

Red Alert for Women's Hearts

Efficacy and safety of cardiovascular drugs from a gender perspective

Angeles Alonso García

Hospital Universitario Puerta de Hierro.

Majadahonda. Madrid. Spain

Member of the Scientific Advice Working Party

European Medicines Agency (EMA)

Efficacy and safety of cardiovascular drugs from a gender perspective

- **Treatment less effective?**
- **Safety concerns?**
- **Past and future perspectives**
- **The Regulator's point of view**
- **Conclusions**

Efficacy and safety of cardiovascular drugs from a gender perspective

- ***The most important strategy to prevent IHD in women is to avoid an underestimation of the risk of disease.***

Efficacy and safety of cardiovascular drugs from a gender perspective

- For the secondary prevention of IHD, the evidence based benefits of several cardiovascular drugs (aspirin, thienopyridines, statins, inhibitors of the renin-angiotensin system, b-blockers) are similar in both genders, despite sex-specific differences in pharmacokinetics and pharmacodynamics.***

Efficacy and safety of cardiovascular drugs from a gender perspective

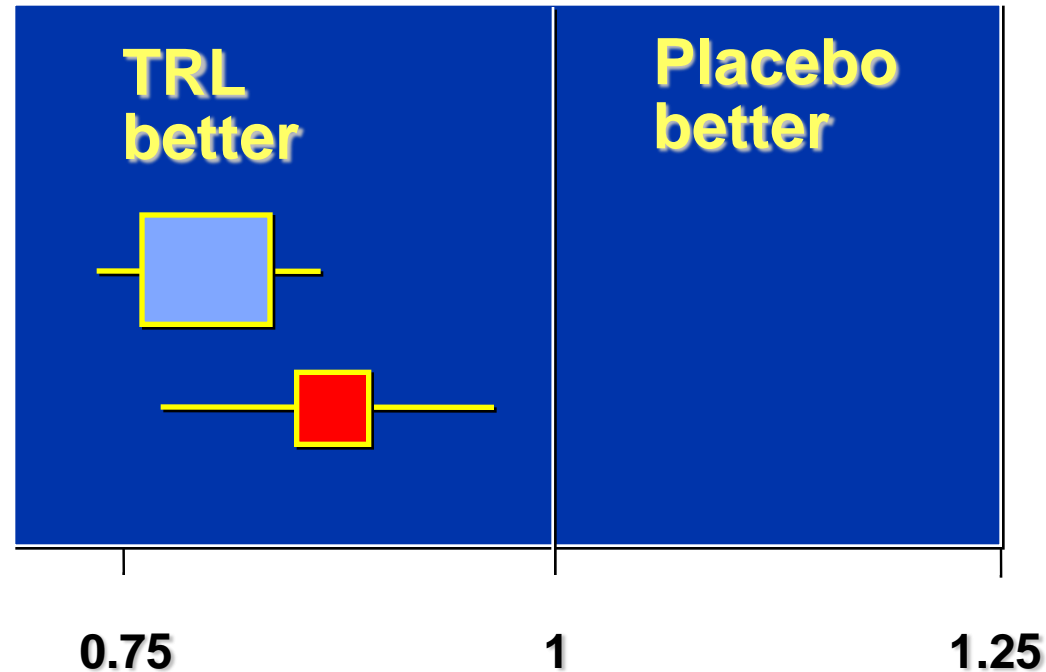
TRL EFFICACY: Mortality at 35 days post-AMI

	TRL	
	Yes	No
Men	8.2	10.1
Women	14.1	16.0

n^o

58.600 IAM

TRL vs Placebo



**Fibrinolytic Therapy Trialist
Collaboration**

Lancet; 1994; 343:311

Efficacy and safety of cardiovascular drugs from a gender perspective

Women Characteristics:

- Older
- More diabetic
- More Hypertension
- More frequently Heart Failure
- Less smoking habit (changing....)
- Less previous AMI
- Delayed presentation (atypical symptoms...)

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Regarding Efficacy Women & Men...:

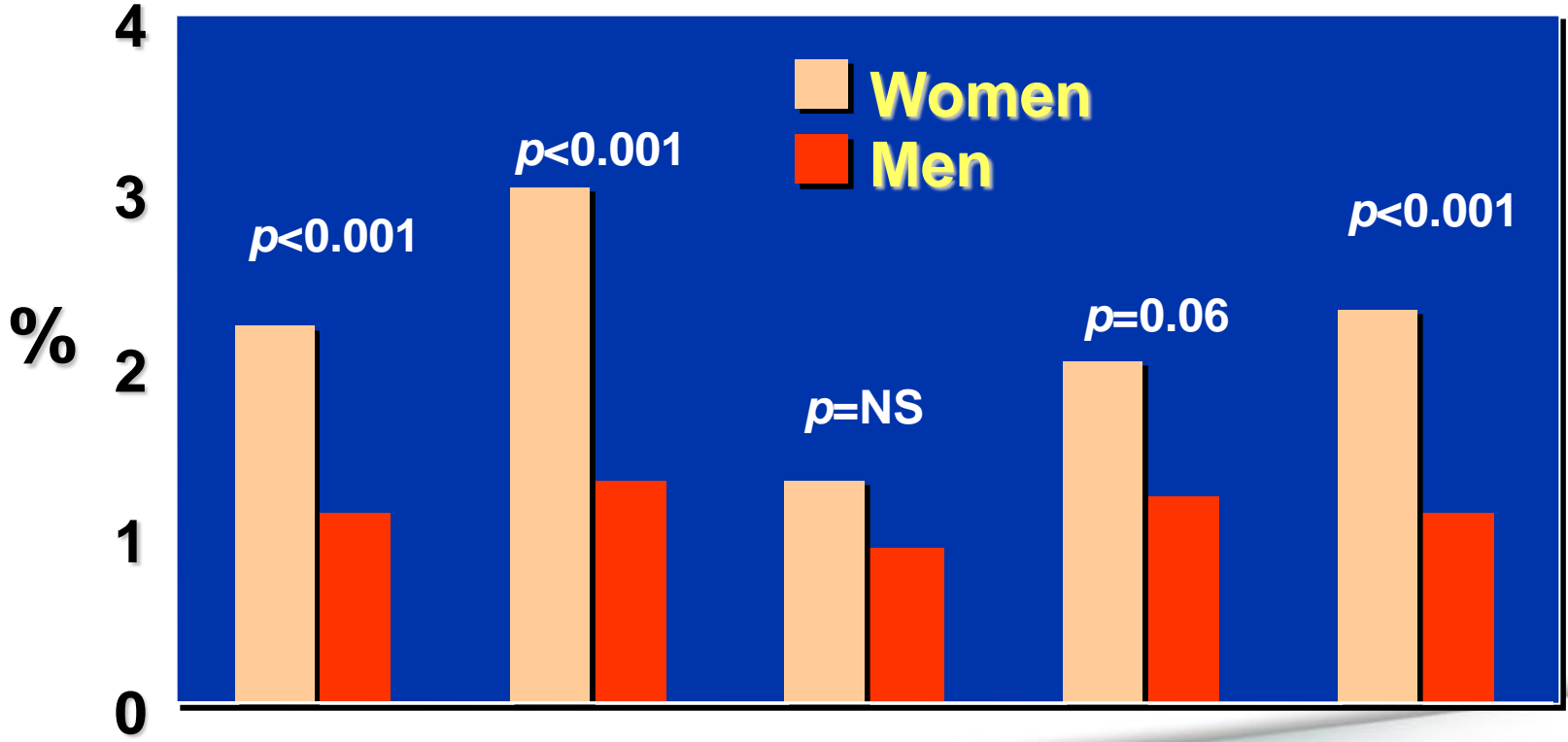
- Different Population characteristics
- Different Clinical Presentation
- ***Due to specific differences in distribution, metabolism, and excretion of drugs for several biological reasons?***

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TRL Treatment: Stroke

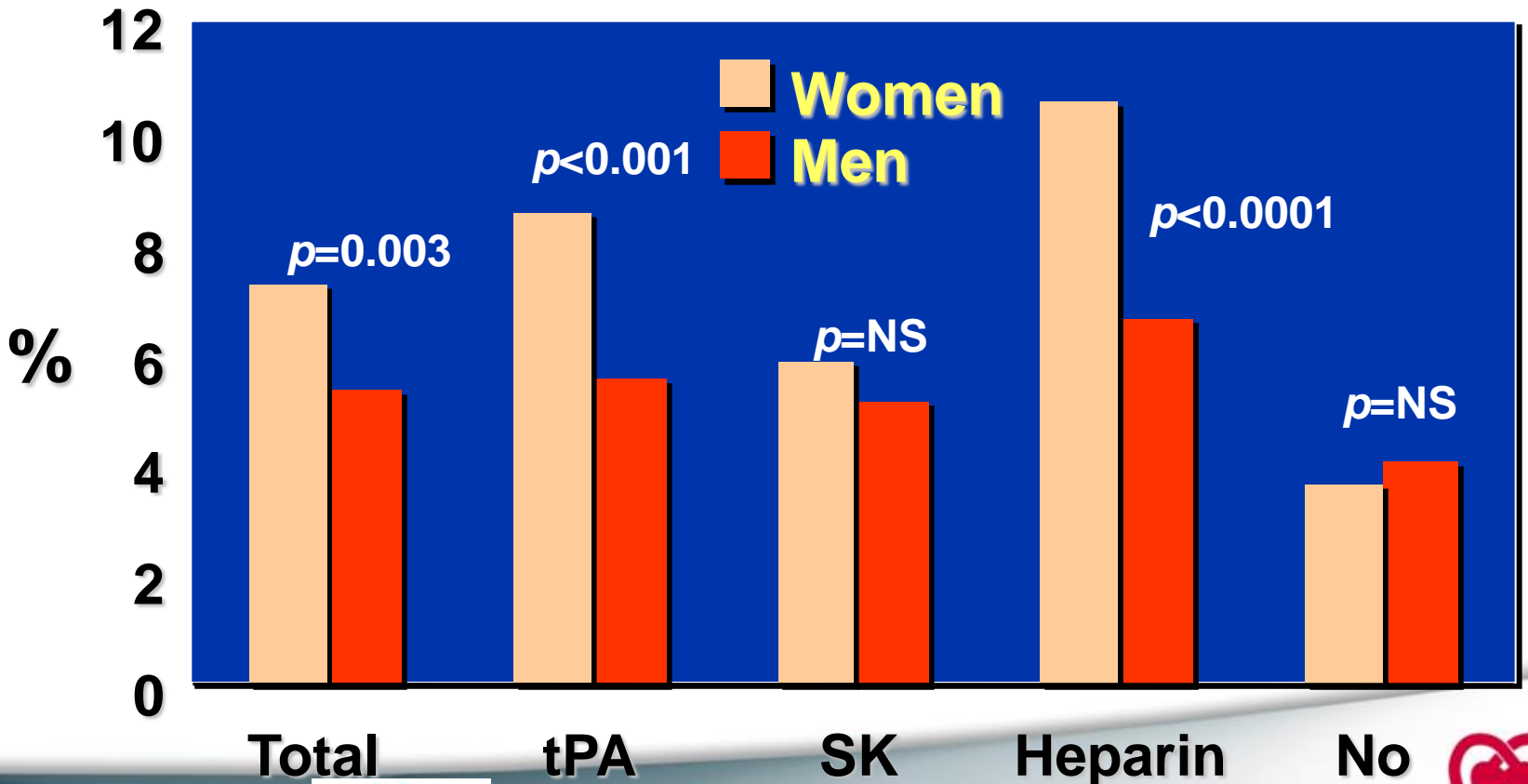


Total tPA SK Heparin No heparin



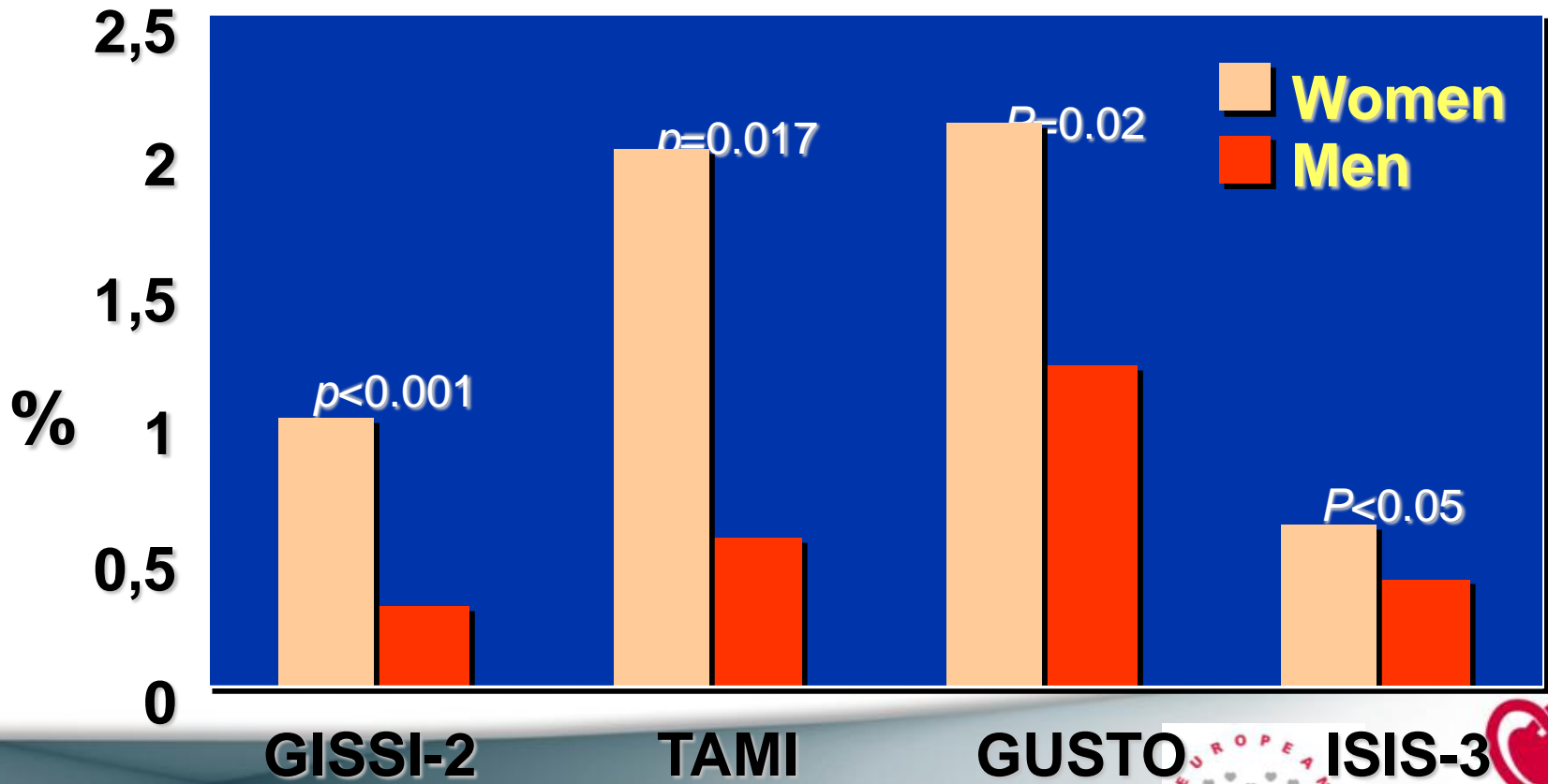
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TRL Treatment: Haemorrhagic Events



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TRL treatment: Haemorrhagic Stroke



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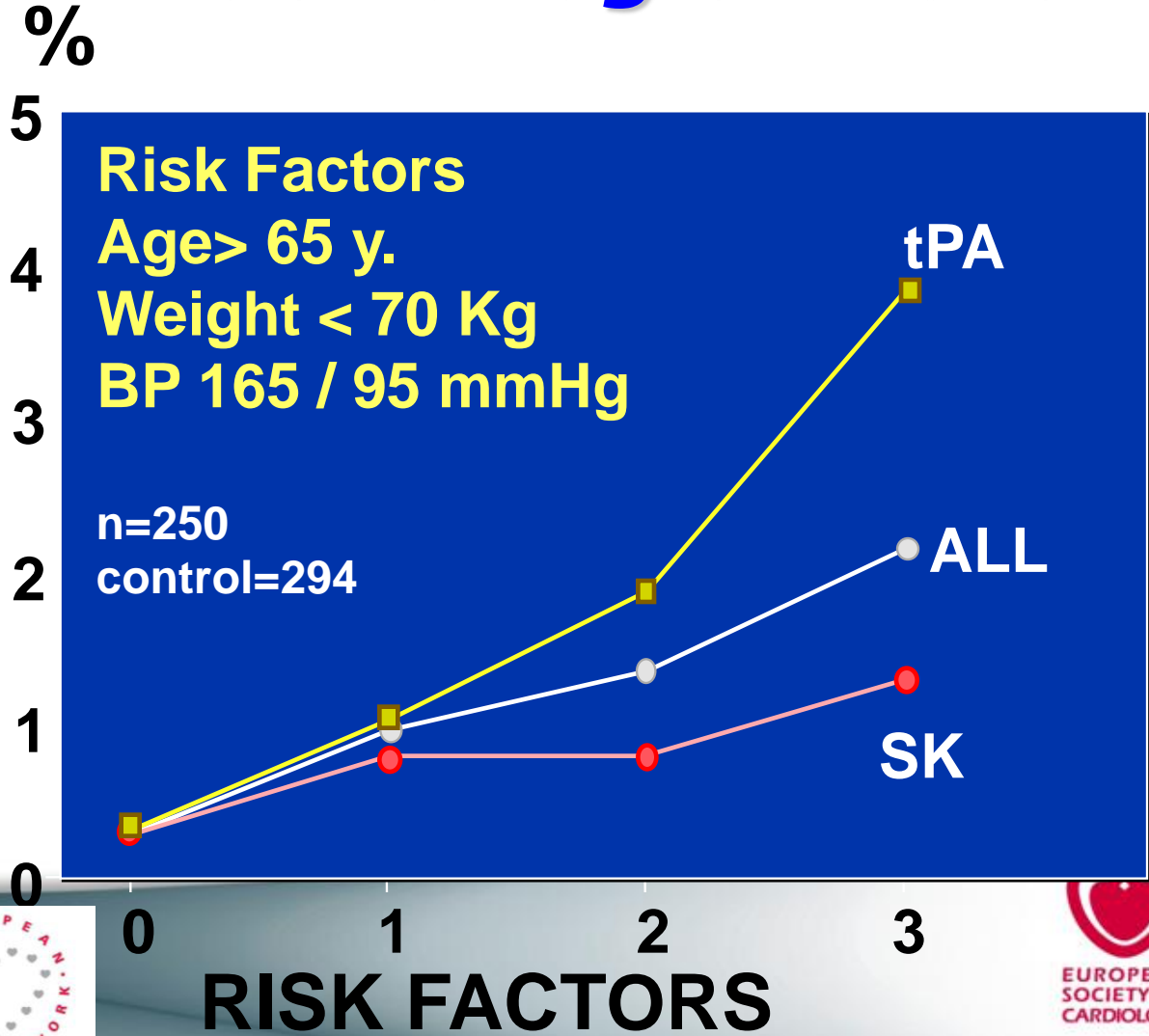
TRL treatment: Haemorrhagic Stroke

WOMEN:

- More Haem. Events
- No Independent Risk Factor

*Simoons M, et al
Lancet 1993;342:1523*

*Netherland registry
European CSG
ISAM
TIMI-II
TAMI
Gissi-2*



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Regarding Safety Women & Men...:

- More events than men
- Due to other associated factors
- *Due to differences in the incidence of adverse drug reactions and pharmacotoxicity?*

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Sex, defined as the biological difference between men and women, and gender, represented by psychosocial differences between the two, do both play important roles in cardiovascular pharmacology.

Estrogens are relevant in these processes, but cannot be regarded as the only responsible mechanism.

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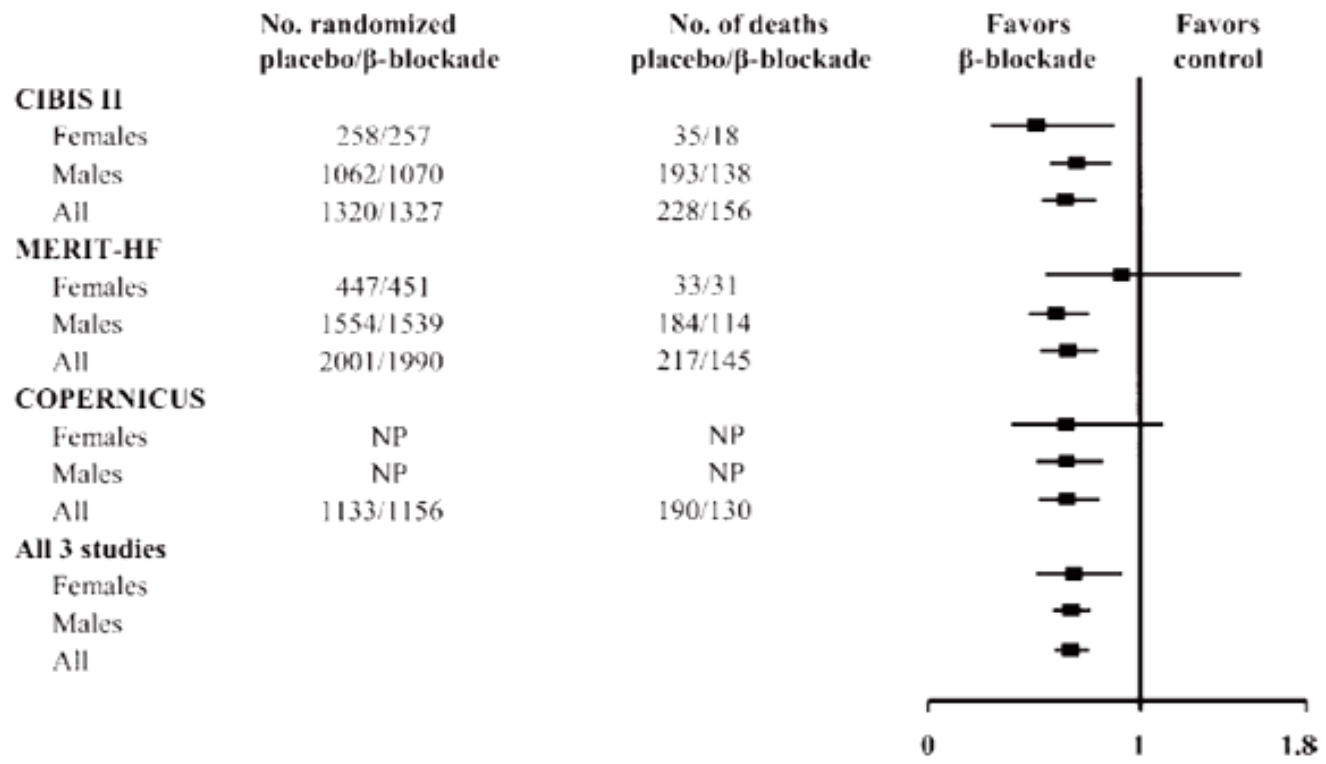
Gender differences in Pharmacokinetics

Mechanism	Gender-specific differences
General differences	
Lean/fat mass ratio	Lower lean/fat mass ratio in female
Distribution volume	Increased volume for lipophilic drugs in women
Drug binding	Smaller and fluctuating distribution volume in females Increased volume for hydrophilic drugs in males Hormonal influences on drug binding
Gastrointestinal differences	Longer gastric emptying time in women due to Slower motility Higher pH
Metabolic differences (phase I)	
CYP	CYP1A2, CYP2E1, CYP2D6 all have higher activity in men
P-glycoproteins	CYP3A4 higher activity in females (maybe rate limiting step is P-glycoprotein)
Metabolic differences (phase II)	Not enough information available
Excretion differences	Females generally have lower GFR, mostly due to body size Active secretion might be reduced in females
Hormonal influences	Estrogens influence inflammation, vasodilation, apoptosis, contractility



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RR and 95%CI: ♀/♂ β-blockers in HF

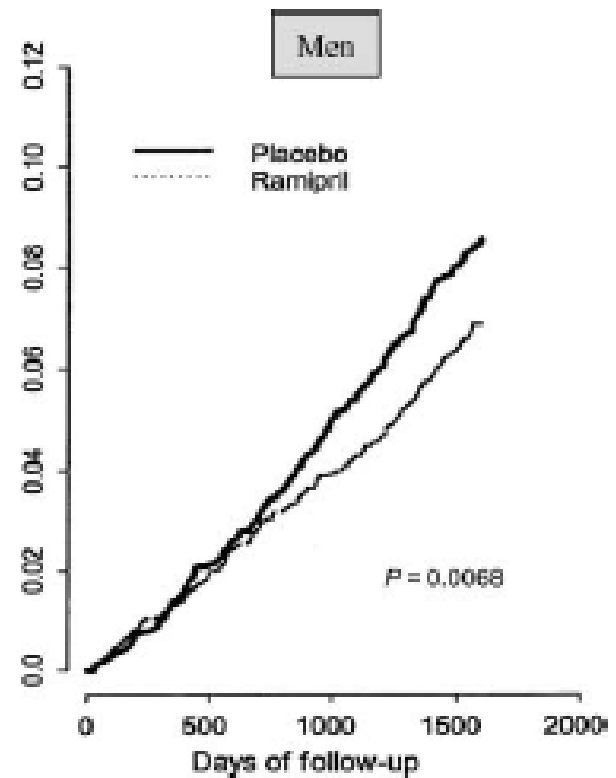
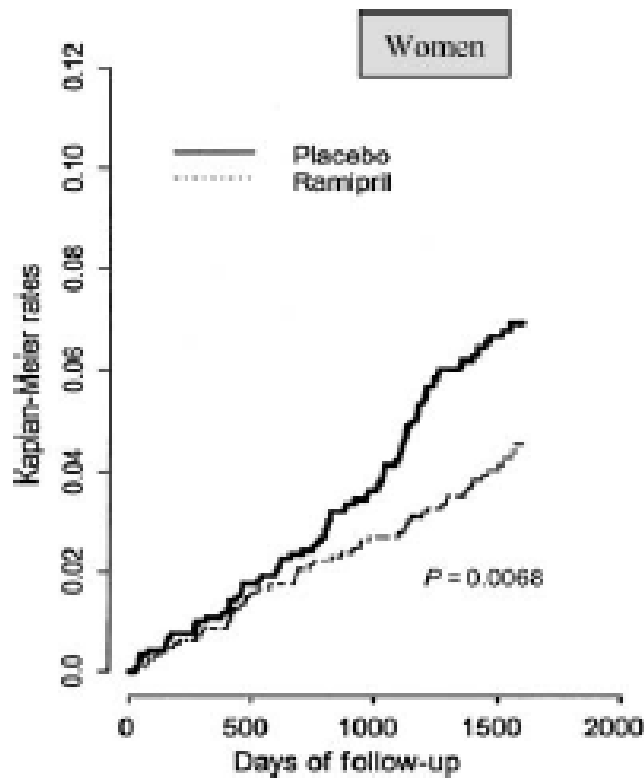


Jochmann: *European Heart Journal* (2005) 26, 1585–1595



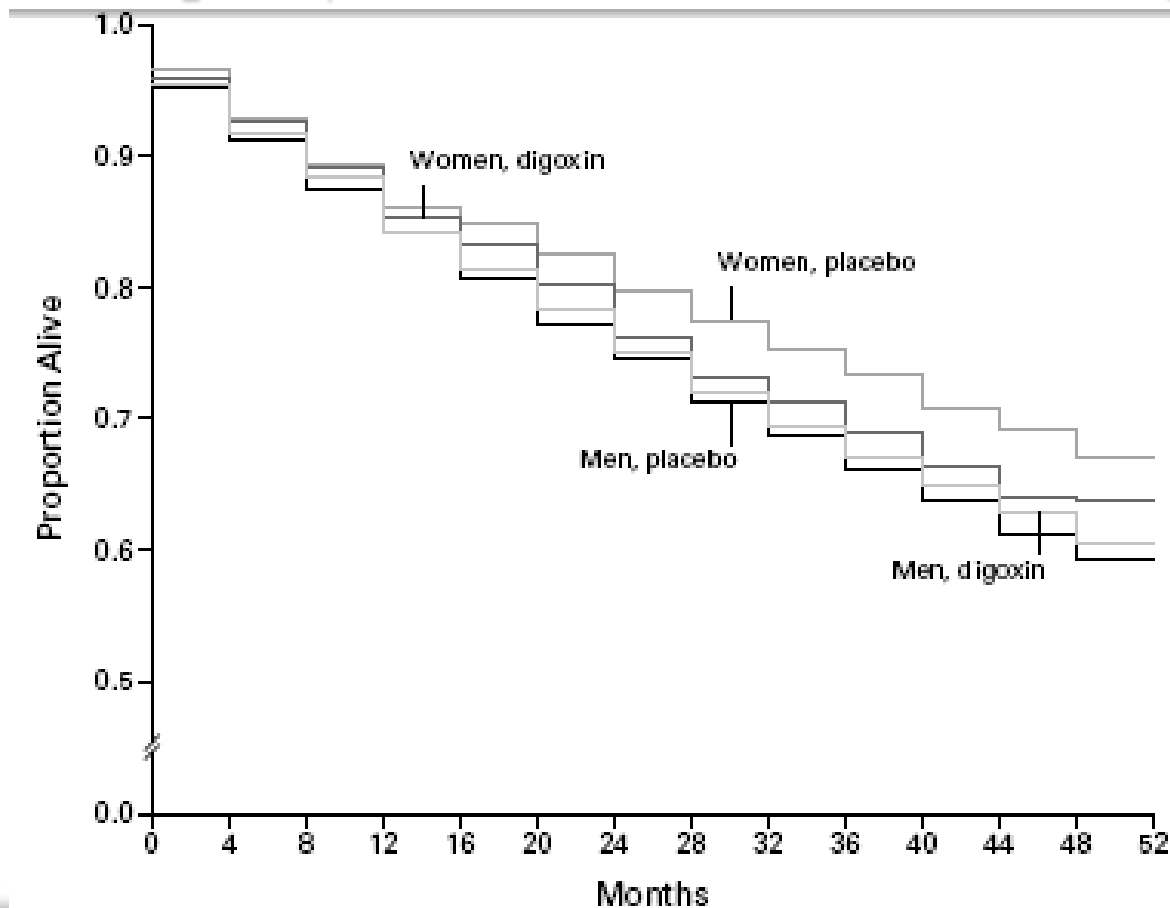
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HOPE trial: ♀/♂ **CV mortality in high risk pts**



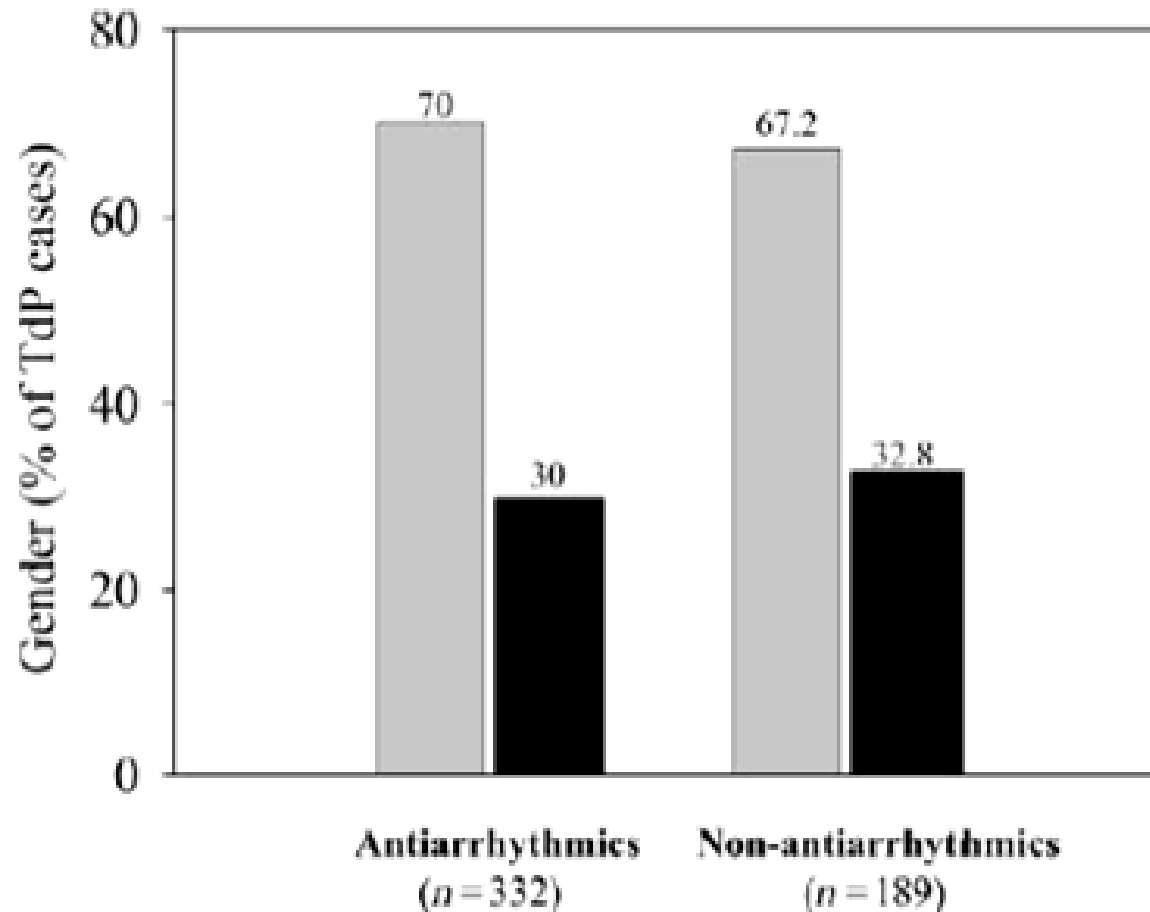
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DIG study: ♀/♂ **Survival according dig/plac**



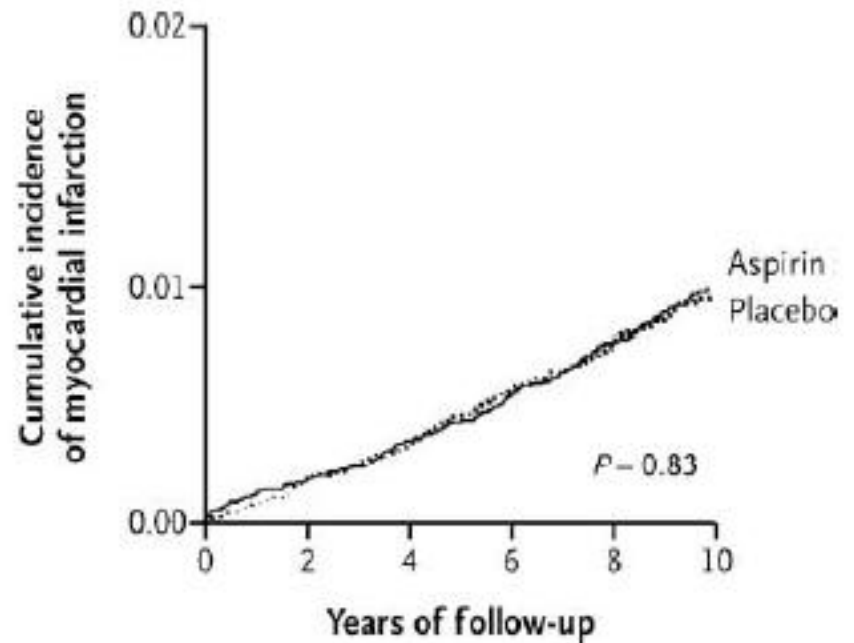
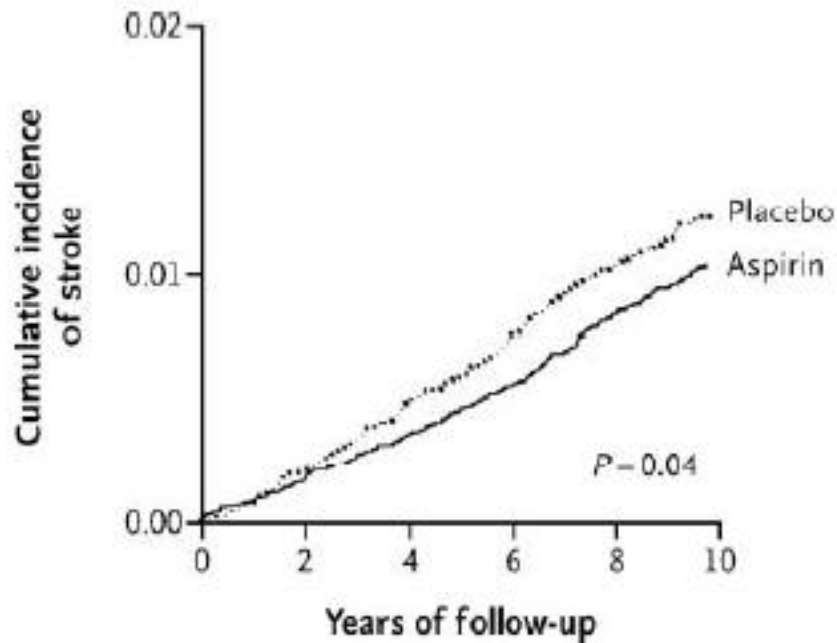
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Relation ♀/♂ and Tde P for antiArr/non-antiArr. drugs



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Stroke/MI with aspirin/control Women's Health Study



Ridker N Eng J Med 2005;352:1293–1304.

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Gender differences in pharmaceutical effects

Drug	Gender-specific effects
Beta blockers	More side effects in women Same benefits in both sexes
Digitalis	Higher mortality in women
ACEI	More side effects in women
ARBs	Gynecomasty only in men Same safety profile in both sexes
Antiarrhythmics	More tachycardia in women Higher incidence of TdP
Aspirin	Effective in primary stroke prevention in women Not effective in primary MI prevention in women Effective in primary MI prevention in men Not effective in primary stroke prevention in men
Thrombolytic agents and anticoagulants	More frequent and severe side effects in women

J. of Cardiovasc. Trans. Res. (2009) 2:258–266

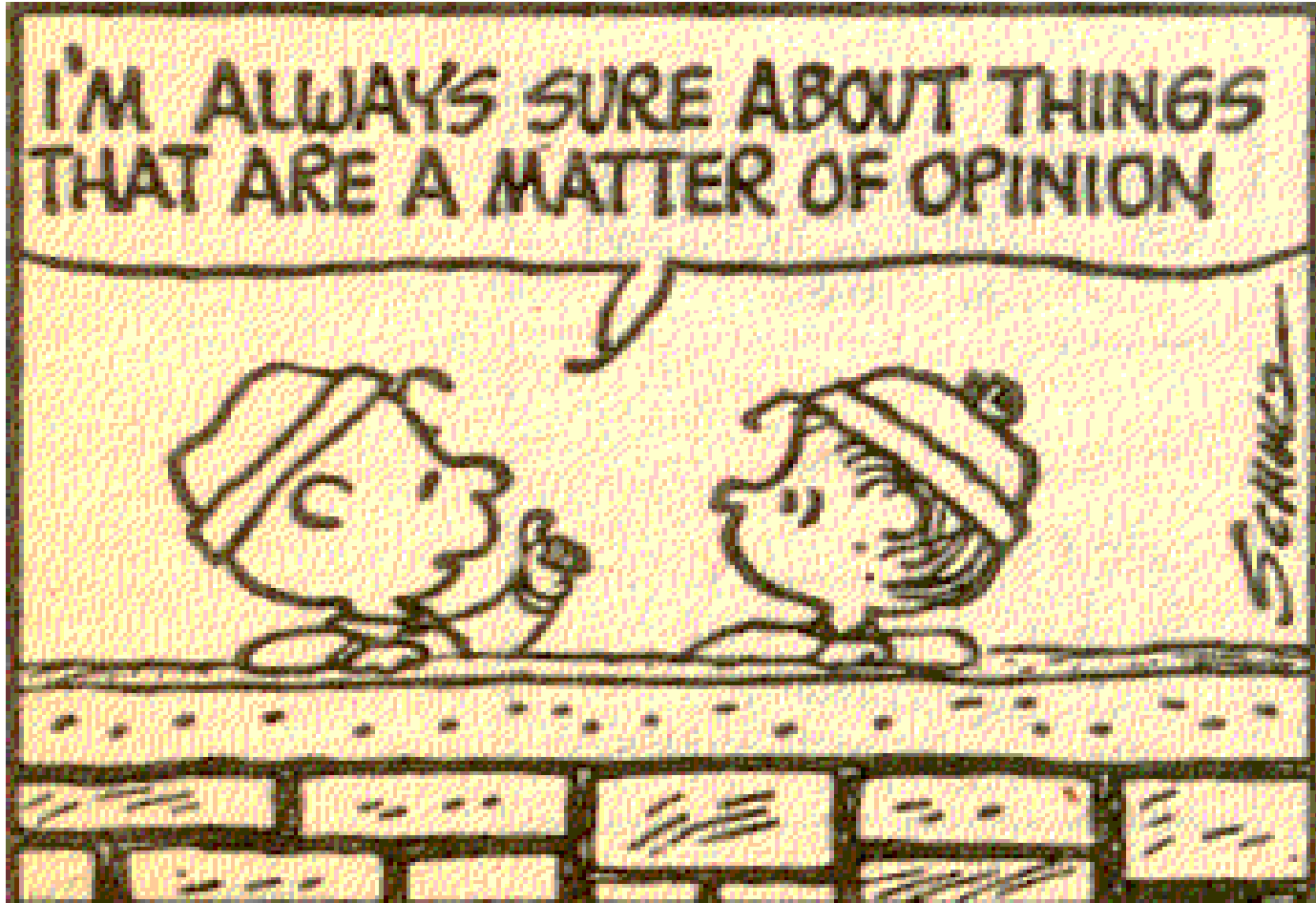
www.escardio.org



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- Increased knowledge has, in fact, been only partially translated into modifications in clinical practice where standardized therapy is still mostly based on the results of clinical trials enrolling low percentages of women.

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Reasons why women are not enrolled in clinical trials

Trials more complex

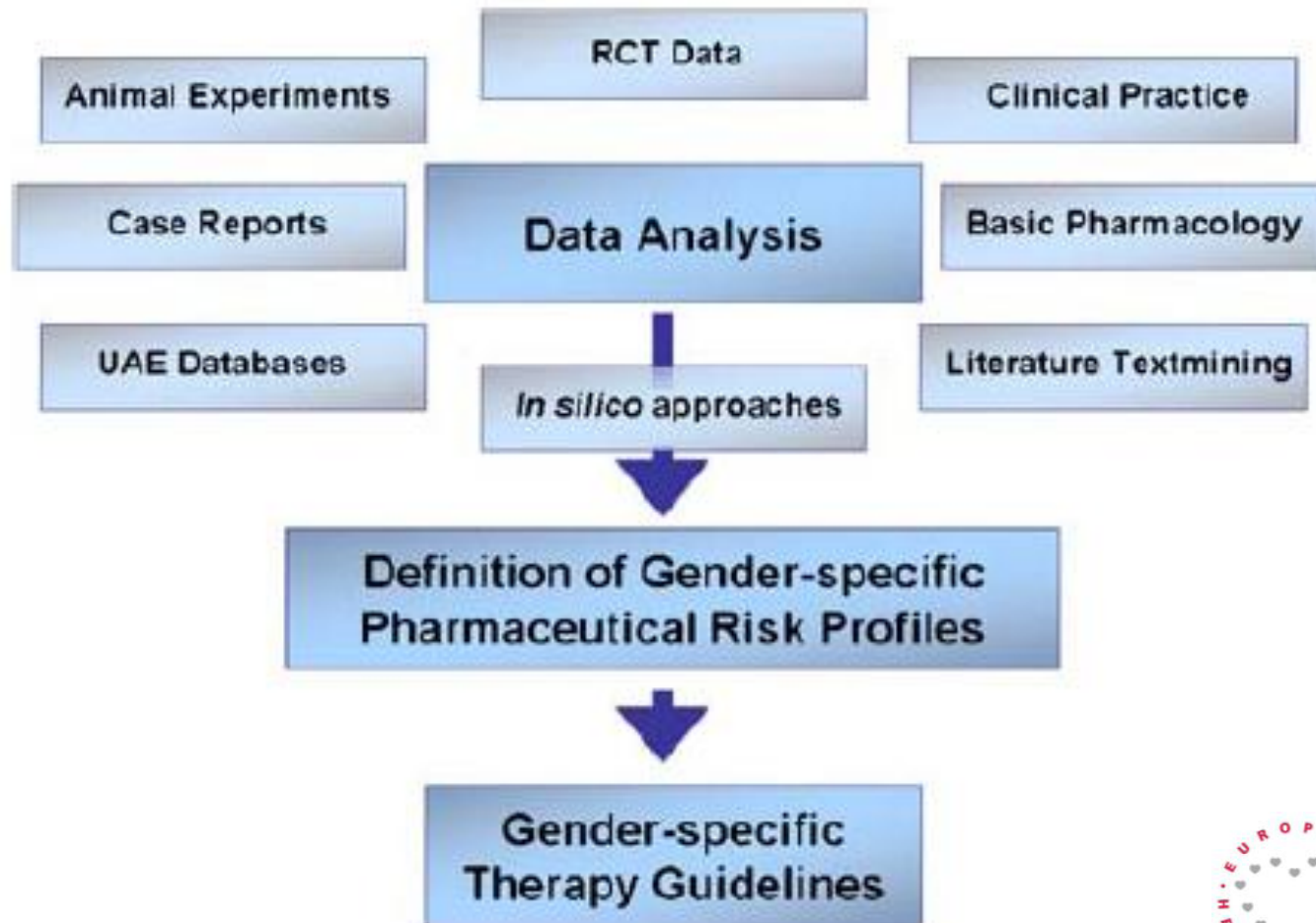
Enrollment more difficult

Pregnancy

Higher cost

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Multiple approach to define gender differences in pharmacology



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EMA Scientific Guidelines for Human Medicinal Products

- *The EMA's Committee for Medicinal Products for Human Use (CHMP) prepares scientific guidelines, in consultation with the competent authorities of the EU Member States, to help applicants prepare marketing-authorisation applications for medicinal products for human use.*

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European Medicines Agency

London, 14 December 2006

Doc. Ref. EMEA/CHMP/EWP/498145/2006

**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

DRAFT

REFLECTION PAPER ON GENDER DIFFERENCES IN CARDIOVASCULAR DISEASES

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- Current regulatory recommendations requires that patients entering clinical trials should reasonably well *represent the population that later will be treated by the drug*, as subpopulations may respond differently to a given drug treatment.

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- This clear statement is fully applicable to the *representation of gender in clinical trials*, and as such is widely reflected in a number of EMEA clinical guidelines and ICH documents.
- Moreover, in the cardiovascular field, several CHMP-EWP documents highlight the importance of an appropriate *representation of women in regulatory clinical trials*.

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- The design of clinical trials should take into consideration that they *should provide answers* to questions related to possible gender diff.
- The *safety issue* requires careful attention. Gender-specific data on safety are scarce. Post hoc analysis of some trials showed that *women in the actively treated group have a higher mortality than women receiving placebo, an effect not observed in men*

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CONCLUSIONS

1. Although there seems not to be any major differences between men and women...,
...*there is a lack of conclusive data* on the magnitude of gender differences in response to cardiovascular therapies.
2. Both females and males are expected to be represented in CV clinical trial in a proportion that *mimics the prevalence of the disease*.

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- The clinical database supporting the *marketing authorisation application* of cardiovascular drugs is expected to satisfactorily address potential *gender related differences in terms of safety and efficacy*, if not this may have regulatory implication and therefore this issue will continue to be a matter of attention.

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Life-Expectancy EU Countries



	HOMBRES		MUJERES	
	1980	1999	1980	1999
España	72,5	75,3	78,6	82,5
Francia	70,2	74,9	78,4	82,3
Suecia	72,8	77,1	78,8	81,9
Italia	70,6	75,5	77,4	81,8
Finlandia	69,2	73,7	77,6	81,0
Austria	69,0	74,4	76,1	80,9
Alemania	69,6	74,5	76,1	80,6
Grecia	72,2	75,5	76,8	80,6
Bélgica	70,0	74,3	76,8	80,5
Luxemburgo	69,1	73,7	75,9	80,5
Holanda	72,7	75,2	79,3	80,5
Reino Unido	70,2	74,3	76,2	79,7
Irlanda	70,1	73,5	75,6	79,1
Portugal	67,7	71,7	75,2	78,9
Dinamarca	71,2	74,0	77,3	78,8
MEDIA UE	70,6	74,6	77,2	80,9

CONCLUSIONS

EU reality

