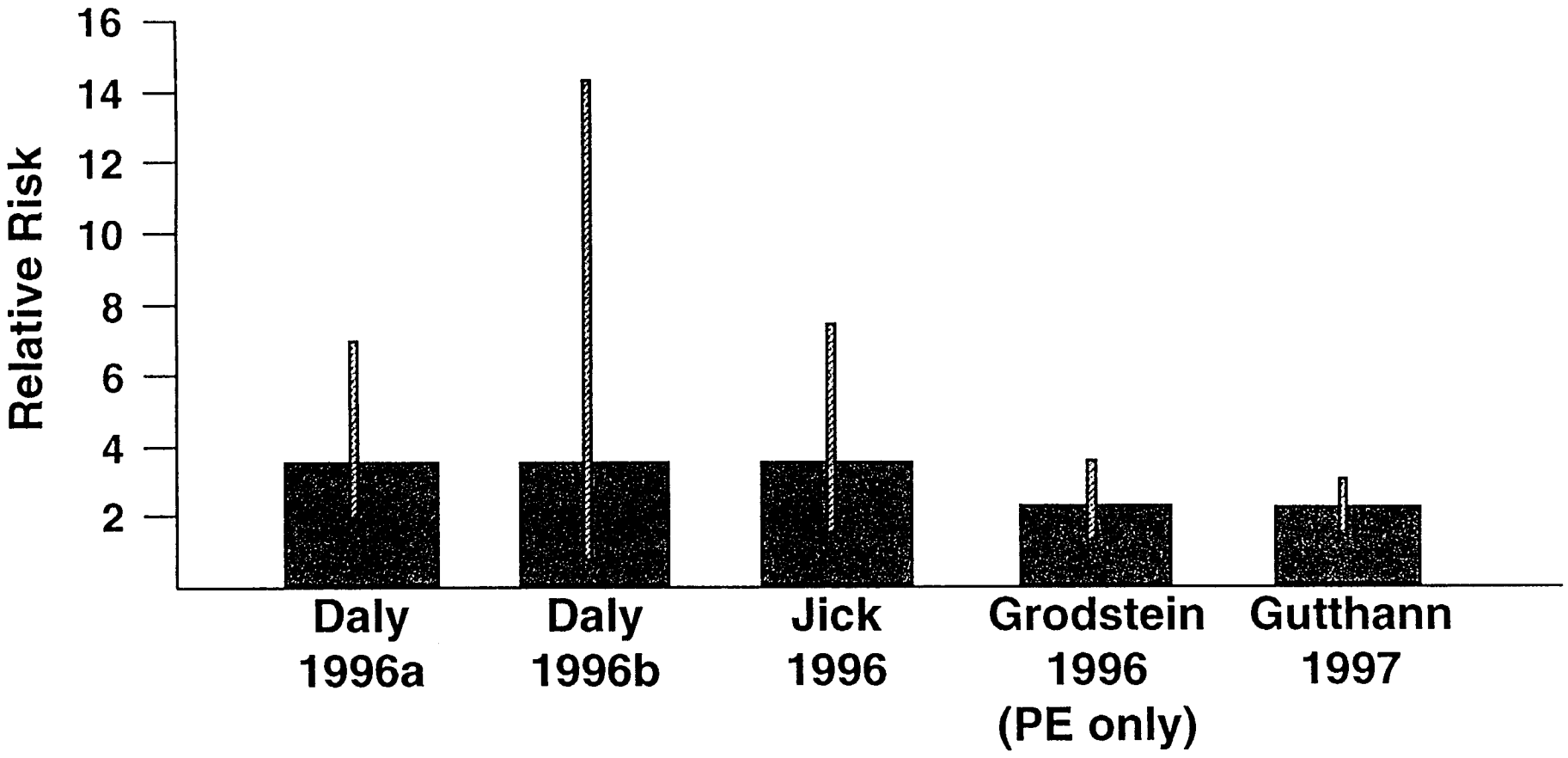
CNS	GU	Skin
depression	urinary tract infection	sweating
insomnia	vaginitis	pruritus
anxiety	cystitis	acne
emotional lability	urinary frequency	alopecia
sleep disorder	urinary incontinence	dry skin
libido decreased	dyspareunia	hirsutism
tolerance decreased		mucous membrane disorder

No therapy difference for any event or group of events

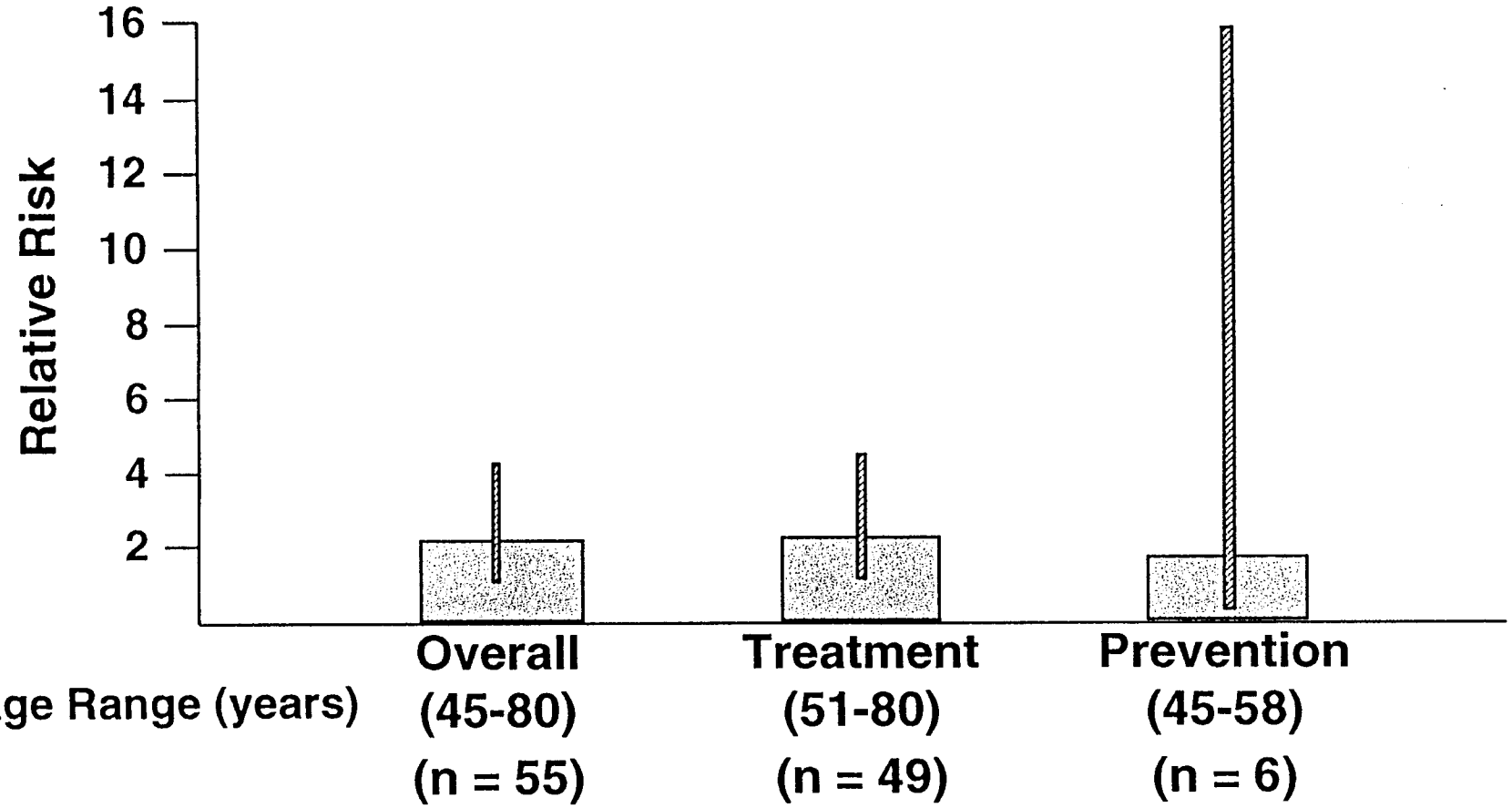
Arterial Events

- Preclinical and clinical efficacy results suggest possible benefits to reduce arterial events
- Few cases of myocardial infarction or stroke in primary placebo-controlled database
- Serious adverse event monitoring of all studies indicates possible risk reductions (not significant)

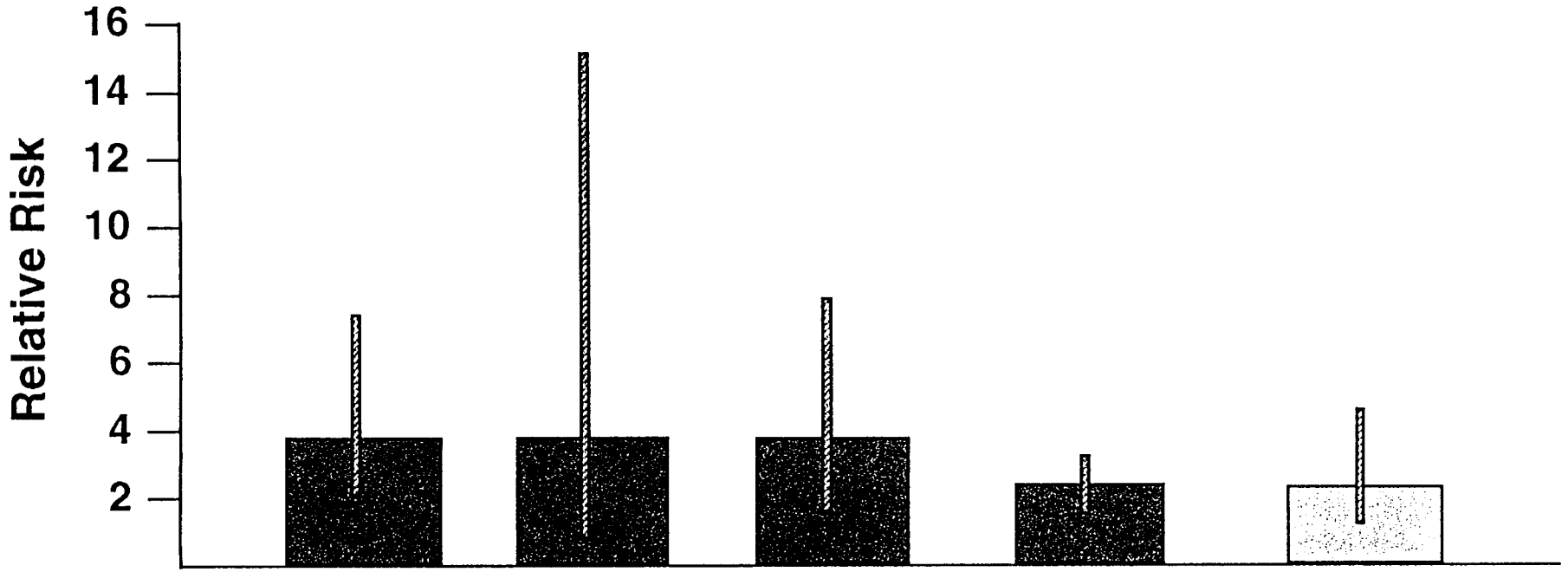
Venous Thromboembolism
Review of HRT Literature



Venous Thromboembolism
Raloxifene Experience

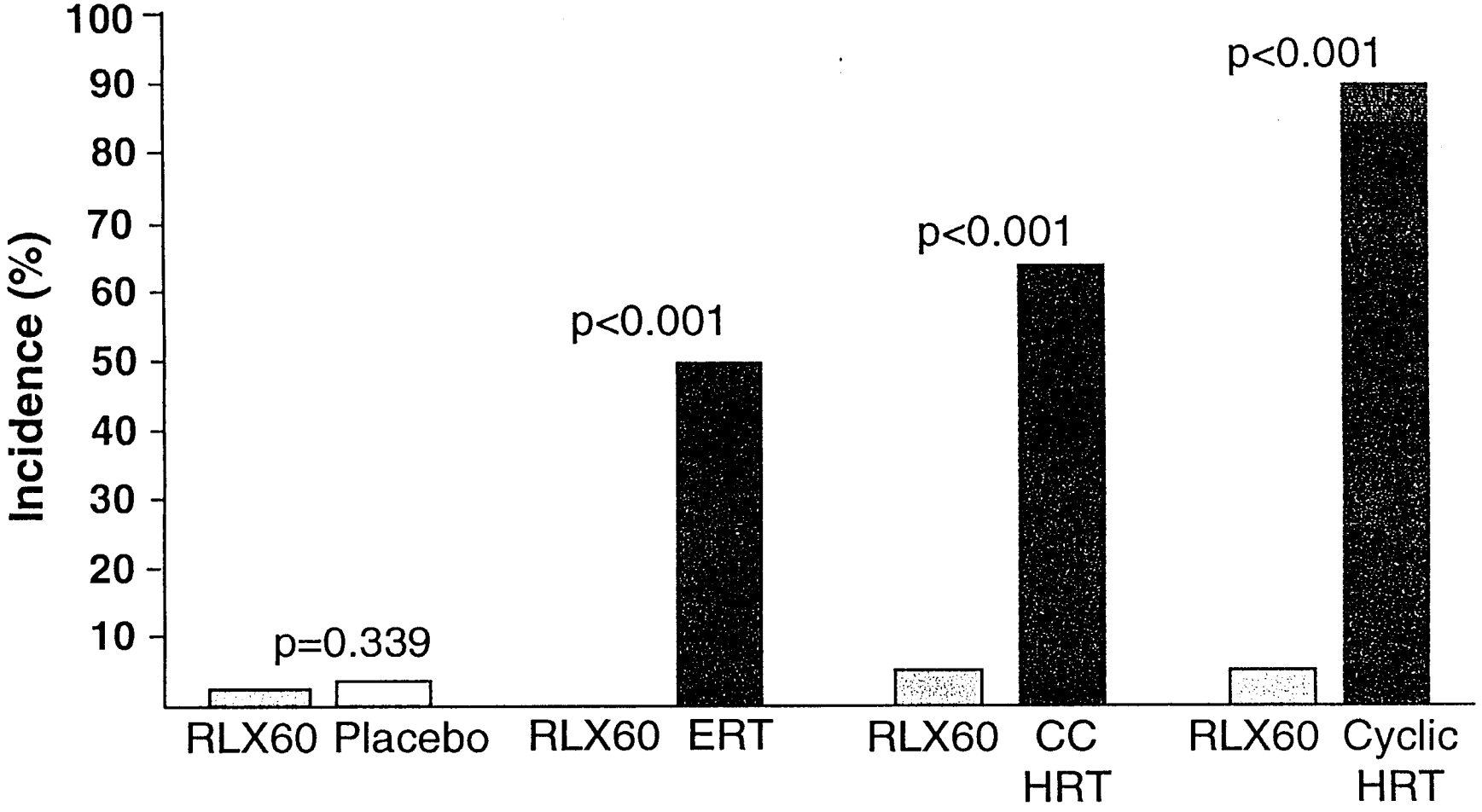


Venous Thromboembolism
Raloxifene versus HRT



	Daly 1996a	Daly 1996b	Jick 1996	Gutthann 1997	Overall Raloxifene
Age Range (years)	(45-64)	(45-64)	(50-74)	(50-79)	(45-80)
Attributable Risk (per 100,000)	16.5	NA	32	27	28

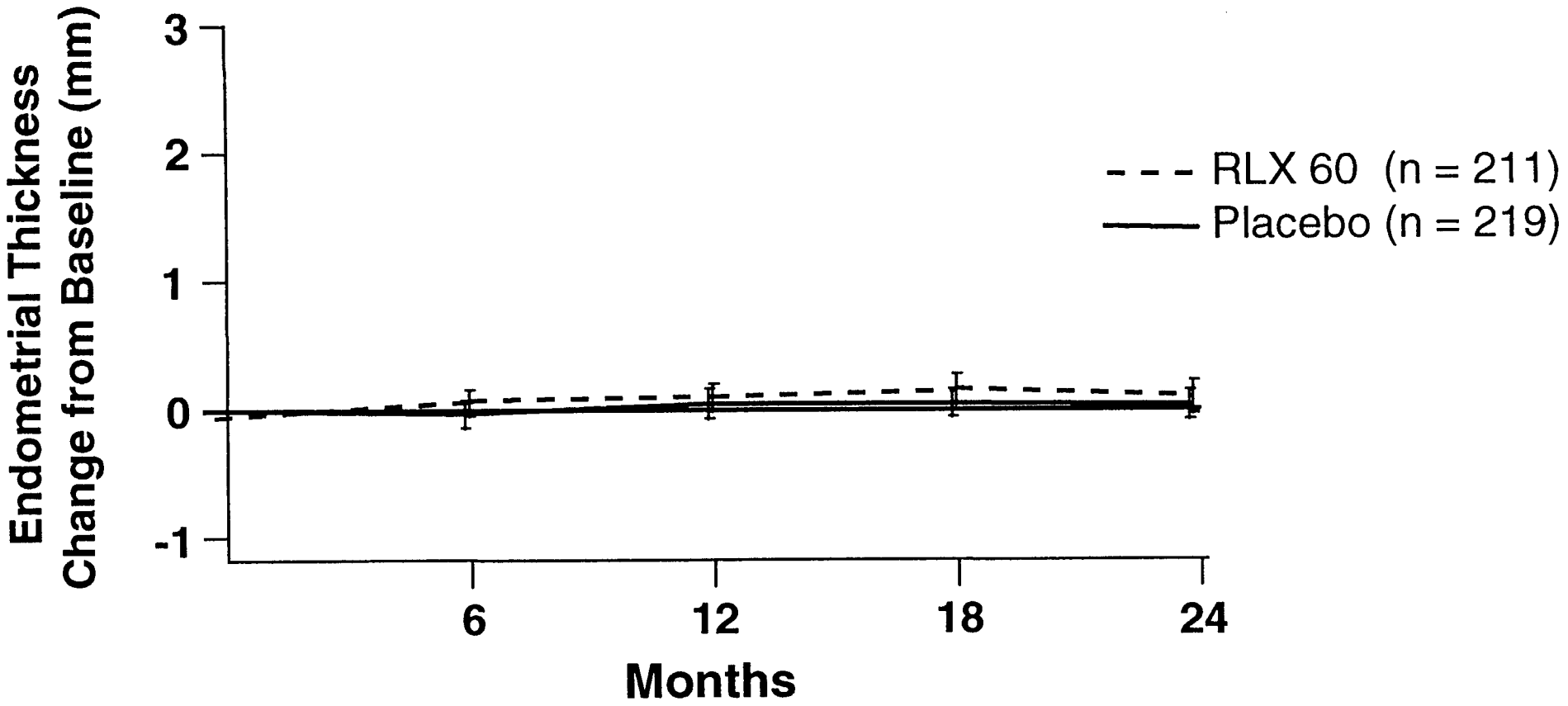
Vaginal Bleeding



Incidence of bleeding during raloxifene same as placebo and less than ERT or HRT

BEST POSSIBLE COPY

Endometrial Thickness



Raloxifene does not increase endometrial thickness

udies GGGF and GGGG

Endometrial Histology

	Placebo N = 247	RLX 60 N = 245
Inadequate (insufficient tissue)	8	8
Surface Endometrium	1	2
Inactive/Atrophic	3	5
Non-proliferative	4	5
Proliferative	2	0
Polyps	3	2
Malignancy	0	0
Total	21	22

Raloxifene does not induce endometrial proliferation

tudies GGGF and GGGG

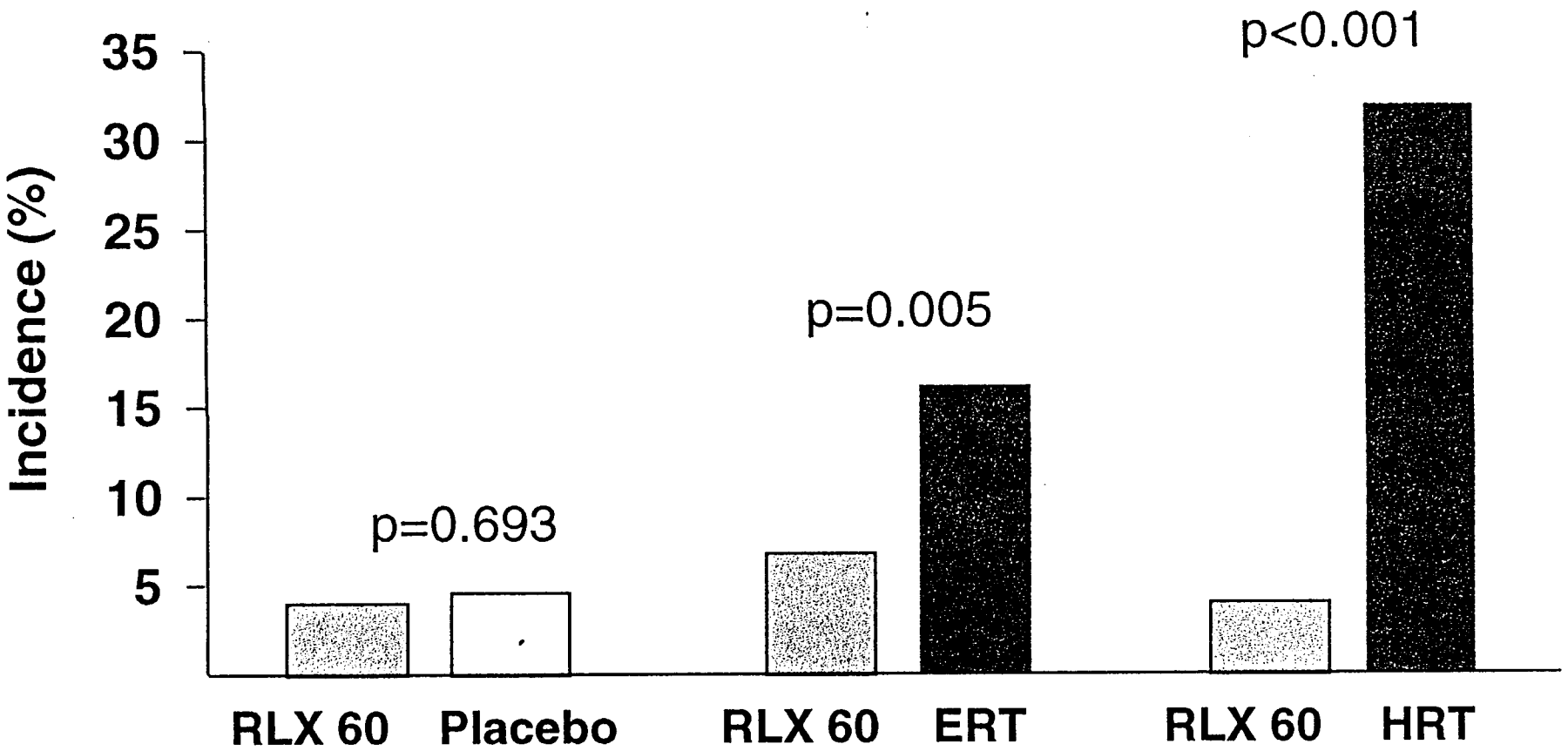
Endometrial Cancer

Overall	**RR**	**(95% CI)**
Raloxifene vs Placebo	0.84	(0.25, 2.87)

After 12 Months	**RR**	**(95% CI)**
Raloxifene vs Placebo	0.12	(0.02, 0.75)

Raloxifene does not increase endometrial cancer risk

Breast Pain



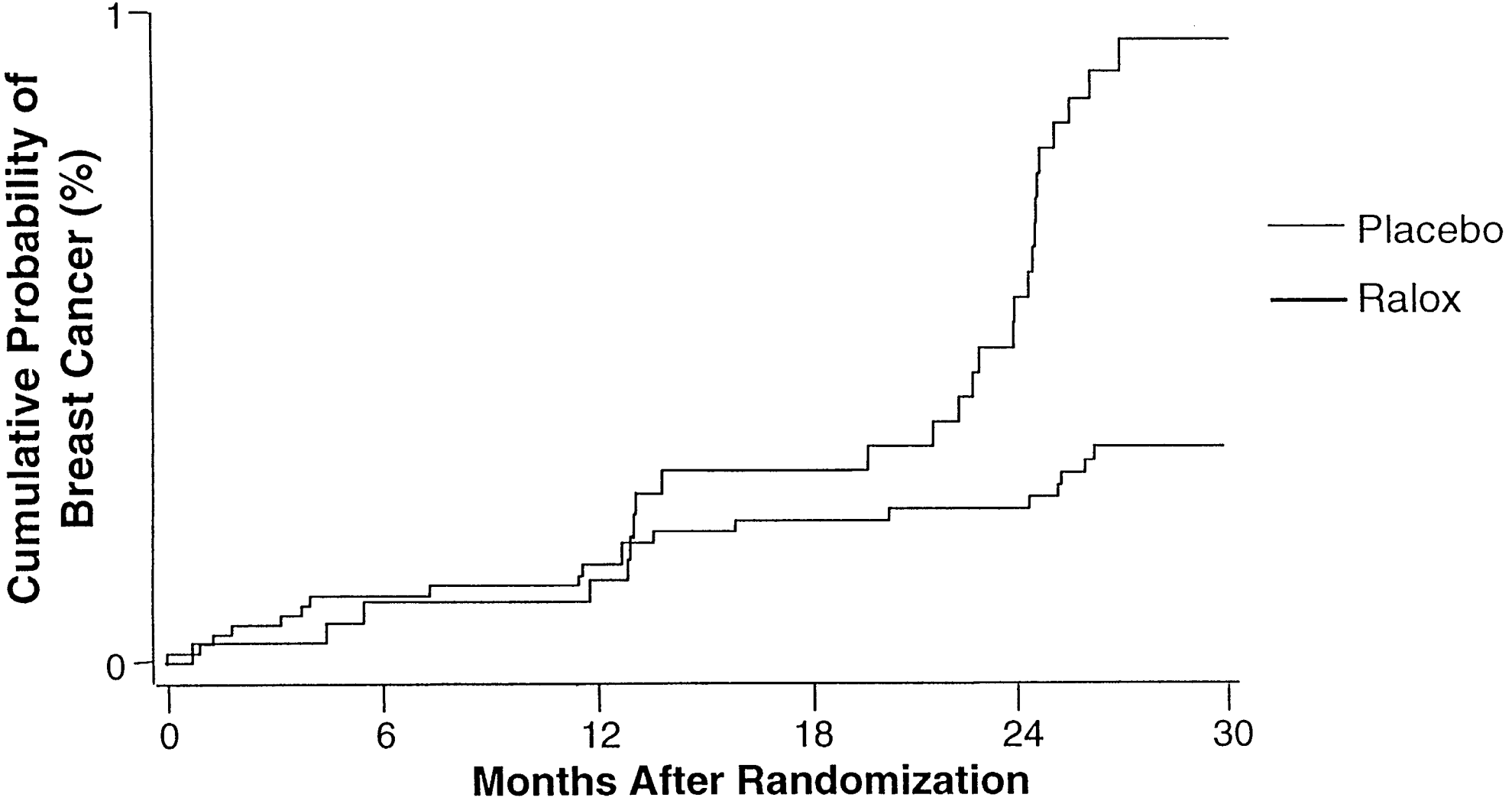
Incidence of breast pain during raloxifene same as placebo and less than ERT or HRT

Breast Cancer Incidence and Relative Risk Raloxifene versus Placebo

Population	Cases After	Placebo n	Raloxifene n	Relative Risk (95% CI)
Overall	1 month	25	20	0.38 (0.22, 0.68)
	18 months	17	8	0.23 (0.10, 0.49)
Treatment	1 month	22	14	0.32 (0.17, 0.60)
	18 months	14	5	0.18 (0.07, 0.44)
Prevention	1 month	3	6	0.79 (0.20, 3.12)
	18 months	3	3	0.39 (0.08, 1.84)

Raloxifene does not increase breast cancer risk and may be protective

Time to Diagnosis of Breast Cancer
All Placebo-Controlled Studies



g rank p-value = 0.001

Data cutoff as of 22 September 19

Safety Considerations for Optimal Dose

- Lowest maximally effective dose
- Most extensively studied
- Safe and well-tolerated

Raloxifene HCl 60 mg is optimal
from a safety perspective

Summary and Conclusions

- Extensively studied in postmenopausal women
- 3 adverse events probably causally related to raloxifene:
    - leg cramps
    - hot flashes
    - venous thromboembolism
- No evidence of effect on other menopausal symptoms
- No evidence of estrogenic effects on breast and uterus
- Does not increase breast cancer risk and may be protective

Raloxifene
Benefit / Risk Profile
and Conclusions

Willard H. Dere, MD

Raloxifene
Preclinical Pharmacology

Mechanism

- High affinity binding and action through the estrogen receptor

Skeleton

- Preserves BMD
- Maintains normal bone quality
- Maintains bone strength

Raloxifene
Preclinical Pharmacology

Cardiovascular

- Improves lipid profile
- Favorable non-lipid effects

Uterus

- Estrogen antagonism

Breast

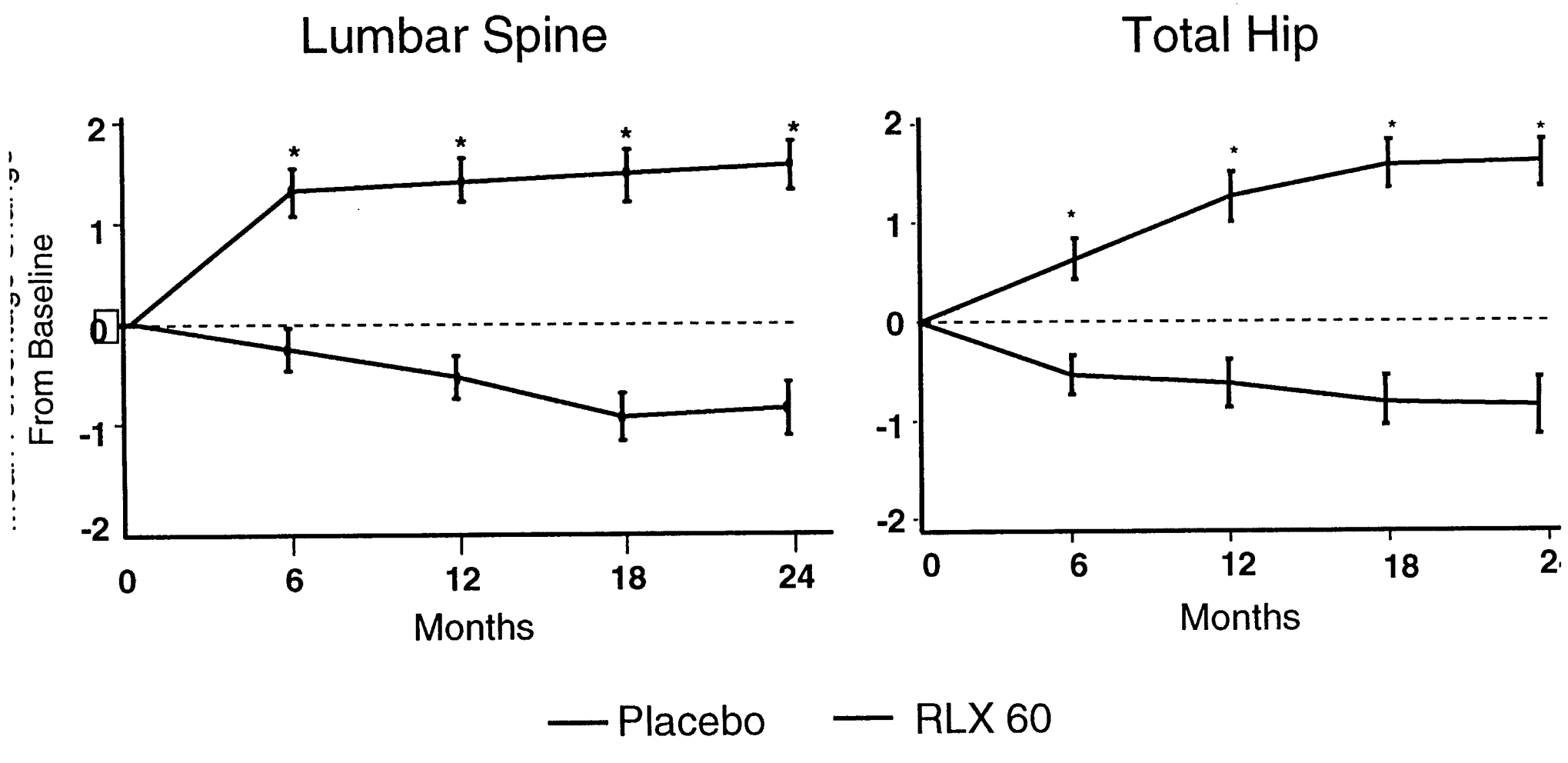
- Estrogen antagonism

Histological Criteria for Normal Bone Quality

- No woven bone
- No marrow fibrosis
- No mineralization defect
- No cellular toxicity (light microscopy)
- Histologically normal appearance

Raloxifene maintains normal bone quality

Raloxifene 60 mg Prevents Osteoporosis



Study GGGF

* p<0.029 compared to placebo

Raloxifene
Clinical Safety

Venous thromboembolism (VTE)

- Comparable to HRT

Hot flashes and leg cramps

- Severity comparable to placebo

Uterus

- Lack of endometrial bleeding and proliferation

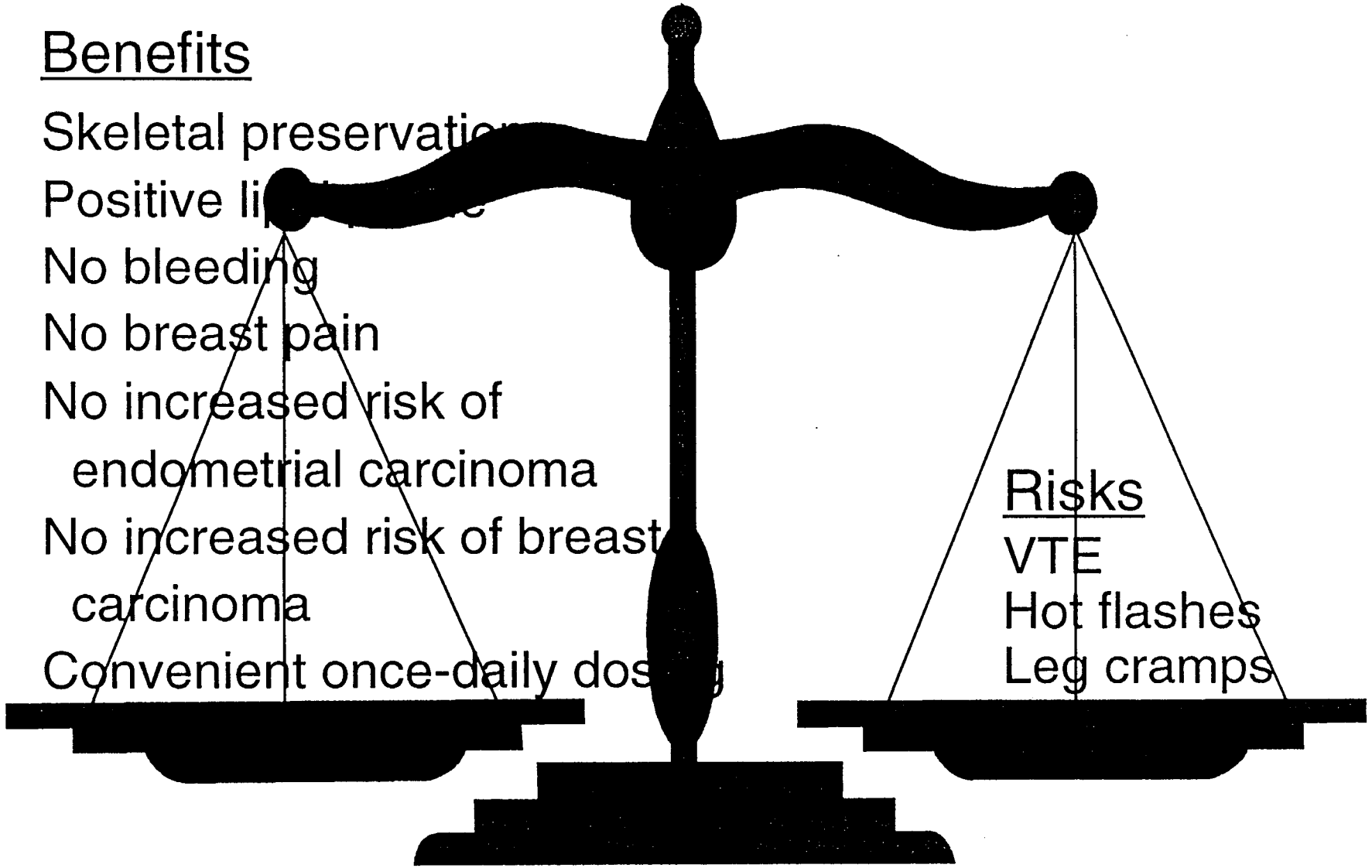
Breast

- Anti-proliferative effects

Raloxifene 60 mg

- Lowest maximally effective dose on BMD
- Improves markers of cardiovascular risk
- Protects the uterus and breast

Raloxifene Benefit / Risk Considerations



Conclusion

- Postmenopausal osteoporosis is an area of unmet medical need
- Raloxifene is estrogen-like in bone
- Raloxifene preserves bone mineral density with normal bone quality
- The 60 mg dose provides the most favorable benefit / risk profile

Raloxifene will provide an important new choice for the prevention of postmenopausal osteoporosis