Farmacologia di genere

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Transparency Declaration

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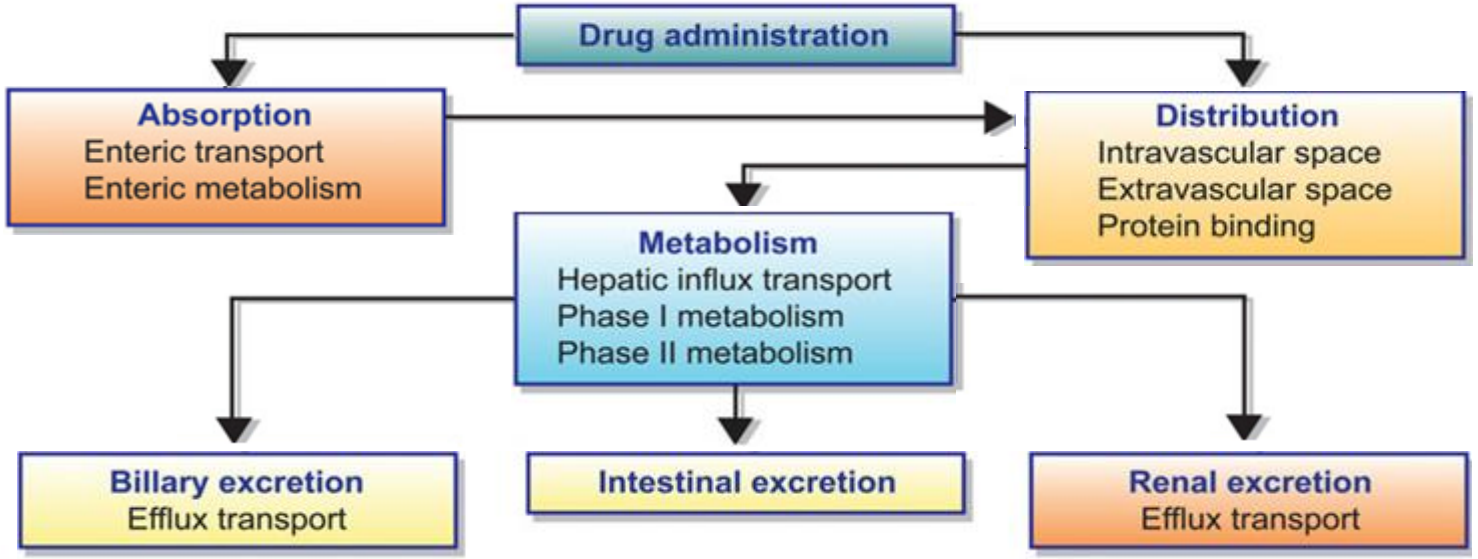
- **Angelini**
- **MSD**
- **Named**
- **Valeas**
- **Zambon Group**

Anatomic differences between men and women

Parameter	Reference adult male	Reference adult female	Pregnant female
Body weight (kg)	78	68	72.5
Body lenght (cm)	176	162	162
Body surface area (m^2)	1.8	1.6	1.65
Total body water (l)	42.0	29.0	33.0
Extracellular water (l)	18.2	11.6	15.0
Intracellular water (l)	23.8	17.4	18.8

Soldin OP & Mattison DR, Clin Pharmacokinet, 2009

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

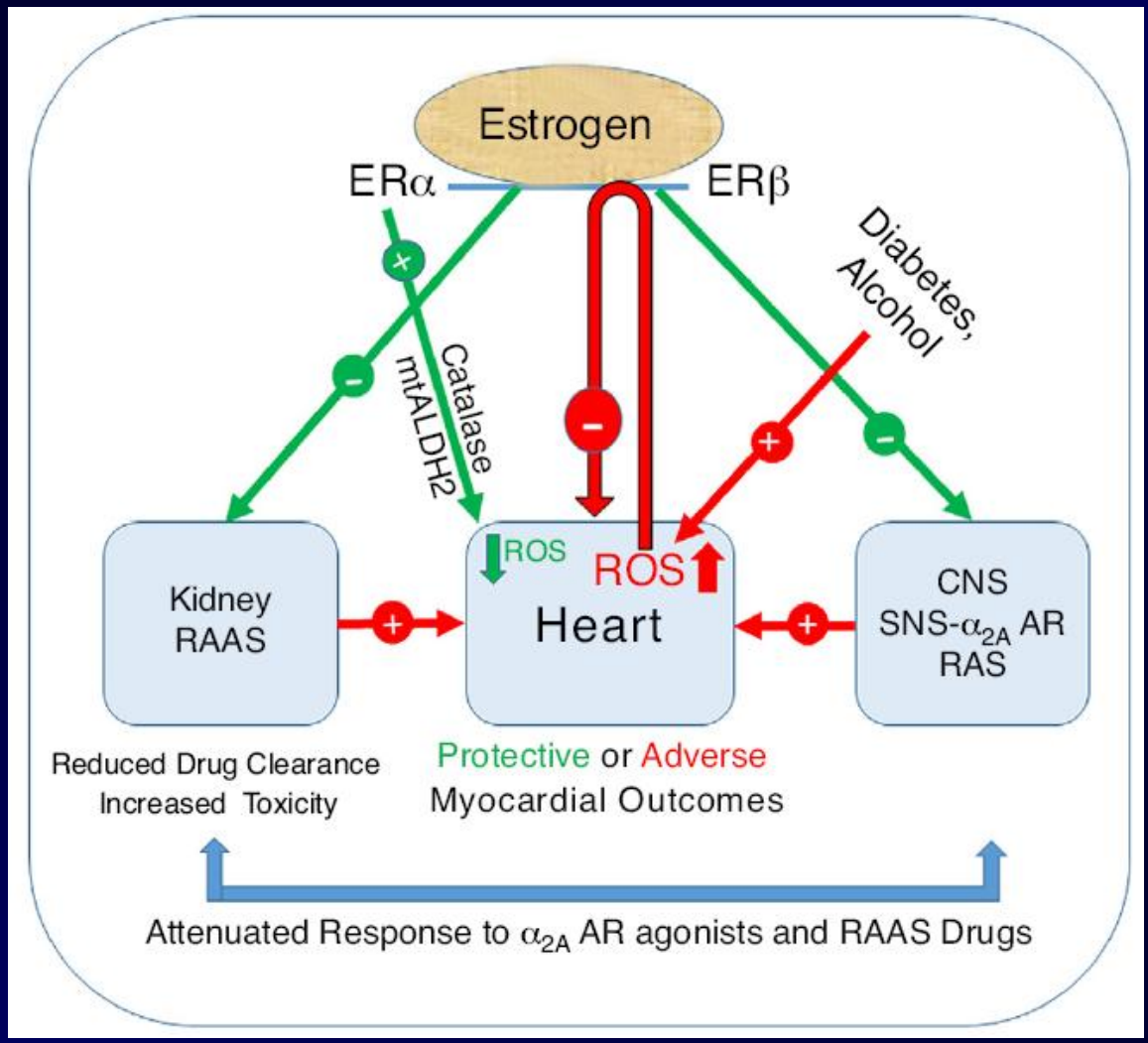
Excretion:
- Lower renal blood flow, glomerular filtration rate (GFR), tubular secretion and reabsorption
- Slower clearance of renally excreted drugs
- Longer elimination half-life

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

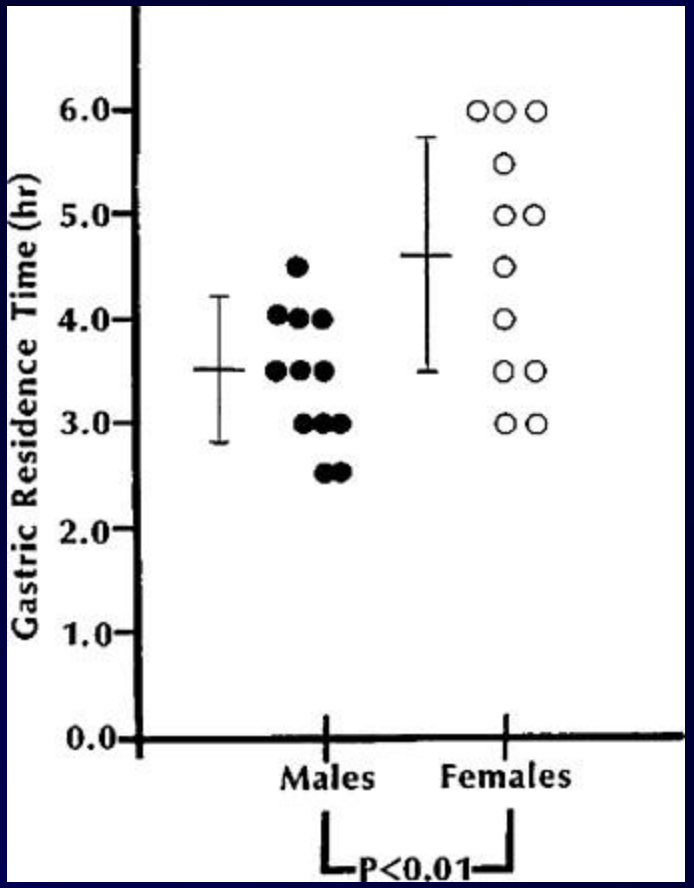
Rosano GMC et al., Eur Heart J, 2015;
Tamargo J et al., Eur Heart J, 2017

Major estrogen dependent signaling events



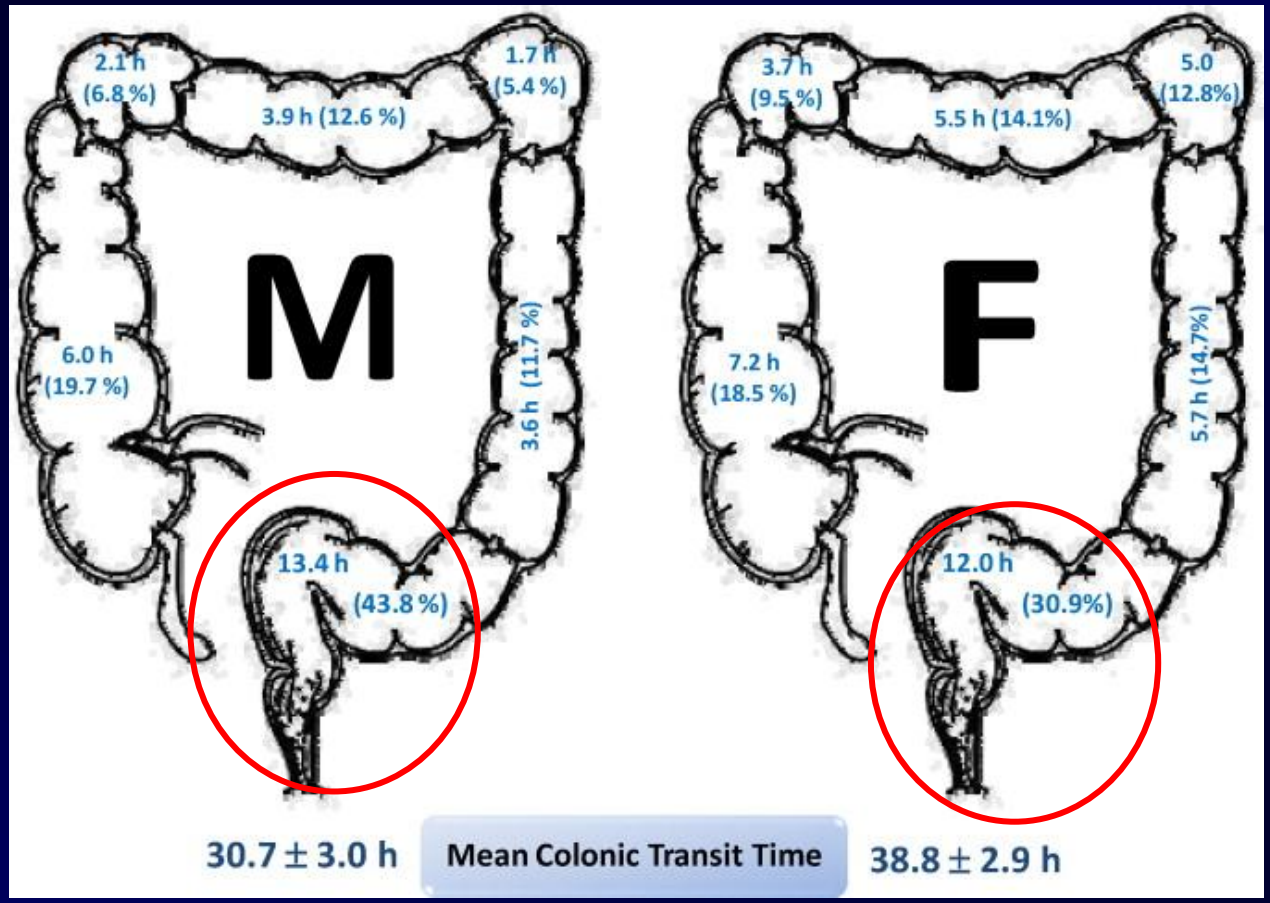
Abdel-Rahman AA, Curr Opin Pharmacol, 2017

Individual and mean (±SD) gastric residence time of Heidelberg capsule of 12 healthy male and 12 aged- and race-matched female counterparts



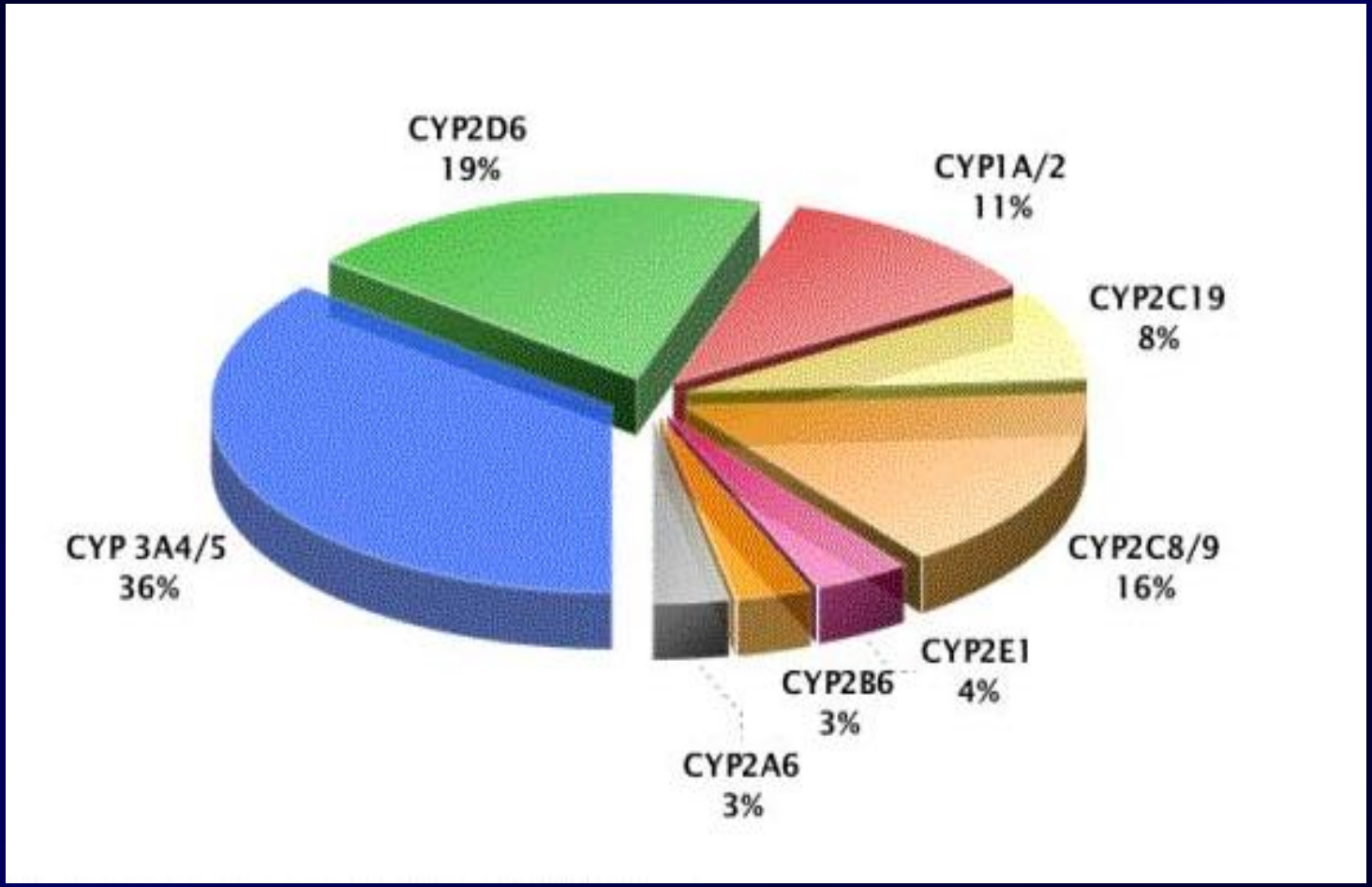
Freire AC et al., Int J Pharm, 2011

Differenze nel tempo di transito nel colon in 34 maschi e 39 femmine



Freire AC et al., Int J Pharm, 2011

Proporzione di farmaci metabolizzati dai citocromi P450



Sex differences in hepatic clearance by route of metabolism

Metabolic route	Drugs metabolized route	Sex-specific activity
CYP1A	Clomipramine, clozapine, paracetamol, methylxanthines	M > F
CYP2E1	—	M > F
CYP2C9	Ibuprofen, (S)-warfarin, tolbutamide, statins, losartan, phenytoin, nelfinavir	M = F
CYP2C19	Omeprazole, mephobarbital, citalopram, celecoxib, imipramine, piroxicam, voriconazole	M = F
CYP2D6	Codeine, fluoxetine, phenformin, propranolol, sertraline, haloperidol, TCA	F > M
CYP3A	Alfentanil, statins, BZDs, carbamazepine, macrolides, cyclosporin, cyclophosphamide, triazoles, ritonavir, verapamil, tacrolimus, VINCA, tamoxifen,	(M = F) F > M

Soldin OP & Mattison DR, Clin Pharmacokinet, 2009

Sex differences in hepatic clearance by route of elimination

Metabolic route	Drugs metabolized route	Sex-specific activity
UDP- glucuronosyl-transferases	Clofibric acid, diflunisal, ibuprofen, paracetamol, zidovudine	M > F
Sulfo- transferases	—	M > F
N-Acetyl- transferases	Catecholamines, mercaptopurine, isoniazid, hydralazine	M = F
Methyl- transferases	Azathioprine, dopamine, levodopa	M > F

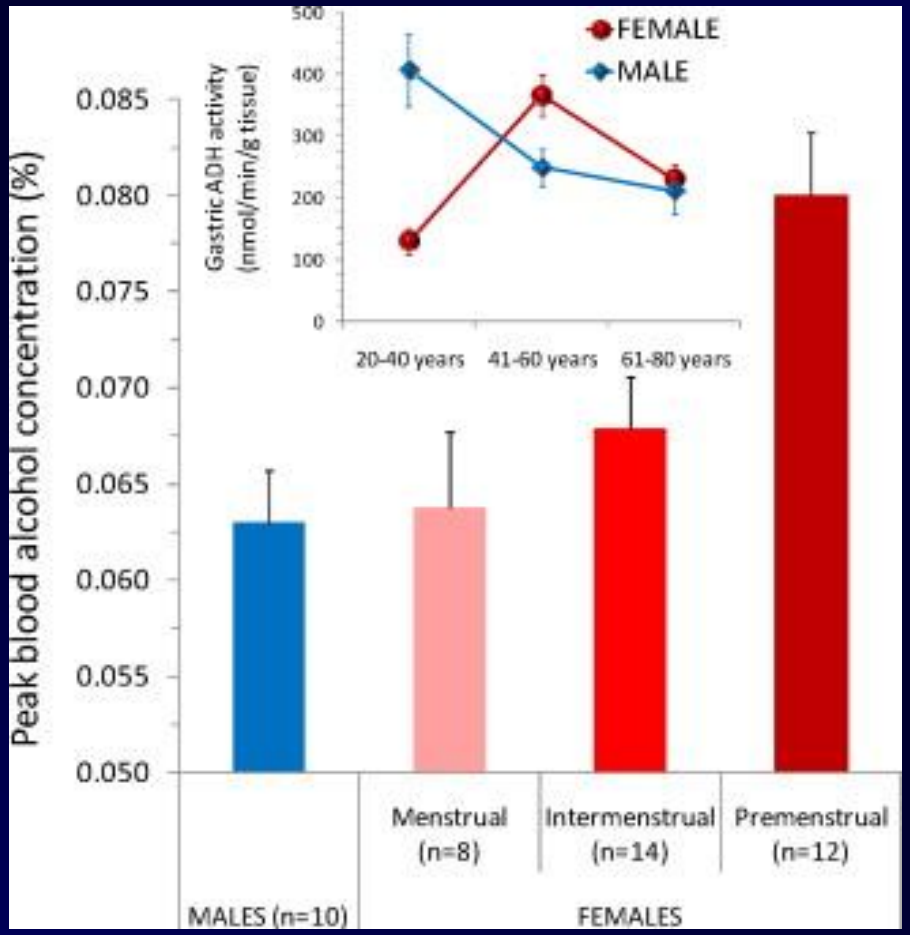
Soldin OP & Mattison DR, Clin Pharmacokinet, 2009

Reasons for sex differences in adverse event reporting

Reasons for sex differences	Pharmacological reason	Pharmacological factors
Women are more frequently overdosed	Pharmacokinetics	• Volume of distribution is smaller • Free fraction of drug is larger • Clearance from the body is slower
Women are more sensitive	Pharmacodynamics	• Alteration in receptor number • Alteration in receptor binding • Alteration in signal transduction pathway following receptor binding
Women take greater amount of medications	Drug interactions	• Alteration in pharmacokinetics • Alteration in pharmacodynamics

Soldin OP & Mattison DR, Clin Pharmacokinet, 2009

Mean (±SE) peak blood alcohol levels for males and females tested at different times in the menstrual cycle



Freire AC et al., Int J Pharm, 2011

Pharmacokinetic parameters that exhibit sex differences for selected drugs

Drug	PK parameter	Male	Female	Comments
Theophylline	Non-smokers	9.3	6.0	The half-life of theophylline is shorter in women compared to men (either smokers or non- smokers), suggesting need for different schedule of administration
	Smokers	6.9	4.6	
Ethanol	Volume of distribution (l/kg)	0.62	0.45	First pass metabolism of ethanol is greater in men than in women. Also, the volume of distribution is smaller in women than men. These suggest the potential for greater blood concentrations among women than men
	Clearance (mg/h/kg)	78.6	88.6	
	First-pass metabolism (nmol/l·h)	5.2	1.2	
Iron	Absorption measured as % of the dose incorporated into red blood cells	35.2%	45.0%	More ingested iron is absorbed by females than males

Soldin OP & Mattison DR, Clin Pharmacokinet, 2009

Pharmacokinetic parameters that exhibit sex differences for selected drugs

Drug	PK parameter	Male	Female	Comments
Acebutolol	AUC (ng·hr/ml)	4861	6410	The AUC profile is larger in women than men, suggesting greater therapeutic and potential side-effects
Propranolol	Total clearance	65.7	40.2	Propranolol is cleared more rapidly in men than women; this is also reflected in the higher clearance of the metabolites. Women have greater potential for therapeutic and adverse effects
	Clearance (glucuronidation)	8.5	5.6	
	Clearance (side chain oxidation)	12.1	5.1	

Drug	Pharmacokinetic parameter	Comments
Verapamil; calcium channel blocker	Clearance following intravenous administration more rapid in women, but oral clearance higher in man than women. Substrate for both CYP3A4 and PGP Oral clearance is lower in women than	Sex-differences in hepatic and gut CYP3A4 and PGP lead to complex differences in clearance between man and women. Bioavailability from the gut is greater in women than in man. The greater bioavailability leads to increased systemic exposure in women

Soldin OP & Mattison DR, Clin Pharmacokinet, 2009

Cardiovascular drugs with gender-specific therapeutic and adverse effects

Drug	Gender-specific effects
Statins	Increased side effects in older women with low body weight
Antiplatelet Agents	Ineffective primary prevention of heart attack in women Decreased stroke prevention in men
Antithrombotic Agents	Increased risk of bleeding
Digoxin	Increased mortality in women
β-Blockers	Enhanced blood pressure lowering and heart rate reduction in exercising women
Antiarrhythmic Agents	Increased risk of prolonged QT and TdP in women
Calcium Channel Blockers	Enhanced blood pressuring lowering in women Increased incidence of edema
ACE Inhibitors	Increased incidence of cough
Diuretics	Increased risk of hyponatremia

TdP, Torsades de Pointes

Stolarz AJ & Rusch NJ. Cardiovasc Drugs Ther, 2015

Abstract Send to:

Thromb Res. 1983 Jan 15;29(2):125-39.

The sex-related differences in aspirin pharmacokinetics in rabbits and man and its relationship to antiplatelet effects.

Buchanan MR, Rischke JA, Butt R, Turpie AG, Hirsh J, Rosenfeld J.

Abstract

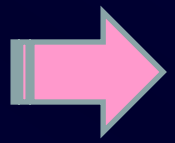
There are a number of reports which suggest that the antithrombotic effect of aspirin is limited to males. It is unclear whether this effect is due to sex-related differences in the effect of aspirin on platelets, the vessel wall, or the pharmacokinetics of aspirin. To test these possibilities we examined the sex-related differences in (1) vessel wall PGI2 release and its inhibition by and recovery from aspirin in rabbits; (2) the effects of aspirin on platelet aggregation, thromboxane B2 and beta-thromboglobulin (BTG) release in man, and (3) the pharmacokinetic characteristics of aspirin, in both rabbits and man. Vascular wall PGI2 measured as 6-keto-PGF1 alpha, was not different in male and females rabbits, and was inhibited to a similar extent by identical concentrations of aspirin. The duration of this inhibitory effect was also the same in males and females. The pattern of inhibition of collagen-induced platelet aggregation, and collagen-induced thromboxane B2 and BTG release by aspirin were not different in either sex. There was, however, a sex-related difference in a number of pharmacokinetic characteristics of aspirin both in rabbits and man. Thus, aspirin was absorbed more rapidly, distributed in larger apparent volume and was hydrolysed more rapidly in females. These observations suggest that the sex-related differences in the antithrombotic effects of aspirin seen in clinical studies are not due to differences in the effects of aspirin on the inhibition of platelet function mediated by the inhibition of cyclo-oxygenase in either the platelet or the vessel wall. An effect of aspirin on platelet function independent of the inhibition of cyclo-oxygenase has been described and it is possible that this effect may be influenced by sex-related differences in the pharmacokinetics of aspirin.

PMID: 6221436 [PubMed - indexed for MEDLINE]

Digoxin

Female gender differences in response to therapy

- Differences in enzyme activities involved in drug metabolism
- Lower glomerular filtration rate
- Lower body weight
- Smaller organ size (heart size is less in women!!)
- Higher proportion of fat
- Different endogenous hormone levels



Digoxin concentrations
> 2.0 ng/mL

2.3% of men
3.4% of women

Torsades des pointes in patients receiving sotalol

1.9% of men
4.1% of women

Whitley H & Lindsey W . Am Fam Physician. 2009

Factors prolonging the QT interval and possibly or probably increasing the risk of cardiac arrhythmias developing after macrolide administration

Risk factor category	Examples
Genetic	Long QT syndrome Unidentified channelopathies Female gender
Underlying cardiac disease	Bradycardia Congestive heart failure Baseline QT prolongation Myocardial ischemia and infarction Cardiomyopathies Atrial fibrillation
Metabolic abnormalities	Hypokalemia Hypomagnesemia Hypocalcemia Acute hypercapnia and/or hypoxia
Taking other medications with risk of QT prolongation without dose adjustment when metabolism or clearance of these medications is impaired	Renal or hepatic insufficiency Genetic polymorphisms Concurrent cytocrome P450 inhibitors
Administration of multiple drugs with QT liability	As summarized in Reference 8

Albert RK et al., Am J Respir Crit Care Med, 2014

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Gender disparity in cardiac electrophysiology: Implications for cardiac safety pharmacology

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A B S T R A C T

Background: Gender differences in cardiac electrophysiology were reported for the first time almost a century ago. The importance for safety pharmacology became significant when modern medicine came into use and women appeared to be more susceptible to drug-induced Torsade de Pointes (TdP). To unravel the underlying mechanisms, the effect of sex hormones on cardiac electrophysiology has been studied in humans, animals and cell models. In this review, these data have been summarized and discussed in regard to possible consequences for safety pharmacology testing.

Results: In man, electrophysiological differences become apparent during adolescence when the QTc interval shortens in males. This protective effect for long-QT related arrhythmias can be correlated to testosterone levels. Testosterone likely suppresses I_{CaL} and enhances I_K which increases the repolarization reserve. Though progesterone may have similar effects in women, these effects are probably balanced out by the small but opposite effects of estrogen. Progesterone levels, however, vary importantly throughout the different phases of the human menstrual cycle, implying that the sensitivity for drug-induced TdP changes too. The consequences for drug safety testing and TdP have not been assessed.

Conclusion: The testosterone-mediated increase in repolarization reserve in men is a likely cause for their lower susceptibility to drug-induced TdP. For the female population, the shifting balance in estrogen and progesterone creates temporal variation in the lability of repolarization to drug-induced TdP. This is a possible confounding factor in the evaluation and comparison of drugs that has to be further tested.

Donne e reazioni avverse a farmaci (ADRs)

- Le donne hanno un rischio maggiore, variabile da 1,5 a 1,7 volte, di sviluppare ADRs rispetto agli uomini
- Il 59% dei ricoveri dovuti a ADRs si riferisce alle donne
- Fattori che possono concorrere sia alla frequenza che ad una maggiore gravità delle ADRs sono i seguenti:
  - Maggiore suscettibilità della donna a specifiche condizioni patologiche farmaco-indotte (ad es. *torsades de point*, aritmia ventricolare)
  - Diversità farmacocinetiche, farmacodinamiche e maggiori interazioni farmacologiche per politerapie
  - Posologie studiate per soggetti di sesso maschile (spesso giovani volontari sani) e di peso medio intorno ai 70 kg
  - Fluttuazioni ormonali in relazione alle fasi della vita riproduttiva
  - Carenza di studi preclinici e clinici genere orientati

Pirmohamed M et al., BMJ 2004; Christianson M et al., Health Care for Women International, 2012; Shah K et al., Am J Physiol Cell Physiol 2014

CLINICAL TRIALS
Gender differences in clinical registration trials: is there a real problem?

Proportion of women in clinical studies, according to development phase

Phase	No. of drugs	Females/total	%	Unknown gender (%)
Phase I	9	788/3600	22	18
Phsase II	9	3477/7268	48	12
Phase I/II	29	3024/11881	25	31
Phase III	38	71049/145296	49	7
Total	38	78338/168045	47	9

Labots G et al., Br J Clin Pharmacol, 2018

Women encounter adverse drug reactions (ADRs) more often than do men

ADRs distribution rate and risk ratio

Population	Male *n* [a] (%)	Female *n* [a](%)	OR[b] 95% CI	*P* value
Overall (adjusted to age)	361 (26.6)	413 (40.8)	1.60 (1.31–1.94)	<0.0001
1 (0–24)	37 (15.6)	25 (13.5)	1.07 (0.59–1.96)	0.8215
2 (25–54)	70 (21.5)	41 (28.9)	1.21 (0.74–1.97)	0.4572
3 (55–64)	77 (28.3)	42 (38.5)	1.67 (0.97–2.79)	0.0631
4 (65–75)	85 (29.0)	104 (52.5)	2.32 (1.54–3.48)	<0.0001
5 (>76)	92 (39.8)	201 (53.2)	1.60 (1.13–2.26)	0.0085

OR, odds ratio, CI confidence interval; [a] number of patients with at least one ADR; [b] adjusted to number of prescribed drugs

Zopf Y et al., Eur J Clin Pharmacol, 2008

Segnalazioni spontanee di ADRs in funzione di sesso ed età*

FASCIA DI ETA’	Uomini	Donne	Totale
MENO DI 1 MESE	9	4	13
DA 1 MESE A MENO DI 2 ANNI	654	570	1.224
DA 2 A 11 ANNI	621	1.793	2.414
DA 12 A 17 ANNI	194	562	756
DA 18 A 64 ANNI	3.752	5.495	9.211
DA 65 ANNI	3.646	4.206	7.852
TOTALE	8.876	12.594 (59%)	21.470

* Rete Nazionale Italiana di Farmacovigilanza 2011

Esempi di classi di farmaci maggiormente responsabili di ADRs in relazione al genere

- Anticoagulanti (ad es. warfarin, acido acetilsalicilico, nuovi anticoagulanti orali)
- Antiaritmici (ad es. digossina, sotalolo)
- Anti-infiammatori non steroidei (FANS)
- Antibiotici (ad es. fluorochinoloni, macrolidi)
- Antivirali (ad es. anti-HIV)
- Antitumorali (ad es. fluoropirimidine)
- Farmaci psicotropi
- Ipoglicemizzanti (ad es. tiazolidinedioni)
- Anti-istaminici
- Analgesici oppioidi

Sex differences in innate Immunity and its impact on opioid pharmacology

Doyle HH and Murphy AZ

- Clinical and animal models investigating sex differences in pain and analgesia demonstrate that morphine is a more potent analgesic in males than in females
- In addition to binding to the neuronal mu opioid receptor, morphine binds to the innate immune receptor TLR4, located on glial cells initiating a neuroinflammatory response that directly opposes morphine analgesia
- Females of many species have a more active immune system than males
- On the other hand women consistently experience higher incidence of side effects including nausea, dysphoria, headache, and vomiting

J Neurosci Res, 2017

Macrolides – Untoward Effects

- **Hepatotoxicity** — 0.4-2/10,000 treated pts
  (Cholestatic hepatitis: jaundice, nausea, vomiting, and abdominal cramps, fever leukocytosis, elevated transaminases)
- **Gastrointestinal toxicity** — 3-20%
  (abdominal cramps, nausea, vomiting and diarrhea)
  Stimulation of GI motility (motilin receptors)
- **Cardiac toxicity**
  (cardiac arrhythmias, QT prolungation, ventricular tachycardia)
  Risk factors; prolonged QT syndrome, lypokalemia or lypomagnesemia, profound bradycardia, antiarrythmics (e.g., quinidine, procainamide, amiodarone) or other drugs that prolong QTc (e.g., cisapride, primozide)
- **Other toxic and irritative effects**
  - Allergic reactions (rare)
  - Transient auditory impairment (rare, high i.v. doses)
  - Visual disturbances in $\simeq$ 1% pts treated with telitromydin (blurred vision, difficulty focusing, diplopia)
- **Drug interactions**

Goodman and Gilman's – The Pharmacological Basis of Therapeutics, 12° Ed, 2011

Incidence of sudden cardiac death in subjects taking oral antibiotics with or without CYP3A inhibitors

Medication(s)	Deaths	Person-years of follow-up	Incidence ratio (95% CI)
Erythromycin with or without CYP3A inhibitor	10	5,305	2.01 (1.08-3.75)
Amoxicillin with or without CYP3A inhibitors	8	6,846	1.18 (0.59-2.36)
No antibiotic with or without CYP3A inhibitors	1,358	1,126.013	1.00
Erythromycin with CYP3A inhibitor	3	194	5.35 (1.72-16.64)
Erythromycin without CYP3A inhibitor	7	4,874	1.79 (0.85-3.76)
Amoxicillin with CYP3A inhibitors	0	254	0
Amoxicillin without CYP3A inhibitors	8	6,304	1.48 (0.74-2.97)
No antibiotic with CYP3A inhibitors	116	36,518	0.93 (0.76-1.13)
No antibiotic without CYP3A inhibitors	1235	1,163,087	1.00

Albert RK et al., Am J Respir Crit Care Med, 2014

Fluroquinolones' drug-drug interaction

Drug	Effect
Anti-acids/bismuth Cimetidine/ranitidine Iron/vitamines	↓ Quinolone bioavailability
Theophylline /caffeine	↑ Methylxanthine serum levels
Warfarin	↑ Warfarin serum levels
Phenazone (antipyrine)	↑ Phenazone serum levels
Opioids	↑ Opioid sereum levels
Digoxin	↑ Digoxin serum levels
Fenbufen	↑ Risk of CNS stimulation
Probenecid	↑ Quinolone serum levels

N.v. Rosenstiel and D. Adam, Drugs, 1994

Moxifloxacina

Valori medi dell'intervallo QT dopo 2h dalla somministrazione orale in 18 soggetti

* P<0.05 vs placebo

Demolis JL et al., Clin Pharmacol Ther, Dec. 2000

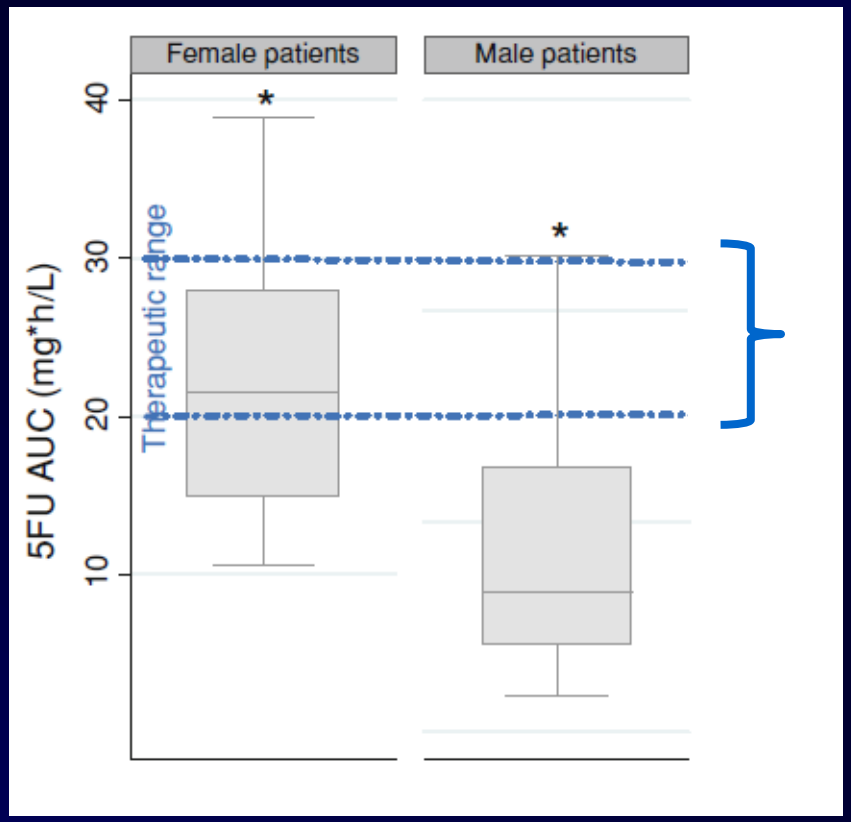
Gender and cancer: the involved areas

- Representation into phase I–II clinical trial
- Pharmacogenetics/pharmacogenomics variability gender-related
- The prevalence and characteristics in certain types of cancer
- The efficacy/toxicity of chemotherapy drugs and biological targeted therapy
- Diversity-related symptoms and their treatment (e.g., pain)
- Impact of comorbidities
- Impact of cancer on relational, social, and family role and caregiver

Baggio G et al., Clin Chem Lab Med, 2013

Gender-specific elimination of continuous-infusional 5-fluorouracil in patients with gastrointestinal malignancies: results from a prospective population pharmacokinetic study

Distribution of 5-fluorouracil area-under-the concentration-time curve (5FU AUC) (mg h/L) (b)*



Toxicity

Therapeutic range

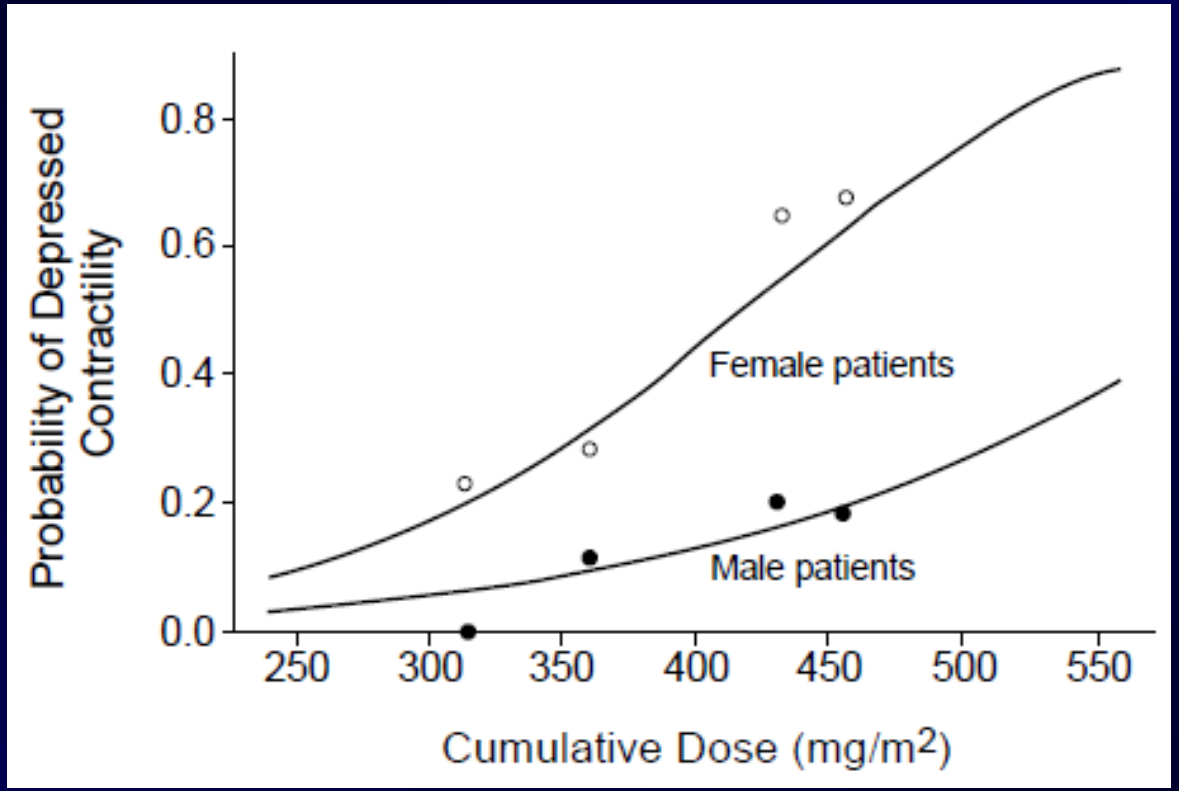
Women have a significantly higher 5FU AUC as compared to men (22 vs. 18 mg h/L, p = 0.04 for Student's T test). The recommended therapeutic range of 5FU AUC is between 20 and 30 mg h/L

Muller et F al ., Cancer Chemother Pharmacol, 2013

Female sex and higher drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer

Probability of Depressed Contractility as a Function of the Cumulative Dose of Doxorubicin in Female and Male Patients

N **= 87 children with ALL**
N **= 33 adult patients with osteogenic sarcoma**



Lipshultz SE et al., New Engl J Med, 1995

Influence of Sex on Treatment Outcome in Small-Cell Lung Cancer

Table 7. Comparison of Response and Survival, by Sex

	Female Patients (n = 319)		Male Patients (n = 564)		
	No.	%	No.	%	*P*
Response					< .0001
Overall	256	80.3	377	66.9	
Complete response	169	53.0	186	33.0	
Partial response	87	27.3	191	33.9	
Stable disease	11	3.4	47	8.3	
Progressive disease	52	16.3	140	24.8	
Survival					< .0001
Median, years	1.31		0.91		
95% CI	1.17 to 1.43		0.87 to 0.97		

Singh S et al., J Clin Oncol, 2005

Influence of Sex on Toxicity and Treatment Outcome in Small-Cell Lung Cancer

Comparison of toxicity by patient sex (I)

	Sex				
	Female (n = 358)		Male (n = 647)		
	No.	%	No.	%	*P*
Nonhematologic toxicity					
≥ grade 1					
Stomatitis	60	16.8	54	8.3	< .0001
Emesis	275	76.8	435	67.2	.0014
Infection	50	14.0	92	14.2	.91
≥ grade 3					
Stomatitis	11	3.1	5	0.8	.0053
Emesis	69	19.3	95	14.7	.059
Infection	16	4.5	87	13.4	.40

Singh S et al., J Clin Oncol, 2005

Influence of Sex on Toxicity and Treatment Outcome in Small-Cell Lung Cancer

Comparison of toxicity by patient sex (II)

	Sex				
	Female (n = 358)		Male (n = 647)		
	No.	%	No.	%	*P*
Hematologic toxicity					
≥ grade 1					
Hemoglobin	200	55.9	250	38.6	< .0001
Platelets	134	37.4	231	35.7	.58
WBC	332	92.7	548	84.7	.0002
≥ grade 3					
Hemoglobin	58	16.2	49	7.6	< .0001
Platelets	39	10.9	53	8.2	.15
WBC	288	80.4	448	69.2	.0001

Singh S et al., J Clin Oncol, 2005

Risk factors at pretreatment predicting treatment-induced nausea and vomiting in Australian cancer patients: a prospective, longitudinal, observational study

Incidence of treatment-induced nausea (TIN) and treatment-induced vomiting (TIV) according to patient and clinical factors

Patient/clinical factor	TIN (n = 119) n (row%)	p	TIV (n = 54) n (row%)	p
Sex				
Male	42 (44.2)	<0.001*	19 (20.0)	0.034**
Female	77 (73.3)		35 (33.3)	
Age				
18–49 years	44 (71.0)	0.027**	23 (37.1)	0.031**
50 years and over	75 (54.3)		31 (22.5)	
Primary diagnosis				
Breast*	43 (74.1)	0.025**	18 (31.0)	0.332
Colorectal	31 (55.4)		11 (19.6)	
Other	45 (52.3)		25 (29.1)	
Treatment duration[a,b]				
≤3 months	24 (38.1)	<0.001*	14 (22.2)	0.32
>3 months	86 (69.4)		36 (29.0)	

*p<0.001; **p<0.05; [a] Patient numbers do not always equal row/column total due to multiple occurrences in patients or missing data; [b] Treatment duration excludes any surgery prior to adjuvant chemotherapy ± radiotherapy received prior to medical oncology presentation

Pirri et al., Support Care Cancer, 2011

Drugs with statistically significant gender differences in bioequivalence

	Variability in AUC (%CV)		Variability in Cmax (%CV)	
	Males	Females	Males	Females
Alprazolam	4.9	29.4		
Drug 2[a]	5.0	10.8		
NAPA	9.0	4.4		
Nitroglycerin	21.3	39.5	13.6	24.4
Phenylacetate	4.3	9.9	6.1	17.4
Cimetidine			26.8	11.8
Ketoprofen			22.2	51.5

NAPA, *N*-acetylprocainamide (major active metabolite of procainamide)
[a] Drug name obscured for trade confidentiality

Koren G et al., Clin Pharmacol Ther, 2013

Test/reference geometric mean differences

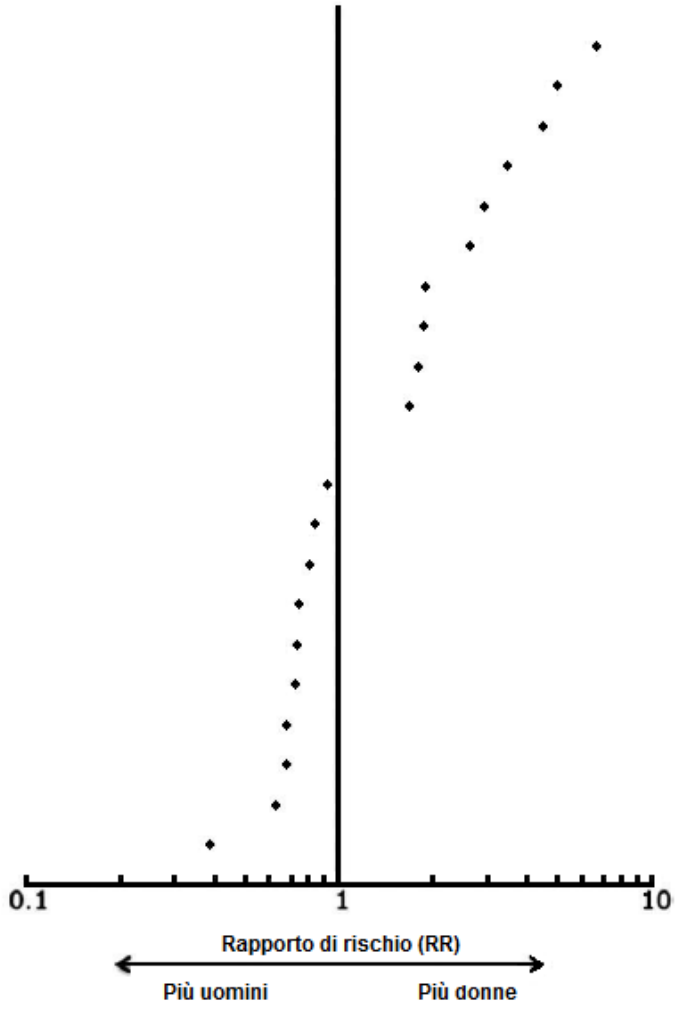
Drug	M – F (%)
Erythromycin	42
Nitroglycerin	16 – 45[a]
NAPA	- 17

NAPA, *N*-acetylprocainamide (major active metabolite of procainamide)
[a] Depending on metabolite (nitroglycerin, 45%; 1,2, nitroglycerin, 16%; 1,3 nitroglycerin, 21%)

Koren G et al., Clin Pharmacol Ther, 2013

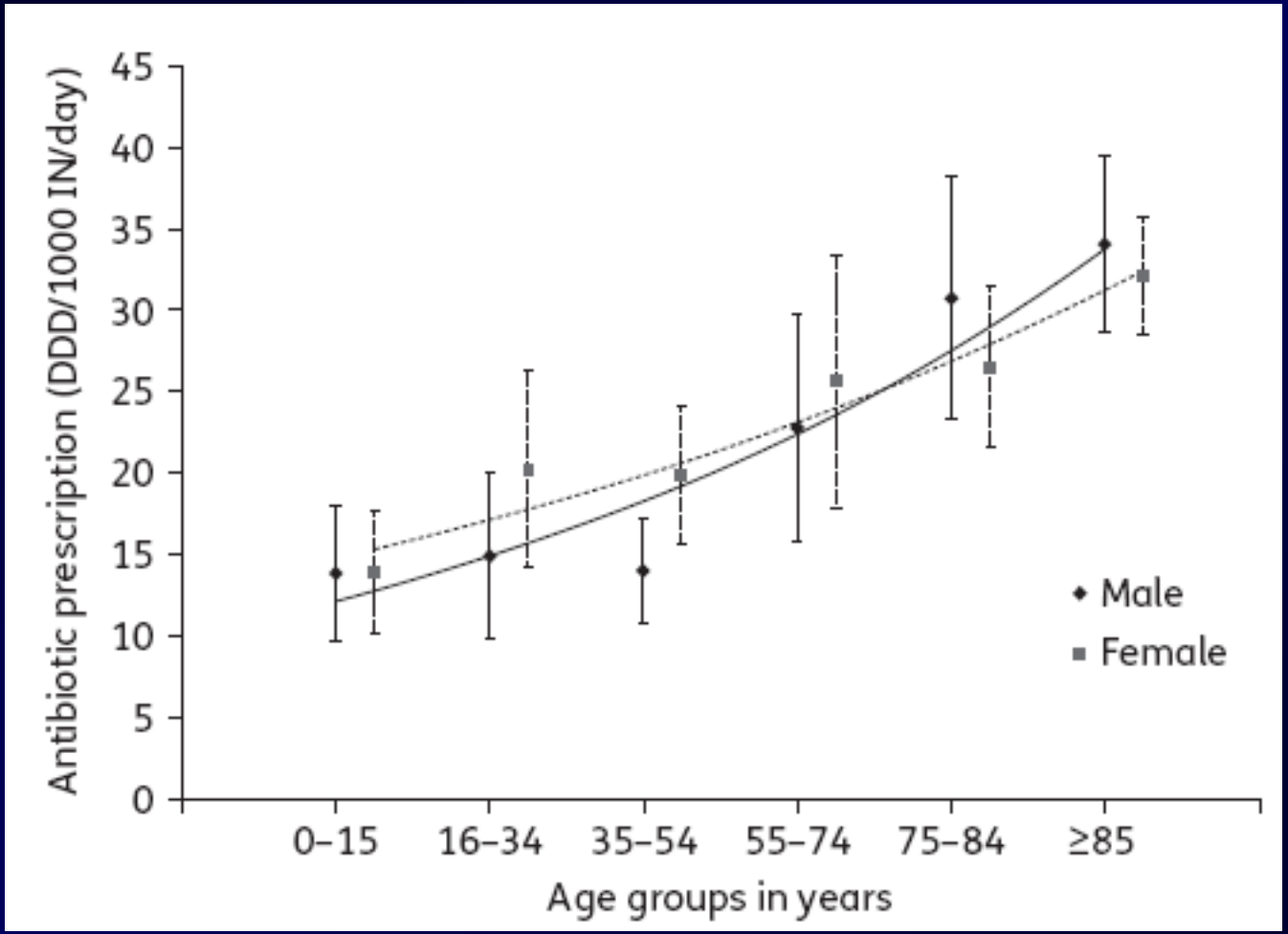
Differenze nella prescrizione dei farmaci M/F in Sweden

ATC	Gruppo farmacologico	Uomini	Donne
J02	Antifungini	2,8	18,9
M05	Farmaci per osteoporosi	3,2	19,3
H03	Farmaci per disfunzioni tiroidee	13,1	65,7
N02C	Farmaci analgesici	5,0	17,2
A12	Supplementi minerali	16,2	57,3
A08	Farmaci antiobesità	1,6	4,1
J05	Antivirali	7,9	14,8
P01	Antiprotozoari	11,0	20,6
N06A	Antidepressivi	55,4	106,6
H01	Ormoni ipofisari e ipotalamici	2,5	4,1
C09C+D	Antagonisti angiotensina II e combinaz	45,2	46,6
C08	Calciotantagonisti	60,8	59,6
C01A	Glicosidi cardiaci	6,0	6,8
C10	Farmaci anti-lipidi	98,0	81,1
C01D	Vasodilatotori	24,9	23,6
B01	Antitrombotici	109,8	97,7
A10	Antidiabetici	45,3	34,5
C09A+B	ACE inibitori	78,1	60,9
N06B	Psicostimolanti	6,9	4,1
M04	Anti-iperuricemici	12,2	5,9



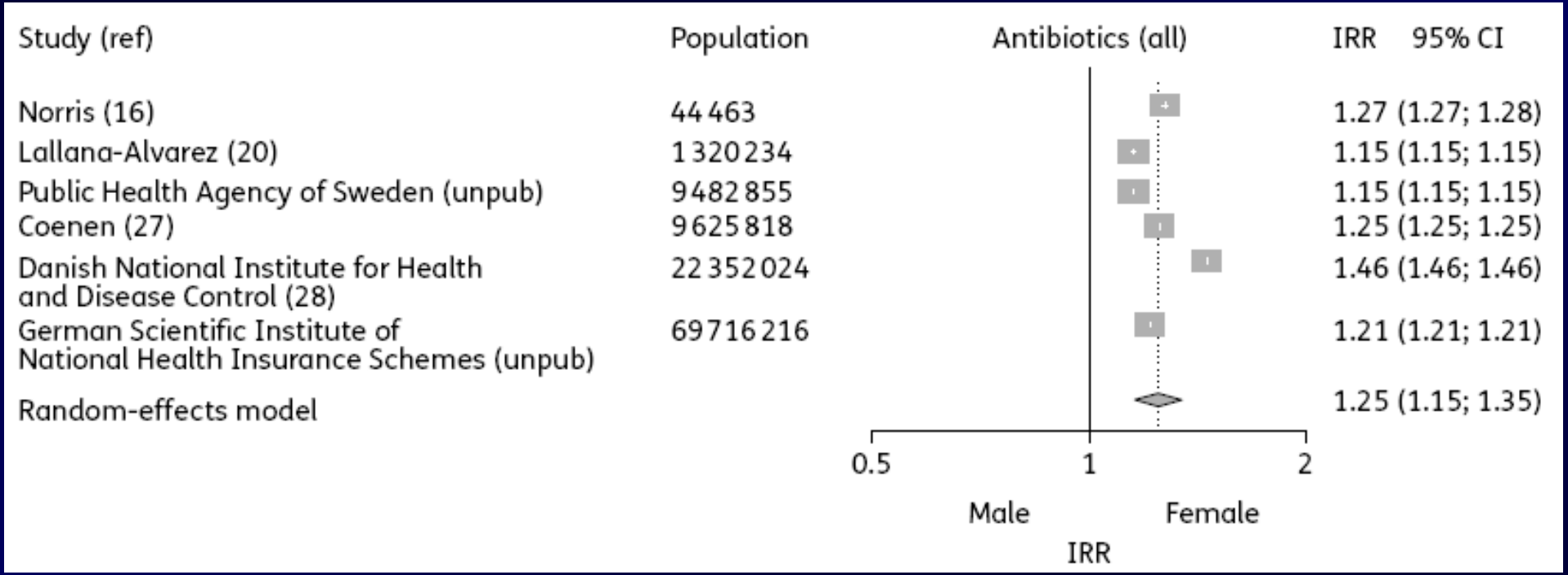
D. Loikas et al., *BMJ Open* , Dec 3, 2013

Pooled estimates of antibiotic prescriptions measured in DDD/1000 IN/day with 95% CI according to age groups and gender



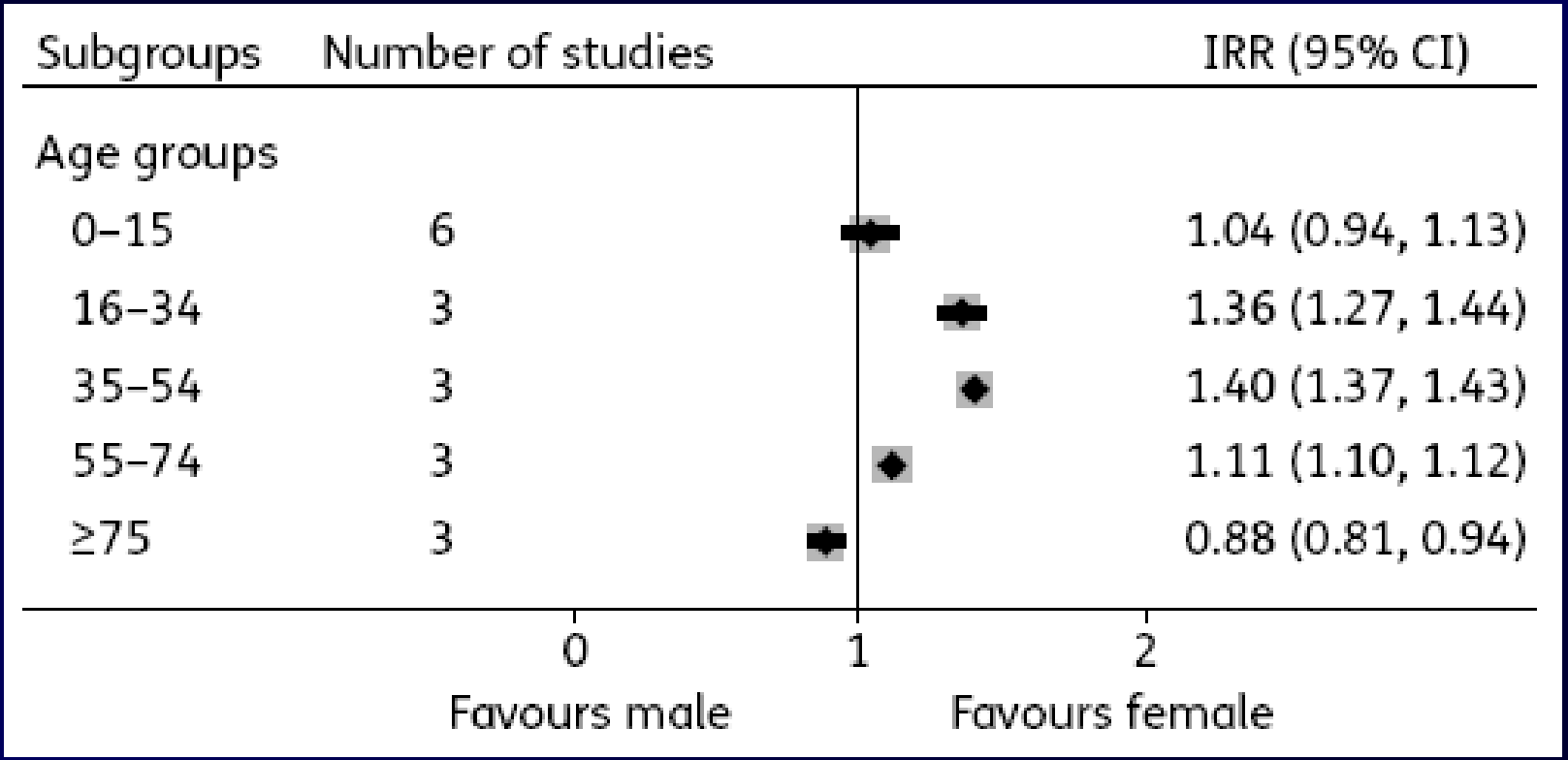
Schröder W et al., J Antimicrob Chemother, 2016

Meta-analysis of antibiotic prescriptions in the community measured as IRR of prescribed DDD/1000 IN/day



Schröder W et al., J Antimicrob Chemother, 2016

Summary forest plot of IRR and 95% CI by age groups



Schröder W et al., J Antimicrob Chemother, 2016

Some drugs that show sex differences in pharmacokinetics during pregnancy

Drug	Pharmacokinetic parameter	Comments
Cefazolin	Clearance, volume of distribution, half-life	Clearance increases during pregnancy
Digoxin	Clearance	Clearance increases during pregnancy, as a result more frequent administration may be needed
Erythromycin	Oral availability	Oral availability decreases during pregnancy, as a result circulating concentrations are decreased
Phenobarbital	Plasma binding, clearance	Plasma binding is unchanged, clearance is increased during pregnancy
Theophylline	Plasma binding, clearance, volume of distribution	Plasma binding decreases during pregnancy. Vd increases as expected from protein binding and changes in physiological spaces. Decreased hepatic clearance is offset by increased renal clearance

Soldin OP & Mattison DR, Clin Pharmacokinet, 2009

Farmacologia di genere

- **Le donne sono le maggiori consumatrici di molte classi di farmaci (es. antidolorifici, antidepressivi, antibiotici, eccetto farmaci cardio vascolari)**

- **Le donne rispondono in maniera diversa rispetto all'uomo ai farmaci (differenze fisiologiche, anatomiche e ormonali)**

- **Le donne mostrano un profilo farmacocinetico peculiare per assorbimento, distribuzione, metabolismo ed eliminazione dei farmaci**

Marazziti D et al., CNS Spectrums, 2013; Franconi F & Campesi I, Expert Rev Clin Pharmacol 2014

Conclusioni

La farmacologia genere-specifica è materia senza dubbio complessa che andrebbe studiata, insegnata e conosciuta maggiormente nel mondo sanitario.