



IL PERCORSO DI AMD per la MEDICINA DI GENERE:

dalle pari opportunità di cura
alla appropriatezza terapeutica

con il patrocinio di



Reggio Emilia
10 e 11 aprile 2015

Centro Internazionale Loris Malaguzzi





Gruppo Donna 2015
**Il percorso di AMD per la medicina di genere:
dalle pari opportunità di cura alla appropriatezza
terapeutica**

Reggio Emilia 10-11 Aprile 2015

**Differenze negli effetti dei farmaci e
genere:
ieri, oggi e domani**

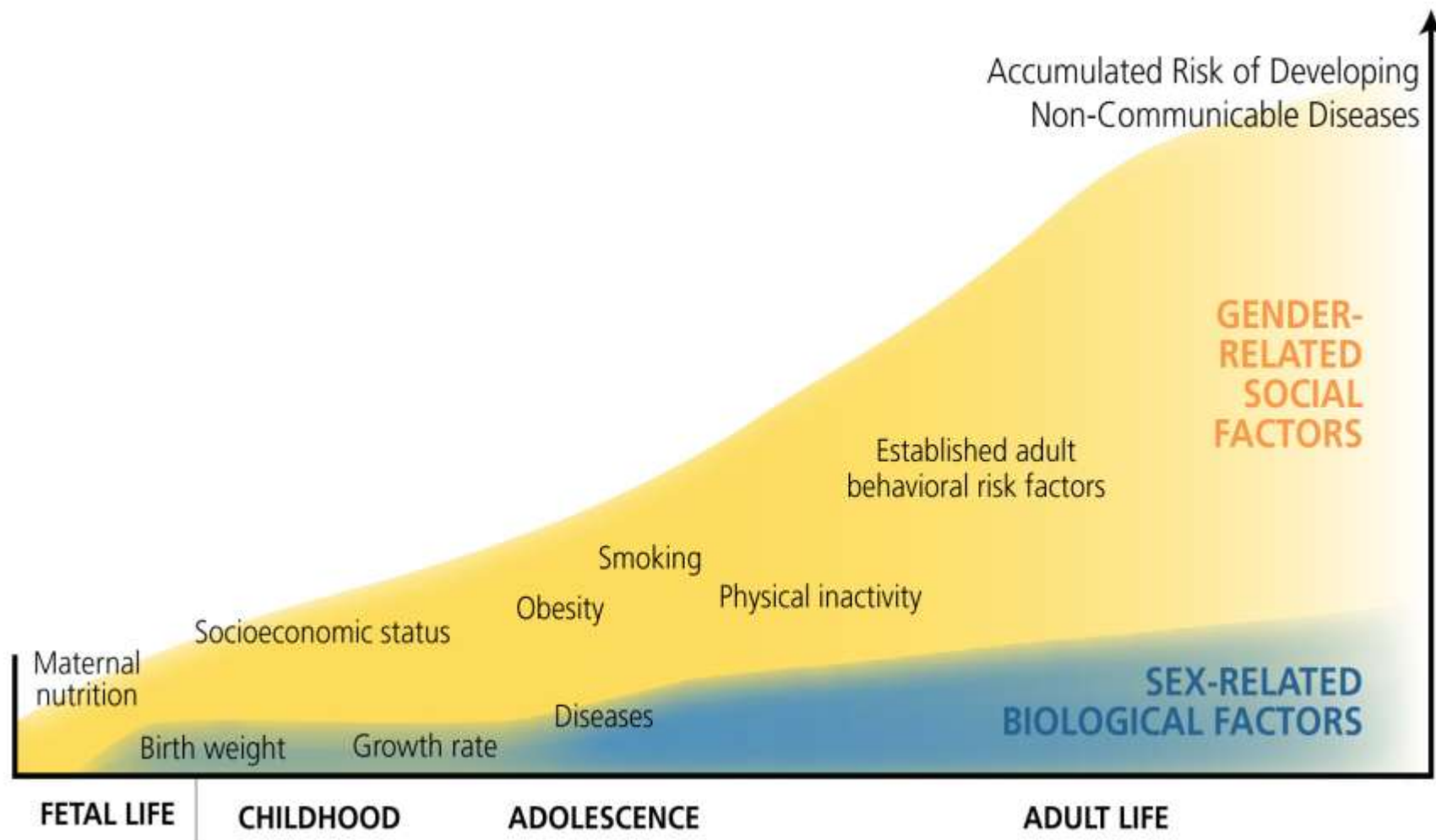
Flavia Franconi

vice presidente – Regione Basilicata



Cumulative Life Course Risk Factors for Non-Communicable Disease (NCD)

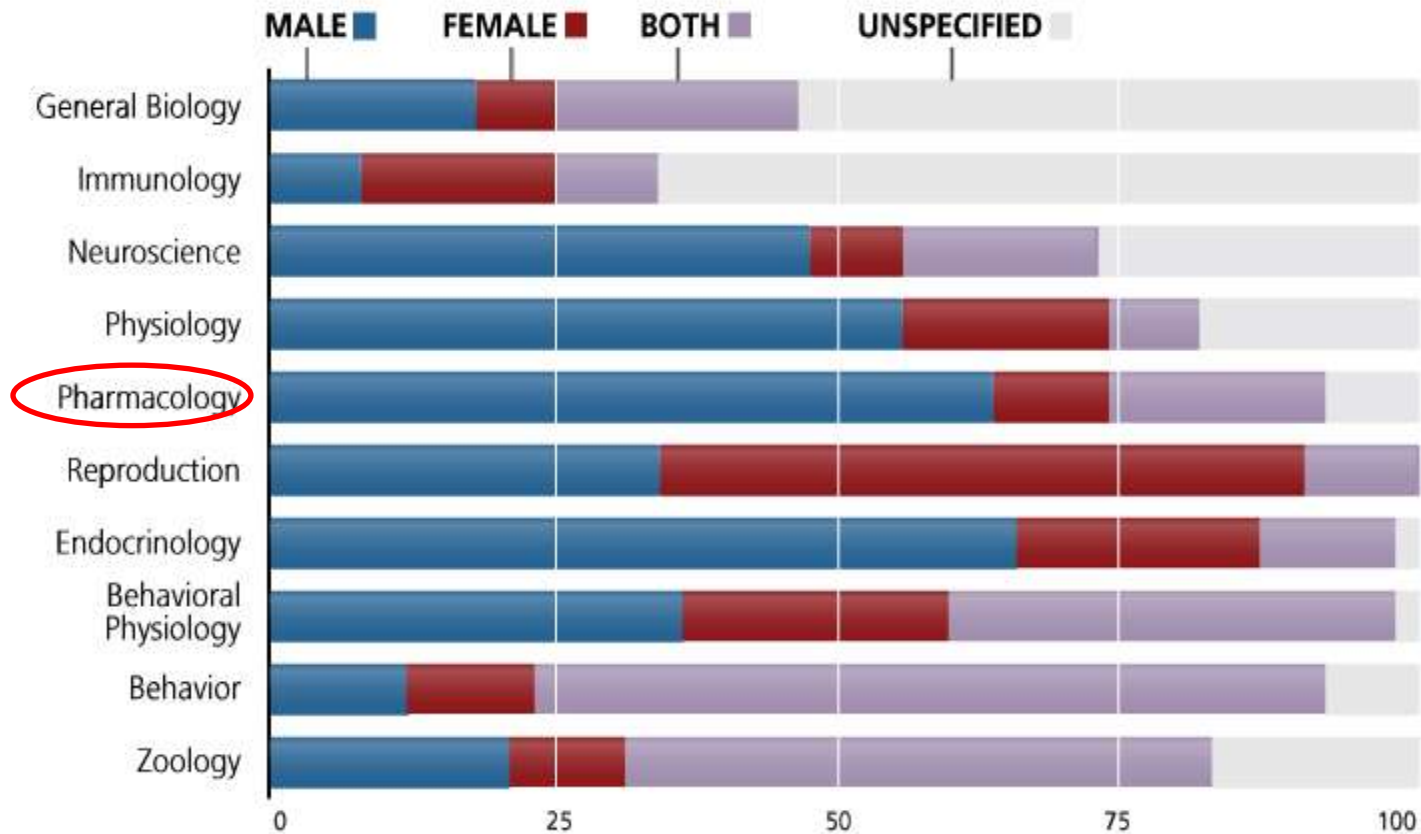
Highlighting the influence of sex and gender-related factors



Adapted from Darton-Hill et al., 2004

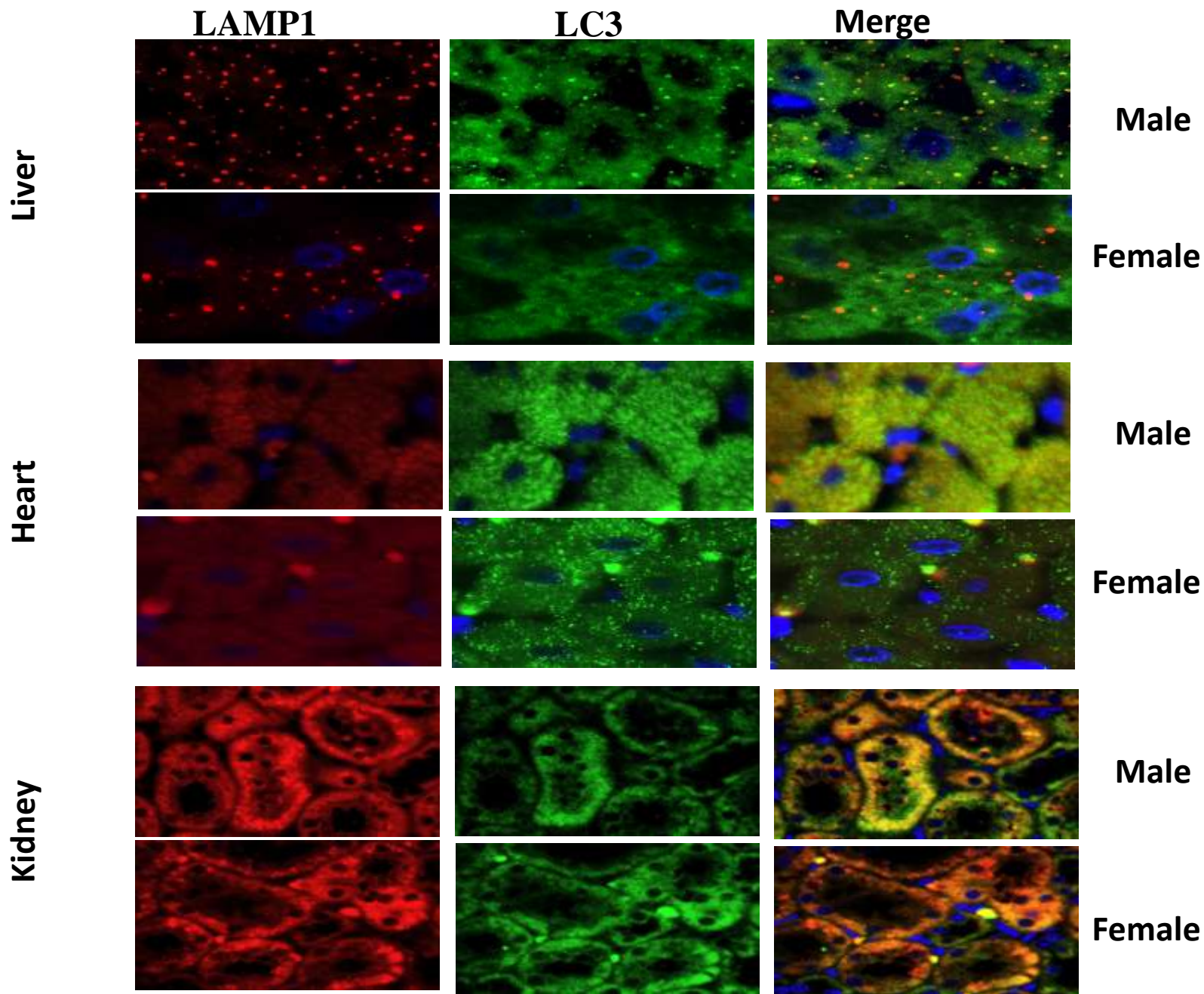
Proportion of Research Studies Using Male and/or Female Animals

From published journal articles within specified biomedical subfield, 2009



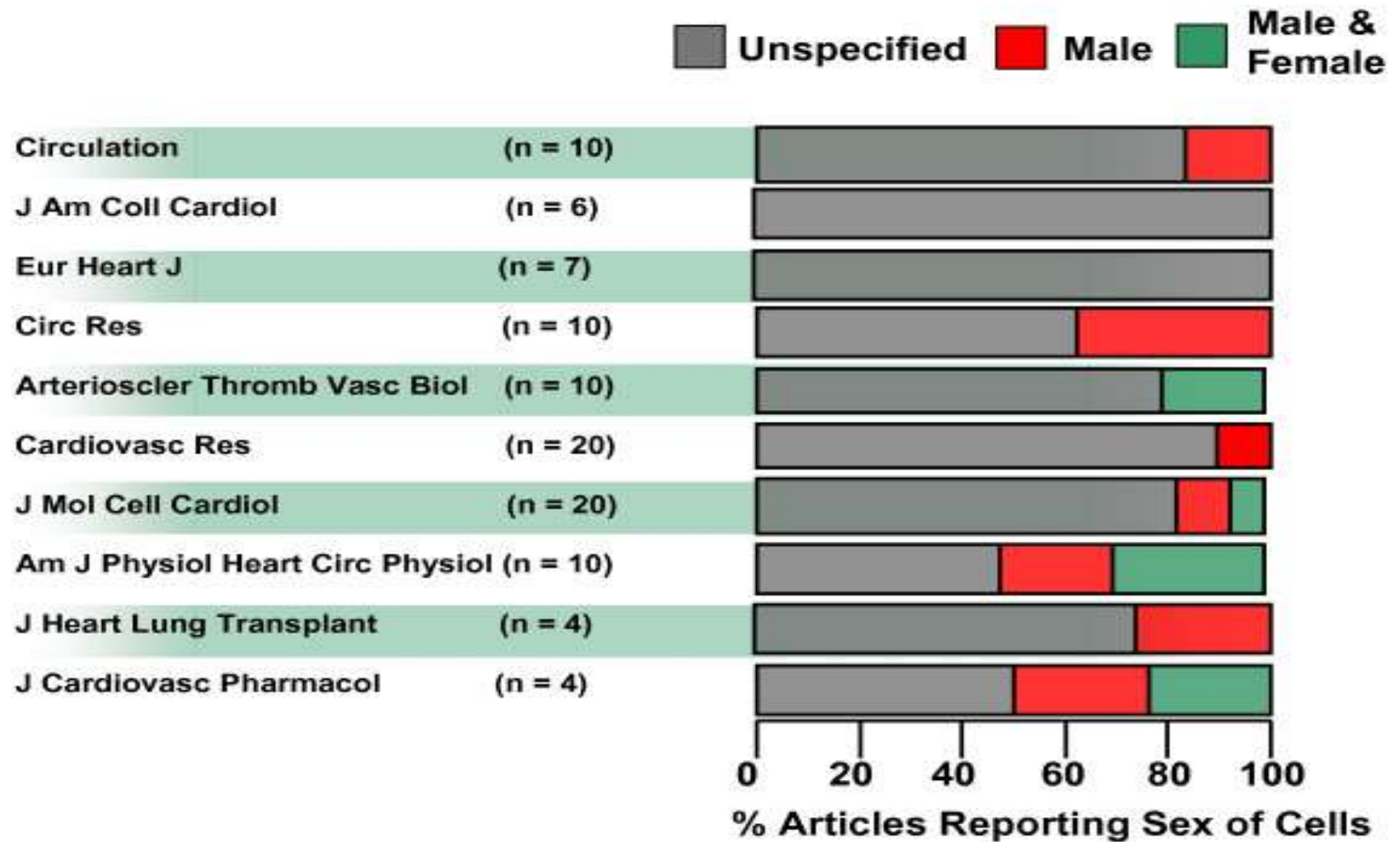
Adapted from Beery et al., 2011

Beery, A., & Zucker, I. (2011). *Neuroscience and Biobehavioral Reviews*, 35 (3), 565-572



Rat

% OF PAPERS REPORTING SEX OF CELLS USED IN THE EXPERIMENTS



Taylor, K et al *Biology of Sex Differences*, 2 (11), 1-7.

HUVEC

VSMC

Migrazione EPCs A 24H: effetto del BPA

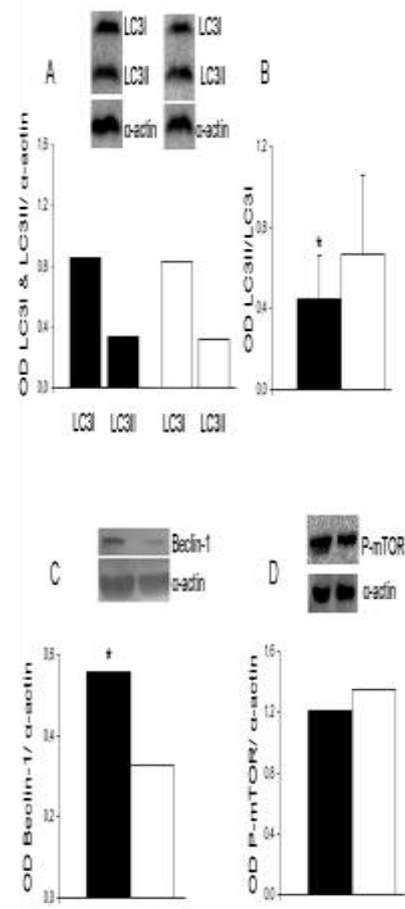
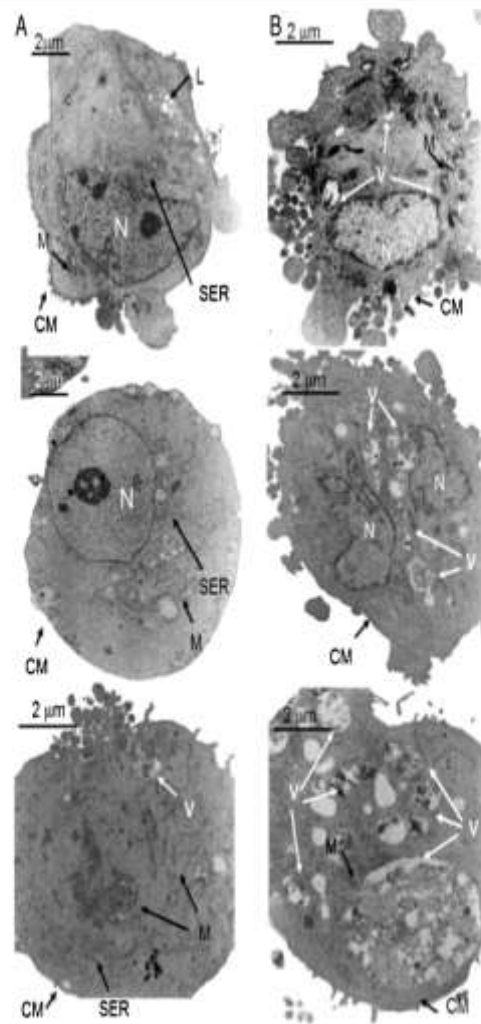
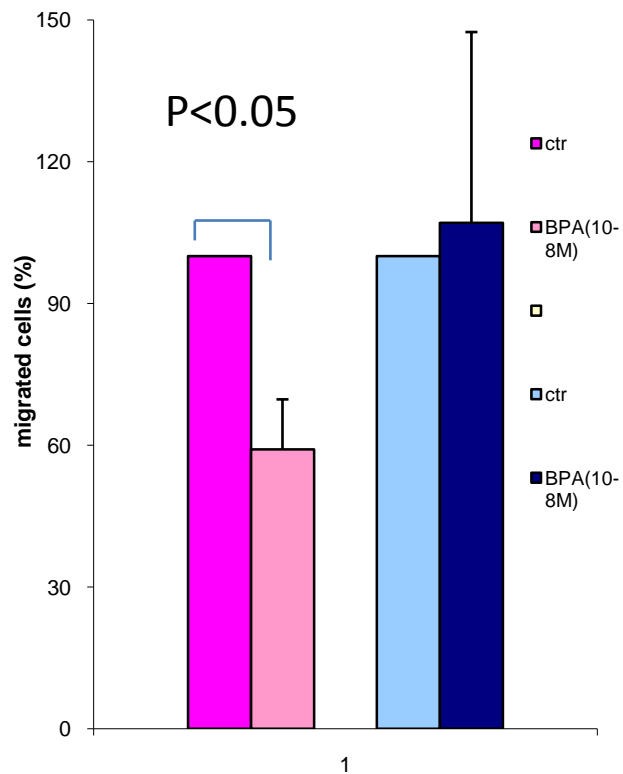


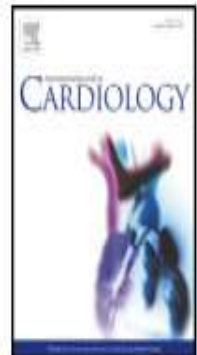
Figure 3 Electron microscopic analysis of HUVECs and VSMCs. (A) HUVECs have little smooth endoplasmic reticulum (SER), abundant lysosomes (L) and a normal cytoplasmic membrane (CM). M and N indicate the mitochondria and nucleus, respectively. (B) VSMCs have abundant autophagic vacuoles (V) in different stages of digestion and a CM with many blebs. M and N indicate the mitochondria and nucleus, respectively. (A) Magnification x 6000, scale bars: 2 μm. (B) Magnification x 4000, scale bars: 2 μm.



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International Journal of Cardiology

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Review

Need for gender-specific pre-analytical testing: The dark side of the moon in laboratory testing



Flavia Franconi ^{a,b,*}, Giuseppe Rosano ^{c,2}, Ilaria Campesi ^{a,3}

^a Department of Biomedical Sciences, University of Sassari, National Laboratory of Gender Medicine of the National Institute of Biostructures and Biosystems, Osilo, Sassari, Italy

^b Vicepresident of Basilicata Region

^c Cardiovascular and Cell Sciences Research Institute, St George's University of London, United Kingdom

Table 5

Questionnaire to be administered to human donors.

Demographic information	Sex Age Actual weight Birth weight Actual height Birth height Race Place of birth Place of house
Lifestyle	Physical activity: how many times a week and type Smoker (yes/no; how long and how many cigarettes/day) Alcohol use (yes/no; type; how many cups/day)
Social status	Occupation Level of education (years) Care giver (h/day)
Health status of subjects	Blood pressure at the time of sampling Diseases at the time of sampling and in the previous 3 months Drug use at the time of sampling and in the previous 3 months (drug type, duration of treatment, generally the use of drug is an exclusion criteria) For women: Oral contraceptives use (how long and type) Date of last menstruation and menstrual cycle phase Pregnancies (number, type) Abortions (number and which month of pregnancy)
Blood collection	Fasting subjects ^a Time of sampling (h) Site of collection, anticoagulants, In fertile women, blood should be collected in the same period of menses cycle

^a Ingestion of food and of some beverages can influence the composition of blood, plasma, and serum [459].

Table 6

Questionnaire to be administered to professionals before the use of animals or animal cells.

Demographic information	Sex Age Actual weight Species
Environmental information	Diet type and parent diet Cross fostering Maternal care and weaning Travelling, stabilisation, acclimatisation period Housing, isolation, spacing and environmental enrichment
Health status of subjects Blood collection	Evaluation of health status Fasting subjects* Time of sampling (h) Site of collection, anticoagulants, blood volume, anaesthesia restraint, handling Blood should be collected in the same oestrous phase determined by vaginal examination

Ingestion of food and of some beverages can influenced the composition of blood, plasma, and serum [459]

Clinical studies have been mainly performed in men

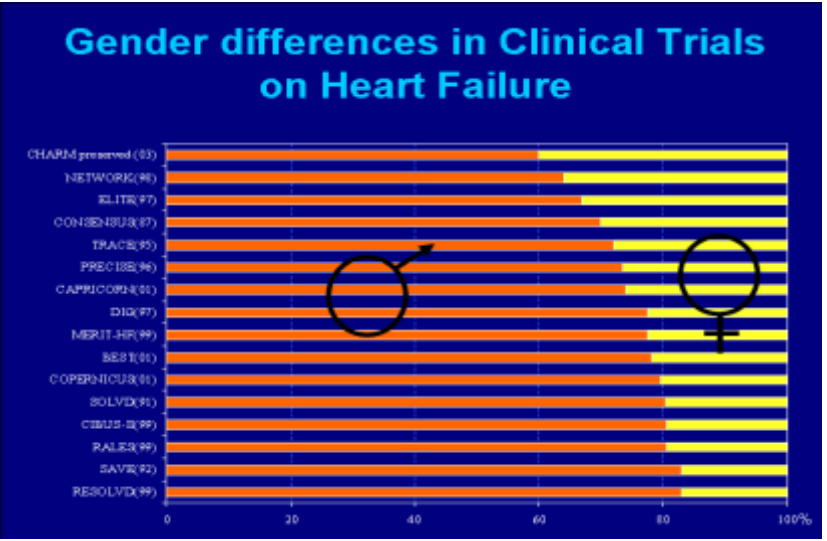
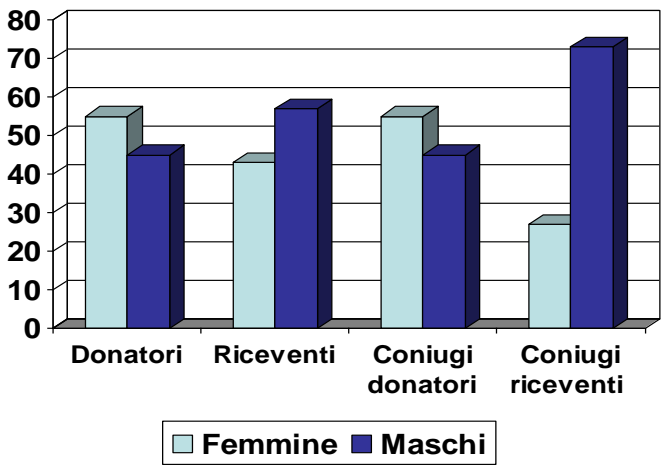
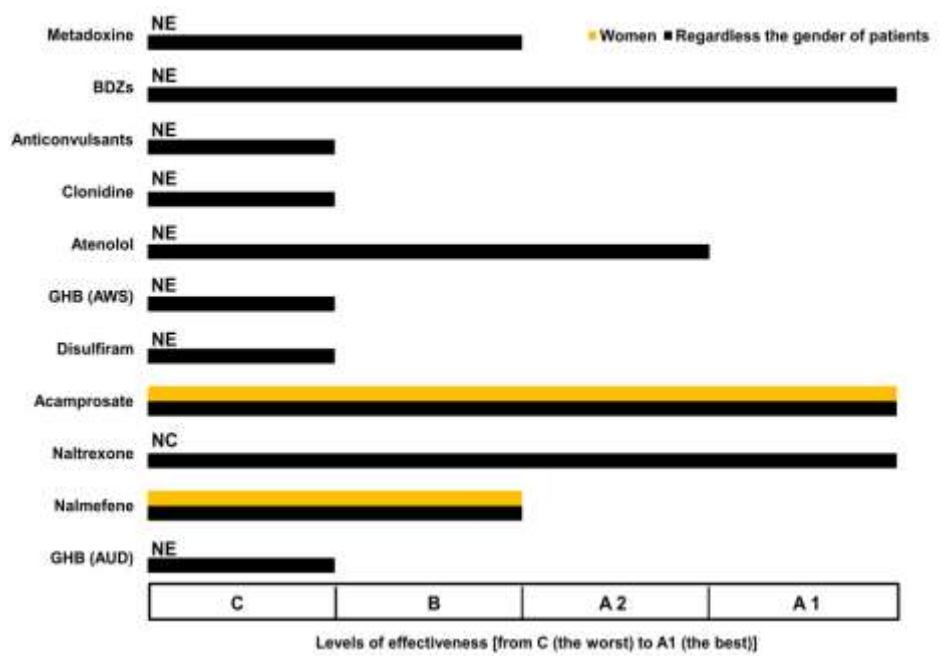
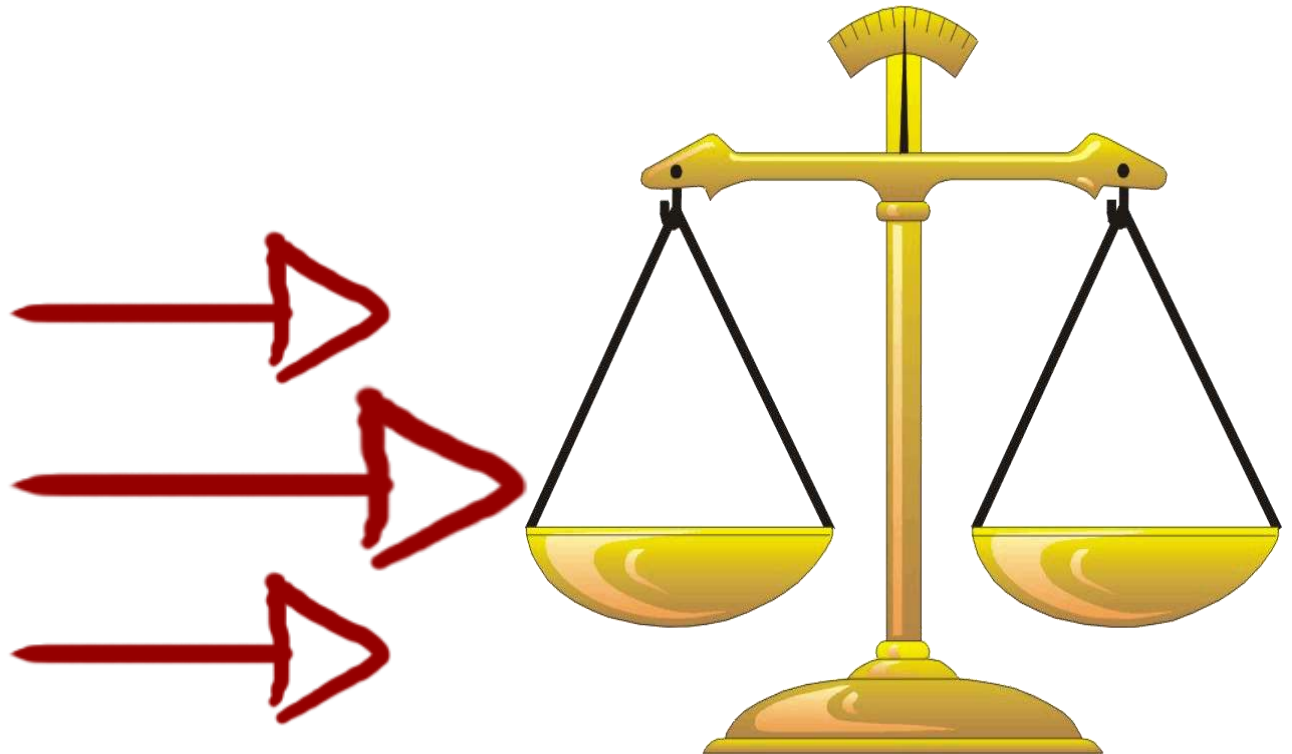


Figure 4

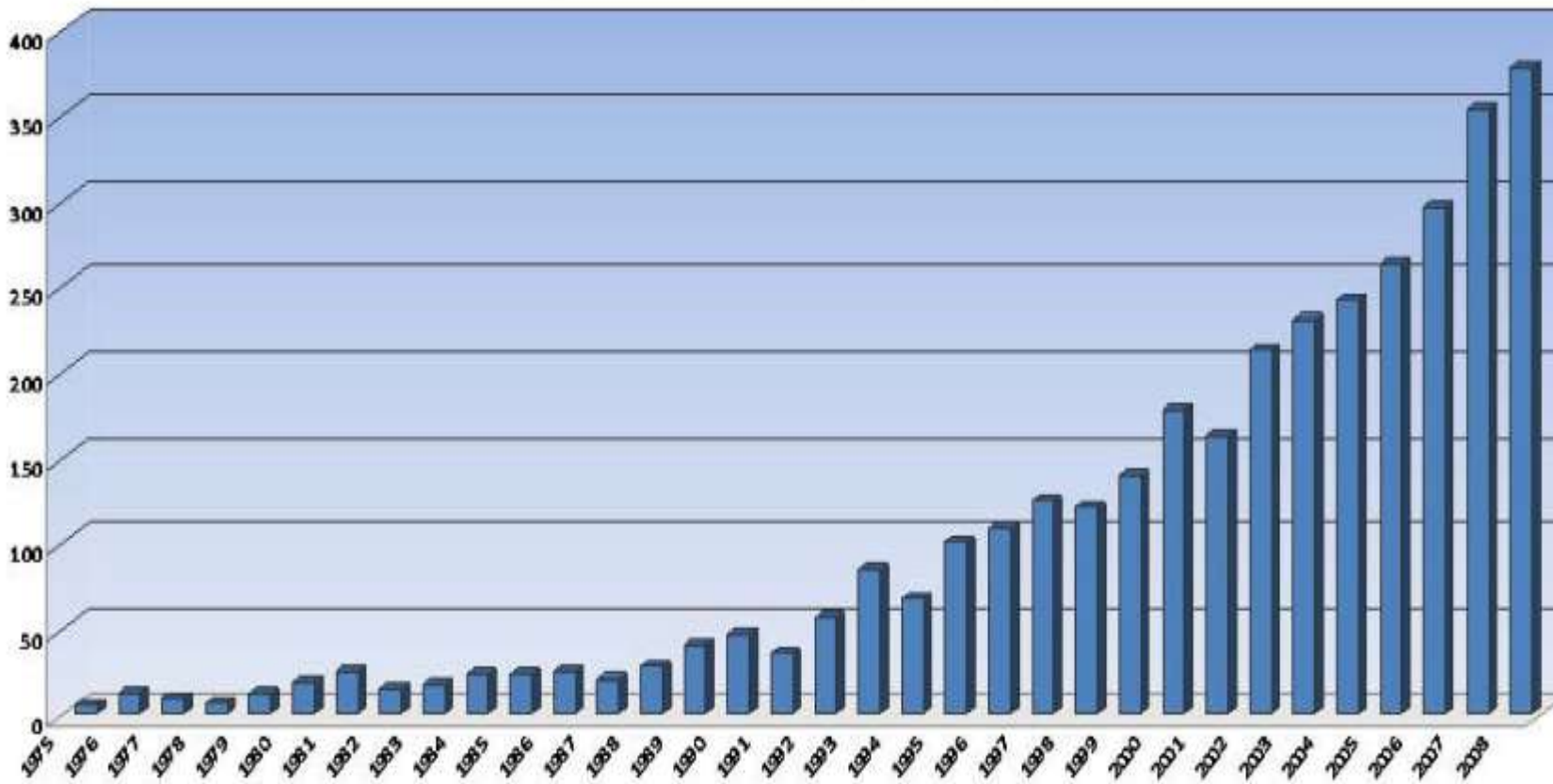
Effectiveness of medications used to treat Alcohol Use Disorder



**1° Take Home message:
E' tempo di bilanciare il reclutamento sia negli
studi preclinici che clinici**



Publication trends (n= 3,466)

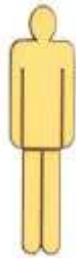


Oertelt-Prigione et al. BMC Medicine
2010, 8:70

SPECIFIC WOMEN ASPECTS

- Menstrual cycle (it can varies the drug metabolism)
- The presence of critical periods (pregnancy, puerperium, menopausa ecc.)
- Oral anticonceptionals use and HRT use
- Care giver and other stressors

Ranitidine



Parameters		in follicular phase	in luteal phase
AUC (ng/ml/h)	11471.9	7312.15	5195.83
clearance l/kg/h		0.65	0.59
Vd (l/kg)		2.0	5.6 1
Cmax (ng/ml)		1086	864

Table 5 Menstrual cycle and fluid balance in age-matched, young adults

Parameter	Males vs. females in early follicular (EF), ovulatory (OV), and mid-luteal (ML) phases	Reference
Systolic blood pressure	$M > [F_{EF} = F_{OV} = F_{ML}]$	3,43
Stroke volume	$M > [F_{EF} = F_{OV} = F_{ML}]$	43
Cardiac output	$[M = F_{ML}] > [F_{EF} = F_{OV}]$	
Plasma volume	$M < [F_{EF} = F_{ML}] < F_{OV}$	
Blood volume	$M < [F_{EF} = F_{ML}] < F_{OV}$	
Vascular conductance (skin, thigh, femoral)	$M = F_{EF} = F_{OV} = F_{ML}$	

Il nodo della sperimentazione

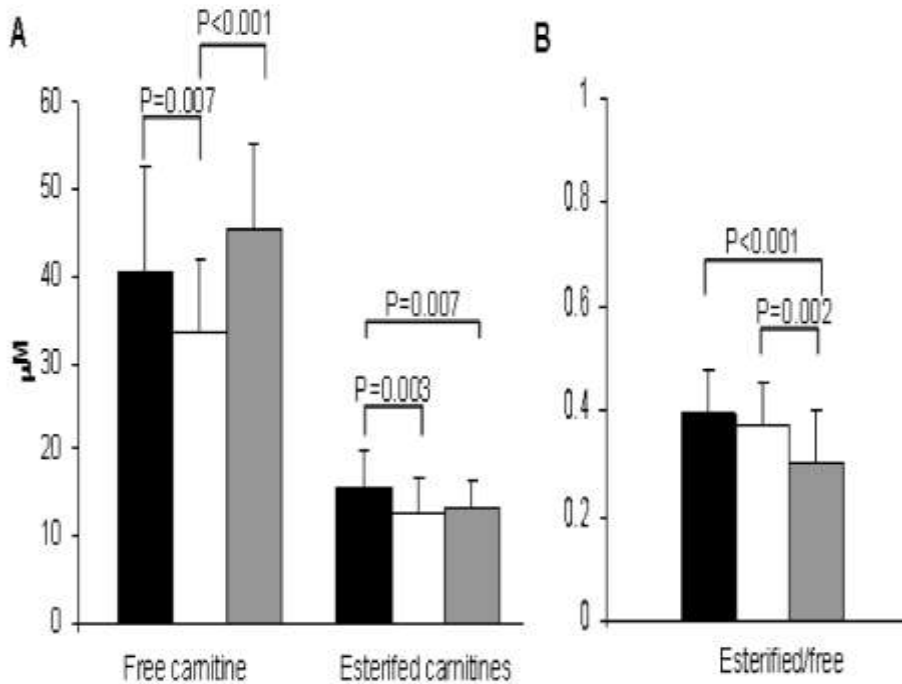


Figure 3

black bars = women, white bars = OC users ; grey bars = men

a) Sex induces specific alteration in the serum metabolome suggesting the need to have reference values for women

b) OC use induces specific alterations in the serum metabolome suggesting that both OC users and non-users should be represented in clinical trials.

Taken together, our results highlight the need to have reference values for women and men

Ruoppolo M, Campesi I, Scolamiero E, Pecce R, Caterino M, Cherchi S, Mercurio G, Tonolo G, Franconi F Am J Transl Res. 2014 Oct 11;6(5):614-24.

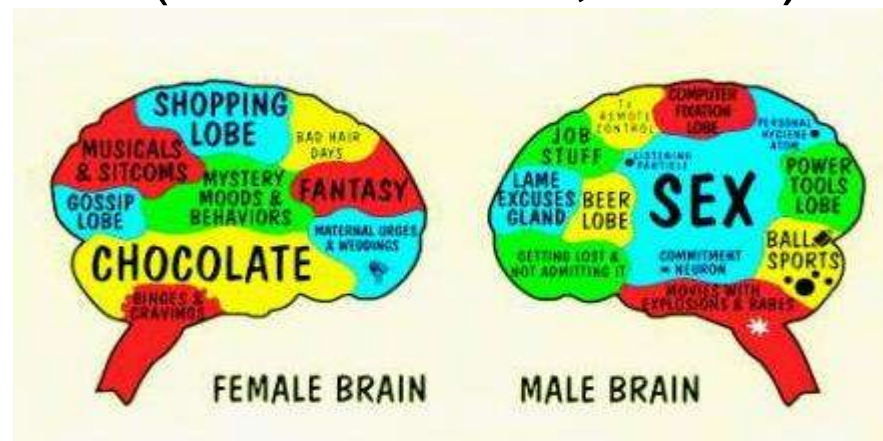
Menopause and drug efficacy

GASTROENTEROLOGY 2011;140:818-829

Early Menopause Is Associated With Lack of Response to Antiviral Therapy in Women With Chronic Hepatitis C

ERICA VILLA,* AIMILIA KARAMPATOU,* CALOGERO CAMMÀ,[‡] ALFREDO DI LEO,[§] MONICA LUONGO,* ANNA FERRARI,* SALVATORE PETTA,[‡] LUISA LOSI,* GLORIA TALIANI,^{||} PAOLO TRANDE,[¶] BARBARA LEI,* AMALIA GRAZIOSI,* VERONICA BERNABUCCI,* ROSINA CRITELLI,* PAOLA PAZIENZA,[§] MARIA RENDINA,[§] ALESSANDRO ANTONELLI,[#] and ANTONIO FRANCAVILLA[§]

Il sistema dello stress lavora in maniera sesso/genere specifica. Quindi lo stesso stimolo può indurre una risposta diversa nella donna e nell'uomo (**Bangasser, Valentino, 2012**). Conseguentemente il ruolo di *care giver* può avere effetti differenti sull'uomo e sulla donna. Pertanto non deve meravigliare che le persone che esercitano la funzione di care giver rispondono di meno (minor risposta anticorpale) alle vaccinazioni (**Glaser et al, 2000**).





A.D. MDLXII

UNIVERSITÀ
degli STUDI
di SASSARI



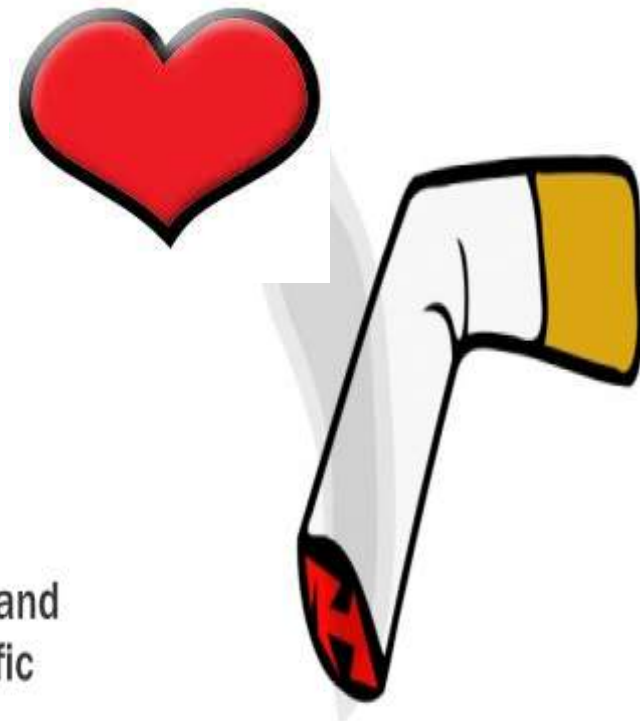
**Laboratorio
Nazionale
di Medicina di
Genere
INBB-Osilo-
Sassari**

Am J Transl Res 2013;5(5):497-509
www.ajtr.org /ISSN:1943-8141/AJTR1305011

Original Article

**Regular cigarette smoking influences the
transsulfuration pathway, endothelial function, and
inflammation biomarkers in a sex-gender specific
manner in healthy young humans**

Ilaria Campesi^{1,2}, Ciriaco Carru², Angelo Zinellu², Stefano Occhioni², Manuela Sanna², Mario Palermo³,
Giancarlo Tonolo⁴, Giuseppe Mercuro⁵, Flavia Franconi^{1,2}

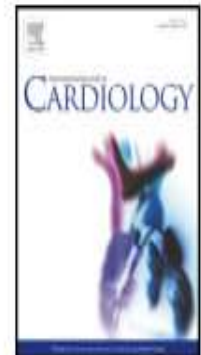




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Farmacogenetica

Il polimorfismo del gene ApoE è predittivo della risposta alla atorvastatina . Infatti, gli uomini, ma non le donne, carrying the epsilon2 allele del Gene dell'ApoE rispondono alla atorvastatina rispetto a coloro che hanno epsilon3 homozygotes e epsilon4 carriers (Pedro-Botet J et al Atherosclerosis. 2001 Sep;158(1):183-93.)

DIADE

I medici sia specialisti che di famiglia attribuiscono più frequentemente un fattore di rischio cardiovascolare più basso alle donne ad alto rischio e ciò altera significativamente il percorso terapeutico (Mosca L et al, Circulation 2005;111:499 e 510; Turnbull F et al Eur J Cardiovasc Prev Rehabil 2011;18:498 e 503).

Le donne diabetiche sono più trattate se seguite da un cardiologo di sesso femminile (Victor BM et al Am J Cardiol 2014;113:1611 e 1615)

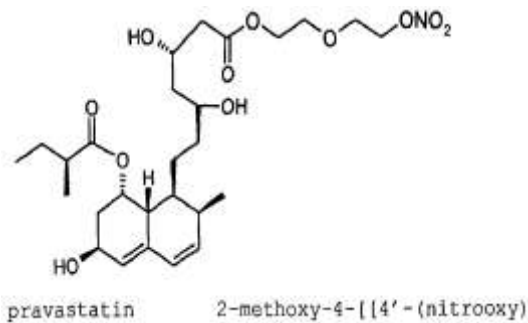
le donne ipertese e le donne diabetiche raggiungono il target terapeutico più facilmente se sono seguite da medici di sesso femminile (Regitz-Zagrosek, 2012).

Uno studio che esamina pazienti con lombosciatalgie evidenzia che l'osservatore è influenzato non solo dal sesso del paziente esaminato ma anche dal suo aspetto fisico (Hadjistavropoulos T et al . Psychol Health. 1996;11:411-20)

2 Take Home message:

L'arruolamento delle donne o l'inclusione nella ricerca clinica del femminile è una condizione necessaria ma non sufficiente per avere una terapia di genere

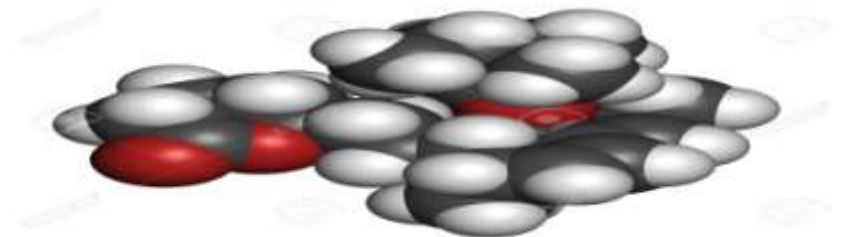
Perché si devono anche considerare le specificità femminili, la farmacogenetica, l'interazione medico paziente, e tutte le variabili preanalitiche



STATINS

In the 1990s, RCTs on statins with an average of more than 500 participants included 18.6% women. By the first decade of the 2000s, women comprised, on average, 31.45%

It is important to recall that WOSCOP study did not enroll any woman ([Farahani P. Clin Invest Med. 2014 1;37\(3\):E163.](#))



The primary outcome measures were the percent of patients who achieved a low-density lipoprotein (LDL) cholesterol goal of <70 mg/dl and a non high-density lipoprotein cholesterol goal of <100 mg/dl

High-potency statins : atorvastatin (40 or 80 mg), rosuvastatin (20 or 40 mg), or simvastatin (80 mg).

Moderate-potency statins : atorvastatin (10 or 20 mg), rosuvastatin (10 mg), simvastatin (40 mg), lovastatin (80 mg), or pravastatin (80 mg).

low-potency statins: All other doses

Combination therapy : statins + Nonstatin lipid-lowering drugs including ezetimibe, bile acid sequestrants, prescription formulation omega-3 polyunsaturated fatty acids, fibrates, and niacin compounds.

Victor BM et al Am J Cardiol 2014;113:1611 e 1615

Table 2

Gender differences in lipid-lowering medications

Lipid-Lowering Medication	Overall (n = 9,950)	Women (n = 3,366)	Men (n = 6,584)	p Value
Statin monotherapy	5,885 (59.1)	2,049 (60.9)	3,836 (58.3)	0.01
High potency	1,691 (17.0)	503 (14.9)	1,188 (18.0)	<0.001
Moderate potency	2,326 (23.4)	794 (23.6)	1,532 (23.3)	0.72
Low potency	1,868 (18.8)	752 (22.3)	1,116 (17.0)	<0.001
Combination therapy	2,730 (27.4)	747 (22.2)	1,983 (30.1)	<0.001
No statin	1,335 (13.4)	570 (16.9)	765 (11.6)	<0.001
No lipid-lowering therapy	946 (9.5)	431 (12.8)	515 (7.8)	<0.001
Other lipid-lowering drugs				
Ezetimibe	1,564 (15.7)	538 (16.0)	1,026 (15.6)	0.60
Niacin	1,036 (10.4)	162 (4.8)	874 (13.3)	<0.001
Fibrates	885 (8.9)	258 (7.7)	627 (9.5)	0.002
Bile acid sequestrant	85 (0.9)	38 (1.1)	47 (0.7)	0.03
Prescription omega-3 PUFA	83 (0.8)	23 (0.7)	60 (0.9)	0.24

p Value relates to comparisons between women and men.

Data are expressed as number (%).

PUFA = polyunsaturated fatty acid.

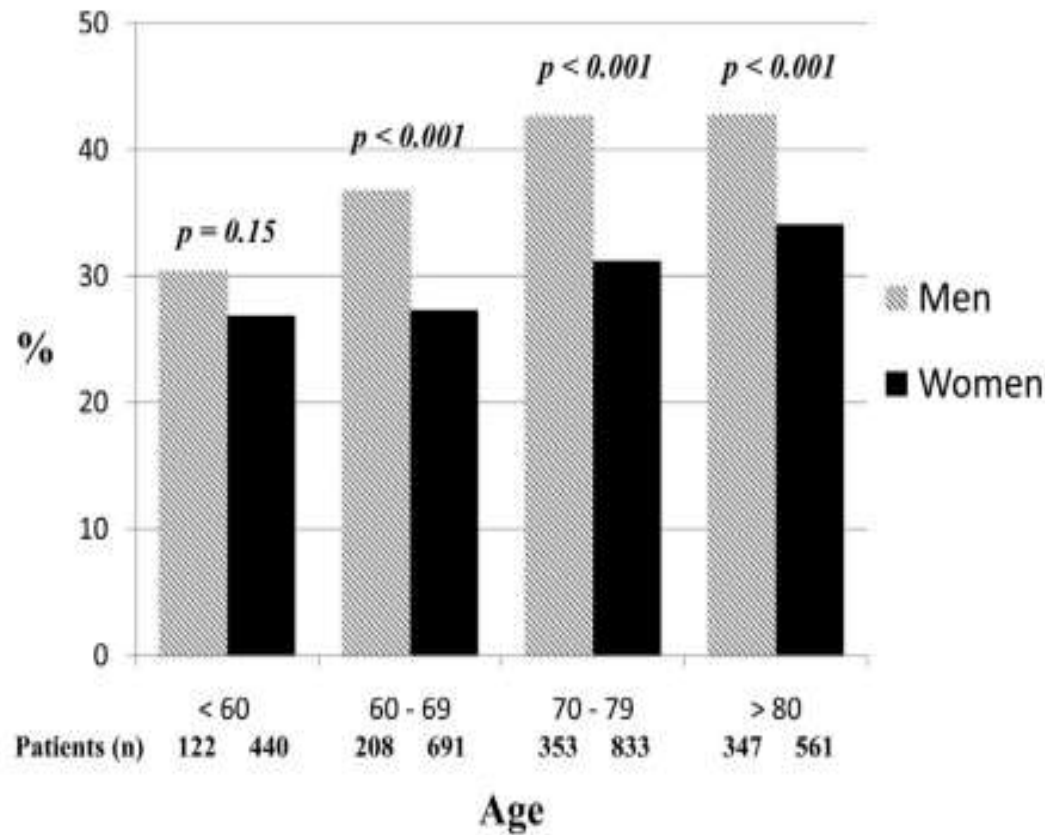
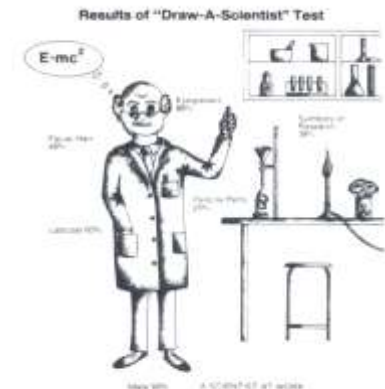


Figure 1. Likelihood of achieving an LDL cholesterol goal of <70 mg/dl in men and women based on age.

Women were older than men, had more hypertension, and had similar rates of diabetes, smoking, and obesity.



ADEHERENCE



Nonadherence to statins is greater in women than men (Chan Dc et al . Med Care 2010;48:196 e 202; Christian et al; J Gen Intern Med 2006;21:231 e 237; Mann DM, et al Ann Pharmacother 2010;44:1410 e 1421.

SAFETY

Some papers provide information on the specific risk for DM associated with different types and doses of statins. The overall increase in diabetes incidence was 25% in JUPITER, sex stratification revealed that the risk was increased by 49% in women and by only 14% in men (Mora S et al Circulation 2010;121:1069 – 1077). A retrospective analysis of the Women ' s Health Initiative (WHI) found that statin use was associated with a 71% increased risk of diabetes (95% CI, 1.61 – 1.83); after adjustment for potential confounders, the hazard ratio (HR) re-mained signi fi cant at 1.48 (1.38 – 1.59) (Culver AL et al Arch Intern Med 2012; 172:144 – 152). Rosuvastatin is more potent and less hydrophilic than pravastatin and is associated with adverse metabolic effects, including increases in insulin resistance and glycosylated hemoglobin; conversely, pravastatin proved to be safe by decreasing these 2 parameters (Navarese et al Am J Cardiol 2013;111:1123e1130).

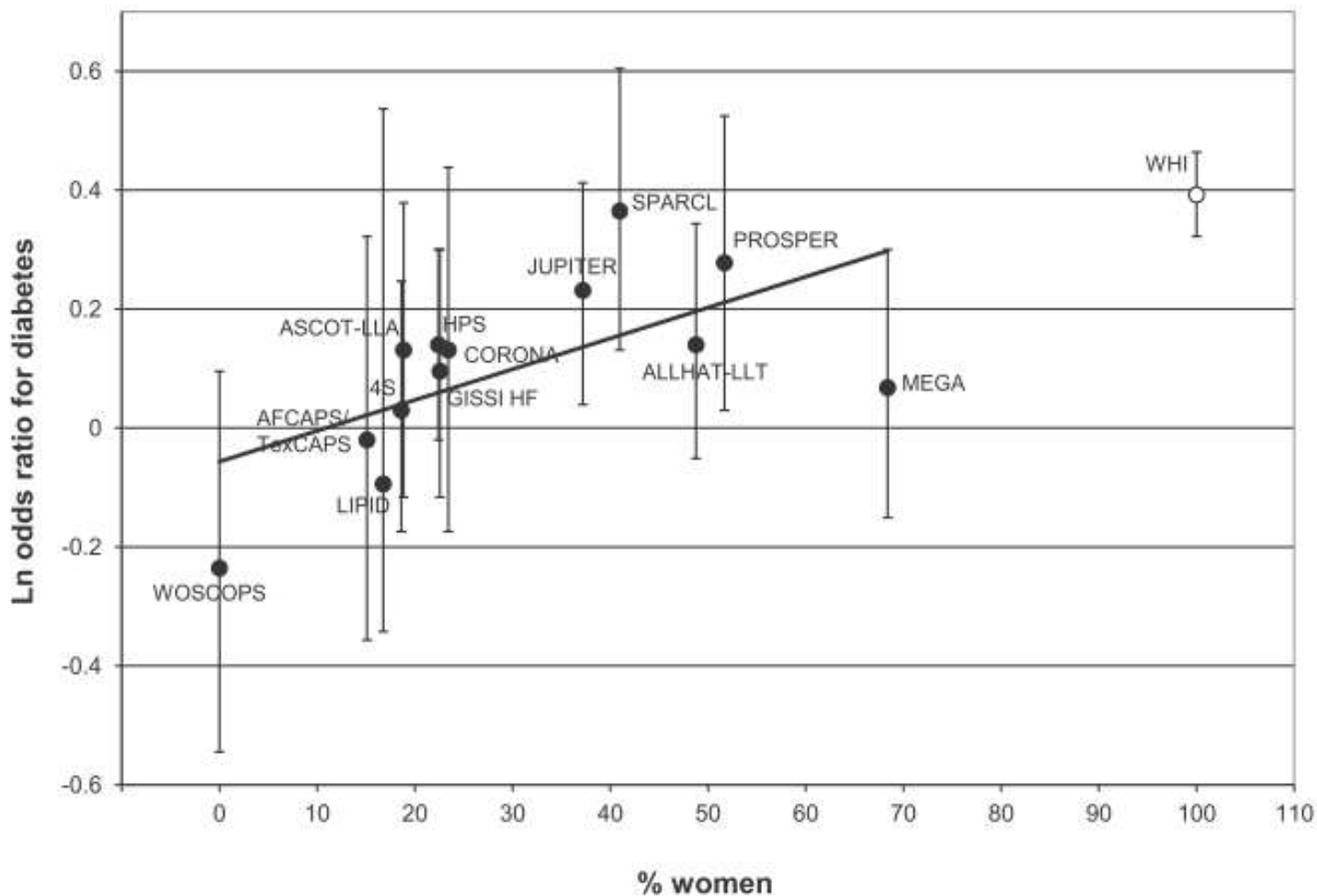


Figure 1—Meta-regression of percent of women on OR for incident diabetes. Only trials examining statin vs. nonstatin placebo or control arms are represented. The percent of women in each trial was obtained from the index publications. When available, the percent of nondiabetic women was used (HPS, LIPID); otherwise, the percent of women in the trial as a whole was used. ORs (natural log-transformed, ln) for diabetes were obtained from the Sattar et al. meta-analysis (3) and from Waters et al. for SPARCL (6). The error bars represent the 95% CIs. The adjusted HR for diabetes from the WHI is plotted for comparison (open circle); its data were not used in the regression calculation.

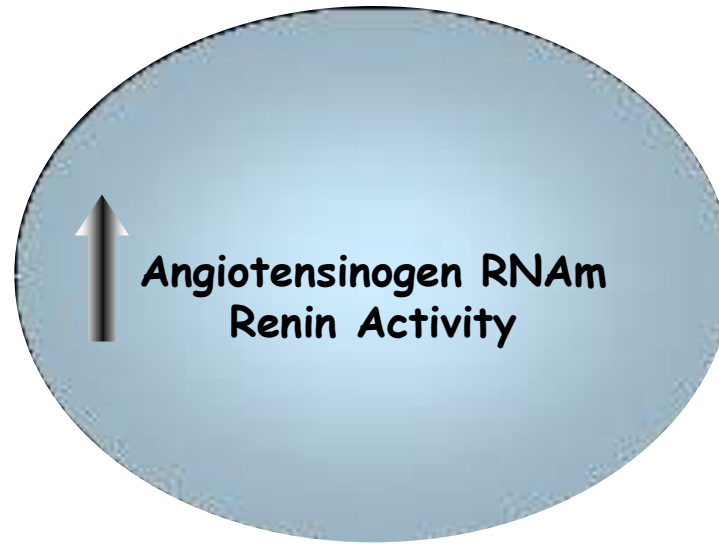
SAFETY

Women may experience more side effects from lipid-lowering therapy compared with men, older women at being at increased risk for statin-associated myopathy (Pasternak RC et al. J Am Coll Cardiol 2002;40:567; Buettner C et al J Gen Intern Med 2008;23:1182). However at this regard there are not univocal results (Bruckert E et al. Cardiovasc Drugs Ther 2005;19:403; Nichols GA, Koro CE. Clin Ther 2007;29:1761 e 1770).

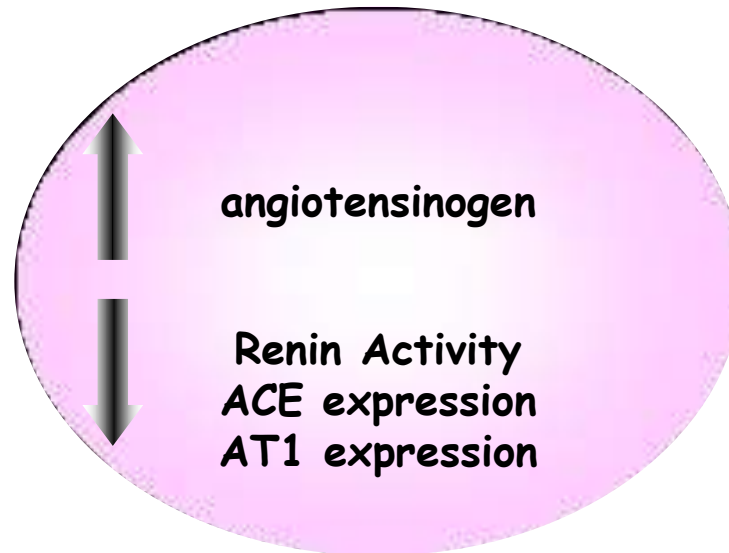
Finally , a recent paper indicates that women in both the lower and higher dose atorvastatin groups discontinue therapy more compared with men either for statin-associated myopathy and persistent liver function test abnormalities compared with men (Wenger NK et al Heart 2008;94:434 e 439).



Testosterone



Oestrogens



Safety profile

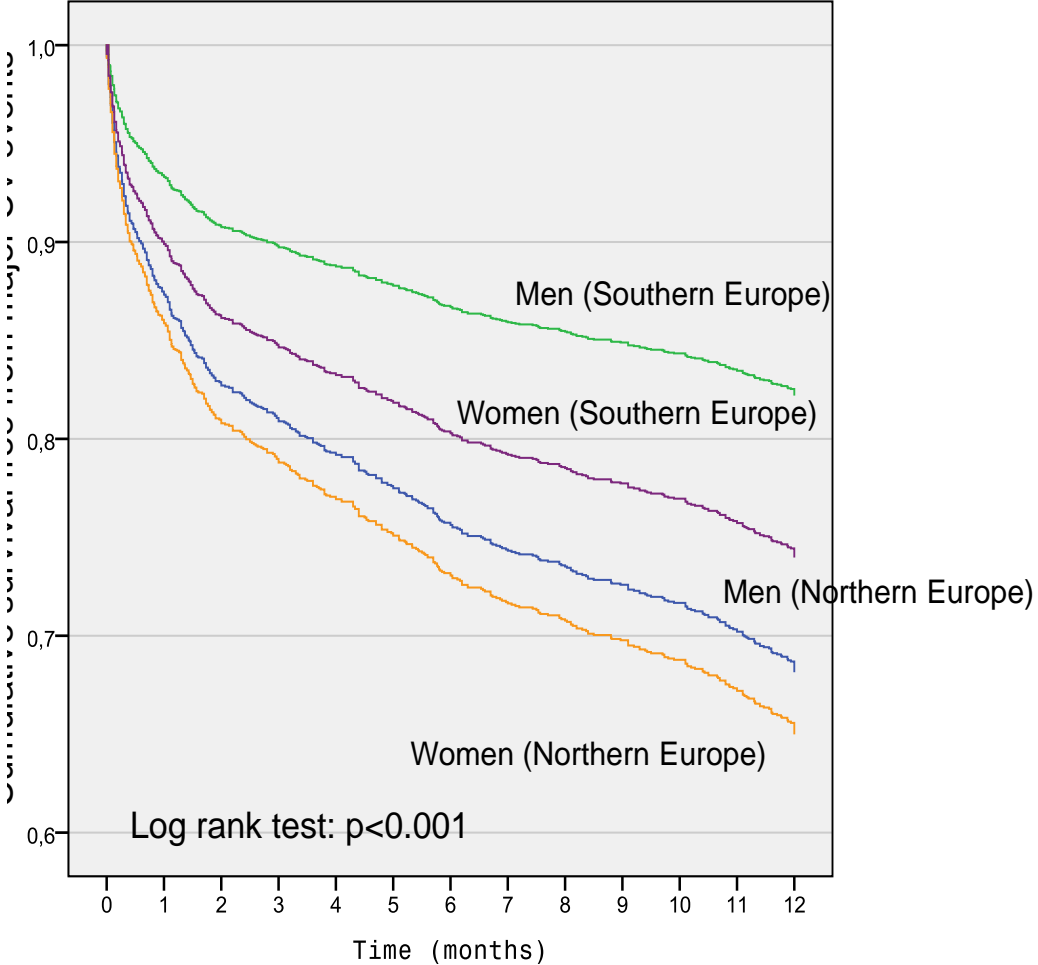
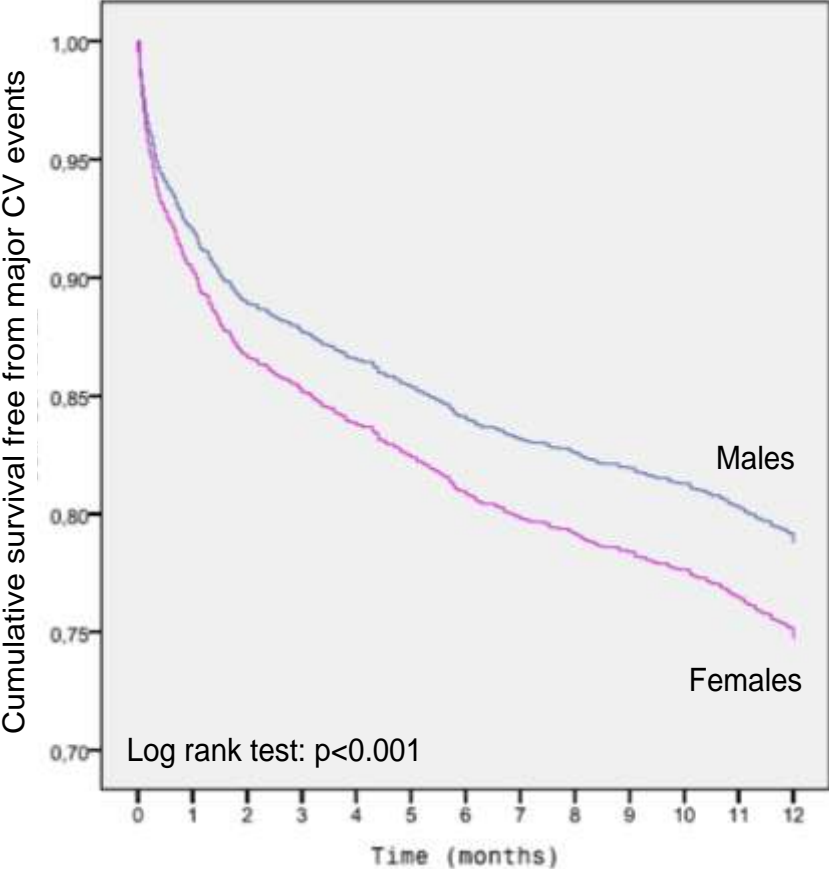
In placebo-treated patients, the incidence of adverse events was slightly, but not significantly larger in women than in men (13.0% vs. 9.9%, $p = 0.174$).

Under zofenopril, the rate of drug related adverse events, expressed by person-time at risk, was comparable in men (0.61) and women (0.56, $p = 0.328$), whereas in patients treated with other ACEIs it was higher in women than in men (0.67 vs. 0.50, $p = 0.009$). Cough, an adverse event which may typically be observed in ACE-inhibitor-treated patients, was reported in a similar low proportion by women and men treated with zofenopril and ramipril, while it occurred more frequently in lisinopril-treated women (7.2%) than men (2.8%, $p = 0.025$), indicating a possible intra-class difference for this type of event.

The incidence of angioedema occurred more frequently in lisinopril-treated women (7.2%) than men (2.8%, $p = 0.025$), indicating a possible intra-class difference for this type of event.

All patients (n=3630)

All patients (n=3630)



Kaplan-Meier cumulative survival curves during 1-year of follow-up in men and women enrolled in the SMILE Programme

Nessuna quantità di esperimenti potrà dimostrare che ho ragione; un unico esperimento potrà dimostrare che ho sbagliato. »

([Albert Einstein](#), lettera a [Max Born](#) del 4 dicembre [1926](#))



.... la salute e la sicurezza non sono cose che si raggiungono come se accadessero per caso, ma il risultato di un consenso collettivo e di un pubblico investimento....”

Nelson Mandela

Manuale di Medicina Sesso-Genere

a cura di Flavia Franconi e Giorgio Caselli Forti



Flavia Franconi
Giorgio Caselli Forti
Silvia Villa

Farmacologia di Genere



GRAZIE