Differenze di genere e risposta ai farmaci cardiovascolari

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SAPIENZA
UNIVERSITÀ DI ROMA

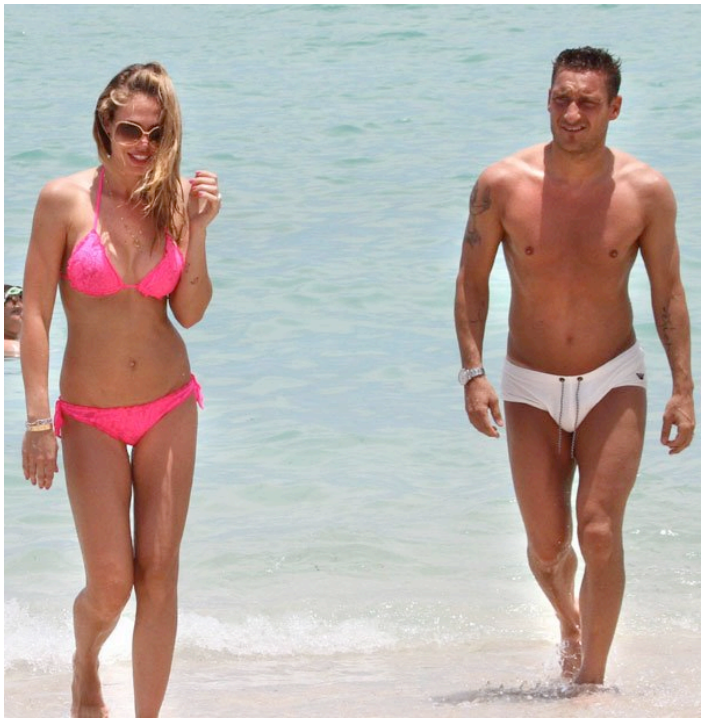
‘all men are created equal’

Declaration of Independence (1776)

Although Thomas Jefferson’s immortal phrase remains true today and includes both men and women having equal human rights, it is clear that important differences between the sexes exist, particularly with respect to diseases and ***therapy****.*

J Womens Health 2010; 6: 1059–72.

Sindrome del bikini



Fino al 1990 la medicina si costruisce sulla nozione che il corpo maschile sia il riferimento. Uniche differenze riconosciute riguardano **l'apparato riproduttivo/ginecologico**

National Institutes of Health
Bethesda, MD 20892

Nel 1991 Bernardine Healy, cardiologa americana, descrisse una malattia che chiamò "Sindrome di Yentl".

Yentl, l'eroina di una storia del Premio Nobel Isaac Bashevis Singer, dovette rasarsi i capelli e vestirsi da uomo per poter accedere alla scuola ebraica e studiare il Talmud, uno dei testi sacri dell'Ebraismo.

La Healy descrisse la ***discriminazione che aveva constatato nell'Istituto di Cardiologia che dirigeva***: le donne erano meno ospedalizzate, meno sottoposte a indagini diagnostiche (coronarografie) e terapeutiche (trombolisi, stent, bypass) rispetto agli uomini; le donne inoltre sottolineava erano per nulla o poco rappresentate nelle sperimentazioni per introdurre nuovi farmaci e nuove tecnologie diagnostiche e terapeutiche.

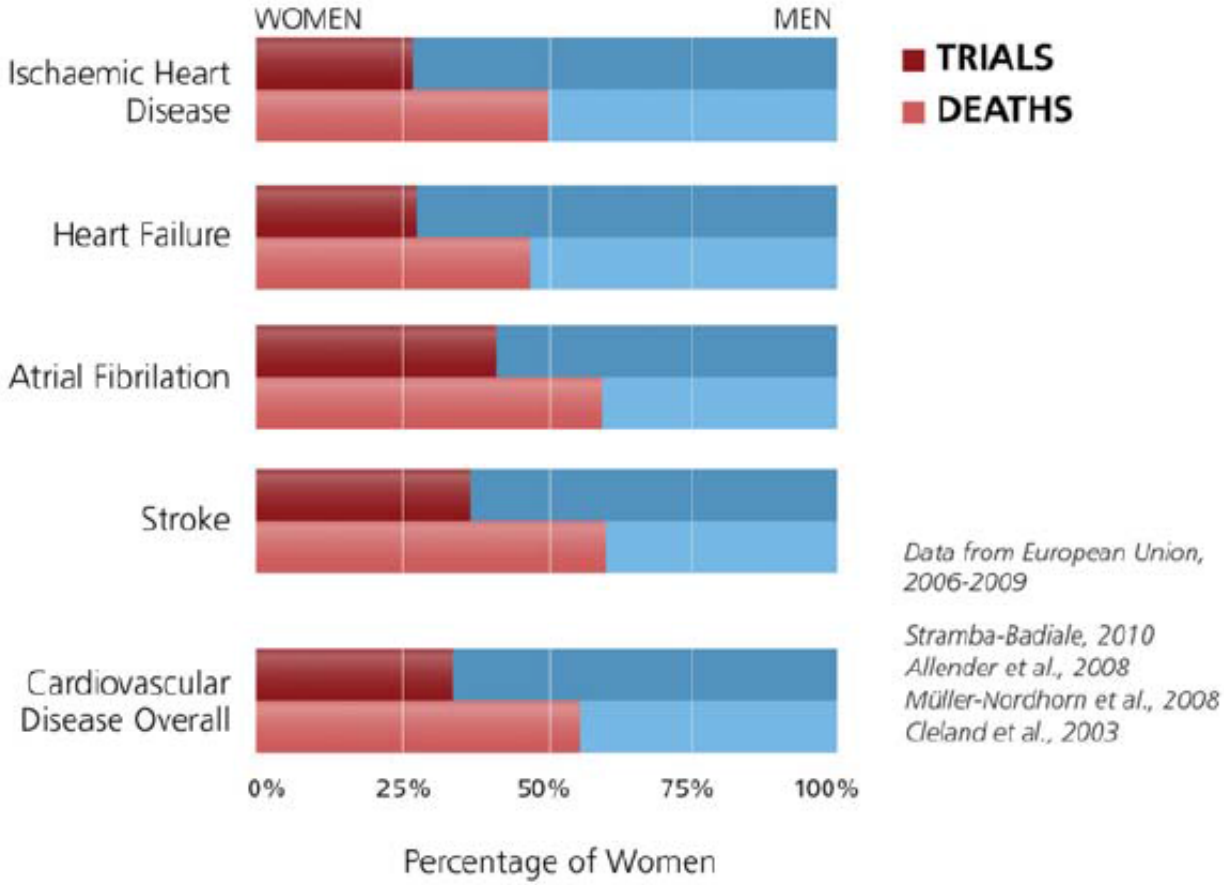
The New England Journal of Medicine

Gender differences in the effect of cardiovascular drugs: a position document of the Working Group on Pharmacology and Drug Therapy of the ESC

- Since the number of women included in CV studies has often bee low, most recommendations in women have often been inferred from effects observed in men.
- This gaps in knowledge on the effects of gender on pharmacokinetics (PK) and pharmacodynamics (PD) of CV drugs have to be discussed.

Percentage of Women in CVD Clinical Trials vs. Deaths

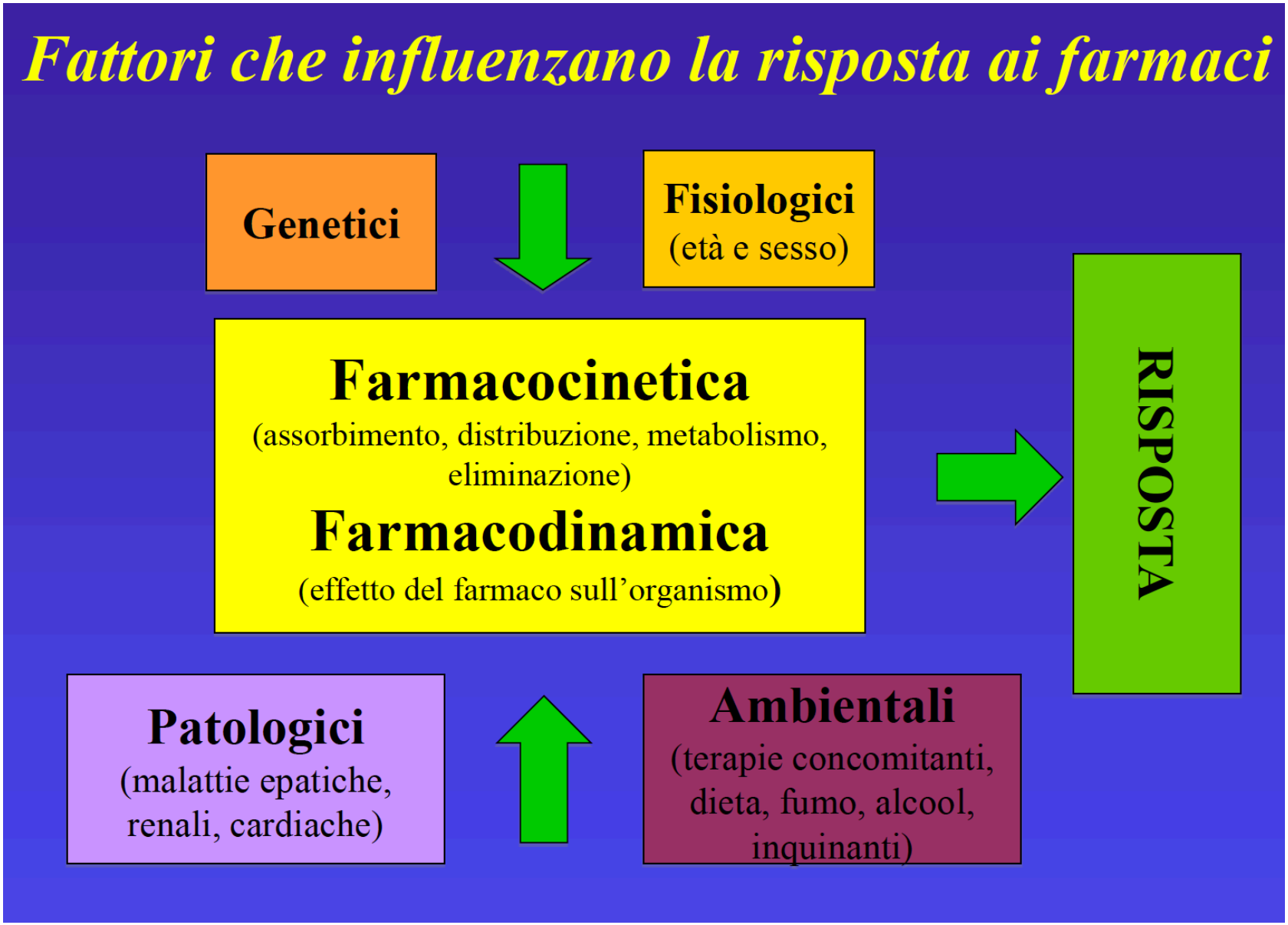
Women are underrepresented in CVD clinical trials

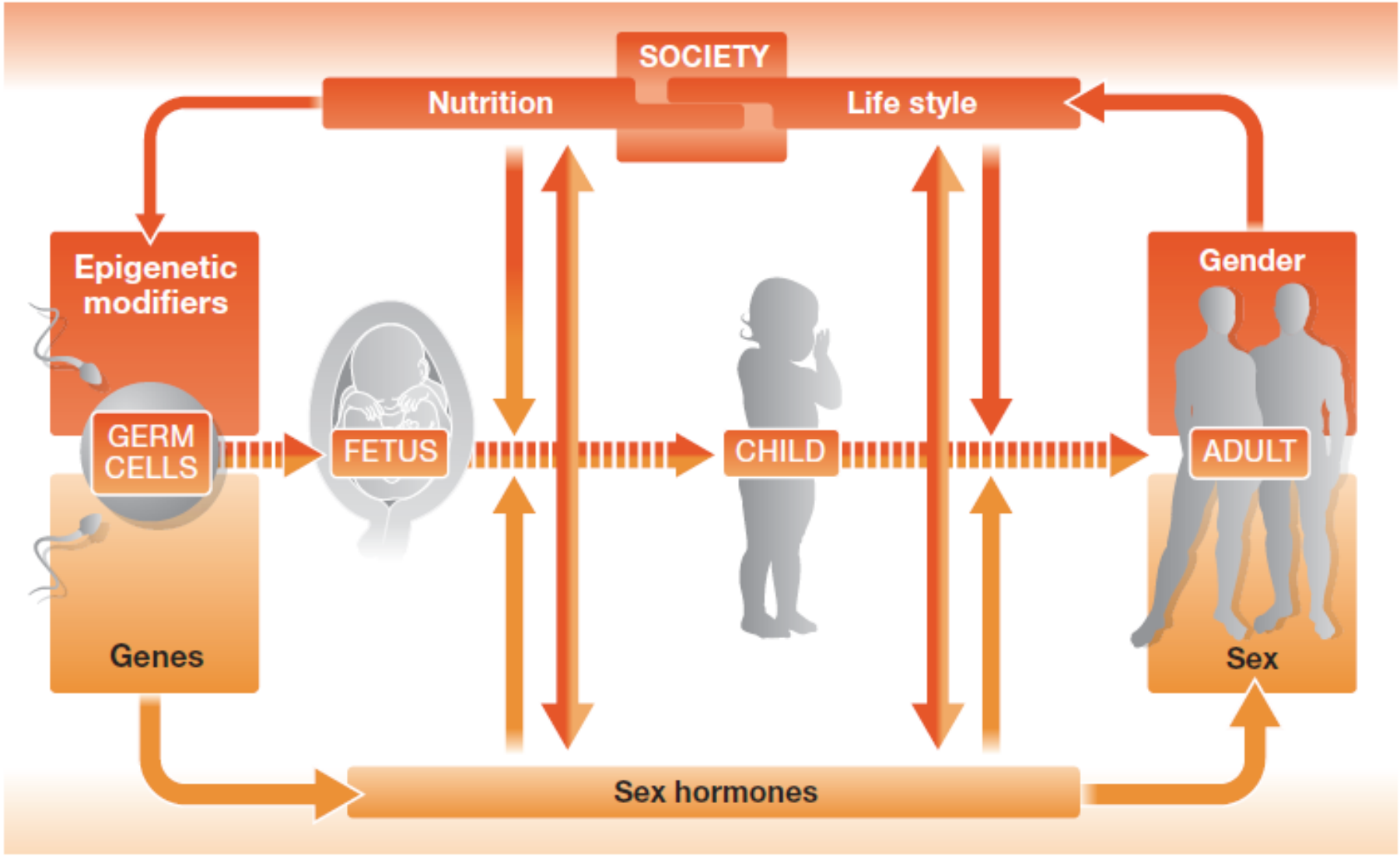


Data from European Union, 2006-2009

Stramba-Badiale, 2010
Allender et al., 2008
Müller-Nordhorn et al., 2008
Cleland et al., 2003

Fattori che influenzano la risposta ai farmaci





Regitz-Zagrosek V - EMBO reports 2012

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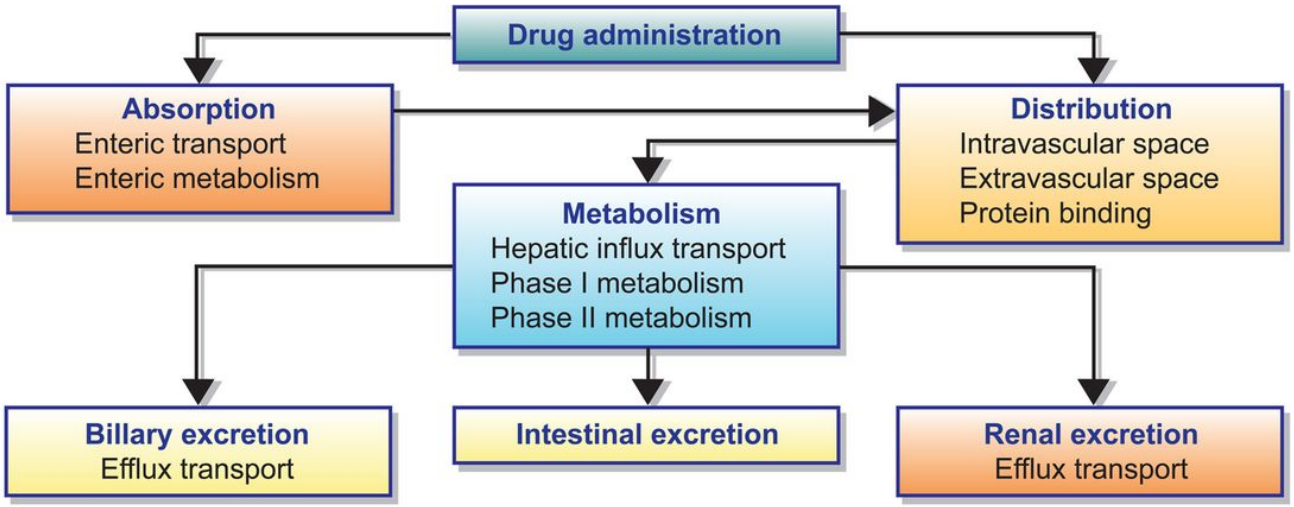
Gender differences in absorption and distribution and excretion of drugs responsible for gender differences in pharmacokinetic and pharmacodynamic actions.



Absorption:
- Slower GI motility and transit time
- Lower gastric acid secretion
- Less drug enzymes and transporters
- Lower absorption rates

Body composition:
- Lower BW, organ size and blood flow

Distribution:
- Greater body fat and lower body water content (Higher Vd for lipophilic drugs, Lower Vd for water-soluble drugs)
- Less α1-acid glycoprotein
- Lower cardiac output

Excretion:
- Lower renal blood flow, glomerular filtration rate (GFR), tubular secretion and reabsorption
- Slower clearance of renally excreted drugs
- Longer elimination half-life

Other Factors:
- Differences in BW, cardiac output, plasma volume and regional blood flow

CYP Enzyme	Enzyme Activity
1A2	M > W
2A6	W > M
2B6	W > M
2C9	M = W
2C19	M = W
2D6	Mostly W > M
3A4	Mostly W > M
UDP-glucuronosyltransferases (UGTs)	M > W
Sulfotransferases	M > W
N-acetyltransferases	M < W
Methyltransferases	M > W

Eur Heart J 2015;eurheartj.ehv161

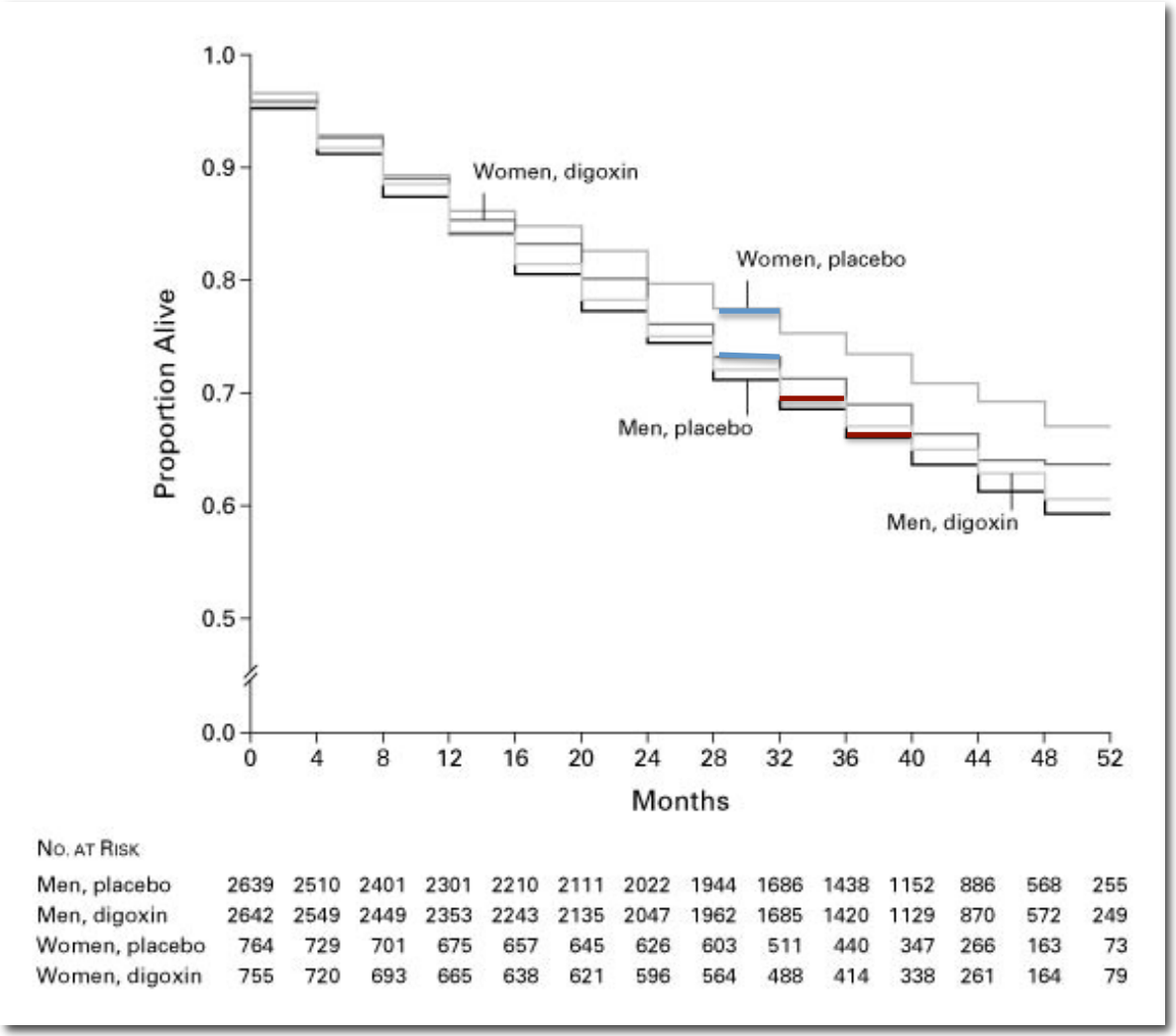
European Heart Journal

Table 1 Gender differences in pharmacokinetics

	Women	Men	Refs
Absorption	↓ gastric acid secretion ↑ GI transit time		[6–11]
Distribution	↓ body weight ↓ intravascular volume ↓ organ volume ↓ muscle volume ↑ adipose tissue		[6–8]
Metabolism	↑ CYP2D6 ↑ CYP3A	↑ CYP1A activity ↑ CYP2E1 activity ↑ P-gp activity	[7, 12, 13]
Excretion	↓ GFR		[6–8, 14]

↑, increased ↓, decreased

Gender differences in the effect of cardiovascular drugs: Digoxin



No. at Risk

Men, placebo	2639	2510	2401	2301	2210	2111	2022	1944	1686	1438	1152	886	568	255
Men, digoxin	2642	2549	2449	2353	2243	2135	2047	1962	1685	1420	1129	870	572	249
Women, placebo	764	729	701	675	657	645	626	603	511	440	347	266	163	73
Women, digoxin	755	720	693	665	638	621	596	564	488	414	338	261	164	79

The increased risk of death among women was possibly related to the relatively excessive dosage of digoxin.

Although the increased mortality was correlated to the higher serum digoxin concentrations, sex-based differences in digoxin PK were absent when actual or ideal body weight was used.

N Engl J Med 2002;347:1403-1411

Gender differences in the effect of cardiovascular drugs: Beta-blockers

Although it is known that plasma levels of beta-blockers do not always correlate with therapeutic efficacy, women present higher plasma level of metoprolol and propranolol due to a **slower Clearance** and lower volume of distribution.

5474 patients (4353 men, 1121 women) have been studied during double-blind therapy with metoprolol 100 mg twice daily or matching placebo.

In total there were 223 deaths in the placebo-treated patients as compared to 188 deaths in the metoprolol-treated patients (P = 0.036).

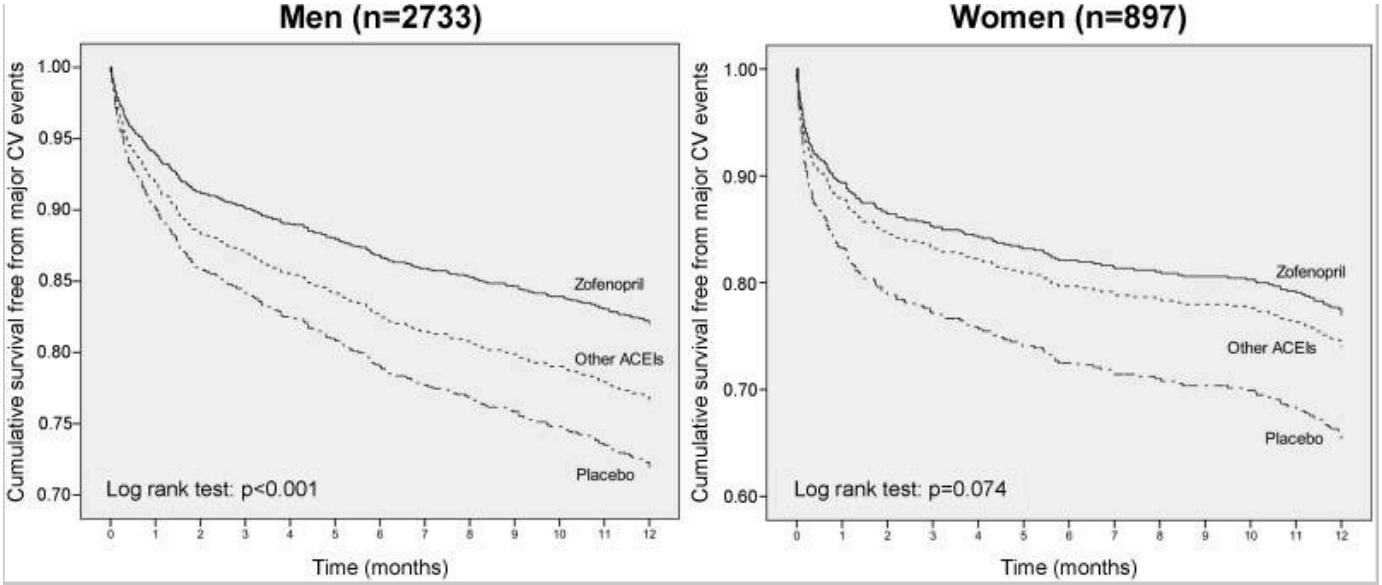
Eur Heart J 1992;13: 28–32.

Despite some trials suggested that beta-blockers improved survival only in males, but not in females, with hypertension or heart failure several a meta-analysis confirmed that beta-blockers produced a similar survival benefit in heart failure or after MI in both sexes.

Gender differences in the effect of cardiovascular drugs:
Inhibitors of the renin-angiotensin-aldosterone system

RAAS are not recommended for use in women during childbearing

Retrospective pooled analysis of SMILE studies. Zofenopril vs. placebo or other ACE-inhibitors (ACEIs) in post-acute myocardial infarction (AMI).



PLoS One. 2014 Nov 3;9(11):e111558

Gender differences in the effect of cardiovascular drugs: Calcium-channel blockers

Gender-specific pharmacokinetics differences have been described for verapamil, nifedipine, and amlodipine.

Oral clearance of verapamil and amlodipine are faster in females compared with men, probably due to the higher activity of CYP3A4 or lower activity of P-gp in females.

Although amlodipine exhibited greater antihypertensive effect and higher incidence of oedema in females than in men, **major hypertension trials with calcium-channel blockers found no evidence for gender-specific differences in outcomes.**

Gender differences in the effect of cardiovascular drugs:
Statins

Plasma concentrations of statins are generally 15–20% higher in women than in men, but dose adjustments are not necessary.
Women, however, have higher concentrations of CYP3A4 and therefore are more capable of metabolizing these statins.

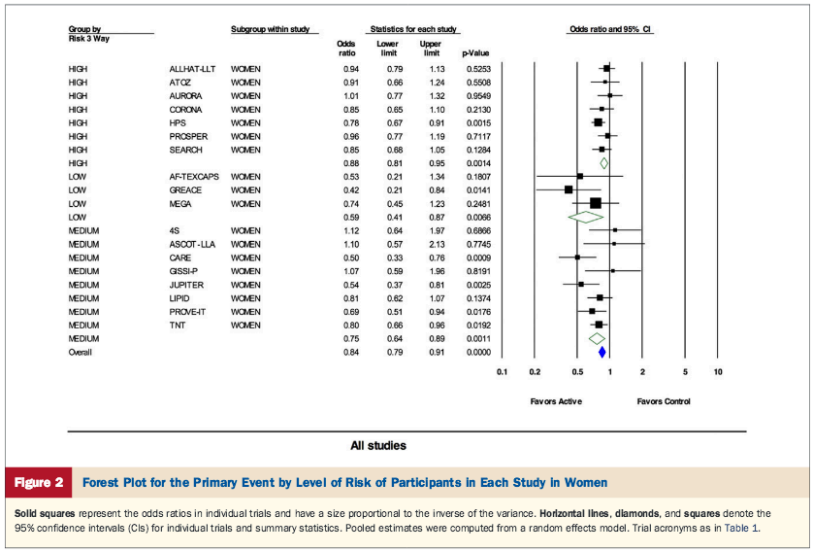


Figure 2 Forest Plot for the Primary Event by Level of Risk of Participants in Each Study in Women

Solid squares represent the odds ratios in individual trials and have a size proportional to the inverse of the variance. **Horizontal lines**, **diamonds**, and **squares** denote the 95% confidence intervals (CIs) for individual trials and summary statistics. Pooled estimates were computed from a random effects model. Trial acronyms as in Table 1.

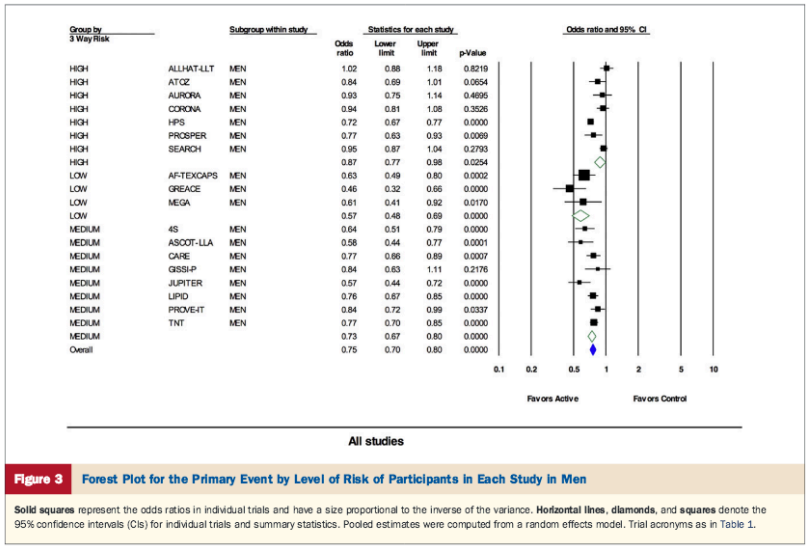


Figure 3 Forest Plot for the Primary Event by Level of Risk of Participants in Each Study in Men

Solid squares represent the odds ratios in individual trials and have a size proportional to the inverse of the variance. **Horizontal lines**, **diamonds**, and **squares** denote the 95% confidence intervals (CIs) for individual trials and summary statistics. Pooled estimates were computed from a random effects model. Trial acronyms as in Table 1.

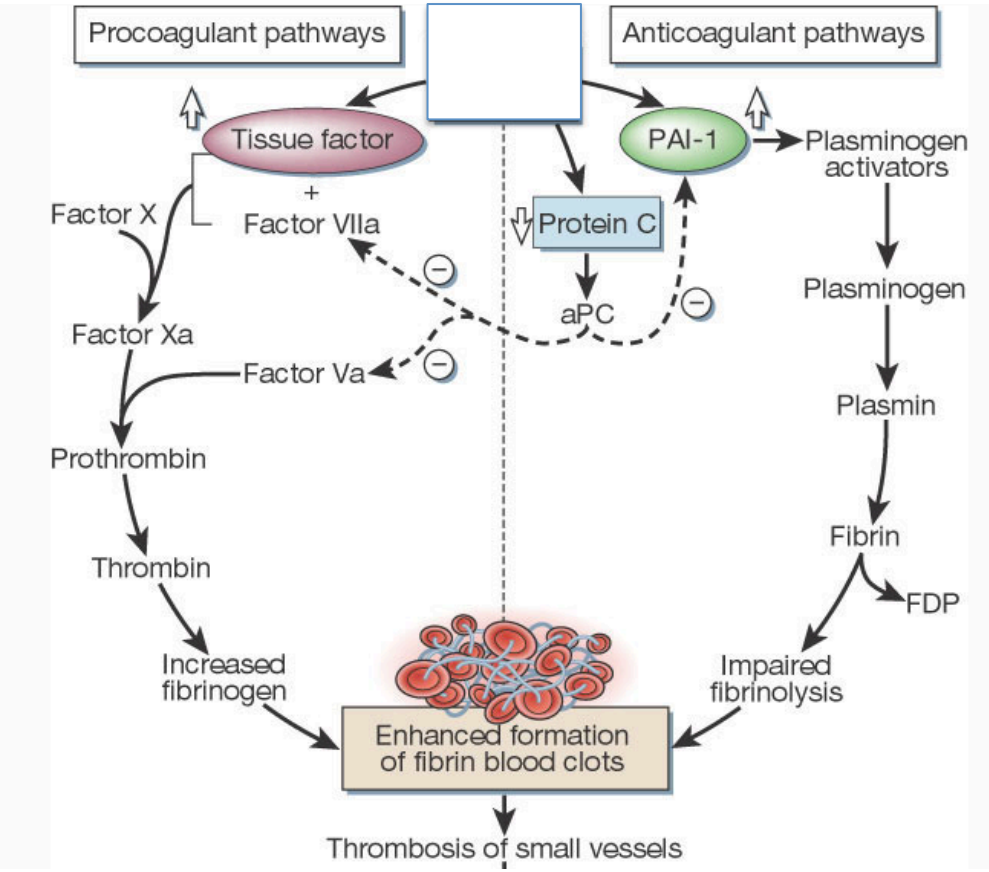
Statins decrease cardiovascular events and all-cause mortality in both women and men. The effect on cardiovascular events is present in both primary and secondary prevention trials.

J Am Coll Cardiol 2012;59:572–82

Haemostasis in females

The cessation of menstrual bleeding

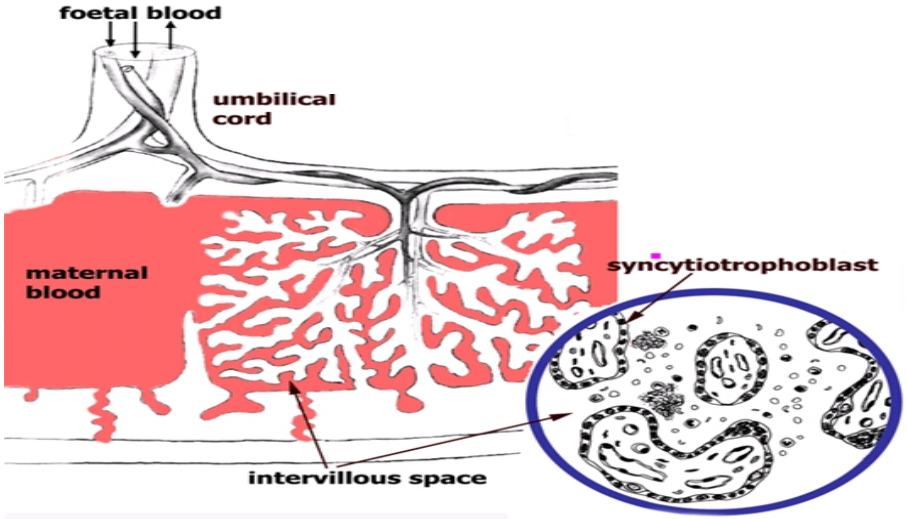
Reviews in Endocrine and Metabolic Disorders 2012; 13: 289-299



Tissue factor and thrombin play a key role locally in the cessation of menstrual bleeding through instigation of the coagulation factors.

On the other hand, fibrinolysis prevents clot organisation within the uterine cavity while plasminogen activator inhibitors (PAI) and thrombin-activatable fibrinolysis inhibitors control plasminogen activators and plasmin activity.

Pregnancy is associated with profound changes in uterine and systemic hemostatic potential.



These changes offer protection from potentially catastrophic hemorrhage during placentation and the third stage of labor.

It is considered that the placental separation provokes an acute maternal blood loss (10–15% of a woman's blood volume or 700 ml/minute)

Pregnancy

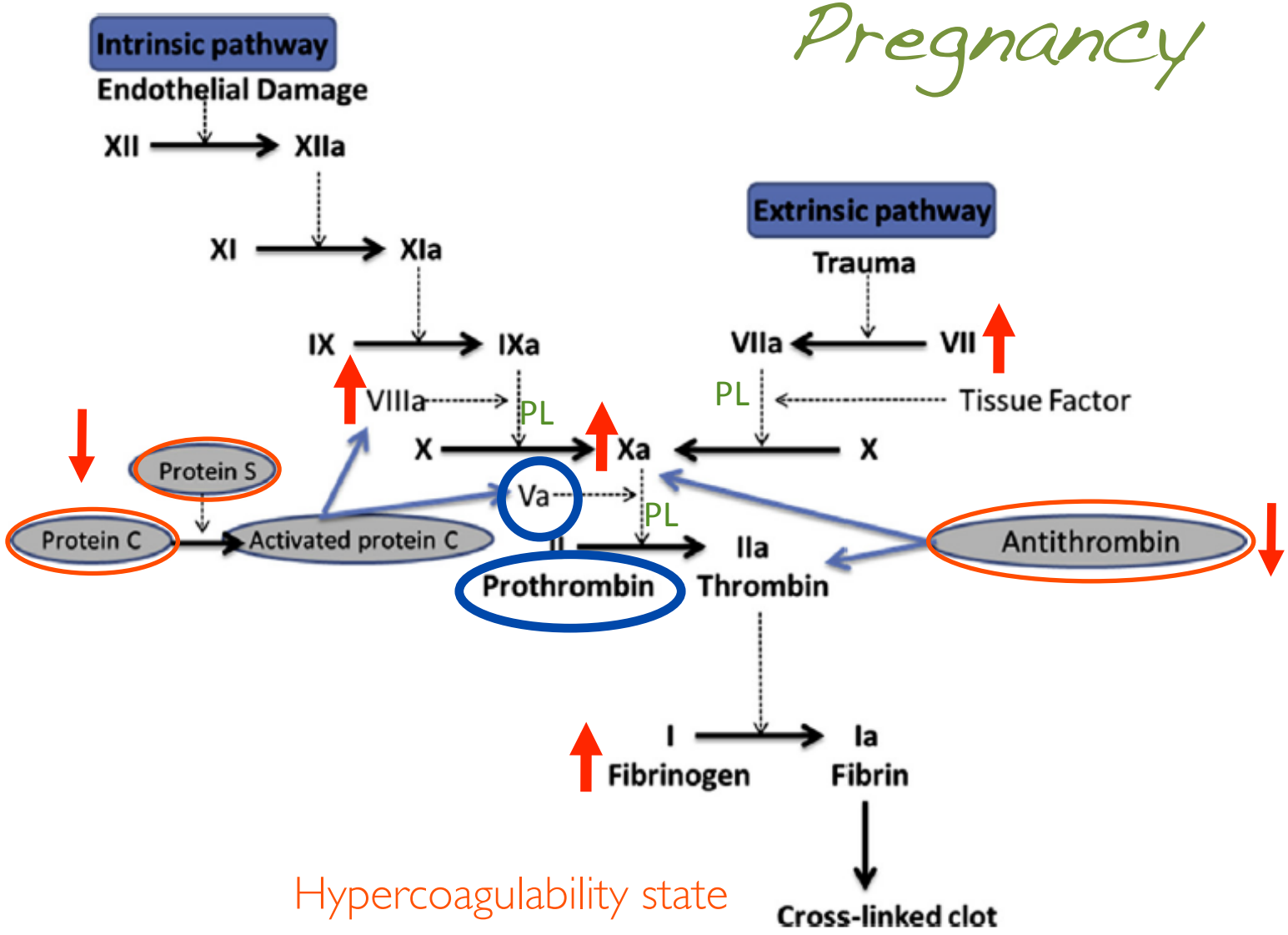
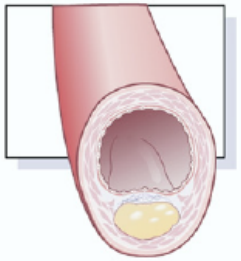
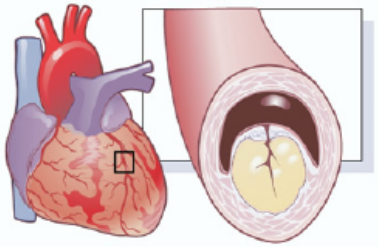
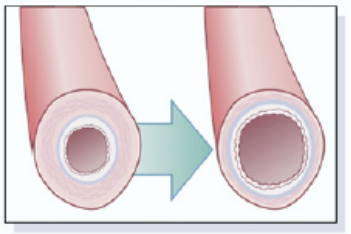
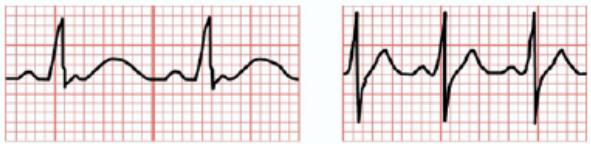


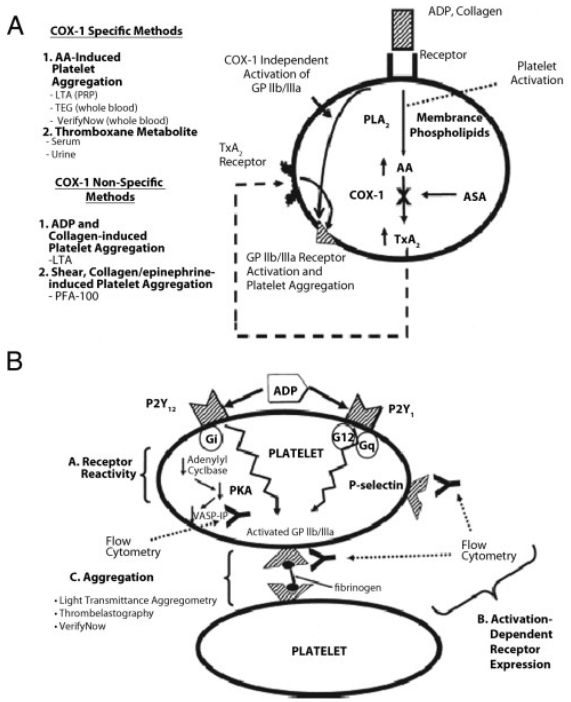
Fig. 1. Cascade of thrombus formation.

Anticoagulant

Estrogens		Progestins
↓ LDL oxidation ↓ LDL binding ↑↓ lipoprotein* *** ↑ blood pressure ↓ oxidation damage ↓ VSMC proliferation ↓ glucose tolerance***	**Atherosclerosis** 	↑↓ HDL effect* ** ↑↓ blood pressure** ↑ glucose tolerance**
↑ coagulation factors ↓ platelet aggregation	**Thrombosis** 	↑ coagulation factors ↓ platelet aggregation ↓ nitric oxide**
↑ nitric oxide ↓ endothelin ↑ Cox-2 ↓ neuroendocrine response ↓ VSMC proliferation	**Vasomotion** 	↑ vasoconstriction** ↓ nitric oxide**
↑ QT prolongation	**Arrhythmogenesis** 	↓ QT prolongation

J Am Coll Cardiol 2009;53:221–31

Antithrombotic Therapy



Studies have shown a higher prevalence of **platelet reactivity and aspirin resistance** in women than in men, suggesting that hormonal differences may play a role.

Platelet Biology and Response to Antiplatelet Therapy in Women

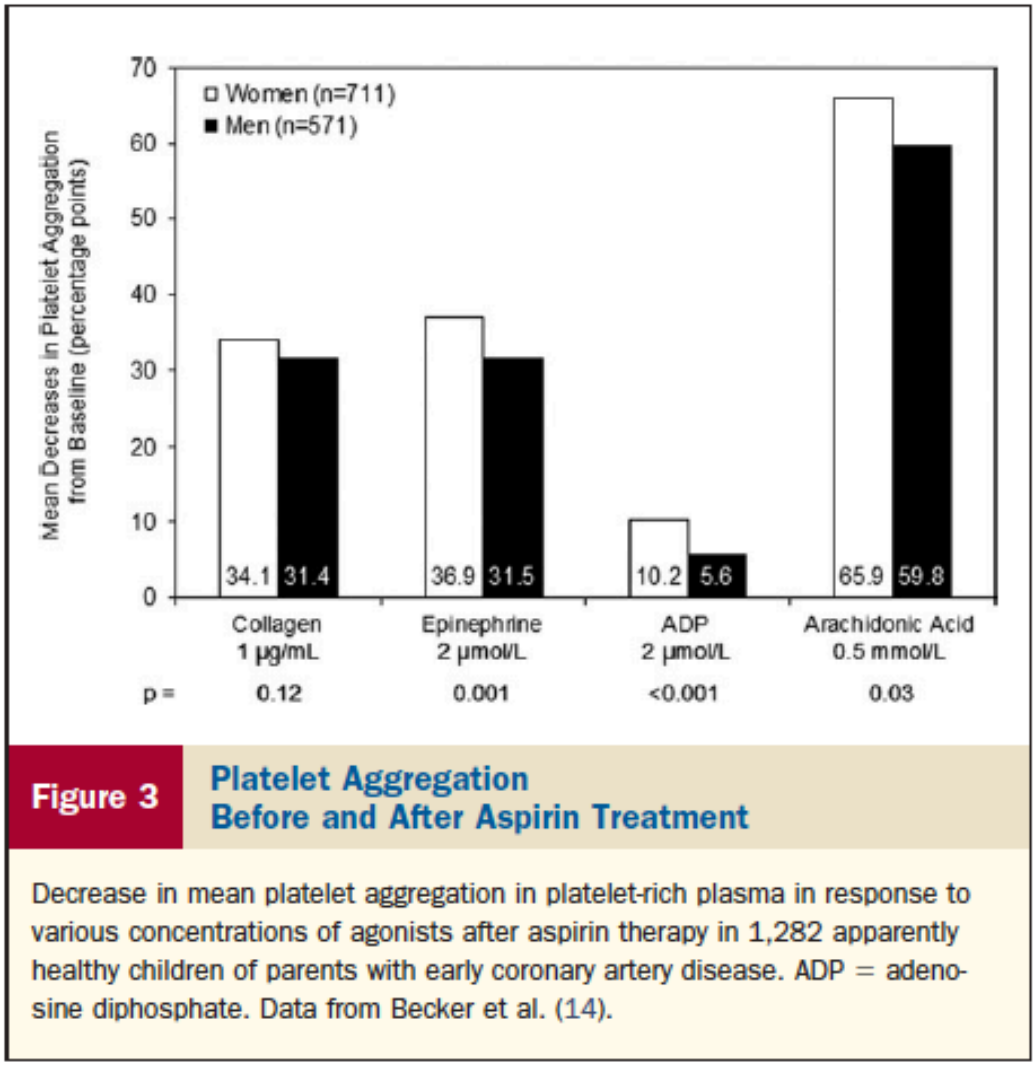


Figure 3 **Platelet Aggregation Before and After Aspirin Treatment**

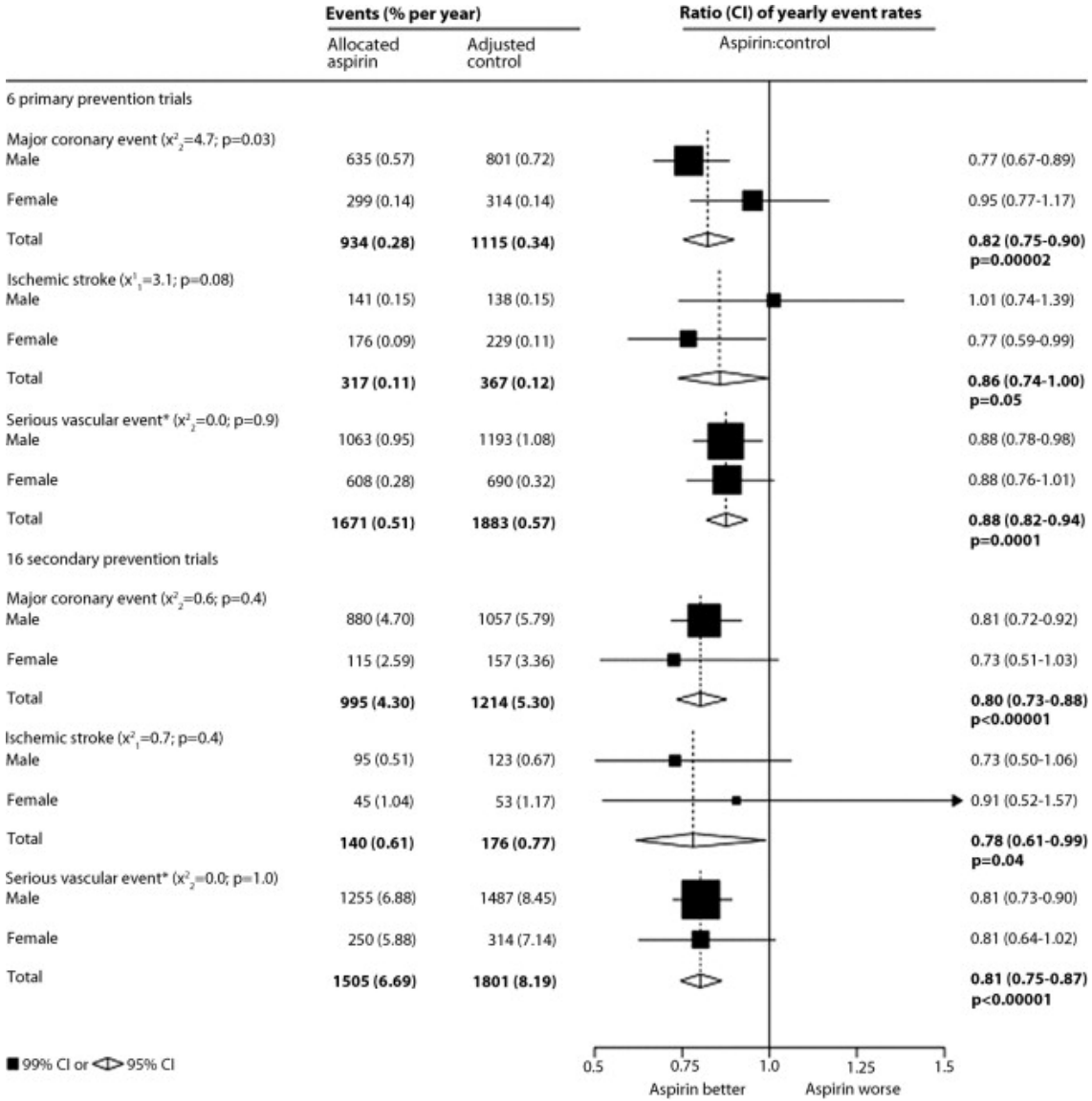
Decrease in mean platelet aggregation in platelet-rich plasma in response to various concentrations of agonists after aspirin therapy in 1,282 apparently healthy children of parents with early coronary artery disease. ADP = adenosine diphosphate. Data from Becker et al. (14).

J Am Coll Cardiol 2012;59:891–900

Selected Outcomes in Primary and Secondary Prevention Trials of Aspirin, by Sex.

Primary Prevention Trials

Secondary Prevention Trials



Journal of the American College of Cardiology, Volume 59, Issue 10, 2012, 891–900

Dual antiplatelet therapy in women and gender-stratified events analyses.

STUDY	YEAR	DESIGN	STUDY POPULATION	ACTIVE GROUP (dual antiplatelet therapy)	CONTROL GROUP (other antiplatelet drug or placebo)	PATIENTS ENROLLED (N)	WOMEN (%)	MEN (%)
CURE [56]	2001	RCT	ACS without ST-segment elevation	CLOP (300 mg loading dose followed by 75 mg/d) + ASA (75-325 mg/d)	ASA (75-325 mg/d) + Placebo	12,562	4,836 (39)	7,726 (61)
CREDO [58]	2003	RCT	Planned PCI or coronary angiogram	CLOP (300-mg loading dose followed by 75 mg/d through 12 months) + ASA (81-325 mg/d)	Placebo (loading dose followed by CLOP 75 mg/d until day 28 then placebo) + ASA (81-325 mg/d)	2,116	606 (29)	1,510 (71)
CHARISMA [62]	2006	RCT	Clinically evident cardiovascular disease or multiple risk factors	ASA (75-162 mg/d) + CLOP (75 mg/d)	ASA (75-162 mg/d) + Placebo	15,603	4,644 (30)	10,959 (70)
CURRENT OASIS-7 [68]	2010	RCT	ACS and intended early PCI	Double-dose CLOP (150 mg for 7 days followed by 75mg/d) High-dose ASA (300-325 mg/d)	CLOP-standard dose (75 mg/d) ASA-Low dose (75-100 mg/d)	17,263	4,234 (25)	13,029 (75)
PLATO [65, 66]	2009	RCT	ACS, with or without ST-segment elevation, with an onset of symptoms during the previous 24 hours	TIC (180 mg loading dose followed by 90 mg twice/d) + ASA (75-100mg/d)	CLOP (300-mg loading dose followed by a dose of 75mg/d) + ASA (75-100 mg/d)	18,624	5,288 (28)	13,336 (72)
TRITON-TIMI 38 [64]	2007	RCT	ACS with scheduled PCI	PRA (60 mg loading dose followed by 10 mg/d) + ASA (75-162 mg/d)	CLOP (300-mg loading dose followed by a dose of 75mg/d) + ASA (75-162 mg/d)	13,608	3,605 (27)	10,003 (73)
GRAVITAS [69]	2011	RCT	Stable CAD or non-ST-elevation acute coronary syndromes. Patients with high on-treatment reactivity 12 to 24 hours after PCI with drug-eluting stents	CLOP (600 mg followed by 150 mg/d) + ASA (75-162 mg/d)	CLOP (loading dose of placebo followed by 75 mg/d and placebo tablet daily) + ASA (75-162 mg/d)	2,214	773 (35)	1,441 (65)

Basili S, Raparelli V, Proietti M, Tanzilli G, Franconi F. J Atheroscler Thromb. 2015;22(2):109-25.

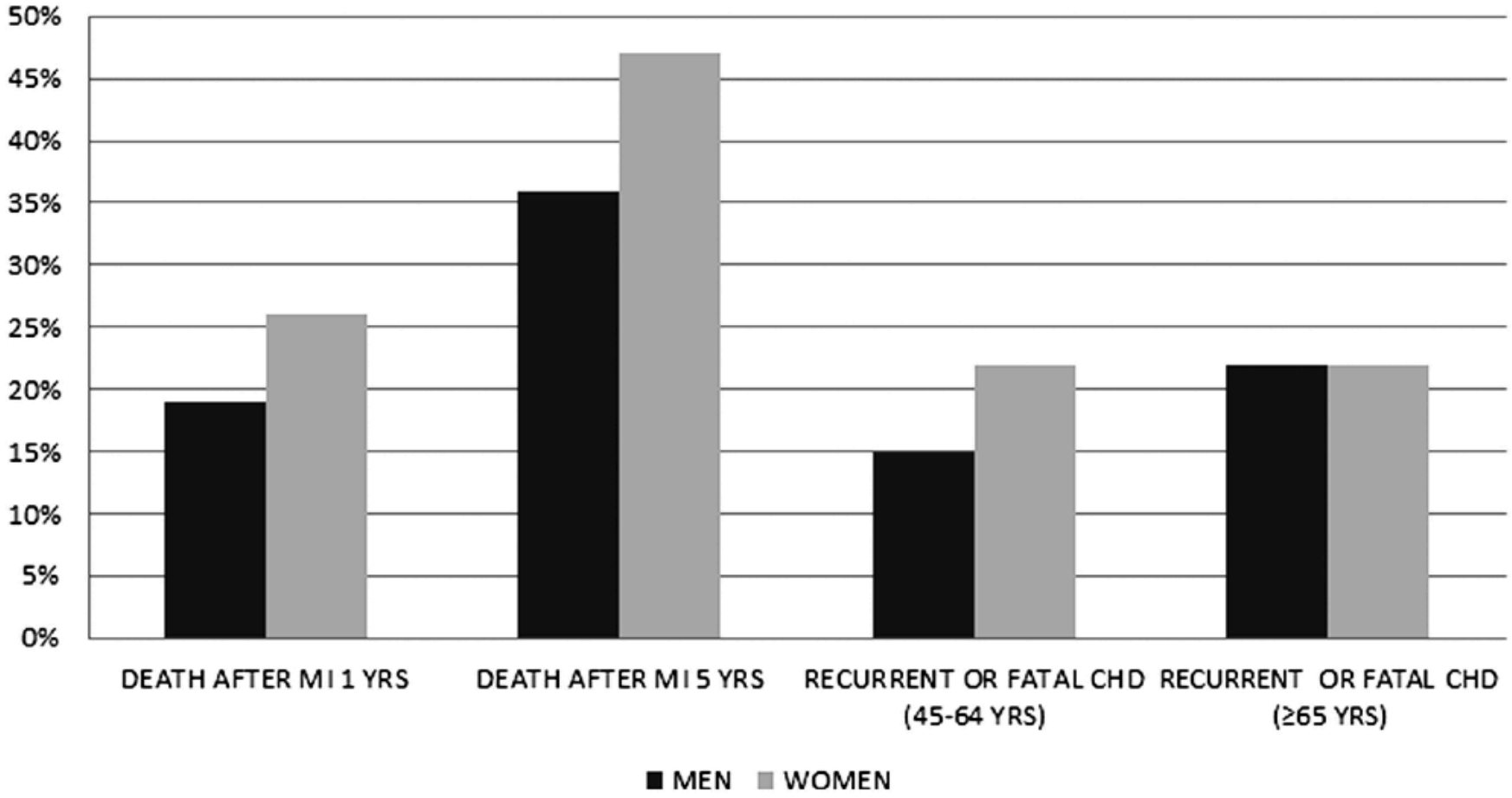


Fig. 3. Rates of cardiovascular events after myocardial infarction[6].

CHD: coronary heart disease; MI: myocardial infarction; YRS: years

J Atheroscler Thromb. 2015;22(2):109-25.

Sex differences in the clinical benefits of aspirin

There has been mention of using higher doses of aspirin in women to achieve the same level of platelet inhibition as in men.

However, studies have shown essentially equal platelet inhibition in both men and women after aspirin administration.

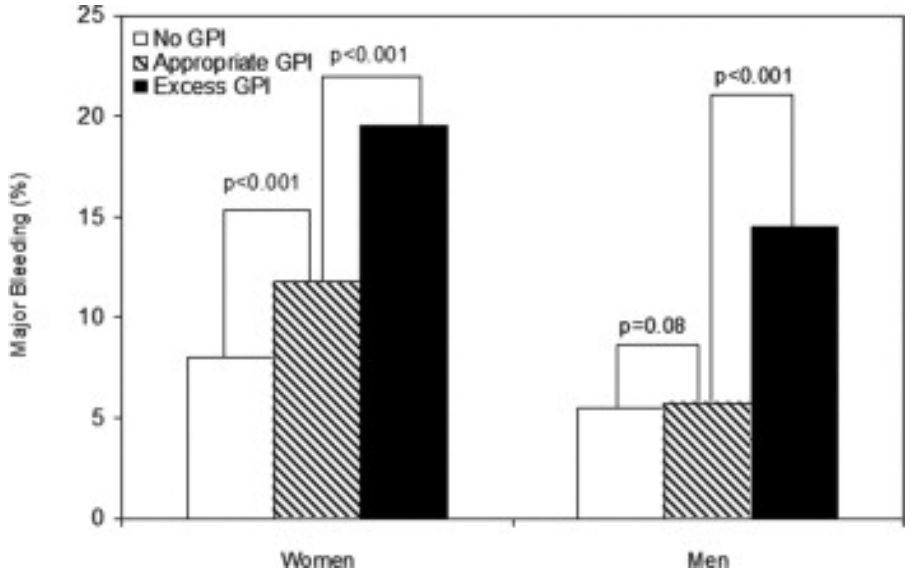
Therefore, more work needs to be done to better understand the observed sex differences in response to aspirin.

- *A clear trend to a higher incidence of **bleeding complications** has been consistently reported in women, which might be related to a more frequent **over-dosage** of antithrombotic treatment in women than in men.*

- *Women are therefore one of the subgroups that might benefit the most from careful dose adjustment of available antithrombotic drugs.*

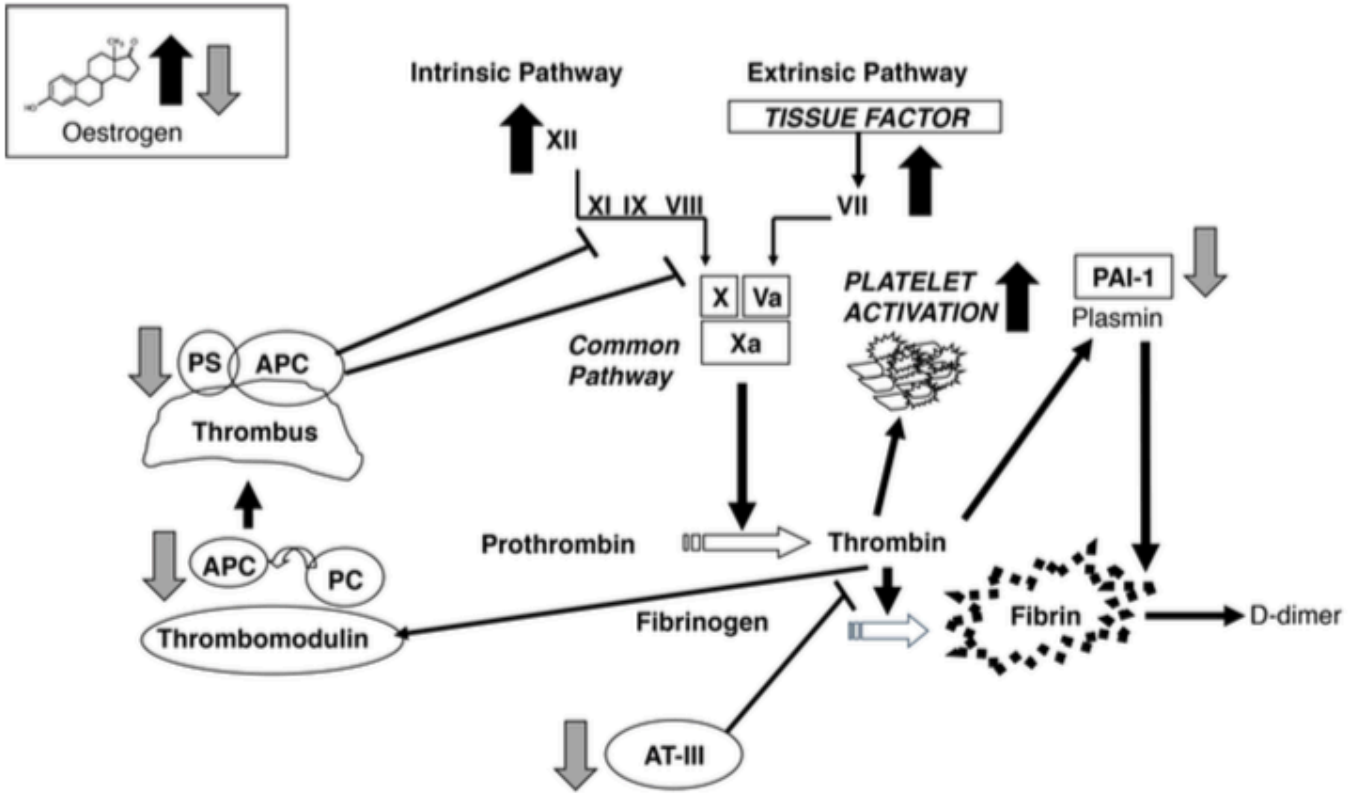
Drugs – 2013; 73: 1921-1933.
Expert Rev Clin Pharmacol. 2014; 7: 469-85.

Major Bleeding by Sex and GPI Dosing Incidence of in-hospital major bleeding among women and men with acute coronary syndromes who did not receive a GP IIb/IIIa inhibitor (GPI), those who received appropriate GPI dosing, and those who received excess GPI dosing in the CRUSADE registry.



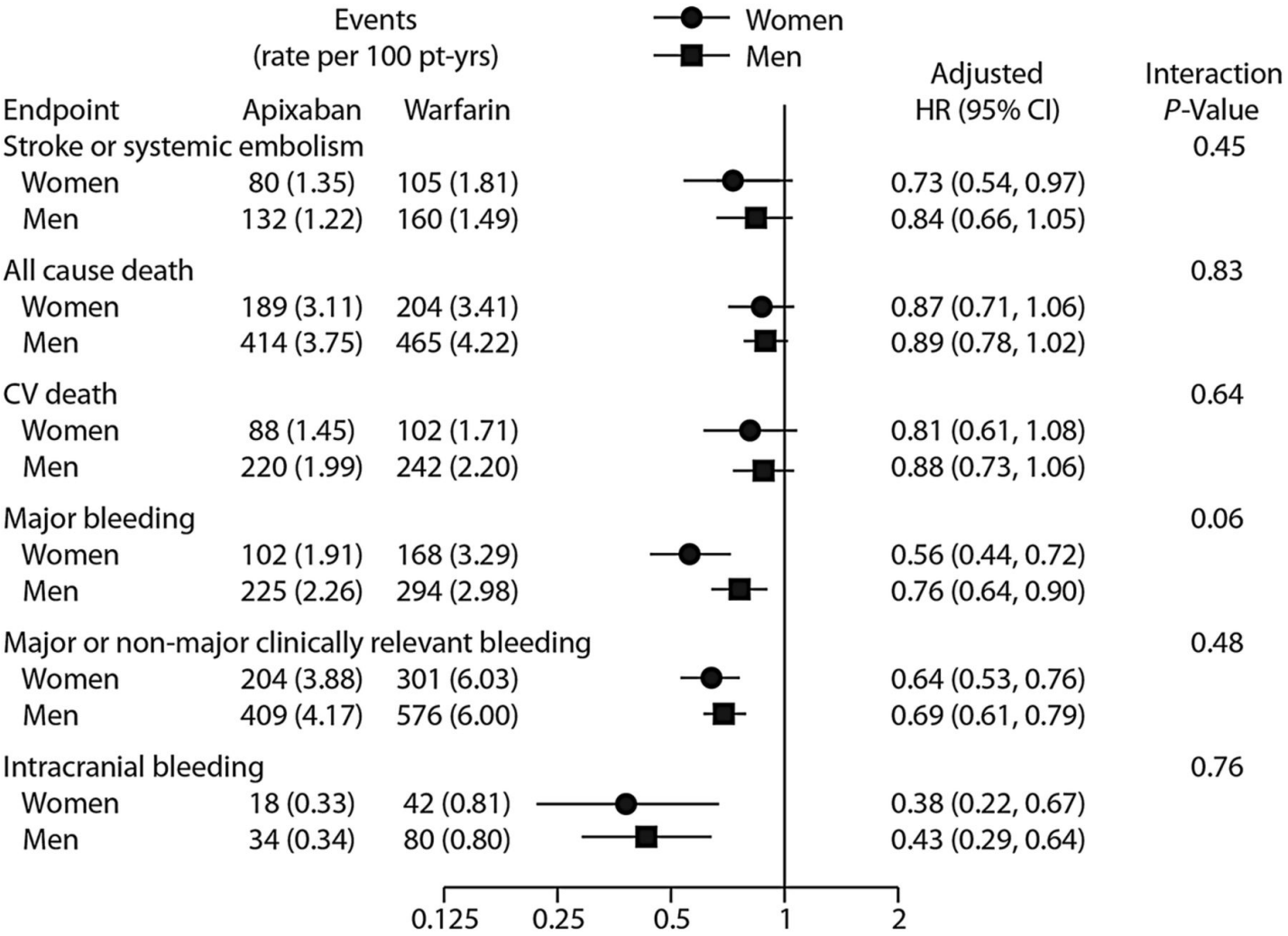
Journal of the American College of Cardiology, Volume 59, Issue 10, 2012, 891–900

Gender-based differences on the efficacy and safety of either "old" (i.e. vitamin K antagonist) or "new" oral anticoagulants (i.e. direct thrombin inhibitors and activated factor X inhibitors) may be relevant in atrial fibrillation management; nevertheless, they are underestimated. Effects of sexual hormones on haemostatic balance are under investigation to clarify the observed disparities in anticoagulation among sexes.



Basili S., Raparelli V., Proietti M., Napoleone L., Ferroni P, Franconi F. ***Old and New Oral Anticoagulants in Management of AtrialFibrillation: A Double-Edged Sword for Women***. Current Vascular Pharmacology, 2015, 13, 000-000.

Treatment effect of apixaban and warfarin on major study outcomes in men (N = 11 785) and women (N = 6416) with NVAF.



Eur Heart J. 2015 Sep 14.

European Heart Journal

Do women bleed more than men when prescribed novel oral anticoagulants for venous thromboembolism?

Study or Subgroup	Male Events	Male Total	Female Events	Female Total	Weight	Risk Ratio M-H, Random, 95% CI
AMPLIFY-ext, 2013	15	468	20	343	8.8%	0.55 [0.29, 1.06]
EINSTEIN- Cont.., 2010	25	351	11	247	8.0%	1.60 [0.80, 3.19]
EINSTEIN-DVT, 2010	75	987	64	731	24.4%	0.87 [0.63, 1.19]
EINSTEIN-PE, 2012	117	1307	132	1105	32.8%	0.75 [0.59, 0.95]
THRIVE III, 2003	60	331	74	281	26.0%	0.69 [0.51, 0.93]
Total (95% CI)		**3444**		**2707**	**100.0%**	**0.79 [0.64, 0.97]**
Total events	292		301			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 6.46$, df = 4 (P = 0.17); $I^2 = 38\%$

Test for overall effect: Z = 2.24 (P = 0.03)

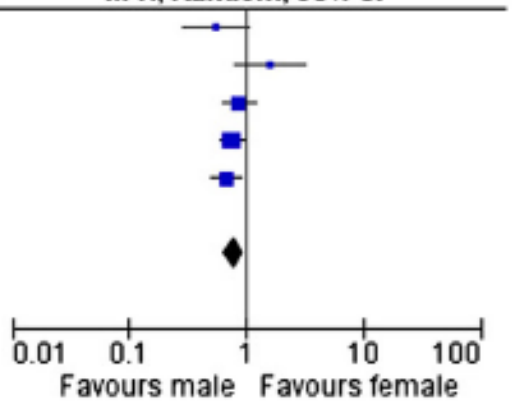


Fig. 3. Bleeding events between male and female patients who were treated with NOACs for venous thromboembolism.

Thromb Res. 2013 Aug;132(2):185-9.

Gender differences in the effect of cardiovascular drugs: a position document of the Working Group on Pharmacology and Drug Therapy of the ESC

EUROPEAN SOCIETY OF CARDIOLOGY®

Gender differences in PD are difficult to quantify as women are often under-represented in trials and the role of sex hormones in the final response is not taken into consideration.

Unfortunately, the appropriate dosage and the gender differences in clinical outcomes are still not recognized for many drugs routinely used in clinical practice.

Eur Heart J. 2015 May 6. pii: ehv161.

The development of a gender-based dosage guideline remains an unmet need in cardiology.