

Women and Cardiovascular Research in Europe

Marco Stramba-Badiale

*Director, Department of Rehabilitation Medicine,
IRCCS Istituto Auxologico Italiano, Milan, Italy*

Red Alert for Women's Hearts
Women and Cardiovascular Diseases Conference
European Heart Health Strategy
EuroHeart Project,
Work Package 6
Sophia Antipolis, November 5th 2009

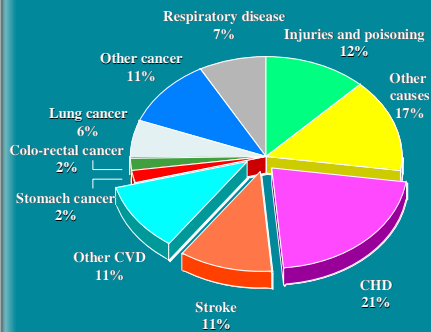


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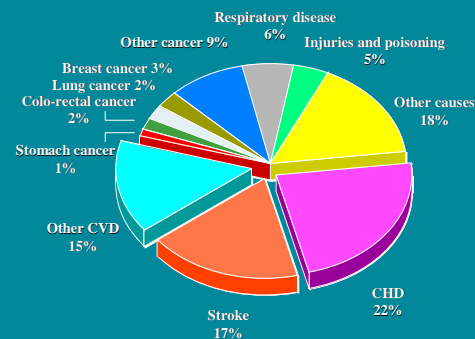


Causes of Death by Gender in the European Countries

Men



Women



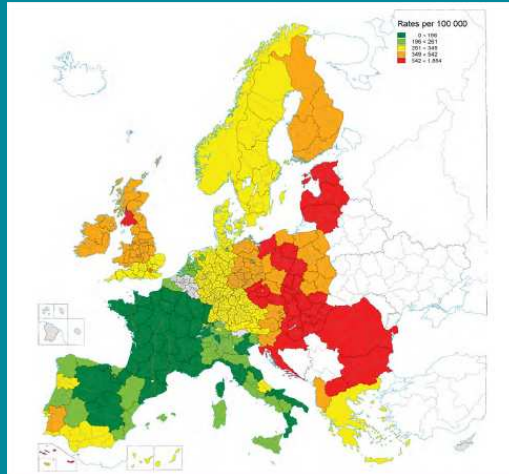
World Health Organization (2008)



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Age-standardized Mortality from Cardiovascular Disease in Men



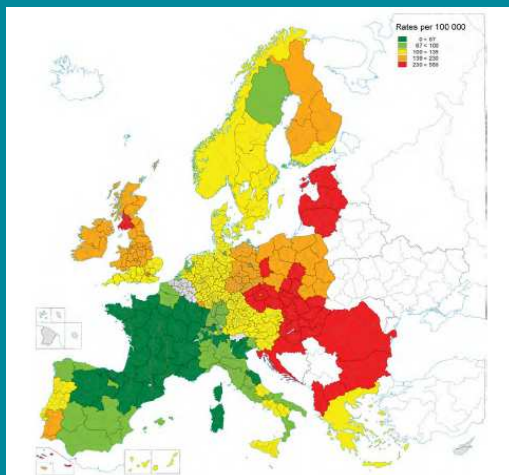
Eur Heart J. 2008;29(10):1316-26



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Age-standardized Mortality from Cardiovascular Disease in Women



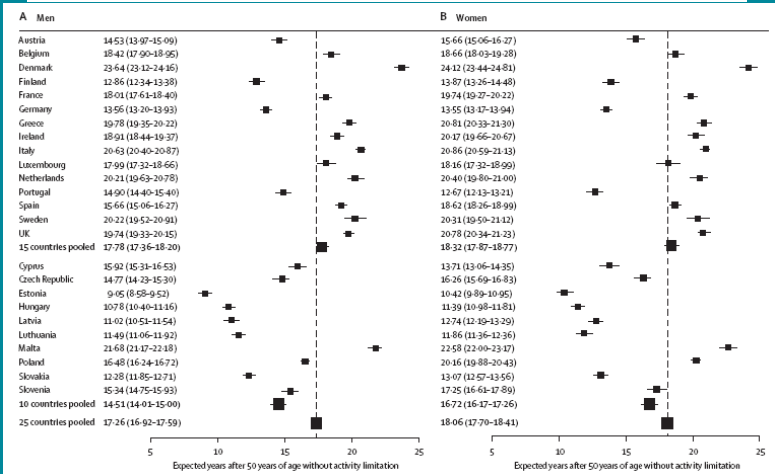
Eur Heart J. 2008;29(10):1316-26



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Inequalities in healthy life years in the 25 countries of the European Union in 2005: a cross-national meta-regression analysis



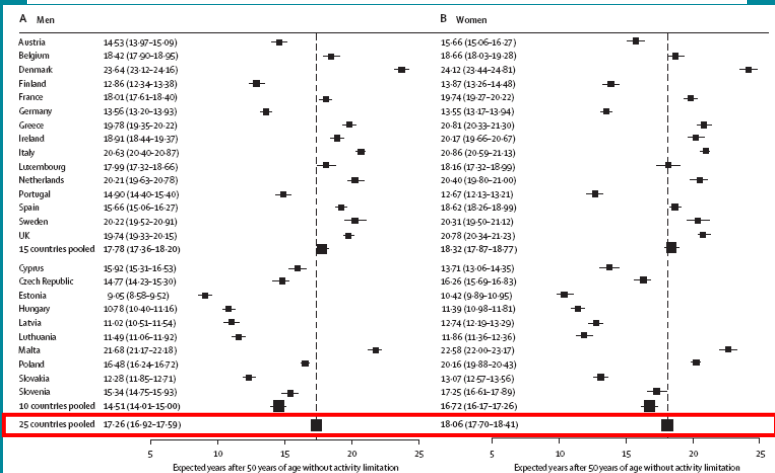
Lancet 2008; 372: 2124-31



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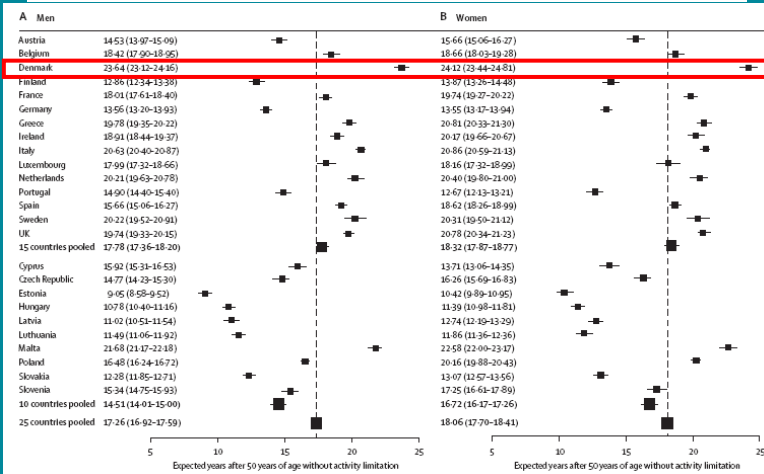
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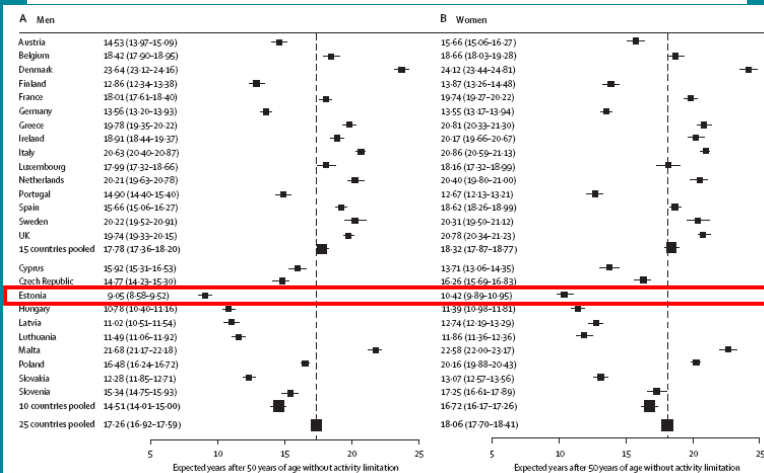
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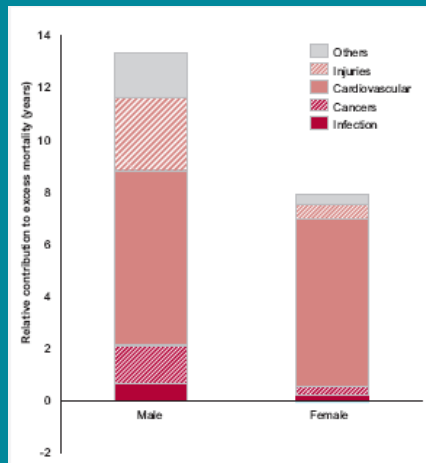
Lancet 2008; 372: 2124-31



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Relative Contribution to the Deficit in Life Expectancy in Eastern Europe



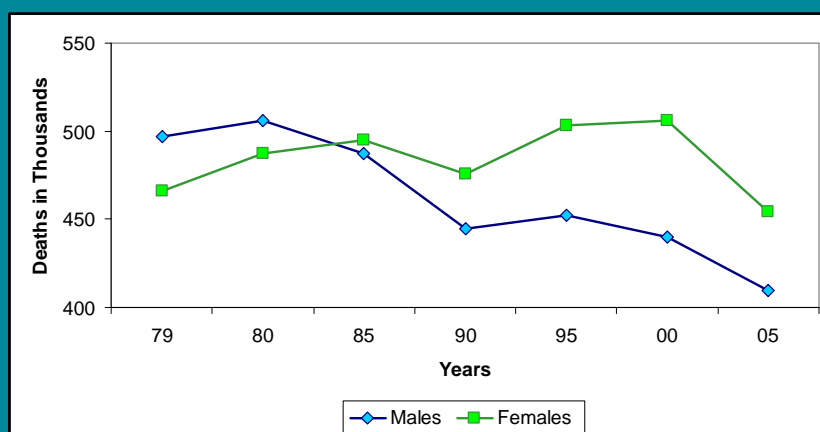
World Health Organization (2008)



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Cardiovascular Disease Mortality Trends for Males and Females



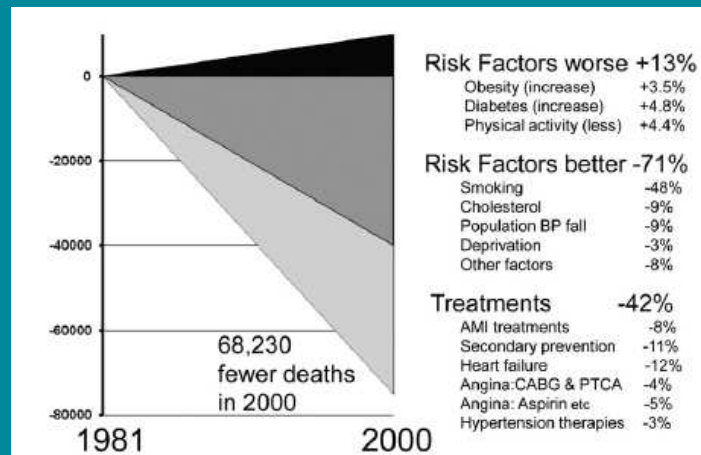
CDC/NCHS and NHLBI 2008



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Determinants of Coronary Heart Disease Deaths Reduction according to the IMPACT Model



Atheroscler Suppl 2009;10:3-21



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Gender and Cardiovascular Diseases

- ♥ Gender differences in the clinical presentation of cardiovascular diseases have been demonstrated and some therapeutic options may not be equally effective and safe in men and women.
- ♥ Furthermore, gender differences in pharmacokinetics, pharmacodynamics and physiology may contribute to a different response to cardiovascular drugs in women when compared with men.
- ♥ Accordingly, preventive and therapeutical interventions should be tested in populations that fairly represent the gender distribution for each specific clinical condition or group at risk.



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Under-representation of Women in Clinical Trials

- ♥ Women, for many years, have been under-represented in randomized clinical trials.
- ♥ The majority of therapeutic interventions were tested for safety and efficacy in predominantly male populations.



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Women in European Clinical Trials

Trial	Enr. pts	Females %	Reference
GISSI-1	11 711	25	Lancet 1986;1:397-402
ISIS-2	17 187	23	Lancet 1988;2:349-360
GISSI-2	12 490	20	Lancet 1990;336:65-71
GISSI-3	18 023	22	Lancet 1994;343:1115-22
4S	4 444	19	Lancet 1994;334:1383-89
ISIS-4	58 050	26	Lancet 1995;345:669-685
SMILE	1 556	27	NEJM 1995;332:80-85
EMIAT	1 486	16	Lancet 1997;349:667-674
GISSI-P	11 324	15	Lancet 1999;354:447-52
CIBIS-2	2 647	19	Lancet 1999;353:9-13



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Under-representation of Women in Clinical Trials

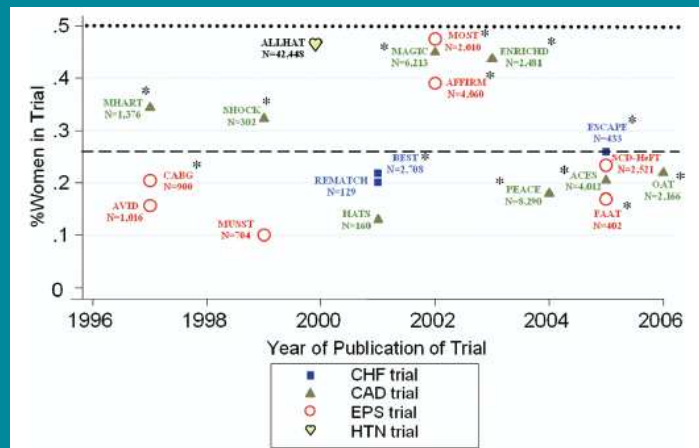
♥ After the FDA Guidelines on gender issues released in 1993 and the 1998 regulation there has been a significant increase in the number and proportion of women who participate in cardiovascular studies and some trials have been conducted specifically in females.



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Enrollment of Women in NHLBI-Sponsored Cardiovascular Randomized Trials From 1997 to 2006



J Am Coll Cardiol 2008;52:672-673



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London, 05 January 2005
EMEA/CHMP/3916/2005 - ICH

ICH
GENDER CONSIDERATIONS IN THE CONDUCT OF CLINICAL TRIALS



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



ESC Report

Cardiovascular diseases in women: a statement
from the policy conference of the European
Society of Cardiology

Marco Stramba-Badiale* (Chairperson of the Policy Conference), Kim M. Fox (Chairperson of the Policy Conference), Silvia G. Priori (Chairperson of Women at Heart), Peter Collins, Caroline Daly, Ian Graham, Benct Jonsson, Karin Schenck-Gustafsson, and Michal Tendera

Eur Heart J 2006;27:994-1005



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Cardiovascular Diseases in Women: A Statement from the Policy Conference of the European Society of Cardiology

♥ *.....it is recommended that based on the specific question addressed, clinical trials enrolling only female patients or clinical trials enrolling a significant proportion of women to allow for pre specified gender analysis will be conducted.*

Eur Heart J 2006;27:994-1005



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European Heart Health Strategy EuroHeart Project, Work Package 6 Women and Cardiovascular Diseases

(European Heart Network and European Society of Cardiology)

Objectives:

- ♥ To address the issue of women representation in cardiovascular research by collecting information on clinical trials and registries in Europe.
- ♥ To identify possible gender differences in the primary outcomes of clinical trials, in the current clinical practice and in the Guidelines of European Scientific Societies.



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European Heart Health Strategy EuroHeart Project, Work Package 6 Women and Cardiovascular Diseases

- ♥ Electronic literature search of PubMed and International Controlled Trials website has been performed.
- ♥ Time period covered: from 2006 (to follow up from ESC 2006 conference on women and cardiovascular disease) to June 2009.



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



European Heart Health Strategy EuroHeart Project, Work Package 6 Women and Cardiovascular Diseases

Four different types of publications (European or international with European representation) have been analysed:

- ♥ Observational/epidemiological studies.
- ♥ Randomized Clinical trials, including meta-analyses, which enrolled women and men or women only.
- ♥ European registries, i.e. the EuroHeart Survey, on the status of clinical practice.
- ♥ Guidelines of European Scientific Societies.



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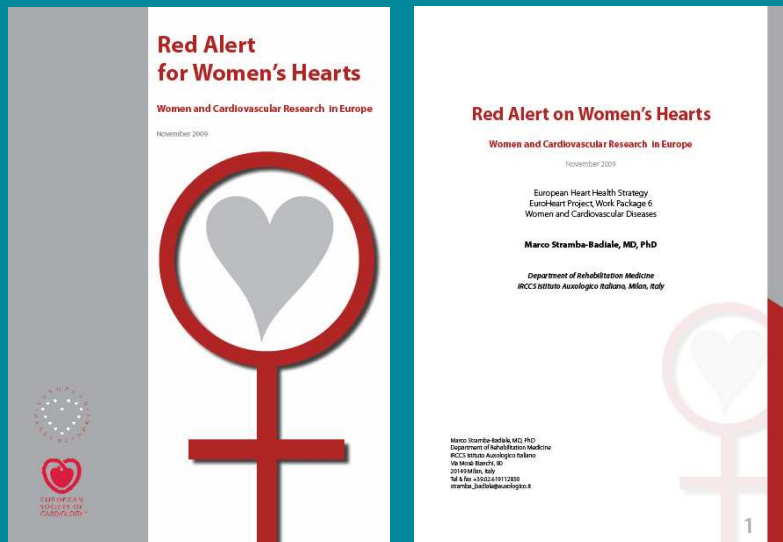
European Heart Health Strategy EuroHeart Project, Work Package 6 Women and Cardiovascular Diseases

The analysis has been focused on:

- ♥ Percentage of women representation.
- ♥ Availability of analysis of outcomes by gender.
- ♥ Gender differences in risk, outcome or clinical practice.
- ♥ Gender issues in scientific guidelines.



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



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Members of the Advisory Board

Members of the Advisory Board of Work Package 6 of the EuroHeart project are:

- ▶ Henrico Brundkules (Dutch: Cardiac Society, GWG)
- ▶ Emanuele Follo (Italian Heart Foundation, Italy)
- ▶ Malcom Mackay (European Heart Network)
- ▶ Suzanne Laganish (European Heart Network)
- ▶ Peggy Maguire (European Institute of Women's Health, Ireland)
- ▶ Rishi Channer (British Heart Foundation, United Kingdom)
- ▶ Soghra Chahly (European Society of Cardiology)
- ▶ Karin Schunck-Gustafsson (Karolinska University Hospital, Sweden)
- ▶ Hans Stam (Netherlands Heart Foundation, Netherlands)
- ▶ Marco Stramba-Badiale (IRCCS Istituto Auxologico Italiano, Italy)
- ▶ Salla Viljanen (Finnish Cardiac Society, Finland)

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Red Alert for Women's Hearts

Women and Cardiovascular Research in Europe

November 2018

Are there gender differences in cardiovascular risk?

Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy

Misperception of Cardiovascular Diseases in Women

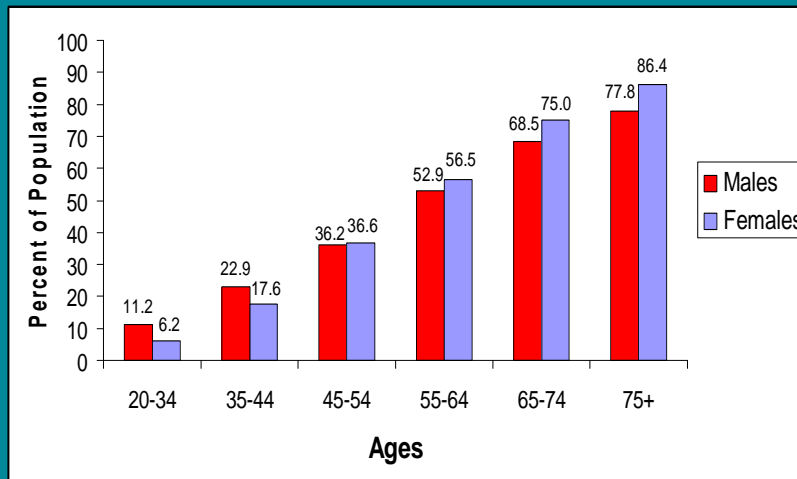
- ♥ The risk of women is underestimated because of the perception that females are “protected” against cardiovascular disease.
- ♥ Women during the fertile age have a lower risk of cardiac events, but this protection fades after menopause thus leaving women with untreated risk factors vulnerable to develop myocardial infarction, heart failure and stroke.



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Prevalence of Cardiovascular Diseases by Age and Gender



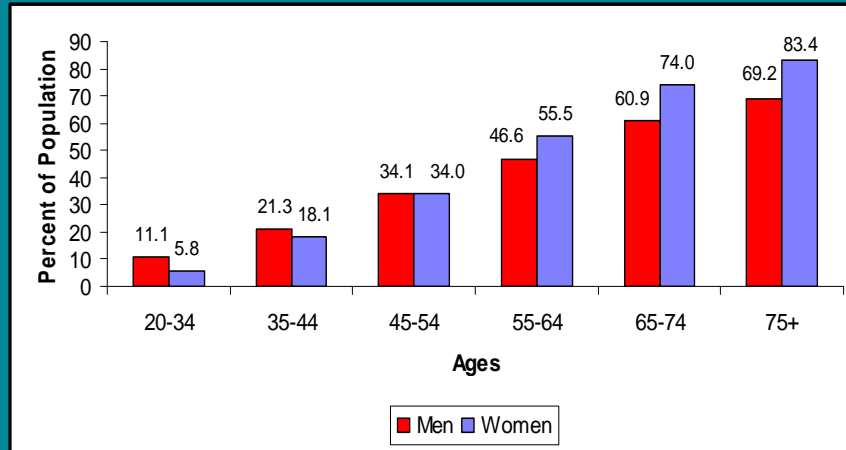
CDC/NCHS and NHLBI 2008



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Prevalence of High Blood Pressure by Age and Sex



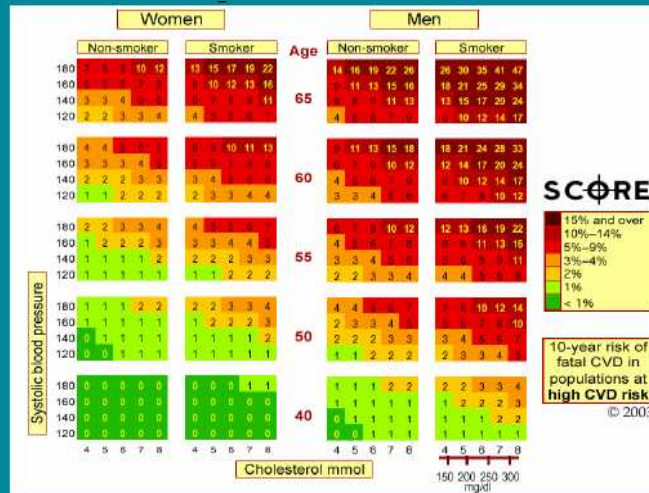
CDC/NCHS and NHLBI 2008



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SCORE Charts for High Risk Countries



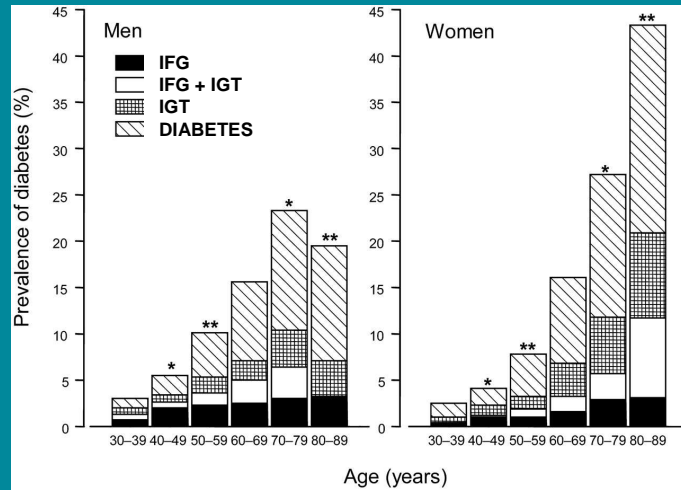
Eur Heart J 2003;24(11):987-1003



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Age- and Gender-specific Prevalence of Diabetes in 13 European Population-based Cohorts Included in the DECODE Study



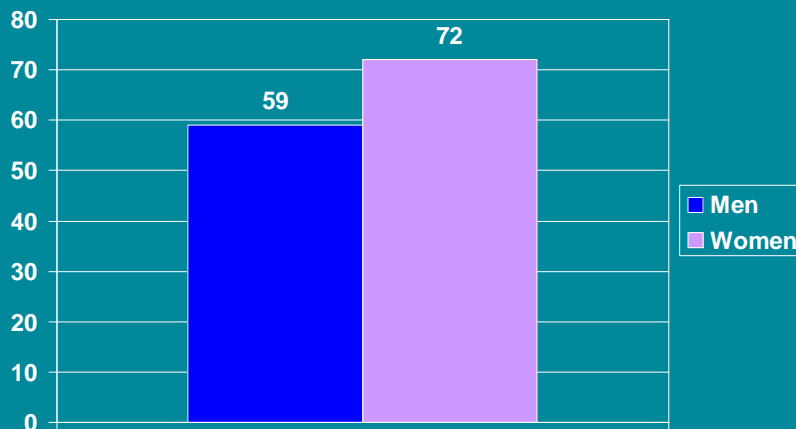
Eur Heart J 2007; 28, 88-136



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Prevalence of metabolic syndrome in 4437 patients by gender according to NCEP and IDF definitions in EUROASPIRE



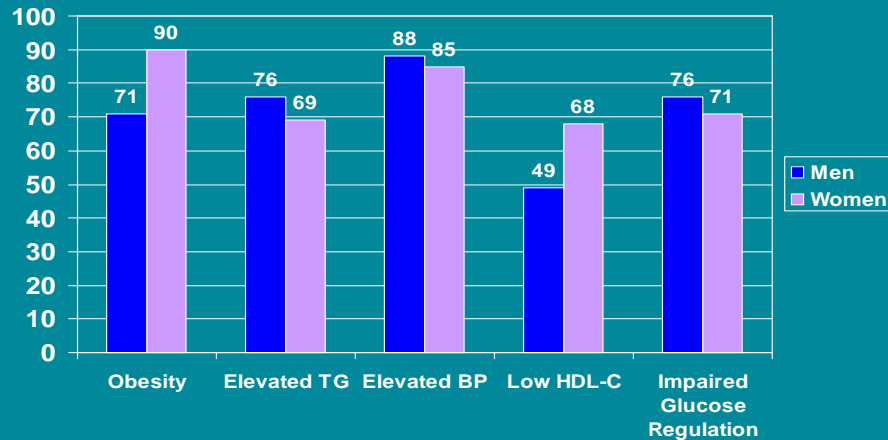
Eur Heart J 2006;27:994-1005



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EUROASPIRE: Components of Metabolic Syndrome by Gender



Eur Heart J 2006;27:994-1005



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Age, Menopause and the Cardiovascular Risk in Women

- ♥ The risk for cardiovascular diseases increases after menopause partly because of ovarian hormone deficiency that favours hypertension, diabetes, hyperlipidemia, central obesity and the metabolic syndrome.
- ♥ Menopause may also contribute to the development of atherosclerosis by inducing the endothelial dysfunction.



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Postmenopausal Hormone Therapy and the Risk of Cardiovascular Diseases Observational Studies

CHD protection

	<i>n</i>	Age-adjusted RR	Risk factor-adjusted RR
Nurses' Health Study	32,317	0.50	0.52
Lipid Research Clinics	2270	0.34	0.37
Walnut Creek	6083	0.90	0.60
Leisure World	8807	0.59	0.69

Eur Heart J 2006;27:994-1005



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Postmenopausal Hormone Therapy and the Risk of Cardiovascular Diseases Meta-analysis of Randomized Trials

	<i>Trials</i>	<i>Subjects</i>	<i>Odds ratio (95% CI)</i>	<i>P-value</i>
Cerebrovascular disease	26	43 549	1.24 (1.09-1.41)	0.001
Coronary heart disease	25	43 159	1.00 (0.90-1.11)	0.97
Venous thromboembolism	22	42 381	2.05 (1.44-2.92)	<0.0001

Eur Heart J 2008;29:2031-41



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Eur Heart J 2008;29:2031-41



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Recommendations on HRT Research

♥ Additional research is needed for the assessment of the efficacy and safety of therapies for the relief of symptoms in postmenopausal women, focused on:

- *age of the population,*
- *time of beginning the therapy since menopause,*
- *type and mode of administration,*
- *duration of therapy,*
- *CVD effects of new agents.*



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Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II, and III surveys in eight European countries

Kornelia Kotseva, David Wood, Guy De Backer, Dirk De Bacquer, Kalevi Pyörälä, Ulrich Keil, for the EUROASPIRE Study Group*

	Raised blood pressure*			Raised cholesterol concentration†			Reported diabetes mellitus		
	EUROASPIRE I	EUROASPIRE II	EUROASPIRE III	EUROASPIRE I	EUROASPIRE II	EUROASPIRE III	EUROASPIRE I	EUROASPIRE II	EUROASPIRE III
Sex									
Men	1345/2388 (56.3%)	1270/2223 (57.1%)	1106/1835 (60.3%)	1686/1794 (94.0%)	1554/2078 (74.8%)	756/1747 (43.3%)	388/2389 (16.2%)	411/2222 (18.5%)	476/1822 (26.1%)
Women	502/790 (63.5%)	460/746 (61.7%)	346/550 (62.9%)	582/605 (96.2%)	568/688 (82.6%)	293/526 (55.7%)	164/791 (20.7%)	187/748 (25.0%)	188/549 (34.2%)
Total‡	1847/3178 (58.1%)	1730/2969 (58.3%)	1452/2385 (60.9%)	2268/2399 (94.5%)	2122/2766 (76.7%)	1049/2273 (46.2%)	552/3180 (17.4%)	598/2970 (20.1%)	664/2371 (28.0%)

Lancet 2009; 373: 929–40



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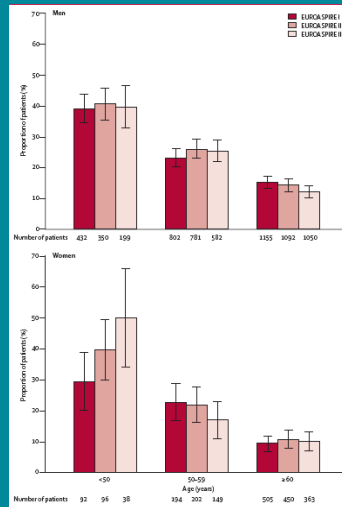
Lancet 2009; 373: 929–40



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Frequency of Smoking by Age and Gender in 1996, 2000 and 2007



Lancet 2009; 373: 929-40



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Recommendations for Cardiovascular Risk Control

- ♥ There is a compelling need for a special effort to prevent smoking initiation and favour smoking cessation in young women.
- ♥ It is important to reach the vast majority of women for the assessment and the management of cardiovascular risk.



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy





European Heart Journal (2007) 28, 2028–2040
doi:10.1093/eurheartj/ehm296

Special article

Management of cardiovascular risk in the peri-menopausal woman: a consensus statement of European cardiologists and gynaecologists

Peter Collins^{1*}, Giuseppe Rosano², Catherine Casey³, Caroline Daly¹, Marco Gambacciani⁴, Peyman Hadji⁵, Risto Kaaja⁶, Tomi Mikkola⁶, Santiago Palacios⁷, Richard Preston⁸, Tabassome Simon⁹, John Stevenson¹, and Marco Stramba-Badiale¹⁰

Eur Heart J 2007; 28: 2028–2040



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



ASSESSMENT AND MANAGEMENT OF CARDIOVASCULAR RISKS IN WOMEN

A SHORT GUIDE FOR GYNAECOLOGISTS

For more information
www.escardio.org

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Professor Peter Collins
Imperial College London
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Tel-Aviv Souraski Medical Center
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Israel

Professor Martin Birkhäuser
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Italy

Faculty members

Cathy Casey (Ireland)
Caroline Daly (UK)
Marco Gambacciani (Italy)
Risto Kaaja (Finland)
Stéphane Laurent (France)
Tomi Mikkola (Finland)

Santiago Palacios (Spain)
Tabassome Simon (France)
John Stevenson (UK)
Marco Stramba-Badiale (Italy)
Eberhard Windler (Germany)

Acknowledgement

We are grateful to the attendees of the meeting on Cardiovascular Risk Assessment and Management in Menopausal Women in the Gynaecological Setting, Seville, 1–2 June 2007, who participated in the Workshop sessions, for their contribution to this guide.



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy





♥ Are there gender differences in the response to cardiovascular therapy?



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Blood Pressure-lowering Treatment

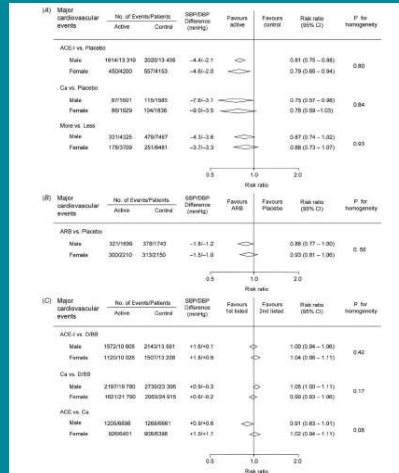
Trials	5
Participants	69,473
Women	28,008
% Women	40,3%
Mean age	70,2 years
Mean follow-up	3,2 years
Analysis by gender	3/5 (60%)



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Gender-wise Response to Blood Pressure Lowering Treatment



Eur Heart J 2008;29:2669-2680



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Diabetes and Metabolic Syndrome

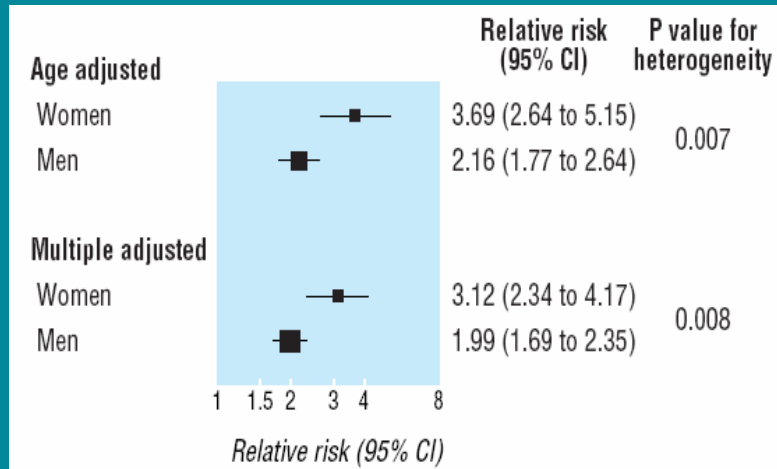
Trials	7
Participants	48,508
Women	20,091
% Women	41,4%
Mean age	61,1 years
Mean follow-up	4,3 years
Analysis by gender	4/7 (57,1%)



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Risk of Fatal Coronary Heart Disease Associated with Diabetes in Men and Women



BMJ 2006; 332:73



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis

Leanne Bellamy, Juan-Pablo Casas, Aroon D'Hingoranj, David Williams

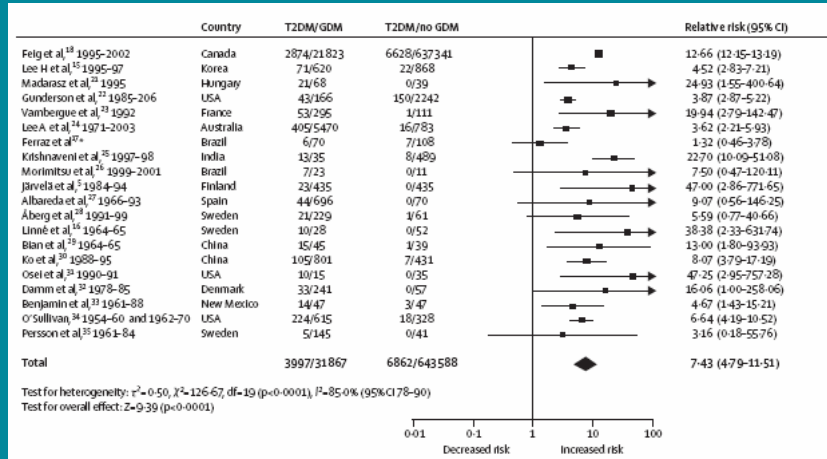
Lancet 2009; 373: 1773-79



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Risk of Type 2 Diabetes after Gestational Diabetes



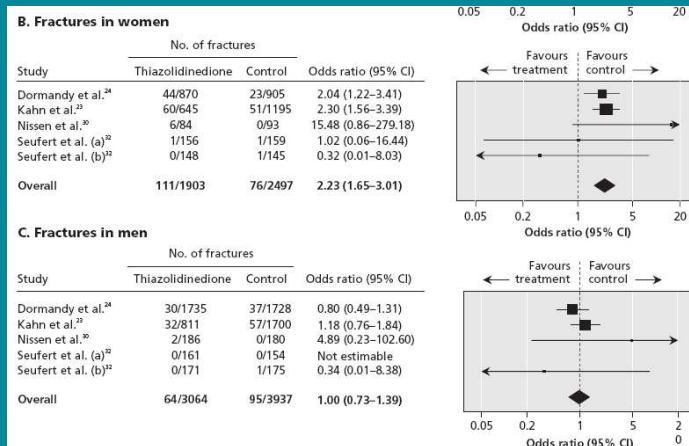
Lancet 2009; 373: 1773-79



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Long-term Use of Thiazolidinediones and Fractures in Type 2 Diabetes



CMAJ 2009;180(1):32-9



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Recommendations on Diabetes Research

- ♥ Encourage research on the risk of developing type 2 diabetes after glycemic alterations during pregnancy.
- ♥ Explore the reasons for gender differences in the adverse effects of hypoglycaemic agents.



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Cholesterol-lowering Therapy

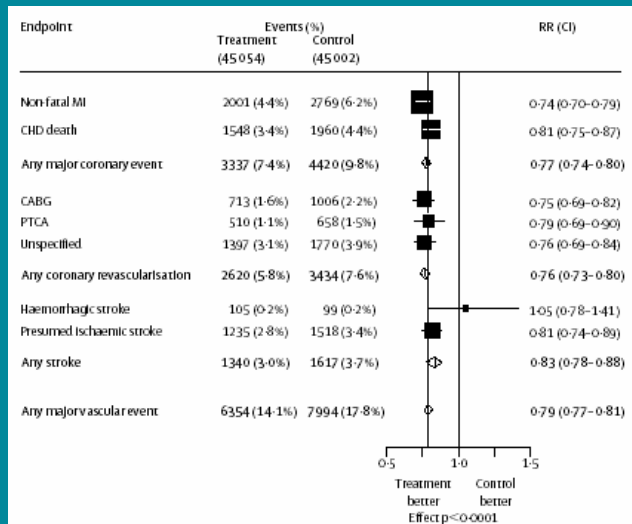
Trials	6
Participants	50,194
Women	15,036
% Women	30,0%
Mean age	60,8 years
Mean follow-up	3,2 years
Analysis by gender	1/6 (16,7%)



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Effects of Statins on Cardiovascular Events



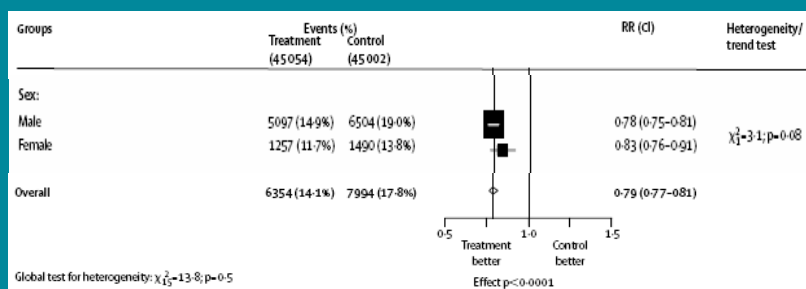
Lancet 2005; 366: 1267-78



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Effects of Statins on Cardiovascular Events by Gender



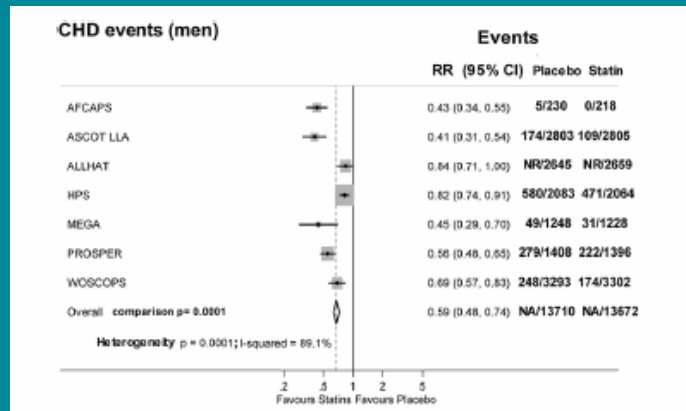
Lancet 2005; 366: 1267-78



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Effects of Statins on Coronary Heart Disease in Primary Prevention Trials in Men



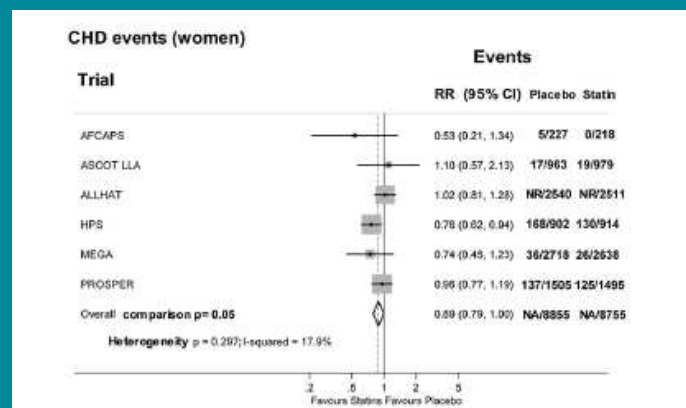
Int J of Cardiology 2008



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Effects of Statins on Coronary Heart Disease in Primary Prevention Trials in Women



Int J of Cardiology 2008



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



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ESTABLISHED IN 1812

NOVEMBER 20, 2008

VOL. 359 NO. 21

Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein

Paul M Ridker, M.D., Eleanor Danielson, M.I.A., Francisco A.H. Fonseca, M.D., Jacques Genest, M.D.,
Antonio M. Gotto, Jr., M.D., John J.P. Kastelein, M.D., Wolfgang Koenig, M.D., Peter Libby, M.D.,
Alberto J. Lorenzatti, M.D., Jean G. MacFadyen, B.A., Børge G. Nordestgaard, M.D., James Shepherd, M.D.,
James T. Willerson, M.D., and Robert J. Glynn, Sc.D., for the JUPITER Study Group*

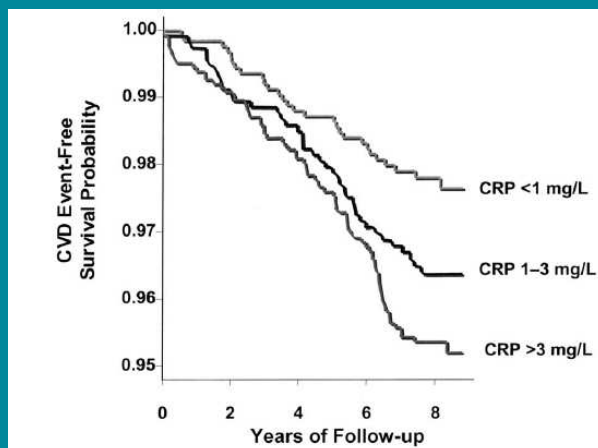
N Engl J Med 2008;359:2195-207



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



High Sensitivity C-reactive Protein (hsCRP) and Risk for Cardiovascular Diseases



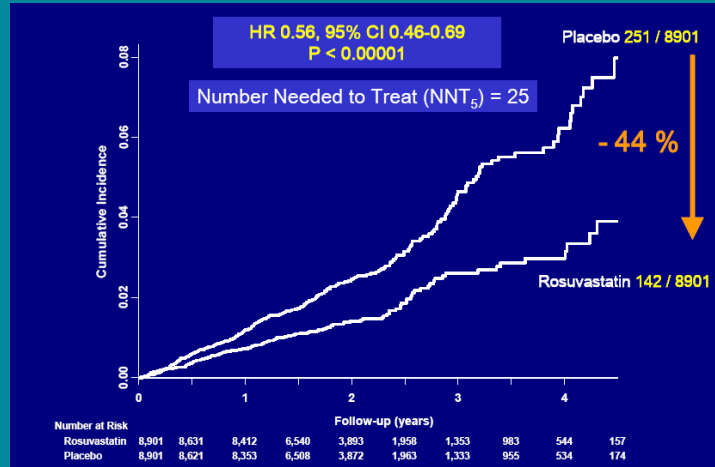
Am J Cardiol 2006;97:33A-41A



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



JUPITER Trial: Primary Endpoint (MI, Stroke, UA/Revascularization, CV Death)



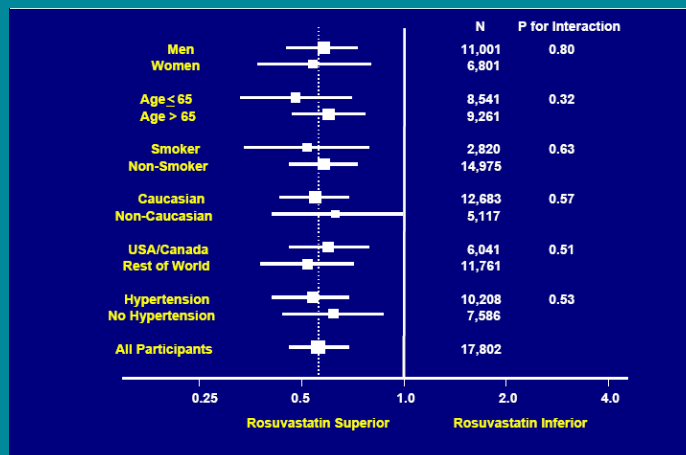
N Engl J Med 2008;359:2195-207



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



JUPITER Trial: Primary Endpoint Subgroups Analysis



N Engl J Med 2008;359:2195-207



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Ischaemic Heart Disease

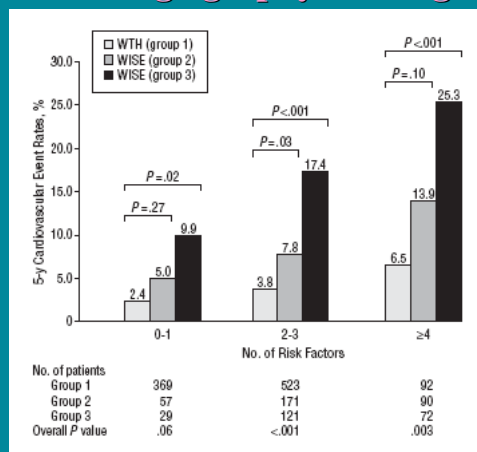
Trials	13
Participants	90,400
Women	24,756
% Women	27,3%
Mean age	62,6 years
Mean follow-up	0,96 years
Analysis by gender	5/13 (38,4%)



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Cardiovascular Events in Women without Obstructive Coronary Disease according to Risk factors and Angiography Findings



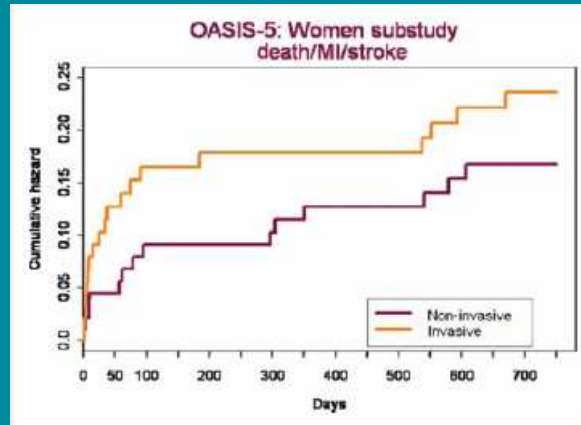
Arch Intern Med 2009;169(9):843-850



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Early Invasive vs Selective Invasive Strategy in Acute Coronary Syndromes



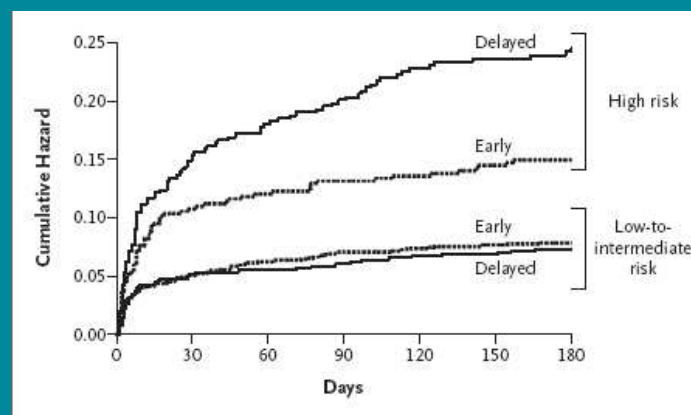
Eur Heart J 2009 Feb 7 [Epub ahead of print]



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Early vs Delayed Invasive Intervention in Acute Coronary Syndromes



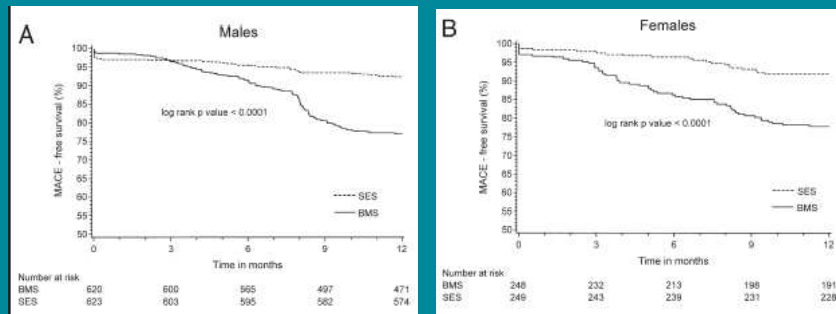
N Engl J Med 2009;360(21):2165-75



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Major Adverse Cardiac Events with Bare Metal Stents vs Drug Eluting Stents in Men and Women



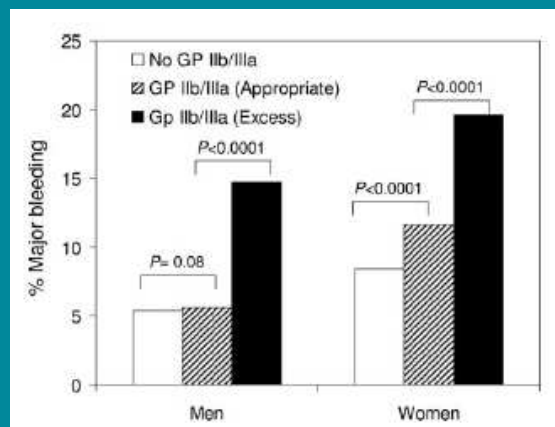
J Am Coll Cardiol 2007;50: 2111-6



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Major Bleedings in Non ST Elevation Acute Coronary Syndromes



Circulation 2006;114:1380-1387



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Recommendations on Ischemic Heart Disease Research

- ♥ Encourage research on women with symptoms and signs suggestive of myocardial ischemia but without obstructive coronary artery disease.
- ♥ Encourage research on the efficacy and safety of early revascularization in acute coronary syndromes in women.



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Heart Failure

Trials	11
Participants	46,141
Women	12,834
% Women	27,8%
Mean age	69,2 years
Mean follow-up	2,4 years
Analysis by gender	8/11 (72,7%)



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The NEW ENGLAND JOURNAL of MEDICINE

Cardiac-Resynchronization Therapy for the Prevention of Heart-Failure Events

Arthur J. Moss, M.D., W. Jackson Hall, Ph.D., David S. Cannom, M.D., Helmut Klein, M.D., Mary W. Brown, M.S., James P. Daubert, M.D., N.A. Mark Estes III, M.D., Elyse Foster, M.D., Henry Greenberg, M.D., Steven L. Higgins, M.D., Marc A. Pfeffer, M.D., Ph.D., Scott D. Solomon, M.D., David Wilber, M.D., and Wojciech Zareba, M.D., Ph.D., for the MADIT-CRT Trial Investigators*

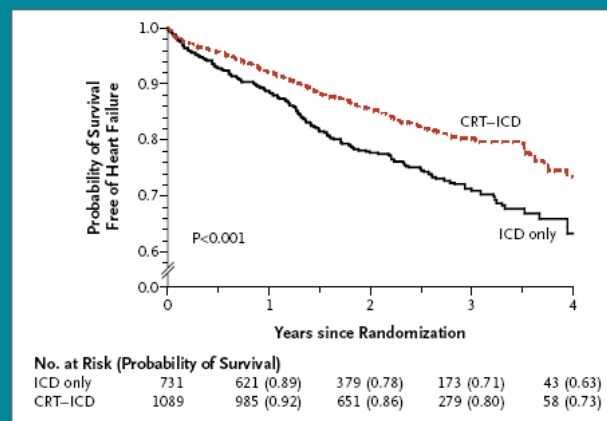
N Engl J Med 2009;361:1329-1338



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Effects of Cardiac Resynchronization Therapy on Heart Failure Events



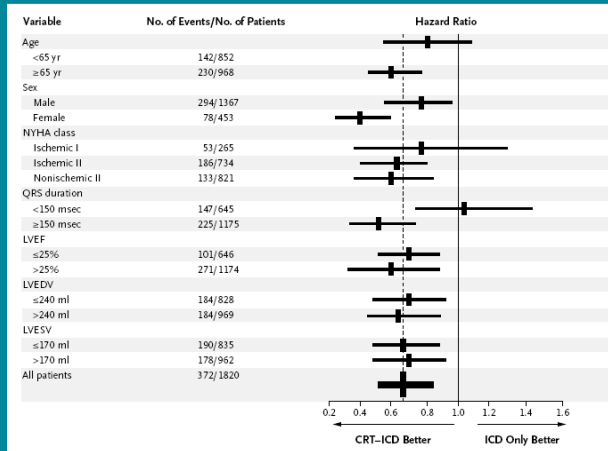
N Engl J Med 2009;361:1329-1338



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Effects of Cardiac Resynchronization Therapy on Heart Failure Events



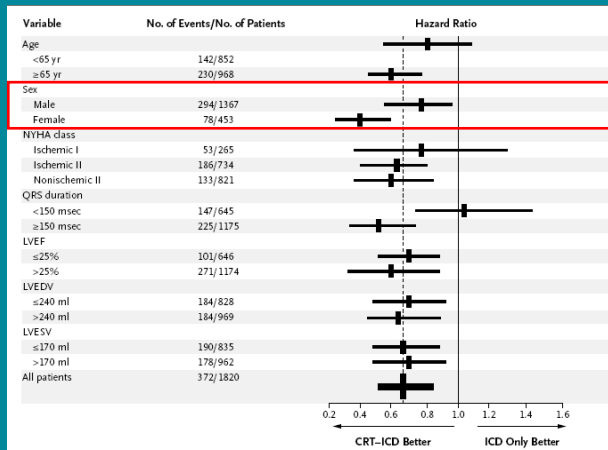
N Engl J Med 2009;361:1329-1338



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Effects of Cardiac Resynchronization Therapy on Heart Failure Events



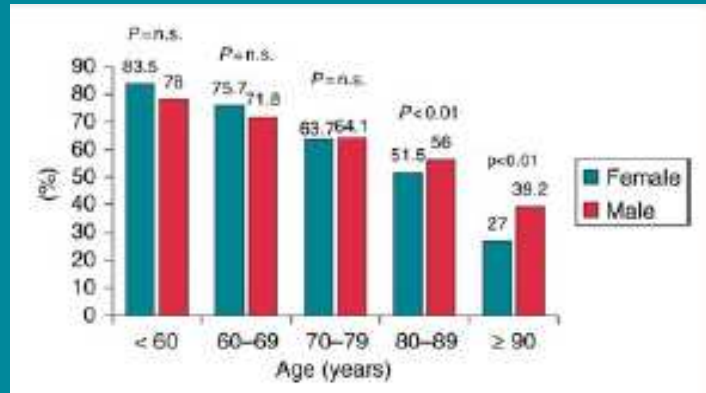
N Engl J Med 2009;361:1329-1338



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Portion of Dual-chamber Pacemaker Implant according to Age and Gender



Europace 2009 published online 28 October

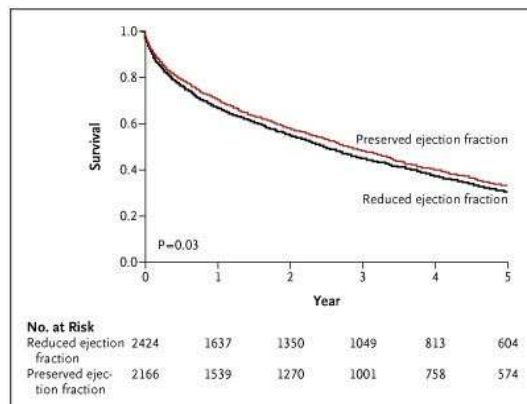


Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Trends in Prevalence and Outcome of Heart Failure with Preserved Ejection Fraction

Theophilus E. Owan, M.D., David O. Hodge, M.S., Regina M. Herges, B.S., Steven J. Jacobsen, M.D., Ph.D., Veronique L. Roger, M.D., M.P.H., and Margaret M. Redfield, M.D.



N Engl J Med 2006;355:251-9



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Trends in Prevalence and Outcome of Heart Failure with Preserved Ejection Fraction

Theophilus E. Owan, M.D., David O. Hodge, M.S., Regina M. Herges, B.S.,
Steven J. Jacobsen, M.D., Ph.D., Veronique L. Roger, M.D., M.P.H.,
and Margaret M. Redfield, M.D.

Table 1. Characteristics of Patients with Heart Failure and Preserved or Reduced Ejection Fraction.*

Characteristic	Reduced Ejection Fraction (N=2429)	Preserved Ejection Fraction (N=2167)	P Value	Adjusted P Value†
Age (yr)	71.7±12.1	74.4±14.4	<0.001	NA
Male sex (% of patients)	65.4	44.3	<0.001	<0.001
Body-mass index‡	28.6±7.0	29.7±7.8	0.002	0.17
Obesity (% of patients)‡§	35.5	41.4	0.007	0.002
Serum creatinine on admission (mg/dl)	1.6±1.0	1.6±1.1	0.31	0.30
Hemoglobin on admission (g/dl)	12.5±2.0	11.8±2.1	<0.001	<0.001
Hypertension (% of patients)	48.0	62.7	<0.001	<0.001
Coronary artery disease (% of patients)	63.7	52.9	<0.001	<0.001
Atrial fibrillation (% of patients)	28.5	41.3	<0.001	<0.001
Diabetes (% of patients)	34.3	33.1	0.42	0.61
Substantial valve disease (% of patients)	6.5	2.6	<0.001	0.05
Ejection fraction (%)	29±10	61±7	<0.001	NA

N Engl J Med 2006;355:251-9



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Trends in Prevalence and Outcome of Heart Failure with Preserved Ejection Fraction

Theophilus E. Owan, M.D., David O. Hodge, M.S., Regina M. Herges, B.S.,
Steven J. Jacobsen, M.D., Ph.D., Veronique L. Roger, M.D., M.P.H.,
and Margaret M. Redfield, M.D.

Table 1. Characteristics of Patients with Heart Failure and Preserved or Reduced Ejection Fraction.*

Characteristic	Reduced Ejection Fraction (N=2429)	Preserved Ejection Fraction (N=2167)	P Value	Adjusted P Value†
Age (yr)	71.7±12.1	74.4±14.4	<0.001	NA
Male sex (% of patients)	65.4	44.3	<0.001	<0.001
Body-mass index‡	28.6±7.0	29.7±7.8	0.002	0.17
Obesity (% of patients)‡§	35.5	41.4	0.007	0.002
Serum creatinine on admission (mg/dl)	1.6±1.0	1.6±1.1	0.31	0.30
Hemoglobin on admission (g/dl)	12.5±2.0	11.8±2.1	<0.001	<0.001
Hypertension (% of patients)	48.0	62.7	<0.001	<0.001
Coronary artery disease (% of patients)	63.7	52.9	<0.001	<0.001
Atrial fibrillation (% of patients)	28.5	41.3	<0.001	<0.001
Diabetes (% of patients)	34.3	33.1	0.42	0.61
Substantial valve disease (% of patients)	6.5	2.6	<0.001	0.05
Ejection fraction (%)	29±10	61±7	<0.001	NA

N Engl J Med 2006;355:251-9



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Recommendations on Heart Failure Research

- ♥ Encourage research on the efficacy and safety of therapeutic interventions for heart failure patients with preserved left ventricular function (more common in women).



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Atrial Fibrillation

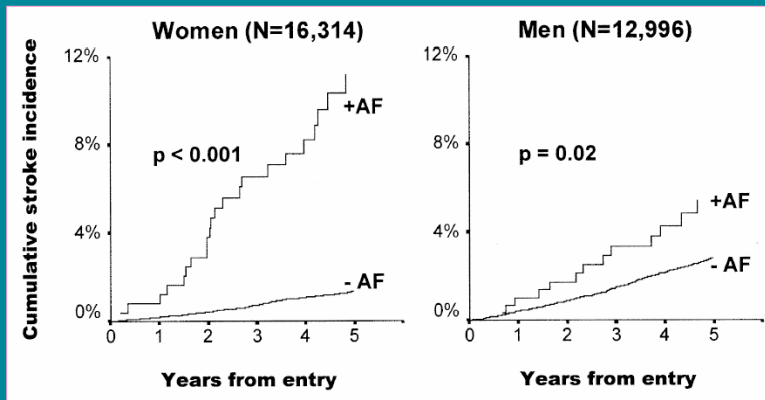
Trials	11
Participants	22,511
Women	9,192
% Women	40,8%
Mean age	72,1 years
Mean follow-up	2,5 years
Analysis by gender	3/7 (42,8%)



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Stroke Incidence in Men and Women with Atrial Fibrillation



Am J Cardiol 2004; 94: 889-94



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CHADS2 Stroke Risk Score in Patients with Atrial Fibrillation

Congestive Heart Failure	1
Hypertension	1
Age > 75 years	1
Diabetes	1
Previous Stroke or TIA	2

Eur Heart J 2006; 27: 1979-2030



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CHADS2 Stroke Risk Score ≥ 2 in Men and Women with Atrial Fibrillation

Men 43%

Women 57%

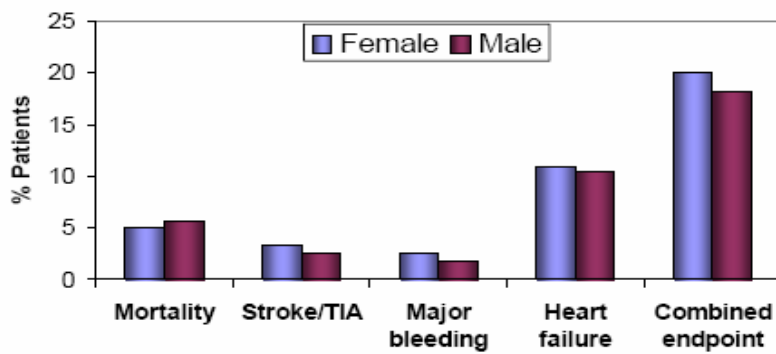


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Atrial Fibrillation

Outcome at 1 Year



J Am Coll Cardiol 2007; 49:572-7

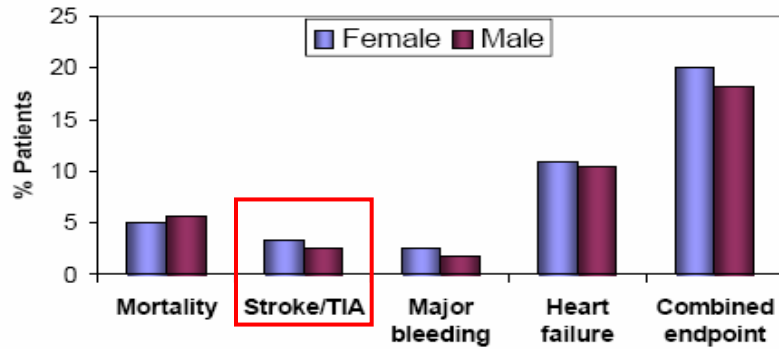


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Atrial Fibrillation

Outcome at 1 Year



J Am Coll Cardiol 2007; 49:572-7

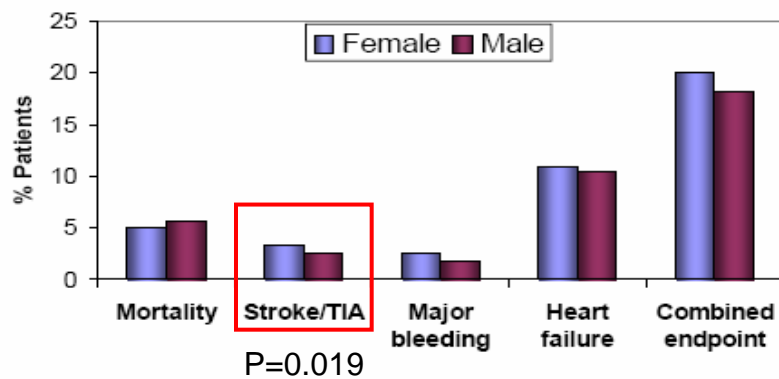


Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Atrial Fibrillation

Outcome at 1 Year



J Am Coll Cardiol 2007; 49:572-7

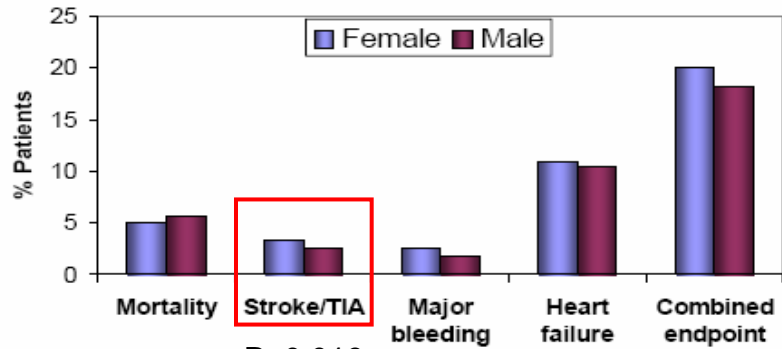


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Atrial Fibrillation

Outcome at 1 Year



P=0.019

Adjusted for age and stroke risk factors

J Am Coll Cardiol 2007; 49:572-7

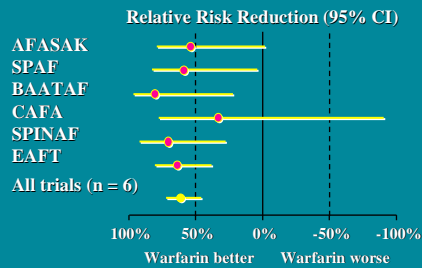


Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy

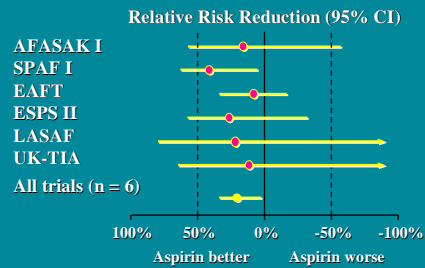


Antithrombotic Therapy for Prevention of Stroke in Patients with Nonvalvular Atrial Fibrillation

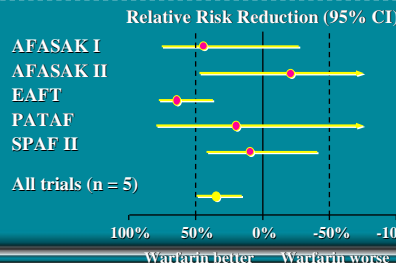
Adjusted-dose Warfarin compared with Placebo



Aspirin compared with Placebo



Warfarin compared with Aspirin



Eur Heart J 2006; 27: 1979-2030

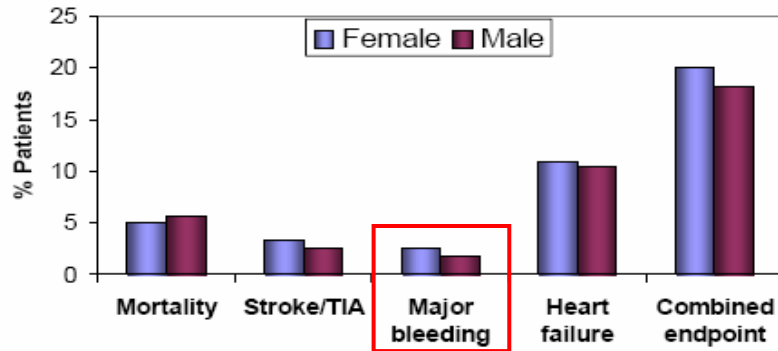


Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Atrial Fibrillation

Outcome at 1 Year



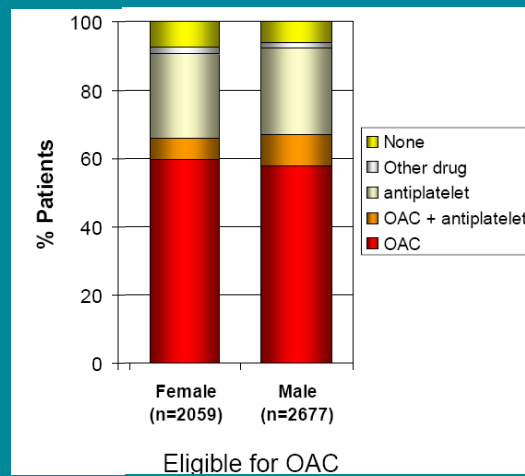
J Am Coll Cardiol 2007; 49:572-7



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Antithrombotic Therapy in Patients with Atrial Fibrillation (The Euro Heart Survey)



J Am Coll Cardiol 2007; 49:572-7



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



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Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

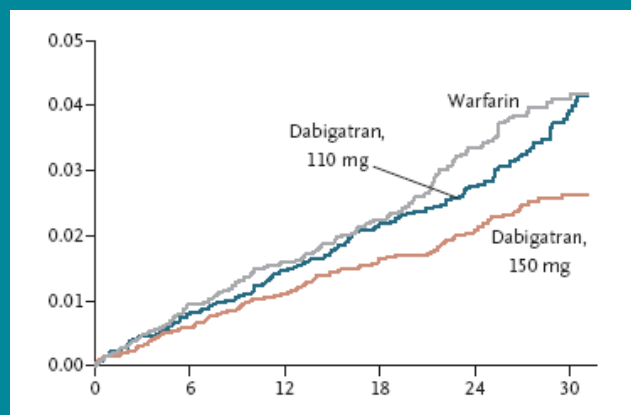
N Engl J Med 2009;361(12):1139-51



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Effects of Dabigatran vs Warfarin in Patients with Atrial Fibrillation



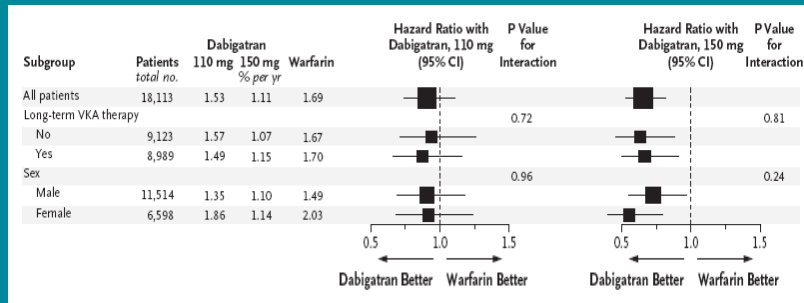
N Engl J Med 2009;361(12):1139-51



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Effects of Dabigatran vs Warfarin in Patients with Atrial Fibrillation



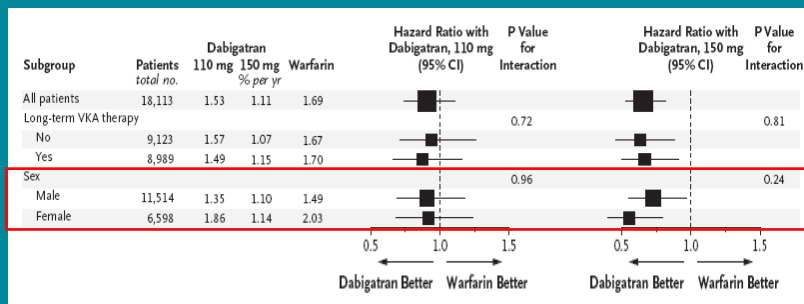
N Engl J Med 2009;361(12):1139-51



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Effects of Dabigatran vs Warfarin in Patients with Atrial Fibrillation



N Engl J Med 2009;361(12):1139-51



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Stroke

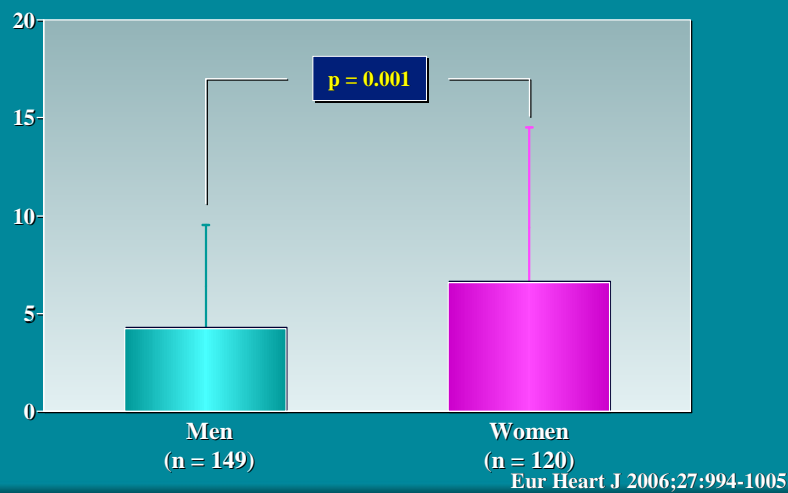
Trials	11
Participants	28,790
Women	10,618
% Women	36,9%
Mean age	69,0 years
Mean follow-up	1,26 years
Analysis by gender	3/7 (42,8%)



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



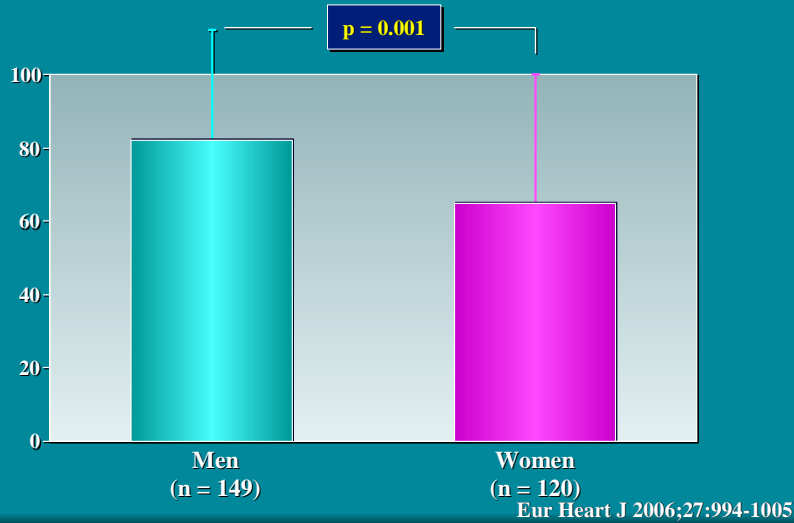
Neurological Impairment after Stroke at Hospital Discharge in Men and Women (NIH Stroke Scale)



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Disability after Stroke in Men and Women (Barthel Index)



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis

Sarah T Pendlebury, Peter M Rothwell

	Number of studies	Patients with factor/total		OR (95% CI)	p value*	I ²	p value†
		With dementia	No dementia				
Demographic factors							
Female sex	24	669/1350	1885/4357	1.3 (1.1-1.6)	0.006	49	0.004

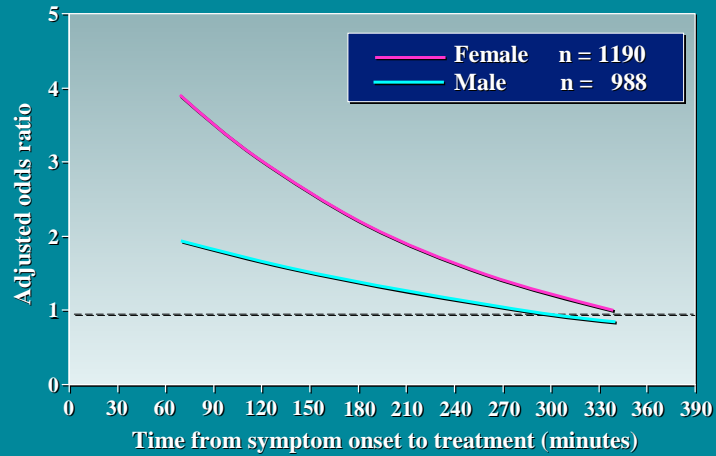
Lancet Neurol 2009; 8: 1006-18



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Effect of Thrombolytic Therapy and Time from Symptom Onset after Stroke in Men and Women



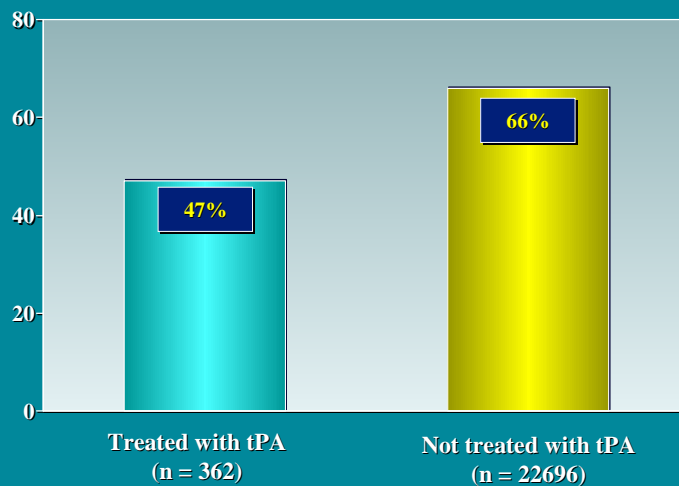
Stroke 2005; 36:62-65



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Female Prevalence among Stroke Patients Treated or Not Treated with Thrombolysis



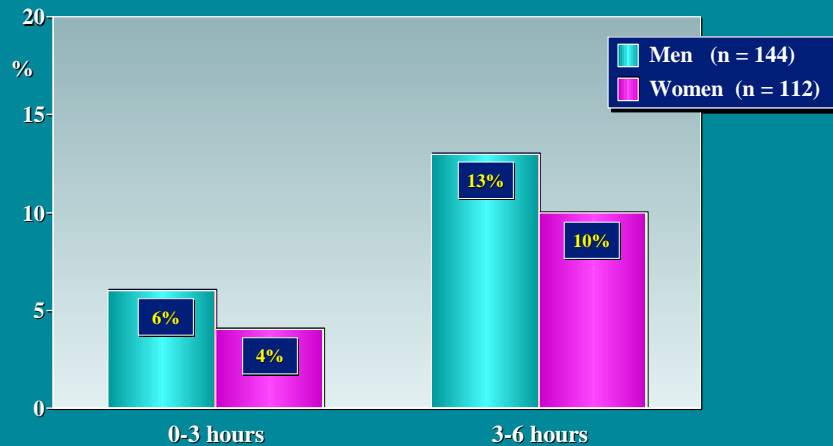
Stroke 2001; 32: 1832-40



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Time from Onset of Symptoms to Hospital Arrival in Men and Women



Eur Heart J 2006;27:994-1005



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Recommendations on Stroke Research

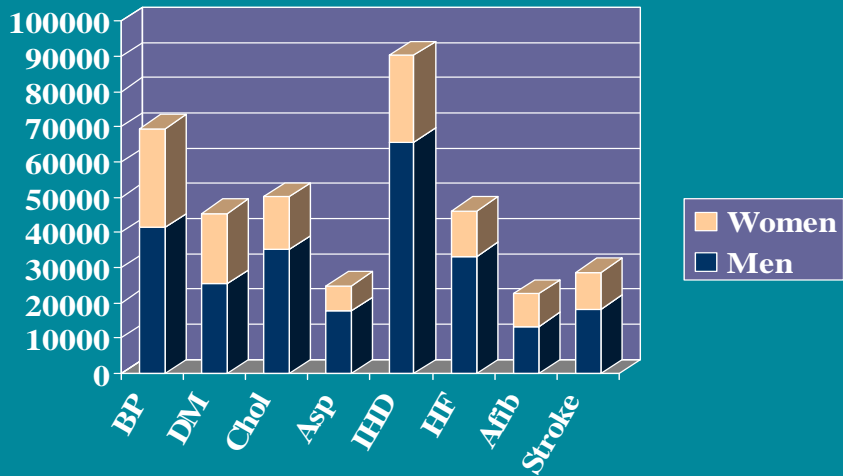
- ♥ Research is needed to clarify the origin on gender differences in stroke incidence and post-stroke disability, and the reasons for the under-treatment of women with thrombolytic therapy.



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



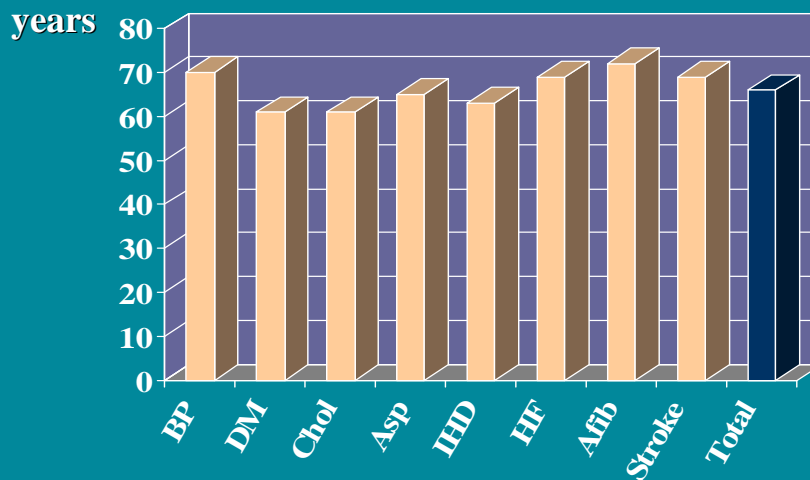
Participants in Clinical Trials by Gender



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



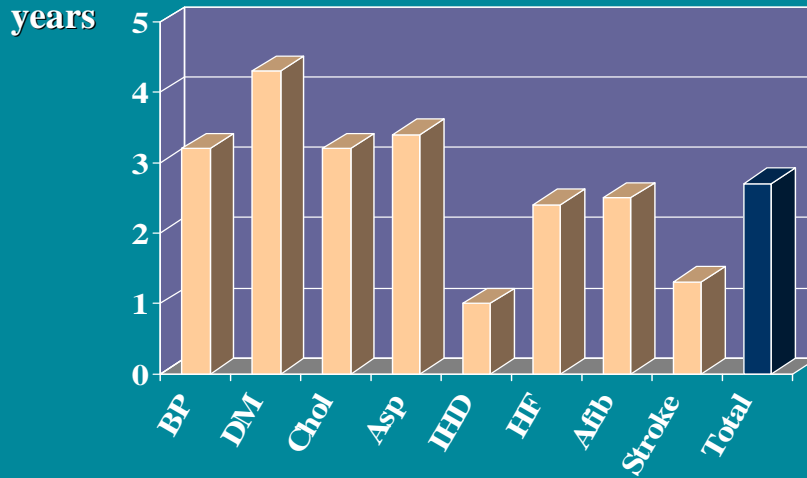
Mean Age of Participants in Clinical Trials



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



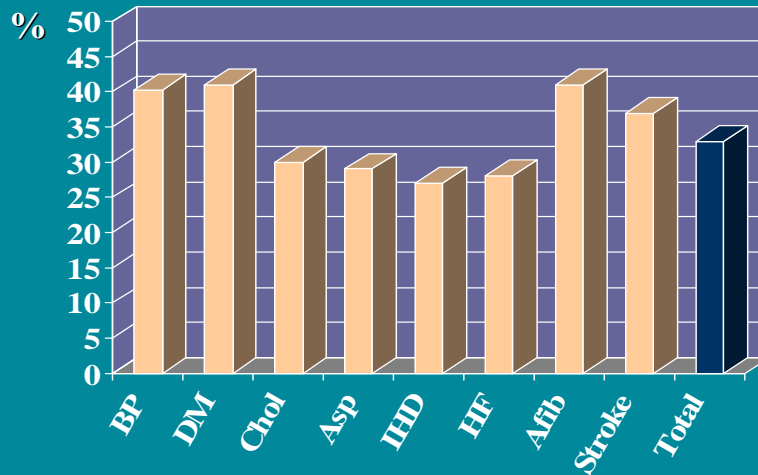
Mean Follow-up of Clinical Trials



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



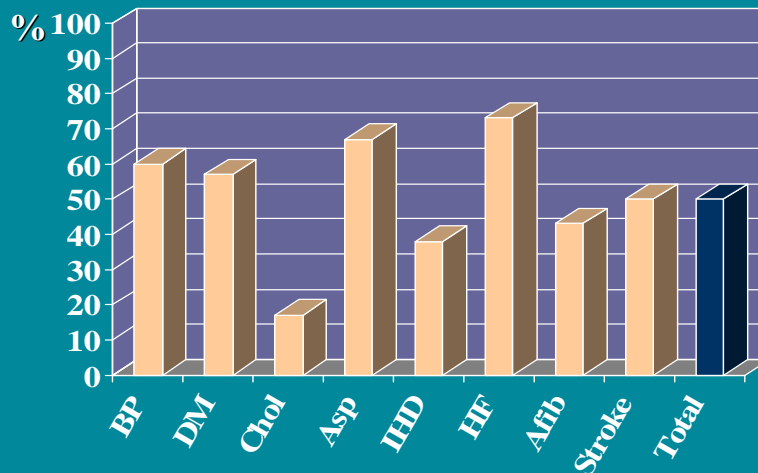
Percentage of Women in Clinical Trials



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Clinical Trials with Analysis by Gender



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Summary

- Despite an increase in the number and proportion of women enrolled in cardiovascular clinical trials, there is still an under-representation of women, particularly in the field of cholesterol-lowering therapy, ischemic heart disease and heart failure, which may have affected the reliability of subgroup analysis.
- Clinical trials and meta-analyses on cardiovascular diseases did not show a significantly lower efficacy of interventions in women when compared with men, although 50% of the studies did not report an analysis of the results by gender. For some therapies there is even a suggestion for greater efficacy in women than in men, as in the case of cardiac resynchronization therapy in heart failure or thrombolysis after ischemic stroke.
- Women may have more frequently adverse effects, such as for newer glucose-lowering agents, or in the treatment of acute coronary syndromes, where they appear to be more prone to bleedings. Some trials provided conflicting results in women, for example in the assessment of the efficacy of early invasive strategies in acute coronary syndromes.



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Reasons for the Under-representation of Women in Clinical Trials

- ♥ Lower occurrence of outcomes in females, which may affect the costs of the study.
- ♥ Lower willingness of women to be enrolled, due to their misperception of risk of cardiovascular diseases.
- ♥ Difficulties in terms of transportation or support for the follow-up visits.



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Reccomendations for Cardiovascular Research

- ♥ Clinical trials enrolling a significant proportion of women to allow for pre-specified gender analysis should be conducted, especially in the fields of ischemic heart disease, cholesterol-lowering therapy and heart failure.
- ♥ Enrolment criteria and follow-up duration should allow the inclusion of women at risk of developing cardiac events.
- ♥ External barriers to the enrolment of women in clinical trials need to be addressed, and in particular transportation difficulties for follow-up visits.
- ♥ Regulatory agencies are urged to adopt strict rules on the inclusion of women in clinical trials and a systematic gender analysis.



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



HEART for Women Act – US Senate 2009



II

111TH CONGRESS
1ST SESSION

S. 422

To amend the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act to improve the prevention, diagnosis, and treatment of heart disease, stroke, and other cardiovascular diseases in women.



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



HEART for Women Act – US Senate 2009

Directs the Secretary to:

- (1) require that a new drug application include any clinical data possessed by the applicant that relates to the safety and effectiveness of the drug involved by gender, age, and racial subgroup;
- (2) develop guidance for the staff of the Food and Drug Administration (FDA) to ensure that new drug applications are adequately reviewed to determine whether they include the required clinical data.



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy



Conclusions

♥ Scientific societies, patients' associations and foundations should cooperate with European institutions, national health care authorities and regulatory agencies to promote scientific research on gender issues in cardiovascular medicine and a larger representation of women in clinical trials.



Marco Stramba-Badiale, Istituto Auxologico Italiano, Milan, Italy

