



# **Correcting for noncompliance in randomized trials**

*an application to the Women's Health Initiative*

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May 22, 2008



## Acknowledgements

- Miguel Hernán, MD, DrPH
  - Department of Epidemiology, HSPH
- Sonia Hernández-Díaz, MD, DrPH
  - Department of Epidemiology, HSPH
- James M. Robins, MD
  - Department of Epidemiology and Biostatistics, HSPH



# Notation

- $R$  Random treatment assignment (1: HRT; 0: placebo)
- $A_k$  Treatment received at time  $k$  (1: HRT; 0: no HRT)
- $V$  Baseline covariates
- $L_k$  Covariates measured at time  $k$
- $C_k$  Censoring status at time  $k$  (1: censored; 0: not censored)
- $\bar{A}_k$  Treatment history through time  $k$
- $\bar{L}_k$  Covariate history through time  $k$
- $\bar{C}_k$  Censoring history through time  $k$
- $Y^r$  (Potential) outcome had  $R=r$



## Randomized clinical trials

- Random treatment assignment at baseline
- Trial investigators have no direct control over participants' treatment decision over time
- Record data as if they were conducting an observational study



## Treatment effects of interest

- Intention-to-treat effect

- *Average effect of treatment initiation*
- *More precisely, average effect of random treatment assignment*

$$\Pr[Y^{r=1} = 1] - \Pr[Y^{r=0} = 1]$$

- Average effect of continuous treatment

- *Average treatment effect in the absence of noncompliance*

$$\Pr[Y^{\bar{a}=1} = 1] - \Pr[Y^{\bar{a}=0} = 1]$$

- Under noncompliance

$$\Pr[Y^{r=1} = 1] - \Pr[Y^{r=0} = 1] \neq \Pr[Y^{\bar{a}=1} = 1] - \Pr[Y^{\bar{a}=0} = 1]$$



## Estimating effect of continuous use

### *Inverse probability weighting – Non dose-response analysis*

- Censor patients when they became non-adherent
- Weight patients by the inverse of their probability of remaining uncensored
- The weight is usually unknown and must be estimated
  - Pooled logistic regression
  - Separately for each randomized arm
  - Baseline and time-varying covariates
- Stabilized weight for a given randomized arm

$$SW(t) = \prod_{k=0}^t \frac{\Pr[C_k = 0 \mid \bar{C}_{k-1} = \bar{0}, R = r, V = v]}{\Pr[C_k = 0 \mid \bar{C}_{k-1} = \bar{0}, R = r, \bar{L}_k = \bar{l}_k]}$$



# Estimating effect of continuous use

## *Inverse probability weighting – Dose-response analysis*

- Do not censor patient when they became noncompliant
- Estimate the probability of received treatment
- Stabilized weight as the inverse of the probability of received treatment

$$SW(t) = \prod_{k=0}^t \frac{f[A_k | R = r, \bar{A}_{k-1} = \bar{a}_{k-1}, V = v]}{f[A_k | R = r, \bar{A}_{k-1} = \bar{a}_{k-1}, \bar{L}_k = \bar{l}_k]}$$

- Assume a (dose-response) marginal structural model
  - Cumulative use
  - Average cumulative use
  - Current use



## Inverse probability weighting *Structural Cox models*

- IPW non dose-response analysis

$$\lambda_{T^r} [t | V] = \lambda_{0_s} [t] \exp[\beta_1 r + \alpha V]$$

- IPW dose-response analysis (marginal structural model)

$$\lambda_{T^{\bar{a}}} [t | V] = \lambda_{0_s} [t] \exp[\beta_1' cum[\bar{a}_t] + \alpha V]$$

where  $cum[\bar{a}_t] = \sum_{k=0}^t a_k$





# Covariates

- **Socio-demographic factors**
  - Ethnicity, income, marital status, etc
- **Major risk factors for CHD**
  - Age, high cholesterol, high blood pressure, diabetes mellitus, physical activity, body mass index, cigarette smoking
- **Medical history (personal and family)**
  - Stroke, fracture, cancer, etc
- **Medication use**
  - Aspirin, statin, oral contraceptives, etc
- **Others**
  - Alcohol intake, multivitamin use, fruit and vegetable intake, screening or diagnostic procedures, age since menopause, and occurrence and severity of menopausal symptoms, etc

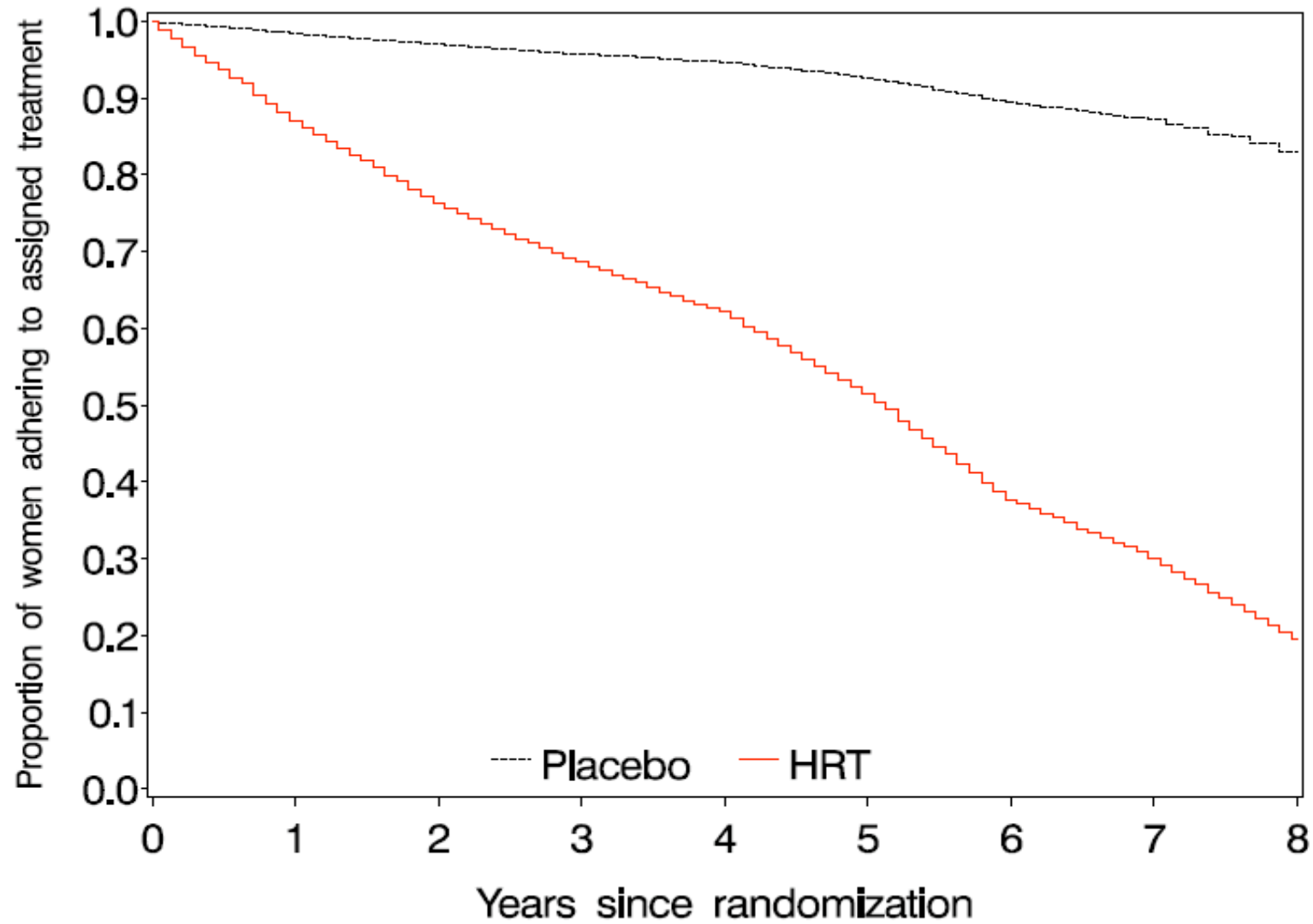


## Intention-to-treat effects

	<i>CHD cases (HRT/placebo)</i>	<i>WHI</i>	<i>Nurses' Health Study</i>
<b>Overall</b>	188/147	1.23 (0.99, 1.53)	1.05 (0.82, 1.34 )
<b>Years since randomization</b>			
≤ 2	80/51	1.54 (1.08, 2.19)	1.43 (0.92, 2.23)
> 2	108/96	1.07 (0.81, 1.41)	0.91 (0.72, 1.16)
<b>Age at baseline</b>			
< 60	37/27	1.27 (0.77, 2.08)	0.89 (0.67, 1.19)
≥ 60	151/120	1.22 (0.96, 1.55)	1.15 (0.85, 1.57)
<b>Years since menopause</b>			
< 10	31/34	0.89 (0.54, 1.44)	0.88 (0.63, 1.21)
≥ 10	137/95	1.46 (1.12, 1.90)	1.13 (0.85, 1.49)



# Adherence during the follow-up





## Baseline characteristics associated with adherence to assigned treatment

<i>Characteristics</i>	<i>Odds ratio (95% confidence interval)</i>	
	Placebo group (N=8,102)	Treatment group (N=8,506)
<b>Baseline age</b>		
50-59	Reference	Reference
60-69	1.20 (1.00, 1.45 )	0.79 (0.72 , 0.86)
70-79	1.55 (1.16, 2.07 )	0.64 (0.57, 0.73 )
<b>Baseline body mass index</b>		
< 25	Reference	Reference
25-30	1.25 (1.07, 1.46 )	0.96 (0.89, 1.03 )
30-35	1.73 (1.40, 2.13 )	0.97 (0.89, 1.05 )
35-40	1.64 (1.23, 2.17 )	0.99 (0.89, 1.11 )
> 40	1.66 (1.14, 2.42 )	0.78 (0.67, 0.92 )
<b>Baseline physical activity</b>		
None	Reference	Reference
< 2.5 per week	0.98 (0.81, 1.19 )	0.96 (0.88, 1.04 )
2.5 – 5.0 per week	1.10 (0.90, 1.35 )	0.97 (0.89, 1.06 )
5.0 – 7.0 per week	0.92 (0.74, 1.14 )	0.94 (0.85, 1.04 )
> 7.0 per week	0.95 (0.77, 1.17 )	0.83 (0.75, 0.91 )
<b>Baseline smoking status</b>		
Never smoker	Reference	Reference
Past smoker	0.88 (0.76, 1.01 )	0.99 (0.93, 1.06 )
Current smoker	1.07 (0.84, 1.36 )	0.96 (0.86, 1.06 )
<b>Baseline medical history</b>		
Cardiovascular disease	0.90 (0.74, 1.08 )	0.86 (0.79, 0.93 )
Diabetes	0.76 (0.54, 1.06 )	0.94 (0.82 , 1.09)
High blood pressure	1.10 (0.94, 1.29 )	0.93 (0.87, 0.99 )
High cholesterol	1.16 (0.93, 1.45 )	0.95 (0.87, 1.04 )



# Adherence-adjusted effects

## *Dose-response analysis*

	<i>Cumulative use (6-yr increase)</i>	<i>Nurses' Health Study</i>	<i>ITT effect</i>
<b>Overall</b>	1.29 (0.82, 2.04)	1.30 (0.76, 2.21)	1.23 (0.99, 1.53)
<b>Years since randomization</b>			
≤ 2	1.68 (0.92, 3.08 ) *	1.71 (1.03, 2.83)	1.54 (1.08, 2.19)
> 2	1.03 (0.95, 1.12) †	1.07 (0.44, 2.63)	1.07 (0.81, 1.41)
<b>Age at baseline</b>			
< 60	1.87 (0.68, 5.14)	0.91 (0.49, 1.69)	1.27 (0.77, 2.08)
≥ 60	1.22 (0.73, 2.03)	1.92 (0.90, 4.10)	1.22 (0.96, 1.55)
<b>Years since menopause</b>			
< 10	0.65 (0.24, 1.77)	0.68 (0.24, 1.91)	0.89 (0.54, 1.44)
≥ 10	1.71 (0.96, 3.03)	1.57 (0.86, 2.85)	1.46 (1.12, 1.90)

\* Two-year cumulative use

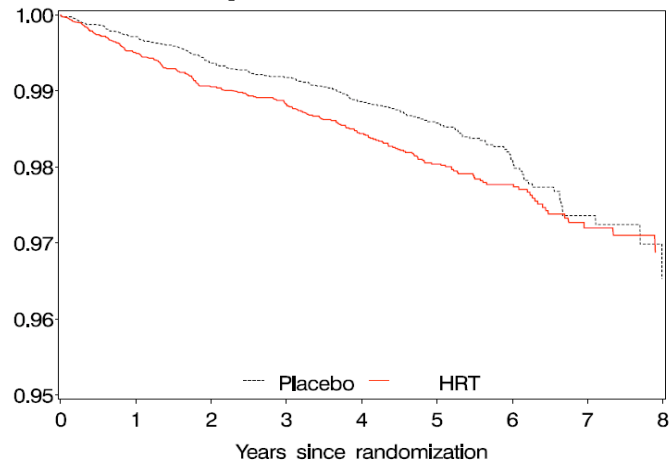
† One-year cumulative use



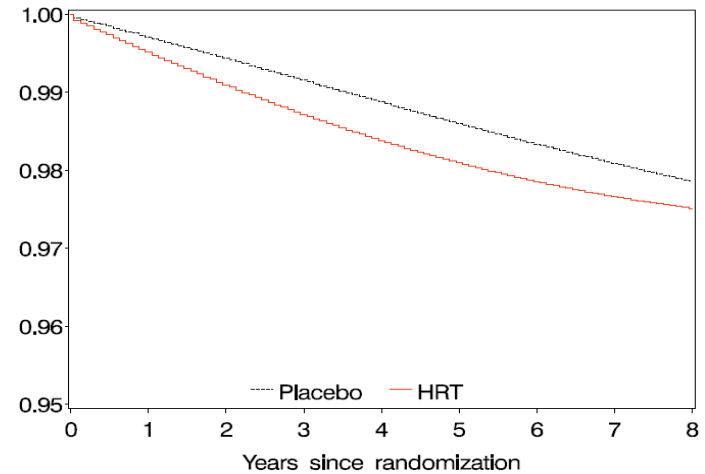
# Proportion of women free of CHD

## *All women*

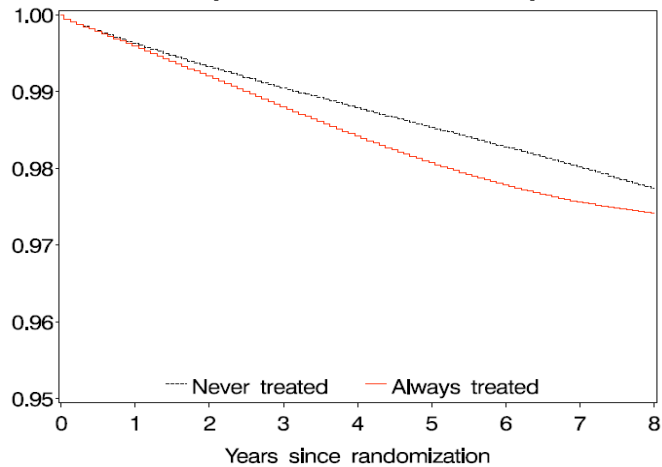
### Kaplan-Meier ITT



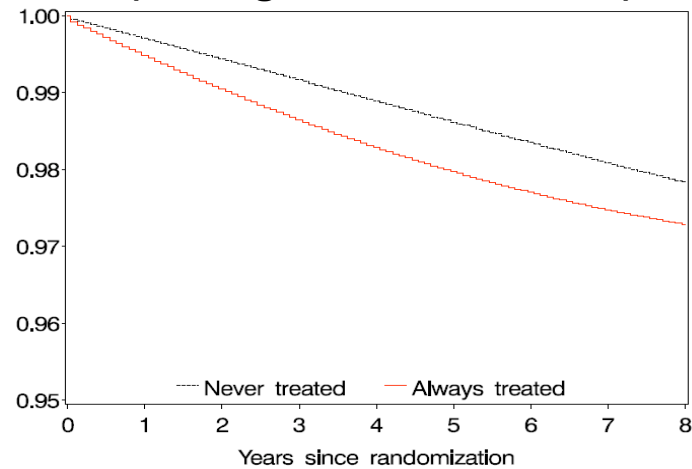
### Estimated ITT



### Adherence-adjusted (cumulative use)



### Adherence-adjusted (average cumulative use)

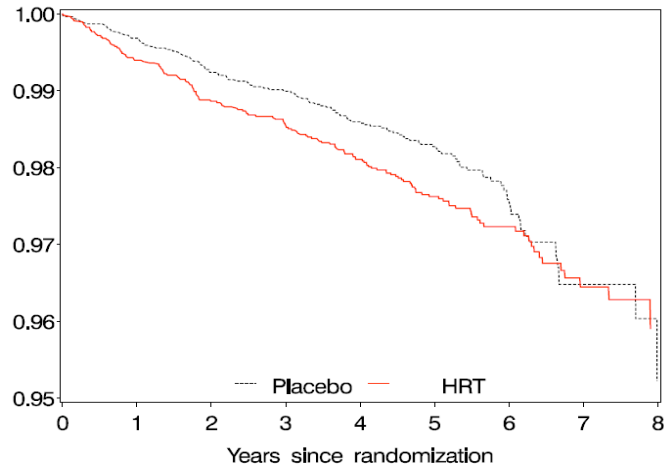




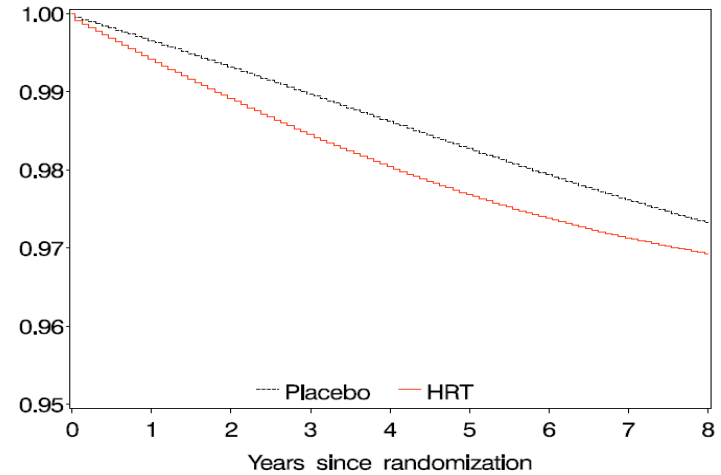
# Proportion of women free of CHD

*Women  $\geq 60$  years old at baseline*

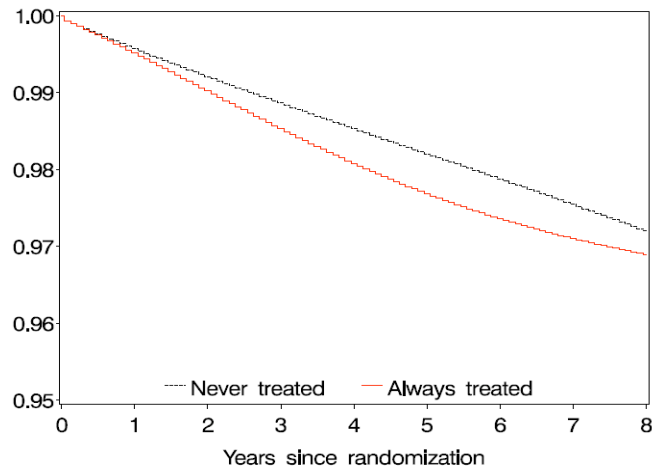
### Kaplan-Meier ITT



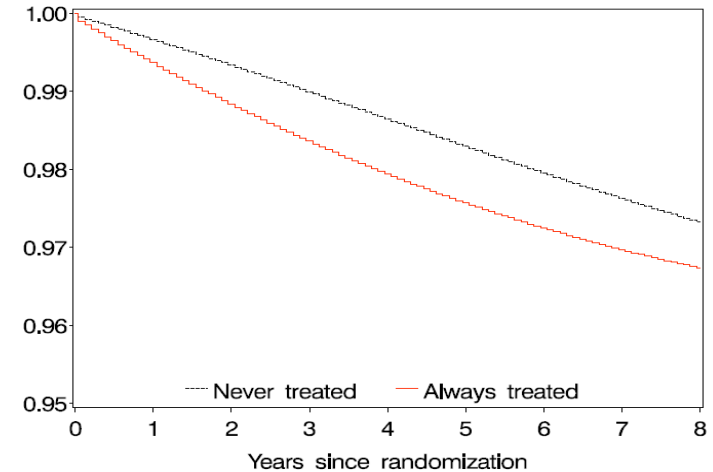
### Estimated ITT



### Adherence-adjusted (cumulative use)



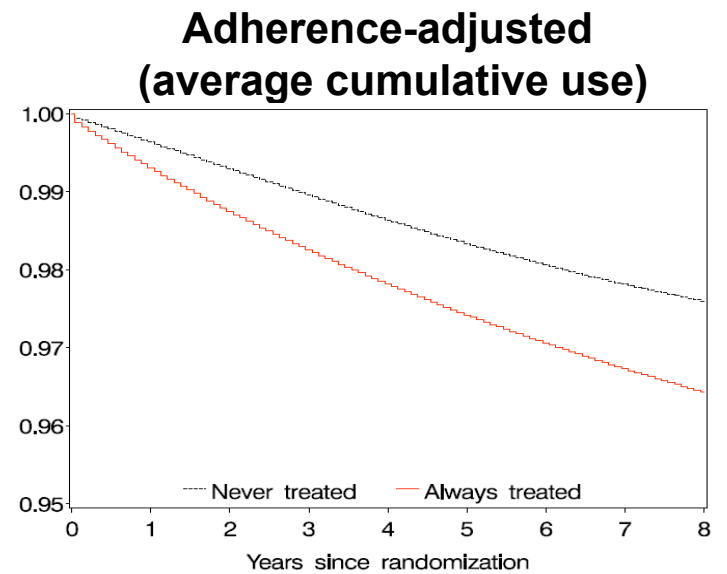
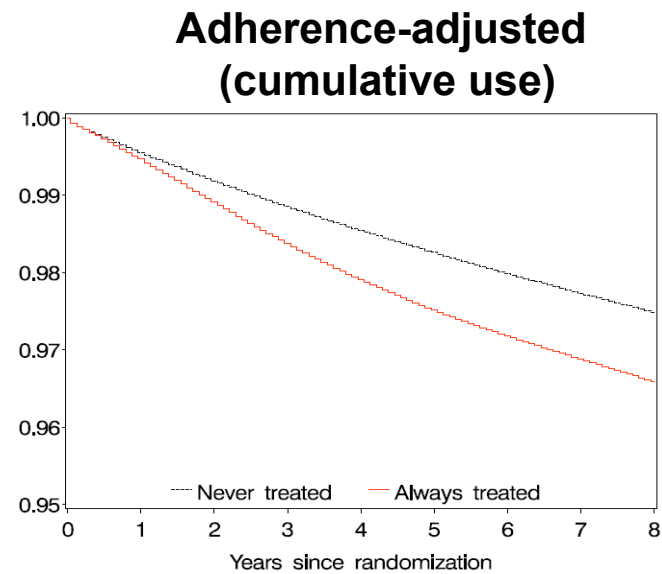
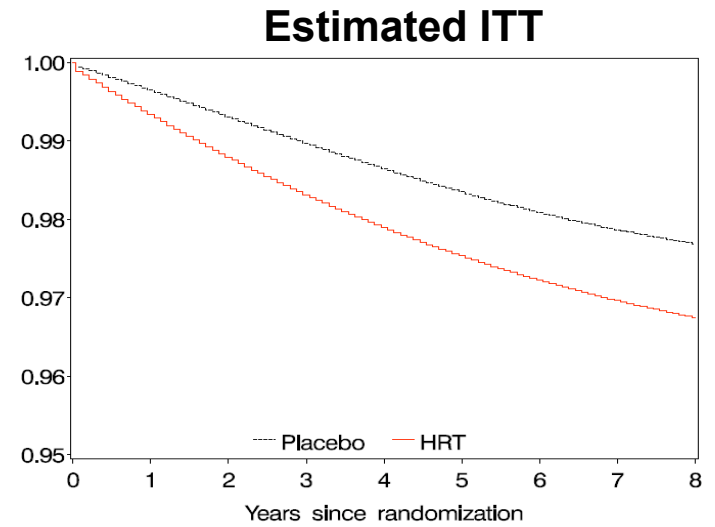
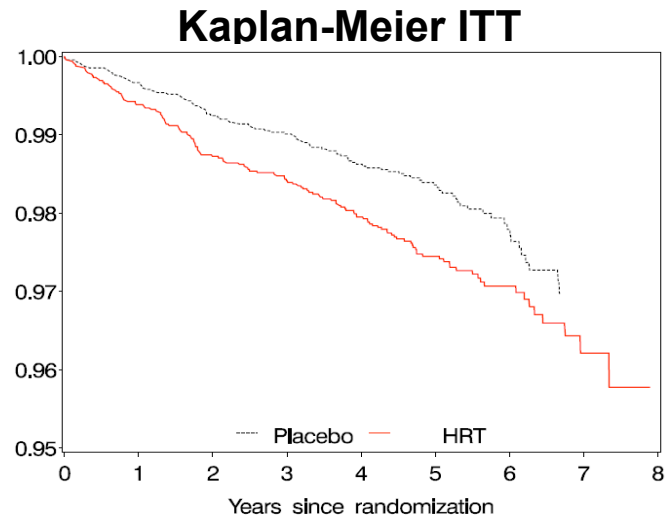
### Adherence-adjusted (average cumulative use)





# Proportion of women free of CHD

*Women  $\geq 10$  years since menopause*



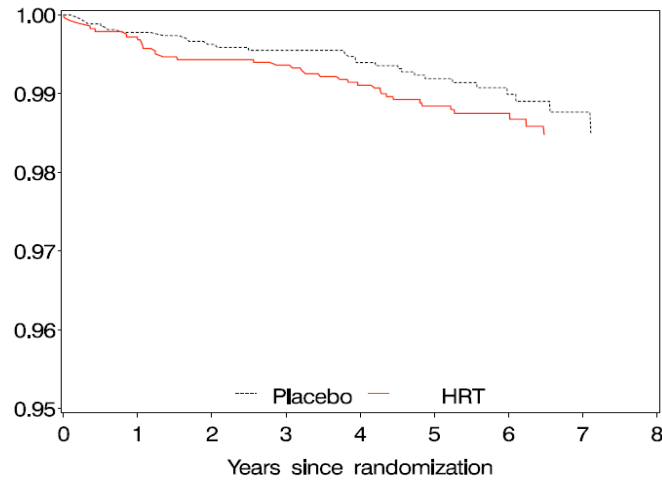




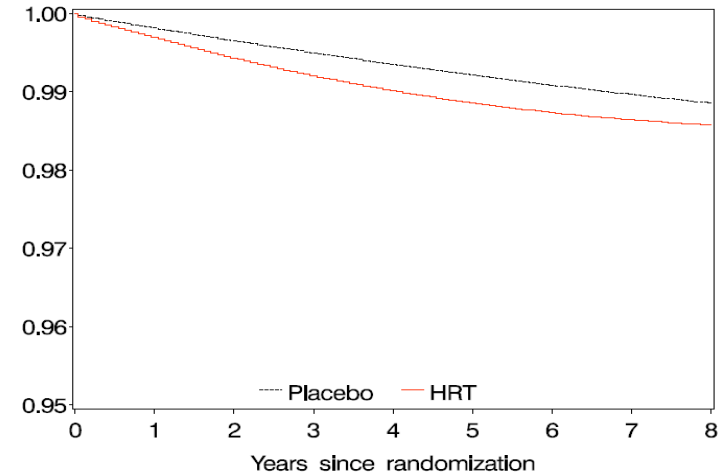
# Proportion of women free of CHD

*Women < 60 years old at baseline*

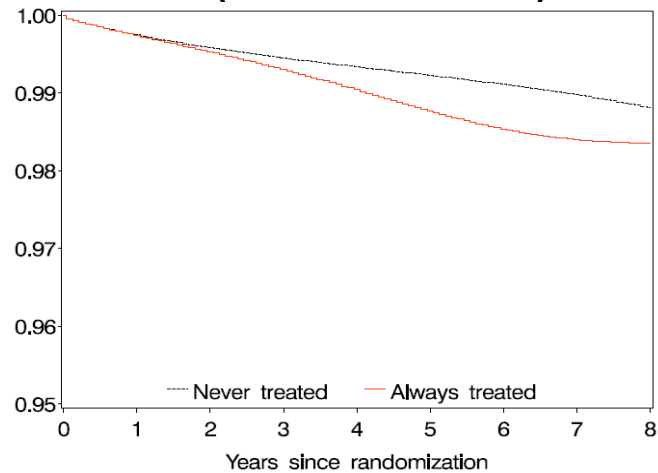
### Kaplan-Meier ITT



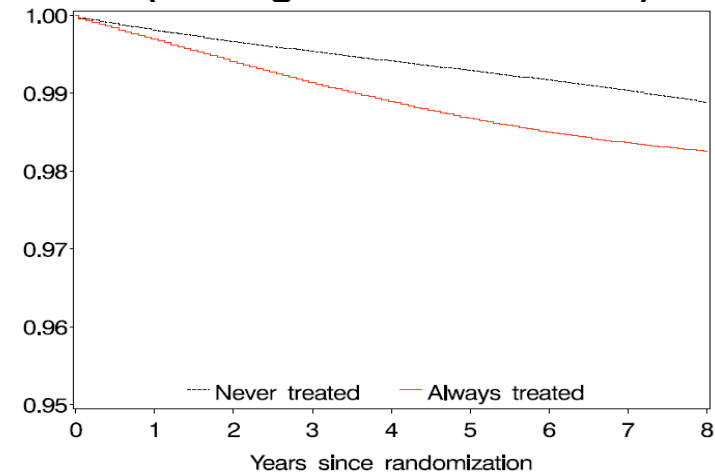
### Estimated ITT



### Adherence-adjusted (cumulative use)



### Adherence-adjusted (average cumulative use)

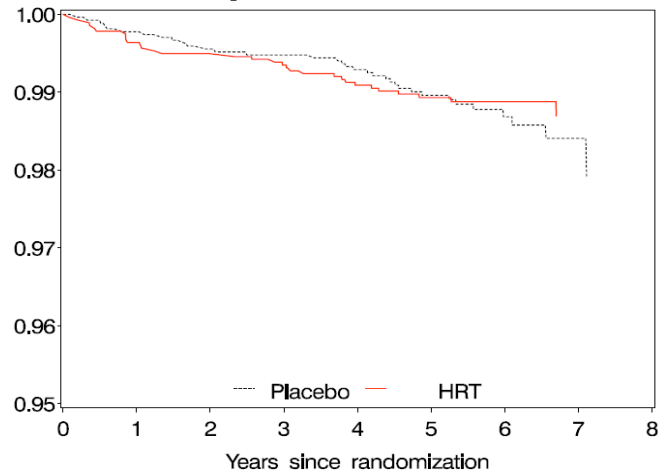




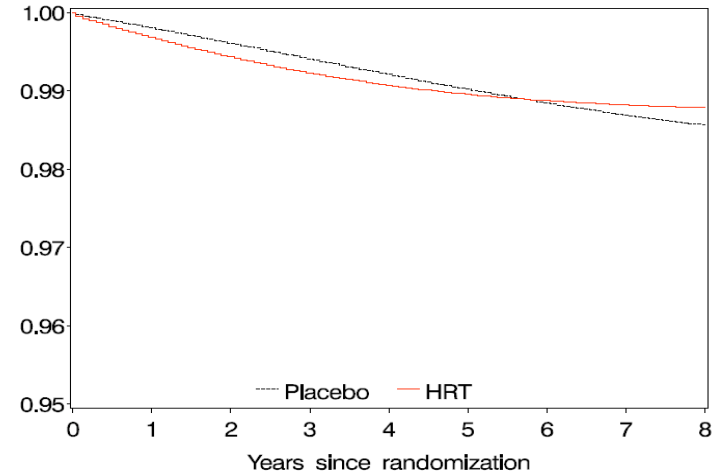
# Proportion of women free of CHD

## *Women < 10 years since menopause*

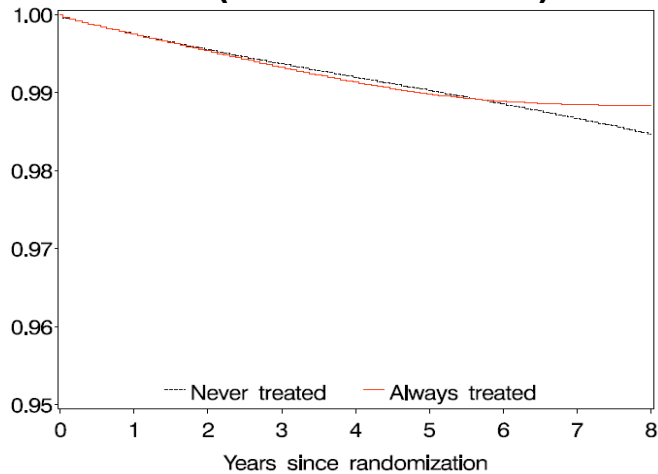
### Kaplan-Meier ITT



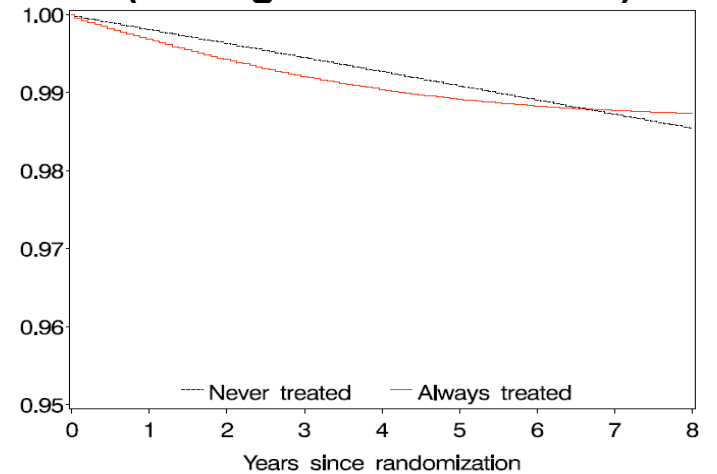
### Estimated ITT



### Adherence-adjusted (cumulative use)



### Adherence-adjusted (average cumulative use)





# Inverse probability weighting

## *Assumptions*

- All joint determinants of treatment and outcome at all times are available
  - *Sequential randomization*
- No model misspecification for estimating the weights
- No model misspecification for the structural model (for dose-response analysis)
- Positivity condition
- Adherence information measured without error
- Covariate information measured without error



# Implications

- Application of inverse probability weighting method to adjust for nonadherence in clinical trials
- Collection of adherence data in clinical trials



# Inverse probability weighting *non dose-response analysis*

	<i>All 65 CHDs occurred before noncompliance</i>	<i>Random date of noncompliance</i>	<i>All 65 CHDs occurred after noncompliance</i>
<b>Overall</b>	1.50 (1.19, 1.90)	1.36 (1.07, 1.74)	0.93 (0.71, 1.21)
<b>Years since randomization</b>			
0-1 year	1.89 (1.13, 3.18)	1.62 (0.93, 2.82)	1.28 (0.70, 2.36)
0-2 years	1.66 (1.16, 2.37)	1.50 (1.03, 2.17)	1.10 (0.74, 1.66)
2-5 years	1.70 (1.15, 2.50)	1.60 (1.08, 2.37)	1.06 (0.69, 1.63)
> 5 years	0.85 (0.45, 1.60)	0.67 (0.34, 1.32)	Do not converge
<b>Age at baseline</b>			
50-59	1.83 (1.05, 3.19)	1.82 (1.03, 3.23)	1.23 (0.67, 2.25)
60-69	1.41 (0.99, 2.02)	1.17 (0.80, 1.72)	0.93 (0.62, 1.39)
70-79	1.59 (1.06, 2.38)	1.48 (0.98, 2.24)	0.79 (0.48, 1.30)
<b>Years since menopause</b>			
<10 year s	1.19 (0.72, 1.97)	1.07 (0.62, 1.83)	0.85 (0.48, 1.53)
10-19 years	1.42 (0.95, 2.12)	1.22 (0.81, 1.85)	0.96 (0.62, 1.48)
≥ 20 years	1.96 (1.24, 3.08)	1.86 (1.17, 2.97)	0.93 (0.54, 1.60)
Unknown	2.22 (0.87, 5.66)	2.10 (0.81, 5.46)	1.39 (0.49, 3.91)

There were 65 CHDs occurred during the same year during which the participants also reported being noncompliant