

**Gender Difference**  
**in Thrombogenicity &**  
**Effect of Antithrombotic**  
**Treatment**



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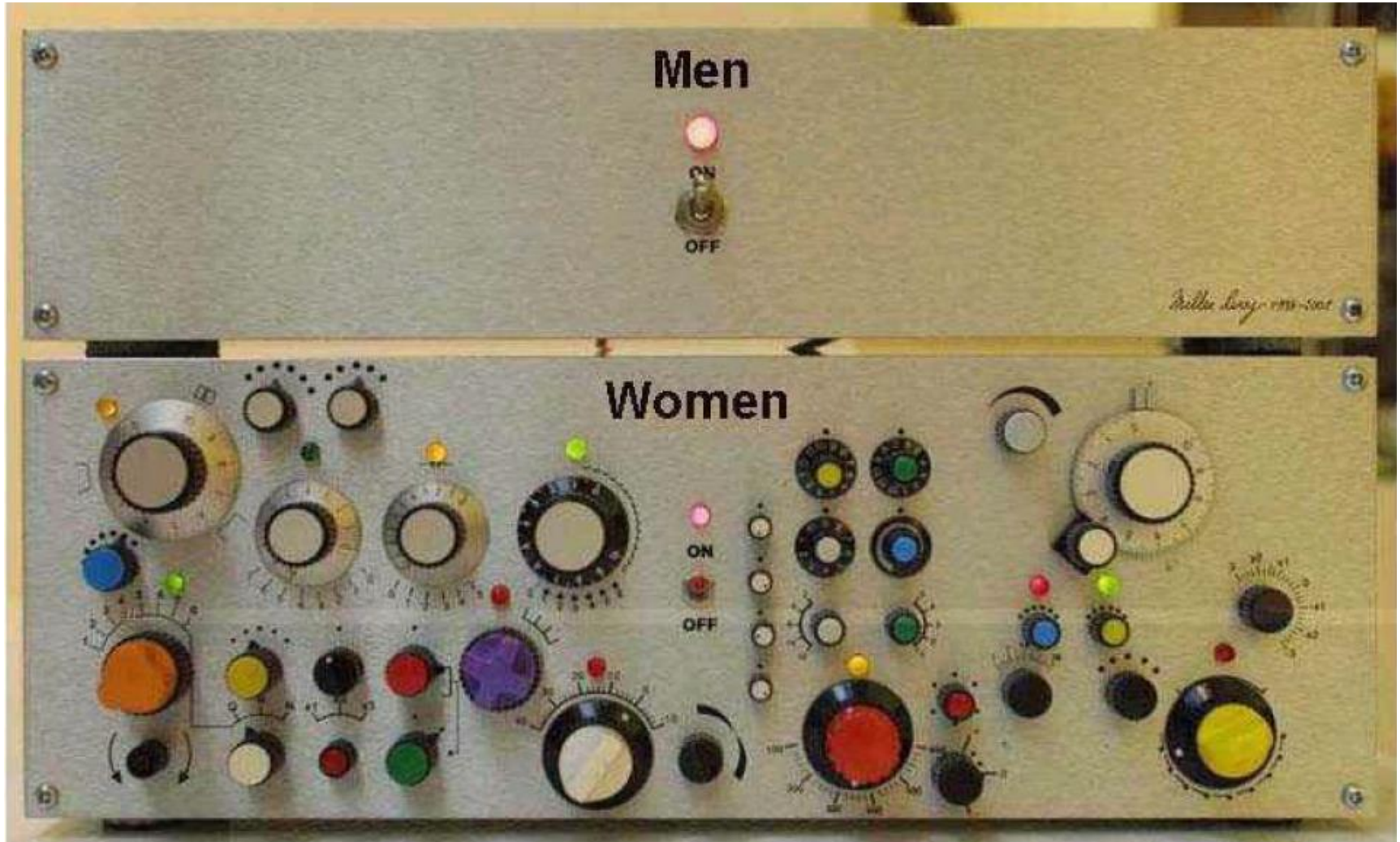
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Gyeongsang National University  
Changwon Hospital, Korea.

# “Women” are like “Small Men”?: No definitely

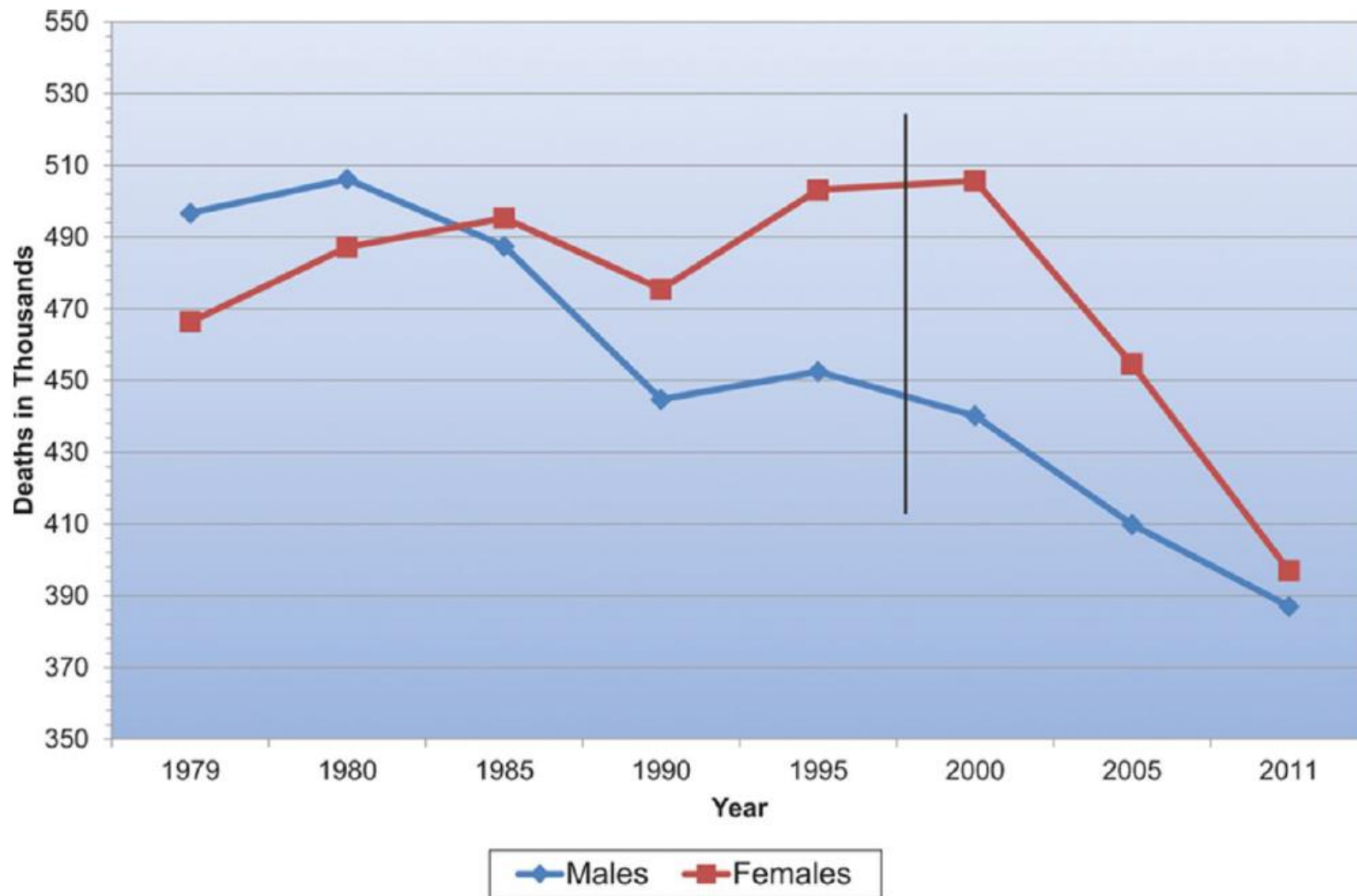




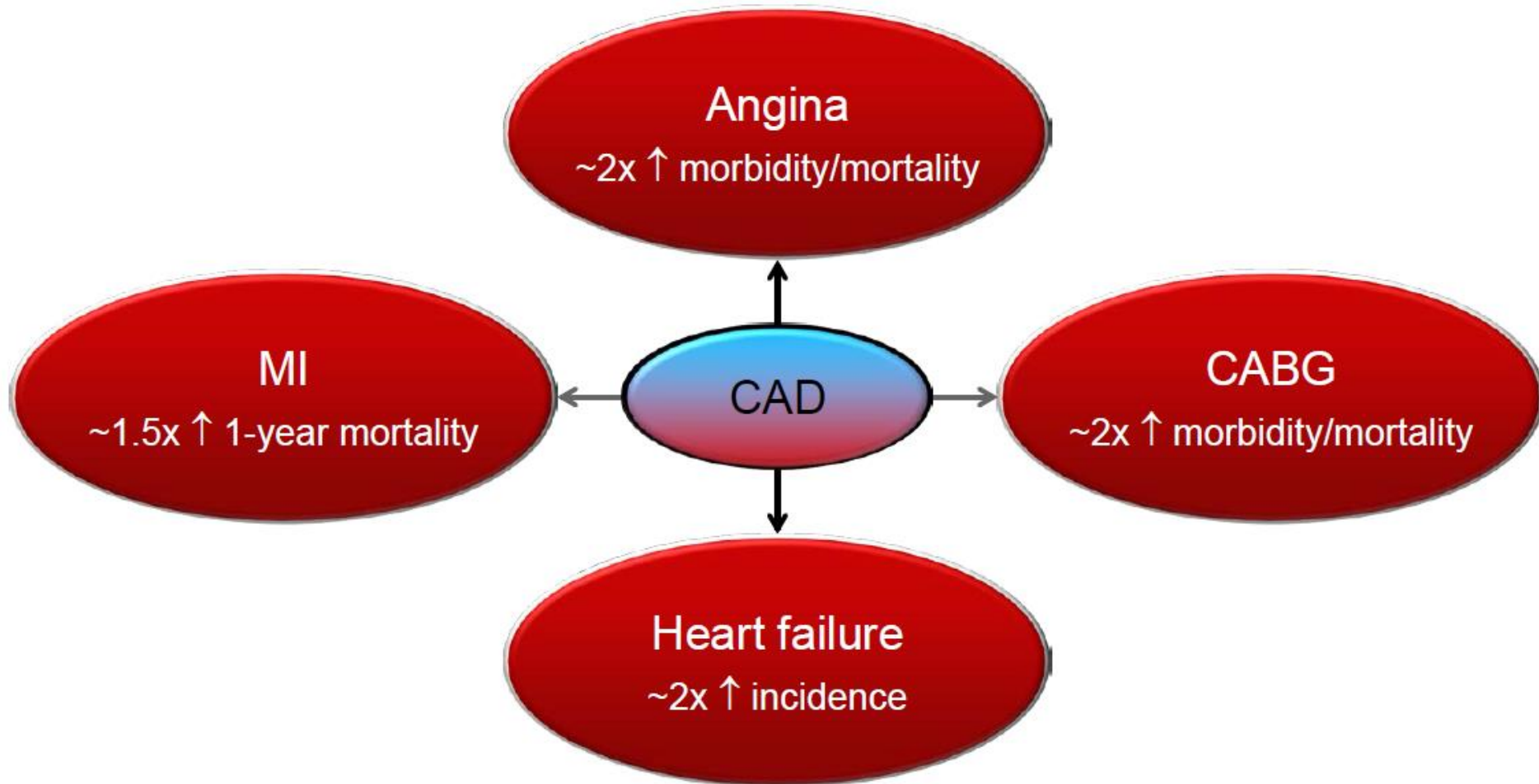
# Women are Just More Complicated Than Men



# CVD Death Trends in the United States



# Women vs. Men Have Poorer Outcomes



- **Under-diagnosed**
- **Under-treated by procedure & medication**

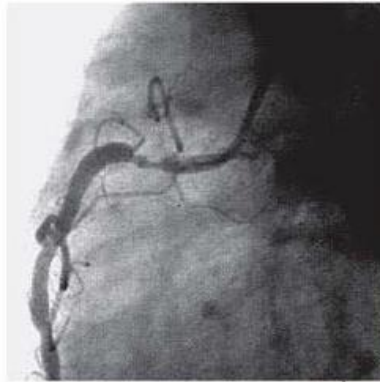


# Pattern of CAD: Men vs. Women

Male-pattern  
Obstructive CAD

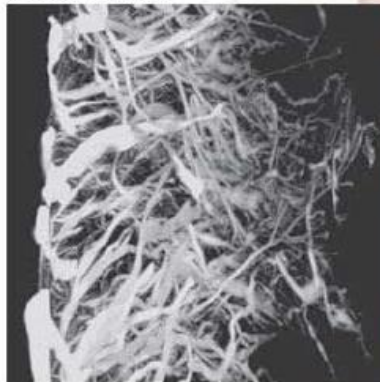
Female-pattern  
Microvascular  
Coronary  
Disease

TYPICAL ANGIOGRAM

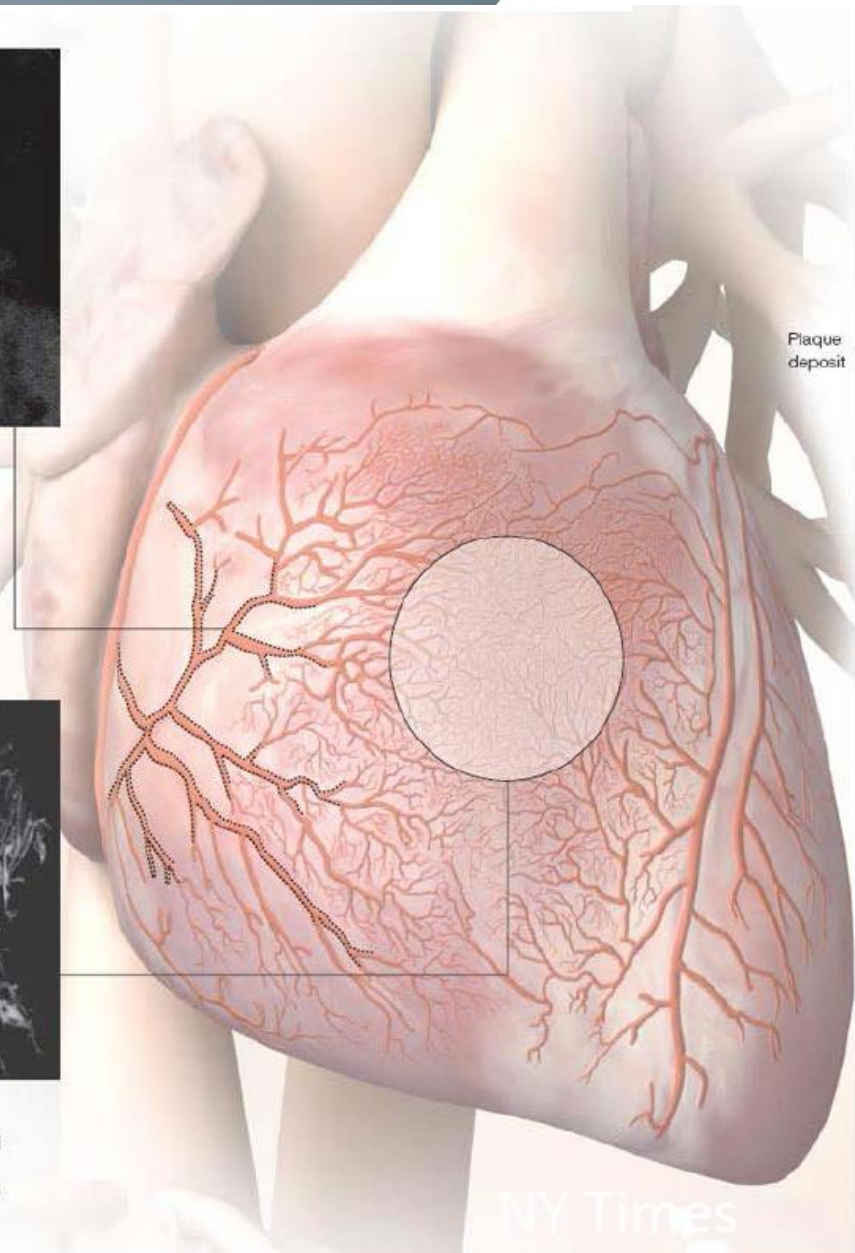


Minneapolis Heart Institute and Foundation  
Larger vessels stand out while smaller ones, because of their microscopic size and the motion of the heart, are lost in a blur.

MICROVASCULATURE



Minneapolis Heart Institute and Foundation  
Other imaging techniques used on hearts removed from the body reveal the vast network of vessels unseen by the angiogram. This image shows the microvessels in a pig's heart.



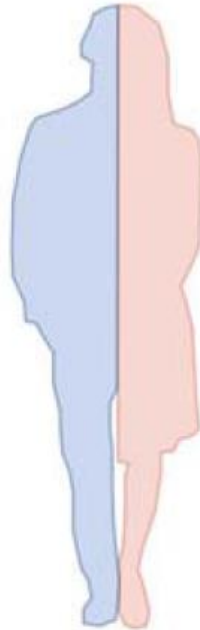
# Specific Features of CAD in Women

## Coronary angiography

- Higher overall prevalence of coronary artery anomalies (> LAD/LCx originating from separate ostia, < myocardial bridge)
- Higher prevalence of normal coronary arteries
- Less severe coronary artery disease

## Fractional flow reserve (FFR)

- Higher FFR values
- Lower proportion of hemodynamically significant stenoses (i.e.,  $FFR < 0.80$ )



## Intravascular ultrasound (IVUS)

- More focal pattern of atherosclerosis (i.e., smaller number of non-culprit plaques, shorter lesions)
- Smaller plaque *plus* media area, smaller plaque volume and plaque burden
- Smaller volumes of necrotic core, fibrous tissue, fibro-fatty tissue and calcium (\*)

## Optical coherence tomography (OCT)

- Similar culprit plaque morphology (~ 50% plaque rupture, ~ 25% plaque erosion)
- Smaller lipid arc and greater reduction in lipid arc after statin therapy
- Lower prevalence of calcification
- Similar prevalence of TCFA, microchannels and macrophages

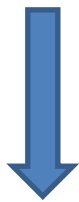
# Antithrombotic Regimen in CAD Patients

Are there gender differences?

✓ platelet physiology

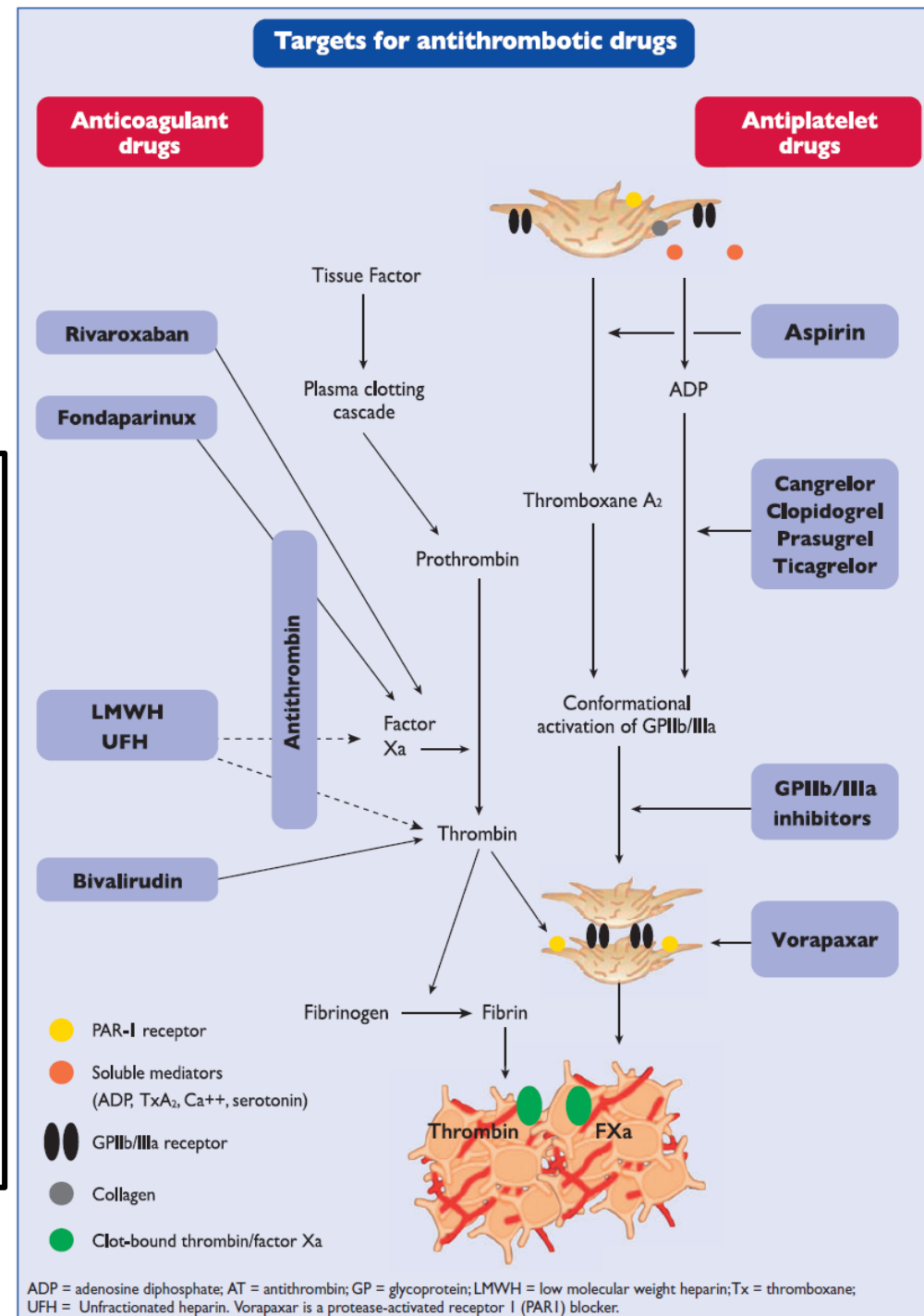
✓ coagulation activity

✓ response to antithrombotics



? Prevalence of CV disease

? Prognosis in CAD patients



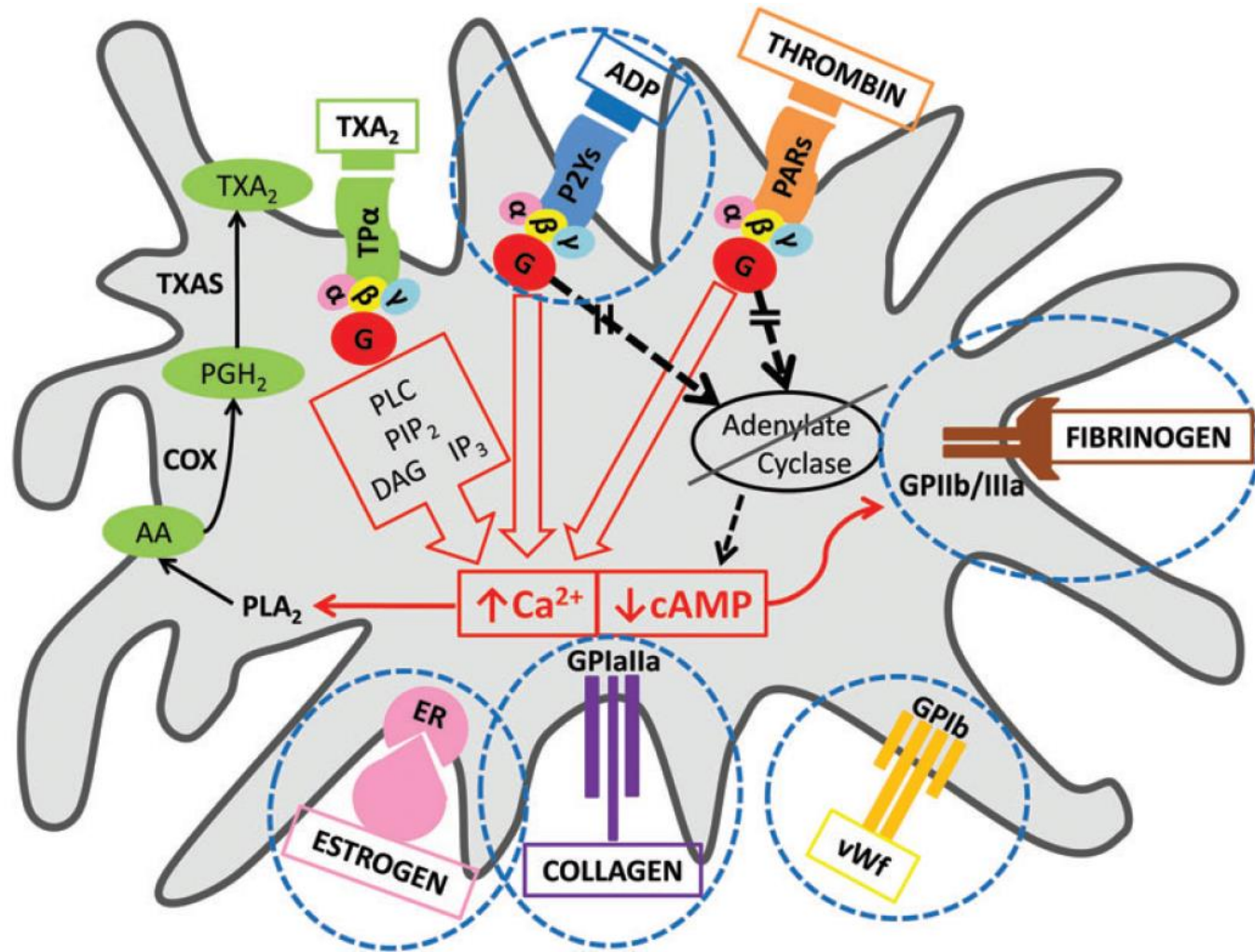


# Sex Differences in Platelet Physiology

- ↑ Platelet count and other platelet indices in women vs. men, regardless of age and menopausal status
- ↑ Number of activated glycoprotein IIb/IIIa receptors per platelet in women
- Platelets from women are characterized by:
  - ↑ Fibrinogen binding upon ADP exposure
  - ↑ Spontaneous aggregation
  - ↑ Plasma thromboxane B2 levels
- ↓ Platelet adhesion and longer bleeding times in women

***Counterbalanced by estrogen system***

# Agonists and Receptors in Platelet Activation



# Sex Differences in Coagulation & Fibrinolysis

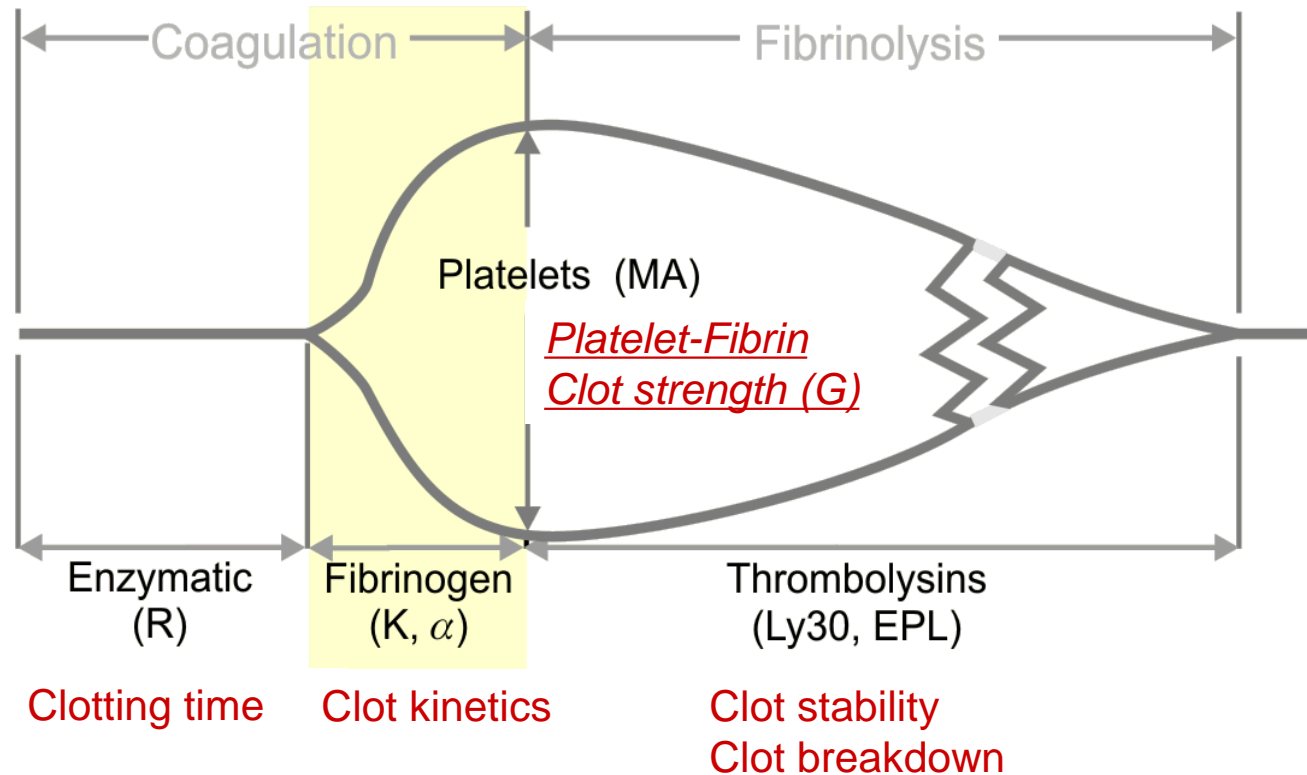
- **Whole blood thromboelastography (TEG®) indicates more coagulability in women than in men**
- **↑ Thrombin generation in women compared to men**
- **No differences in coagulation factors (fibrinogen and coagulation factor VII) and natural anticoagulants (antithrombin and protein C) between men and women**
- **No difference in fibrinolytic measures (PAI-1 and tPA) among men and women**



# TEG<sup>®</sup> System

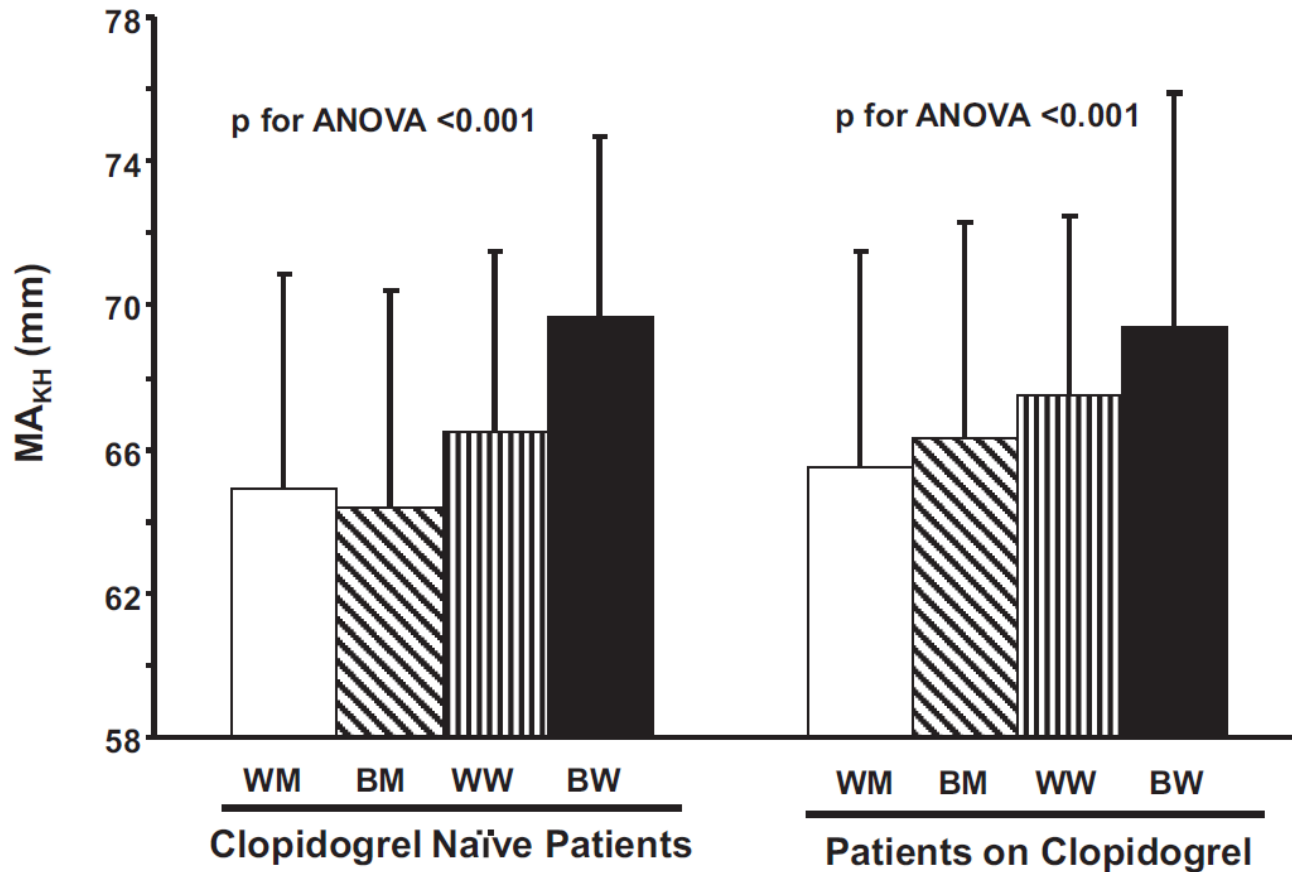


- Physiologic whole blood test
- Use: hematologic disorder, surgery, trauma, burn...
- Measures global hemostasis
  - From clot initiation to clot lysis
  - Net effect of components



# Clot Strength: Influence of Race and Gender

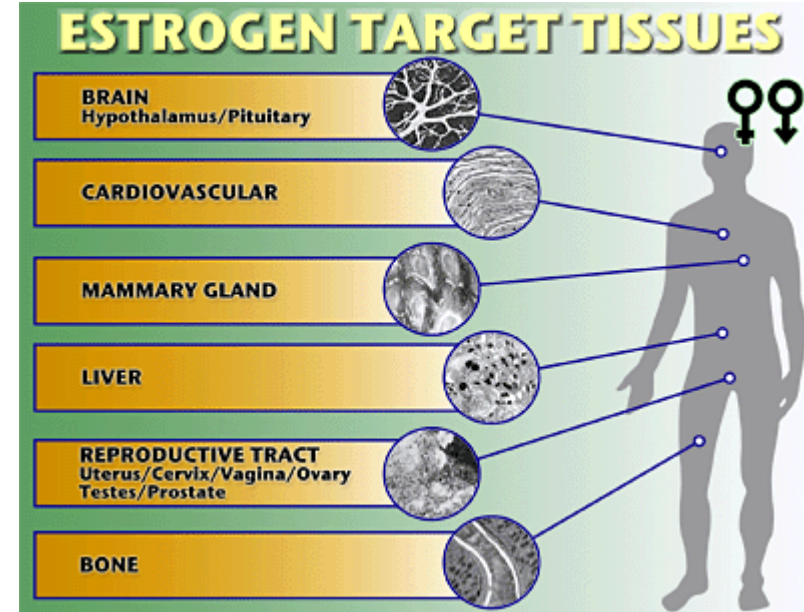
- Patients on aspirin therapy with known or suspected CAD undergoing non-urgent cardiac catheterization (n=1172)



BM, black men; **BW, black women**; WM, white men; WW, white women.

# Beneficial Effect of Endogenous Estrogen

- **Effect on vasculature**
  - Induction of the prostacyclin synthesis
  - ↑ NO bioavailability
- **Direct inhibition of platelet aggregation**
  - Estrogen receptors on the platelet surface
- **Transcriptional regulation of coagulation protein genes**



Hvas AM, et al. Expert Review of Hematology 2017.



# Effect of Antithrombotic Tx: Men vs. Women

- **Aspirin**
- **Clopidogrel**
- **Potent P2Y<sub>12</sub> inhibitor**
- **GP IIb/IIIa inhibitor**
- **Bivalirudin vs. Heparin**
- **NOAC**

# Response of Low-Dose Aspirin According to Gender

Aspirin at 81 mg/d for 14 days

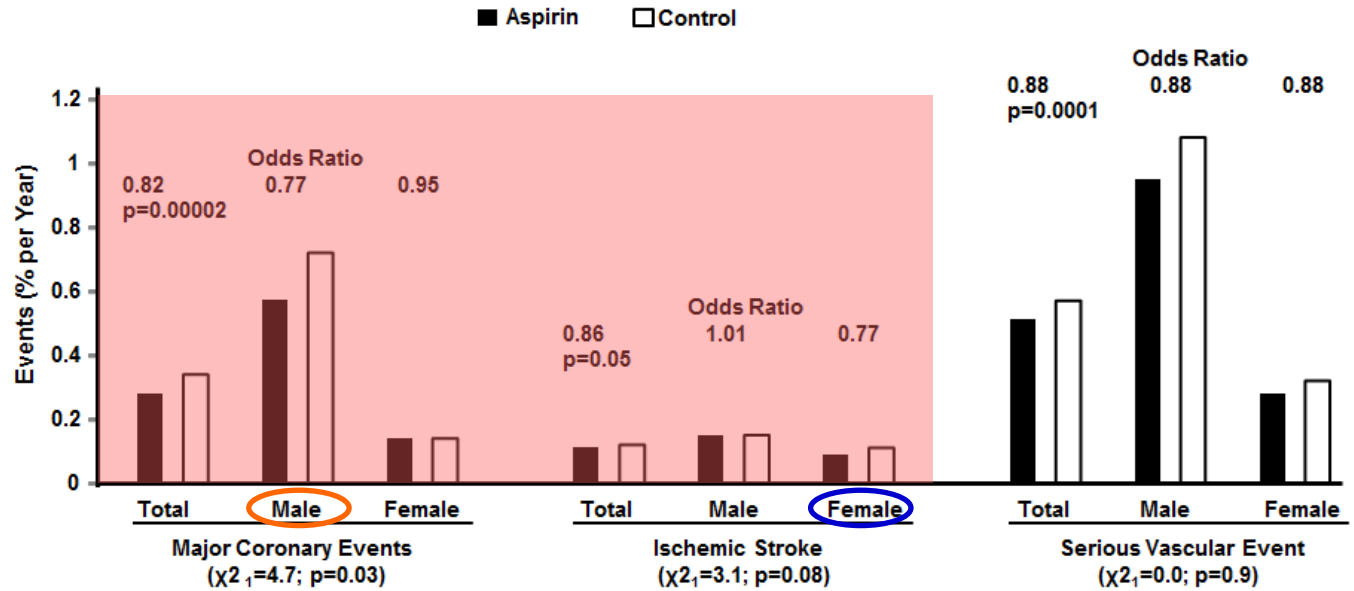
Baseline and post-aspirin platelet function: Whole blood agg. and LTA

Aggregation	Before Aspirin Therapy			After Aspirin Therapy		
	Men (n = 571)	Women (n = 711)	<i>P</i> Value	Men (n = 571)	Women (n = 711)	<i>P</i> Value
Whole blood indirect COX-1 pathways						
Collagen 1 µg/mL, Ω	20.9 (5.3)	22.0 (5.7)	<.001	6.3 (5.4)	7.1 (5.6)	.004
Collagen 5 µg/mL, Ω	28.2 (6.5)	28.8 (6.2)	.11	25.8 (6.8)	26.4 (6.2)	.13
ADP 10 µM, Ω	10.7 (6.1)	14.7 (5.4)	<.001	10.5 (6.2)	14.5 (6.2)	<.001
Whole blood direct COX-1 pathways						
Arachidonic acid 0.5 mM, %	94.9	98.0	.002	4.38	3.80	.60
Platelet-rich plasma indirect COX-1 pathways						
Collagen 1 µg/mL, %	37.4 (34)	41.9 (35)	.02	6.03 (8.3)	7.79 (9.7)	.01
Collagen 5 µg/mL, %	81.7 (17)	83.0 (17)	.19	27.2 (21)	31.8 (22)	<.001
Epinephrine 2 µM, %	52.8 (35)	59.8 (34)	<.001	21.2 (13)	22.8 (14)	.03
Epinephrine 10 µM, %	69.0 (29)	73.4 (28)	.007	28.1 (15)	29.7 (16)	.07
ADP 2 µM, %	36.9 (26)	46.6 (28)	<.001	31.1 (17)	36.6 (17)	<.001
ADP 10 µM, %	77.5 (15)	81.0 (13)	<.001	65.6 (13)	70.3 (12)	<.001

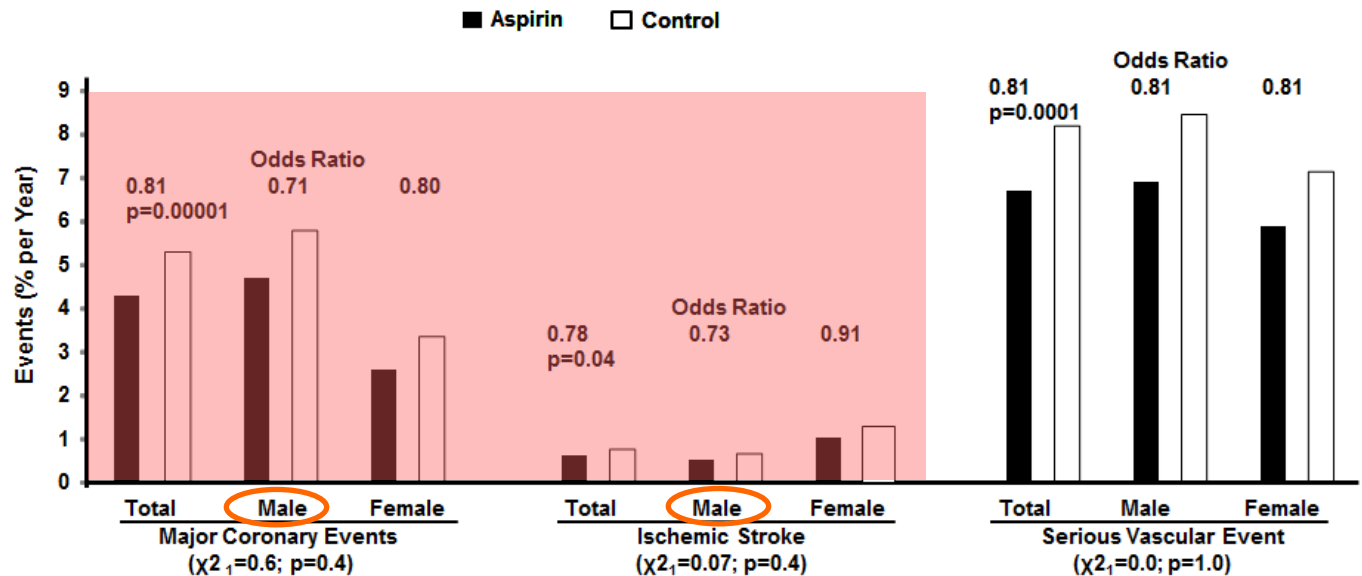
**Women: activated baseline platelet reactivity**

# Effect of Aspirin Therapy According to Gender

## Primary Prevention Trials



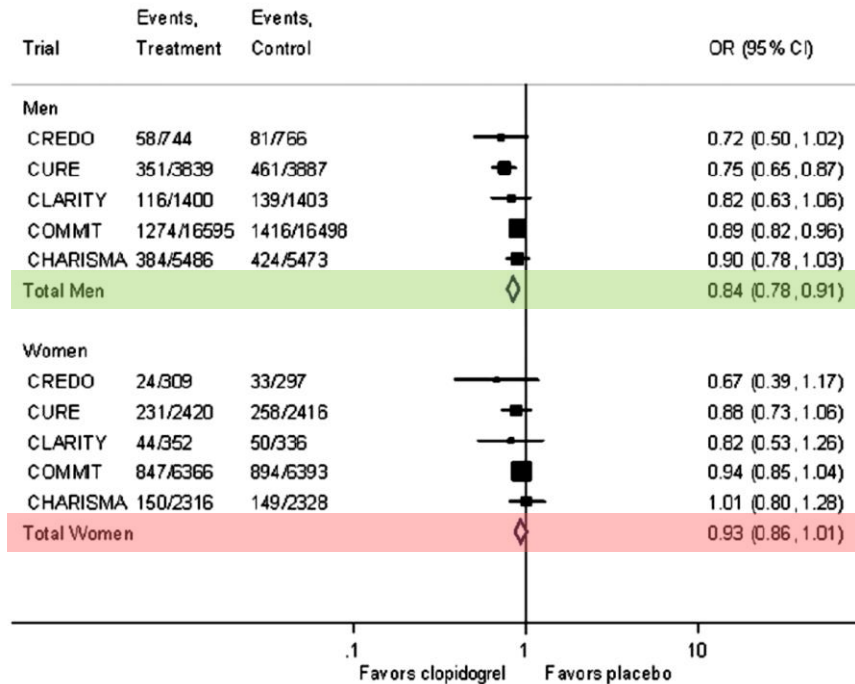
## Secondary Prevention Trials





# Efficacy & Safety of Clopidogrel: Women vs. Men

- Men vs. women: no difference in plasma level of active metabolite
- Meta-analysis: CURE, CREDO, CLARITY, COMMIT, CHARISMA (n=79,613: 30% of women)



Berger JS, et al. JACC 2009;54:1935–45.

**Table 3 Random-Effects ORs (95% CIs) for Clopidogrel Therapy Versus Placebo In Subgroup Analyses**

	Major Cardiovascular Event	All-Cause Mortality	Myocardial Infarction	Stroke	Major Bleeding
<b>Enrollment for ACS</b>					
Women	0.93 (0.85–1.01)	0.99 (0.90–1.09)	0.80 (0.68–0.94)	0.80 (0.45–1.45)	1.50 (1.14–1.97)
Men	0.83 (0.74–0.93)	0.89 (0.82–0.97)	0.82 (0.73–0.91)	0.83 (0.68–1.00)	1.18 (0.96–1.44)
<b>Established CVD</b>					
Women	0.93 (0.85–1.01)	0.98 (0.89–1.07)	0.81 (0.70–0.94)	0.92 (0.67–1.27)	1.43 (1.14–1.79)
Men	0.84 (0.78–0.92)	0.90 (0.83–0.96)	0.82 (0.74–0.90)	0.81 (0.69–0.94)	1.19 (1.02–1.40)

# Efficacy and Safety of Prasugrel in ACS Patients

- Men vs. women: similar plasma level of active metabolite
- TRITON-TIMI 38: Ischemic events on Prasugrel vs. Clopidogrel

	Prasugrel	Clopidogrel	Relative reduction	Absolute reduction
<b>Men</b>	9.5%	11.9%	<u>21%</u>	<u>2.4%</u>
<b>Women</b>	11.0%	12.6%	12%	1.6%

## Predictors of Non-CABG–Related Serious Bleeding

	HR (95% CI)	<i>P</i>	Strength of Association With Bleeding*
Female sex	1.77 (1.44–2.18)	<0.001	28.79
GPIIb/IIIa inhibitor used	1.59 (1.29–1.95)	<0.001	19.33
Duration of intervention, per 10-min intervals	1.07 (1.04–1.10)	<0.001	17.98
Age, by decade	1.22 (1.09–1.38)	<0.001	11.07
Assignment to prasugrel, vs clopidogrel	1.34 (1.12–1.60)	0.001	10.19

Wiviott SD, et al. NEJM 2007;  
Hochholzer W, et al. Circulation 2011,

# Efficacy and Safety of Ticagrelor in ACS Patients

- Men vs. women: similar plasma level of active metabolite
- PLATO: Ischemic events on Ticagrelor vs. Clopidogrel

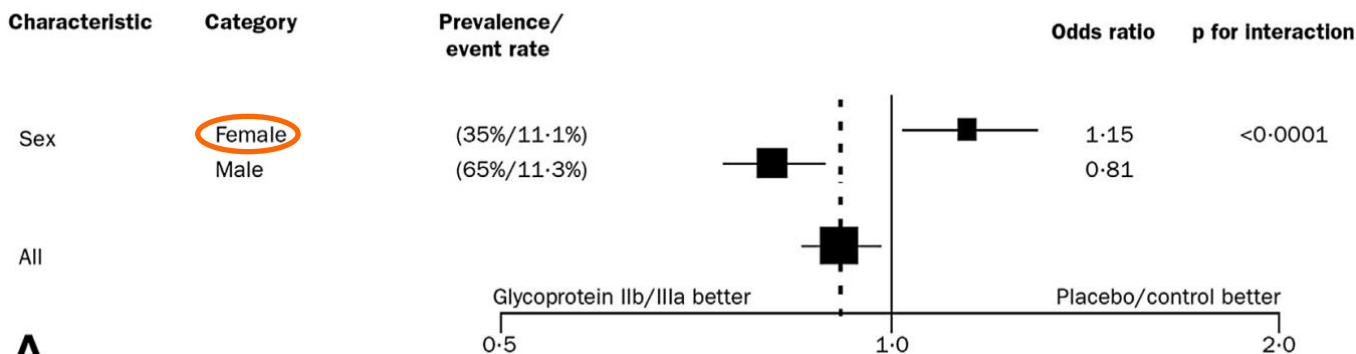
	Ticagrelor	Clopidogrel	Relative reduction	Absolute reduction
Men	9.2%	11.1%	15%	1.9%
Women	11.2%	13.2%	17%	2.0%

- PCI-related major bleeding
  - Age (HR 1.272, 95% CI 1.140–1.420 for a 5-year increase)
  - Female sex (HR 2.245, 95% CI 1.416–3.559)
  - Weight (HR 0.898, 95% CI 0.818–0.986 for a 5 kg increase)

# Efficacy & Safety of GPIIb/IIIa Inhibitor in ACS Pts

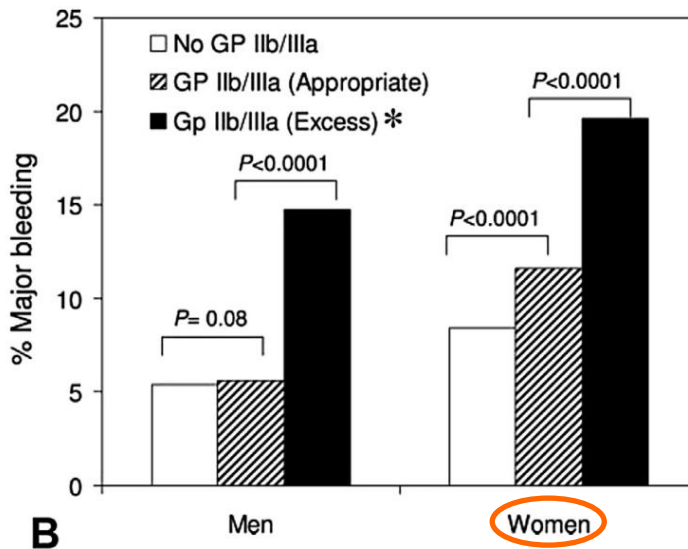
## Meta-analysis on 6 RCTs

### 30-day death & MI



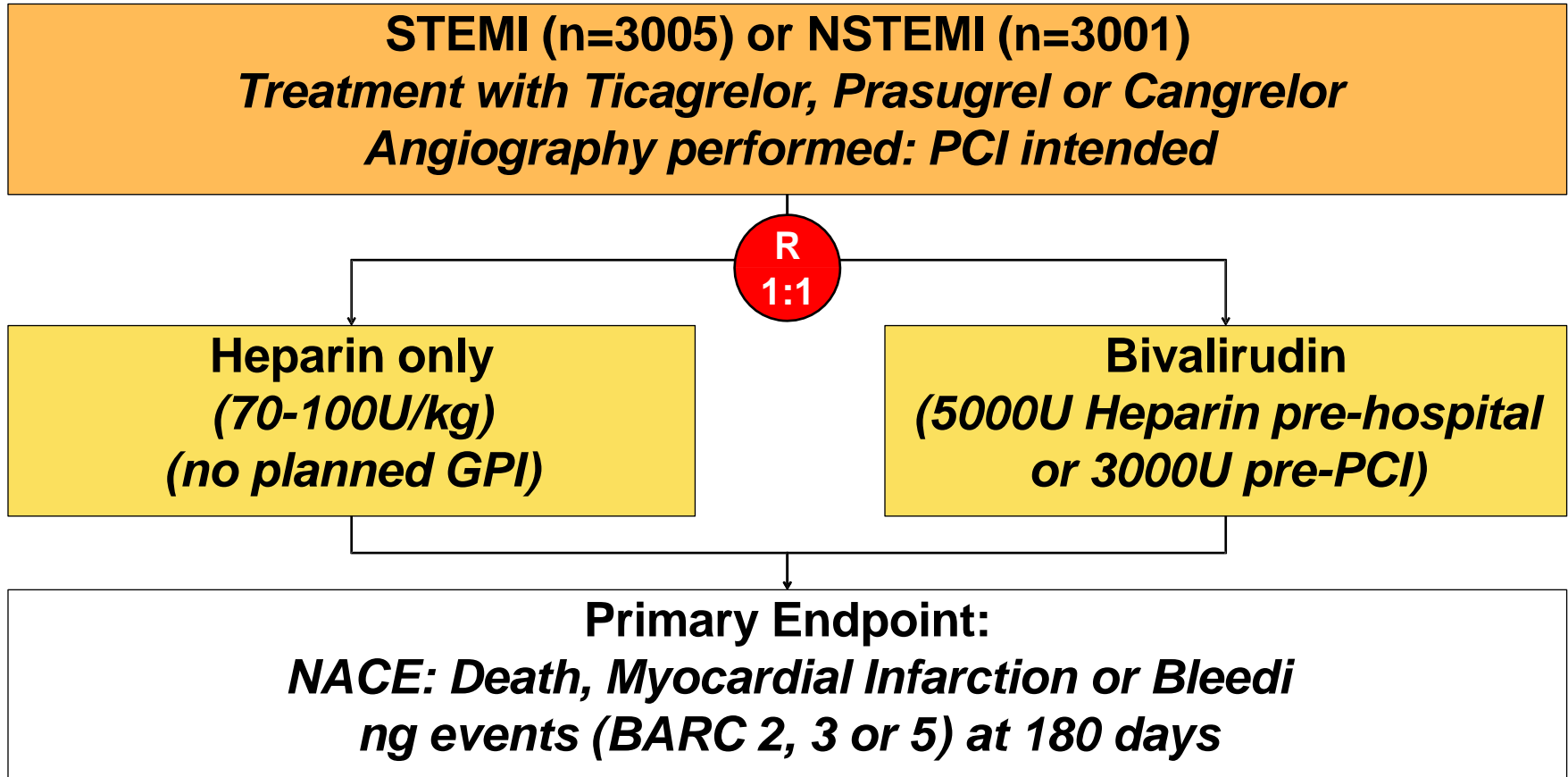
A

### Major bleeding



B

# Bivalirudin vs. Heparin in ACS



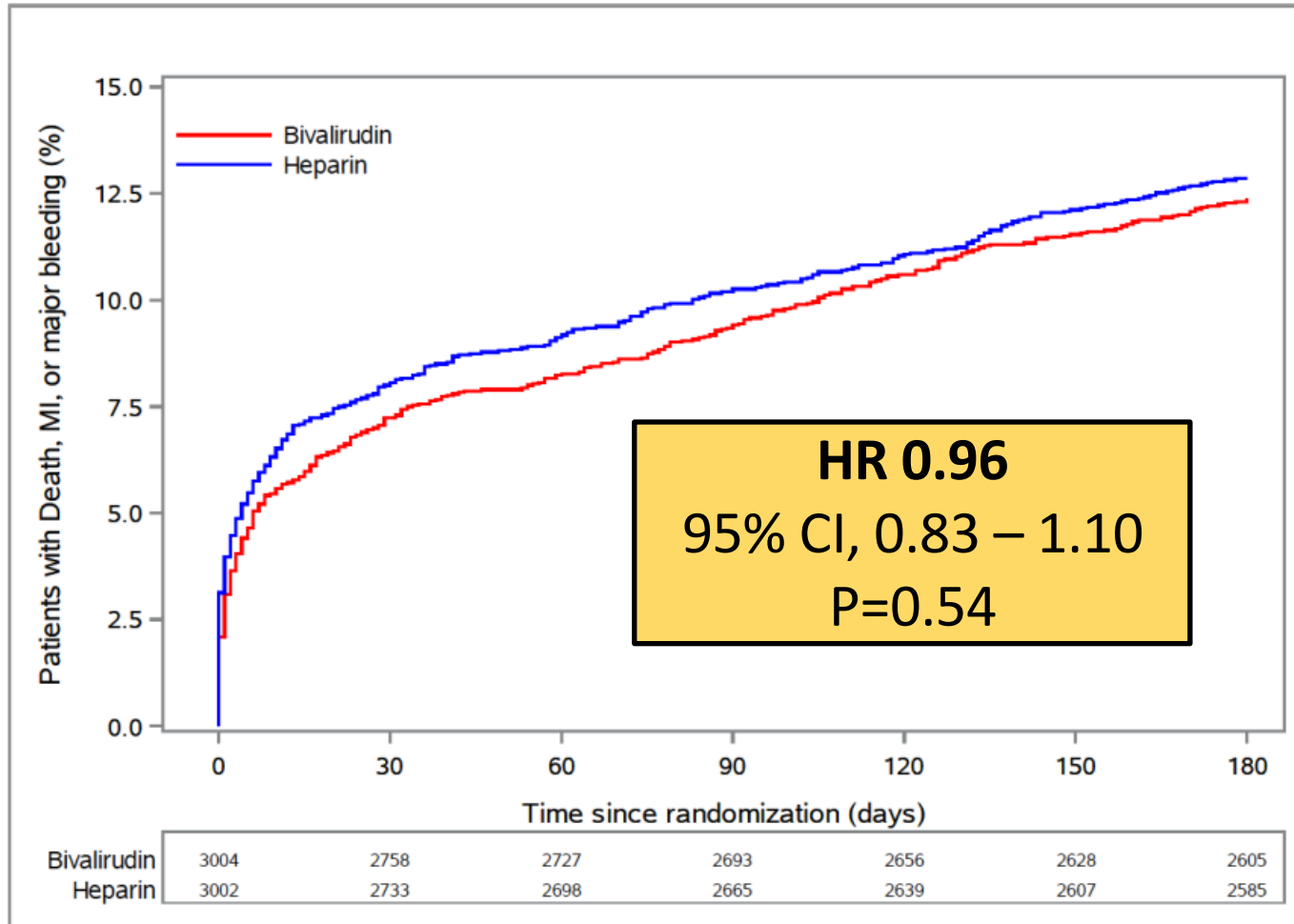
**Coordinating PI:** David Erlinge, Lund University, Sweden

**Chairman:** Stefan James, Uppsala University, Sweden



# Outcomes of Bivalirudin vs. Heparin in ACS

## Death, MI or major bleeding at 180 days



# Female vs. Male: Outcomes of Bivalirudin vs. Heparin

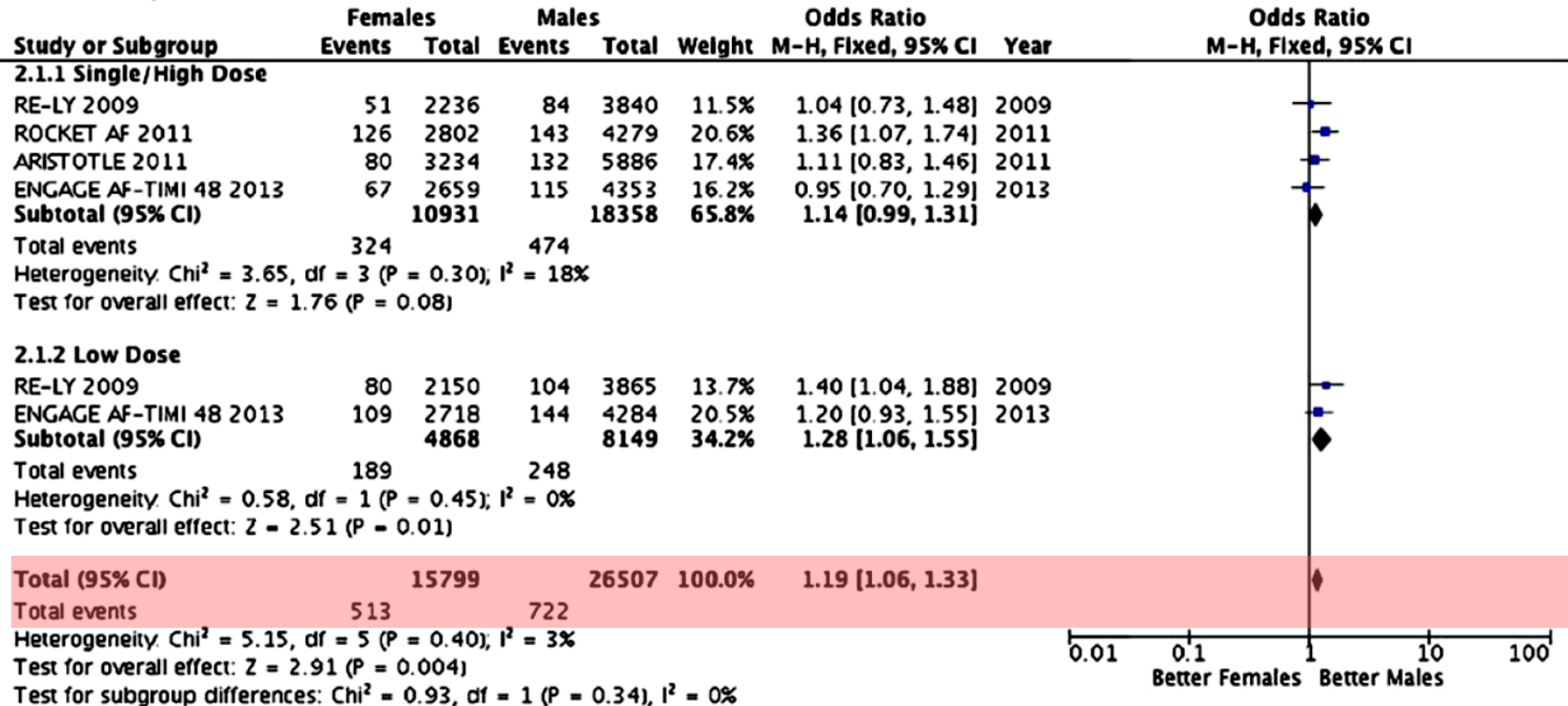
## Death, MI or major bleeding at 180 days

	Bivalirudin		Heparin			HR (95% CI)	P-value
	Patients	Events, N(%)	Patients	Events, N(%)			
<b>Death, MI, or major bleeding</b>							
Women	771	105 (13.6%)	821	140 (17.1%)		0.78 (0.60-1.00)	0.05
Men	2229	263 (11.8%)	2177	243 (11.2%)		1.06 (0.89-1.26)	
<b>Death, MI, Major bleeding, or Stroke</b>							
Women	771	106 (13.7%)	821	146 (17.8%)		0.75 (0.58-0.96)	0.02
Men	2229	272 (12.2%)	2177	252 (11.6%)		1.05 (0.89-1.25)	
<b>Death, MI, or bleeding BARC 3 or 5</b>							
Women	771	78 (10.1%)	821	92 (11.2%)		0.90 (0.66-1.21)	0.46
Men	2229	142 (6.4%)	2177	134 (6.2%)		1.03 (0.82-1.31)	
<b>Death or MI</b>							
Women	771	54 (7.0%)	821	55 (6.7%)		1.04 (0.72-1.52)	0.65
Men	2229	89 (4.0%)	2177	93 (4.3%)		0.93 (0.70-1.25)	
<b>Death</b>							
Women	771	35 (4.5%)	821	31 (3.8%)		1.20 (0.74-1.94)	0.52
Men	2229	53 (2.4%)	2177	53 (2.4%)		0.98 (0.67-1.43)	
<b>CV death</b>							
Women	771	28 (3.6%)	821	26 (3.2%)		1.14 (0.67-1.95)	0.70
Men	2229	45 (2.0%)	2177	44 (2.0%)		1.00 (0.66-1.52)	
<b>MI</b>							
Women	771	21 (2.7%)	821	27 (3.3%)		0.83 (0.47-1.46)	0.90
Men	2229	39 (1.7%)	2177	44 (2.0%)		0.86 (0.56-1.33)	
<b>Stent thrombosis [a]</b>							
Women	771	18 (2.3%)	821	16 (1.9%)		1.20 (0.61-2.35)	0.42
Men	2229	38 (1.7%)	2177	43 (2.0%)		0.86 (0.56-1.34)	
<b>ST within 24-48h [a c]</b>							
Women	771	12 (1.6%)	821	11 (1.3%)		1.16 (0.51-2.66)	0.72
Men	2229	25 (1.1%)	2177	25 (1.1%)		0.98 (0.56-1.71)	
<b>Definite ST [b]</b>							
Women	771	5 (0.6%)	821	3 (0.4%)		1.77 (0.42-7.40)	0.06
Men	2229	7 (0.3%)	2177	19 (0.9%)		0.36 (0.15-0.86)	
<b>Definite ST within 24-48h [b c]</b>							
Women	771	0 (0.0%)	821	2 (0.2%)		N/A	

# NOAC in AF Patients: Women vs. Men

## Meta-analysis (4 RCTs)

### A. Stroke/SEE

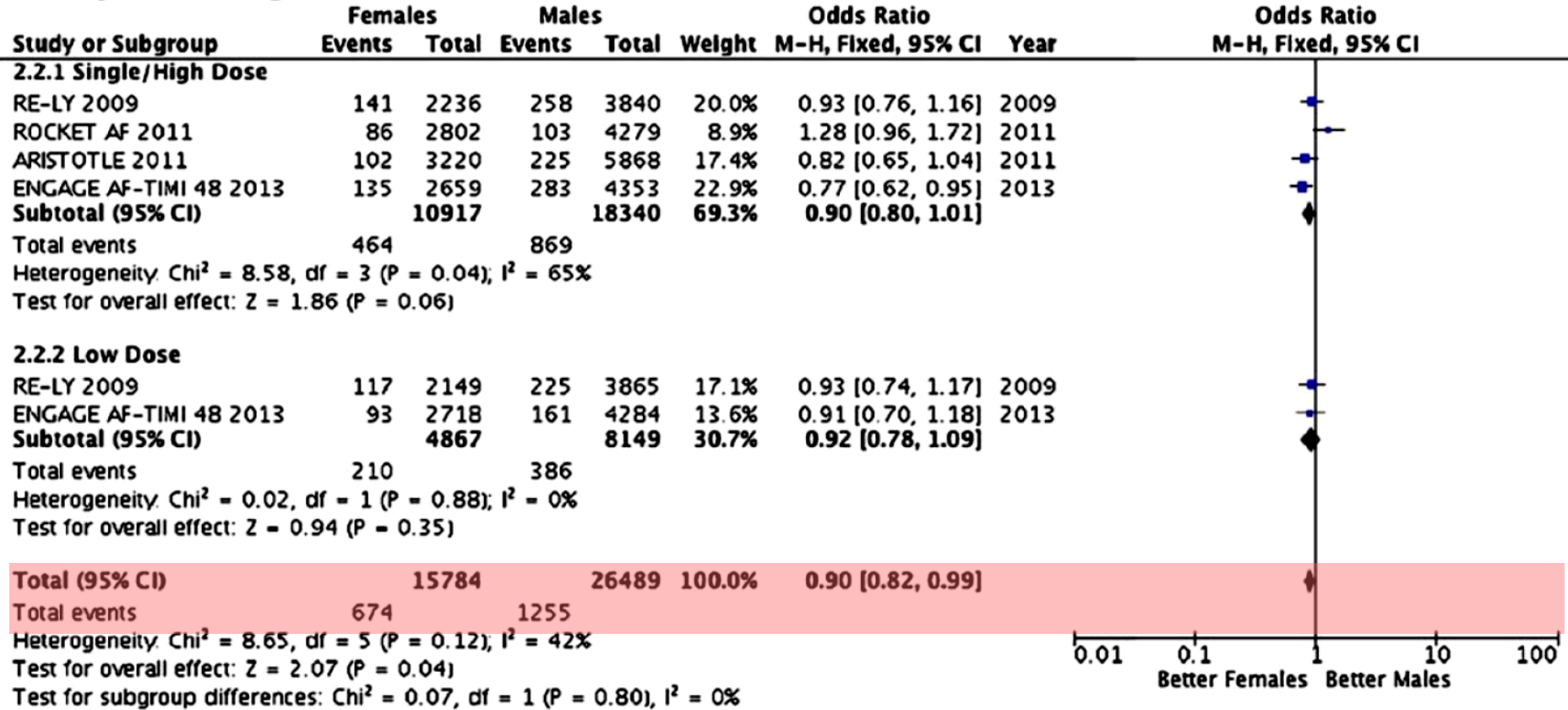


**Male patients are more protective of stroke/SEE**

# NOAC in AF Patients: Women vs. Men

## Meta-analysis (4 RCTs)

### B. Major Bleeding



**Female patients are more protective of major bleeding**

# Perspectives

## 1. Hemostatic profiles of Women vs. Men:

- ↑Platelet reactivity & ↑Thrombogenicity
- Protective effect of estrogen: pre- vs. post-menopause

## 2. Risk/benefit profiles of Women vs. Men:

- Similar PK/PD data of antithrombotic regimen
- Women vs. Men: ↓Efficacy & ↑Bleeding on antithrombotics

## 3. How to solve a mysterious story about Women?:

↓Efficacy: ↑Platelet reactivity & ↑Thrombogenicity

↑Bleeding: ??Fragile vasculature

*Are we ready for a gender-specific approach in CVD?*