

The Trudy Bush Lecture:  
Estrogens & Cardiovascular  
Disease in Women:



*What to Make of Genomes*

**David Herrington, MD**  
Wake Forest University

1



**Trudy L. Bush**  
(1949 – 2001)

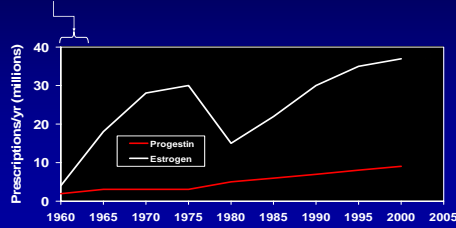
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**History of HRT Use in the US**

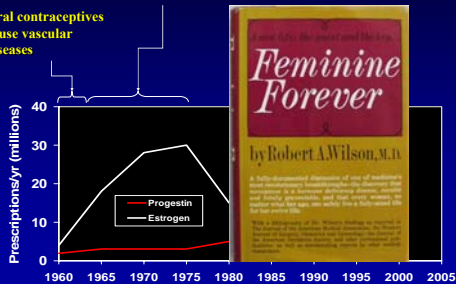
Failed estrogens trials in men  
Oral contraceptives cause vascular diseases



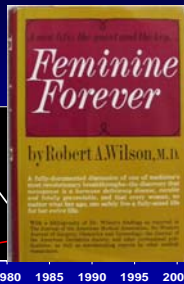
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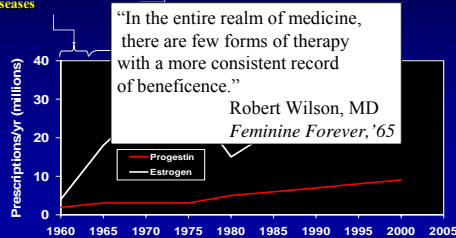


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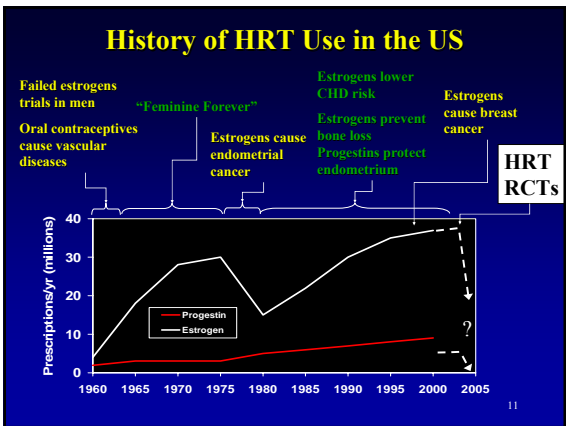
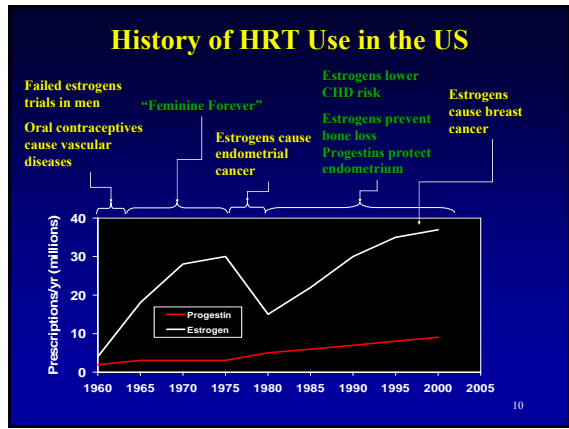
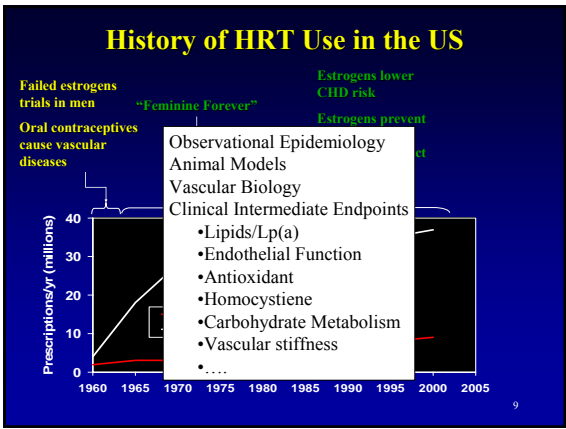
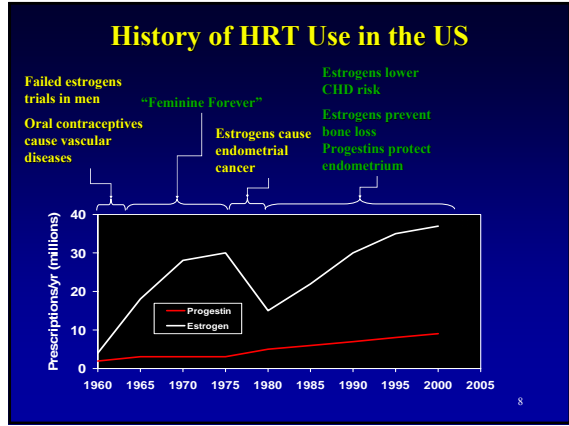
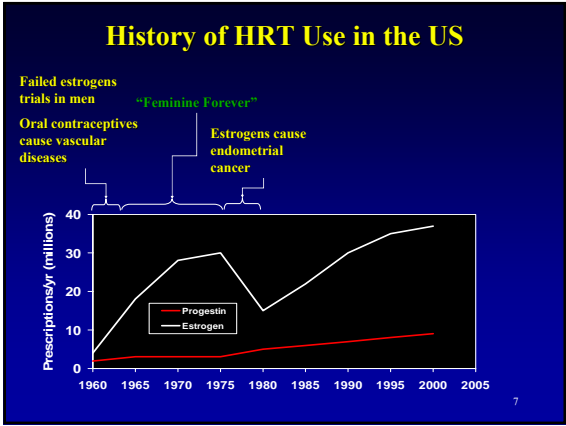


**History of HRT Use in the US**

Failed estrogens trials in men  
Oral contraceptives cause vascular diseases



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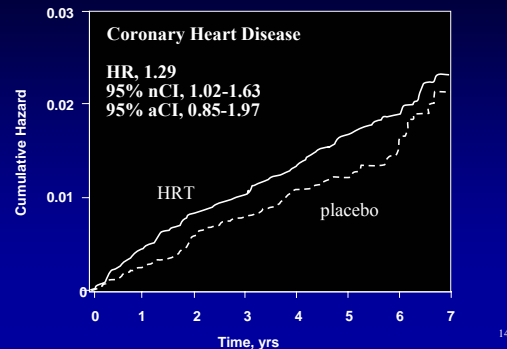
### 2° Prevention Trials of HRT

Study	Outcome	Results
♦ <b>HERS</b> CEE + MPA	MI/CHD Death	no benefit
♦ <b>ERA</b> CEE or CEE + MPA	QCA	no benefit
♦ <b>PHASE</b> TD 17β-E <sub>2</sub> 2 mg (+ cyclic NE)	Death/MI/UA	no benefit
♦ <b>PHOREA</b> 17-β E <sub>2</sub> 1 mg (+ cyclic gestodene)	Carotid IMT	no benefit
♦ <b>WEST</b> 17-β E <sub>2</sub> 1 mg (+ yearly MPA)	Stroke/TIA	no benefit
♦ <b>Schulman et.al.</b> 17-β E <sub>2</sub> or 17-β E <sub>2</sub> + MPA	MI/CHD Death	no benefit
♦ <b>ESPRIT</b> Estradiol valerate 2mg	MI/CHD Death	no benefit
♦ <b>WAVE</b> CEE +/- cont MPA	QCA + death	no benefit
♦ <b>WELL-HART</b> 17-β E <sub>2</sub> + cyclic MPA	QCA	no benefit

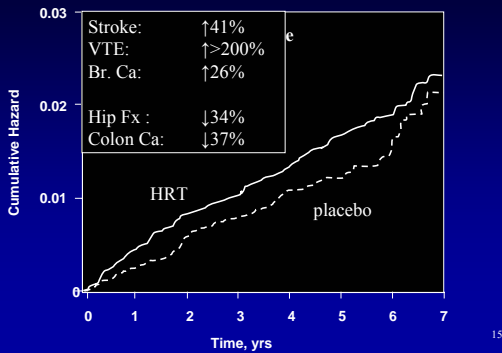
## 2° Prevention Trials of HRT

Study	Outcome	Results
• <b>HERS</b> CEE + MPA	MI/CHD Death	possible harm
• <b>ERA</b> CEE or CEE + MPA	QCA	no benefit
• <b>PHASE</b> TD 17B-E <sub>2</sub> 2 mg (+ cyclic NE)	Death/MI/UA	possible harm
• <b>PHOREA</b> 17-β E <sub>2</sub> 1 mg (+ cyclic gestodene)	Carotid IMT	no benefit
• <b>WEST</b> 17-β E <sub>2</sub> 1 mg (+ yearly MPA)	Stroke/TIA	possible harm
• <b>Schulman et.al.</b> 17-β E <sub>2</sub> or 17-β E <sub>2</sub> + MPA	MI/CHD Death	possible harm
• <b>ESPRIT</b> Estradiol valerate 2mg	MI/CHD Death	no benefit
• <b>WAVE</b> CEE +/- cont MPA	QCA + death	possible harm*
• <b>WELL-HART</b> 17-β E <sub>2</sub> + cyclic MPA	QCA	no benefit

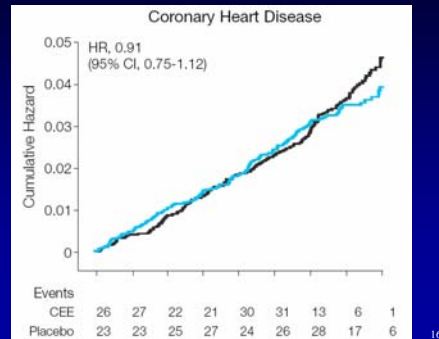
## Effects of E+P on CHD Events in WHI



## Effects of E+P on CHD Events in WHI

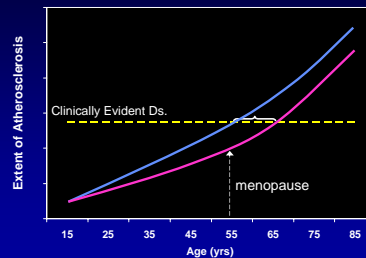


## Effect of E Alone on CHD in WHI

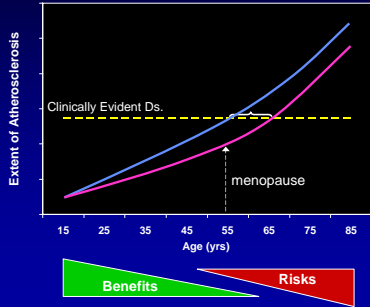


Dear Dr. Herrington 3/22/2000  
 I was 90 years old last June 29<sup>th</sup> and thought you might like to know I have been taking 5 Premarin 0.625 mg per week since I was 38 years old when I had to have a complete hysterectomy...  
 I have outlived my four sisters and their husbands and my two daughters and husband.  
 I do not have any wrinkles and people find it hard to believe I am 90+. I live alone with a bird...  
 Yours truly, ...  
 PS. I forgot to tell you I have a computer and have had one for years XXX@Juno.com

## Does Timing of Estrogen Exposure Influence the Risk/Benefit Ratio?

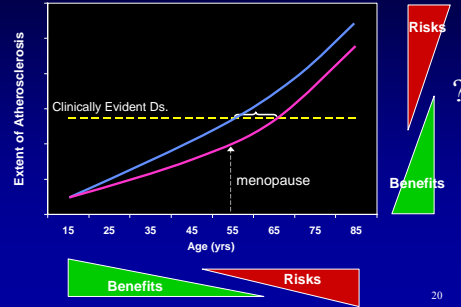


### Does Timing of Estrogen Exposure Influence the Risk/Benefit Ratio?



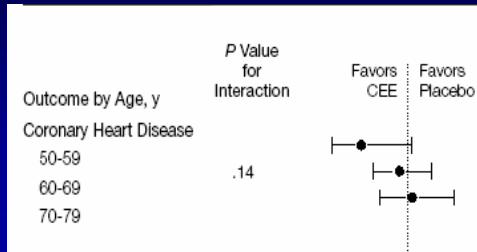
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### Does Timing of Estrogen Exposure Influence the Risk/Benefit Ratio?



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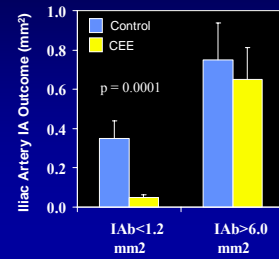
### Does Age at Initiation of HT Matter? Data from WHI (E alone)



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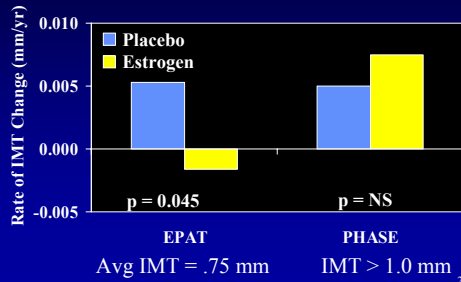
### Additional Evidence Concerning 1° vs 2° Prevention

*Iliac Atherosclerosis in Monkeys*



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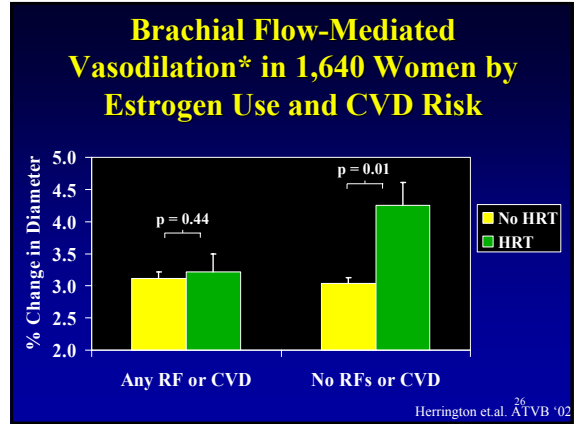
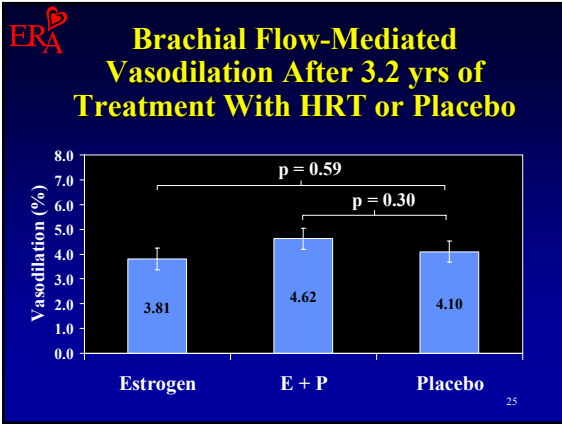
### Comparison of Results from the EPAT and PHASE Trials



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### Brachial Flow-Mediated Vasodilation





“You are as old as your endothelium”  
Ralph Altschul, 1954

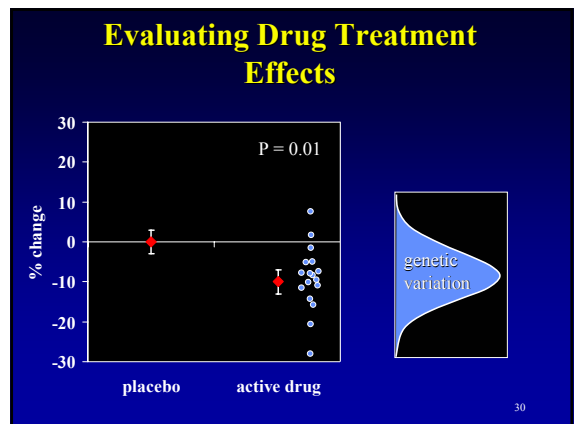
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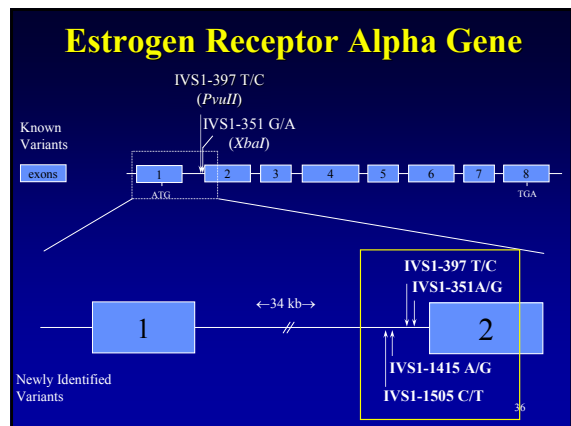
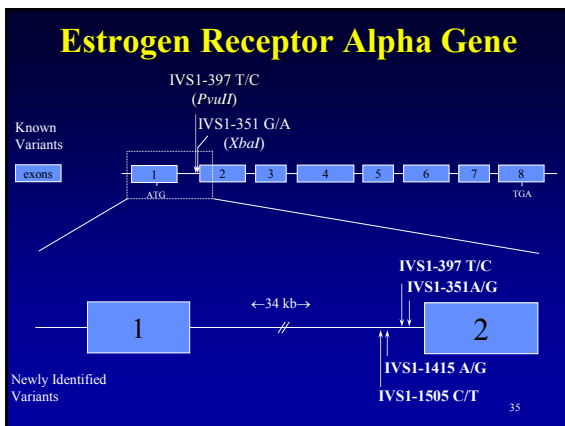
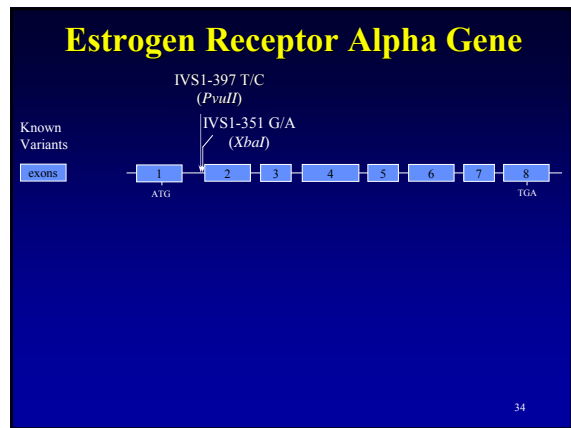
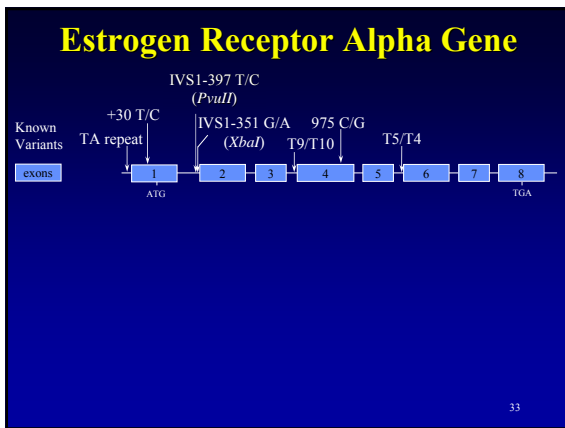
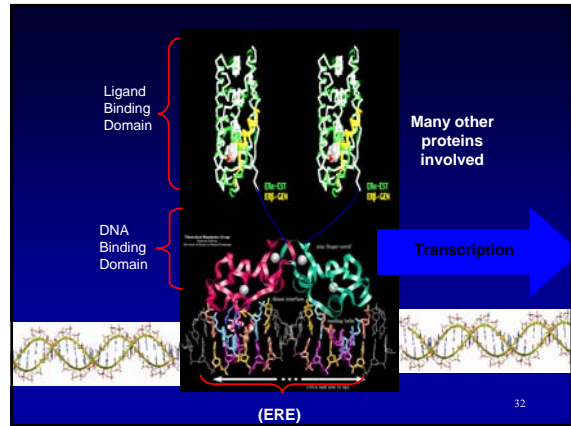
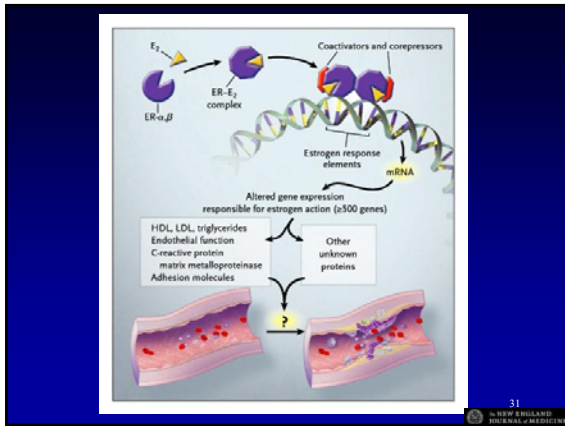
“All who drink of this treatment recover in a short time. Except those who it does not help, who all die. It is obvious, therefore, that it fails only in incurable cases.”  
Galen, Ancient Rome

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**Pharmacogenetics:**  
The study of the hereditary (genetic) basis for variation in individual responses to drugs.

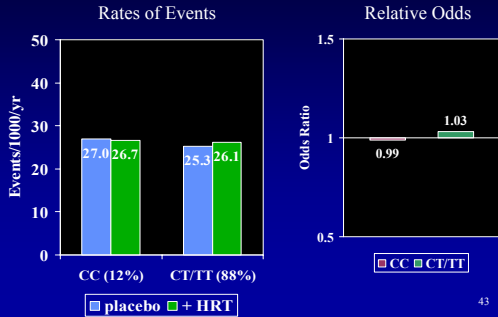
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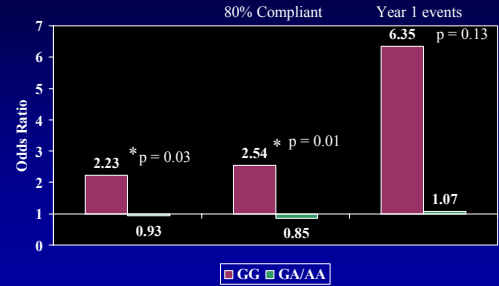


### Absolute and Relative Risks of MI/CHD Death by ESR1 +30 T/C



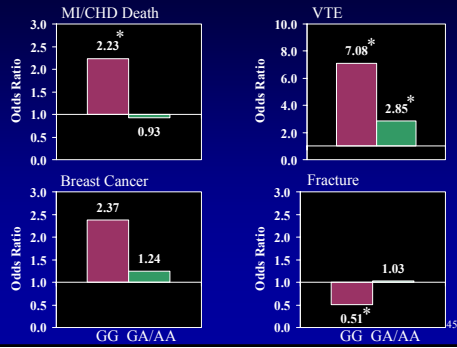
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### Relative Odds for MI/CHD Death by ESR1 IVS1 -354 A/G Genotype



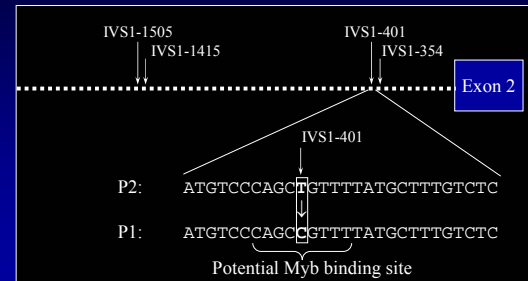
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### Relative Odds for Clinical Events by ESR1 IVS1 -354 A/G Genotype



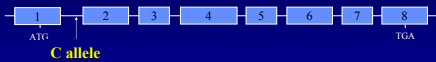
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### Possible Myb Binding Site



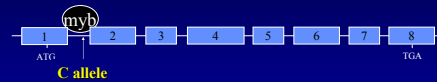
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### Potential effects of a myb factor binding site



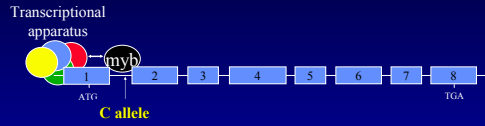
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### Potential effects of a myb factor binding site



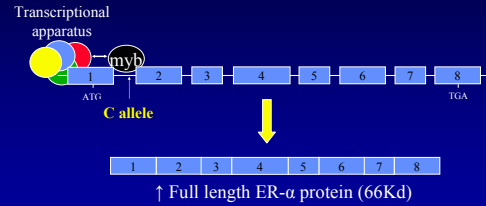
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## Potential effects of a myb factor binding site



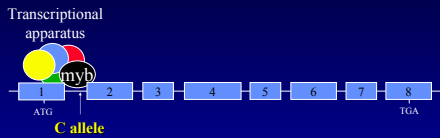
49

## Potential effects of a myb factor binding site



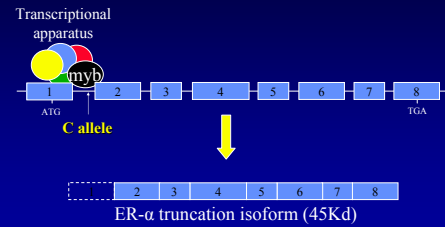
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## Potential effects of a myb factor binding site



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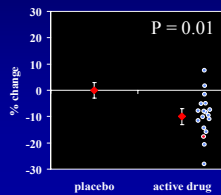
## Potential effects of a myb factor binding site



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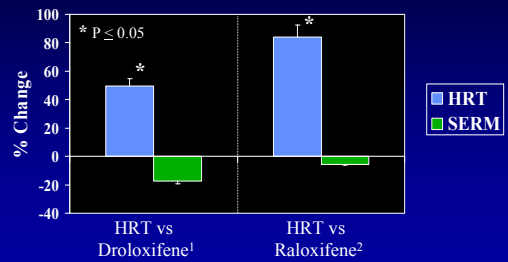
“Variation is absolute, and in physiology averages give nothing real.”

Claude Bernard  
Cahier Rouge, 1860

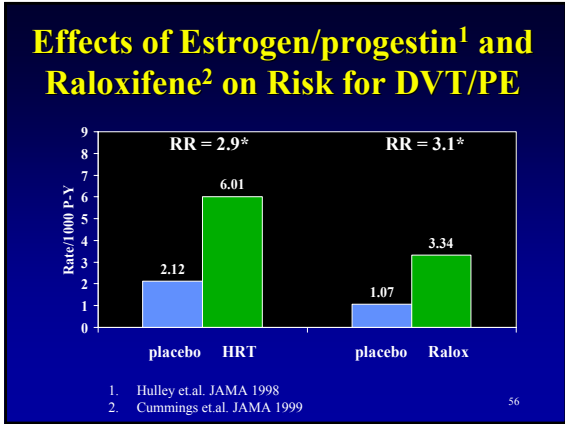
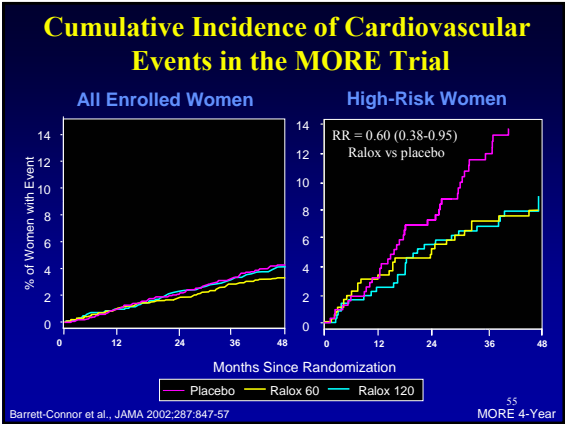


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## Effects of Oral Estrogen vs SERMs on CRP



<sup>1</sup>Herrington et al. J Clin Endocrinol Metab 2001;86:4216-4222. 54  
<sup>2</sup>Walsh BW, et al. J Clin Endocrin Metab. 2000;35:1-214-218.



“Estrogens for Prevention of CHD: Putting the Brakes on the Bandwagon”  
*Circulation 1996;94:2699-702*

“HRT and Heart Disease Prevention: Experimentation Trumps Observation”  
*JAMA 1998;280:650-2*

“The HERS Trial: Paradigms Lost?”  
*Ann Intern Med 1999;131:463-6*

“Lessons from HERS: The Null and Beyond”  
*J Womens Health 1998;7:781-3*

“The Time Has Come to Stop Letting the HERS Tale Wag the Dogma”  
*Circulation 2001;104:2256-9*

“Looking for the Pony in the HERS Data”  
*Circulation 2002;105:902-3*

“The medical profession ... is slow to make use of new knowledge. The history of medicine is full of unrecognized prophets, missed opportunities, and embarrassed hindsight.”

Robert Wilson, *Feminine Forever*

“Each time we learn something new, the astonishment comes from the recognition that we were wrong before. In truth, whenever we discover a new fact, it involves the elimination of old ones. We are always, as it turns out, fundamentally in error.”

Lewis Thomas

