



Medicina, Cura e Genere

Venerdì 6 maggio 2016

Museo MAGI'900
Pieve di Cento (Bologna)

Il Segretario
Prof. C. Feo

Il Presidente
Prof. R. Manfredini

Sono stati richiesti i crediti formativi ECM
per Medici, Biologi, Farmacisti, Professioni Sanitarie
Sono disponibili attestati di partecipazione per gli studenti in
Medicina

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**Morte improvvisa:
differenze o disparità di genere**

B. Sassone

UO Cardiologia
Ospedale SS.ma Annunziata – Cento
Ospedale del Delta – Lagosanto
AUSL di Ferrara

Dimensioni del problema

Definizione di morte improvvisa

- Morte naturale, inaspettata, con perdita repentina dello stato di coscienza e decesso entro 1 ora dall'inizio dei sintomi
- Improvvisa cessazione della funzione di pompa del cuore
- Può essere reversibile mediante tempestive manovre rianimatorie



La morte dell'emerodromo Filippide

Dimensione del problema

Dati OMS



- **17 milioni** morti/anno nel mondo
- **25%** morti improvvise
- **10-20%** morti improvvise cardiache

Dimensione del problema

Dati OMS

Stati Uniti d'America



300.000/anno

Europa



400.000/anno

Incidenza morte improvvisa nella popolazione generale

USA, Olanda, Irlanda, Cina



0.5 -1.0 casi/1.000 abitanti/anno

Prospective studies using multiple sources

J Am Coll Cardiol. 2004;44:1268 –1275

J Am Coll Cardiol. 1997;30:1500–1505

Eur Heart J. 2008;29:1418 –1423

J Am Coll Cardiol. 2009;54:1110 –1118

Incidenza morte improvvisa nella popolazione generale in Italia

Friuli (studio Monica)



0.95 casi/1.000 abitanti/anno

Brianza (studio Monica)



0.88 casi/1.000 abitanti/anno (maschi 55-64 anni)

The **WHO MONICA** multinational project (Monitoring of Trends and Determinants in Cardiovascular Disease)

**Incidenza
di morte improvvisa
in Italia**

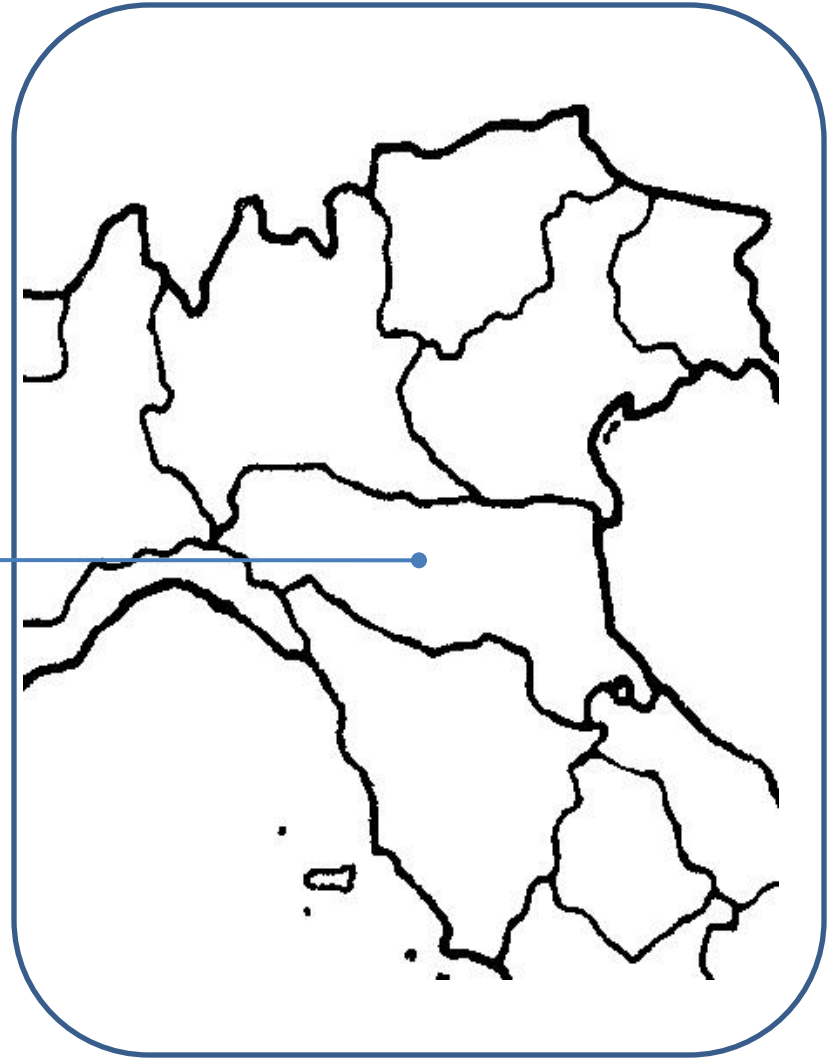


57.000/ anno

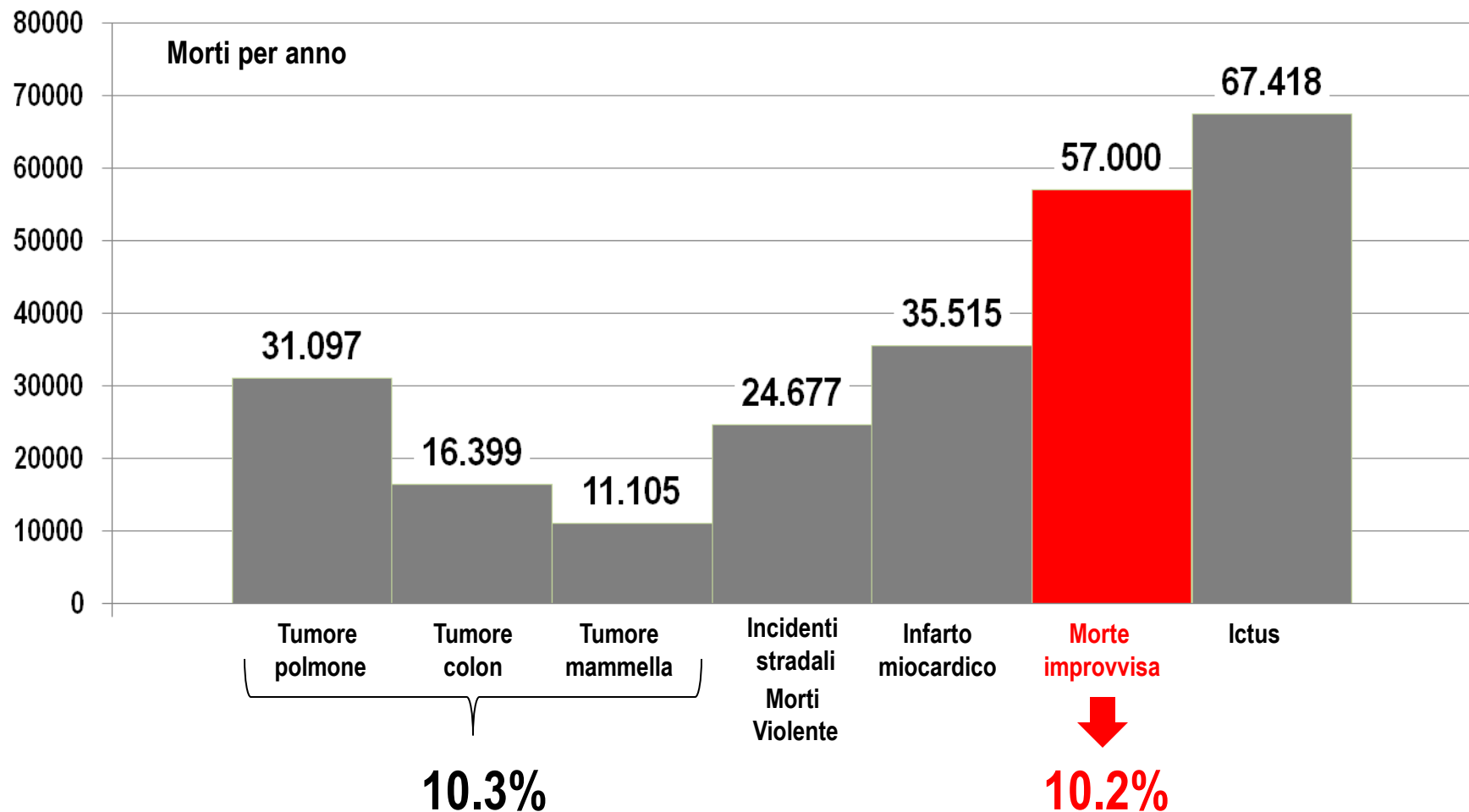


Emilia-Romagna

1 caso ogni 2.5 ore



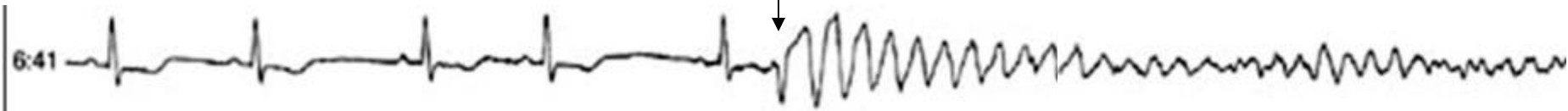
Cause di morte in Italia



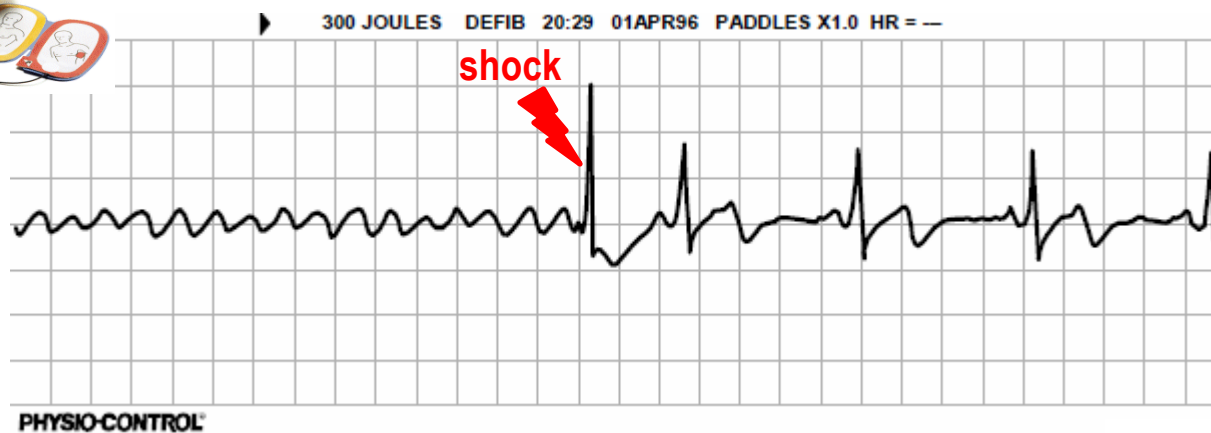
Meccanismo aritmico della morte improvvisa

Ritmo cardiaco normale

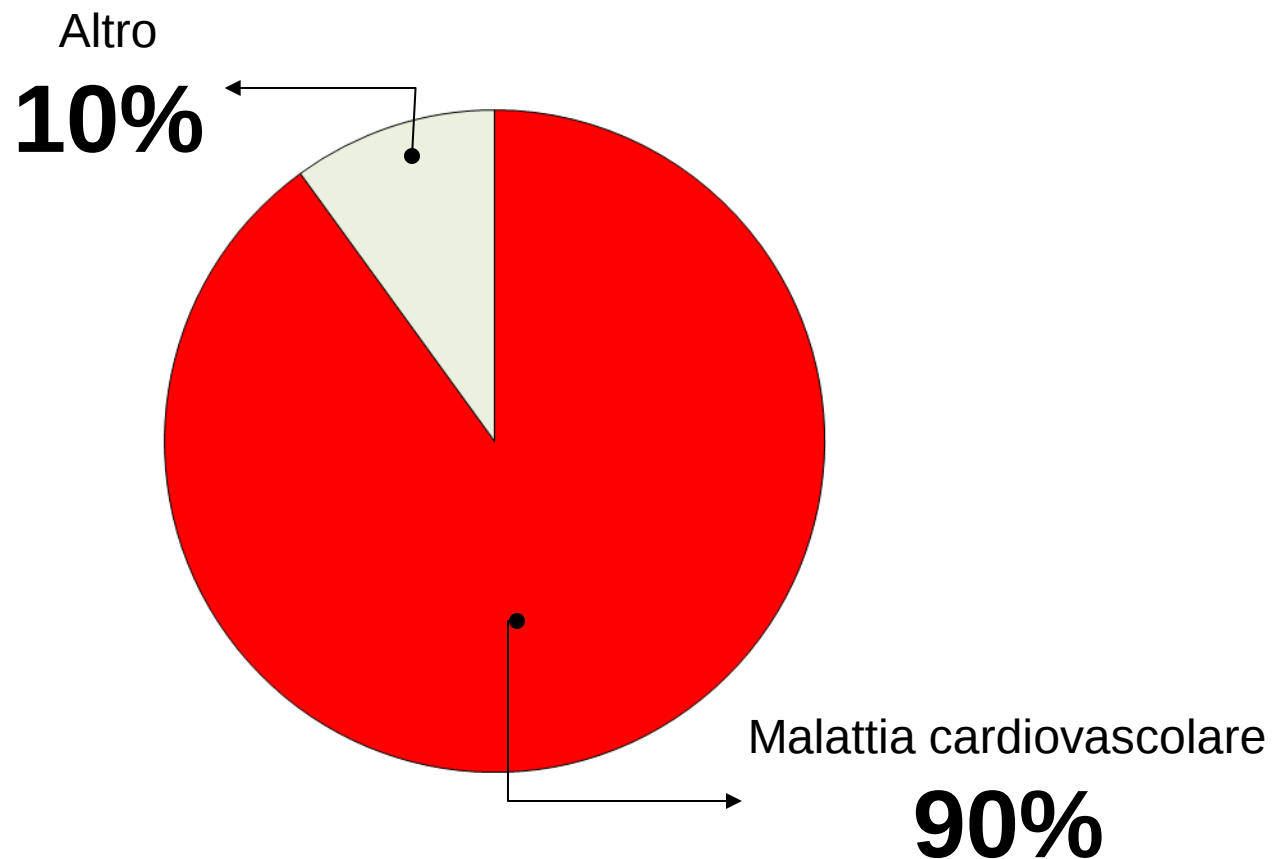
Fibrillazione ventricolare (arresto cardiaco)



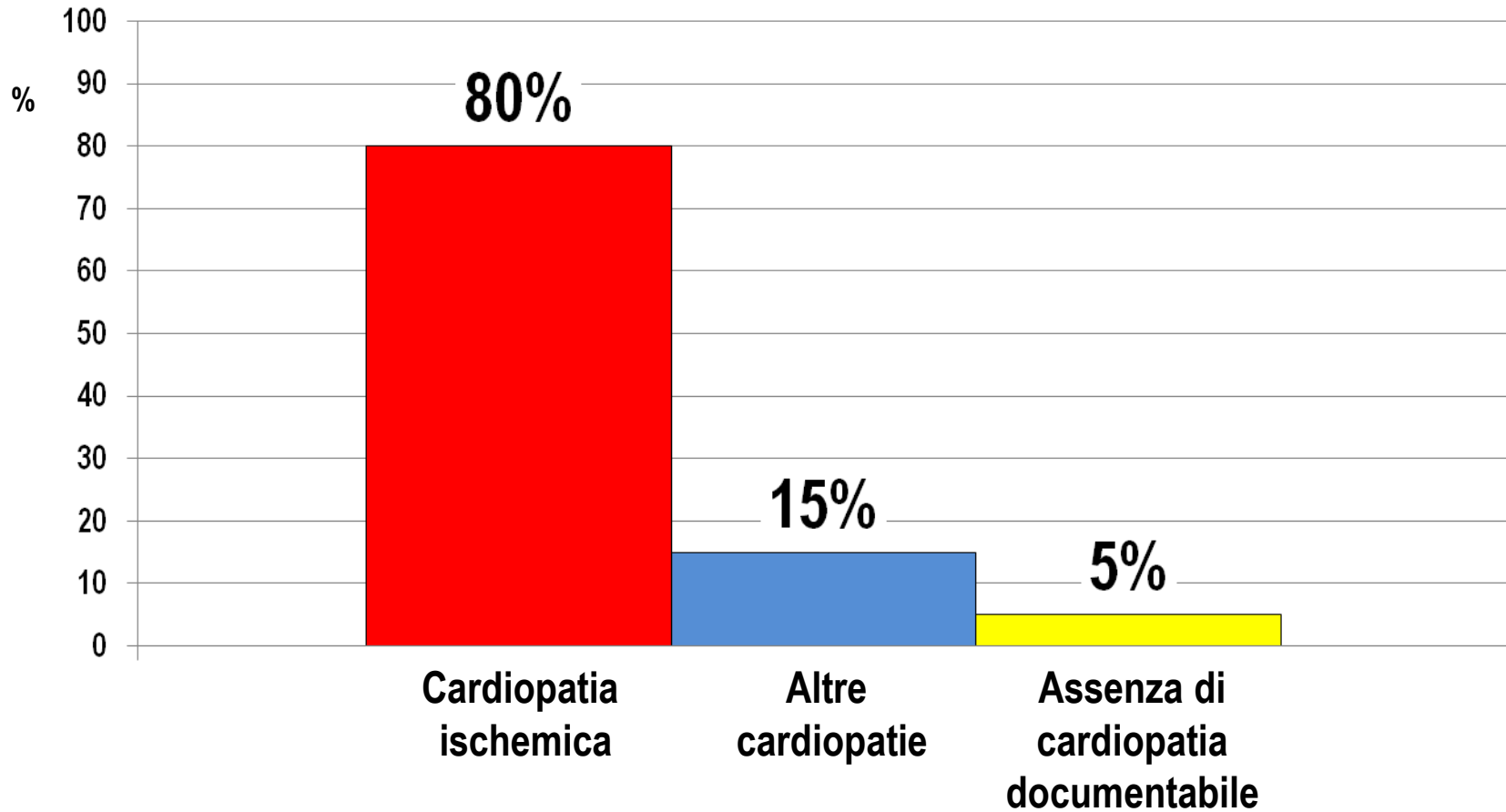
Unico trattamento: la defibrillazione precoce



Morte improvvisa cardiaca

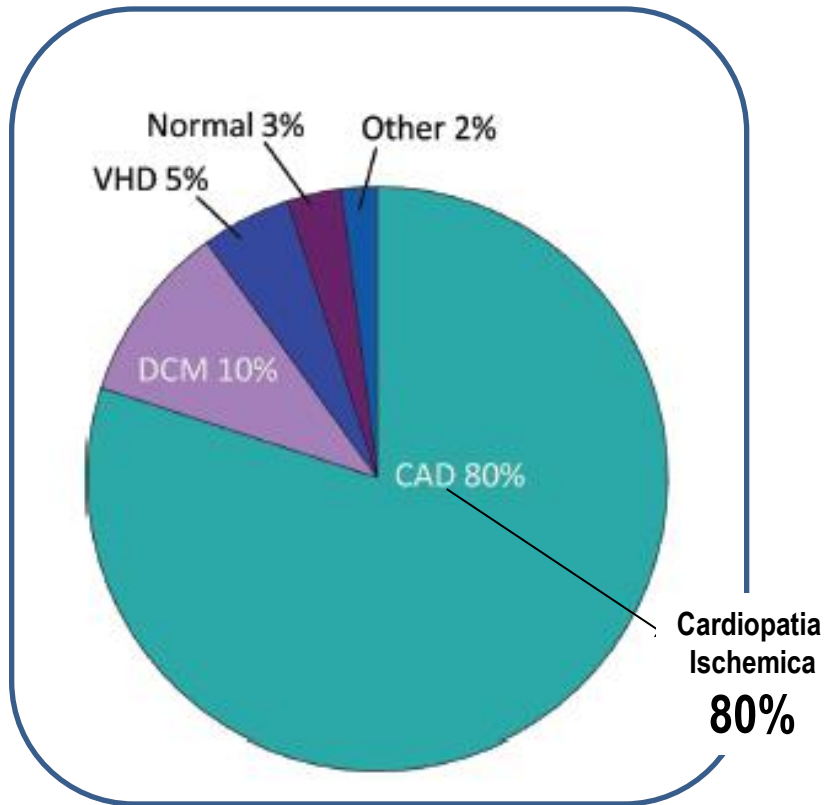


Cardiopatía e morte improvvisa

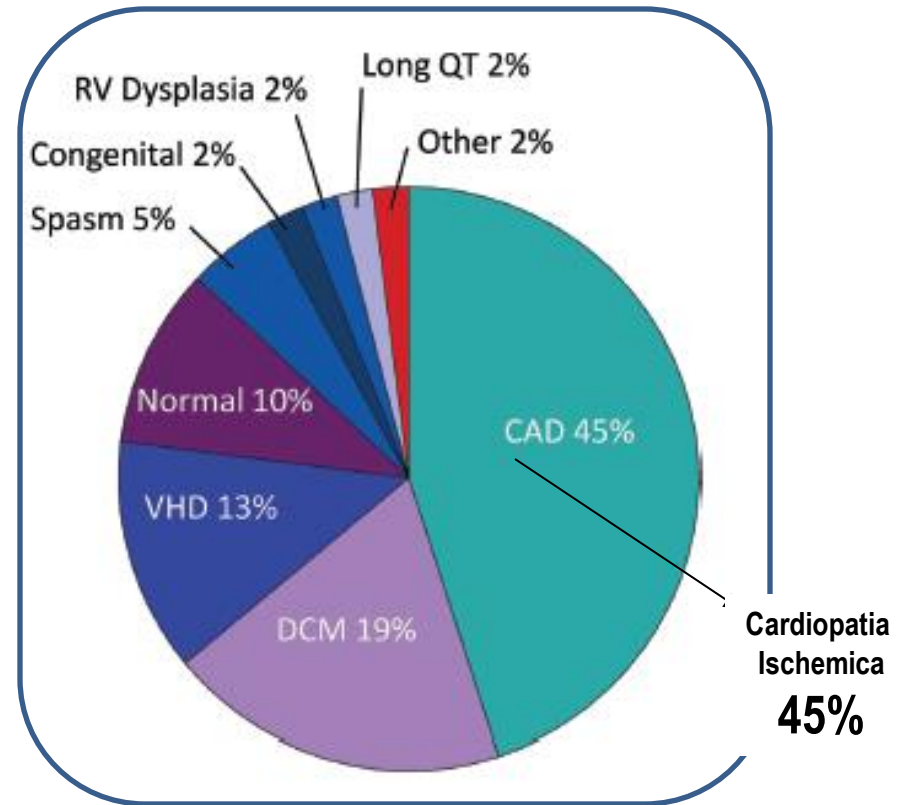


Differenze di sesso

Cardiopatia nei sopravvissuti a morte improvvisa



Uomini



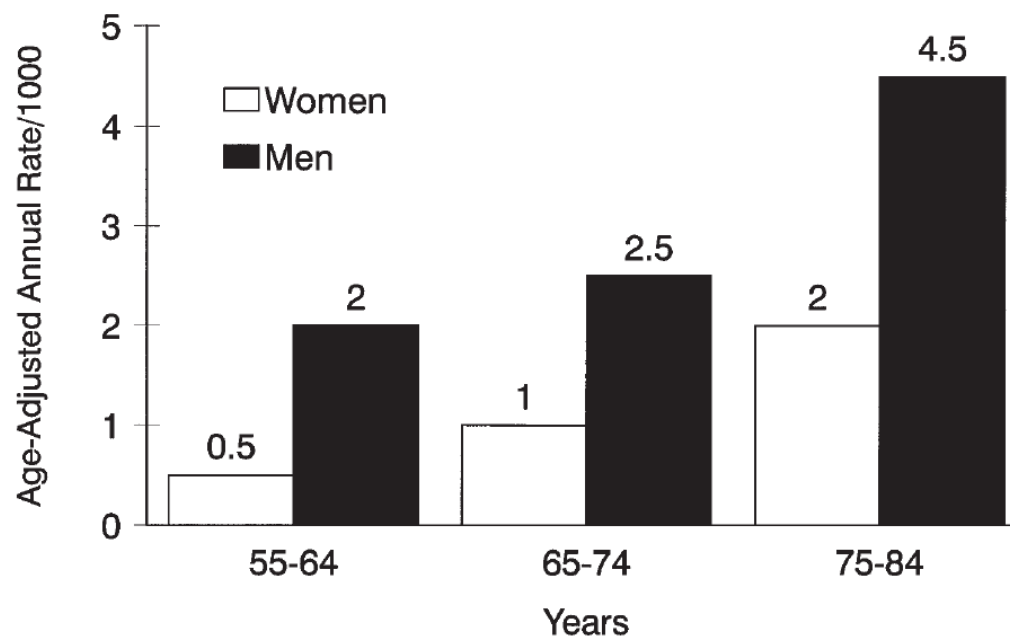
Donne

Morte improvvisa nei pazienti ischemici

“Framingham study”

Cohort of 2.873 women, aged 30-62 yrs, monitored over 38 yrs

Incidenza annuale di morte improvvisa

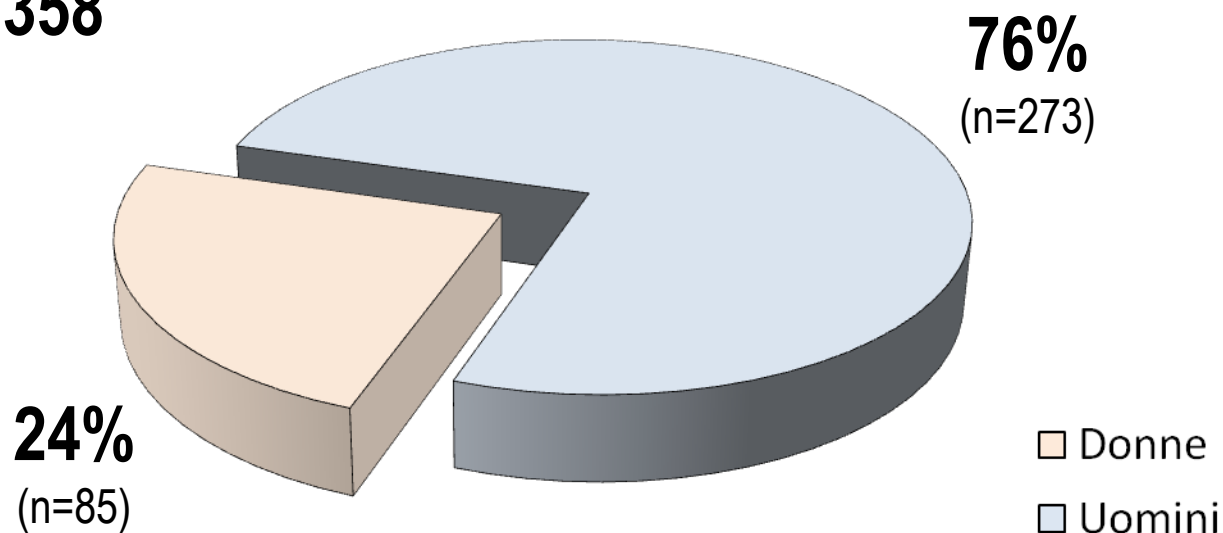


Differenza di sesso nella morte improvvisa

“Framingham study”: 5.209 soggetti, età 28-62 anni, periodo 1948 to 1999

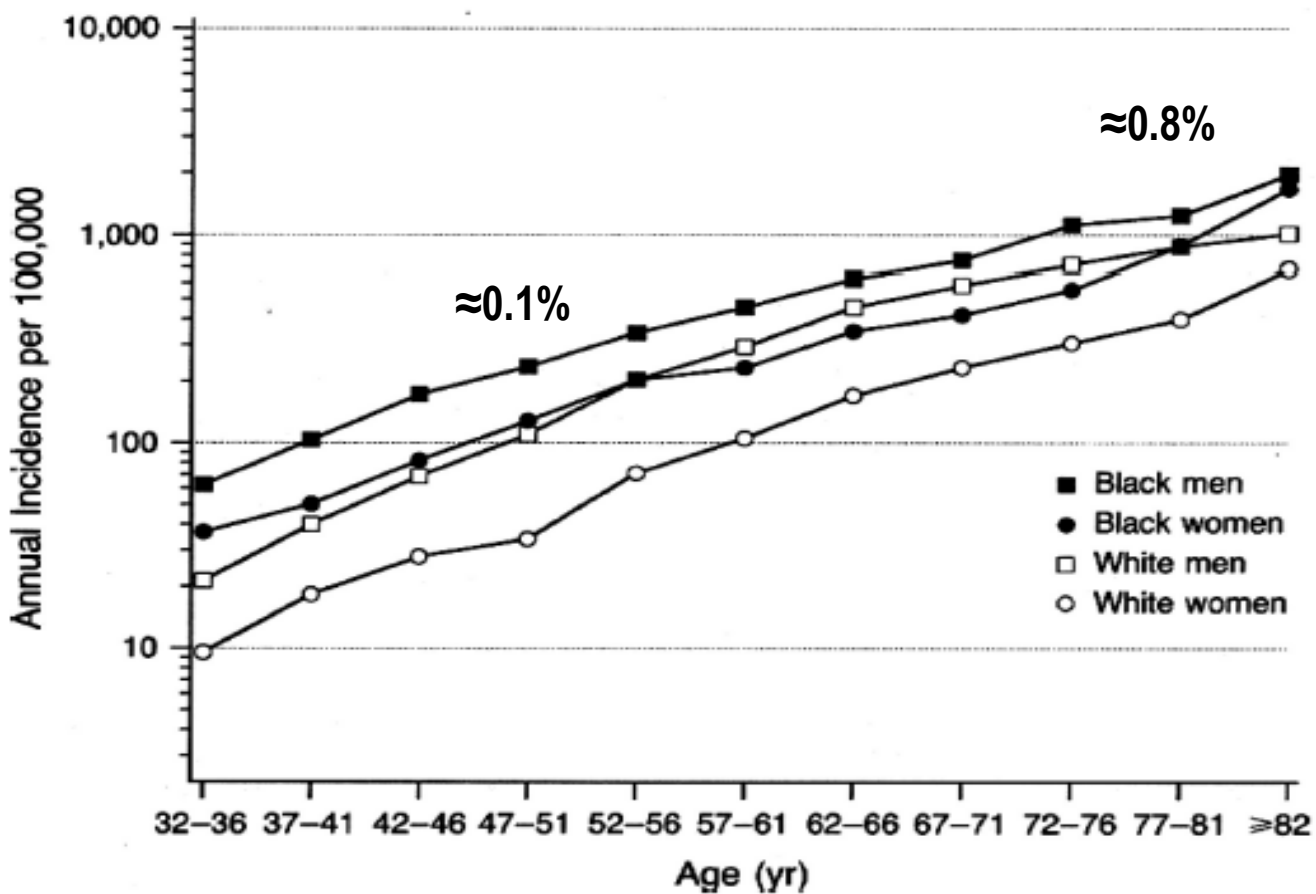
Numero di morti improvvise in 50 anni di osservazione

Totale = 358



Chicago CPR project

6.451 soggetti (3.207 bianchi e 2.910 afroamericani)



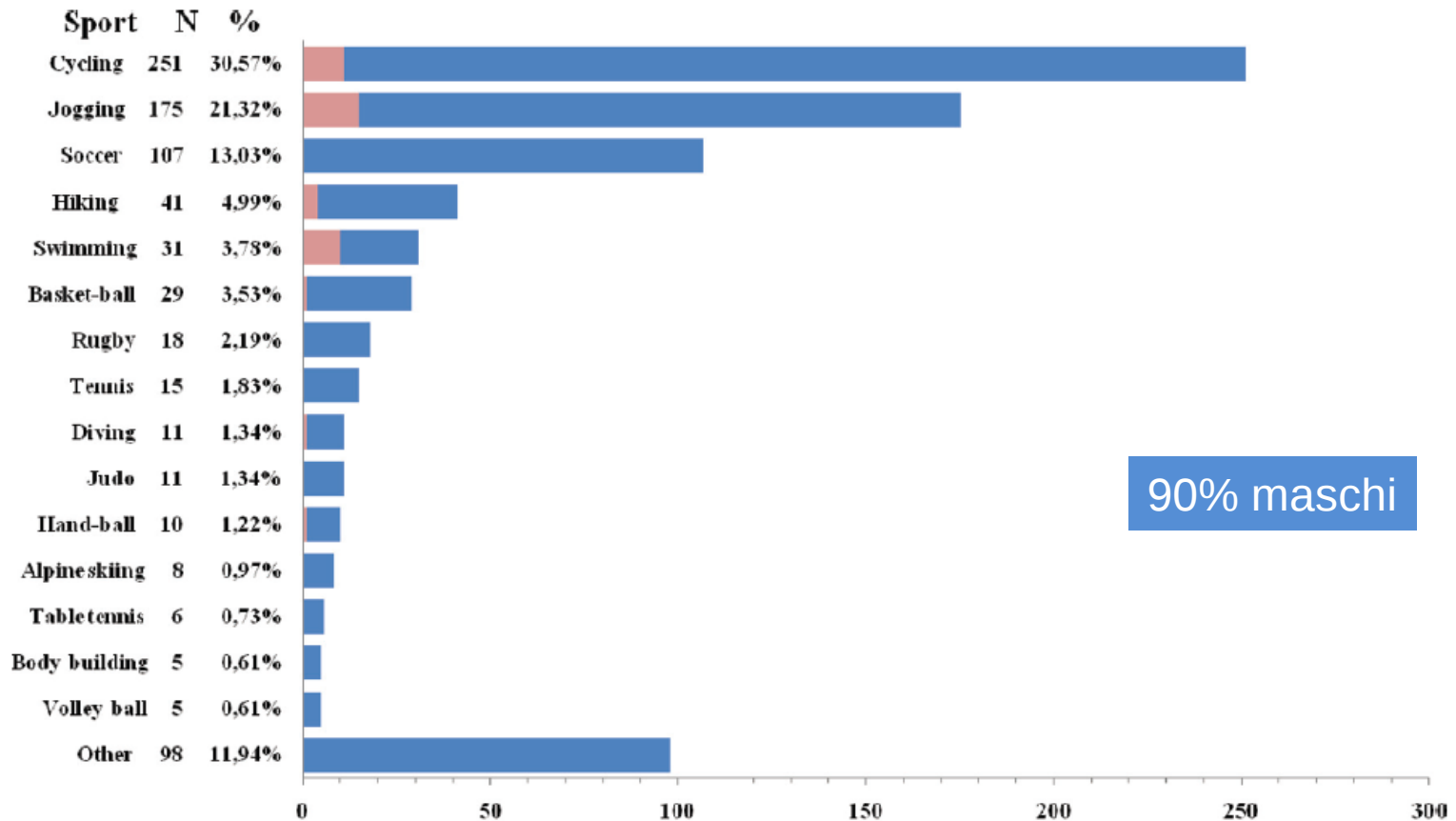
Incidenza di morte improvvisa nello sport

USA (atleti dei “college”, range 12-24 anni, 34% femmine)  <1/100.000 atleti/anno

Italia (atleti competitivi, range 12-35 anni, 20% femmine)  $\approx 3/100.000$ atleti/anno

Morte improvvisa e sport

(820 casi di morte durante attività sportiva in Francia)



Ormoni ovarici e aterosclerosi

The vasoprotective effects of estrogen

Stimulation of endothelial repair in damaged vessels

Restoration of endothelium-dependent vasomotor mechanisms

Termination of lipid peroxidation

Inhibition of platelet adhesion

Lipid lowering

Inhibition of clotting factor synthesis

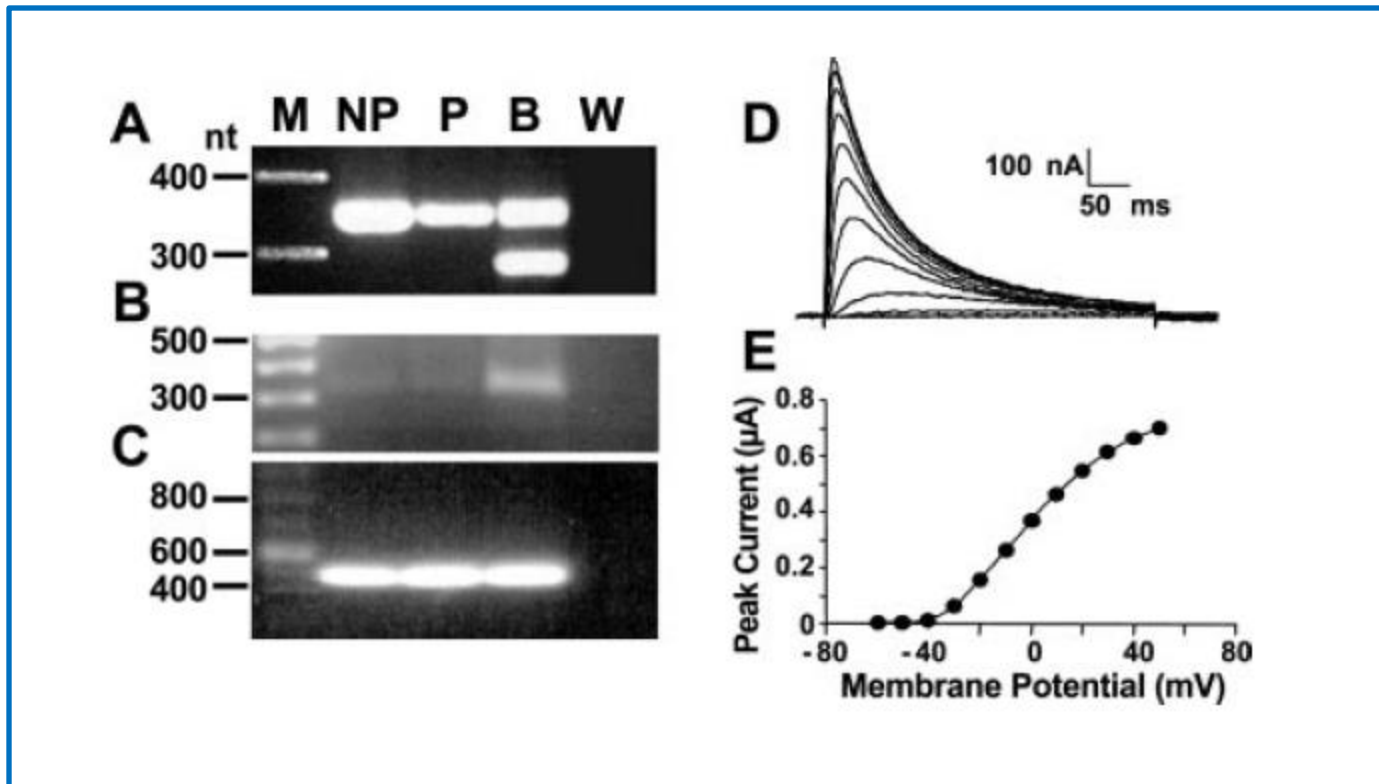
Ann Intern Med. 1992;117:1016 –1037.

N Engl J Med. 1997;336:1769 –1775

Trends Cardiovasc Med. 1997;7:94 –100.

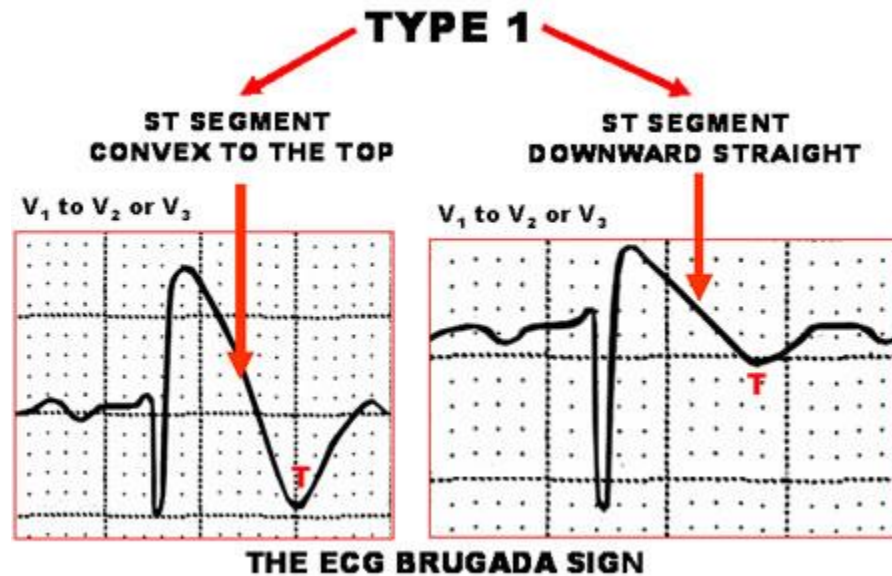
N Engl J Med. 1997;336:683–690.

Ormoni ovarici e proprietà elettriche del cuore



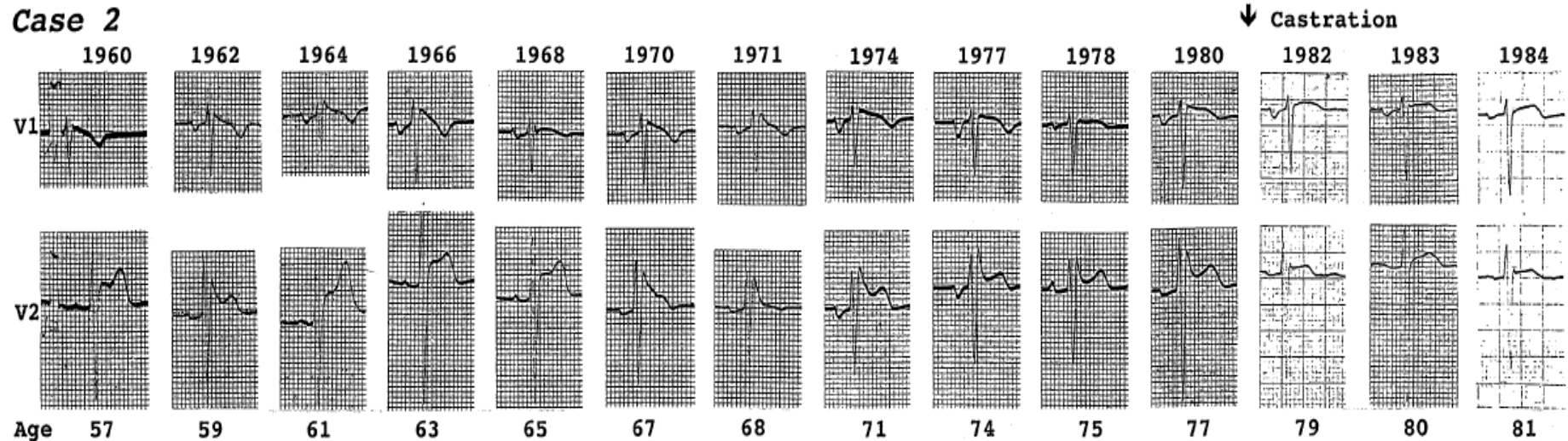
Sindrome di Brugada

(Ereditaria autosomica dominante)

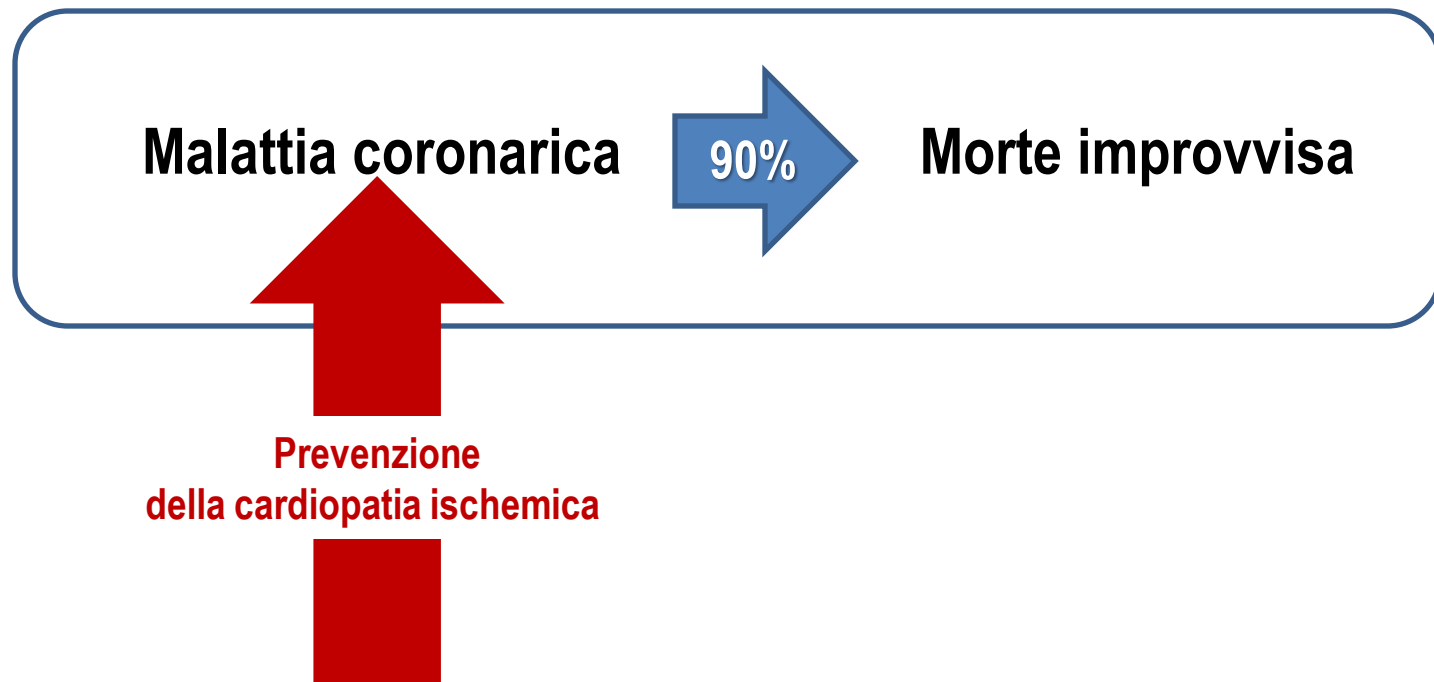


Disappearance of the Brugada-Type Electrocardiogram After Surgical Castration: A Role for Testosterone and an Explanation for the Male Preponderance?

KIYOTAKA MATSUO,*† MASAZUMI AKAHOSHI,* SHINJI SETO,†
and KATSUSUKE YANO†



Strategia di prevenzione di massa....sostenibile



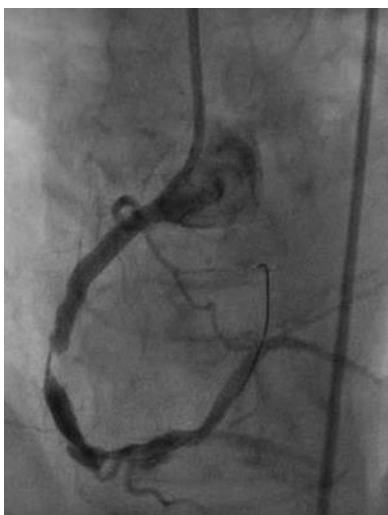
Disparità di sesso

Terapia farmacologica



Beta-bloccanti
ACE-inibitori
Antiaggreganti
PUFA -3

Rivascolarizzazione miocardica



Angioplastica
By-pass

Defibrillatore impiantabile



ICD

Table 1
Number of women enrolled

Trials	Year	Women
<i>ACE-inhibitors/AT 2 inhibitors trials</i>		
SOLVD prevention (Enalapril vs. placebo)	1992	486 (11.5%)
SOLVD treatment (Enalapril vs. placebo)	1990	594 (23%)
CONSENSUS (Enalapril vs. placebo)	1992	75 (30%)
V-HeFT II (Enalapril vs. idralazina)	1991	— *
ELITE (Losartan vs. captopril)	1997	240 (33%)
ELITE II (Losartan+captopril vs. placebo)	2000	966 (30.5%)
ATLAS (Lisinopril vs. placebo)	1999	648 (20%)
RESOLVD (Candesartan vs. enalapril vs. both)	1999	127 (15%)
VAL-HeFT (Valsartan vs. placebo)	2001	1000 (20%)
<i>Beta-blockers</i>		
US Carvedilol (Carvedilol)	1996	57 (25.5%)
MDC (Metoprolol vs. placebo)	1993	105 (28%)
CIBIS (Bisoprolol vs. placebo)	1994	112 (17%)
CIBIS II (Bisoprolol vs. placebo)	1999	515 (29%)
PRECISE (Carvedilol vs. placebo)	1996	74 (34%) *
MOCHA (Carvedilol vs. placebo)	1996	109 (24%)
MERIT-HF (Metoprolol vs. placebo)	2000	898 (22.5%)
RESOLVD (Metoprolol vs. placebo)	2000	76 (18%)
COPERNICUS (Carvedilol vs. placebo)	2001	452 (20%)
BEST (Bucindolol vs. placebo)	2001	593 (22%)
<i>Amiodarone and ICD</i>		
GESICA (Amiodarone)	1994	56 (11%)
MADIT (Implanted defibrillator vs. medical)	1996	16 (9%)
DIAMOND (Dofetilide vs. placebo)	1999	404 (26.5%)
MADIT II (Implanted defibrillator vs. medical)	2002	190 (15.5%)
<i>Other</i>		
PROMISE (Milrinone vs. placebo)	1991	556 (24%)
PRAISE (Amlodipine vs. placebo)	1996	1520 (22.4%)
DIG (Digitalis vs. placebo)	1997	374 (20%)
PRIME II (Ibopamide vs. placebo)	1997	446 (27%)
RALES (Spironolactone vs. placebo)	1999	26 (20%)
REMATCH (Left ventricular device vs. medical)	2001	17 (25%)
MUSTIC (Atrioventricular pacemaker)	2001	

0% ↓

34% ↑

EuroHeart Survey on Heart Failure

EuroHeart Survey on Heart Failure

Observational study totalling 8.914 patients (47% women) between year 2000 and 2001

Table 5 Pharmacological treatment by gender, including unadjusted and adjusted ORs for the association with treatment (incl. total population and stratified to patients with depressed and preserved left ventricular function)

			Gender differences		
			Unadjusted OR* (95% CI)	OR* adjusted for age (95% CI)	Adjusted OR* (95% CI)†
<i>Total population (n = 8914)</i>	<i>Men (n = 4748) (%)</i>	<i>Women (n = 4166) (%)</i>			
➡ ACE-inhibitors	69	60	0.67 (0.62 to 0.74)	0.77 (0.70 to 0.84)	0.70 (0.64 to 0.77)
➡ β-Blockers	41	32	0.70 (0.65 to 0.77)	0.86 (0.79 to 0.94)	0.90 (0.83 to 0.99)
➡ Spironolactone	26	19	0.67 (0.61 to 0.75)	0.76 (0.69 to 0.85)	0.77 (0.69 to 0.85)
Diuretics	85	88	1.25 (1.11 to 1.42)	1.07 (0.94 to 1.22)	1.05 (0.92 to 1.19)
Cardiac glycosides	38	40	1.12 (1.03 to 1.22)	1.09 (1.00 to 1.19)	1.06 (0.97 to 1.17)
➡ Antithrombotic agents	82	75	0.65 (0.58 to 0.71)	0.67 (0.60 to 0.74)	0.71 (0.63 to 0.79)

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DIFFERENCES IN THE USE OF PROCEDURES BETWEEN WOMEN AND MEN HOSPITALIZED FOR CORONARY HEART DISEASE

JOHN Z. AYANIAN, M.D., M.P.P., AND ARNOLD M. EPSTEIN, M.D., M.A.

Abstract *Background and Methods.* Previous studies at individual hospitals have reported differences in the use of major diagnostic and therapeutic procedures for women and men with coronary heart disease. To assess whether these differences can be generalized, we performed retrospective analyses of coronary angiography and revascularization (coronary-artery bypass surgery or percutaneous transluminal coronary angioplasty) in women and men hospitalized for coronary heart disease in 1987, using abstract data on 49,623 discharges in Massachusetts and 33,159 discharges in Maryland. We used multiple logistic regression to estimate the adjusted odds of the use of a procedure, controlling for principal diagnosis, age, secondary diagnosis of congestive heart failure or diabetes mellitus, race, and insurance status.

Results. The adjusted odds of undergoing angiography were 28 percent and 15 percent higher for men than for women in Massachusetts and Maryland, respectively (95 percent confidence intervals for the odds ratios, 1.22 to 1.35 and 1.08 to 1.22). The respective adjusted odds of

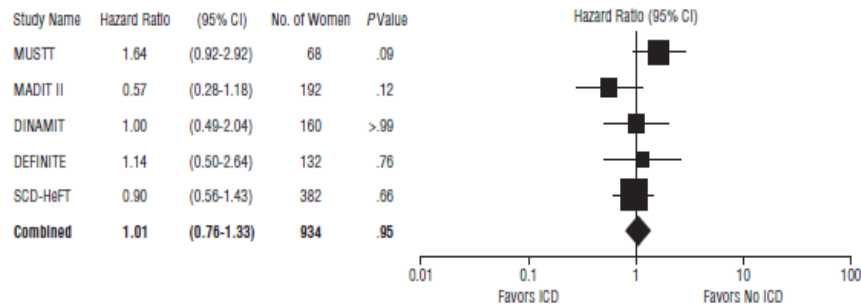
undergoing revascularization were 45 percent and 27 percent higher for men than for women (95 percent confidence intervals, 1.35 to 1.55 and 1.16 to 1.40). Because these differences could be related to differing thresholds for hospital admission, we performed a second analysis limited to patients with diagnosed acute myocardial infarction (11,865 discharges in Massachusetts and 6894 discharges in Maryland), a group in which all patients would be expected to receive hospital care. The male-to-female odds ratios in both states remained similar in magnitude and were statistically significant for angiography and revascularization.

Conclusions. These findings demonstrate that women who are hospitalized for coronary heart disease undergo fewer major diagnostic and therapeutic procedures than men. These differences may represent appropriate levels of care for men and women, but it is also possible that they reflect underuse in women or overuse in men. Further study should assess the cause of these differences and their effect on patients' outcomes. (N Engl J Med 1991; 325:221-5.)

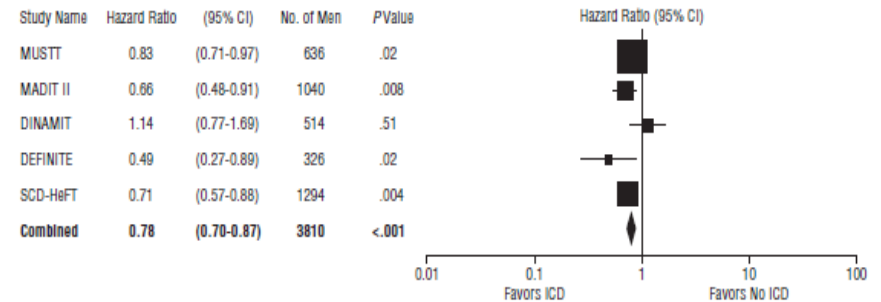
Il defibrillatore nelle donne: studi clinici

A Meta-analysis of 5 RCTs totalling 934 women and 3.810 men

Women



Men



Disparità di sesso negli studi clinici



A randomized trial of aspirin and beta-carotene among U.S. physicians: Physicians' Health Study

Prev Med. 1985;14:165–168



Multiple Risk Factor Intervention Trial Research Group. Multiple Risk Factor Intervention Trial (MRFIT). Risk factor changes and mortality results

JAMA 1982;248:1465–1477

Guidance for Industry



U.S. Department of Health and Human Services
Food and Drug Administration

US FDA guideline for the study and evaluation of gender differences in the clinical evaluation of drugs.

1993;58:39406–39416



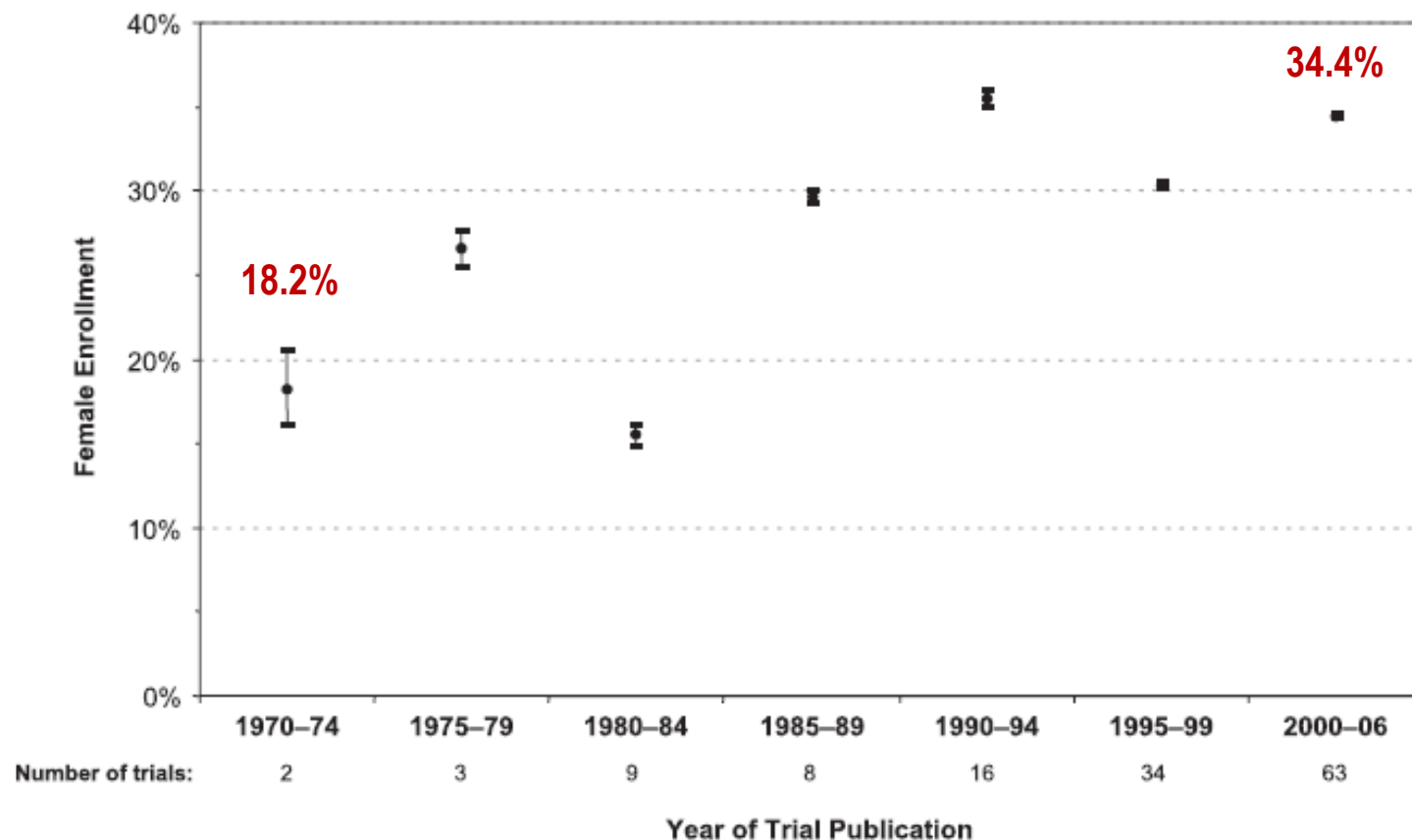
National Institutes
of Health

**NIH guidelines on the inclusion of
women and minorities as subjects in
clinical research.**

1994;59(part VIII):14508–14513

Rappresentazione delle donne nei grandi studi clinici

Both women and men were represented in 135 of 156 (86.5%) trials;
20 trials enrolled only men; 1 enrolled only women





Il defibrillatore nel mondo reale

“Get With the Guidelines” heart failure database

Only 35% of 13.034 patients eligible for ICD, between January 2005-June 2007 at 217 participating hospitals, received an implant at discharge

Device implantation in eligible patients for ICD	
White men	43.6%
Black men	33.4%
White women	29.8%
Black women	28.2%

Differenze biologiche o disparità di genere

Perché differenze ?

- Fattori intrinseci (genetici, ormonali, massa corporea, fisiologia sesso-dipendente, etc)
- Fattori estrinseci (dieta, problemi socioculturali, ambientali, etc)

Perché disparità ?

- Mancanza di letteratura, tutti i dati disponibili sono *post-hoc*, manca uno studio che abbia come obiettivo primario la valutazione delle differenze di sesso
- Barriere nell'arruolamento di donne negli studi clinici (responsabilità familiare, paura della gravidanza e delle conseguenze sul feto, timore di un maggior consumo di tempo e risorse economiche nel follow-up)