Università degli Studi di Padova
Dipartimento di Scienze Ginecologiche e della Riproduzione Umana
Scuola di Specializzazione in Ginecologia e Ostetricia
Direttore Prof. Giovanni Battista Nardelli

UPDATE on RALOXIFENE:mechanism of action, Clinical Efficacy, Adverse Effects and Controindications

Dott. Salvatore Gizzo

Volume 68, Number 6
OBSTETRICAL AND GYNECOLOGICAL SURVEY

CME REVIEW ARTICLE 1

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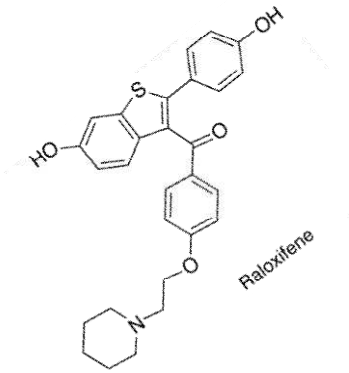
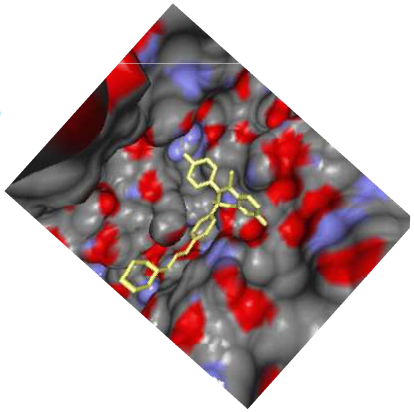


Update on Raloxifene: Mechanism of Action, Clinical Efficacy, Adverse Effects, and Contraindications

Salvatore Gizzo, MD*, Carlo Saccardi, MD, PhD*, Tito Silvio Patrelli, MD†, Roberto Berretta, MD†, Giampiero Capobianco, MD‡, Stefania Di Gangi, MD*, Antonio Vacilotto, MD*, Anna Bertocco, MD*, Marco Noventa, MD*, Emanuele Ancona, MD*, Donato D'Antona, MD*, and Giovanni Battista Nardelli, MD*

*Department of Woman and Child Health, University of Padua, Padua; †Department of Surgical Sciences, University of Parma, Parma; and ‡Department of Microsurgery, Specialized and Miniinvasive Surgery, University of Sassari, Sassari, Italy.



Dott. Salvatore Gizzo

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THE BEST DRUG FOR

OSTEOPOROSIS TREATMENT & PREVENTION

IN HEALTY POST-MENOPAUSAL WOMEN

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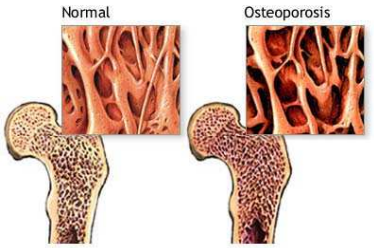
- Warning Letters 2003
- Warning Letters 2002

Warning Letters 1997

November 1997				
Acular (Ketorolac Tromethamine)	Hoffman-LaRoche	DDMAC	11/18/1997	5/21/1998
Allegra (Fexofendadine HCl) Capsules	Hoechst Marion Roussel	DDMAC	11/26/1997	5/21/1998
Coreg (Carvedilol) Tablets	SmithKline Beecham	DDMAC	11/20/1997	5/21/1998
Covera-HS (verapamil hydrochloride) Extended Release Tablets Controlled-Onset	G.D. Searle	DDMAC	11/21/1997	11/26/1997
Evista (Raloxifene HCl)	Eli Lilly	DDMAC	11/26/1997	5/21/1998
Pravachol (Pravastatin Sodium) Tablets	Bristol-Myers Squibb	DDMAC	11/26/1997	5/21/1998
Prevacid (Lansoprazole) Delayed-Release Capsules	TAP Holdings	DDMAC	11/7/1997	5/21/1998
Raxar (Grepafloxacin HCl) Tablets	GlaxoWellcome	DDMAC	11/25/1997	5/21/1998
Soma (Carisoprodol) Tablets/Soma Compound	Wallace Laboratories	DDMAC	11/14/1997	5/21/1998
Vancenase (Beclomethasone Dipropionate) Pockethaler Nasal Inhaler	Schering	DDMAC	11/7/1997	5/21/1998



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http://www.fda.gov/downloads/Drugs/DrugSafety/ucm088593.pdf

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000395.jsp&mid=WC0b01ac058002956d

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Cancer Drug Information

Reviewed: 01/17/2011

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NCI Drug Dictionary
Search for Clinical Trials

FDA Approval for Raloxifene Hydrochloride

Brand name(s): Evista®

- Approved for breast cancer risk reduction

Full prescribing information is available, including clinical trial information, safety, dosing, drug-drug interactions and contraindications.

On September 13, 2007, the U. S. Food and Drug Administration approved raloxifene hydrochloride tablets (Evista® tablets, made by Eli Lilly and Company) for reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis and in postmenopausal women at high risk for invasive breast cancer.

Related Pages

Breast Cancer Home Page
NCI's gateway for information about breast cancer.

Drug Information Summaries
NCI's drug information summaries provide consumer-friendly information about certain drugs that are approved by the U.S. Food and Drug Administration (FDA) to treat cancer or conditions related to cancer.

REVOLUTIONARY DRUG FOR

REDUCTION INVASIVE BREAST CANCER RISK
&
PREVENTION BREAST CANCER IN HIGH RISK WOMEN

http://www.cancer.gov/cancertopics/druginfo/fda-raloxifene-hydrochloride

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CME REVIEW ARTICLE 1

Update on Raloxifene: Mechanism of Action, Clinical Efficacy, Adverse Effects, and Contraindications

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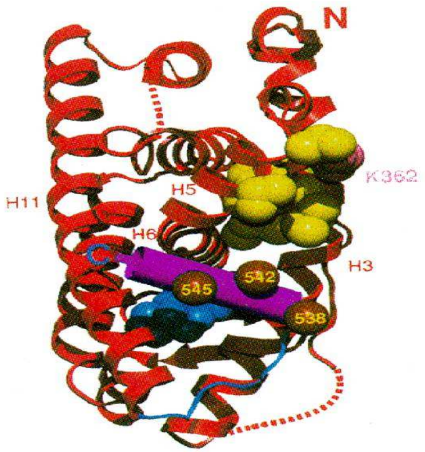
Raloxifene is the only SERM approved for long-term treatment in the prevention of osteoporotic fractures. The demonstrated beneficial effects on bone and mammalian tissue led clinical and molecular research to focus mainly on these organs, giving less attention to all other systemic effects of this SERM, even the beneficial or the adverse ones.

The aim of this review was to evaluate all described systemic effects of RAL, investigating its molecular tissue mechanism of action. Moreover, it was focused on all the positive or adverse effects within endometrium, lipid profile, and coagulation pattern.

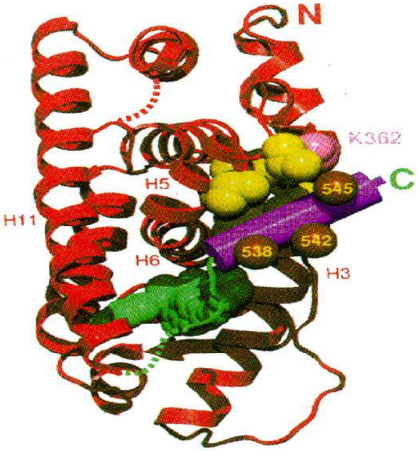
Concept of a SERM

Selective
Estrogen
Receptor
Modulator

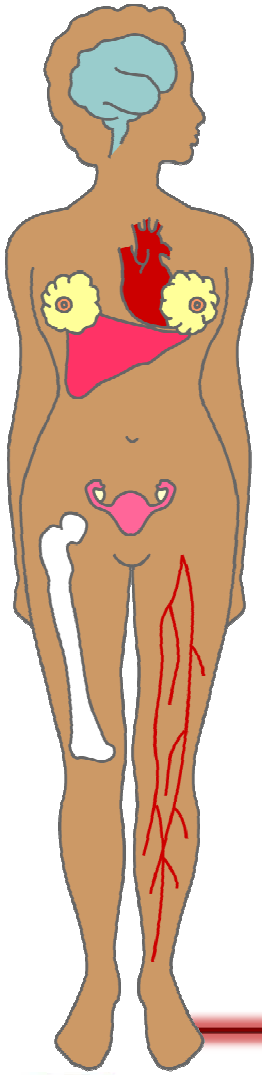
- Not an estrogen, progestin or other hormone
- Binds to estrogen receptors
- Has estrogen-like effects in some tissues
- Blocks estrogen effects in some tissues



Estradiol, K_d= 86 pM



Raloxifene, K_d= 54 pM



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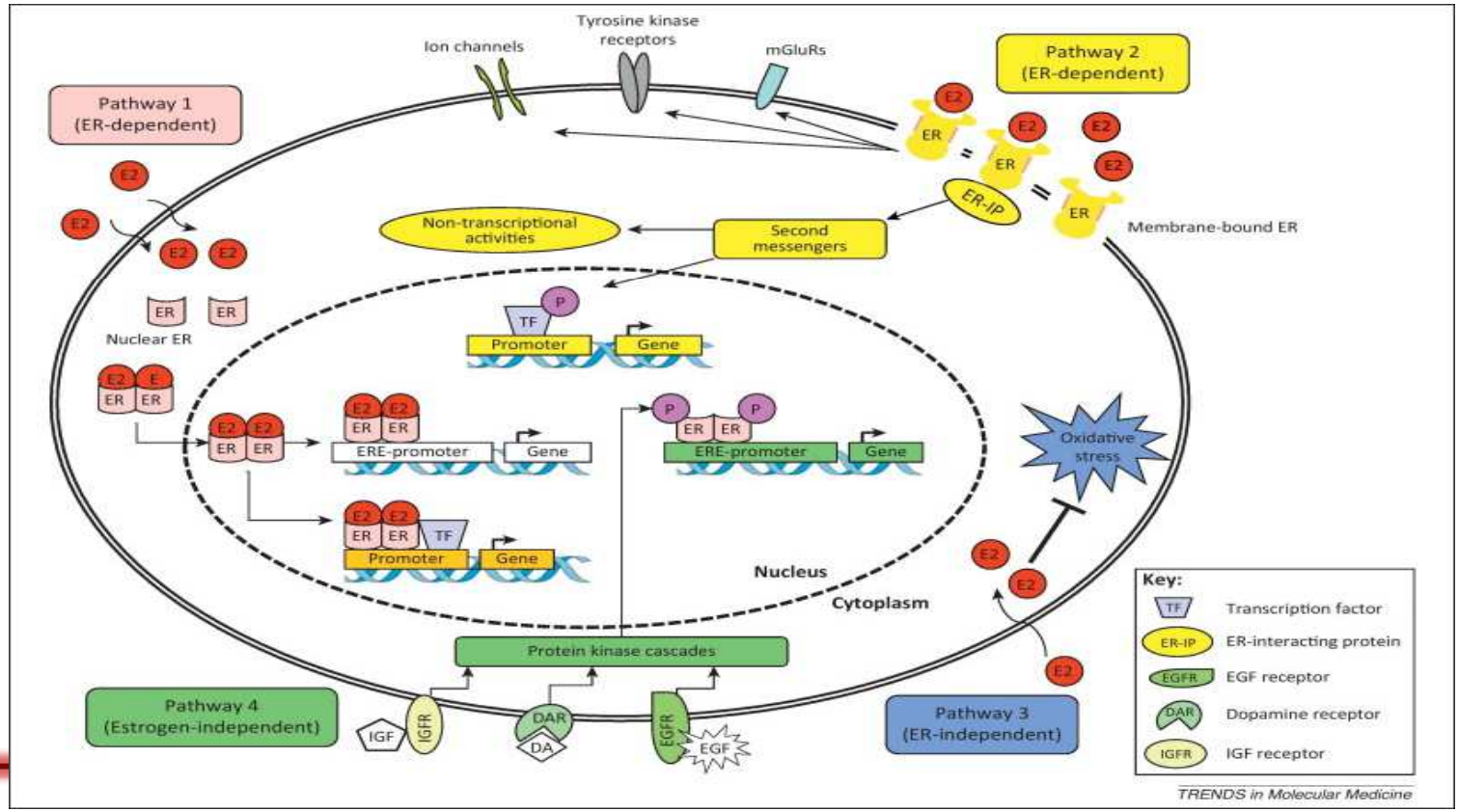
*Department of Woman and Child Health, University of Padua, Padua; †Department of Surgical Sciences, University of Parma, Parma; and ‡Department of Microsurgery, Specialized and Minimvasive Surgery, University of Sassari, Sassari, Italy.

Mechanisms of Action

Raloxifene, as all SERMs, acts as an estrogen agonist or antagonist depending on the tissue. This feature is related to specific actions on at least 2 distinct ERs, whose proportions vary according to tissue type.[3]



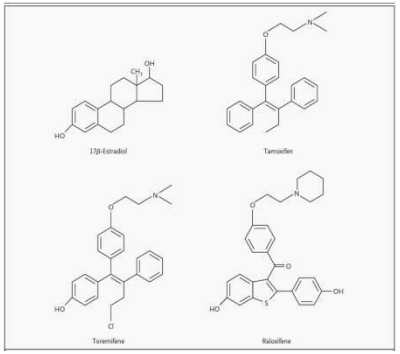
REVIEW ARTICLE

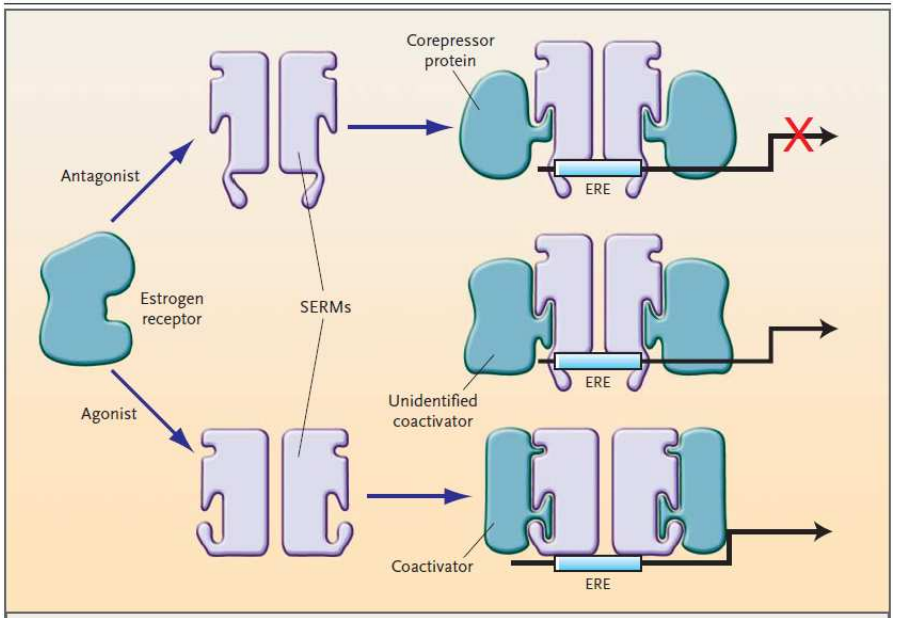
DRUG THERAPY

Alastair J.J. Wood, M.D., *Editor*

Selective Estrogen-Receptor Modulators — Mechanisms of Action and Application to Clinical Practice

B. Lawrence Riggs, M.D., and Lynn C. Hartmann, M.D.





When it binds ER, estradiol induces its dimerization and subsequently interacts with a specific sequence of DNA known as the estrogen-responding element.

It is also known that ERs do not have a single molecular binding site, but that they present 2 different domains: one for estrogen-type ligands and another one for anti–estrogen-type ligands such as SERM.[4]

Most of the peculiar pharmacology of SERMs can be explained by 3 interactive mechanisms: differential ER expression in a given target tissue, differential ER conformation on ligand binding, and differential ER expression and binding to the coregulator proteins.

CME REVIEW ARTICLE 1

Update on Raloxifene: Mechanism of Action, Clinical Efficacy, Adverse Effects, and Contraindications

Search for the Perfect SERM

The "ideal" SERM would:

- Strengthen bones
- Lower LDL cholesterol and raise HDL cholesterol
- Relieve hot flashes
- Reduce breast cancer risk
- Reduce uterine cancer risk

Clinical profiles of commercially available and investigational SERMs for postmenopausal osteoporosis

SERM	Bone	Breast	Endometrium	Cardiac	Vasomotor
First generation					
Tamoxifen	(+)[a]	(–)	(+)	(+)[b]/(–)[c]	(–)[d]
Second generation					
Raloxifene	(+)[a,e]	(–)	(+)[f]	(+)[b]/(–)[c]	(–)[d]
Third generation					
Bazedoxifene	(+)[a,e,g]	0	0	(+)[b]/(–)[h]	(–)[d]
Lasofoxifene	(+)[a,e,i]	(–)	(+)[f]	(+)[b]/(–)[c]	(–)[d]
Ospemifene	(+)[a]	Unk	(+)[f]	0	(+)/0
Arzoxifene[j]	(+)[a]	(–)	0	(–)[c]	(–)[d]

Abbreviations: SERM, selective estrogen receptor modulator; (+), pro-estrogenic (agonist) effect; (–), antiestrogenic (antagonist) effect; 0, neutral effect; Unk, unknown effect.

[a]Increases bone mineral density.
[b]Beneficial effects on lipid levels.
[c]Increased risk of venous thromboembolic events.
[d]Increased risk of hot flushes.
[e]Decreased vertebral fracture risk.
[f]Increased endometrial thickness, but no increased risk of endometrial cancer.
[g]Decreased nonvertebral fracture risk in women at higher risk for fracture.
[h]Increased risk of deep vein thrombosis.
[i]Decreased nonvertebral fracture risk.
[j]Development recently discontinued based on interim results of large phase 3 study.

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FASE III and IV pharmacological and clinical RCTs…

The NEW ENGLAND JOURNAL of MEDICINE

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Effects of Raloxifene on Cardiovascular Events and Breast Cancer in Postmenopausal Women

zabeth Barrett-Connor, M.D., Lori Mosca, M.D., Ph.D., M.P.H., Peter Collins, M.D., Mary Jane Geiger, M.D., Ph.D., eborah Grady, M.D., M.P.H., Marcel Kornitzer, M.D., Michelle A. McNabb, M.S., and Nanette K. Wenger, M.D., for the Raloxifene Use for The Heart (RUTH) Trial Investigators*

Printed in U.S.A.

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ORIGINAL RESEARCH

Efficacy of Raloxifene on Vertebral Fracture Risk Reduction in Postmenopausal Women with Osteoporosis: Four-Year Results from a Randomized Clinical Trial

PIERRE D. DELMAS, KRISTINE E. ENSRUD, JONATHAN D. ADACHI, KRISTINE D. HARPER, SOMNATH SARKAR, CARLO GENNARI, JEAN-YVES REGINSTER, HUIBERT A. P. POLS, ROBERT R. RECKER, STEVEN T. HARRIS, WENTAO WU, HARRY K. GENANT, DENNIS M. BLACK, AND RICHARD EASTELL, FOR THE MULTIPLE OUTCOMES OF RALOXIFENE EVALUATION (MORE) INVESTIGATORS

Safety and Adverse Effects Associated With Raloxifene: Multiple Outcomes of Raloxifene Evaluation

Deborah Grady, MD, MPH, Bruce Ettinger, MD, Elena Moscarelli, MD, Leo Plouffe Jr, MD, CM, Somnath Sarkar, PhD, Angelina Ciaccia, PhD, and Steven Cummings, MD, for the Multiple Outcomes of Raloxifene Evaluation Investigators*

ORIGINAL CONTRIBUTION

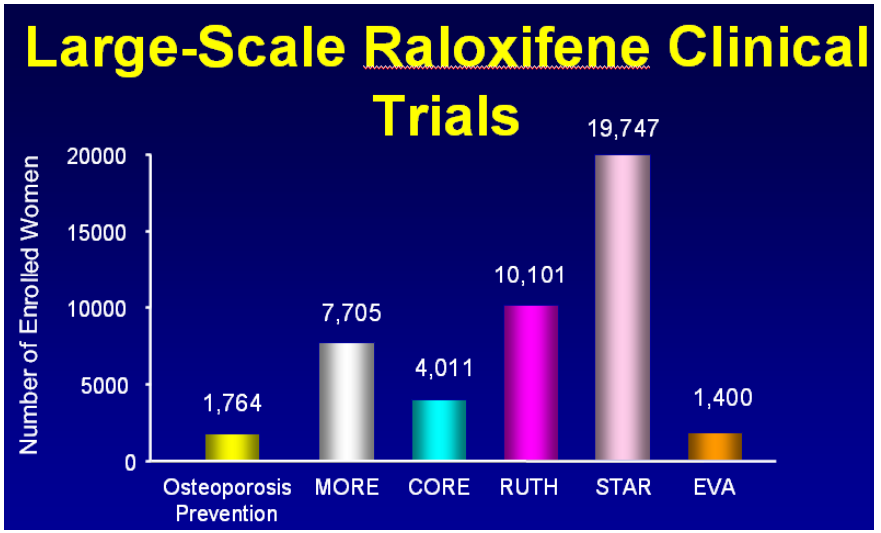
Continuing Outcomes Relevant to Evista: Breast Cancer Incidence in Postmenopausal Osteoporotic Women in a Randomized Trial of Raloxifene

Silvana Martino, Jane A. Cauley, Elizabeth Barrett-Connor, Trevor J. Powles, John Mershon, Damon Disch, Roberta J. Secrest, Steven R. Cummings

For the CORE Investigators

Patient-Reported Symptoms and Quality of Life During Treatment With Tamoxifen or Raloxifene for Breast Cancer Prevention

The NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 Trial



MORE: Multiple Outcomes of Raloxifene Evaluation;
CORE: Continuing Outcomes Relevant to EVISTA;
RUTH: Raloxifene Use for The Heart;
STAR Study of Tamoxifen and Raloxifene;
EVA: EVISTA-Alendronate Comparison

Bone effects…

CME REVIEW ARTICLE 1

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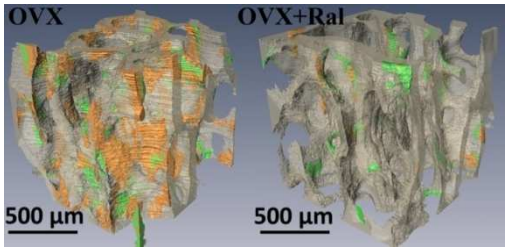
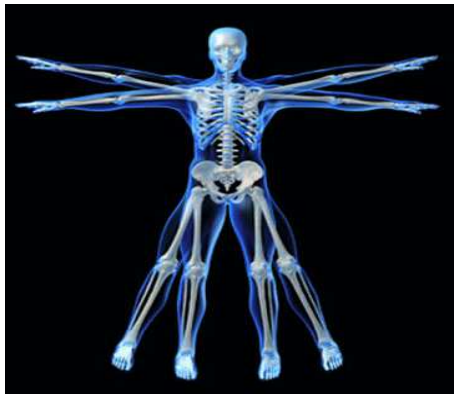
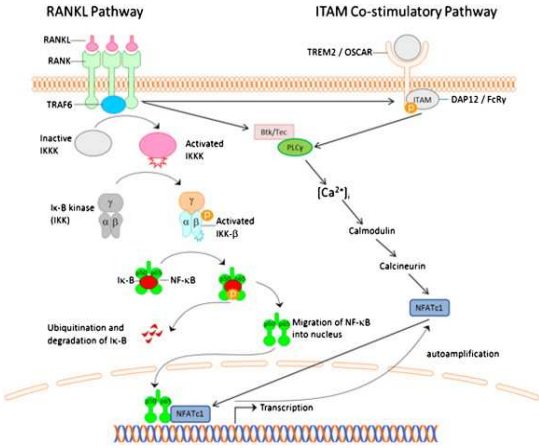
*Department of Woman and Child Health, University of Padua, Padua; †Department of Surgical Sciences, University of Parma, Parma; and ‡Department of Microsurgery, Specialized and Minimyvasive Surgery, University of Sassari, Sassari, Italy.

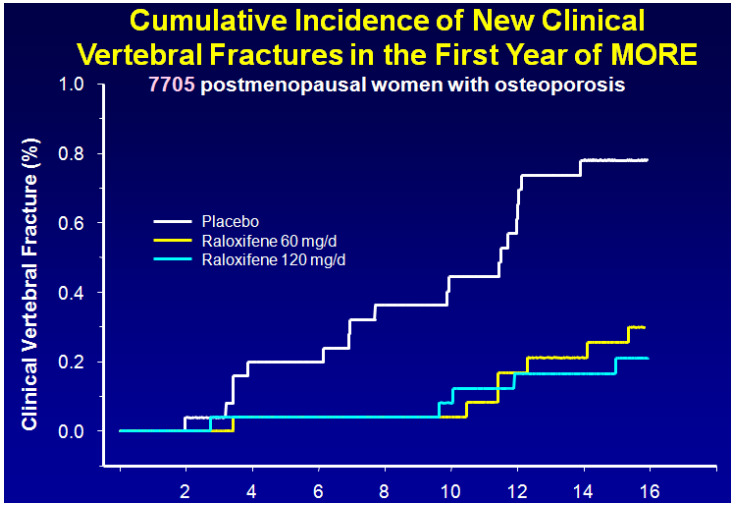
TABLE 1
Raloxifene and Bone Tissue: Study Design, Main Outcomes, and Adverse Effects of Principal Trials

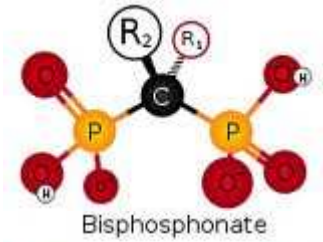
Trial	Authors (Year)	Study Design	Number of Patients (Age)	Trial Duration	Treatment	Main Outcomes	Adverse Effects
	Johnston et al[27] (2000)	Double-blind placebo-controlled clinical trial	1145 Postmenopausal women (45–60 y)	36 mo	• RAL 30 mg/d ➢RAL 60 mg/d ❖ RAL 150 mg/d – Placebo	BMD increasing: • +0.71% ± 0.23% ➢+1.28% ± 0.23% ❖ +1.20% ± 0.24%	Higher incidence in RAL: hot flashes Only associated with RAL: deep vein thrombophlebitis Lower incidence in RAL: breast carcinoma No significant differences in RAL vs placebo: leg cramps, abdominal pain, nausea, peripheral edema, vaginitis, breast pain, leukorrhea, vaginal hemorrhage
MORE	Delmas et al[28] (2002)	Randomized clinical trial	7705 postmenopausal women; age: placebo 66.6 ± 7.0 y; RAL 66.2 ± 7.1 y	4 y	• RAL 60 mg/d ➢RAL 120 mg/d – Placebo	Cumulative RR for 1/> new vertebral fractures: • 0.64 ➢0.57	Higher incidence with RAL: flu syndrome, vasodilatation, leg cramps, endometrial cavity fluid, peripheral edema, diabetes Rare but serious adverse events occurring more frequently in RAL: venous thromboembolism, deep vein thrombosis, pulmonary embolism, retinal vein thrombosis Lower incidence in RAL: hypertension, hypercholesterolemia, hematuria, bradycardia, all breast cancer
CORE	Siris et al[29] (2005)	Multicenter, double-blind, placebo-controlled clinical trial	4011 Women (mean age, 65.8 y)	4 Additional y then the 4 y of the MORE trial (8 y)	• RAL 60 mg/d – Placebo	Risk of at least 1 new nonvertebral fracture: similar in RAL and in placebo BMD in RAL: 4.3% from MORE baseline, 2.2% from placebo Increase (%) in femoral neck BMD in RAL: 1.9% from MORE baseline, 3.0% from placebo	Higher incidence in RAL: hot flashes and leg cramps Higher incidence in RAL, no statistical significance: thromboembolic disease, including deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis No significant differences in RAL vs placebo: ovarian cancer, breast symptoms (eg, breast pain), pelvic prolapse, cataracts, stroke, or myocardial infarction, peripheral edema
RUTH	Barrett-Connor et al[31] (2006)	Multicenter, double-blind, placebo-controlled clinical trial	10,101 Postmenopausal women (mean age, 67.5 y)	5.6 y	• RAL 60 mg/d – Placebo	Absolute risk reduction of clinical vertebral fractures: • 1.3/1000	Higher incidence with RAL: arthritis, cholelithiasis, dyspepsia, hot flush, intermittent claudication, muscle spasm, and peripheral edema, leg cramps, gallbladder disease Lower incidence in RAL: acute coronary syndrome, anxiety, constipation, and osteoporosis No significant differences in RAL vs placebo: rates of cholecystectomy, incidences of endometrial cancer and all cancers other than breast cancer

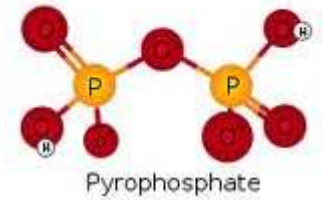


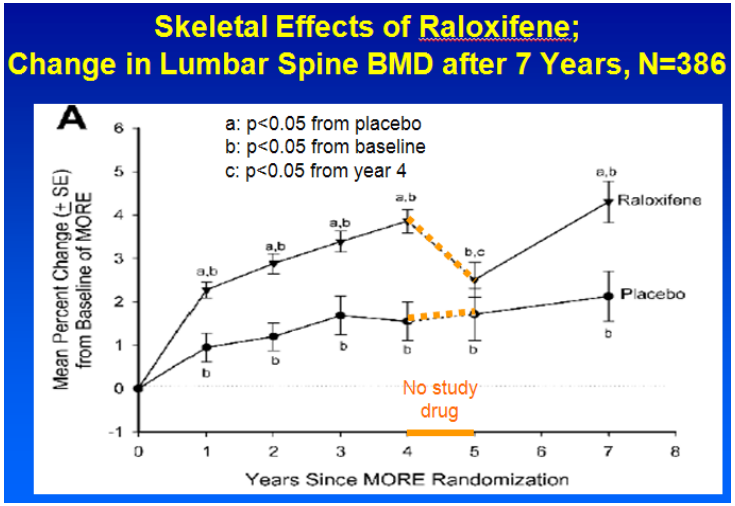


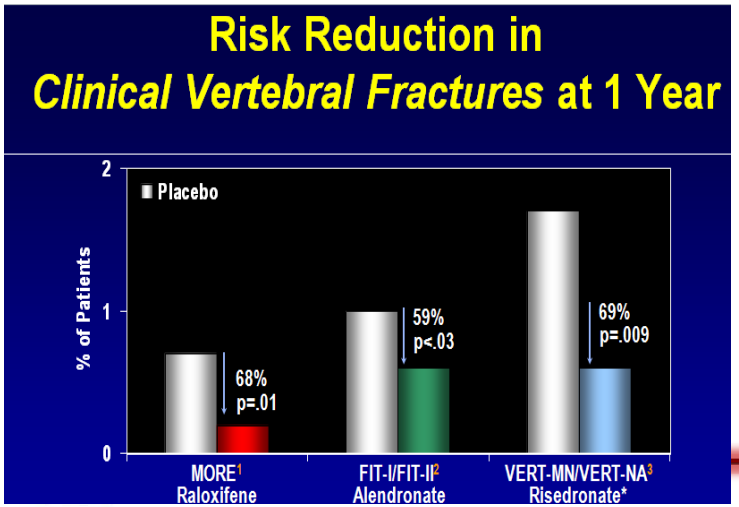


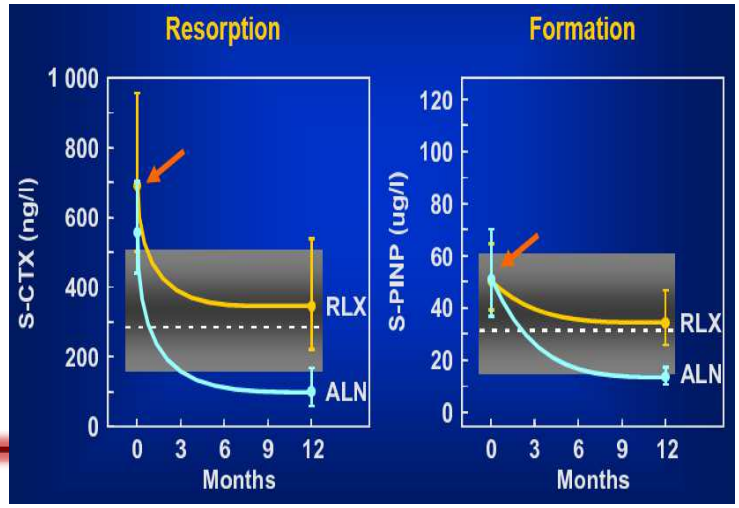

Cumulative Incidence of New Clinical Vertebral Fractures in the First Year of MORE
7705 postmenopausal women with osteoporosis
Clinical Vertebral Fracture (%)
1.0
0.8
0.6
0.4
0.2
0.0
Placebo
Raloxifene 60 mg/d
Raloxifene 120 mg/d
2
4
6
8
10
12
14
16


R2
R1
C
P
P
H
Bisphosphonate


P
P
H
Pyrophosphate


Skeletal Effects of Raloxifene;
Change in Lumbar Spine BMD after 7 Years, N=386
A
a: p<0.05 from placebo
b: p<0.05 from baseline
c: p<0.05 from year 4
Mean Percent Change (± SE) from Baseline of MORE
Raloxifene
Placebo
No study drug
Years Since MORE Randomization


Risk Reduction in
Clinical Vertebral Fractures at 1 Year
Placebo
% of Patients
68%
p=.01
59%
p<.03
69%
p=.009
MORE1
Raloxifene
FIT-I/FIT-II2
Alendronate
VERT-MN/VERT-NA3
Risedronate*


Resorption
Formation
S-CTX (ng/l)
S-PINP (ug/l)
RLX
ALN
Months

Breast effects…

CME REVIEW ARTICLE 1

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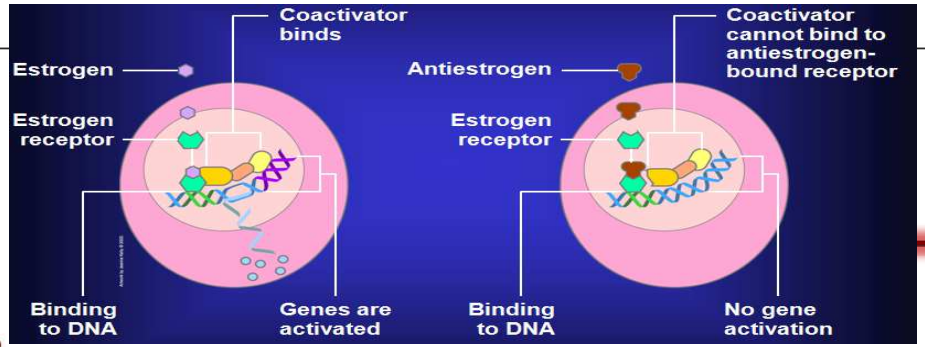
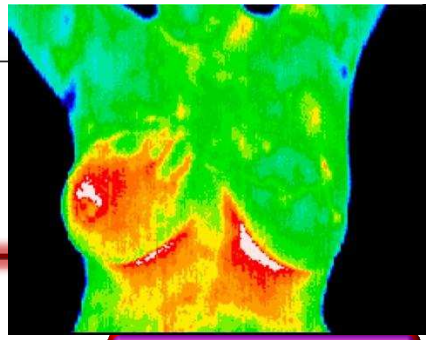
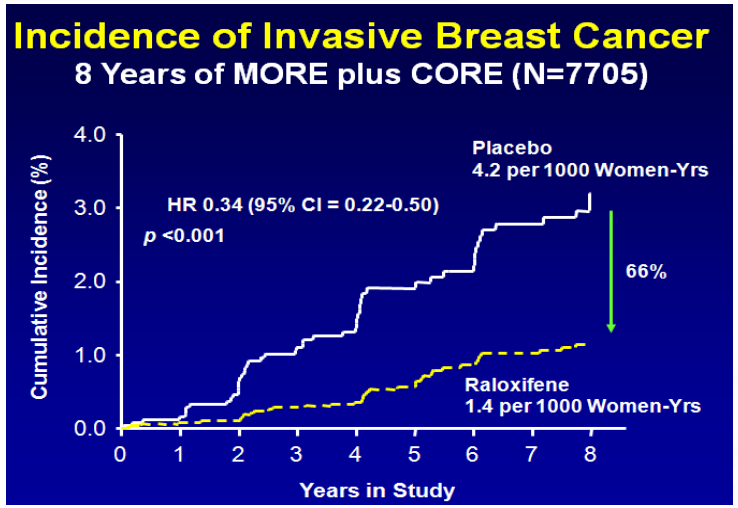
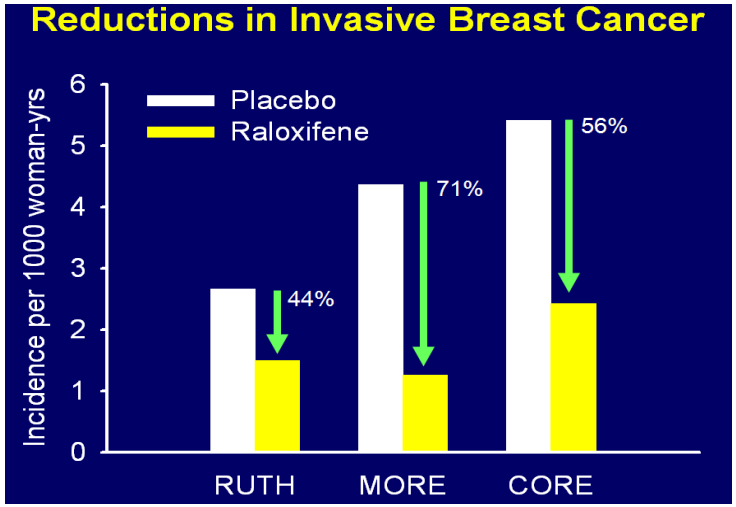
TABLE 2
Raloxifene and Breast: Study Design, Main Outcomes, and Adverse Effects of Principal Trials

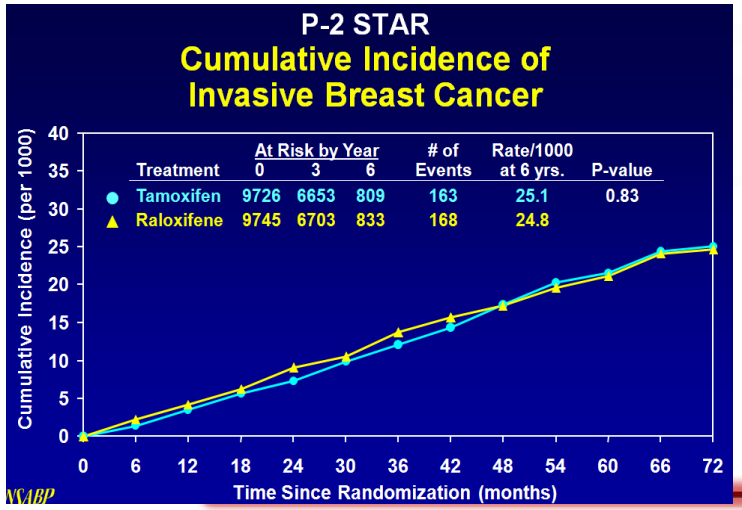
Trial	Authors (Year)	Study Design	No. Patients (Age)	Trial Duration	Treatment	Main Outcomes	Adverse Effects
NSABP	Vogel et al[32] (2006)	Prospective, double-blind, randomized clinical trial	19,747 Postmenopausal women (mean age, 58.5 y)	5 y	Randomly receiving RAL 60 mg/d or tamoxifen 20 mg/d	Risk reduction of invasive breast cancer: comparable for both drugs	Lower risk in RAL: thromboembolic events and cataracts; similar risk in RAL vs tamoxifen: other cancers than breast cancer, fractures, ischemic heart disease, stroke
MORE	Cauley et al[31] (2001)	Multicenter, randomized, double-blind clinical trial	7705 Postmenopausal women (placebo: 66.6 ± 7.0 y; RAL: 66.2 ± 7.1 y)	4 y	Randomly receiving RAL 60 mg/d or RAL 120 mg/d or placebo	Incidence reduction of all types of breast cancer (RAL vs placebo): 62% in RAL group (RR, 0.38)	Vide supra
CORE	Martino et al[26] (2004)	Multicenter, double-blind, placebo-controlled clinical trial	4011 Women (mean age, 65.8 y)	4 Additional y than the 4 y of the MORE trial (8 y)	RAL 60 mg/d or placebo	Incidence reduction in RAL group: 59% invasive breast cancer, 66% invasive ER-positive breast cancers	Vide supra
RUTH	Grady et al (2006)	Multicenter, double-blind, placebo-controlled clinical trial	10,101 Postmenopausal women (mean age, 67.5 y)	5.6 y	RAL 60 mg/d or placebo	Incidence reduction in RAL group: 44% invasive breast cancer; 55% invasive ER-positive breast cancers	Vide supra

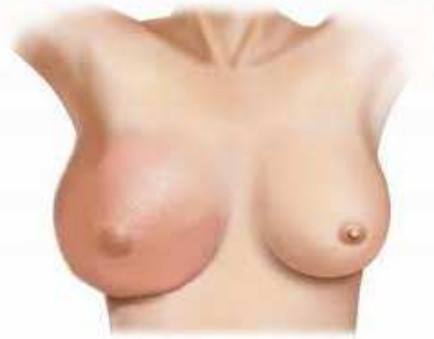


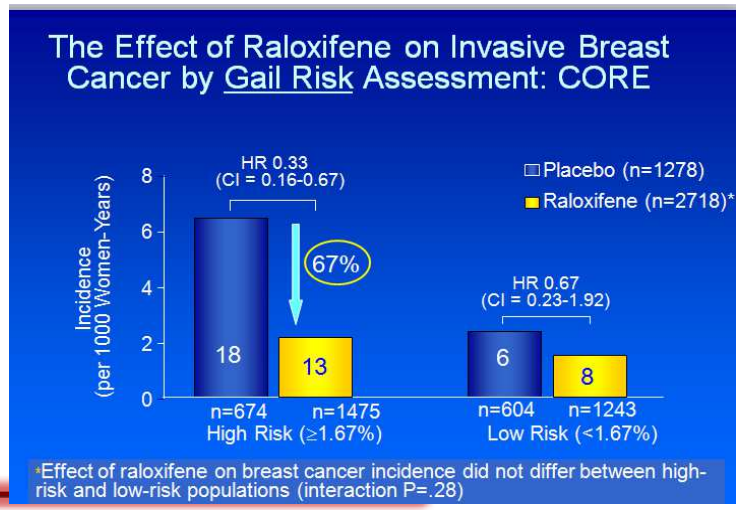



Incidence of Invasive Breast Cancer
8 Years of MORE plus CORE (N=7705)
Cumulative Incidence (%)
4.0
3.0
2.0
1.0
0.0
Placebo
4.2 per 1000 Women-Yrs
HR 0.34 (95% CI = 0.22-0.50)
p <0.001
66%
Raloxifene
1.4 per 1000 Women-Yrs
0 1 2 3 4 5 6 7 8
Years in Study


Reductions in Invasive Breast Cancer
Incidence per 1000 woman-yrs
6
5
4
3
2
1
0
Placebo
Raloxifene
44%
71%
56%
RUTH
MORE
CORE


P-2 STAR
Cumulative Incidence of Invasive Breast Cancer
Cumulative Incidence (per 1000)
40
35
30
25
20
15
10
5
0
Treatment | At Risk by Year 0 | 3 | 6 | # of Events | Rate/1000 at 6 yrs. | P-value
Tamoxifen | 9726 | 6653 | 809 | 163 | 25.1 | 0.83
Raloxifene | 9745 | 6703 | 833 | 168 | 24.8
0 6 12 18 24 30 36 42 48 54 60 66 72
Time Since Randomization (months)
NSABP




The Effect of Raloxifene on Invasive Breast Cancer by Gail Risk Assessment: CORE
Incidence (per 1000 Women-Years)
8
6
4
2
0
HR 0.33
(CI = 0.16-0.67)
67%
18
13
HR 0.67
(CI = 0.23-1.92)
6
8
Placebo (n=1278)
Raloxifene (n=2718)*
n=674
n=1475
High Risk (≥1.67%)
n=604
n=1243
Low Risk (<1.67%)
*Effect of raloxifene on breast cancer incidence did not differ between high-risk and low-risk populations (interaction P=.28)

Endometrial effects…

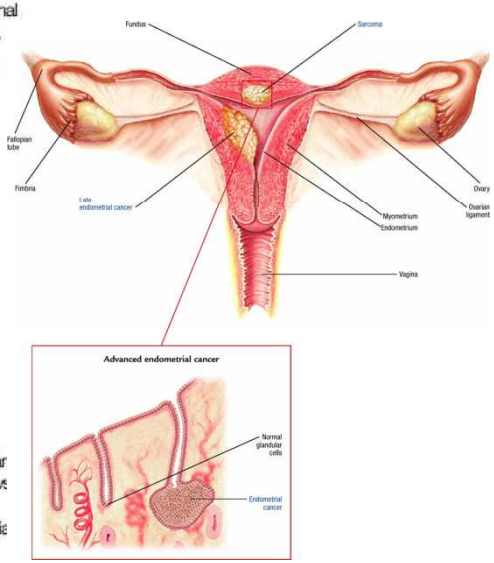
CME REVIEW ARTICLE 1

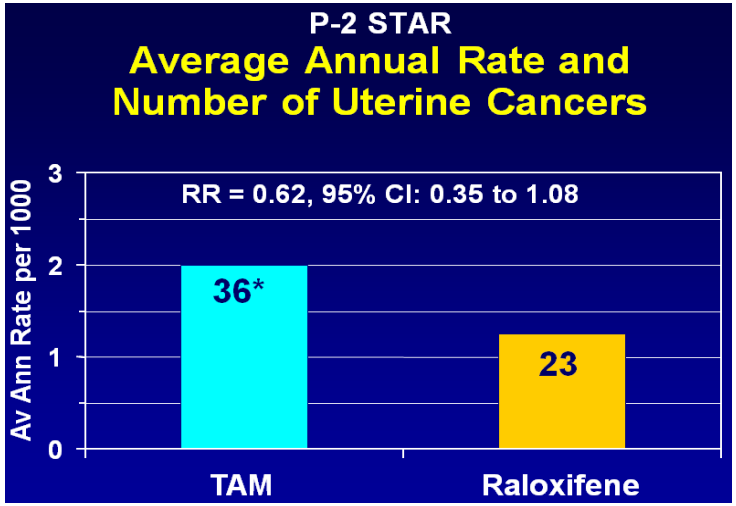
Update on Raloxifene: Mechanism of Action, Clinical Efficacy, Adverse Effects, and Contraindications

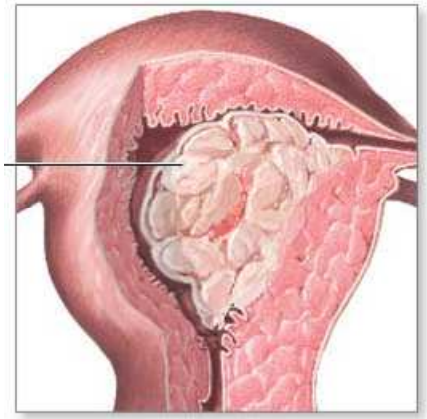
Salvatore Gizzo, MD*, Carlo Saccardi, MD, PhD*, Tito Silvio Patrelli, MD†, Roberto Berretta, MD†, Giampiero Capobianco, MD‡, Stefania Di Gangi, MD*, Antonio Vacilotto, MD*, Anna Bertoceo, MD*, Marco Noventa, MD*, Emanuele Ancona, MD*, Donato D'Antona, MD*, and Giovanni Battista Nardelli, MD*

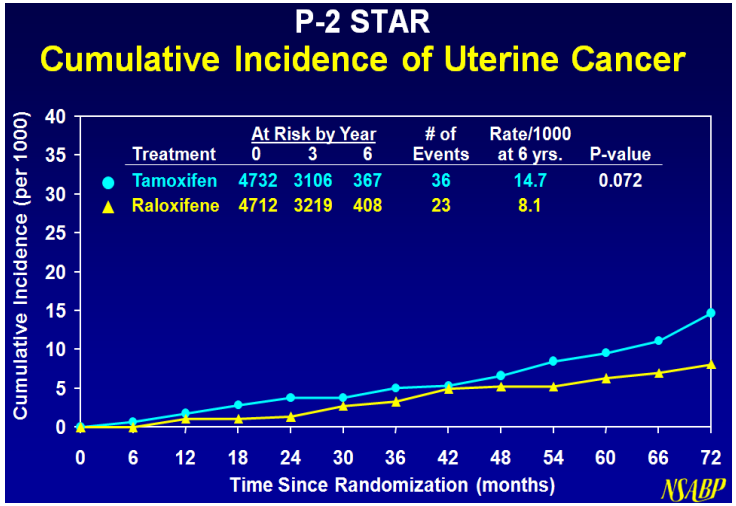
TABLE 3
Raloxifene and Endometrium: Study Design, Main Outcomes, and Adverse Effects of Principal Trials

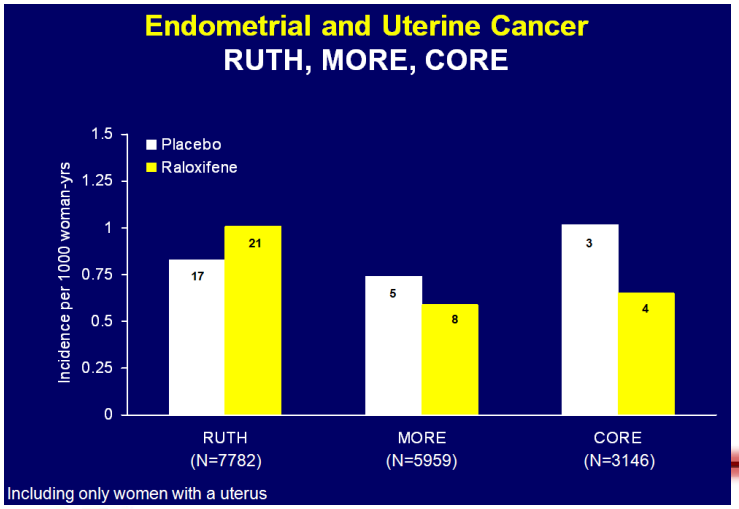
Trial	Authors (Year)	Study Design	No. Patients (Age)	Trial Duration	Treatment	Main Outcomes	Adverse Effects
	Cohen and Lu[48] (2000)	Data from 2 identically designed, randomized, double-masked, placebo-controlled clinical trials	969 Healthy women (45–60 y)	3 y	Randomly receiving 30 mg/d, 60 mg/d, 150 mg/d, or placebo	Endometrial thickness: unchanged in RAL group; incidence of vaginal bleeding, spotting, other uterine-related adverse events: no significant difference in RAL vs placebo groups	No significant differences in RAL vs placebo: leukorrhea and uterovaginal prolapse
	Goldstein et al[39] (2000)	Multicenter, double-masked, placebo-controlled, randomized, parallel study	415 Healthy postmenopausal women (47–60 y)	1 y	Randomly receiving RAL 60 mg/d, RAL 150 mg/d; hormone replacement therapy: 0.625 mg/d conjugated equine estrogens; placebo	Endometrial thickness, morphology, and uterine volume: no significant difference in RAL vs placebo groups	Higher incidence in the hormone replacement therapy group: vaginal bleeding, mastalgia, abdominal or pelvic pain, leukorrhea
	de Azevedo et al (2002)	Prospective longitudinal study	25 Healthy postmenopausal women (56.0 ± 4.8 y)	6 mo	RAL 60 mg/d or placebo	Endometrial thickness: mean endometrial thickness at the pretreatment period 3.38 ± 0.73 mm → practically unaltered at 1, 3, and 6 mo of treatment with RAL (3.04 ± 0.82, 3.30 ± 0.83, and 3.37 ± 0.79, respectively); uterine volume (UV): no significant alterations in the 6-mo follow-up period. Mean UV: 40.4 ± 17.8 cm^3 at baseline → similar values at 1, 3, and 6 mo of treatment (40.4 ± 16.8, 40.2 ± 14.6, and 39.9 ± 14.4, respectively). Blood perfusion parameters in the uterine arteries: no significant alterations were observed during treatment	Not reported
	Jolly et al[30] (2003)	Data from 2 identically designed, prospective, double-blinded trials	328 Women (mean age, 55 y)	5 y	RAL 60 mg/d or placebo	Incidence of vaginal bleeding, endometrial hyperplasia, or endometrial carcinoma: not increased in RAL	Higher incidence in RAL group: hot flashes. No significar differences in RAL vs placebo: vaginal bleeding, endometria thickness
NSABP	Vogel et al[32] (2006)	Prospective, double-blind, randomized clinical trial	19,747 Postmenopausal women (mean age, 58.5 y)	5 y	Randomly receiving RAL 60 mg/d or tamoxifen 20 mg/d	Annual incidence rate of uterine cancer rates: 2 per 1000 in the tamoxifen-treated group, 1.25 per 1000 in the RAL-treated group. Incidence of uterine hyperplasia for hyperplasia both with and without atypia: 84% less in RAL group than in the tamoxifen-treated group. No. hysterectomies performed: 111 in those assigned to RAL vs 244 hysterectomies performed in those assigned to tamoxifen	Vide supra











Summary of Adverse Outcomes over the 8 Years of MORE-CORE (N=4011)

	%Percentage of participants who experienced event (n)		P-value
	Placebo (N=1286)	Raloxifene (N=2725)	
Mortality	2.3 (29)	1.7 (47)	0.07
All cancers†	8.6 (110)	5.7 (156)	0.001
All cancers† excluding breast cancer	6.3 (81)	4.6 (126)	0.027
Hospitalization	40.9 (526)	38.8 (1057)	0.21
Treatment-emergent AEs	99.0 (1273)	98.6 (2688)	0.45
Treatment-emergent serious AEs	45.5 (585)	42.3 (1154)	0.07
Study discontinuation CORE due to AE	2.4 (31)	1.9 (53)	0.35

†Excluding non-melanoma skin cancers

Title page

In-vitro studies on Ishikawa cell lines could explain the endometrial safety of Raloxifene?

Salvatore Gizzo[1] M.D.; Carlo Saccardi[1] M.D, PhD, Omar Anis[1] M.D.; Antonio Vacilotto[1] M.D.; Emanuele Ancona[1] M.D.; Bruno Mozzanega[1] M.D.; Prof. Donato D'Antona[1] M.D & Prof Giovanni Battista Nardelli[1] M.D.

1 - Department of Woman and Child Health – University of Padua, Padua (ITALY)

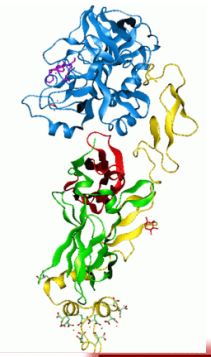
Concerning this, studies conducted in Ishikawa cells confirmed that expressing estrogen-responsive finger protein (E-rFP) and VEGF mRNA are increased after E2 and TAM treatment but not after RAL treatment[18].

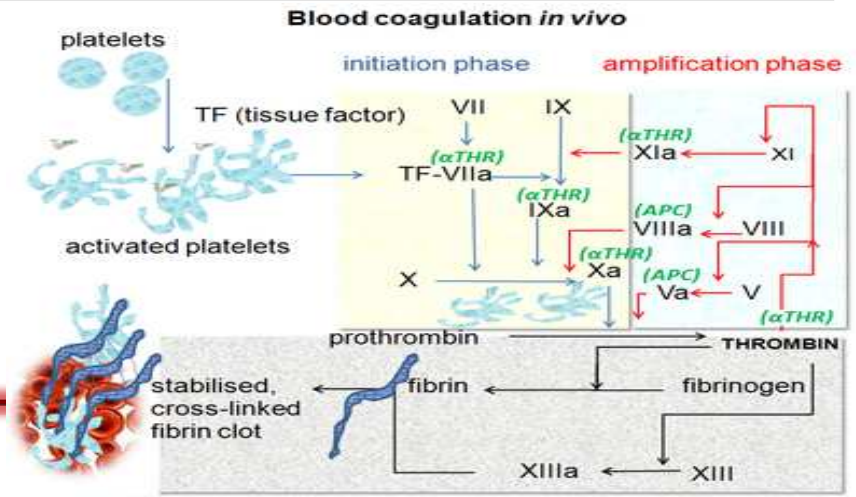
invasion. In Estrogen-related tumors most of this process are linked to ERs and different from TAM and E2: when compared to E2 and TAM, RAL did not showed any influence in this cellular rearrangement[20].

Finally, the antagonist effects of RAL in endometrial cell proliferation could also be explained by the evidences that it induces the most potent antiangiogenic factors, thrombospondin-1 (TSP-1), and actives the mitochondria-mediated apoptotic cell death probably not via the Bid-mitochondria pathway linked to both the death receptor and the mitochondrial pathway[17].

TABLE 5
Raloxifene and Coagulation Profile: Study Design, Main Outcomes, and Adverse Effects of Principal Trials

Trial	Authors (Year)	Study Design	Number of Patients (Age)	Trial Duration	Treatment	Main Outcomes	Adverse Effects
MORE	Grady et al[46] (2004)	Multicenter, randomized, double-blind, clinical trial	7705 Postmenopausal women (placebo: 66.6 ± 7.0 y; RAL: 66.2 ± 7.1 y)	4 y	Randomly receiving RAL 60 mg/d, RAL 120 mg/d, or placebo	Any venous thrombosis: 3.5/1000 woman-years at risk with RAL vs 1.7/1000 woman-years with placebo (RR, 2.1). Deep vein thrombosis: 2.5/1000 woman-years at risk with RAL vs 0.8/1000 woman-years with placebo (RR, 3.1). Pulmonary embolism: 1.1/1000 woman-years at risk with RAL vs 0.2/1000 woman-years with placebo (RR, 4.5)	Vide supra
CORE	Martino et al[26] (2004)	Multicenter, double-blind, placebo-controlled clinical trial	4011 Women (mean age, 65.8 y)	4 Additional y than the 4 y of the MORE trial (8 y)	Randomly receiving RAL 60 mg/d or placebo	Incidence rate for venous thromboembolic events (deep vein thrombosis, pulmonary embolism, retinal vein thrombosis): 2.2 in RAL group 1.3 events per 1000 woman-years	Vide supra
RUTH	Barrett-Connor et al[31] (2006)	Multicenter, double-blind, placebo-controlled clinical trial	10,101 postmenopausal women (mean age, 67.5 y)	5.6 y	RAL 60 mg/d or placebo	Incidence of venous thromboembolic events: 44% higher in RAL	Vide supra





CME REVIEW ARTICLE 1

Update on Raloxifene: Mechanism of Action, Clinical Efficacy, Adverse Effects, and Contraindications

Salvatore Gizzo, MD*, Carlo Saccardi, MD, PhD*, Tito Silvio Patrelli, MD†, Roberto Berretta, MD†, Giampiero Capobianco, MD‡, Stefania Di Gangi, MD*, Antonio Vacilotto, MD*, Anna Bertoceo, MD*, Marco Noventa, MD*, Emanuele Ancona, MD*, Donato D'Antona, MD*, and Giovanni Battista Nardelli, MD*

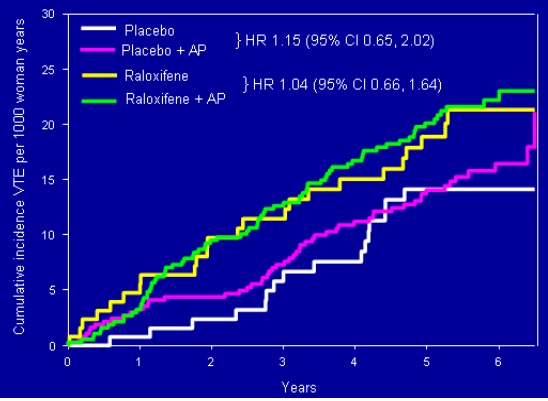
*Department of Woman and Child Health, University of Padua, Padua; †Department of Surgical Sciences, University of Parma, Parma; and ‡Department of Microsurgery, Specialized and Minimvasive Surgery, University of Sassari, Sassari, Italy.

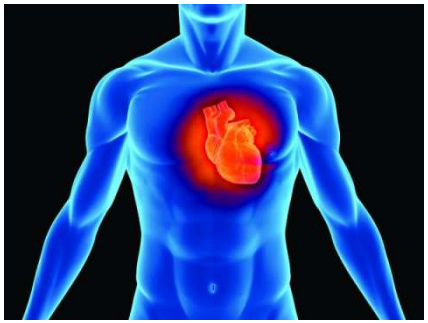
Obstetrical and Gynecological Survey

Coagulative System

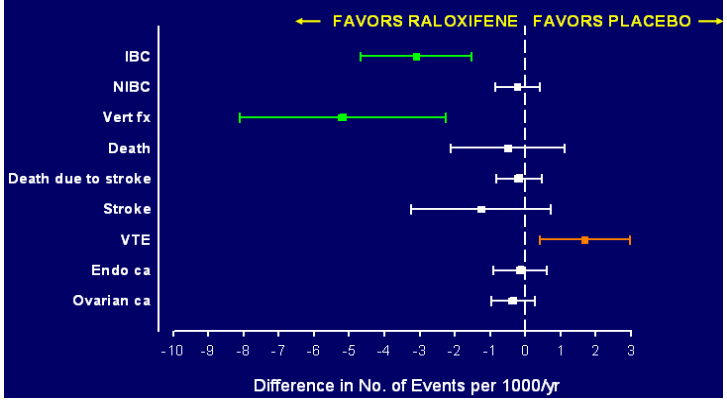
Recently, some clinical trials have tried to define the mechanisms by which RAL increases the risk of thromboembolic events. Azevedo et al[21] in a prospective study on 16 postmenopausal women who has been administered RAL hydrochloride orally (60 mg once daily) for a period of 6 months showed that factor VIII activity increased by 17.1% and 26.9% (at 3 and 6 months of treatment, respectively), and factors XI and XII activities significantly increased from baseline by 10.9% and 43.1%, respectively, after 6 months of treatment.[21] The increased plasma levels of VIII, XI, and XII factors and a significant reduction of APC sensitivity ratio demonstrate that RAL therapy in postmenopausal women is associated with a procoagulant state. Sgarabotto et al[22] have proved that a 6-month RAL treatment increases procoagulant blood parameters and decreases anticoagulant parameters 12 months later. By the way, factor VIII and fibrinogen plasma levels significantly increased at 6 months, prothrombin fragments 1 and 2 significantly increased at 12 months, and protein C activity and antithrombin significantly decreased at 12 months.[22]

Cumulative Incidence of VTE by Treatment Group and Antiplatelet Use



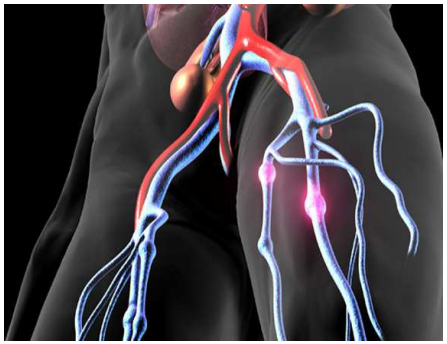


Balance of Efficacy and Safety Outcomes MORE

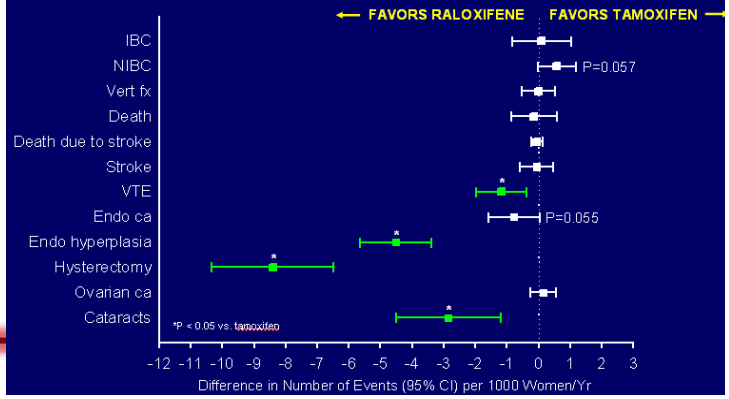


RUTH: Venous Thromboembolic Events (VTE) for All Randomized Women (N=10,101)

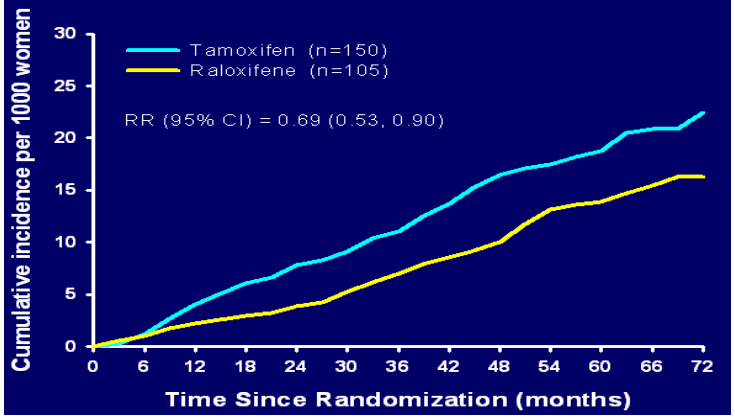
Endpoint	No. of events (%)		Hazard Ratio (95% CI)	P value
	Placebo (N=5057)	Raloxifene (N=5044)		
VTE event	71 (1.40)	103 (2.04)	1.44 (1.06-1.95)	0.02
Deep vein thrombosis	47 (0.93)	65 (1.29)	1.37 (0.94-1.99)	0.10
Pulmonary embolism	24 (0.47)	36 (0.71)	1.49 (0.89-2.49)	0.13



Efficacy and Important Safety Outcomes STAR



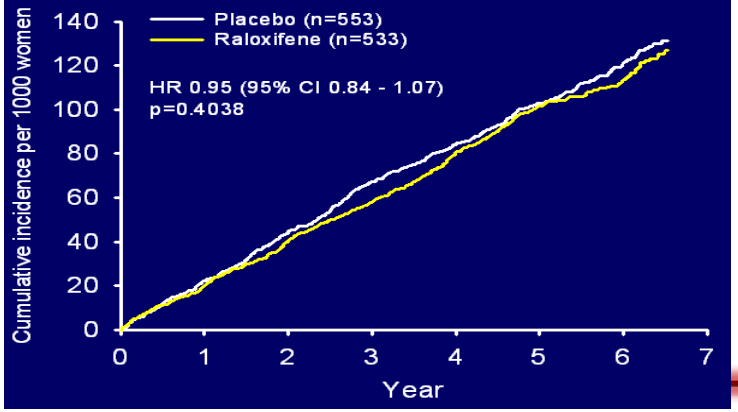
Venous Thromboembolic Events
STAR

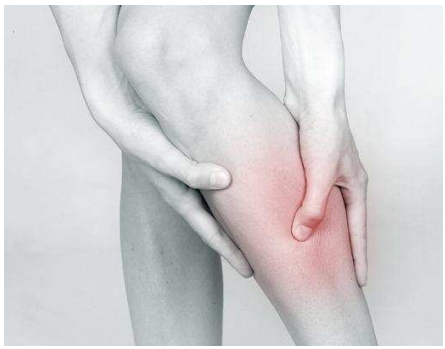


Adverse Events
MORE – 4 Years

	Percent (%)		
	Placebo (n=2576)	Raloxifene (n=5129)	p-value
Thromboembolic disease	17 (0.7)	64 (1.3)	0.017
- deep vein thrombosis	8 (0.3)	44 (0.9)	0.005
- pulmonary embolism	4 (0.2)	22 (0.4)	0.060
Death	36 (1.4)	64 (1.2)	0.584

No Effect on Coronary Events*
RUTH





Adverse Events Reported
During MORE Plus CORE – 8 Years

	Number (%)		
	Placebo (n=1286)	Raloxifene (n=2725)	p-value
Flushing (hot flushes)	89 (6.9)	342 (12.6)	<0.001
Leg cramps	152 (11.8)	407 (14.9)	0.008
Peripheral edema	120 (9.3)	288 (10.6)	0.240

Estrogen Replacement During Menopause

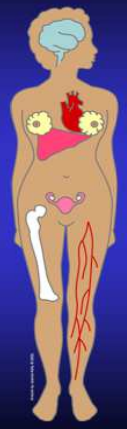
Estrogen

Good effects
- Strengthens bones
- Lowers LDL cholesterol
- Raises HDL cholesterol
- Reduces menopausal symptoms (e.g., hot flashes)

Bad effects
- Increases breast cancer risk
- Increases uterine cancer risk
- Increases blood clot risk

Search for the Perfect SERM

The "ideal" SERM would:
- Strengthen bones
- Lower LDL cholesterol and raise HDL cholesterol
- Relieve hot flashes
- Reduce breast cancer risk
- Reduce uterine cancer risk



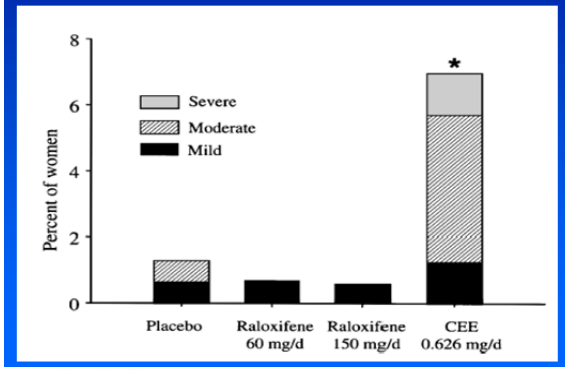
Estrogen Plus Progesterone Replacement

Estrogen plus Progesterone *reported effects*

Good effects
- Strengthens bones
- Decreases colon cancer risk
- Reduces menopausal symptoms (e.g., hot flashes)

Bad effects
- Increases invasive breast cancer risk
- Increases heart attacks
- Increases strokes
- Increases blood clots

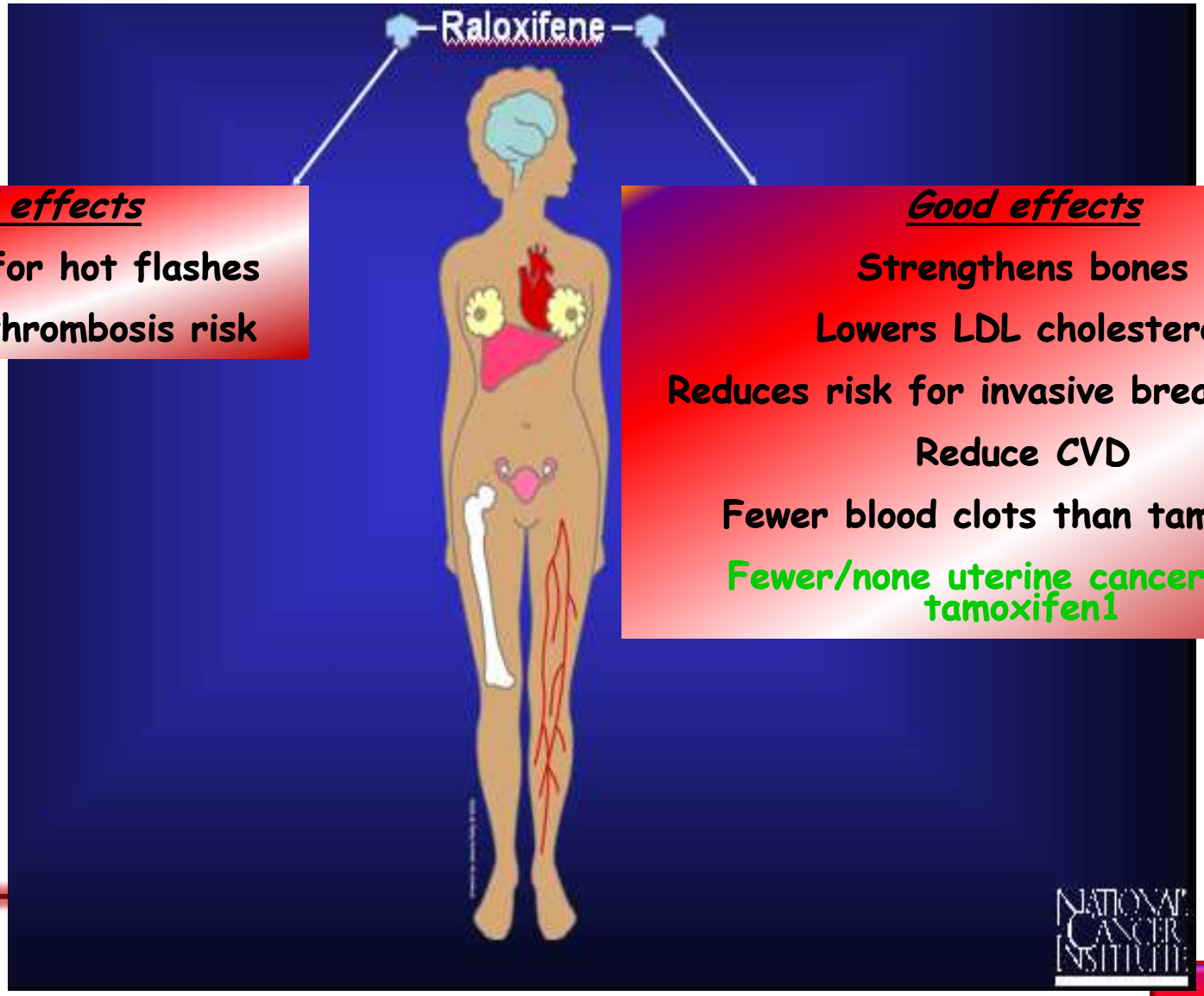
Incidence & Severity of Urinary Incontinence in Postmenopausal Women Treated with Raloxifene or Estrogen



* Significantly different from placebo and both doses of raloxifene ($P \leq 0.020$)

Effect of Raloxifene on Prevention of Dementia and Cognitive Impairment

Cognitive outcome	Treatment group	RR	P
Mild cognitive impairment	RLX 60 mg	1.18	0.32
	RLX 120mg	0.67	0.04
Alzheimer's dis.	RLX 60 mg	0.82	0.60
	RLX 120mg	0.52	0.12
Any dementia	RLX 60 mg	0.90	0.76
	RLX 120mg	0.91	0.78
Dementia or mild cognitive impairment	RLX 60 mg	1.12	0.45
	RLX 120mg	0.73	0.054



Bad effects

No relief for hot flashes

Increase thrombosis risk

Good effects

Strengthens bones

Lowers LDL cholesterol

Reduces risk for invasive breast cancer

Reduce CVD

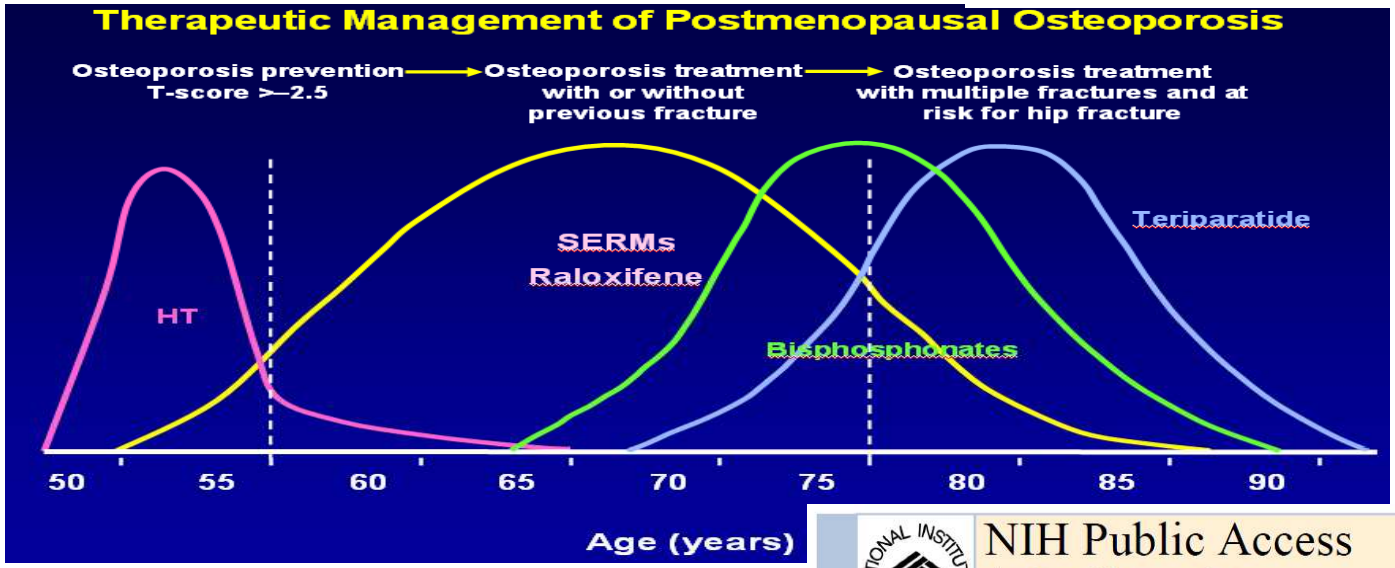
Fewer blood clots than tamoxifen

Fewer/none uterine cancers than tamoxifen1

ORIGINAL CONTRIBUTION

Patient-Reported Symptoms and Quality of Life During Treatment With Tamoxifen or Raloxifene for Breast Cancer Prevention

The NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 Trial



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Cognitive changes associated with endocrine therapy for breast cancer

UNIVERSITÀ DEGLI STUDI DI PADOVA

REPRODUCTIVE ENDOCRINOLOGY

Antiproliferative and proapoptotic effects of raloxifene on uterine leiomyomas in postmenopausal women

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Raloxifene slows down the progression of intima-media thickness in postmenopausal women

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ORIGINAL ARTICLE

Role of raloxifene on platelet metabolism and plasma lipids

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ABSTRACT

Background This study was performed to understand the metabolic effects of raloxifene, a selective oestrogen receptor modulator, on platelets in healthy non-obese postmenopausal women. The data were compared to untreated subjects.

Materials and methods Platelet nitric oxide activity (NO) and peroxynitrite level, platelet inducible and endothelial nitric oxide synthase expression and plasma lipids were evaluated at baseline and after 12 months of raloxifene or placebo treatment.

Results A significant increase of platelet NO and reduction of platelet peroxynitrite levels, as well as a decrease of inducible nitric oxide synthase expression, was observed 12 months after raloxifene therapy as compared to baseline or placebo treatment. Moreover, raloxifene treatment caused a significant increase in high-density lipoprotein cholesterol and a decrease of total cholesterol and low-density lipoprotein cholesterol were observed versus baseline values ($P < 0.05$). A significant positive correlation was observed between high-density lipoprotein cholesterol and platelet NO ($r = 0.76$, $P < 0.005$) in the raloxifene group.

Conclusion Our results showed that raloxifene improves platelet metabolism in healthy postmenopausal women through an increase of the bioavailability of platelet NO by a reduction of iNOS and the beneficial effects on lipid metabolism. This mechanism of action of raloxifene on platelet activity may explain some cardiovascular protective effects of this selective oestrogen receptor modulator.

Keywords Nitric oxide, NOS, peroxynitrite, platelets, postmenopausal women, raloxifene.

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CLINICAL RESEARCH STUDY

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Effect of Raloxifene on All-cause Mortality

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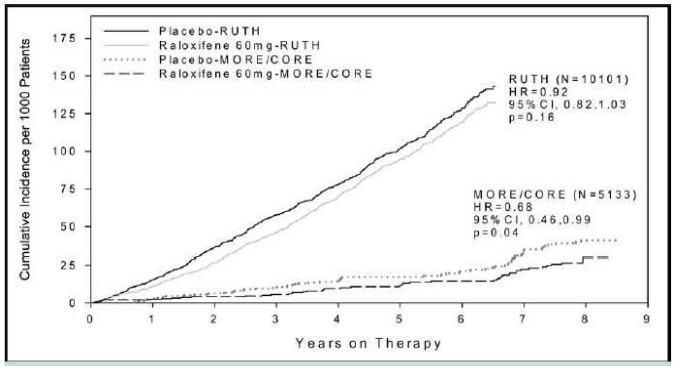


Figure 1 Cumulative incidence of death in patients receiving raloxifene 60 mg/day or placebo throughout the MORE, CORE, and RUTH studies. MORE = Multiple Outcomes of Raloxifene Evaluation trial; CORE = Continuing Outcomes Relevant to Evista trial; RUTH = Raloxifene Use for the Heart trial; CI = confidence interval.

Table 3 Mortality Outcomes from RUTH

Adjudicated Cause	Placebo n = 5057	Raloxifene (60 mg/day) n = 5044	Hazard Ratio (95% CI)	*P* Value
All	595 (11.8%)	554 (11.0%)	0.92 (0.82-1.03)	.16
Cardiovascular death	355 (7.0%)	362 (7.2%)	1.01 (0.87-1.17)	.91
Coronary	274 (5.4%)	255 (5.1%)	0.92 (0.78-1.09)	.34
Cerebrovascular	39 (0.8%)	59 (1.2%)	1.49 (1.00-2.24)	.05
Other cardiovascular*	42 (0.8%)	48 (1.0%)	1.13 (0.75-1.71)	.57
Noncardiovascular death	231 (4.6%)	188 (3.7%)	0.80 (0.66-0.98)	.03
Cancer	103 (2.0%)	97 (1.9%)	0.93 (0.70-1.23)	.61
Noncancer	128 (0.5%)	91 (0.3%)	0.70 (0.54-0.92)	.01
	9 (<0.1%)	4 (<0.1%)	N/A	N/A

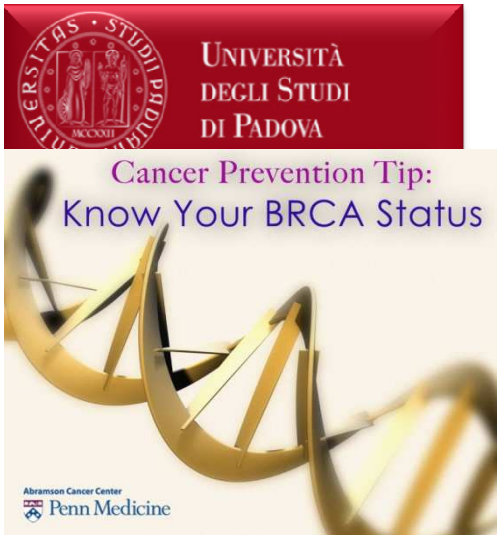
ne Use for the Heart trial; CI = confidence interval.
due to venous thromboembolism (5 in placebo; 10 in raloxifene [HR 1.98; 95% CI, 0.68-5.79; *P* = .20]).

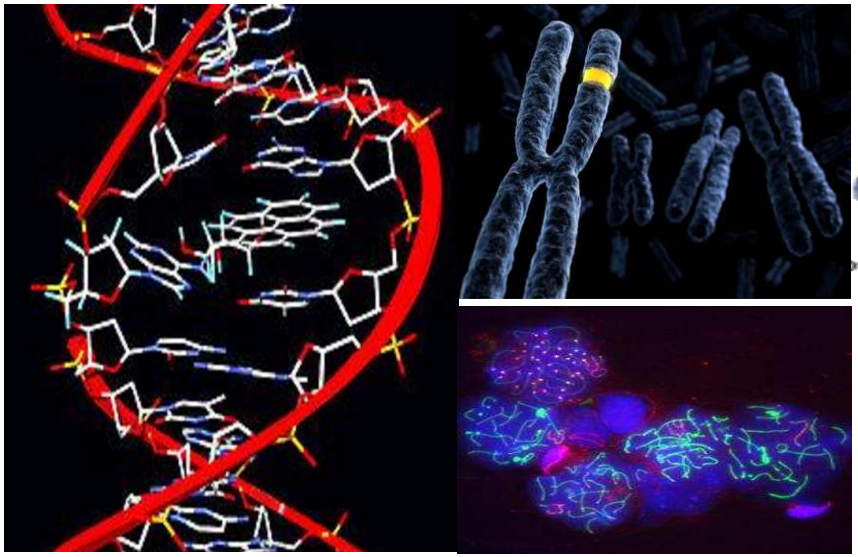
Table 5 Adjudicated Noncardiovascular, Noncancer Deaths in MORE/CORE, RUTH, and Pooled Trials

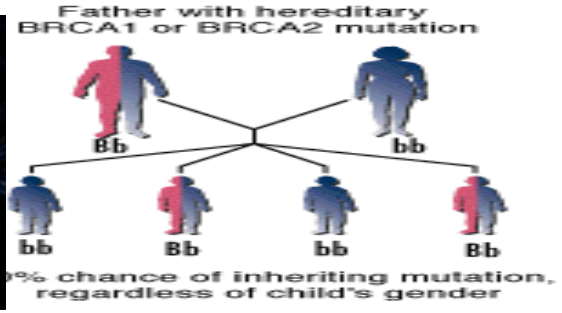
	MORE/CORE		RUTH		Pooled	
	Placebo	Raloxifene (60 mg/day)	Placebo	Raloxifene (60 mg/day)	Placebo	Raloxifene (60 mg/day)
Infection/sepsis	8	3	43	25	51	28
Respiratory	3	4	19	18	19	18
Renal failure	0	0	10	4	10	4
Gastrointestinal	0	1	8	6	8	7
Hepatobiliary	0	1	4	1	4	2
Pancreatic	2	0	3	2	5	2
Central nervous system	0	1	4	3	4	4
Other (accident, suicide, homicide, N/A)	4	5	40	36	44	41
Total	17	15	128	91	145	106

MORE/CORE = Multiple Outcomes of Raloxifene Evaluation/Continuing Outcomes Relevant to Evista; RUTH = Raloxifene Use for the Heart.

Perspective Clinical Trail…PADUA UNIVERSITY







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see you next update…Bye