MEDICINA DI GENERE: COME PRENDERSI CURA DELLE DIFFERENZE

AHA Scientific Statement

Acute Myocardial Infarction in Women

A Scientific Statement From the American Heart Association

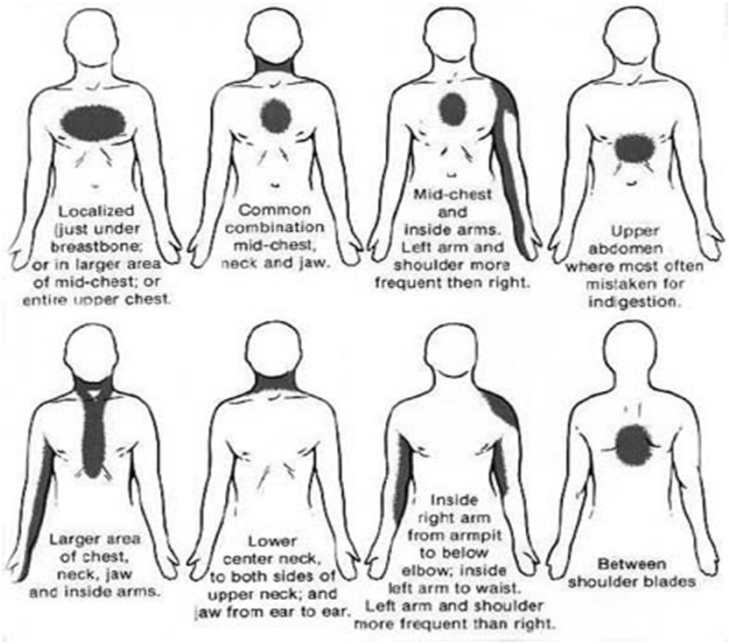
Laxmi S. Mehta, MD, FAHA, Chair; Theresa M. Beckie, PhD, FAHA, Co-Chair; Holli A. DeVon, PhD, RN, FAHA; Cindy L. Grines, MD; Harlan M. Krumholz, MD, SM, FAHA; Michelle N. Johnson, MD, MPH; Kathryn J. Lindley, MD; Viola Vaccarino, MD, PhD, FAHA; Tracy Y. Wang, MD, MHS, MSc, FAHA; Karol E. Watson, MD, PhD; Nanette K. Wenger, MD, FAHA; on behalf of the American Heart Association Cardiovascular Disease in Women and Special Populations Committee of the Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council on Cardiovascular and Stroke Nursing, and Council on Quality of Care and Outcomes Research

Table 1. Typical Versus Atypical Symptoms in Women Presenting With AMI

Typical Symptoms	Atypical Symptoms
Chest pain/discomfort (pressure, tightness, squeezing)	Chest pain: sharp, pleuritic, burning, aching, soreness, reproducible
Additional symptoms with chest pain Radiation of pain to jaw, neck, shoulders, arm, back, epigastrium Associated symptoms: dyspnea, nausea, vomiting, lightheadedness, diaphoresis	Other symptoms excluding chest pain Unusual fatigue Unusual shortness of breath Upper back/chest pain Neck, jaw, arm, shoulder, back, epigastric pain Flu-like symptoms Dizziness Generalized scared/anxiety feeling Generalized weakness Indigestion Palpitations

AMI indicates acute myocardial infarction.

Mehta et al, Circulation 2016



AHA Scientific Statement

Preventing and Experiencing Ischemic Heart Disease as a Woman: State of the Science

A Scientific Statement From the American Heart Association

Jean C. McSweeney, PhD, RN, FAHA, Chair; Anne G. Rosenfeld, PhD, RN, FAHA, Vice Chair; Willie M. Abel, PhD, RN, ACNS-BC; Lynne T. Braun, PhD, CNP, FAHA; Lora E. Burke, PhD, MPH; Stacie L. Daugherty, MD, MSPH; Gerald F. Fletcher, MD; Martha Gulati, MD, MS, FAHA; Laxmi S. Mehta, MD, FAHA; Christina Pettey, PhD, APRN, FAHA; Jane F. Reckelhoff, PhD; on behalf of the American Heart Association Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council on Hypertension, Council on Lifestyle and Cardiometabolic Health, and Council on Quality of Care and Outcomes Research

McSweeney et al, Circulation 2016

Table 1. Sex-Related Differences in the Cardiovascular System

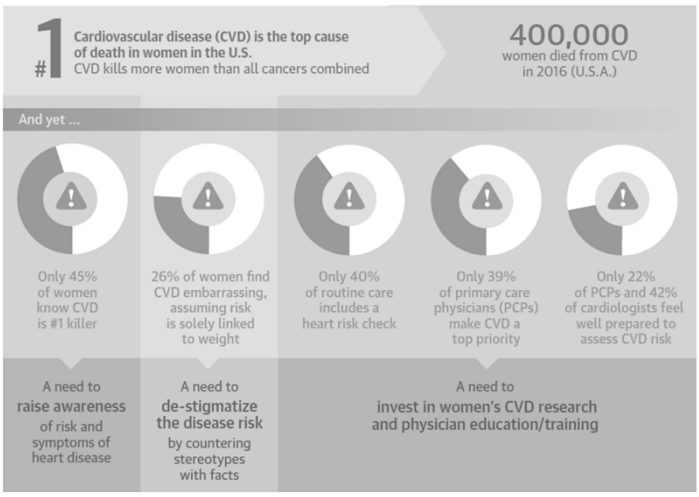
Parameter	Manifestations
Anatomy	Dimensions that are smaller in women (adjust for age and race): left ventricular mass, ventricular wall thickness, left atrial dimension, left ventricular end-diastolic dimension, and vessel size
Hormonal influences	Estrogen and progesterone are most influential in women; testosterone is predominant in men
	Menstruation can affect hematologic and electrocardiographic indexes
Cardiovascular function	Stroke volume is women is 10% less
	Pulse rate in women is 3–5 bpm faster
	Ejection fraction is higher in women
Physiology	Women have reduced sympathetic and enhanced parasympathetic activity
	Women have lower plasma concentrations of norepinephrine
Cardiovascular adaptations	In response to stress, women experience an increased pulse rate, resulting in increased cardiac output; men have increased vascular resistance, resulting in increased BP
	Women are more sensitive to altitude or body positioning changes and experience more orthostatic hypotension and syncope
Hematologic indexes	Women have a lower number of circulating red blood cells per unit volume of plasma (resulting in a lower hematocrit)
	Because of a lower hemoglobin, women have a lower oxygen-carrying capacity; this is balanced by women having a lower oxygen consumption
Electrocardiographic and electrophysiological indexes	Women on average have a longer corrected QT interval and a shorter sinus node recovery time
	Drug-induced torsades de pointes is more common in women
	Sudden cardiac death and atrial fibrillation are less common in women

McSweeney et al, Circulation 2016

Knowledge, Attitudes, and Beliefs Regarding Cardiovascular Disease in Women

The Women's Heart Alliance

C. Noel Bairey Merz, MD,[a] Holly Andersen, MD,[b] Emily Sprague, MA,[c] Adam Burns, MPP,[c] Mark Keida, PhD,[c] Mary Norine Walsh, MD,[d] Phyllis Greenberger, MSW,[e] Susan Campbell, MPH,[f] Irene Pollin, MSW, PhD(Hon),[g] Cassandra McCullough, MBA,[h] Nancy Brown, BA,[i] Marjorie Jenkins, MD,[j] Rita Redberg, MD,[k] Paula Johnson, MD,[l] British Robinson, MA, JD(Hon)[m]



Bairey Merz et al, J Am Coll Cardiol 2017

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 70, NO. 2, 2017
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2017.05.037

EDITORIAL COMMENT

What Women (and Clinicians) Don't Know Hurts Them*

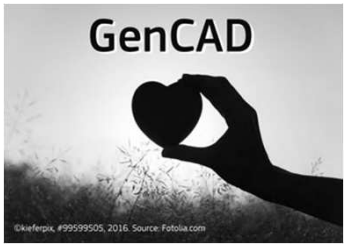
Jennifer G. Robinson, MD, MPH

Robinson et al, J Am Coll Cardiol 2017

GenCAD: Gender-specific mechanisms in coronary artery disease in Europe

European Commission

Public Health



GENCAD Conference 2: Gender and health – awareness, facts, and European perspectives
Brussels, 11th October 2017

Gender differences in classical risk factors

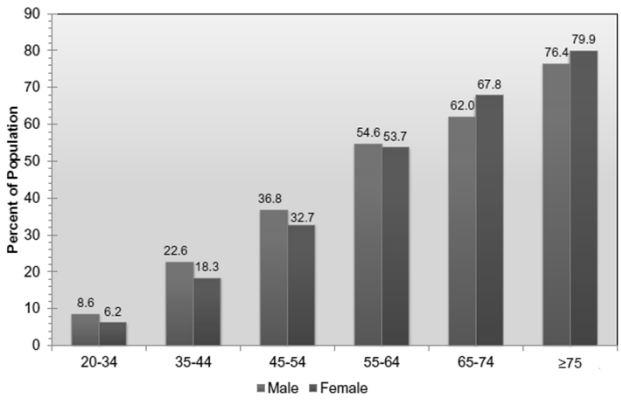
- Hypertension occurs more frequently in men before the age of 50, and in women after the age of 50. Hypertension leads to more strokes and heart failure in women than in men.

Gender differences in classical risk factors

- Coronary heart disease develops 7-10 years later in women compared to men. Overall, more women are affected, since they live longer and the disease develops in old age.

Heart Disease and Stroke Statistics
2016 Update

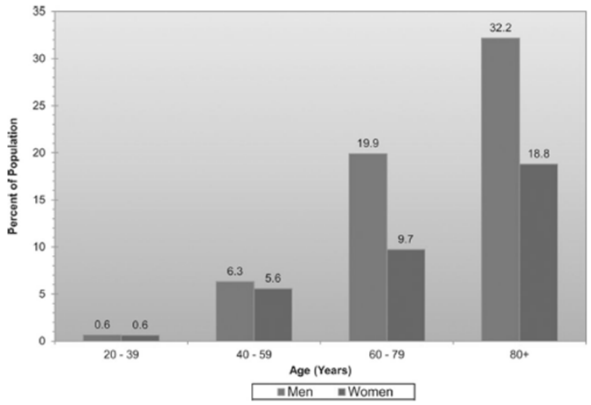
Prevalence of hypertension, by age & sex



AHA Statistical 2016 Update, Circulation 2016

Heart Disease and Stroke Statistics
2016 Update

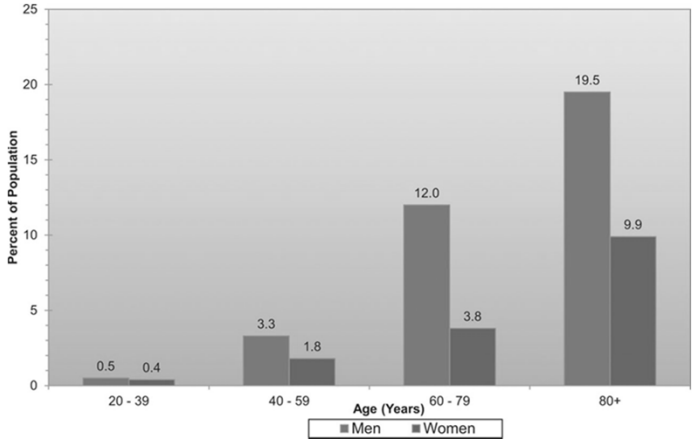
Prevalence of coronary artery disease, by age & sex



AHA Statistical 2016 Update, Circulation 2016

Heart Disease and Stroke Statistics
2016 Update

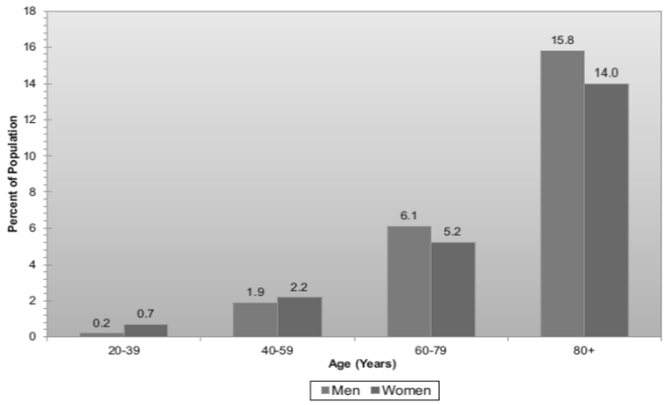
Prevalence of myocardial infarction, by age & sex



AHA Statistical 2016 Update, Circulation 2016

Heart Disease and Stroke Statistics
2016 Update

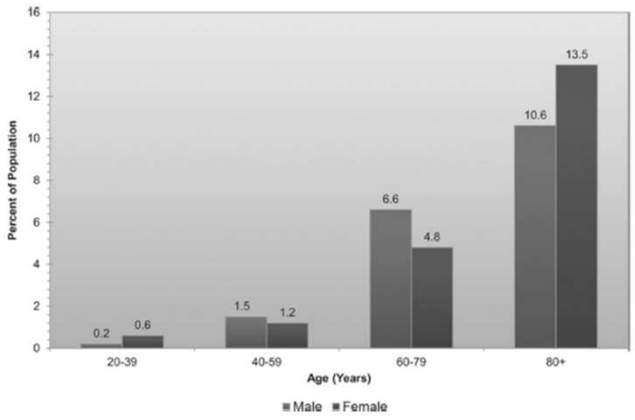
Prevalence of stroke, by age & sex



AHA Statistical 2016 Update, Circulation 2016

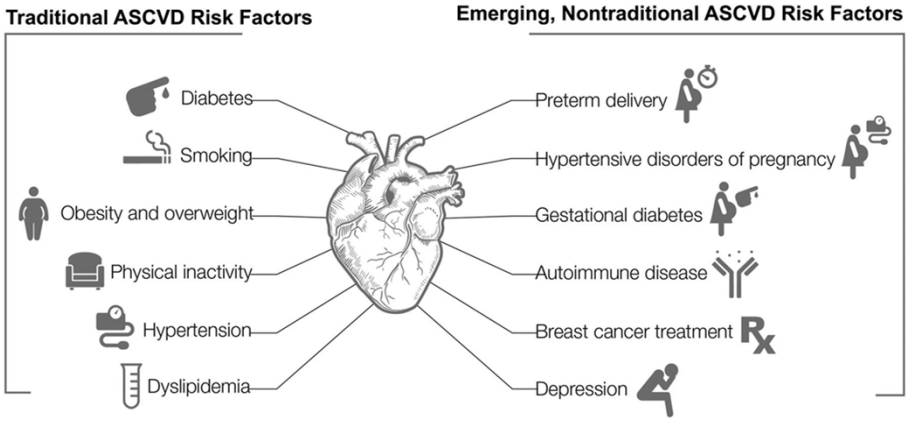
Heart Disease and Stroke Statistics
2016 Update

Prevalence of heart failure, by age & sex



AHA Statistical 2016 Update, Circulation 2016

Traditional and nontraditional atherosclerotic cardiovascular disease (ASCVD) risk factors in women.



American Heart Association.

Mariana Garcia et al. Circ Res. 2016;118:1273-1293

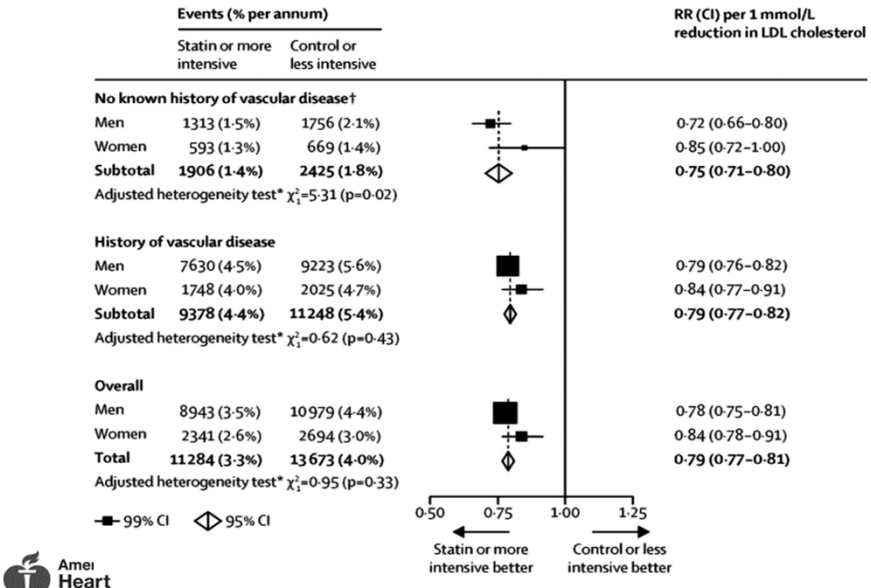
Gender differences in classical risk factors

- Diabetes increases the risk of cardiovascular disease more in women than in man. Women with diabetes and associated risk factors are high risk patients, and need intense management and treatment.

Gender differences in classical risk factors

- Dyslipidemia is an equally strong risk factor in women and in men.Lipid lowering therapy should therefore be used in both.

Effects on major vascular events per 1.0 mmol/L reduction in low-density lipoprotein (LDL) cholesterol, subdivided by history of vascular disease and sex.



Mariana Garcia et al. Circ Res. 2016;118:1273-1293

PubMed

Format: Abstract

Full text links

BenthamScience Full-Text Article

Curr Med Chem. 2017;24(24):2628-2638. doi: 10.2174/0929867324666161118094711.

Treatment and Response to Statins: Gender-related Differences.

Raparelli V[1], Pannitteri G[2], Todisco T[3], Toriello F[3], Napoleone L[1], **Manfredini R**[4], Basili S[5].

Author information

Abstract

Response to drug administration is a primary determinant for treatment success. Sex and gender disparities play a role in determining the efficacy and safety of the most commonly used medications suggesting the need for a sex-tailored approach in prescription. Statins are a cost-effective strategy for cardiovascular disease (CVD) prevention. While statins are similarly effective in secondary CVD prevention, some concerns raised by conflicting data reported in primary CVD prevention clinical trials. The small representation of women in clinical trials and the fewer rates of events due to the lower female baseline CVD risk may have conditioned contradictory meta-analysis findings. Specifically, benefits outweigh disadvantages of statin therapy in women with a high CVD risk, while several doubts exist for the primary prevention of women at low-intermediate CVD risk. Furthermore, disparities between women and men in medication adherence may influence statin efficacy in CVD prevention. The sex-dependent impact of adverse side effects is one of the reasons advocated for explaining the gender gap, but it is not evidence-proved. The present review summarizes the sex and gender differences in the use of statins, pointing out new perspectives and opening issues in sex-tailored CVD prevention strategy.

KEYWORDS: Statin; cardiovascular disease; gender; medication adherence; prevention; sex

Gender differences in classical risk factors

- Smoking is a relatively greater risk factor in younger women than in men and smoking rate in women has been reduced less than in men.

Gender differences in non-classical risk factors

- Poor socioeconomic status contributes to gender disparities in cardiovascular health.
- Depression and sustained marital stress occur more often in women than in men and are more important risk factors in women.

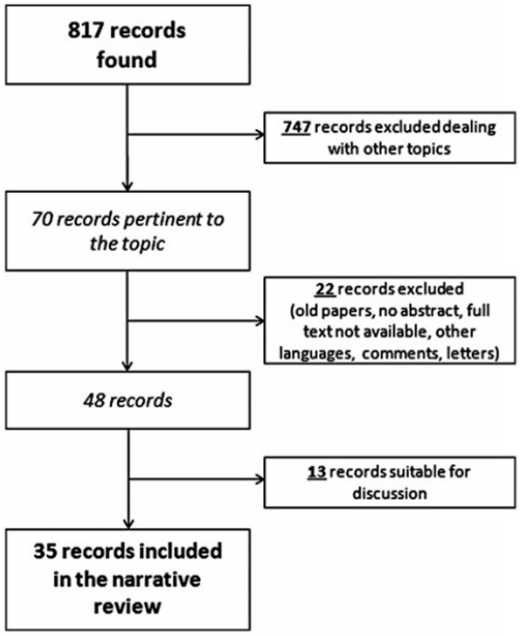
JOURNAL OF WOMEN'S HEALTH
Volume 26, Number 6, 2017

DOI: 10.1089/jwh.2016.6103

Marital Status, Cardiovascular Diseases, and Cardiovascular Risk Factors: A Review of the Evidence

Roberto Manfredini, MD,[1,2] Alfredo De Giorgi, MD,[1,2] Ruana Tiseo, MD,[2] Benedetta Boari, MD,[2] Rosaria Cappadona, MT,[1] Raffaella Salmi, MD,[2] Massimo Gallerani, MD,[2] Fulvia Signani, PsyD,[1] Fabio Manfredini, MD,[1,2] Dimitri P. Mikhailidis, MD,[3] and Fabio Fabbian, MD[1,2]

Marital Status, Cardiovascular Diseases, and Cardiovascular Risk Factors: A Review of the Evidence



Marital Status, Cardiovascular Diseases, and Cardiovascular Risk Factors: A Review of the Evidence

Abstract

Background: There is evidence showing that marital status (MS) and marital disruption (*i.e.*, separation, divorce, and being widowed) are associated with poor physical health outcomes, including for all-cause mortality. We checked for the available evidence on the association between MS and cardiovascular (CV) diseases, outcomes, and CV risk factors.

Methods: A search across the PubMed database of all articles, including the term ''marital status'' in their title, was performed. All articles were then manually checked for the presence of the following terms or topic: CV diseases, acute myocardial infarction, acute coronary syndrome, coronary artery disease, cardiac arrest, heart failure, heart diseases, and CV mortality. Moreover, other search terms were: CV risk factors, hypertension, cholesterol, obesity, smoking, alcohol, fitness and/or physical activity, and health. Systematic reviews, meta-analyses, controlled trials, cohort studies, and case–control studies were potentially considered pertinent for inclusion. Case reports, comments, discussion letters, abstracts of scientific conferences, articles in other than English language, and conference abstracts or proceedings were excluded.

Results: In total, 817 references containing the title words ''marital status'' were found. After elimination of articles dealing with other topics, 70 records were considered pertinent. Twenty-two were eliminated for several reasons, such as old articles, no abstract, full text unavailable, other than English language, comments, and letters. Out of the remaining 48 articles, 13 were suitable for the discussion, and 35 (accounting for 1,245,967 subjects) were included in this study.

Conclusions: Most studies showed better outcomes for married persons, and men who were single generally had the poorest results. Moreover, being married was associated with lower risk factors and better health status, even in the presence of many confounding effects.

Gender differences in non-classical risk factors

- Autoimmune and rheumatic diseases occur more often in women and are frequently associated with cardiovascular diseases.
- Pre-eclampsia is an increasing recognized risk factor in women. Women who develop pre-eclampsia have a twofold elevated risk of developing cardiovascular diseases later in life.

Gender differences in non-classical risk factors

- Genetic factors are important in premature heart disease in women and in men.
- Erectile Dysfunction is associated with general metabolic and cardiovascular health risks in men.
- Menopause, polycystic ovary syndrome, andropause and hypogonadism are associated with increased cardiovascular risk in women and men.

Gender-specific mechanism of disease

- In men, arteriosclerosis of large coronary arteries is the dominant mechanism leading to myocardial ischemia and infarction.
- Middle-aged women frequently have angina pectoris and myocardial ischemia in the presence of normal coronary arteries. The term ischemic heart disease is suitable for this form of disease.

Gender-specific mechanism of disease

- Fuctional disorders and spasms of large arteries and the smaller vessels (the microcirculation) of the heart or an increased demand of the myocardial tissue may cause ischemic heart disease, which occurs preferentially in women.
- Stress induced heart disease, coronary artery spasms and spontaneous coronary artery dissections (longitudinal ruptures in the wall) cause relatively more acute coronary syndromes in women than in men.

Gender-specific mechanism of disease

- In pregnancy and in the peripartum period, pre-eclampsia, peripartum cardiomyopathy and coronary artery dissection should be suspected in symptomatic women.

Gender in prevention

- Women underestimate their risk for cardiovascular disease and are less open for preventive actions than men. Secondary prevention goals are less often achieved in women than in men.
- Exercise is a stronger protective factor in women, but women exercise less then men.
- Smoking cessation is more difficult for women than for men.

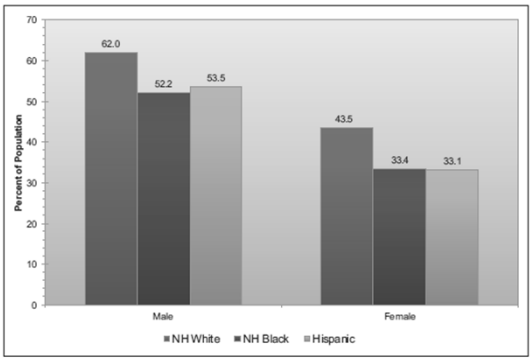


Chart 4-2. Prevalence of students in grades 9 to 12 who met currently recommended levels of physical activity during the past 7 days by race/ethnicity and sex.

Benjamin et al, Circulation 2017

Gender in prevention

- Healthy nutrition is a strong and underused protective factor in women and men. Men generally use less healthy nutrition than women.
- Hormone therapy and selective estrogen-receptor modulators (SERMs) should not be used in the primary or secondary prevention of cardiovascular diseases.
- Routine use of aspirin in healthy women under 65 years of age is not recommended to prevent myocardial infarction. However, aspirin in primary prevention for myocardial infarction is useful in men.

Gender in clinical manifestation and diagnosis

- Women with myocardial ischemia and infarction may have a greater variety of symptoms than men.
- The ECG normally is an indicator of myocardial ischemia. However, women exhibit changes in ECG more often than men, caused by factors other than myocardial ischemia.
- Women have relatively lower exercise tolerance than men and the exercise-ECG is less sensitive for CAD.

Gender in clinical manifestation and diagnosis

- The use of high-sensitive Troponins and sex-specific thresholds improve the diagnosis of myocardial infarction in women.
- Coronary angiography should not be used ad a first test to diagnose myocardial ischemia in young or middle-aged women that have few other risk factors for CAD. Newer imaging tecniques are recommended by the ESC Guidelines in these patients.
- Non-radiation imaging tecniques should be preferred in younger women with suspected myocardial ischemia.

JOURNAL OF WOMEN'S HEALTH
Volume 20, Number 11, 2011

DOI: 10.1089/jwh.2011.2734

Seasonal and Weekly Patterns of Occurrence of Acute Cardiovascular Diseases: Does a Gender Difference Exist?

Roberto Manfredini, M.D.,[1] Fabio Fabbian, M.D.,[1] Marco Pala, M.D.,[1] Ruana Tiseo, M.D.,[1] Alfredo De Giorgi, M.D.,[1] Fabio Manfredini, M.D.,[2] Anna Maria Malagoni, M.D.,[2] Fulvia Signani, PsyD,[3] Candida Andreati, M.D.,[3] Benedetta Boari, M.D.,[4] Raffaella Salmi, M.D.,[4] Davide Imberti, M.D.,[4] and Massimo Gallerani, M.D.[4]

Seasonal and Weekly Patterns of Occurrence of Acute Cardiovascular Diseases: Does a Gender Difference Exist?

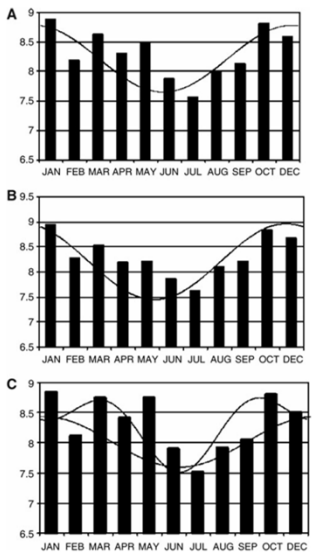


FIG. 1. Monthly distribution of hospital admissions (percentage of events) for acute cardiovascular (CV) events. (A) All cases. (B) Women. (C) Men. Cosinor fit is superimposed on the graphs.

TABLE 1. MONTHLY DISTRIBUTION OF ACUTE CARDIOVASCULAR EVENTS (% OF EVENTS) ACCORDING TO GENDER

	Aneurysms[a]		*Pulmonary embolism*[b]		*Acute myocardial infarction*[c]		*TIA*[d]		*All*[e]	
	Women n = 1,243 26.9%	*Men* n = 3,372 73.1%	*Women* n = 11,102 57.7%	*Men* n = 814 42.3%	*Women* n = 23,805 37.1%	*Men* n = 40,386 62.9%	*Women* n = 23,765 54.5%	*Men* n = 19,877 45.5%	*Women* n = 23,765 54.5%	*Men* n = 19,877 45.5%
January	8.7%	9.5%	9.4%	9.6%	9.1%	9.0%	8.3%	8.5%	8.8%	8.9%
February	8.8%	7.8%	8.4%	8.2%	8.0%	8.2%	7.7%	7.4%	8.0%	8.0%
March	9.0%	9.4%	8.7%	8.5%	8.5%	8.7%	8.6%	8.9%	8.6%	8.7%
April	8.0%	8.6%	8.7%	8.5%	8.2%	8.5%	8.2%	8.4%	8.1%	8.4%
May	8.4%	8.0%	7.7%	7.3%	8.0%	8.5%	8.5%	8.9%	8.2%	8.4%
June	8.2%	8.6%	6.4%	6.6%	7.6%	7.6%	8.5%	8.4%	7.8%	7.7%
July	8.8%	8.8%	7.6%	7.5%	7.2%	7.3%	8.0%	8.0%	7.6%	7.6%
August	7.8%	7.3%	8.3%	8.8%	7.4%	7.3%	8.3%	8.1%	7.9%	7.7%
September	7.9%	8.5%	8.0%	8.9%	8.4%	7.9%	8.5%	8.0%	8.4%	8.1%
October	8.7%	8.6%	9.5%	8.7%	9.2%	9.1%	8.8%	8.9%	9.1%	9.0%
November	7.0%	7.5%	9.3%	9.1%	9.2%	8.7%	8.4%	8.3%	8.9%	8.6%
December	8.6%	7.4%	9.2%	8.9%	9.0%	9.3%	8.1%	8.1%	8.7%	8.8%

[a]Between women and men: chi-square = 0.291, p = NS; [b]chi-square = 0.127, p = NS; [c]chi-square = 0.062, p = NS; [d]chi-square = 0.044, p = NS; [e]chi-square = 0.024, p = NS.
TIA, transient ischemic attack.

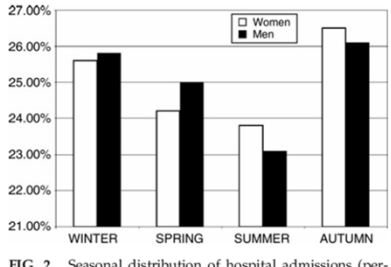


FIG. 2. Seasonal distribution of hospital admissions (percentage of events) for acute CV events. White bars, women; black bars, men.

Sex and Circadian Periodicity of Cardiovascular Diseases

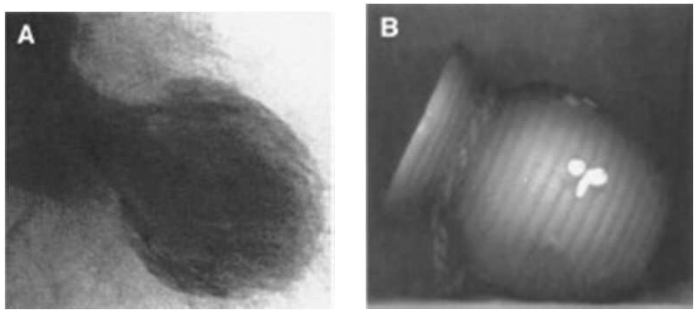
Are Women Sufficiently Represented in Chronobiological Studies?

Roberto Manfredini, MD[a,*], Raffaella Salmi, MD[b], Rosaria Cappadona, MW[c], Fulvia Signani, PsyD[d], Stefania Basili, MD[e], Niki Katsiki, MD, MSc, PhD, FRSPH[f]

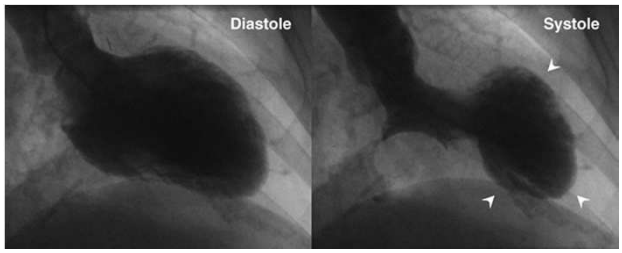
Cardiomiopatia da stress

Cardiomiopatia Tako-Tsubo

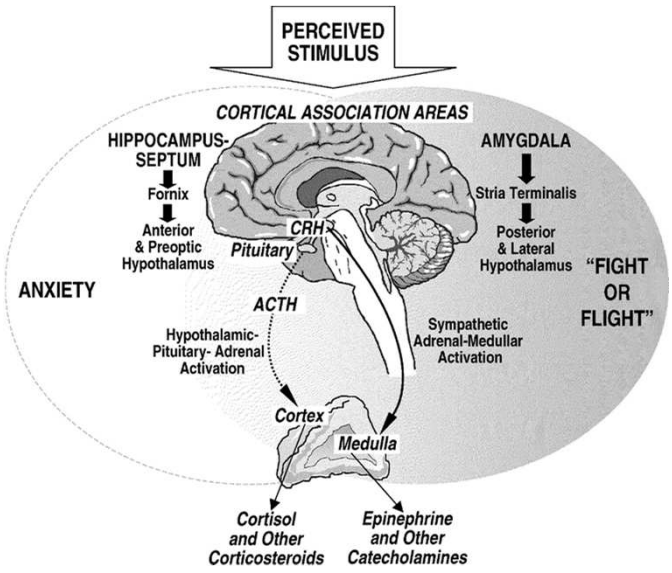
Descritta per la prima volta in Giappone nel 1990. Il nome deriva dalle parole Tako (polpo) e Tsubo (giara)



Disfunzione transitoria delle sezioni apicale e medio-ventricolare del ventricolo sx, in assenza di malattia coronarica significativa, e spesso scatenata da uno stress (emotivo o fisico).



- Fino al 2% delle sospette sindromi coronariche acute (SCA) (donne 6-9%, uomini 0.5%)
- Più frequente nelle donne (~90%), >80% dei casi in postmenopausa
- Mortalità intra-ospedaliera: 1-2%
- Recupero della funzione del Vsx: 1-4 sett.
- Recidive (10% ad un follow-up di 4 anni)



Triggers 'emotivi'

- Morte, malattia grave o grave lesione riguardante un membro della famiglia, un amico, il proprio animale
- Cattive notizie (diagnosi di grave malattia, divorzio di un famigliare)
- Grave litigio
- Aggressione
- Coinvolgimento in azione legale
- Incidente d'auto
- Trasloco
- Perdita economica (affari, gioco, licenziamento)
- Disastri naturali (terremoti..)
- Party a sorpresa
- Public speaking

European Heart Journal Advance Access published March 2, 2016

European Heart Journal
doi:10.1093/eurheartj/ehv757

CLINICAL RESEARCH
Heart failure/cardiomyopathy

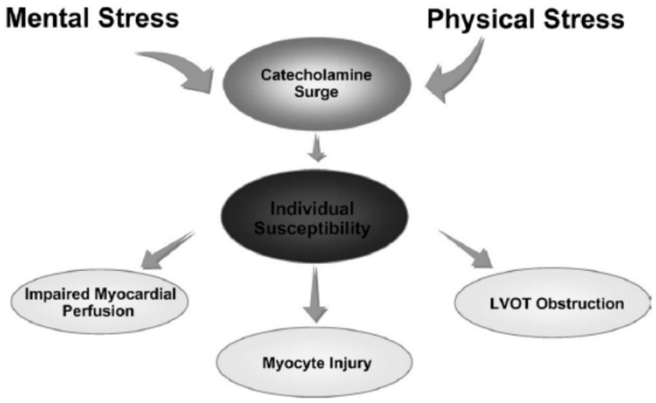
Happy heart syndrome: role of positive emotional stress in takotsubo syndrome

Table 1 Happy heart events (n = 20)

Patient 1	Birthday party
Patient 2	Son's wedding
Patient 3	Meeting after 50 years with friends from high school
Patient 4	Preparing 50th wedding anniversary (pleasant anticipation)
Patient 5	Positive job interview
Patient 6	Wedding
Patient 7	Favourite driver won race car competition
Patient 8	Becoming grandmother
Patient 9	Surprise farewell celebration
Patient 10	Son's company opening
Patient 11	Favourite rugby team won game
Patient 12	Emotional speaking during a friend's birthday
Patient 13	Celebrating 80th birthday
Patient 14	Winning several jackpots at the casino
Patient 15	Celebration of normal PET-CT scan
Patient 16	Visiting opera with her family
Patient 17	Family party
Patient 18	Unexpected visit from favourite nephew
Patient 19	Grandchildren visiting from London (abroad)
Patient 20	Becoming great grandmother

Triggers 'fisici'

- Procedure chirurgiche e cardiochirurgiche
- Cause respiratorie
- Patologie gastroenteriche
- Patologie reumatologiche
- Patologie endocrine
- Patologie ematologiche
- Patologie infettive
- Dialisi
- Patologie neurologiche
- Sostanze illecite o farmaci: cocaina, abuso di antidepressivi, β2 stimolanti, adrenalina…
- Altri: traumi, ustioni, colpo di calore, abuso di energy drinks, puntura di medusa, ..



Prasad et al, *Am Heart J* 2008

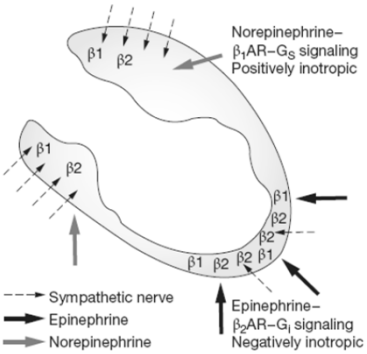


Figure 3 Schematic representation of the regional differences in response to high catecholamine levels, explaining stress cardiomyopathy.

High levels of circulating E might trigger a switch in intracellular signal trafficking, from G8 protein to Gi protein signaling through the β2AR. This change in signaling is negatively inotropic, and the effect is greatest at the apical myocardium, in which the density of β-adrenoceptors is highest.

Lyon et al, *Nat Clin Pract Cardiovasc Med* 2009

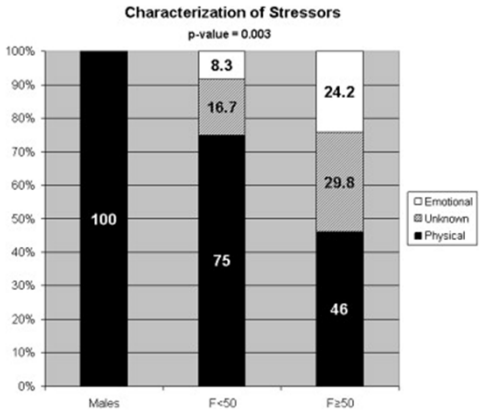
Tako-Tsubo & genere

- Netta preponderanza nelle donne (90%, età media da 62 a 76)
- Circa 2% delle SCA: donne 6-9%, uomini <0.5%
- Contrariamente alle SCA, sintomi clinici e pre-hospital delay sono simili tra donne e uomini
- L'aumento della troponina è più frequente negli uomini
- Le complicanze tipo shock cardiogeno e arresto cardiaco sono più frequenti nell'uomo, così come le aritmie maligne (aumento del QTc?)

Schneider et al, *Heart Fail Clin J* 2013

Distinctive Clinical Characteristics According to Age and Gender in Apical Ballooning Syndrome (Takotsubo/Stress Cardiomyopathy): An Analysis Focusing on Men and Young Women

SANDEEP M. PATEL, MD,[1] RAMESH G. CHOKKA, MD,[2] KAVITA PRASAD, MD,[3] AND ABHIRAM PRASAD, MD, FRCP, FACC[2]



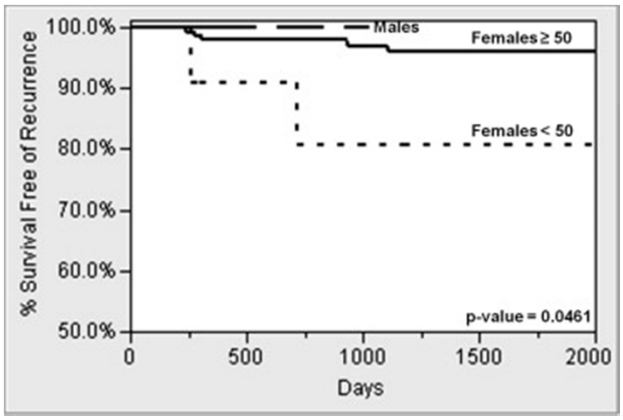
Patel et al, *J Cardiac Fail* 2013

Distinctive Clinical Characteristics According to Age and Gender in Apical Ballooning Syndrome (Takotsubo/Stress Cardiomyopathy): An Analysis Focusing on Men and Young Women

SANDEEP M. PATEL, MD,[1] RAMESH G. CHOKKA, MD,[2] KAVITA PRASAD, MD,[3] AND ABHIRAM PRASAD, MD, FRCP, FACC[2]

N=224
M=12 (RR 0%)
F<50=12 (RR 16%)
F>50=200 (RR 3%)

RR recurrence rate



Patel et al, *J Cardiac Fail* 2013

Gender Differences in Patients with Takotsubo Cardiomyopathy: Multi-Center Registry from Tokyo CCU Network

Tsutomu Murakami, Tsutomu Yoshikawa*, Yuichiro Maekawa, Tetsuro Ueda, Toshiaki Isogai, Konomi Sakata, Ken Nagao, Takeshi Yamamoto, Morimasa Takayama

The Tokyo CCU Network Scientific Committee, Tokyo, Japan

		All patients (n = 368)	Male (n = 84)	Female (n = 284)	*P* value
Age (years) [range]		76 [67–82]	72 [64–81]	76 [68–83]	0.040
Hospitalization within 24 hours		86.7%	92.9%	84.9%	0.058
Symptom					
	Chest pain	48.6%	39.3%	51.4%	0.051
	Dyspnea	33.4%	35.7%	32.8%	0.613
Preceding stress					
	No stress	36.1%	31.0%	37.7%	0.260
	Physical stress [a]	35.6%	50.0%	31.3%	0.002
	Emotional stress	28.3%	19.0%	31.0%	0.039
Vital signs					
	Systolic blood pressure (mm Hg) [range]	133 [111–160]	131 [110–164]	134 [112–160]	0.690
	Diastolic blood pressure (mm Hg) [range]	79 [66–91]	80 [64–92]	79 [67–91]	0.719
	Heart rate (bpm) [range]	87 [75–108]	88 [72–114]	87 [75–104]	0.921
	Arterial oxygen saturation (%) [range]	98 [95–99]	98 [94–99]	98 [95–99]	0.857

[a] Physical stress included acute respiratory failure, central nervous system disorders, infection, post-surgery, trauma, etc.

doi:10.1371/journal.pone.0136655.t001

Murakami et al, *PLoS ONE* 2015

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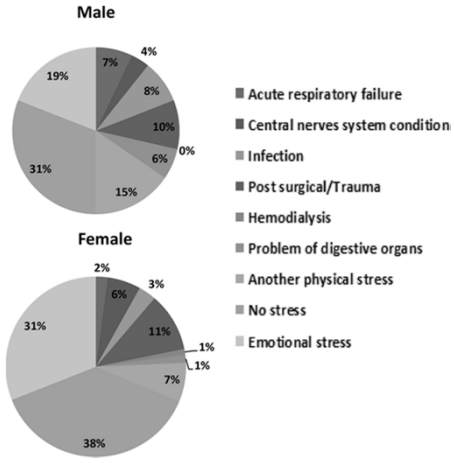

Murakami et al, *PLoS ONE* 2015

Gender Differences in Patients with Takotsubo Cardiomyopathy: Multi-Center Registry from Tokyo CCU Network

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	Odds ratio	95% Confidence	*P* value
Male gender	4.32	1.41–13.6	0.011
Chronic kidney disease present	1.46	0.48–4.84	0.511
High age	1.12	0.36–3.47	0.839
High White blood cell count	4.38	1.38–16.9	0.011
High C-reactive protein level	1.42	0.45–4.70	0.548
High brain natriuretic peptide level	2.61	0.78–9.48	0.119
Low left ventricular ejection fraction	2.09	0.68–7.08	0.198
Physical stress present	0.92	0.28–2.79	0.878

doi:10.1371/journal.pone.0136655.t004

Stepwise multiple logistic regression analysis.

Murakami et al, *PLoS ONE* 2015

Gender differences in the manifestation of tako-tsubo cardiomyopathy

Birke Schneider [a,*], Anastasios Athanasiadis [b], Claudia Stöllberger [c], Wolfgang Pistner [d], Johannes Schwab [e], Uta Gottwald [f], Ralph Schoeller [g], Birgit Gerecke [h], Ellen Hoffmann [i], Christian Wegner [j], Udo Sechtem [b]

Clinical characteristics of 324 female and male patients with tako-tsubo cardiomyopathy.

Characteristics	Female		Male		p Value	
Patients	296	(91%)	28	(9%)		
Age (years)	68 ± 12	(27–90)	66 ± 12	(37–84)	0.31	
Symptoms						
Chest pain	217	(73%)	16	(57%)	0.08	
Dyspnea	45	(15%)	5	(18%)	0.78	
Syncope	9	(3%)	1	(4%)	0.60	
Shock/Resuscitation	2	(1%)	4	(14%)	**<0.001**	⇦
Other	16	(5%)	1	(4%)	1.00	
None	7	(2%)	1	(4%)	0.52	
Triggering event	226	(76%)	24	(86%)	0.35	
Emotional stress	111	(38%)	6	(21%)	0.10	
Physical stress	88	(30%)	16	(57%)	**0.005**	⇦
Both	27	(9%)	2	(7%)	1.00	
None	70	(24%)	4	(14%)	0.93	
Time from symptom onset to hospital admission						
Hours	7.6 ± 6.8	(0–23.8)	7.2 ± 7.1	(0–23.0)	0.57	
Cardiac markers						
CK median × ULN	1.17	(0.72–1.80)	1.55	(1.10–2.11)	0.05	
CK-MB median × ULN	1.34	(0.85–2.20)	1.28	(0.75–1.77)	0.76	
Troponin median × ULN	7.2	(2.9–17.9)	10.7	(7.6–29.0)	**0.03**	⇦
Angiography						
Symptom onset to angiography (days)	1	(0–2)	1	(0–2.75)	0.48	
LV ejection fraction	49 ± 14	(18–81)	46 ± 15	(23–80)	0.23	
Apical ballooning	189	(64%)	18	(64%)	1.00	
Mid-ventricular ballooning	107	(36%)	10	(36%)		
Intraaortic balloon pump	2	(1%)	1	(4%)	0.24	

Schneider et al, *Int J Cardiol* 2016

In-hospital mortality among patients with takotsubo cardiomyopathy: A study of the National Inpatient Sample 2008 to 2009

Waleed Brinjikji, MD,[a] Abdulrahman M. El-Sayed, DPhil,[b,c] and Samer Salka, MD, FACC[d] *Dearborn, MI; and New York, NY*

	Takotsubo patients	n (%), mortality	Unadjusted mortality OR (95% CI)
n	24701	1027 (4.2)	–
Age, mean ± SD	66.9 ± 30.7	–	–
Age group			
<50 y	2689 (10.9)	105 (3.9)	Ref
50-64 y	7290 (29.5)	245 (3.4)	0.86 (0.68-1.08)
>64 y	14722 (59.6)	677 (4.6)	1.19 (0.96-1.46)
Gender			
Female, n (%)	21994 (89.0)	799 (3.6)	Ref
Male, n (%)	2707 (11.0)	228 (8.4)	2.44 (2.09-2.84)*
Race, n (%)			
White	16680 (84.0)	668 (4.0)	Ref
Black	1178 (5.9)	49 (4.2)	1.04 (0.77-1.40)
Hispanic	1032 (5.2)	50 (4.9)	1.22 (0.91-1.64)
Asian	353 (1.8)	15 (4.2)	1.06 (0.63-1.79)
Mean ± SD CCI	1.4 ± 2.7	–	–
Chronic comorbidities			
Obesity	1494 (6.1)	29 (2.0)	0.44 (0.31-0.64)*
HTN	14434 (58.4)	428 (3.0)	0.49 (0.44-0.56)*
Hyperlipidemia	9261 (37.5)	119 (1.3)	0.21 (0.17-0.25)*
Diabetes mellitus	4661 (18.9)	157 (3.4)	0.77 (0.64-0.91)*
Smoking	3250 (13.2)	81 (2.5)	0.56 (0.44-0.70)*
Malignancy	3547 (14.4)	288 (8.1)	2.45 (2.13-2.82)*
Anxiety disorder	2204 (8.9)	22 (1.0)	0.22 (0.14-0.34)*
Mood disorder	3696 (15.0)	67 (1.8)	0.39 (0.30-0.50)*

HTN, Hypertension; *Ref*, reference.
*$P < .001$.

Brinjikji et al, *Am Heart J* 2012

In-hospital mortality among patients with takotsubo cardiomyopathy: A study of the National Inpatient Sample 2008 to 2009

Waleed Brinjikji, MD,[a] Abdulrahman M. El-Sayed, DPhil,[b,c] and Samer Salka, MD, FACC[d] *Dearborn, MI; and New York, NY*

	OR (95% CI)	P
Age group		
<50 y	Ref	Ref
50-64 y	1.01 (0.77-1.32)	.95
>64 y	1.04 (0.82-1.35)	.73
Gender		
Female	Ref	Ref
Male	2.07 (1.71-2.49)	<.0001
Race		
White	Ref	Ref
Black	0.87 (0.63-1.17)	.35
Hispanic	0.92 (0.67-1.24)	.59
Asian	0.65 (0.36-1.09)	.10
CCI*	1.19 (1.13-1.26)	<.0001
Underlying critical illness		
No	Ref	Ref
Yes	10.87 (9.08-13.08)	<.0001

Brinjikji et al, *Am Heart J* 2012

Out-of-hospital *versus* in-hospital Takotsubo cardiomyopathy: Analysis of 3719 patients in the Diagnosis Procedure Combination database in Japan ☆

Toshiaki Isogai [a,b], Hideo Yasunaga [a,*], Hiroki Matsui [a], Hiroyuki Tanaka [b], Tetsuro Ueda [b], Hiromasa Horiguchi [c], Kiyohide Fushimi [d]

Multivariable logistic regression model for in-hospital mortality in patients with TC.

	Odds ratio	95% CI	p-Value
In-hospital TC (reference: out-of-hospital TC)	2.02	1.43 to 2.85	<0.001
Age (years), by 10-year increase	1.33	1.15 to 1.53	<0.001
Male sex (reference: female)	1.24	0.91 to 1.70	0.176
Ambulance use (reference: non-use)	1.09	0.82 to 1.47	0.550
Hospital volume (case/year)	1.03	0.98 to 1.07	0.216
Academic hospital (reference: non-academic hospital)	0.97	0.68 to 1.37	0.845
Japan Coma Scale at admission (reference: 0 [alert])			
1–3 (drowsy)	2.10	1.43 to 3.07	<0.001
Chronic pulmonary disease	1.11	0.67 to 1.84	0.684
Chronic liver disease	2.69	1.33 to 5.42	0.006
Chronic renal failure	1.62	0.95 to 2.77	0.078
Peptic ulcer disease	0.99	0.53 to 1.85	0.966
Thyrotoxicosis	0.85	0.11 to 6.65	0.879
Rheumatic disease	2.92	1.46 to 5.83	0.002
Psychiatric disease	0.43	0.19 to 0.96	0.039
Sepsis	2.02	1.17 to 3.49	0.011
Pneumonia	3.07	2.15 to 4.38	<0.001
Cerebrovascular diseases	1.99	1.24 to 3.20	0.004
Acute renal failure	3.76	1.80 to 7.84	<0.001
Acute gastrointestinal diseases	2.51	1.16 to 5.41	0.019
Status asthmaticus	0.72	0.09 to 5.50	0.751
Seizure or status epilepticus	0.87	0.26 to 2.92	0.824
External injury	1.25	0.60 to 2.60	0.549
Surgical operation under general anesthesia within 7 days after admission	1.15	0.62 to 2.13	0.661

CI = confidence interval.

Male sex (reference: female) 1.24

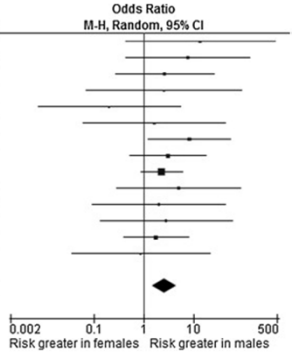
Isogai et al, Int J *Cardiol* 2014

Meta-Analysis of Clinical Correlates of Acute Mortality in Takotsubo Cardiomyopathy

Kuljit Singh, MD[a,*], Kristin Carson, Dip Lab Med[b], Ranjit Shah, MD[a], Gagandeep Sawhney, MD[c], Balwinder Singh, MD[d], Ajay Parsaik, MD[e], Harel Gilutz, MD[f], Zafar Usmani, MD[b], and John Horowitz, PhD[a]

Study or Subgroup	Males Events	Total	Females Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bonello 2007	1	1	2	13	2.6%	13.80 [0.42, 448.21]
Buja 2012	1	7	1	47	3.8%	7.67 [0.42, 139.26]
Eitel 2011	1	29	3	227	6.0%	2.67 [0.27, 26.52]
Elian 2006	0	1	1	12	2.4%	2.56 [0.07, 95.87]
Fang 2008	0	4	2	6	2.9%	0.20 [0.01, 5.45]
Jabara 2009	0	6	1	32	2.9%	1.62 [0.06, 44.24]
Joe 2012	4	10	2	27	8.7%	8.33 [1.23, 56.67]
Kurisu 2010	2	13	5	89	10.3%	3.05 [0.53, 17.69]
Kwon 2012	8	57	10	151	32.9%	2.30 [0.86, 6.16]
Lee 2009	2	4	1	6	3.8%	5.00 [0.27, 91.52]
Parodi 2011	0	10	2	106	3.3%	1.99 [0.09, 44.27]
Sharkey 2010	0	6	3	130	3.4%	2.80 [0.13, 60.14]
Song 2009	3	23	5	64	13.8%	1.77 [0.39, 8.08]
Vriz 2013	0	4	2	21	3.1%	0.87 [0.04, 21.36]
Total (95% CI)		**175**		**931**	**100.0%**	**2.62 [1.49, 4.60]**
Total events	22		40			

Heterogeneity: Tau² = 0.00; Chi² = 6.28, df = 13 (P = 0.94); I² = 0%
Test for overall effect: Z = 3.34 (P = 0.0008)



Singh et al, *Am J Cardiol* 2014

Gender Differences and Predictors of Mortality in Takotsubo Cardiomyopathy: Analysis from the National Inpatient Sample 2009–2010 Database

Parasuram Krishnamoorthy[a] Jalaj Garg[b] Abhishek Sharma[c]
Chandrasekar Palaniswamy[d] Neeraj Shah[b] Gregg Lanier[d] Nainesh C. Patel[b]
Carl J. Lavie[e,f] Hasan Ahmad[d]

Variable	Total (n = 7,510)	Males (n = 705; 9.4%)	Females (n = 6,805; 90.6%)	p value[a]
Age, years	65.6 (64.9–66.2)	59.5 (56.6–62.3)	66.2 (65.5–66.8)	**<0.001**
Length of stay, days	4.9 (4.5–5.2)	5.9 (4.5–7.2)	4.8 (4.4–5.1)	0.12
Cardiometabolic risk factors				
Diabetes	1,507 (20)	112 (15.9)	1,395 (20.5)	0.19
Hypertension	4,619 (61.5)	393 (55.8)	4,226 (62.1)	0.14
Hyperlipidemia	3,304 (44)	249 (35.3)	3,055 (44.9)	**0.03**
Obesity	638 (8.5)	44 (6.3)	594 (8.7)	0.32
Tobacco	1,247 (16.6)	162 (22.9)	1,085 (15.9)	**0.03**
Prior CAD	3,525 (46.9)	335 (47.4)	3,190 (46.8)	0.89
Other risk factors				
Anxiety	753 (10)	48 (6.8)	705 (10.3)	0.17
Alcohol	244 (3.3)	64 (9.1)	180 (2.6)	**<0.001**
Cocaine	37 (0.5)	5 (0.8)	32 (0.5)	**0.01**
Amphetamine	9 (0.1)	9 (1.3)	–	**<0.001**
Depression	1,100 (14.7)	42 (5.9)	1,058 (15.6)	**<0.01**
Migraine	179 (2.4)	11 (1.5)	168 (2.5)	0.48
Seizure	95 (1.3)	20 (2.8)	75 (1.1)	0.08
Malignancy	360 (4.7)	48 (6.8)	312 (4.5)	0.23
Acute critical illness				
Sepsis	347 (4.6)	63 (9)	284 (4.2)	**<0.01**
Acute CVA	161 (2.2)	30 (4.2)	131 (1.9)	0.07
Respiratory failure	987 (13.1)	129 (18.2)	858 (12.6)	0.06
Acute renal failure	626 (8.33)	78 (11.1)	548 (8.1)	0.21
Complications				
Mortality	180 (2.4)	34 (4.8)	146 (2.1)	**0.04**
Ventricular arrhythmia	425 (5.7)	54 (7.7)	371 (5.4)	0.27
Sudden cardiac death	173 (2.3)	39 (5.6)	134 (1.9)	**<0.01**

Krishnamoorthy et al, *Cardiology* 2015

Takotsubo cardiomyopathy, sepsis and clinical outcome: does gender matter?☆

Takotsubo cardiomyopathy and sepsis: in-hospital vs. out-of-hospital mortality

	Overall	Out-of-hospital	In-hospital	*P*
	3719	3300	419	
Male	833 (22.4%)	702 (21.3%)	131 (31.3%)	<.001
Female	2886 (77.6%)	2598 (78.7%)	288 (68.7%)	
Sepsis	105 (2.8%)	63 (1.9%)	42 (10.0%)	<.001
Multivariate analysis				
		Odds ratio	95% CI	*P*
In-hospital TC		2.02	1.43-2.85	<.001
Age (by 10-year increase)		1.33	1.15-1.53	<.001
Male sex (reference: female)		1.24	0.91-1.70	NS
Sepsis		2.02	1.17-3.49	.011

(Japan, Diagnosis Procedure Combination database 2010-2013) [19].

Takotsubo cardiomyopathy and sepsis: in-hospital mortality

			Mortality (OR, 95% CI)	*P*
All	24701 (100%)	Female 21994 (89.0%)		
		Male 2707 (11.0%)	2.44 (2.09-2.84)	<.05
Sepsis (all)		Female 1426 (6.5%)		
		Male 336 (12.4%)	2.04 (1.80-2.32)	<.001
Sepsis (fatal)	380 (21.6)	Female 296 (20.8%)	10.48 (8.97-12.25)	
		Male 84 (24.9)	5.12 (3.80-6.91)	<.001
Multivariate analysis				
Age				
>50 y			ref	
50-64 y			1.01 (0.77-1.32)	NS
>64 y			1.04 (0.82-1.35)	NS
Gender				
Female			ref	
Male			2.07 (1.71-2.49)	<.001
Underlying critical illness (including sepsis)				
NO			ref	
YES			10.87 (9.08-13.08)	<.001

(USA, National Inpatient Sample 2008 to 2009) [18].

Manfredini et al, *Am J Emerg Med* 2015