L'assistenza specialistica alle persone con diabete nel contesto della medicina di genere

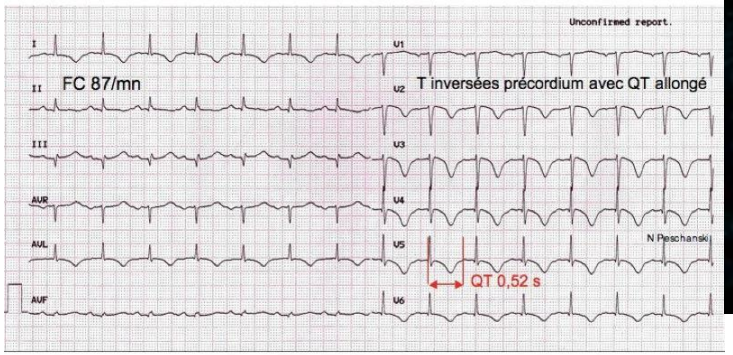
Valeria Manicardi

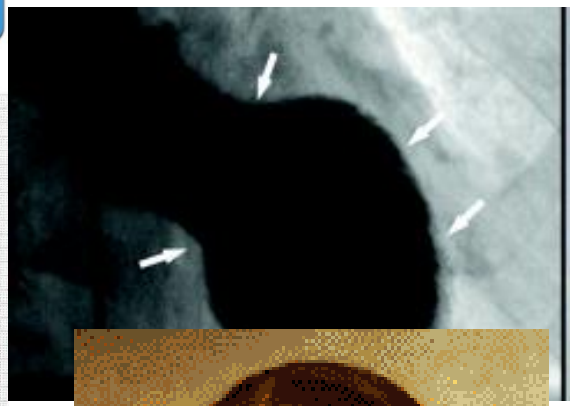
AUSL di Reggio Emilia – Coordinatore Gruppo Donna AMD

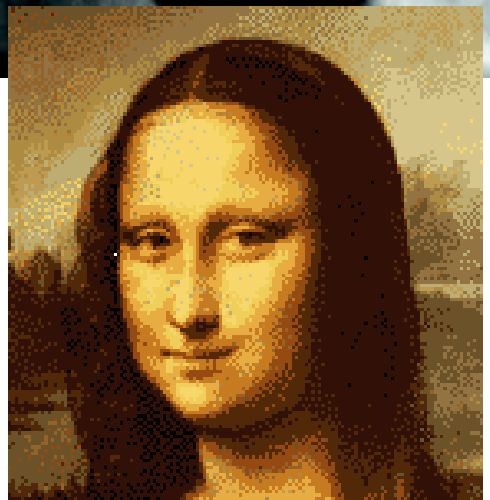
Il Cuore delle Donne: Sindrome di Takotsubo

La S di Takotsubo : Morire di crepacuore .
Perché solo nelle donne ?

Tako-tsubo
Cardiomyopathie de stress







Le differenze di genere nelle espressioni della Cardiopatia ischemica sono oggetto di studio da molto tempo.

Pari Opportunità .... di rischio :

Le donne Diabetiche sono colpite da Infarto tanto come gli uomini:

- hanno perso la protezione ormonale dall'infarto in età fertile

Editorial

Type 2 Diabetes and Cardiovascular Risk in Women

Giuseppina T. Russo,[1] Giovannella Baggio,[2] Maria Chiara Rossi,[3] and Alexandra Kautzky-Willer[4]

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[3]*Laboratory of Clinical Epidemiology of Diabetes and Chronic Diseases, Fondazione Mario Negri Sud, Via Nazionale 8/A, 66030 Santa Maria Imbaro, Italy*
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Intern J Endocrinology ,2015

Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies

Rachel Huxley, Federica Barzi, Mark Woodward

BMJ, 21 December 2006

Abstract

Objective To estimate the relative risk for fatal coronary heart disease associated with diabetes in men and women.
Design Meta-analysis of prospective cohort studies.
Data sources Studies published between 1966 and March 2005, identified through Embase and Medline, using a combined text word and MESH heading search strategy, in addition to studies from the Asia Pacific Cohort Studies Collaboration.
Review methods Studies were eligible if they had reported estimates of the relative risk for fatal coronary heart disease comparing men and women with and without diabetes. Studies were excluded if the estimates were not adjusted at least for age.
Results 37 studies of type 2 diabetes and fatal coronary heart disease among a total of 447 064 patients were identified. The rate of fatal coronary heart disease was higher in patients with diabetes than in those without (5.4 *v* 1.6%). The overall summary relative risk for fatal coronary heart disease in patients with diabetes compared with no diabetes was signifi[illegible] 3.50, 9[illegible] After [illegible] age, th[illegible] reduced but still highly significant. The pooled ratio of the relative risks (women: men) from the 29 studies with multiple adjusted estimates was 1.46 (1.14 to 1.88).
Conclusions The relative risk for fatal coronary heart disease associated with diabetes is 50% higher in women than it is in men. This greater excess coronary risk may be explained by more adverse cardiovascular risk profiles among women with diabetes, combined with possible disparities in treatment that favour men.

RR F vs M nei 29 studi corretti per fattori confondenti = 1,49

Le Donne Diabetiche hanno il 50% in più di rischio di Eventi CV fatali rispetto ai Maschi.

Cause :

- Peggiore profilo di rischio
- Sottotrattamento con Statine, ASA, Antiipertensivi

Donne con DM2 hanno un rischio aumentato di eventi CV e di mortalità del 50% rispetto ai maschi

Recent studies found that men with diabetes or established cardiovascular disease are more likely to receive aspirin, statins, or antihypertensive drugs than are women. For example, one study [illegible] cardiovascular [illegible]% of men with [illegible] reported from the United Kingdom prospective diabetes study,[39] where women with diabetes were significantly less likely to use aspirin compared with men. In two recent studies from the United States, women with diabetes were also less likely to be treated with aspirin and lipid lowering agents or to achieve recommended levels of blood pressure or low density lipoprotein cholesterol than were men.[40 41] Therefore more

Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies

Rachel Huxley, Federica Barzi, Mark Woodward

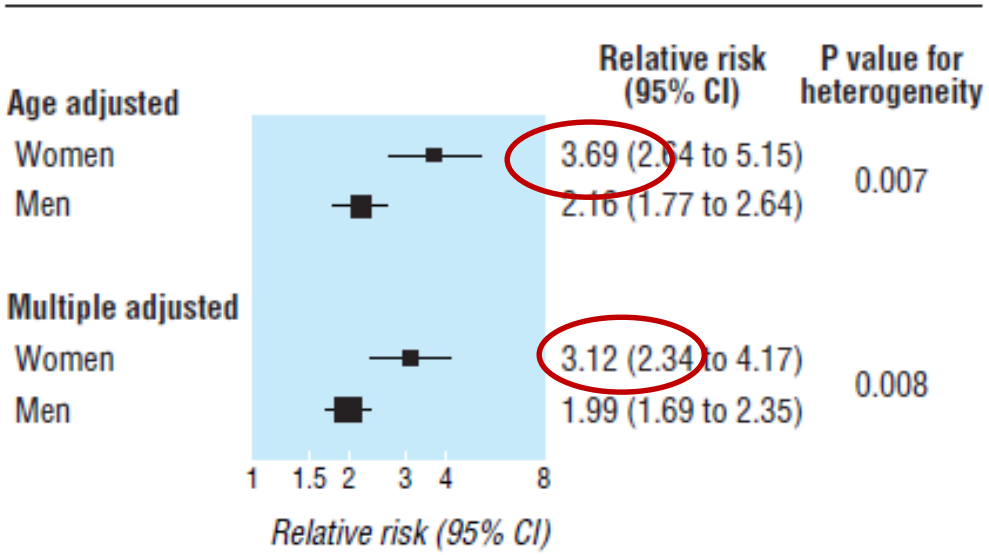


Fig 2 Overall summary estimates of relative risks and 95% confidence intervals for fatal coronary heart disease in men and women with and without diabetes in 22 studies that reported both age and multiple adjusted coefficients

Huxley, BMJ 2006

Le donne con T2DM hanno anche un aumentato rischio di Stroke

Diabetologia (2006) 49:2859–2865
DOI 10.1007/s00125-006-0493-z

ARTICLE

Risk of stroke in people with type 2 diabetes in the UK: a study using the General Practice Research Database

H. E. Mulnier · H. E. Seaman · V. S. Raleigh · S. S. Soedamah-Muthu · H. M. Colhoun · R. A. Lawrenson · C. S. De Vries

Age-adjusted HR for stroke in DM2 subjects vs non diabetic subjects was:
- 2.08 (95%CI:1.94-2.24) in men
- 2.32 (95%CI: 2.16-2.49) in women.

The increase in risk attributable to diabetes was highest
- in young women (HR 8.18; 95%CI 4.31-15.51) and decreased with age.

Table 4 Hazard ratios (95% CI) for stroke in diabetes compared with no diabetes stratified by sex and attained age-group

	All	Men	Women
Diabetes/no diabetes (*n*)	41,799/ 202,733	22,178/ 107,285	19,621/ 95,448
Age (years)			
35–54	5.64 (3.91–8.13)	4.66 (2.96–7.33)	8.18 (4.31–15.51)
55–64	3.81 (3.23–4.49)	3.31 (2.69–4.07)	4.89 (3.71–6.45)
65–74	2.54 (2.31–2.79)	2.35 (2.07–2.65)	2.83 (2.45–3.28)
75–84	1.90 (1.75–2.06)	1.69 (1.49–1.90)	2.10 (1.89–2.34)
≥85	1.69 (1.49–1.92)	1.60 (1.28–1.99)	1.74 (1.49–2.03)
All ages	2.19 (2.09–2.32)	2.08 (1.94–2.24)	2.32 (2.16–2.49)

Research Article

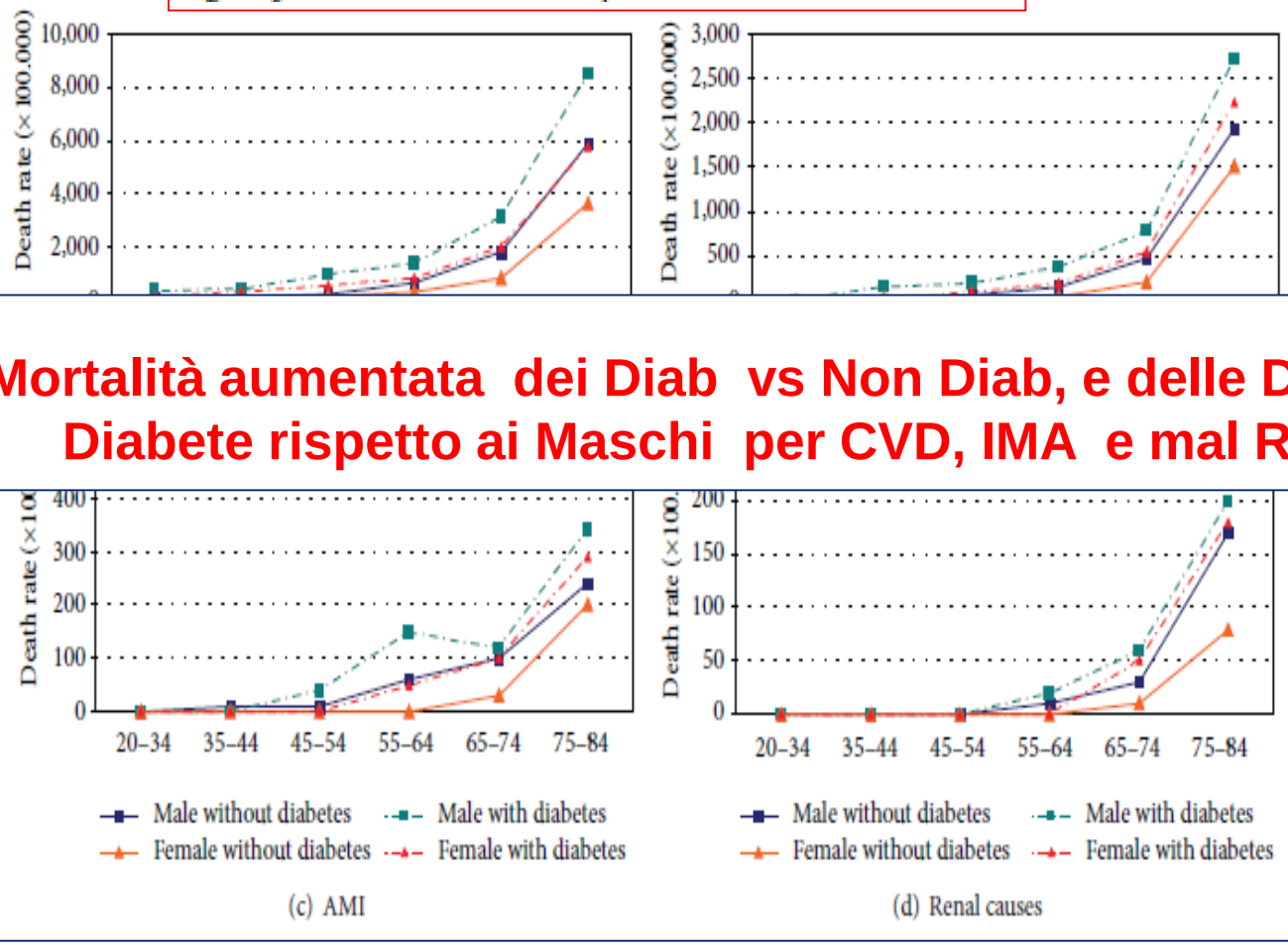
Sex Differences in Cardiovascular Mortality in Diabetics and Nondiabetic Subjects: A Population-Based Study (Italy)

Paola Ballotari,[1,2] Sofia Chiatamone Ranieri,[3] Ferdinando Luberto,[1,2] Stefania Caroli,[1,2] Marina Greci,[4] Paolo Giorgi Rossi,[1,2] and Valeria Manicardi[5]

Hindawi Publishing Corporation
International Journal of Endocrinology
Article ID 914057

Dati della Provincia di Reggio Emilia, 2014

Age-specific death rates by sex and diabetes status:



Mortalità aumentata dei Diab vs Non Diab, e delle Donne con Diabete rispetto ai Maschi per CVD, IMA e mal Renale.

Dati della Provincia di RE :

I DM2 HANNO UN MAGGIOR RISCHIO DI INCORRERE IN UN EVENTO CARDIOVASCOLARE MAGGIORE (MACE) vs AI NON DIABETICI?

Tassi standardizzati (x10.000) e rischio relativo per sesso (i soggetti senza DM2 sono il riferimento)

	UOMINI			DONNE		
EVENTO:	**SENZA DM2**	**CON DM2**	**IRR (95%CI)**	**SENZA DM2**	**CON DM2**	**IRR (95%CI)**
ICTUS	37.28	74.70	**1.86 (1.68-2.06)**	30.10	61.73	**1.81 (1.60-2.04)**
INFARTO	39.04	78.02	**1.78 (1.60-1.98)**	16.13	47.58	**2.58 (2.22-2.99)**
SCOMPENSO	**21.47**	**63.71**	**2.78 (2.48-3.12)**	**17.10**	**48.83**	**2.59 (2.27-2.97)**

I D HANNO UN MAGGIOR RISCHIO, QUASI DOPPIO PER ICTUS E INFARTO, QUASI TRIPLO PER SCOMPENSO, ma le Donne hanno un Rischio di IMA > dei Maschi

La Medicina di Genere in Diabetologia nasce in AMD nel 2010 : il patrimonio degli ANNALI in ottica di genere

Esistono differenze legate al genere

- nell' accesso alle cure ?
- nella Qualità della Cura erogata ?
- nel profilo di rischio CV ?
- nella appropriatezza ed intensità di cura ?

Le Monografie di genere

Differenze di Genere

Nel DT2

Nel DT1

415.320 DT2 seguiti da 236 servizi in Italia nel 2009.

28.802 DT1 seguiti da 320 servizi di diabetologia in Italia nel 2011

2012

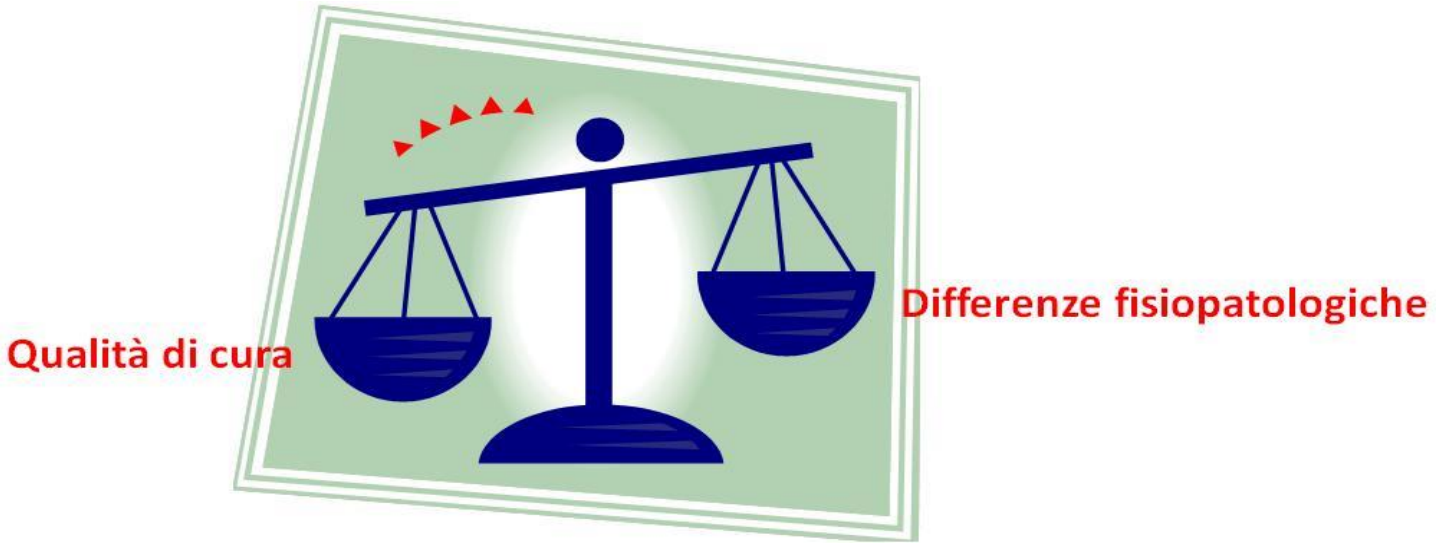
2014

(Diabetes Care 36:3162-3168,2013).

PLOS One – Ottobre 2016

Annali AMD

- Le differenze di genere sono giocate tra differenze di natura fisiopatologica e differenze di natura assistenziale.
- **Cosa ci dicono gli Annali AMD sulle differenze di genere nel diabete di tipo 1 e di T2 ?**



Epidemiology/Health Services Research

ORIGINAL ARTICLE

DT2

Sex Disparities in the Quality of Diabetes Care: Biological and Cultural Factors May Play a Different Role for Different Outcomes

A cross-sectional observational study from the AMD Annals initiative

MARIA CHIARA ROSSI, MSCPHARMCHEM[1]
MARIA ROSARIA CRISTOFARO, MD[2]
SANDRO GENTILE, MD[3]
GIUSEPPE LUCISANO, MSCSTAT[1]
VALERIA MANICARDI, MD[4]
MARIA FRANCA MULAS, MD[5]
ANGELA NAPOLI, MD[6]
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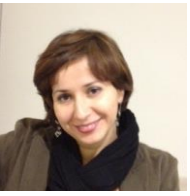
CONCETTA SURACI, MD[7]
CARLO GIORDA, MD[8]
ON BEHALF OF THE AMD ANNALS STUDY GROUP*

Gender medicine integrates aspects of biology, sociology, ethnicity, and culture responsible for different responses to care in women and men (1). Gender medicine applied to the field of diabetes care is particularly relevant because women with diabetes, regardless

OBJECTIVE—To investigate the quality of type 2 diabetes care according to sex.



- ✓236 centri
- ✓188,125 donne
- ✓227,169 uomini

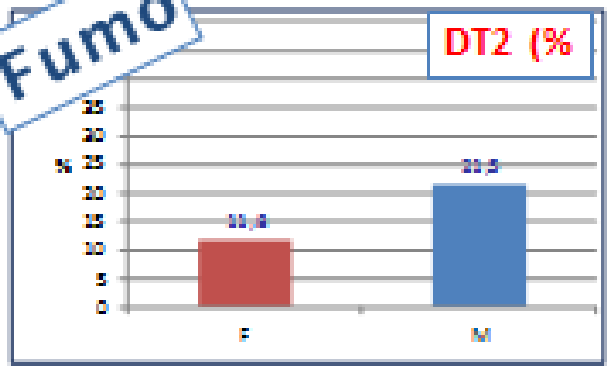
Differenze di genere nel DT2

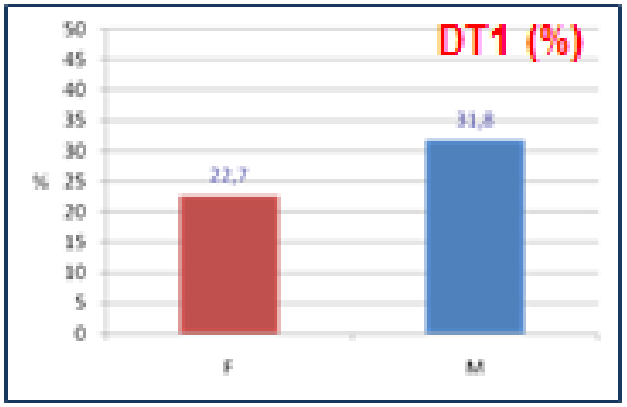
- **OBESITA' (BMI)**
- **COMPENSO METABOLICO (HbA1c)**
- **PROFILO LIPIDICO (LDL-C)**

Figure 1. Favorable outcomes in diabetic men and women and age (*AMD Annals*). The intermediate outcomes (target of HbA1c, PA, C-LDL, BMI) are systematically in favor of men, independently of age.

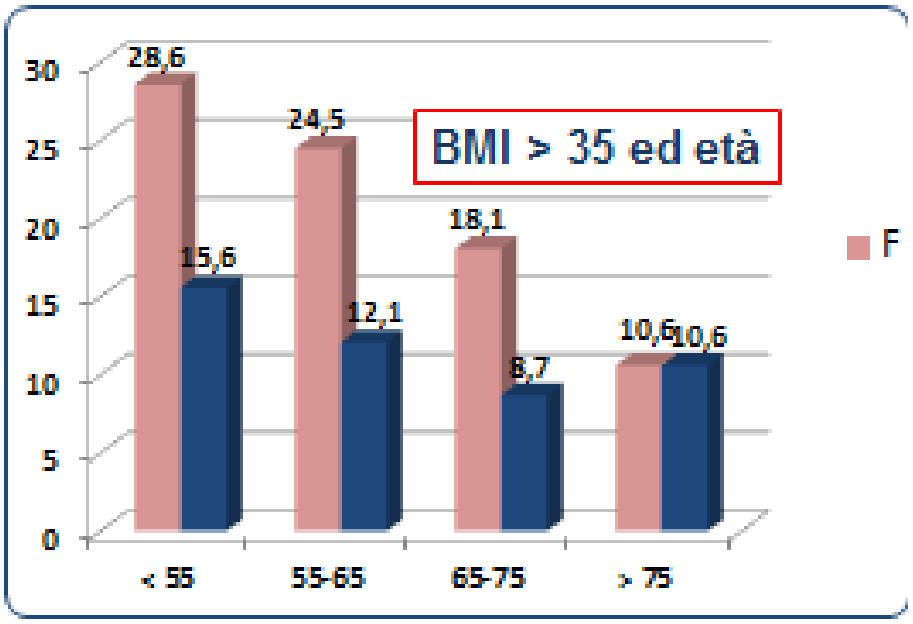
FUMO e BMI nel Diabete

Fumo





DT2



Compenso Metabolico peggiore nel DT2 :

Età, BMI e Durata di Malattia sono più elevati , Ma Dopo aggiustamento :

	M	F
Età (anni)	65.7±11.1	68.4±11.4
BMI (Kg/m2)	29.1±4.6	30.2±5.9
Fumo (%)	21.5%	11.8%
Durata del diabete (anni)	10.0±9.	11.1±9.7

Indicatori di esito intermedio:	F	M	delta
HbA1c ≤7.0% →	41.0	44.8	- 3.8
HbA1c >8.0% →	29.9	27.2	+ 2.7

Profilo Lipidico nel DT2

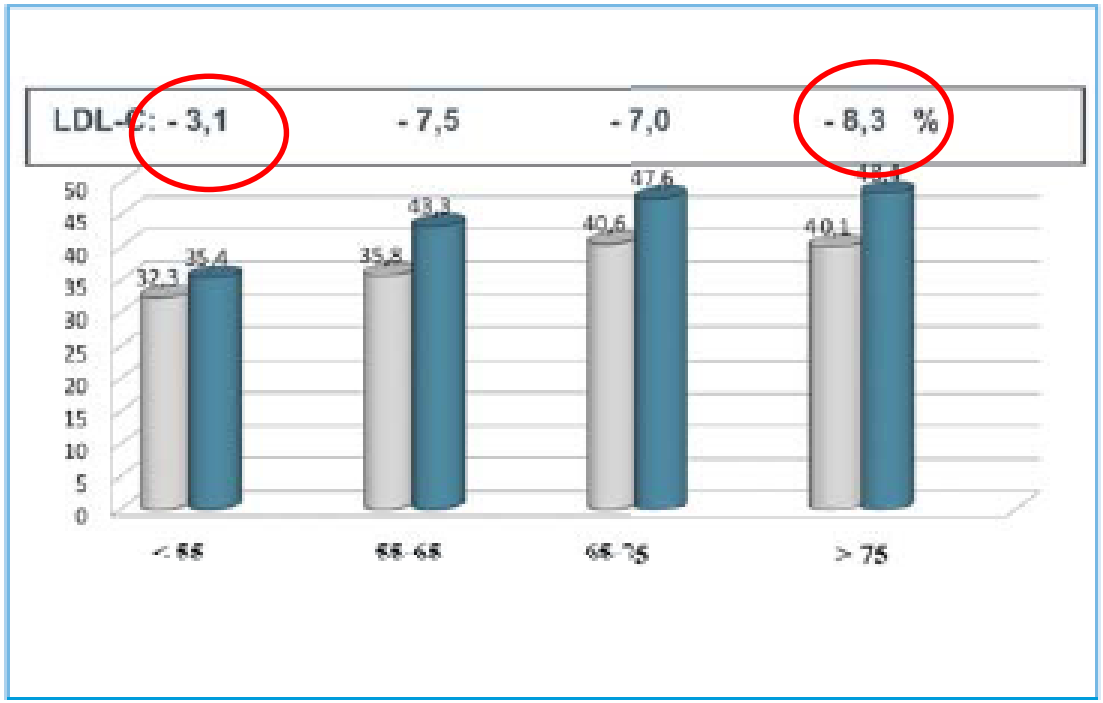


Figure 2. Target of LDL-C in men (blue) and women (grey) and age. The intermediate outcomes (target of HbA1c, PA, C-LDL, BMI) are systematically in favor of men, independently of age. The proportion of men and women with LDL-C target value is unfavorable to women, and the gap increases with age.

LDL Col < 100 mg/dl

L'outcome favorevole per LDL a target è sistematicamente a Sfavore delle donne, ed il gap aumenta con l'età e la durata del DM

Il mancato raggiungimento dei target di LDL-C è sempre a sfavore delle Donne con DT2 :

- Sia trattate che non tratte con Statine

- le differenze aumentano con età e durata del DM.

Le Donne con DT2 più anziane sono a maggior rischio di CHD.

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Volume 2015, Article ID 957105, 8 pages
http://dx.doi.org/10.1155/2015/957105

Hindawi

Research Article

Age- and Gender-Related Differences in LDL-Cholesterol Management in Outpatients with Type 2 Diabetes Mellitus

Giuseppina Russo,[1] Basilio Pintaudi,[2] Carlo Giorda,[3] Giuseppe Lucisano,[2] Antonio Nicolucci,[2] Maria Rosaria Cristofaro,[4] Concetta Suraci,[5] Maria Franca Mulas,[6] Angela Napoli,[7] Maria Chiara Rossi,[2] and Valeria Manicardi[8]

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[7]*Department of Clinical and Molecular Medicine, Faculty of Medicine and Psychology, S. Andrea Hospital, Sapienza University, 00189 Rome, Italy*

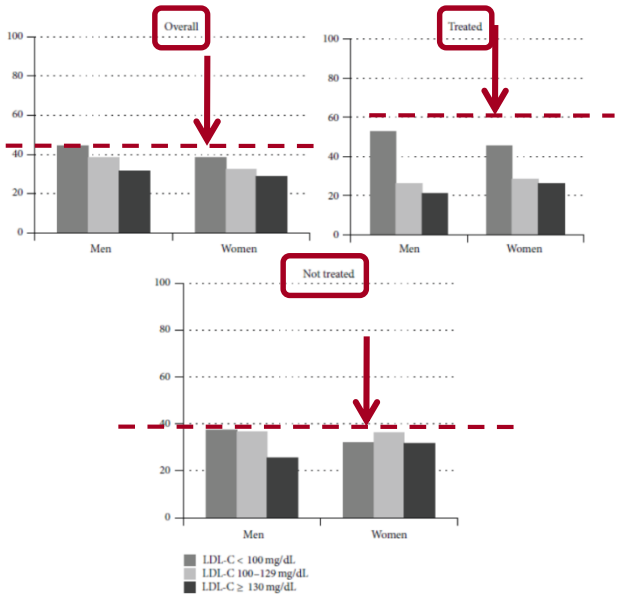


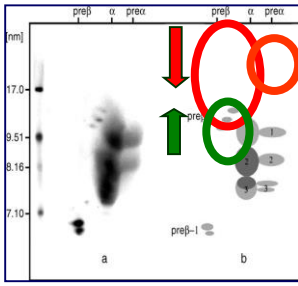
FIGURE 1: LDL-C classes according to gender and lipid-lowering treatment.

Atherosclerosis 210 (2010) 294–301

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis



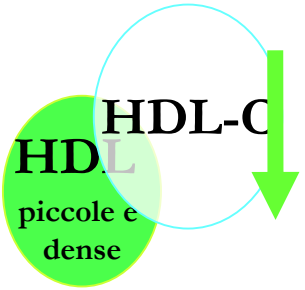
Influence of menopause and cholesteryl ester transfer protein (CETP) *Taq*IB polymorphism on lipid profile and HDL subpopulations distribution in women with and without type 2 diabetes

Giuseppina T. Russo[a,*], Kathleen V. Horvath[b], Antonino Di Benedetto[a], Annalisa Giandalia[a], Domenico Cucinotta[a], Bela Asztalos[b]

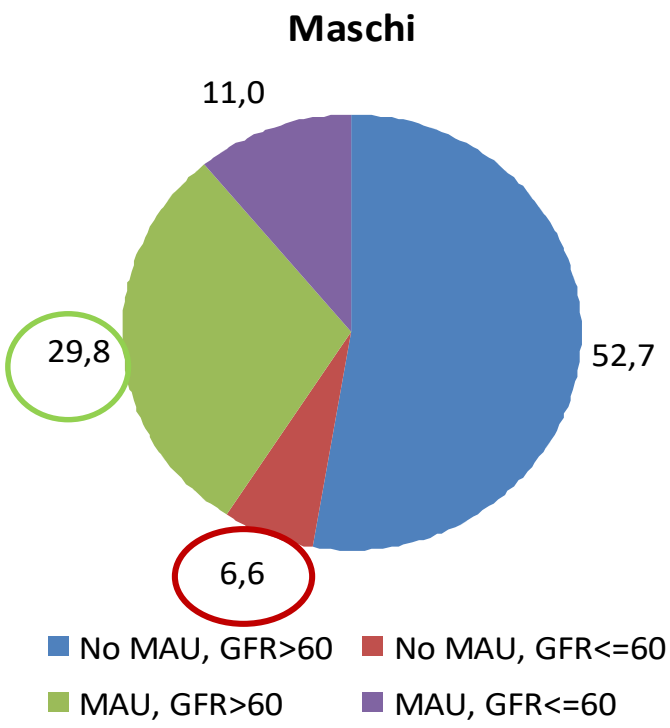
[a] Department of Internal Medicine, University of Messina, Italy
[b] Lipid Metabolism Laboratory, JM USDA Human Nutrition Research

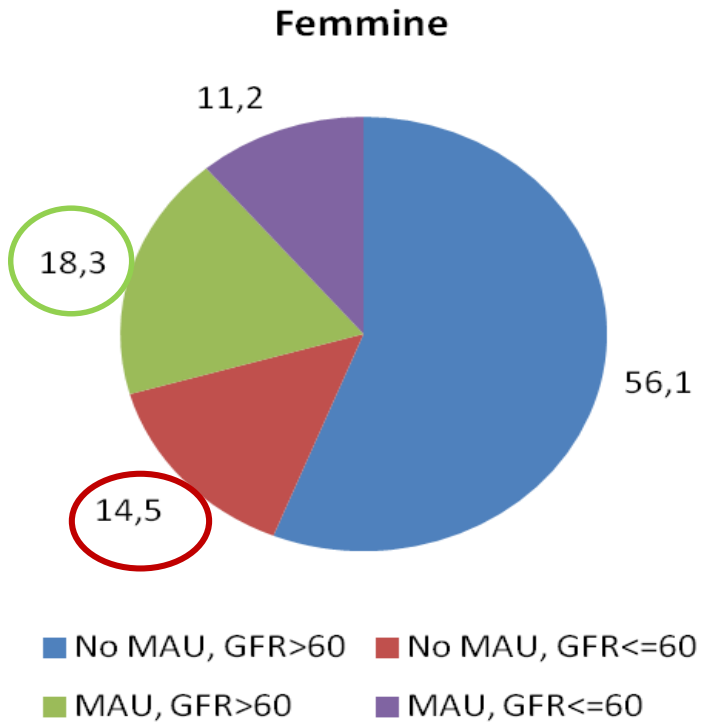
	Donne con DM2	Controlli	P
α-1 (mg/dl)	19.32±8.97	23.35±9.58	0.006
α-2 (mg/dl)	41.29±9.62	45.47±8.99	0.005
α-3 (mg/dl)	18.18±5.56	16.36±3.74	0.02
α-4 (mg/dl)	10.90±3.58	9.71±3.07	0.02
Pre-α1 (mg/dl)	5.51±3.39	6.74±3.46	0.02
Pre-α2 (mg/dl)	6.77±2.99	7.10±2.48	-
Pre-α3 (mg/dl)	2.46±0.97	1.95±0.63	0.0001
Pre-β1 (mg/dl)	15.30±7.96	15.16±9.81	-
Pre-β2(mg/dl)	1.84±1.02	2.36±1.24	0.004

Donne DM2 senza CHD hanno lo Stesso profilo sottopopolazioni HDL degli uomini con pregresso IMA



Distribuzione della popolazione divisa per SESSO in relazione alla presenza di MAU e di riduzione del GFR (%)





I dati raccolti nel corso della normale pratica clinica da 251 Servizi di Diabetologia diffusi sull'intero territorio nazionale

415.346 soggetti con diagnosi di diabete di tipo 2 (DM2) sono stati visti nel corso dell'anno 2009.

I dati raccolti mediante cartella clinica informatizzata e costituzione del File Dati AMD.


Nephrol Dial Transplant (2014) 29: 657–662
doi: 10.1093/ndt/gft506
Advance Access publication 6 January 2014

Kidney dysfunction and related cardiovascular risk factors among patients with type 2 diabetes

Salvatore De Cosmo[1], Maria Chiara Rossi[2], Fabio Pellegrini[2], Giuseppe Lucisano[3], Simonetta Bacci[1], Sandro Gentile[3], Antonio Ceriello[4], Giuseppina Russo[5], Antonio Nicolucci[2], Carlo Giorda[6], Francesca Viazzi[7], Roberto Pontremoli[7] and the AMD-Annals Study Group

Nutrition, Metabolism & Cardiovascular Diseases (2013) 23, 235–241

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/nmcd

Nutrition, Metabolism & Cardiovascular Diseases

Women show worse control of type 2 diabetes and cardiovascular disease risk factors than men: Results from the MIND.IT Study Group of the Italian Society of Diabetology

L. Franzini [a,*,1], D. Ardigò [a,1], F. Cavalot [b,1], R. Miccoli [c,1], A.A. Rivellese [d,1], M. Trovati [b,1], I. Zavaroni [a,1], O. Vaccaro [d,1]

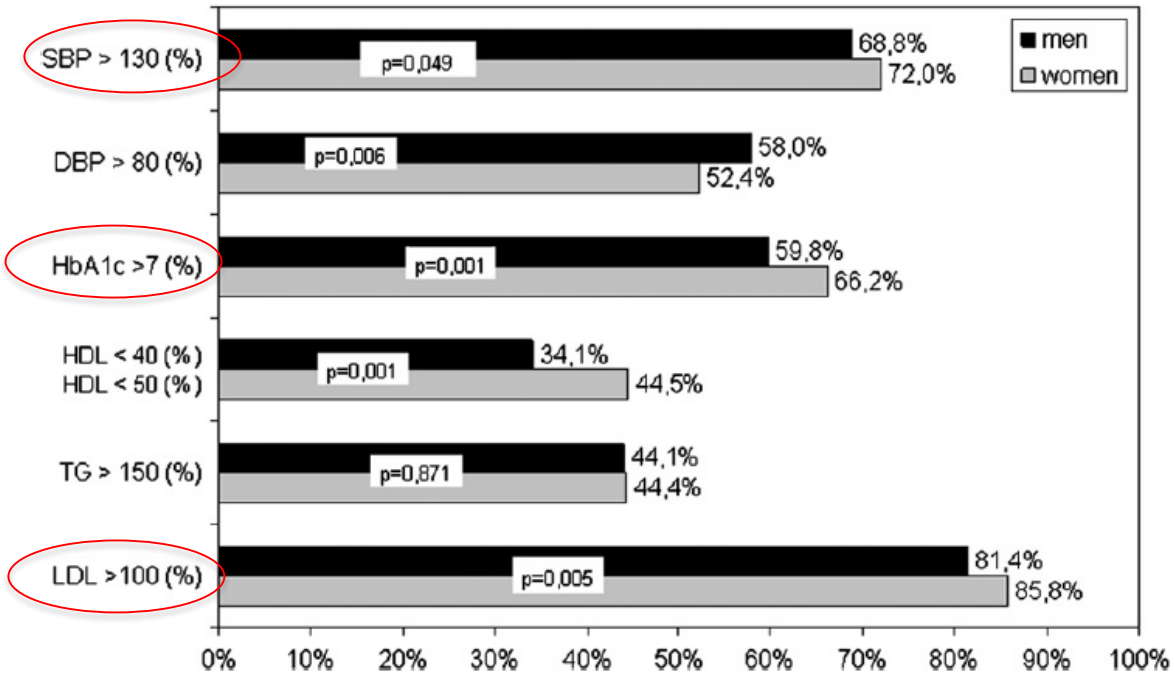


Figure 1 Proportion (%) of men and women out of target for glycated haemoglobin and the cardiovascular risk factors measured in the study. Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated haemoglobin; HDL, HDL cholesterol; TG, triglycerides; LDL, LDL cholesterol.

AHA Scientific Statement

Sex Differences in the Cardiovascular Consequences of Diabetes Mellitus

A Scientific Statement From the American Heart Association

Table 1. Sex Differences in CVD Risk Factors and Outcomes in DM

Cardiovascular risk profile	More adverse in women with DM: impaired endothelium-dependent vasodilation, worse atherogenic dyslipidemia, prothrombotic coagulation profile, higher metabolic syndrome prevalence
	Compared with men, women have worse HbA_{1c} and blood pressure control
	CHD predictors in T1DM (Pittsburgh Epidemiology of Diabetes Complications Study)
	Women only: abdominal adiposity, insulin resistance, HbA_{1c}
	Men and women: inflammatory markers (fibrinogen, white blood cell count), microalbuminuria
Adiposity	Abdominal adiposity was more strongly associated with cardiovascular mortality in women compared with men with DM in a Finnish population
Outcome	
CHD	Women with DM have a 2-fold excess CHD risk compared with men
	Myocardial infarction occurs earlier and has higher mortality in women with DM compared with men
	Revascularization rates (angioplasty, coronary artery bypass grafting) are lower in women with DM compared with men
Heart failure	Risk of incident heart failure is greater in women than men
Stroke	Male stroke patients have a higher prevalence of DM than female stroke patients
	DM is a stronger risk factor for stroke in women compared with men

Table 2. Sex Differences in CVD Treatments and Interventions in DM

CVD Treatment/Intervention	Sex Differences
Prescription of pharmacotherapy	Compared with men, women have lower frequency of lipid-lowering (statin) therapy, lower aspirin use, and lower ACE inhibitor and β-blocker use
	Lower medication adherence in women compared with men in some but not all studies

Il genere influenza le scelte Terapeutiche ?

European Heart Journal (2011) **32**, 1337–1344
doi:10.1093/eurheartj/ehr027

CLINICAL RESEARCH

Factors influencing underutilization of evidence-based therapies in women†

Raffaele Bugiardini [1]*, Andrew T. Yan [2], Raymond T. Yan [2], David Fitchett [2], Anatoly Langer [2], Olivia Manfrini [1], and Shaun G. Goodman [2], on behalf of the Canadian Acute Coronary Syndrome Registry I and II Investigators*

[1]Dipartimento di Medicina Interna, Cardioangiologia, Epatologia (Padiglione 11), University of Bologna, Via Massarenti 9, 40138 Bologna, Italy; and [2]Terrence Donnelly Heart Centre, Division of Cardiology, St. Michael's Hospital, University of Toronto and the Canadian Heart Research Centre, Toronto, Ontario, Canada

Received 18 October 2010; revised 8 January 2011; accepted 25 January 2011; online publish-ahead-of-print 7 March 2011

See page 1313 for the editorial comment on this article (doi:10.1093/eurheartj/ehr083)

Aims Previous studies have reported differences in the use of cardiovascular medications for acute coronary syndromes (ACSs) according to the sex of the patient. We analysed which clinical factors are associated with underutilization of evidence-based therapies in women.

Methods and results From the Canadian Registry of ACS I and II, 6558 patients (4471 men and 2087 women) with a final diagnosis of ACS were selected for the current analysis. Covariates were chosen using the approach described by Blackstone. The final selected model included 23 patient clinical variables. Women were less likely than men to receive beta-blockers (75.76 vs. 79.24%; $P < 0.01$), lipid-modifying agents (56.37 vs. 65.44%; $P < 0.0001$), and angiotensin-converting enzyme (ACE)-inhibitors (55.52 vs. 59.99%; $P < 0.01$). Female sex and clinical decision not to investigate with cardiac catheterization were the strongest independent predictors for not receiving lipid-modifying agents and ACE-inhibitors. Age, Killip class 2, and Killip class 3/4 were significant independent predictors of underutilization of beta-blocker use. Women were older (69 ± 12 vs. 64 ± 12; $P < 0.01$) with a higher prevalence of Killip class ≥ 2 (19.95 vs. 15.54%; $P < 0.068$), and they were less likely to be referred for cardiac catheterization (41.9 vs. 49.6%; $P < 0.001$).

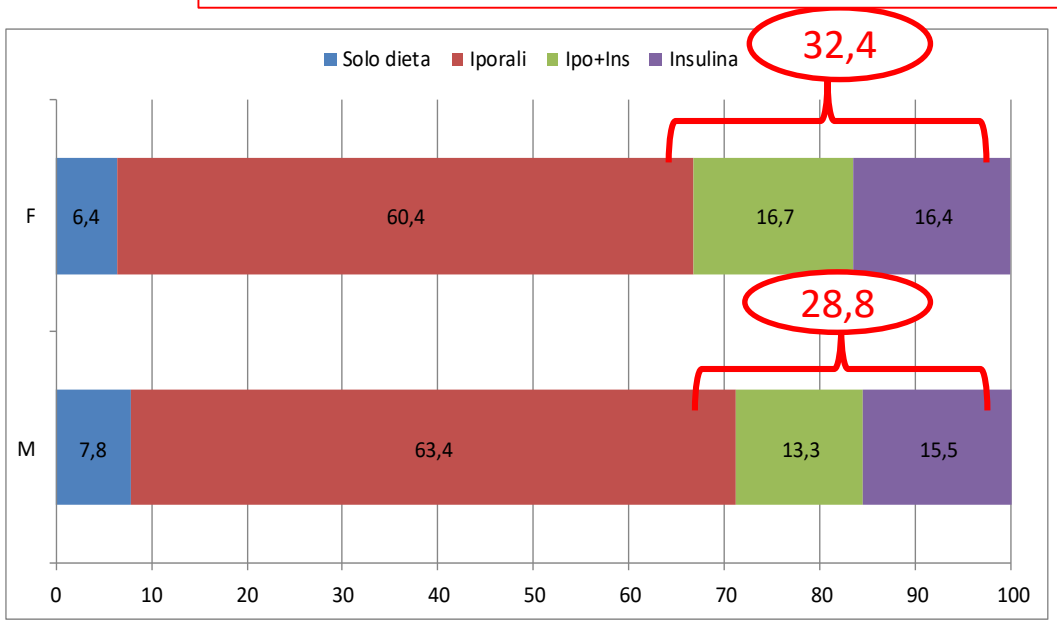
Conclusions The current findings demonstrate that underutilization of evidence-based therapies in women with ACS compared with men is associated with multiple factors related to the patient (age), the consequences of the disease (congestive heart failure), and the physician's assessment of patient risk (decision to catheterize). Female gender remains associated with underutilization of lipid-modifying agents and ACE-inhibitors despite adjustment for these confounders.

Keywords Women • Evidence-based therapies

Il genere femminile Resta un predittore indipendente di sotto Utilizzo di Statine e ACE-I

Sottotrattamento delle donne con Diabete vs uomini

DT2 – Trattamento del diabete . Appropriatezza e Intensità



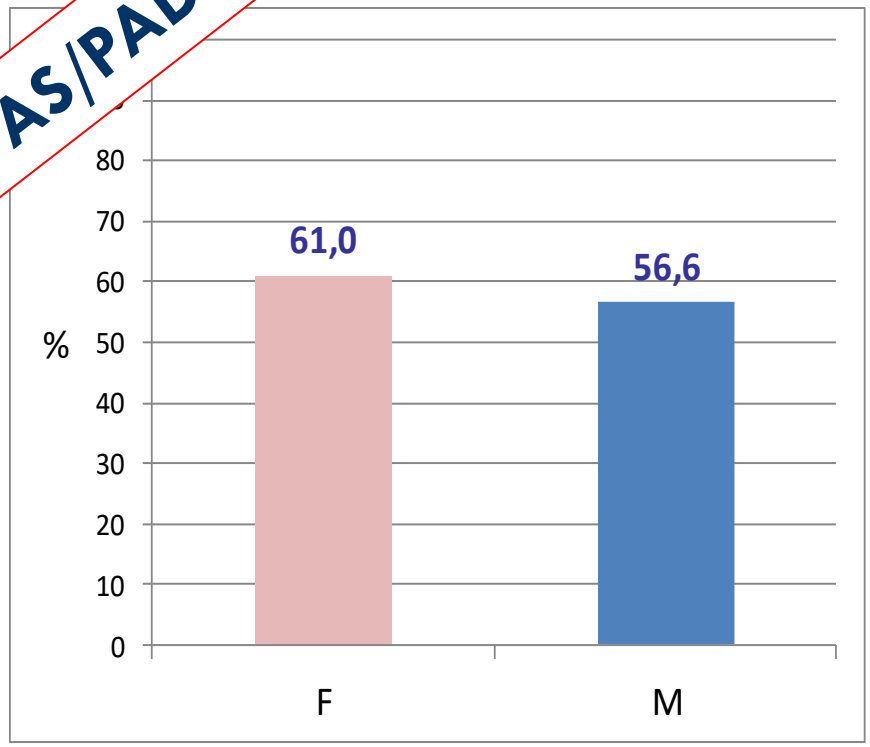
Compenso Glicemico E terapia nel DT2

Le donne con DT2 sono trattate più intensamente :
con Insulina e Insulina + Ipo-Orali

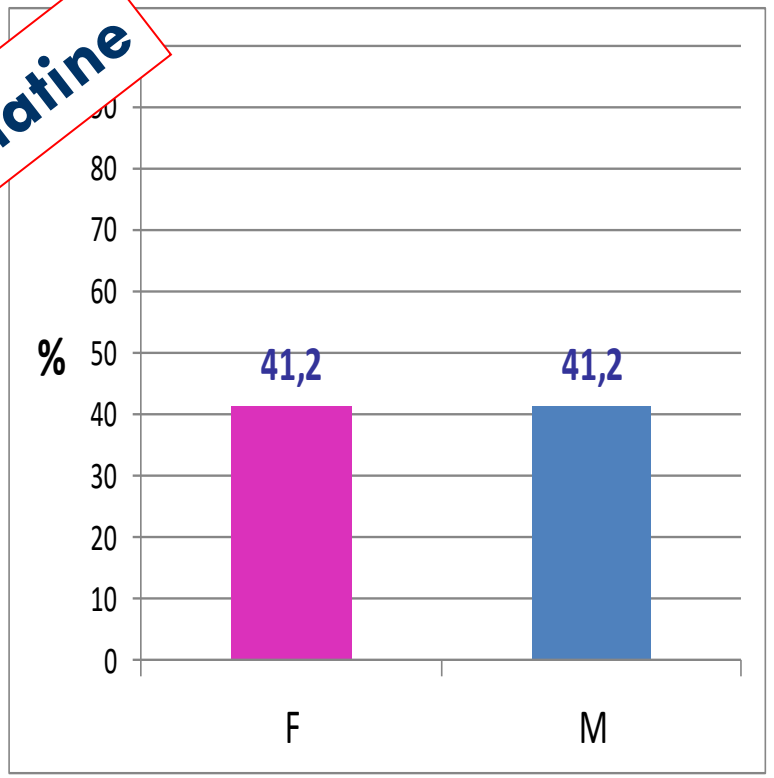
DT2 – Appropriatezza e Intensità di Trattamento

Farmaci Ipolipemizzanti

PAS/PAD



Statine



Le donne sono più frequentemente trattate con farmaci antiipertensivi e con più di 2 farmaci.

Stessa % di M e F trattati con ipolipemizzanti (statine)

Ital J Gender-Specific Med 2016; 2(2): 60-68

Gender differences in type 2 diabetes (Italy)

Valeria Manicardi[1], Maria Chiara Rossi[2], Elisabetta L Romeo[3], Annalisa Giandalia[3], Mariella Calabrese[4], Elena Cimino[5], Daniela Antenucci[6], Paola Bollati[7], Patrizia Li Volsi[8], Ada Maffettone[9], Guglielmina Speroni[10], Concetta Suraci[11], Elisabetta Torlone[12], Giuseppina Russo[3] (on behalf of Gruppo Donna AMD)

1. Department of Int
Research and Epider
4. Diabetology Depa
7. Department of Int
9. Metabolic Unit, Hc
Lodi), Italy; 11. Diabe
Received 2 March 201

RCH - Center for Outcomes
Jniversity of Messina, Messina, Italy;
ology, Lanciano (Chieti), Italy;
Department, AAS5, Pordenone, Italy;
ology, Hospital of Codogno (ASST
aly.

Summary. The im
is particularly evid
major cardiovascu
tion, and have a l
protection by estr
from the *AMD Ann*

ere nell'utilizzo di questi farmaci.
n solo, non ancora del tutto cono-
differenze e vanno esplorati.
abete di tipo 2, rischio cardiova-

Key messages

- Gender-differences have been reported in diabetic patients: in Italy they are less pronounced than in other countries, but it exists despite equal access to specialist care.
- The likelihood to reach metabolic targets (HbA1c, LDL-C, BMI, PA) is systematically unfavorable in diabetic women as compared with men.
- Diabetic women have a worse lipid profile than men, and have a 2-fold higher CHD risk compared with men. Myocardial infarction occurs earlier and has higher mortality in women with DM compared with men.
- Diabetic women are systematically undertreated with CV therapy, such as ASA, ACE – I, β-blockers, hypoglycemic agents, but not in Italy.
- Pathophysiological factors are involved in the greater difficulty to reach LDL-C targets in diabetic women, despite the same drug treatment in Italy.

- **Non ci sono diversità di trattamento ,**

ma esiti peggiori :

- Differenze biologiche /genetiche ?
- Diversa risposta ai farmaci ?
- Resistenza a Statine, ASA, Insulina ?
- Mancata aderenza alle terapie ?

Gershoni and Pietrokovski *BMC Biology* (2017) 15:7
DOI 10.1186/s12915-017-0352-z

BMC Biology

Differenze genetiche tra M e F in 6.500 geni

RESEARCH ARTICLE Open Access

The landscape of sex-differential transcriptome and its consequent selection in human adults

Moran Gershoni* and Shmuel Pietrokovski

Researchers Identify 6,500 Genes That Are Expressed Differently in Men and Women

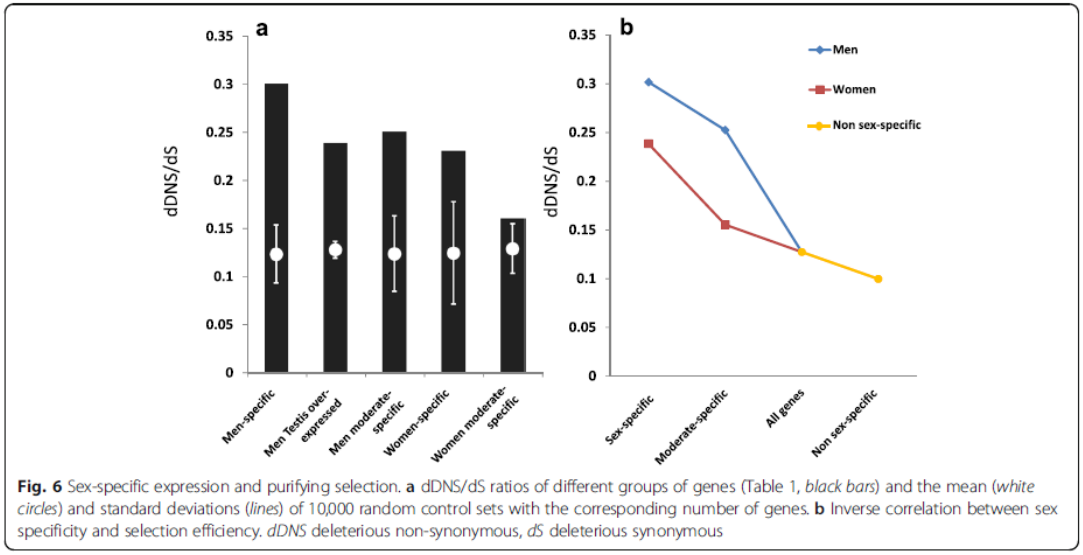


Fig. 6 Sex-specific expression and purifying selection. **a** dDNS/dS ratios of different groups of genes (Table 1, *black bars*) and the mean (*white circles*) and standard deviations (*lines*) of 10,000 random control sets with the corresponding number of genes. **b** Inverse correlation between sex specificity and selection efficiency. *dDNS* deleterious non-synonymous, *dS* deleterious synonymous

Human evolution should be viewed as co-evolution

6500 geni diversi tra M e F potrebbero condizionare
- diverse espressioni delle stesse malattie o diverse risposte ai farmaci

RISPOSTA alle STATINE

Statin Therapy for Secondary Prevention: Is There a Gender Difference? Test for Interaction in Meta-Analysis Revisited

Gutierrez et al,[1] in an analysis of 11 trials with 43,193 patients, concluded that statin therapy has no benefit on stroke and all-cause mortality in women. The investigators found statistically significant 21% and 18% reductions in mortality and stroke with statins for men but only 19% and 8% reductions in women, which did not reach statistical signifi-

Statine in prev 2aria
Meno efficaci nelle donne

1 – donne meno rappresentate

2 – la terapia con Statine non ha effetti benefici sullo Stroke e su tutte le cause di morte nelle Donne Diabetiche in Prev 2aria.

BMJ

RESEARCH

Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials

Giorgia De Berardis, research officer,[1] Michele Sacco, research officer,[1] Giovanni F M Strippoli, editor and regional coordinator of the Cochrane Renal Group,[1,2] Fabio Pellegrini, senior biostatistician,[1] Giusi Graziano, biostatistician,[1] Gianni Tognoni, institute director,[3] Antonio Nicolucci, department head[1]

[1]Department of Clinical

ABSTRACT

(I^2=52.5%; P=0.08). Aspirin significantly reduced the risk of myocardial infarction in men (0.57, 0.34 to 0.94) but not in women (1.08, 0.71 to 1.65; P for interaction=0.056). Evidence relating to harms was inconsistent.

Results Of 157 studies in the literature searches, six were eligible (10 117 participants). When aspirin was compared with placebo there was no statistically significant reduction in the risk of major cardiovascular events (five studies, 9584 participants, relative risk 0.90, 95% confidence interval 0.81 to 1.00), cardiovascular mortality (four studies, n=8557, 0.91, 0.72 to 1.23), or all cause mortality (four studies, n=8557; 0.93, 0.82 to 1.05). Significant heterogeneity was found in the analysis for myocardial infarction (I^2=62%; P=0.02) and stroke (I^2=52.5%; P=0.08). Aspirin significantly reduced the risk of myocardial infarction in men (0.57, 0.34 to 0.94) but not in women (1.08, 0.71 to 1.65; P for interaction=0.056). Evidence relating to harms was inconsistent.

Conclusions A clear benefit of aspirin in the primary prevention of major cardiovascular events in people with diabetes remains unproved. Sex may be an important effect modifier. Toxicity is to be explored further.

INTRODUCTION

Aspirin is recommended by key guideline agencies for the primary prevention of cardiovascular events in people with diabetes, although with some inconsistencies (see web extra on bmj.com).[1-6] Existing mixed, some arguing for definite proof on the lack of aspirin's efficacy in the primary prevention of cardiovascular events,[11] others raising claims that data are still inconclusive and more trials are warranted.[12 13] The persisting uncertainties form the basis of our meta-analysis of trials on the benefits and harms of aspirin in people with diabetes and no pre-existing cardiovascular disease.

METHODS

We included prospective, randomised, controlled, open or blinded trials of participants with diabetes mellitus who were allocated to aspirin treatment or a control group (placebo or no treatment) for the primary prevention of cardiovascular disease. The outcomes of interest were all cause mortality, death from cardiovascular causes, non-fatal myocardial infarction, and non-fatal stroke.

We also included data on subsets of people with diabetes who were enrolled in larger studies of the general population or patients with a mixed baseline risk for cardiovascular events, where aspirin was tested against placebo or no treatment.

ASA in prev 1aria meno efficace nelle donne nella prevenzione dell'Infarto

Pharmacological Research 119 (2017) 195–207

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

Sex-gender-related therapeutic approaches for cardiovascular complications associated with diabetes

Ilaria Campesi[a,*], Flavia Franconi[a,b], Giuseppe Seghieri[c], Marco Meloni[d]

[a] Department of Biomedical Sciences, University of Sassari, Sassari, Italy
[b] Dipartimento Politiche della Persona, Regione Basilicata, Italy
[c] Centro Studi Salute di Genere, AUSL3, Pistoia, Italy
[d] BHF Centre for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh, UK

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Keywords:
Diabetes mellitus
Sex-gender differences
Risk factors
Cardiovascular complications
Therapeutic approaches

ABSTRACT

Diabetes is a chronic disease associated with micro- and macrovascular complications and is a well-established risk factor for cardiovascular disease. Cardiovascular complications associated with diabetes are among the most important causes of death in diabetic patients. Interestingly, several sex-gender differences have been reported to significantly impact in the pathophysiology of diabetes. In particular, sex-gender differences have been reported to affect diabetes epidemiology, risk factors, as well as cardiovascular complications associated with diabetes. This suggests that different therapeutic approaches are needed for managing diabetes-associated cardiovascular complications in men and women. In this review, we will discuss about the sex-gender differences that are known to impact on diabetes, mainly focusing on the cardiovascular complications associated with the disease. We will then discuss the therapeutic approaches for managing diabetes-associated cardiovascular complications and how differences in sex-gender can influence the existing therapeutic approaches.

Diversa risposta ai farmaci ; necessità di nuovi studi e di nuovi farmaci

These novel biomarkers can be considered as promising biomarkers for early detection of diabetes in women, and might be used as basis for developing sex-gender specific treatments for diabetes-associated cardiovascular (or also other) complications.

PLOS ONE | DOI:10.1371/journal.pone.0162960 October 3, 2016

DT1

RESEARCH ARTICLE

Gender-Disparities in Adults with Type 1 Diabetes: More Than a Quality of Care Issue. A Cross-Sectional Observational Study from the AMD Annals Initiative

Valeria Manicardi[1☯], Giuseppina Russo[2☯], Angela Napoli[3☯], Elisabetta Torlone[4☯], Patrizia Li Volsi[5☯], Carlo Bruno Giorda[6☯], Nicoletta Musacchio[7☯], Antonio Nicolucci[8☯], Concetta Suraci[9☯], Giuseppe Lucisano[8☯], Maria Chiara Rossi[8☯*], AMD Annals Study Group[¶]

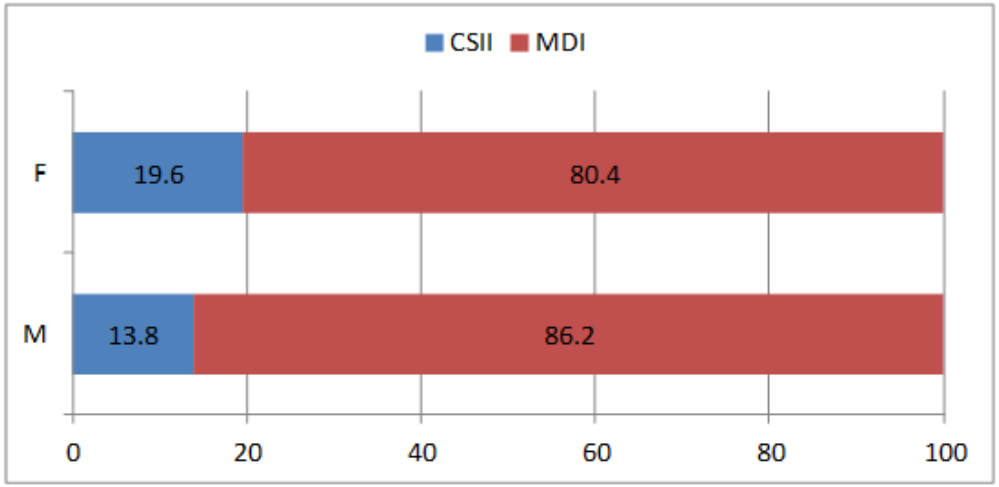
Favorable outcome indicators	M (%)	F (%)	p-value
HbA1c ≤7.0% (≤53 mmol/mol)	25.6	20.4	<0.0001
LDL-C <100 mg/dl	41.4	41.5	0.91
BP ≤130/80 mmHg	61.5	69.5	<0.0001
Unfavorable outcome indicators			
HbA1c >8.0% (>64 mmol/mol)	41.6	47.3	<0.0001
LDL-C ≥130 mg/dl	22.1	20.7	0.02
BP ≥140/90 mmHg	31.5	25.2	<0.0001
BMI ≥30 Kg/m2	8.7	9.8	0.002
GFR ≤60 ml/min	7.8	9.6	<0.0001
MAU	30.1	24.7	<0.0001

Multiiniettiva (MDI) vs Microinfusore (CSII)

- **Le F sono più spesso trattate con CSII dei M (19,6 vs 13,2%), ma raggiungono il target di HbA1c sempre in % inferiore vs i M**

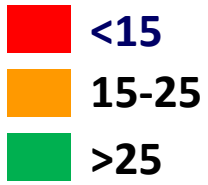
- Da MDI a CSII:

F a target da 19,3 a 25,1%;
M a target da 24,7 a 31,2%

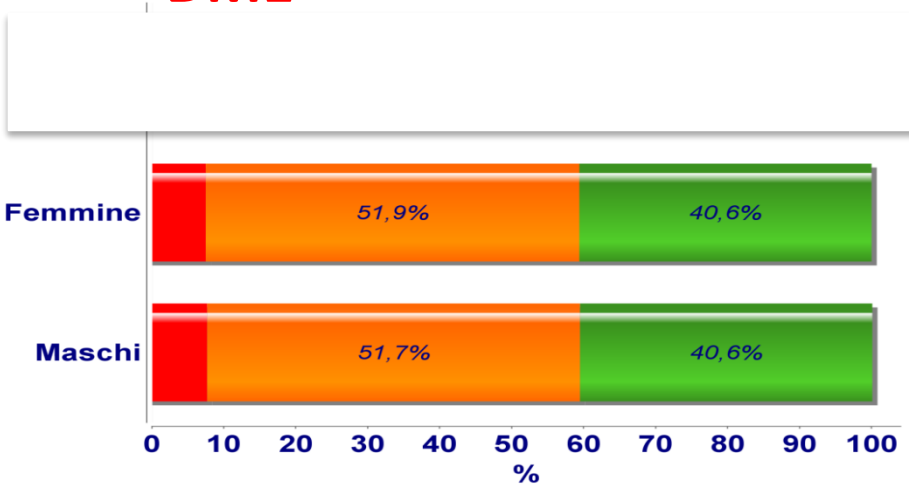


Score Q :

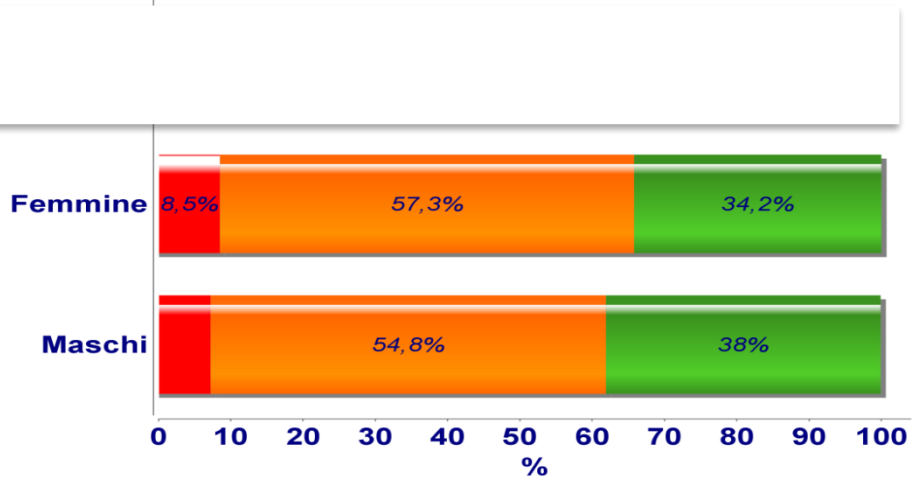
Misura riassuntiva di qualità di cura.
Correla con il rischio
di eventi Cardio-Vascolari



DM1



DM2



L'analisi per genere mostra come, **nel DM1**, non ci sia alcuna differenza tra i sessi riguardo le classi di score di qualità. **Nel DM2,** la quota di soggetti con punteggi <15 e fra 15 e 25 è invece superiore nelle donne.

SCORE Q nel DT1 :Qualità di cura complessiva per genere e per schema di trattamento nel DM1 (N=28.802)

Score Q medio			
	Uomini	Donne	p
MDI	24.9±8.5	24.7±8.5	0.26
CSII	25.8±8.3	26.2±8.4	**0.03**

Lo Score Q medio migliora in modo significativo nelle Donne trattate con CSII rispetto a quelle trattate con MDI

Rischio di morte nel DT1 : Metanalisi

Risk of all-cause mortality and vascular events in women versus men with type 1 diabetes: a systematic review and meta-analysis

Lancet Diabetes Endocrinol 2015;
198–206

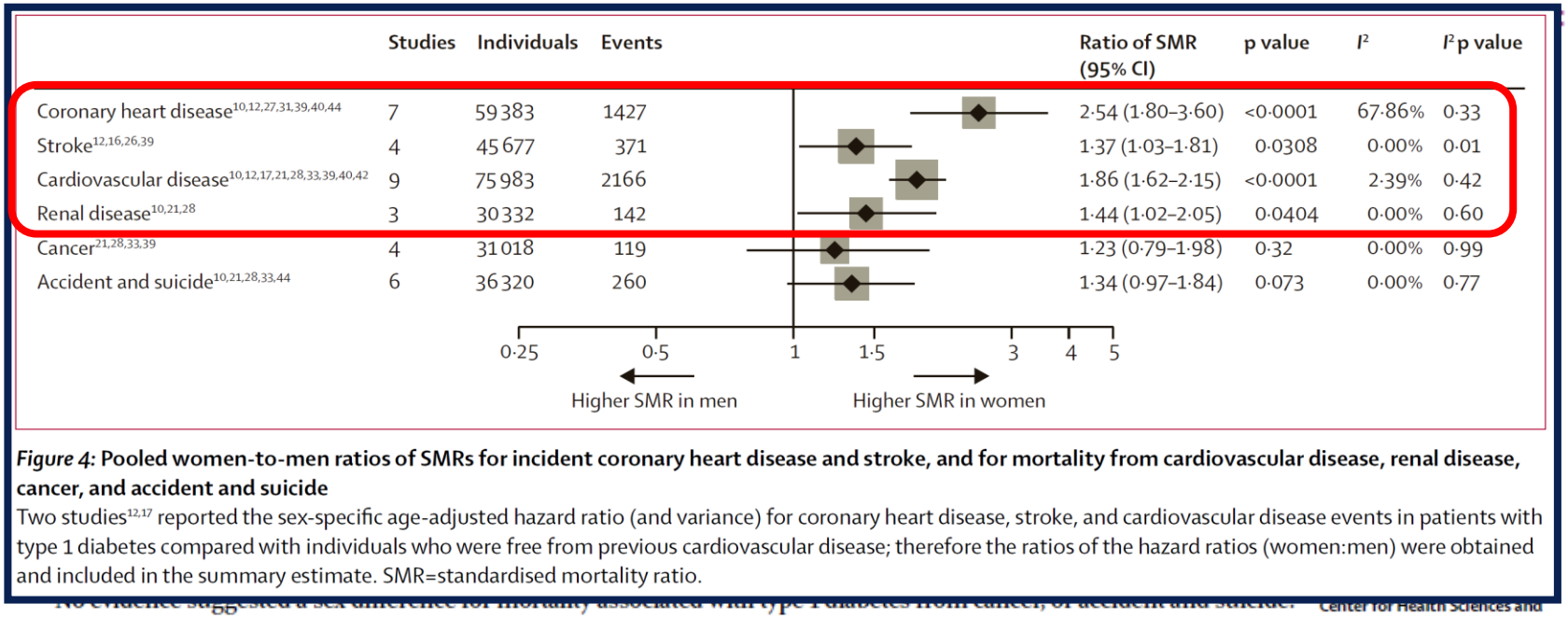


Figure 4: **Pooled women-to-men ratios of SMRs for incident coronary heart disease and stroke, and for mortality from cardiovascular disease, renal disease, cancer, and accident and suicide**

Two studies[12,17] reported the sex-specific age-adjusted hazard ratio (and variance) for coronary heart disease, stroke, and cardiovascular disease events in patients with type 1 diabetes compared with individuals who were free from previous cardiovascular disease; therefore the ratios of the hazard ratios (women:men) were obtained and included in the summary estimate. SMR=standardised mortality ratio.

Mortalità per tutte le cause nelle Donne :+ 40%

- **Quale Assistenza in un'ottica di genere** per ridurre il Rischio CV delle donne con Diabete ?

- Per l'Obesità

- Per il compenso metabolico

- Per il profilo lipidico

Circulation 2016

AHA Scientific Statement

Acute Myocardial Infarction in Women

A Scientific Statement From the American Heart Association

***Abstract*—**Cardiovascular disease is the leading cause of mortality in American women. Since 1984, the annual cardiovascular disease mortality rate has remained greater for women than men; however, over the last decade, there have been marked reductions in cardiovascular disease mortality in women. The dramatic decline in mortality rates for women is attributed partly to an increase in awareness, a greater focus on women and cardiovascular disease risk, and the increased application of evidence-based treatments for established coronary heart disease. This is the first scientific statement from the American Heart Association on acute myocardial infarction in women. Sex-specific differences exist in the presentation, pathophysiological mechanisms, and outcomes in patients with acute myocardial infarction. This statement provides a comprehensive review of the current evidence of the clinical presentation, pathophysiology, treatment, and outcomes of women with acute myocardial infarction. (*Circulation*. 2016;133:00-00. DOI: 10.1161/CIR.0000000000000351.)**

Obesity and Type 2 DM

compared with lean women.[169] Obesity is a major risk factor for AMI in women and increases their risk almost 3-fold.[170] The risk of AMI associated with the metabolic syndrome is higher in younger women than any of the other groups, increasing their odds of AMI almost 5-fold.[171] DM, related to obesity and the metabolic syndrome, is associated with a higher relative risk of coronary events in women compared with men, in part as a result of a higher rate of coexisting risk factors in women with DM[170] and better survival (relative to men) of women without DM.[172] DM is an especially powerful risk factor in young women, increasing their risk of CHD, including ACS, by 4- to 5-fold.[173] For both men and women with DM, mortality after STEMI or UA/NSTEMI is significantly increased compared with their nondiabetic counterparts at 30 days and 1 year.[174]

OBESITA':
Maggior fattore di rischio di Infarto nella donna(x3)

S.Meabolica e DM : x 4 - 5
Nelle donne giovani

Stroke
Journal of the American Heart Association

American Heart Association | American Stroke Association

-20 maggio 2017
GRESSO ONALE AMD

AHA/ASA Guideline

Guidelines for the Prevention of Stroke in Women

A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.
Endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons

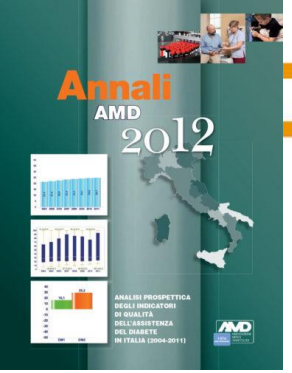
Purpose—The aim of this statement is to summarize data on stroke risk factors that are unique to and more common in women than men and to expand on the data provided in prior stroke guidelines and cardiovascular prevention guidelines for women. This guideline focuses on the risk factors unique to women, such as reproductive factors, and those that are more common in women, in l fibrillation.

Obesity, Metabolic Syndrome, and Lifestyle Factors: Recommendations

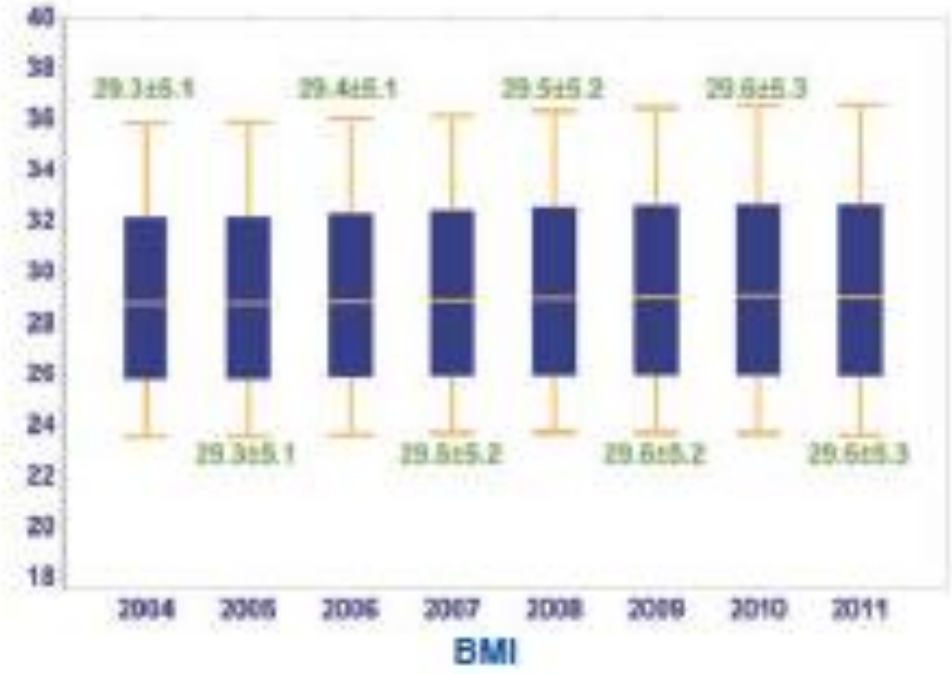
1. A healthy lifestyle consisting of regular physical activity, moderate alcohol consumption (<1 drink/d for nonpregnant women), abstention from cigarette smoking, and a diet rich in fruits, vegetables, grains, nuts, olive oil, and low in saturated fat (such as the DASH [Dietary Approaches to Stop Hypertension] diet) is recommended for primary stroke prevention in women with cardiovascular risk factors *(Class I; Level of Evidence B)*.
2. Lifestyle interventions focusing on diet and exercise are recommended for primary stroke prevention among individuals at high risk for stroke *(Class I; Level of Evidence B)*.

OBESITA', S. METABOLICA

Stile di Vita :
Alimentazione
E
Attività Fisica regolare



BMI : indagine longitudinale 2004 - 2011



Nessuna Variazione negli anni del BMI medio e della prevalenza di OBESITA'

Work In Progress: Analisi Longitudinale dei FdR CV per genere – Gr Donna

Annali AMD 2004-2011 :
BMI = > 30

Obesita

L'obesita rappresenta oggi il quarto fattore di rischio per mortalità a livello planetario. I dati degli Annali non inducono all'ottimismo.

In media, **il 40,1%** dei pazienti diabetici era obeso nel 2004, contro **il 42,9%** dei pazienti valutati nel 2011, con un **aumento assoluto di 2,8** punti percentuali. Sebbene il trend appaia uniforme,
alcune regioni mostrano delle medie superiori a quella nazionale

Attività Fisica e genere

EURODIAB : 1415 DT1 , attività fisica settimanale, lieve o intenso, ha ottenuto risultati sul rischio CV solo nei maschi

women with prediabetes than in men. Observational studies suggest that women with DM may require greater frequency and intensity of physical activity than their male counterparts to reduce cardiovascular events. From a practical standpoint, at least 2 h/wk of activity was associated with lower cardiovascular events for women with T2DM in the Nurses' Health Study cohort,[273] and this finding is consistent with the US physical activity guidelines and the joint American Diabetes Association/American College of Sports Medicine guidelines for people with DM, which recommend at least 150 minutes of weekly physical activity for all adults.[274,275]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease

Amit V. Khera, M.D., Connor A. Emdin, D.Phil., Isabel Drake, Ph.D., Pradeep Natarajan, M.D., Alexander G. Bick, M.D., Ph.D., Nancy R. Cook, Ph.D., Daniel I. Chasman, Ph.D., Usman Baber, M.D., Roxana Mehran, M.D., Daniel J. Rader, M.D., Valentin Fuster, M.D., Ph.D., Eric Boerwinkle, Ph.D., Olle Melander, M.D., Ph.D., Marju Orho-Melander, Ph.D., Paul M Ridker, M.D.,

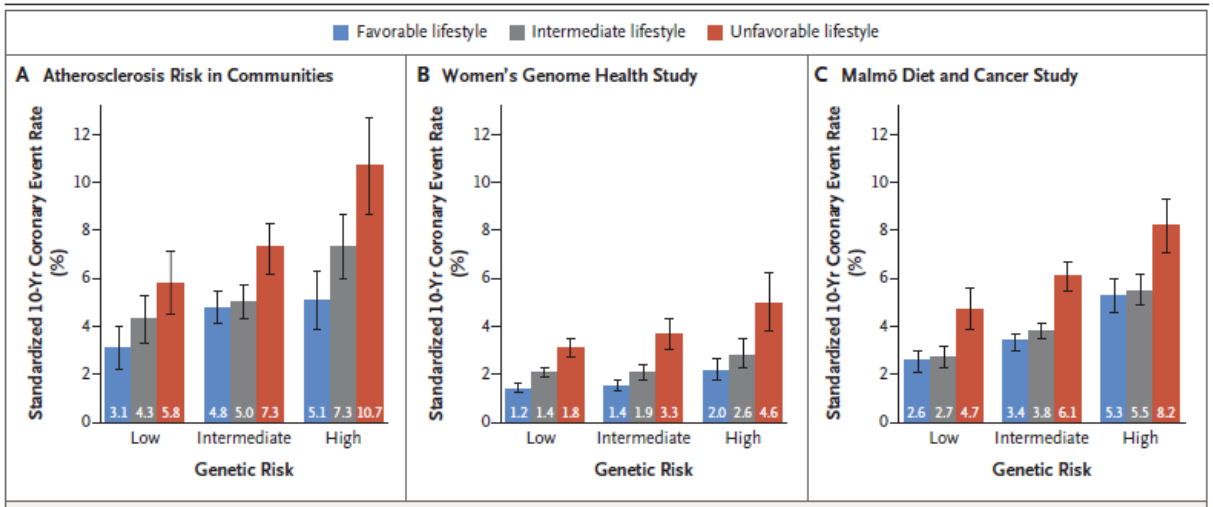


Figure 3. 10-Year Coronary Event Rates, According to Lifestyle and Genetic Risk in the Prospective Cohorts.

Shown are standardized 10-year cumulative incidence rates for coronary events in the three prospective cohorts, according to lifestyle and genetic risk. Standardization was performed to cohort-specific population averages for each covariate. The I bars represent 95% confidence intervals.

within each genetic risk category.

Stile di vita:
Studi di Coorte
7814 ARIC
21.222 WGHS
22.389 MDCS
4260 BISt

L'attività fisica, comunque associata a livelli di rischio genetici diversi è efficace

CONCLUSIONS

Across four studies involving 55,685 participants, genetic and lifestyle factors were independently associated with susceptibility to coronary artery disease. Among participants at high genetic risk, a favorable lifestyle was associated with a nearly 50% lower relative risk of coronary artery disease than was an unfavorable lifestyle. (Funded by the National Institutes of Health and others.)

Rossi et al. Health and Quality of Life Outcomes (2017) 15:41
DOI 10.1186/s12955-017-0613-0

Bench-D

Health and Quality of Life Outcomes

RESEARCH Open Access

The complex interplay between clinical and person-centered diabetes outcomes in the two genders

Maria Chiara Rossi[1*], Giuseppe Lucisano[1], Basilio Pintaudi[2], Angela Bulotta[3], Sandro Gentile[4], Marco Scardapane[1], Soren Eik Skovlund[5], Giacomo Vespasiani[6], and Antonio Nicolucci[1] on behalf of the BENCH-D Study Group

Abstract

Background: New approaches to cope with clinical and psychosocial aspects of type 2 diabetes (T2DM) are needed; gender influences the complex interplay between clinical and non-clinical factors. We used data from the BENCH-D study to assess gender-differences in terms of clinical and person-centered measures in T2DM.

Methods: Clinical quality of care indicators relative to control of HbA1c, lipid profile, blood pressure, and BMI were derived from electronic medical records. Ten self-administered validated questionnaires (SF-12 Health Survey; WHO-5 well-being index; Problem Areas in Diabetes (PAID) 5, Health Care Climate Questionnaire, Patients Assessment of Chronic Illness Care, Diabetes Empowerment Scale, Diabetes Self-care Activities, Global Satisfaction for Diabetes Treatme
indicatc

Results
reached
BMI <27
functior
distress,
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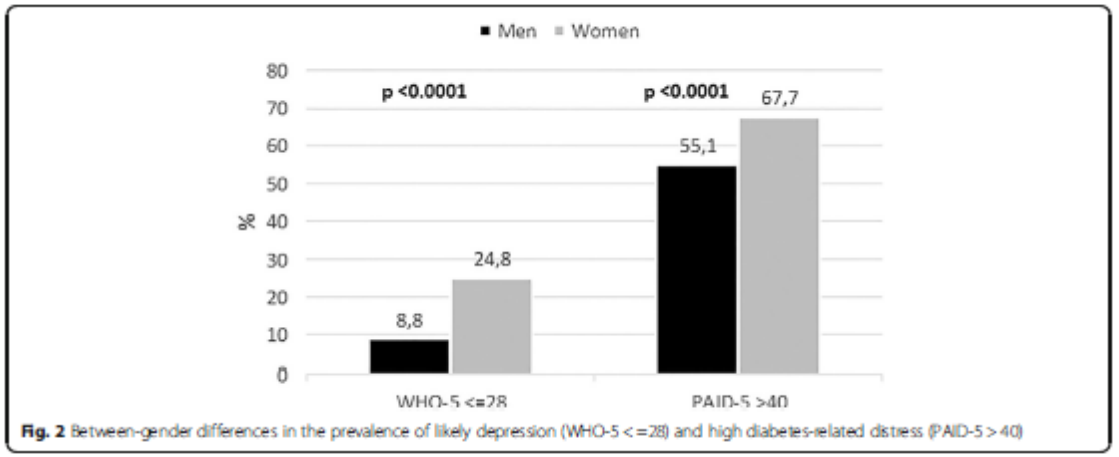

Fig. 2 Between-gender differences in the prevalence of likely depression (WHO-5 <=28) and high diabetes-related distress (PAID-5 > 40)

WHO-5 = depressione

PAID - 5 = peso della malattia

Questionari Validati

Table 1 Questionnaires used and validated in the BENCH-D study

Questionnaire	Abbreviation	Domain	Brief description	No. of items	Scoring	References
SF-12 Health Survey - physical component	SF-12 PCS	Physical functioning	SF-12 is a widely used generic health status measure. It includes 12 items which can be aggregated into two summary measures: the Physical (PCS) and Mental (MCS) Component Summary scores. Both scores range from 0 (worst possible health state) to 100 (best possible health state); they are normalized to a general population mean of 50 and an SD of 10.	6	0-100	[14]
WHO-5 well-being index	WHO-5	Psychological well-being	WHO-5 assesses the psychological well-being, a core component of overall quality of life. It is also a valid and reliable risk assessment measure for mild, moderate and severe depression. A score <50 indicates poor psychological well-being, a score <=28 indicates probable depression.	5	0-100	[10, 15]
Problem Areas in Diabetes	PAID-5	Diabetes distress	PAID-5 evaluates diabetes related emotional distress, i.e. specific worries and negative emotions related to diabetes. A score >40 indicates high diabetes-related distress	5	0-100	[9, 16–20]
Health Care Climate Questionnaire - Short Form	HCC-SF	Person centered communication	HCC-SF evaluates the extent to favor the autonomy of the pati assume a paternalistic attitude scores correspond to a higher			

Influenze psicosociali sui livelli di compenso metabolico nel DT2 , nelle donne

In a multivariate analysis, factors associated with an increased likelihood of having elevated HbA1c levels (≥8.0%) were different in men and women (Table 4). In particular:

- Both in men and in women, insulin treatment alone or in association with OHAs increased the likelihood of having HbA1c ≥ 8.0% from 13 to 33% vs. OHAs only;
- In men but not in women, the likelihood of having HbA1c ≥ 8.0% decreased as age increased (–3% for each additional 5 years) and was associated with the level of school education;
- In women but not in men, high levels of diabetes related distress were associated with a higher likelihood of poor metabolic control.

Quale Assistenza in un'ottica di genere ?

- **Occorrono strategie educative e approcci terapeutici personalizzati e differenziati per genere per colmare questi gap.**
- **ma occorre anche modificare i ruoli**

OBESITA' → meno attività fisica ?

Problemi aperti

- **Se il peggiore profilo di rischio CV nelle donne con DT2 può spiegare la maggiore mortalità CV nelle donne vs gli uomini con DT2**
- **Il peggior compenso metabolico nel DT1 può spiegare la maggiore mortalità CV e per tutte le cause nelle donne con DT1 ? *(metanalisi)***
- **I medici sottostimano il rischio cardiovascolare delle loro pazienti donne?**
- **Le donne sottostimano per motivi diversi (culturali, economici, depressione ecc) la malattia, i sintomi, i segni e soprattutto il prendersi cura di sè ?**

Quale Assistenza in ottica di genere ?

- **LIPIDI:** l'aderenza e la continuità terapeutica sono fattori essenziali per raggiungere i target.
- Le donne più frequentemente sospendono le Statine dopo l'Infarto.
- Verificare l'aderenza alla terapia e ai dosaggi
- Intensificare il trattamento
- Non riusciamo a convincerle che sono farmaci salva-vita

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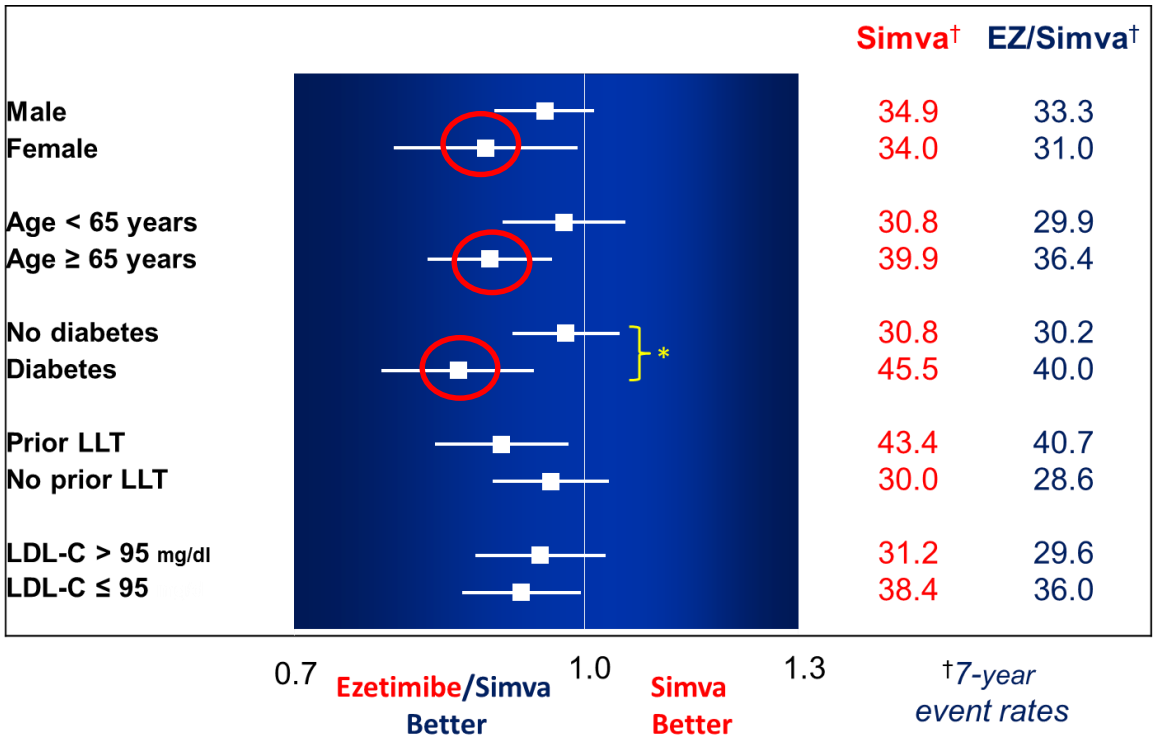
Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes

Christopher P. Cannon, M.D., Michael A. Blazing, M.D., Robert P. Giugliano, M.D., Amy McCagg, B.S., Jennifer A. White, M.S., Pierre Theroux, M.D., Harald Darius, M.D., Basil S. Lewis, M.D., Ton Oude Ophuis, M.D., Ph.D., J. Wouter Jukema, M.D., Ph.D., Gaetano M. De Ferrari, M.D., Witold Ruzyllo, M.D., Paul De Lucca, Ph.D., KyungAh Im, Ph.D., Erin A. Bohula, M.D., D.Phil., Craig Reist, Ph.D., Stephen D. Wiviott, M.D., Andrew M. Tershakovec, M.D., M.P.H., Thomas A. Musliner, M.D., Eugene Braunwald, M.D., and Robert M. Califf, M.D., for the IMPROVE-IT Investigators*

Improve-it

Lipidi



*p-interaction = 0.023, otherwise > 0.05

Migliori risultati
- nei Diabetici
- nelle donne
- Età > 65 a.

In prevenzione secondaria
Follow up di 7 anni

Quale Assistenza in ottica di genere ?

Compenso Metabolico :

- **I nuovi Farmaci ci possono aiutare ?**
- **SGLT2i (Empa-Reg)**
  riduzione del rischio CV e del peso
- **Liraglutide (Leader): riduzione eventi CV , e riduzione Peso**

Ma anche

- **Migliorare l'aderenza ai corretti stili di vita, anche con approcci personalizzati**

Diabetologia
DOI 10.1007/s00125-015-3804-4

ARTICLE

The impact of gender on the long-term morbidity and mortality of patients with type 2 diabetes receiving structured personal care: a 13 year follow-up study

Marlene Ø. Krag[1] · Lotte Hasselbalch[1] · Volkert Siersma[1] · Anni B. S. Nielsen[1] · Susanne Reventlow[1] · Kirsti Malterud[1,2,3] · Niels de Fine Olivarius[1]

- **1381 DT2 di nuova diagnosi →**

randomizzati **a trattamento intensivo**, **strutturato** vs trattamento routinario **per 6 anni**: follow up di 13 anni

- Follow up regolare , ob personalizzati, educazione continua ,formazione continua MMG

- **L'intervento strutturato e personalizzato ha portato ad una riduzione dei livelli di HbA1c, e una riduzione di morbilità e mortalità per cause CV e legate al diabete, nella donna, ma non nell'uomo (- 30 %)**

- Un trattamento personalizzato potrebbe portare le donne a prendersi cura di se e potrebbe incentivarle ad una maggiore aderenza al trattamento.
- Le donne in genere accettano meglio la malattia e i cambiamenti ad essa correlati. I maschi invece tendono a rifiutare la malattia e le difficoltà che comporta.

Quale Assistenza in un'ottica di genere

per ridurre il rischio CV Globale

nella Donna con Diabete ?

- **Trattare SUBITO !**
- **Verificare l'aderenza !**
- **Intensificare il trattamento !**
- **Perseguire i Target !**
- **Personalizzare gli interventi**
- **Usare le tecnologie**

tenendo conto delle differenze ....

WORK in PROGRESS

finanziato da AMD 5 x 1000

Titolo	**Differenze di genere riguardanti le abitudini alimentari, lo stile di vita, l'aderenza al trattamento farmacologico e la qualità di vita nel DM1 e nel DM2**
Tipo di Studio	Studio osservazionale trasversale
Proponente	Gruppo Donna AMD, coordinatrice Valeria Manicardi (Reggio Emilia)
Referenti	Maria Chiara Rossi – CORESEARCH, Pescara Giuseppina Russo – Policlinico Universitario, Messina
Altre Strutture Partecipanti	Centri diabetologici della rete di ricerca AMD

Grazie al Gruppo Donna