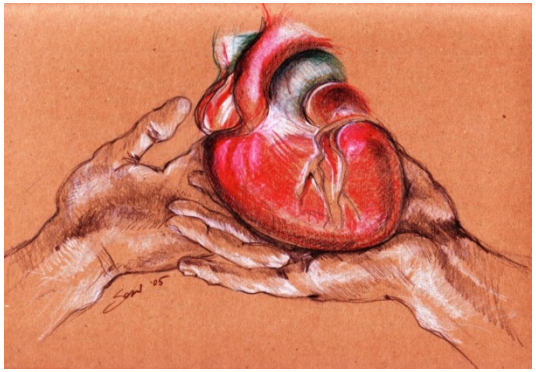
Stress cardiomyopathy: always benign?

Francesco Maria Bovenzi

Declaration of interest



I have nothing to declare!

Heartwire from Medscape

Twitter Seen as Fertile Ground for Cardiovascular Research

Patrice Wendling

October 07, 2016

550,338 tweets associated with CVD

EDITORS' RECOMMENDATIONS

Technology Rekindling the Doctor-Patient Relationship

Social Media Shaping How Drugs Are Made, Monitored

PHILADELPHIA, PA — A new study mining the Twittersphere for references to CVD reveals a distinct rhythm and pattern to the posts, even if the likes of Justin Bieber are driving some of the dialogue[1].

"There were these cyclical patterns where at times there was a lot of conversation about certain types of heart disease and at other times it seemed to be the usual chatter. But we realized if there was a big trial that came out or a big change in how we

#Takotsubo

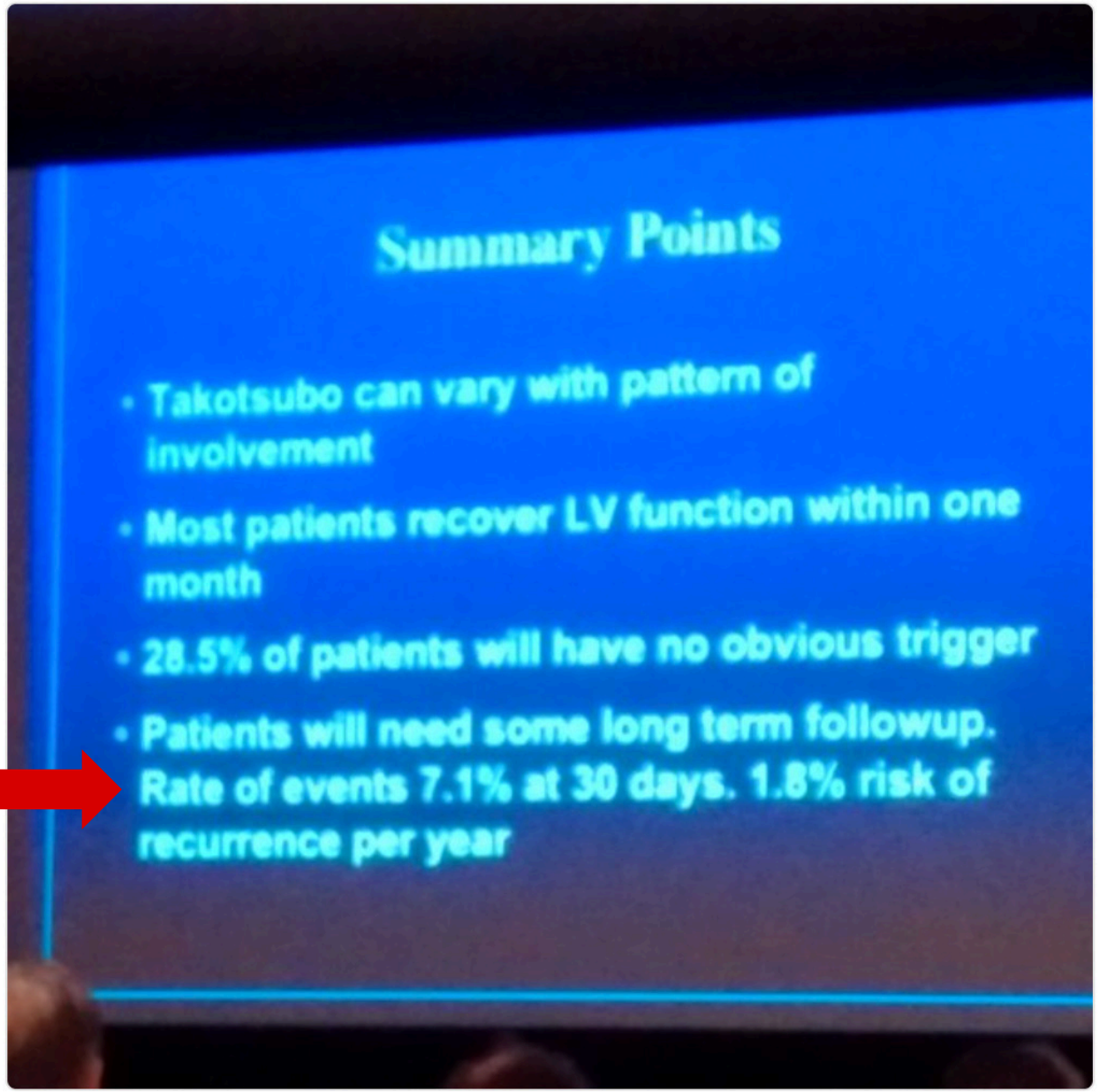
Cardio Debate @CardioDebate · 17 dic 2015

#Takotsubo cardiomyopathy: benign condition or malignant acute #heartfailure syndrome? buff.ly/1lSs0Fg

2 1

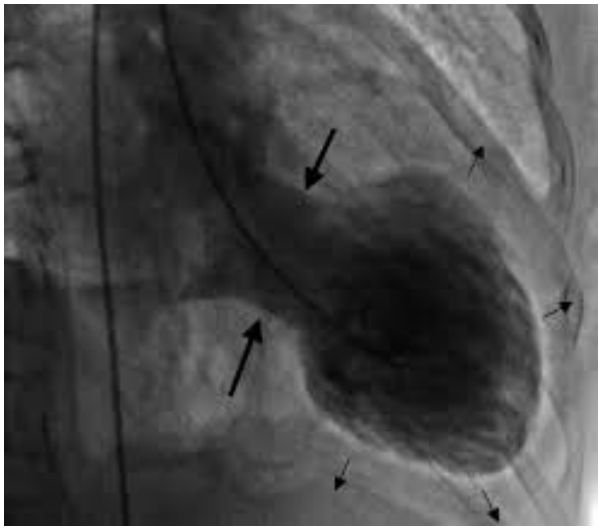
A. Shekhar Pandey @Dr_Pandey_Heart · 9 apr 2016

Great review of #takotsubo #stress induced #brokenheart syndrome #chf: not a benign condition #cse2016 @CSEchoCa



The first description

Was in *1990 by Sato* and colleagues from Hiroshima General Hospital

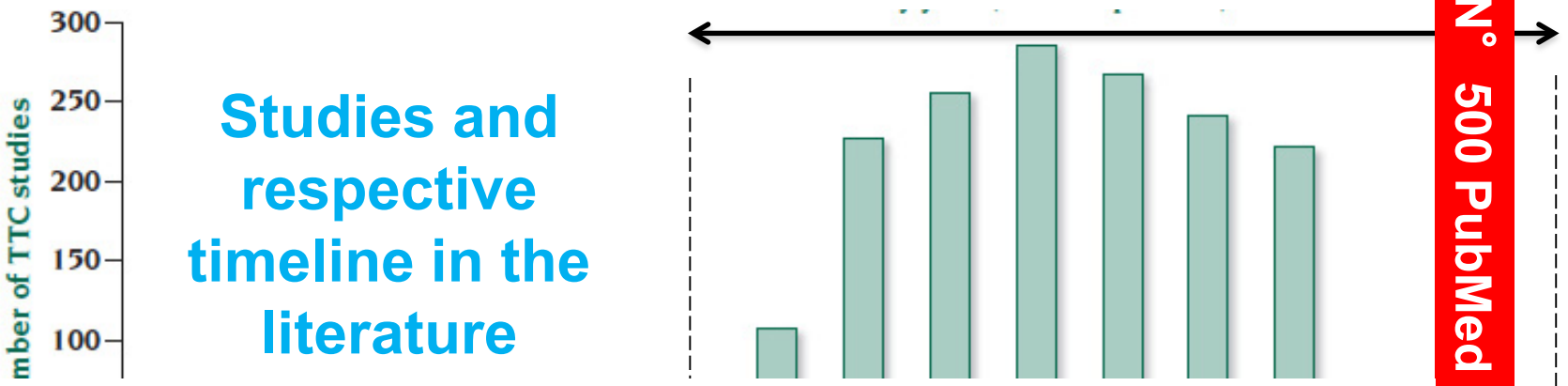


"Octopus trap" **… a reference to the ballooning shape of left ventriculography during an attack.**

Various names have been used to describe the acute appearance now classically described as a **'Takotsubo Cardiomyopathy'** or **'Takotsubo Syndrome'**

European Heart Journal (2016) 37, 2806–2815

The enormous interest in this disease is best **reflected** by the increasing numbers of **publications on TTS** during the last years..



European Journal of Heart Failure (2016) 18, 8–27
doi:10.1002/ejhf.424

REVIEW

Current state of knowledge on Takotsubo syndrome: a position statement from the task force on Takotsubo syndrome of the Heart Failure Association of the European Society of Cardiology

Alexander R. Lyon[1,2,*], Eduardo Bossone[3], Birke Schneider[4], Udo Sechtem[5], Rodolfo Citro[6], S.Richard Underwood[1,2], Mary N. Sheppard[7], Gemma A. Figtree[8,9], Guido Parodi[10], Yoshihiro J. Akashi[11], Frank Ruschitzka[12], Gerasimos Filippatos[13], Alexandre Mebazaa[14], and Elmir Omerovic[15]

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REVIEW

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Clinical subtypes: primary and secondary

1. Physical or Emotional Stressful Trigger or Spontaneous (Primary)
Medical/Surgical/Psychiatric Emergency* (Secondary)*

2. Diagnosis: Takotsubo Syndrome

Admit to CCU or HDU
Risk Stratification
(see Box 2)

Lower Risk Takotsubo Syndrome

Higher Risk Takotsubo Syndrome

* In pts already hospitalized for another medical, surgical, anaesthetic, obstetric, or psychiatric condition.

3. **Box 4 Heart Failure Association risk stratification in Takotsubo syndrome**

Risk factor	Higher risk	Lower risk
MAJOR RISK FACTORS		
Age	≥75 years	See minor risk factors[a]
Systolic BP	<110 mmHg	≥110 mmHg
Clinical pulmonary oedema[b]	Present	Absent
Unexplained syncope, VT or VF	Present	Absent
LVEF	<35%	See minor risk factors[a]
LVOTO	≥40 mmHg	Absent or <40 mmHg
Mitral regurgitation[c]	Present	Absent
Apical thrombus	Present	Absent
New VSD or contained LV wall rupture	Present	Absent
MINOR RISK FACTORS		
Age	70–75 years	<70 years
ECG		
QTc	≥500 ms	<500 ms
Pathological Q waves	Present	Absent
Persistent ST elevation[d]	Present	Absent
LVEF	35–45%	≥45%
Physical stressor	Present	Absent
Natriuretic peptides		
BNP	≥600 pg/mL	<600 pg/mL
NT-proBNP	≥2000 pg/mL	NT-proBNP <2000 pg/mL
Bystander obstructive CAD	Present	Absent
Biventricular involvement	Present	Absent

Lyon AR, EJHF 2016

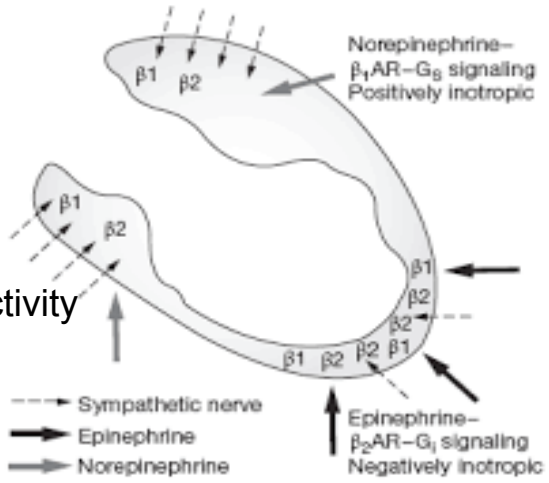
Takotsubo's Clinical Review

- **90% women (90% post-menopausal)**
- **Triggers (70%)**
- **Typical**: apical akinesia [ballooning] and hypercontractile base
- **Atypical**: midventricular akinesia, basal and focal

4 wall motion patterns

- ***90% an acute completely reversible HF syndrome*** *(4-53 days)*
- ***No relevant CAD***
- ***New ECG abnormalities, > modest cardiac troponin***
- ***No Pheochromocytoma, Hypertrophic CMP, Myc***
- **> BNP e NT-ProBNP** during the acute phase
- **Catecholamine theory**
- **Mimics symptoms of ACS**

  - Myocardium toxicity
  - Stunning
  - Decreased inotropic activity
  - Ballooning



Akashi Y, et al. Circulation, 2008
Lyon AR, EJHF 2016

European Heart Journal (2016) 37, 2816–2820
doi:10.1093/eurheartj/ehw057

EDITOR'S NOTE

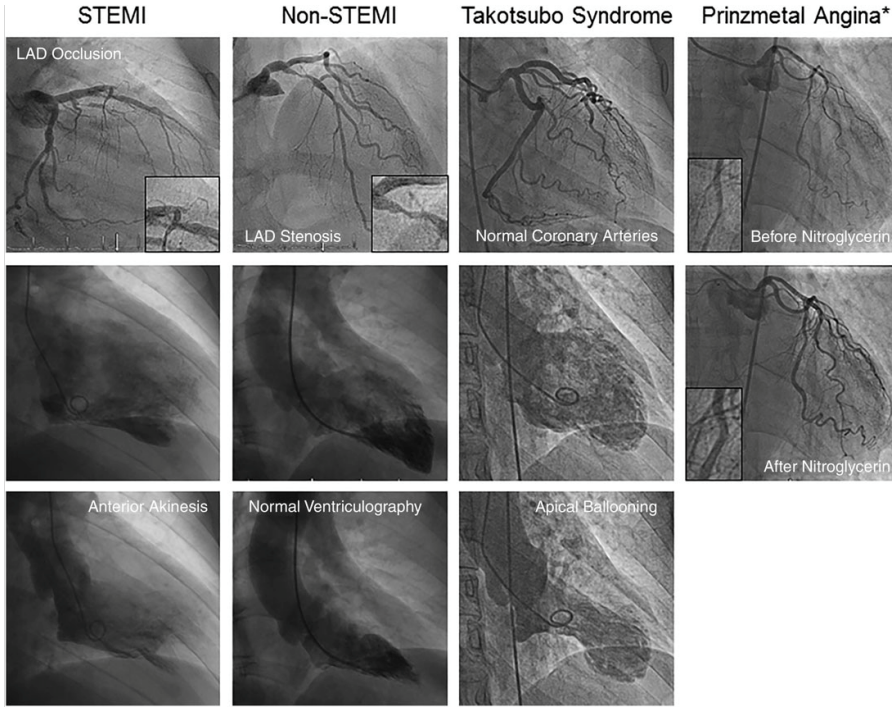
1. Is takotsubo syndrome a microvascular acute coronary syndrome? Towards of a new definition

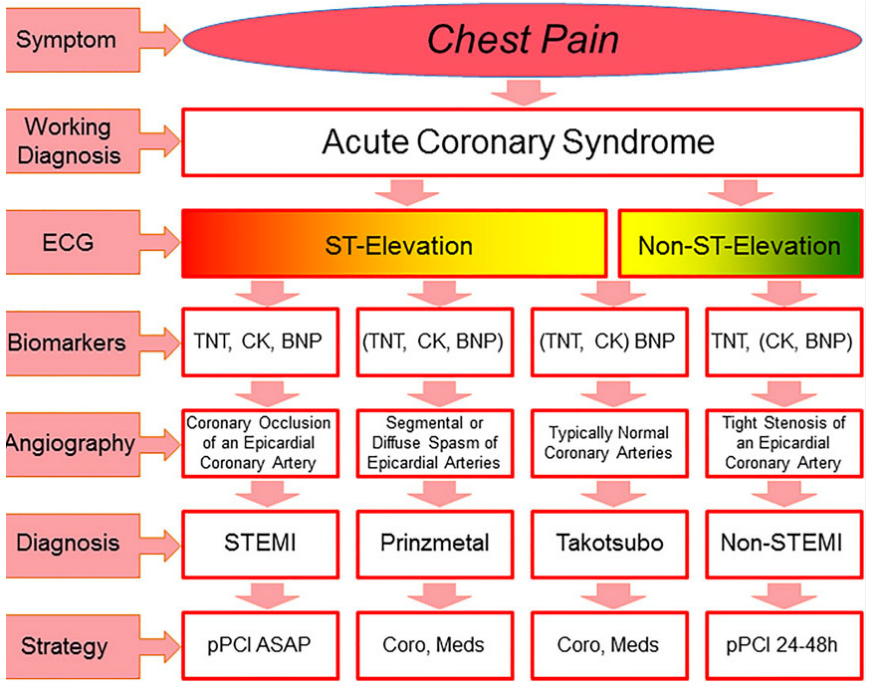
Thomas F. Lüscher* and Christian Templin

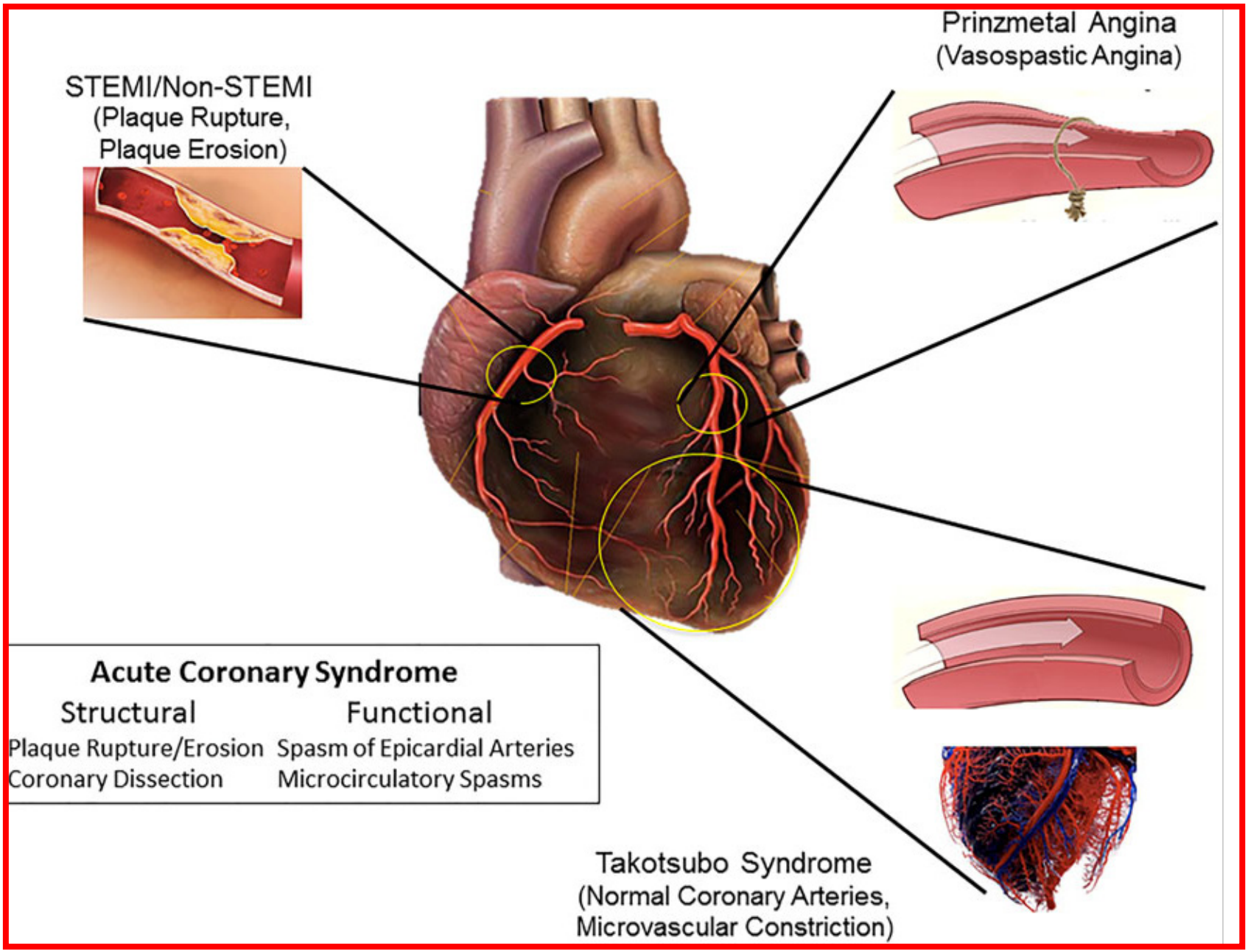
Editorial Office, European Heart Journal, Zurich Heart House, Careum Campus, University Heart Center, University Hospital Zurich and Center for Molecular Cardiology, Campus Schlieren, University Zurich, Zurich, Switzerland

Online publish-ahead-of-print 10 March 2016

2. Is TTS a novel form of an ACS?







Luscher TF., European Heart Journal (2016) 37, 2816–2820

Dialogues in Cardiovascular Medicine - Vol 19 · No. 2 · 2014

DIALOGUES

Takotsubo cardiomyopathy: is it a benign heart failure syndrome?

Birke Schneider, MD, FESC

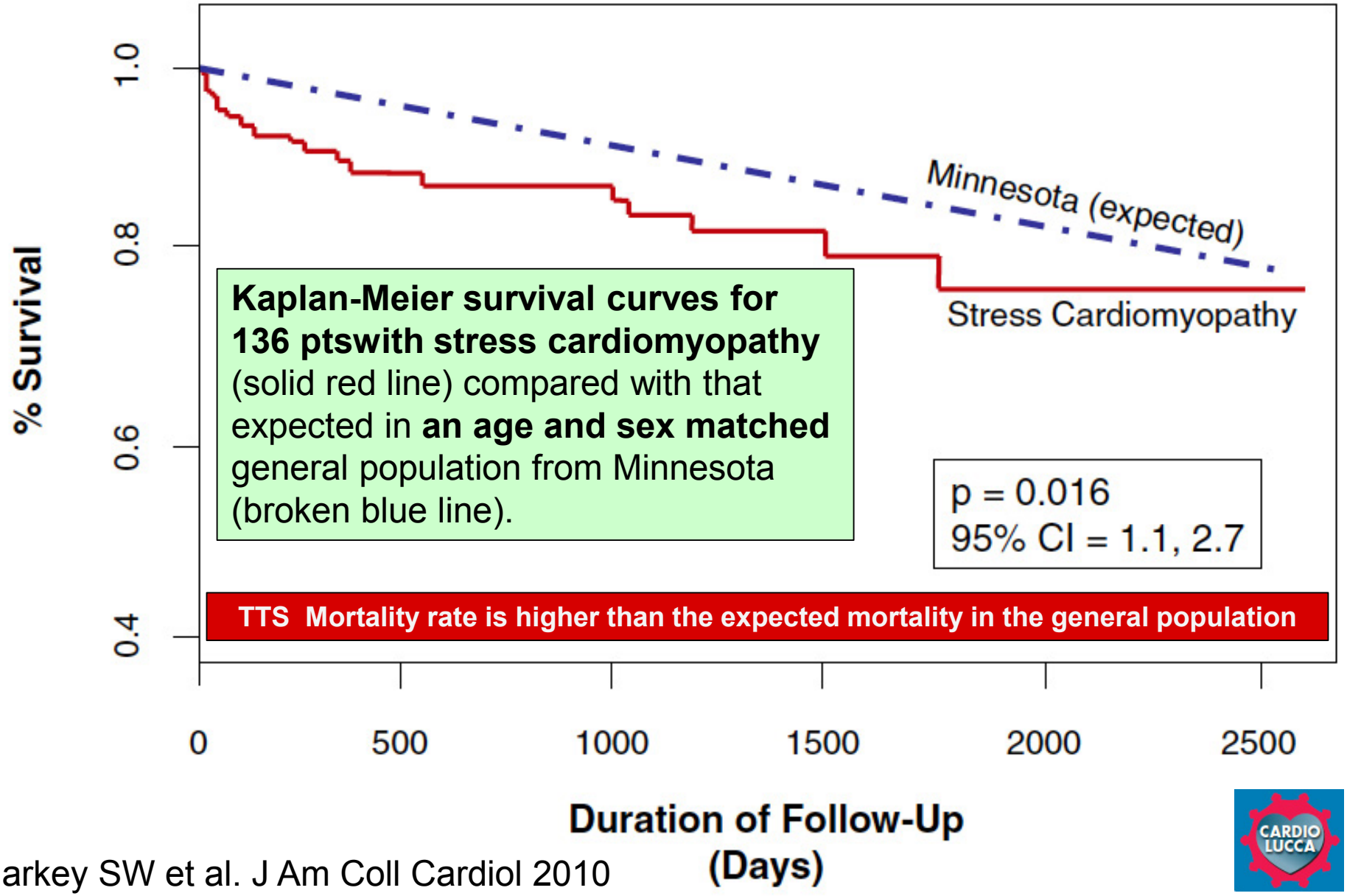
Department of Cardiology - Sana Kliniken - Lübeck - GERMANY

… has to be regarded as a clinical entity with a potentially complicated **clinical course similar to patients with ACS.**

… although has long been considered a benign disease with a good prognosis, **severe complications may occur.**

Schneider B, Dialogues in Cardiovascular Medicine, **2014**

Survival Curves for Stress Cardiomyopathy Patients Vs That Expected in the General Population



Sharkey SW et al. J Am Coll Cardiol 2010

The International Takotsubo Registry

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Clinical Features and Outcomes of Takotsubo (Stress) Cardiomyopathy

C. Templin, J.R. Ghadri, J. Diekmann, L.C. Napp, D.R. Bataiosu, M. Jaguszewski, V.L. Cammann, A. Sarcon, V. Geyer, C.A. Neumann, B. Seifert, J. Hellermann, M. Schwyzer, K. Eisenhardt, J. Jenewein, J. Franke, H.A. Katus, C. Burgdorf,

Background: The natural history, management, and outcome of takotsubo (stress) cardiomyopathy **are incompletely understood**.

Methods: … a consortium of 26 centers in Europe and the United States (1.750 pts), was established to investigate clinical features, prognostic predictors, and outcome of TTC cardiomyopathy. **Pts were compared with age and sex-matched pts who had an ACS.**

Conclusions: Our study demonstrates that takotsubo (stress) cardiomyopathy **represents an acute heart failure syndrome** that **is associated with a risk for adverse events (with substantial morbidity and mortality).**

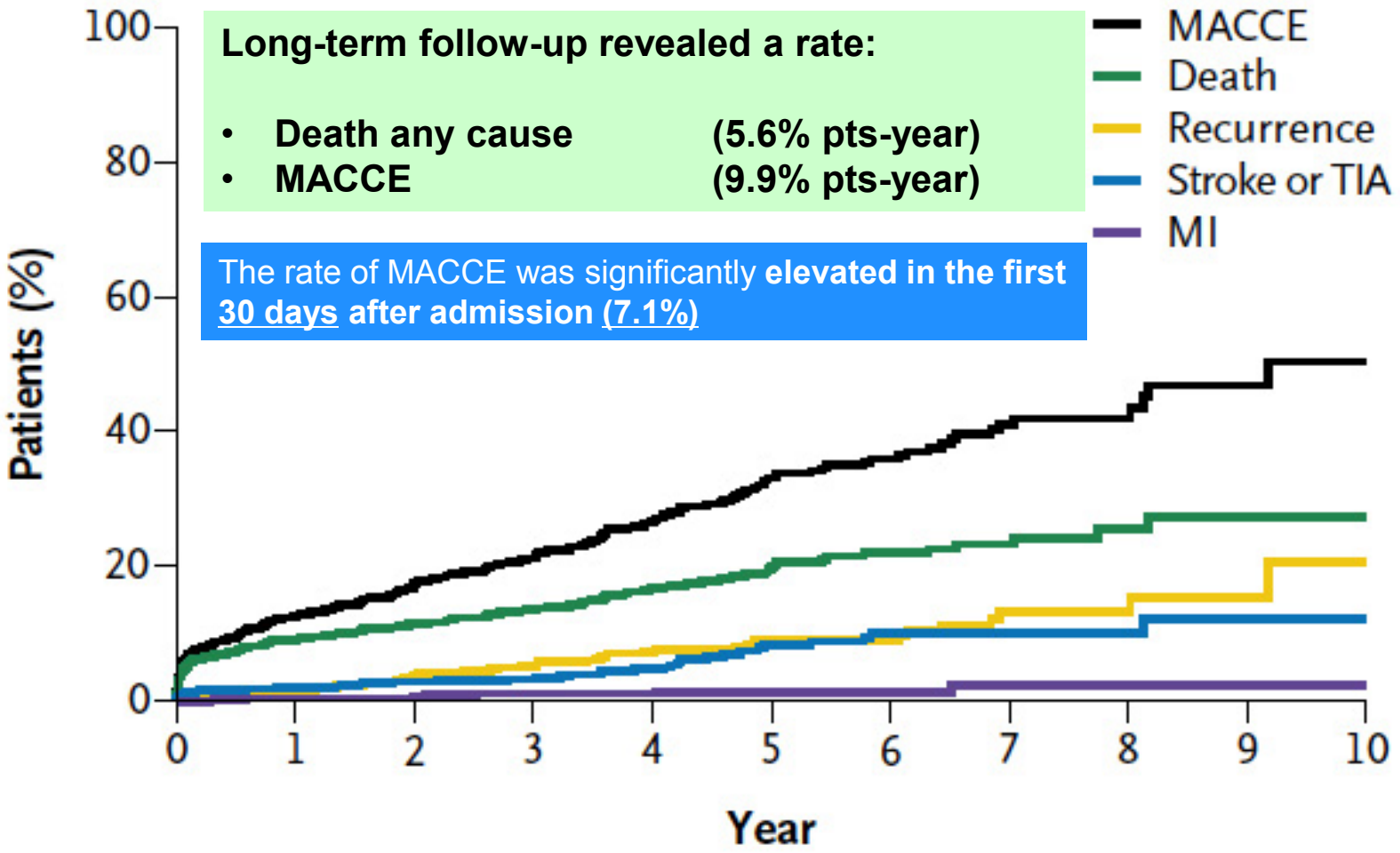
Templin C., et al. N Engl J Med 2015; 373:929-938

Kaplan–Meier Estimates of **10-Year** Outcome Events

Long-term follow-up revealed a rate:

- **Death any cause** **(5.6% pts-year)**
- **MACCE** **(9.9% pts-year)**

The rate of MACCE was significantly **elevated in the first 30 days after admission (7.1%)**



No. of Patients	1750	786	570	431	300	191	126	71	38	17	9

Templin C., et al. N Engl J Med 2015; 373:929-938

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

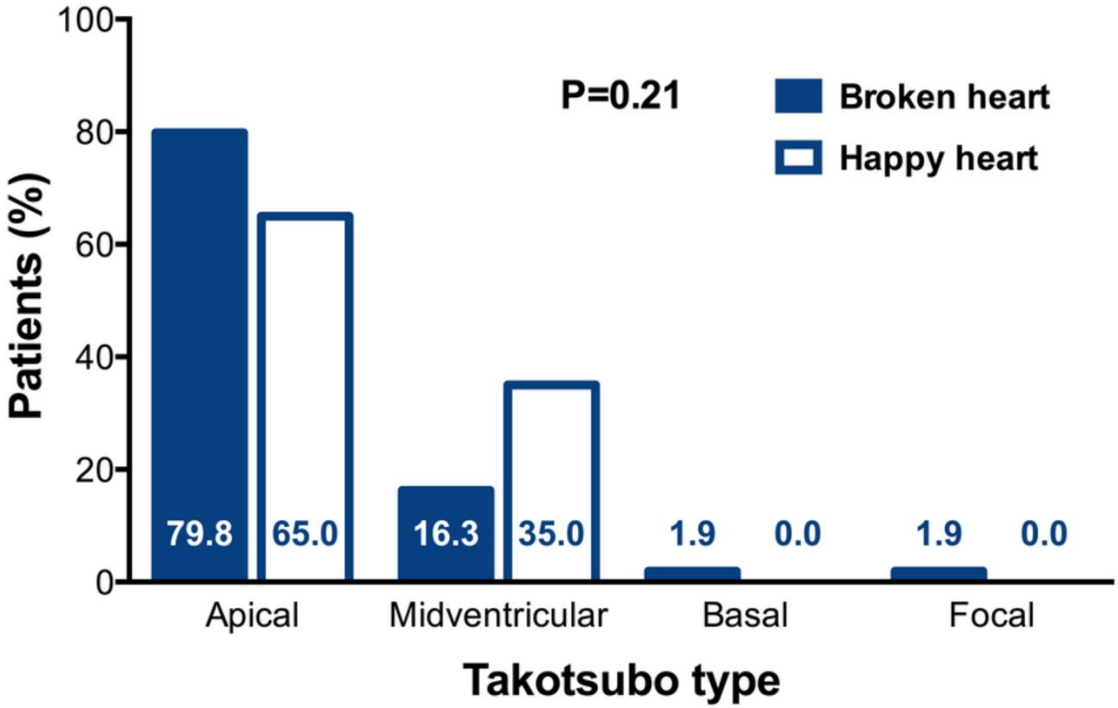
Jelena R. Ghadri[1], Annahita Sarcon[2], Johanna Diekmann[1], Dana Roxana Bataiosu[1], Victoria L. Cammann[1], Stjepan Jurisic[1], Lars Christian Napp[3], Milosz Jaguszewski[1], Frank Scherff[1], Peter Brugger[4], Lutz Jäncke[5], Burkhardt Seifert[6], Jeroen J. Bax[7], Frank Ruschitzka[1], Thomas F. Lüscher[1], and Christian Templin[1]*

TTS can be triggered by not only negative but also positive life events

InterTAKRegistry: Methods and Results

- Of 1750 TTS pts, we identified a total of **485 with a definite emotional trigger (27.7% pts)**
- Of these, **4.1% (n. 20) presented with pleasant preceding events** and 95.9% (n. 465) with unequivocal negative emotional events associated with TTS.
- **Clinical presentation** of pts with '**happy heart syndrome**' **was similar** to those with the '**broken heart syndrome**' including symptoms such as **chest pain [89.5% (17/19) vs. 90.2% (412/457), P = 1.0]**. Similarly, electrocardiographic parameters, laboratory findings, **and 1-year outcome did not differ.**

TTS pts with preceding **pleasant** events were **compared** to those with **negative** emotional triggers **from the International Takotsubo Registry**.



STUDIO OSSERVAZIONALE

Epidemiologia della sindrome di tako-tsubo nel mondo reale: dati del Registro Toscano della Miocardiopatia da stress tipo Tako-tsubo

Benedetta Bellandi[1], Claudia Salvadori[2], Guido Parodi[1], Alberto Genovesi Ebert[3], Nunzia Petix[4], Stefano Del Pace[1], Andrea Boni[5], Francesco Pestelli[6], Massimo Fineschi[7], Antonio Giomi[8], Alberto Cresti[9], Gabriele Giuliani[10], Francesco Venditti[1], Loreno Querceto[10], Gian Franco Gensini[1], Leonardo Bolognese[2], Francesco Bovenzi[5]

Sintomo d'esordio	
Dolore toracico	90 (86%)
Dispnea	8 (8%)
Sincope	10 (10%)
Altro	12 (11%)
Evento stressante	
Fisico	13 (12%)
Psicologico	65 (63%)
Alterazioni del tratto ST-T	
Sopraslivellamento	62 (59%)
Sottoslivellamento	13 (12%)
Inversione onda T	58 (56%)
Lunghezza del QT corretto (ms)	440 ± 75

FE all'ingresso (%)	40 ± 9
FE alla dimissione (%)	51 ± 9

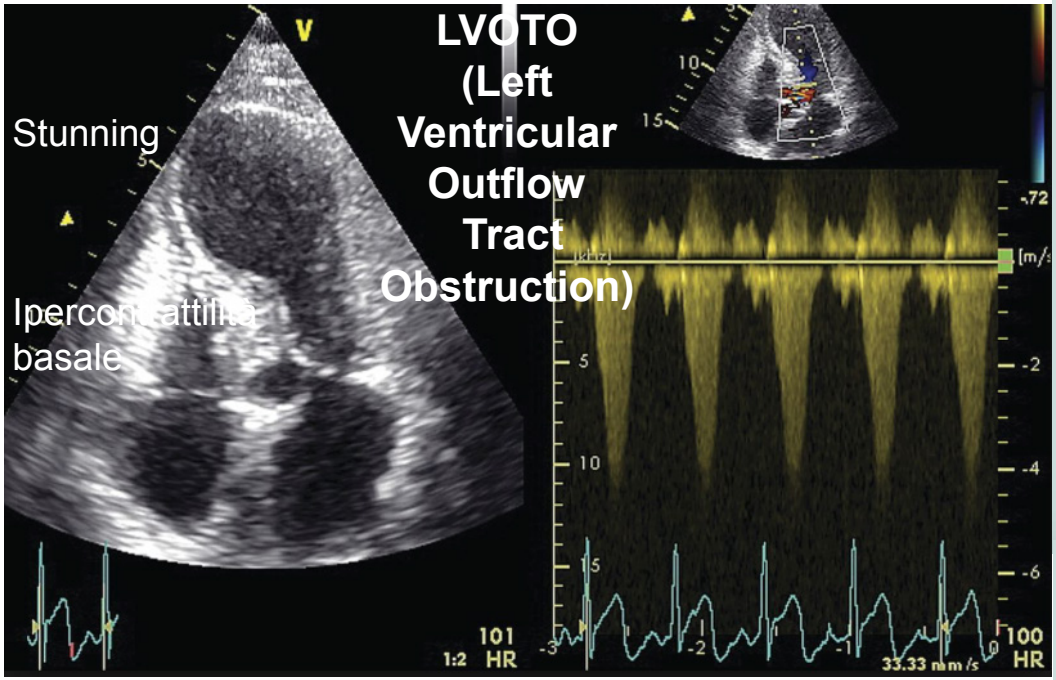
Classe Killip all'ingresso	
I	84 (80%)
II	9 (9%)
III	2 (2%)
IV	4 (4%)

6%

… **rischio** di **complicanze** legate all'**insufficienza cardiaca nella fase acuta** **non tascurabile.**

G Ital Cardiol 2012;13(1):59-66

A variety of serious complications may occur during the **acute clinical course in up to 52% of the patients**



Schneider B,
Dialogues in Cardiovascular Medicine, **2014**

Heart Failure
- Pulmonary edema
- Pleural effusion

Cardiogenic shock

Mitral regurgitation

Intraventricular pressure gradient

Left ventricular thrombus formation
- Stroke
- Peripheral embolism

Right ventricular involvement

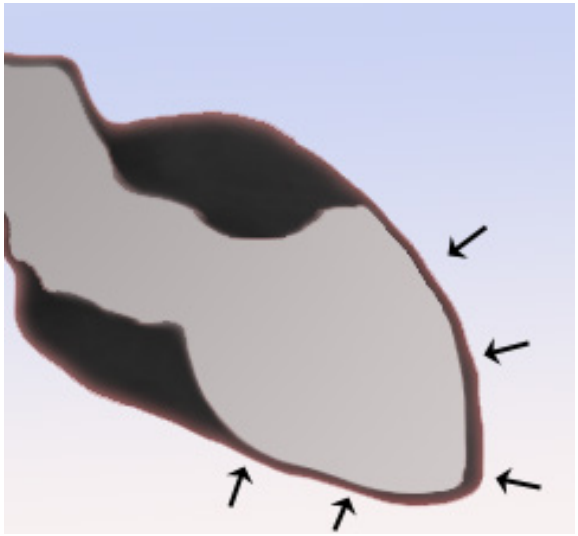
Pericardial tamponade

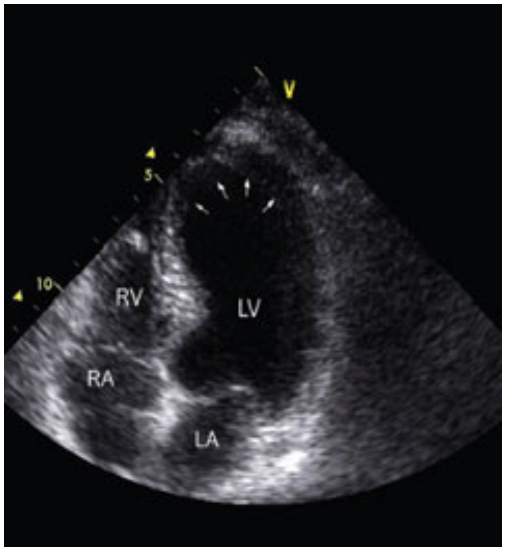
Myocardial rupture
- Free wall rupture
- Perforation of the interventricular septum

Death

Arrhythmias
- Ventricular tachycardia/fibrillation
- Atrial fibrillation
- Atrioventricular block
- Resuscitation

Acute heart failure





- **Systolic heart failure is the most common complication in the acute phase, occurring in 12% to 45%.**
- **Independent predictors: > age, low EF on presentation, > troponin levels and a physical stressor.**
- **Mechanical ventilation, inotropic support,** and **IABP** had been required in a substantial number of cases, respectively **28%, 38%,** and **17%.**

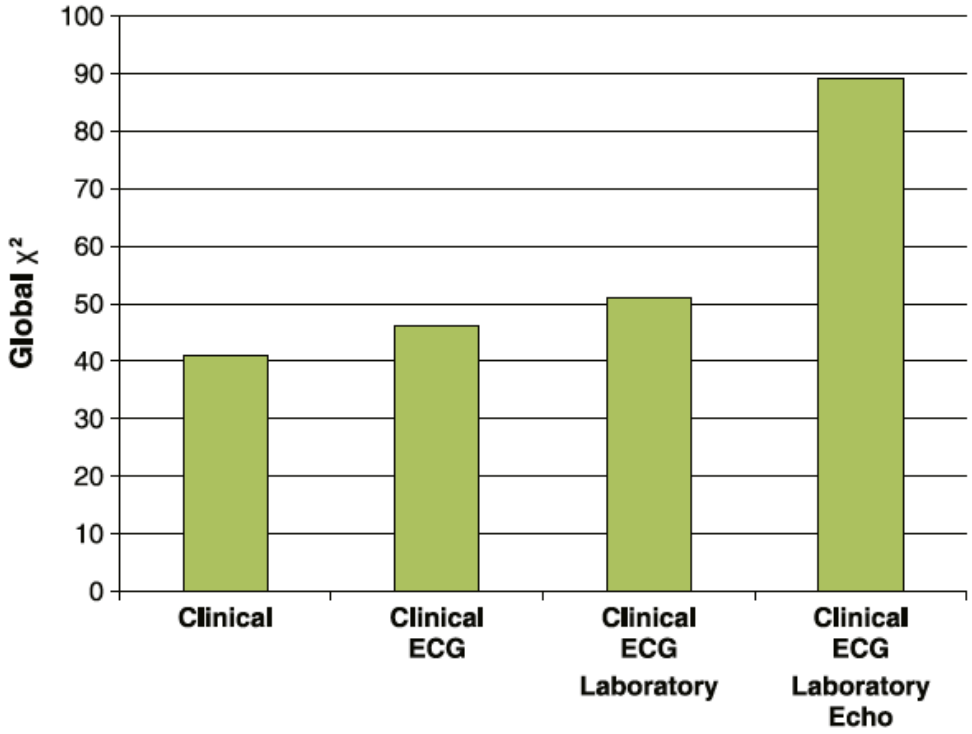
Schneider B, Dialogues in Cardiovascular Medicine, 2014
Madhavan M, JACC, 20111

Cardiogenic shock

- The prevalence ranging **from 6% to 20%**
- **Primarily due to acute LV dysfunction, may be aggravated by:**
    1. ***Right ventricular involvement***
    2. ***LVOTO***
    3. ***Acute mitral regurgitation***
- The **mortality is high (between 17% and 30%), but appears to be lower than the reported 40% to 62% mortality in reperfused STEMI**, due to the early spontaneous reversibility of LV dysfunction in TTC
- **Repeat echocardiography plays an important role** in determining the exact mechanism of cardiogenic shock in each patient in order to apply an appropriate therapy

Schneider B, Dialogues in Cardiovascular Medicine, 2014

Incremental Prognostic Value of Echocardiography



Conclusions: Echocardiographic parameters **provide additional information** compared to other variables routinely used in clinical practice **to identify patients at higher risk of hemodynamic deterioration and poor in-hospital outcome (1. acute mitral regurgitation, 2. LVOTO),** allowing prompt institution of appropriate pharmacological treatment and adequate mechanical support.

Citro R et al J Am Coll Cardiol Img 2014

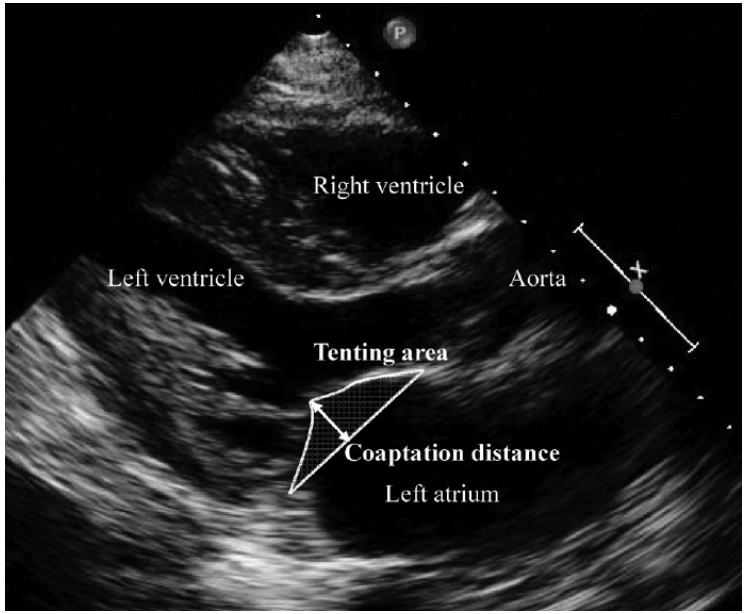
Acute mitral regurgitation

- Is another potentially serious complication occurring **in 14% to 25%**

- Two independent mechanisms:

  1. **Systolic anterior motion of the mitral valve with dynamic LVOTO**
  2. **Apical tethering of the apparatus**

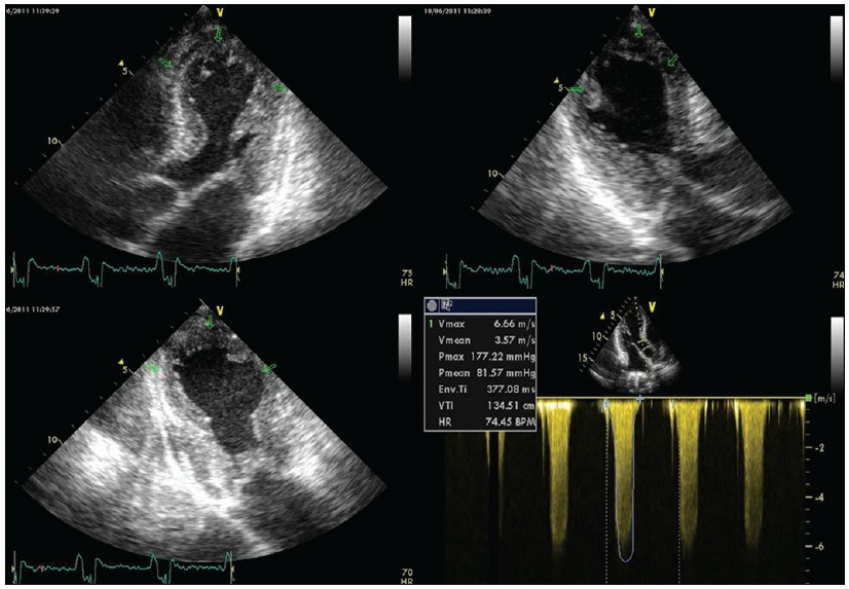
Early improvement of acute mitral regurgitation can be observed in conjunction with normalization EF



Izumo M et al, Circ Cardiovasc Imaging, 2011

Left ventricular outflow tract obstruction

- Dynamic intraventricular pressure gradient, **due to stunning apical segments and hypercontraction basal**.



- LVOTO with gradients ranging from 20 to 140 mm Hg **in 10% to 25%**, **often accompanied by mitral regurgitation**.
- **Hypotension and cardiogenic shock are more frequent.**
- Use of inotropic drugs or nitrates may aggravate LVOTO whereas **b -blocker treatment < the gradient.**
- Normally, the outflow tract obstruction **resolves spontaneously over a few days.**

Schneider B, Dialogues in Cardiovascular Medicine, 2014

Other severe complications

- **Pericardial effusion** (pericardial tampanade requiring pericardiocentesis is rare)
- **Ventricular wall rupture** (observed in **less than 1%** of cases)
- **Thrombus formation**

Rischio aritmico nella cardiomiopatia tako-tsubo: è davvero così innocua la malattia del cuore infranto?

Francesco Rotondi, Fiore Candelmo, Ferdinando Alfano

U.O. di Cardiologia-UTIC, Dipartimento Medico Chirurgico del Cuore e dei Vasi, Azienda Ospedaliera di Rilievo Nazionale ed Alta Specialità "San Giuseppe Moscati", Avellino

RIASSUNTO

È noto che la cardiomiopatia tako-tsubo presenta a medio e lungo termine una buona prognosi. Ciononostante, è sempre più spesso segnalato il rischio aritmico legato a questa condizione clinica. Alla luce della letteratura corrente, sono qui riportati i criteri per una stratificazione prognostica accanto ad alcuni suggerimenti pratici per la gestione di questi pazienti "vulnerabili".

1. **La questione** relativa all'incidenza di aritmie cardiache **è stata ignorata** nei primi studi, dove il termine "*arrhythmias*" veniva raramente preso in considerazione.
2. **I dati risultavano sottostimati e le aritmie ventricolari letali non venivano riconosciute come prima manifestazione clinica**.

EUROPEAN SOCIETY OF CARDIOLOGY®

Europace (2011) **13**, 780–788
doi:10.1093/europace/euq435

REVIEW

Arrhythmia occurrence with takotsubo cardiomyopathy: a literature review

Faisal F. Syed[1], Samuel J. Asirvatham[2,3]*, and Johnson Francis[4]

[1]Department of Internal Medicine, Mayo Clinic College of Medicine, Rochester, MN, USA; [2]Department of Medicine, Division of Cardiovascular Diseases, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, USA; [3]Department of Pediatrics and Adolescent Medicine, Mayo Clinic College of Medicine, Rochester, MN, USA; and [4]Malabar Institute of Medical Sciences, Calicut, Kerala, India

Received 28 August 2010; accepted after revision 3 November 2010; online publish-ahead-of-print 3 December 2010

Aims Takotsubo cardiomyopathy (TC) or the apical ballooning syndrome is a reversible cardiomyopathy mimicking acute myocardial infarction (AMI). Although malignant arrhythmia is considered less likely to occur in TC than with AMI, sporadic reports of malignant arrhythmia with TC, however, have been reported. We reviewed the medical literature on TC and arrhythmias and describe in the summary the reported findings and discuss possible specific scenarios where arrhythmia may be more likely in patients with TC.

Methods and results Articles were identified o PubMed sing the MeSH terms 'Takotsubo Cardiomyopathy' or 'Apical Ballooning Syndrome'. Seventy-four unique case series with five or more TC patients were identified, with a cumulative total of 1876 cases. Twelve series (242 cases) were excluded because Mayo criteria were not met. Twenty-five series (816 cases, 43.5%) reported on arrhythmia and were included in the analysis.

FA 4.7%, BAV 2.9%, FV 2.2%, TVS 1.2%, TVNS 1%

rhythmia, although there is little evidence to support their use beyond convalescence when used for this indication alone. Those in heart failure and cardiogenic shock should be managed with established evidence-based therapies fo these conditions. The use of internal defibrillators in TC requires consideration only on a case-by-case basis.

Keywords Arrhythmia • Tachycardia • Bradycardia • Takotsubo cardiomyopathy • Apical ballooning syndrome

CARDIO LUCCA

Takotsubo cardiomyopathy: a novel "proarrhythmic" disease

Michael A. Nault, Adrian Baranchuk, Christopher S. Simpson, Damian P. Redfearn

Queen's University , Kingston General Hospital, Division of Cardiology, FAPC 3, Kingston, Ontario, Canada

Introduction

Transient left ventricular apical dyskinesis accompanied by ischemic-like electrocardiographic abnormalities in the absence of obstructive epicardial coronary artery disease is characteristic of Takotsubo cardiomyopathy (TC) (1). Clinical manifestations and morbidity are related to the degree of left ventricular dysfunction with symptom resolution paralleling the course of improvement in systolic function of the left ventricle (LV). Treatment, if required, consists of supportive therapy while the dysfunctional LV recovers (2). Whether TC may represent a possible anatomical substrate for severe arrhythmia or conduction disturbance remains unknown. We present two cases of TC associated with life-threatening arrhythmias and speculate that such arrhythmias may identify a subpopulation of TC patients at

lasting ≥7.8 seconds (Fig. 1B). The patient was stabilized and urgently transferred to our centre for further management. Subsequent investigations identified mild hypokalemia of 3.3 mmol/L secondary to intravenous bicarbonate. Potassium levels normalized within 18 h following discontinuation of forced alkaline diuresis. By 48 hours T wave abnormalities and prolongation of the QTc interval have resolved (Fig. 1A). Cardiac catheterization revealed marked akinesis of the mid and apical left ventricle with hyperkinesis of the basal segments (Figs. 2A, 2B) with normal epicardial coronary vessels (Fig. 2C). Echocardiography confirmed dilation and akinesis of the mid and apical LV with preservation of basal function. Follow-up echocardiography at one month was normal.

Case 2

Nault MA, et al. Anatol J Cardiol 2007

The etiology, optimal managment and outcome of this acute cardiac syndrome are still unknown.

Prognostic impact of QT intervals in takotsubo cardiomyopathy: still a long way to trap the octopus

- The **intracellular myocyte calcium overload** may be **responsible for myocyte dysfunction and for QT prolongation and cardiac arrhythmias**
- An **increased concentration of catecholamines** has an important pathogenetic role in TTS, the use of **beta-blockers would theoretically reasonable, despite the absence of large randomized trials**
- **Prolongation of the QT interval is very frequent** and the **combination with another condition associated with the QT prolongation** (drugs, hypokalemia, hypomagnesemia, hypocalcemia) could adversely affect clinical outcome
- **The prevention** and treatment of life-threatening arrhythmias should be based on **elimination of all the causes that increase the risk of long QT**

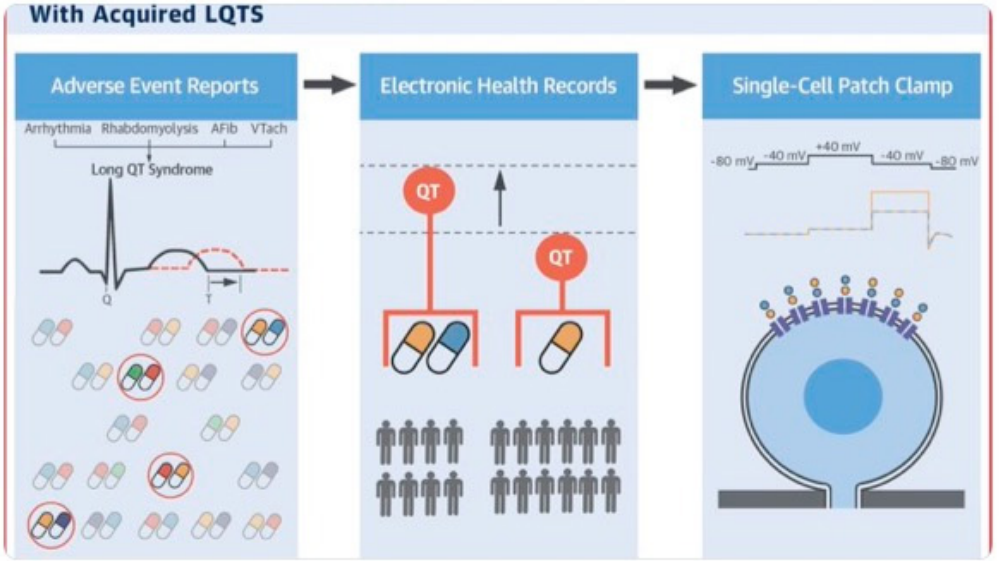
Editorial Comment: Rotondi F, et al Anatol J Cardiol 2007

13. X. 2016

Twitta le tue idee

JACC Journals @JACCJournals · 33m

Data mining & laboratory experiments reveal combination of ceftriaxone & lansoprazole prolongs QT interval #JACC ow.ly/KpAO3057nvP



2

Blocco di branca sinistra di nuova insorgenza come prima manifestazione elettrocardiografica della cardiomiopatia takotsubo

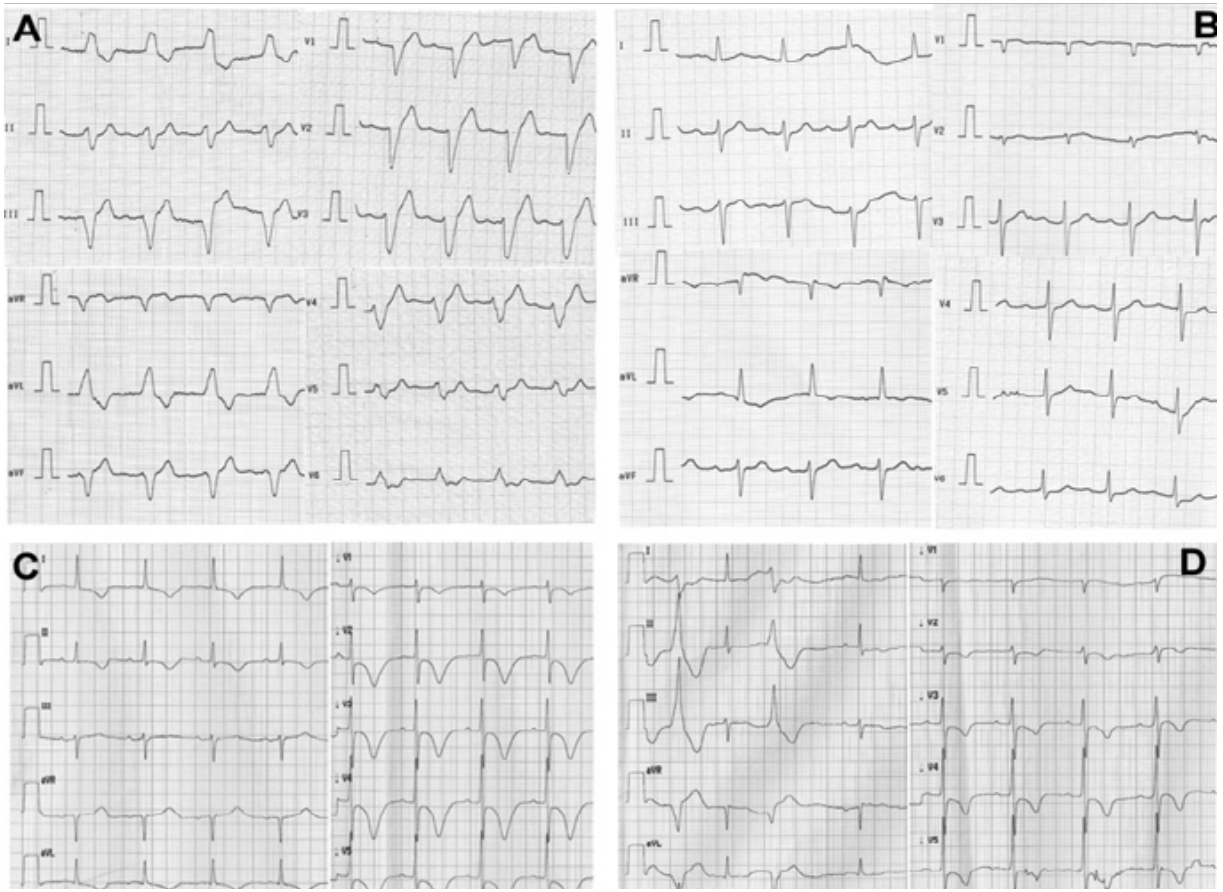
Andrea Di Cori, Cristina Gemignani, Mauro La a Boni, Lauro Cortigiani, Francesco Bovenzi

U.O. di Cardiologia, Ospedale Campo di Marte, Lucca

Takotsubo cardiomyopathy is a recently described syndrome characterized by reversible left ventricular dysfunction, chest pain, ST-segment elevation, and minor elevation in serum levels of cardiac enzymes, in the absence of significant coronary artery disease. ST-segment elevation is the most common electrocardiographic finding on the admission ECG of patients, followed by evolutionary T-wave inversions. We report a case of takotsubo cardiomyopathy characterized by the unusual feature of a new onset transient left bundle branch block as first electrocardiographic manifestation. New left bundle branch block increases heterogeneity in the broad spectrum of electrocardiographic findings of takotsubo syndrome, contributing to ambiguity in ly recognition and affecting potential management strategies.

(G Ital Cardiol 2010; 11 (5): 442-445)

Evoluzione delle anomalie dell'ECG a 12 derivazioni durante l'ospedalizzazione



A: Blocco di branca sinistra di nuova insorgenza al ricovero
B: Precoce normalizzazione dell'ECG nel Cath-Lab
C: Inversione onda T con prolungamento QTc in 2° giornata
D: Inversione onda T e normalizzazione del QTc dimissione

Di Cori A., Bovenzi F., et al. G Ital Cardiol 2010

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EDITORIAL

Takotsubo cardiomyopathy and the long-QT syndrome: an insult to repolarization reserve

Elijah R. Behr[1]* and Saagar Mahida[2]

[1]Cardiac and Vascular Division, St George's University of London, London SW17 0RE, UK; and [2]Leeds General Infirmary, Leeds, UK

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This editorial refers to 'A fatal combination in an old lady: Tako-Tsubo cardiomyopathy, long QT syndrome, and cardiac hypertrophy' by H. Wedekind *et al.*, on page 820

Despite these consistent findings, ventricular arrhythmias in patients with TCM are relatively uncommon. In a review of seven case series containing a total of 180 cases, Bybee *et al.*[1] reported a 1–1.5% incidence of ventricular arrhythmias. In a more recent series of 14 patients, Bonello *et al.*[8] reported two

A cut-off of acute phase QTc > 500ms is a potential risk predictor for the development of TdP
(sensitivity 82%) (specificity 85%)

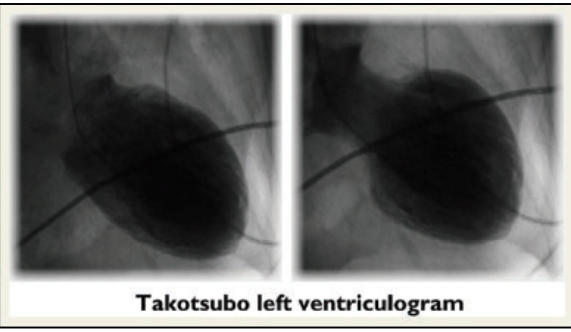
looning and hypokinesia with the preservation of basal contraction. Electrocardiogram changes include ST-segment elevation, the evolution of marked anterior T-wave inversion, and prolongation of the QT interval. These features all appear to resolve with time.[1]

Torsades de pointes and QTc prolongation as a predictor of risk

Take Home Message (*from Sato*)

Sato: Tako-tsubo-like left ventricular dysfunction due to multivessel coronary spasm. In: Kodama K, Haze K, Hori M, eds. Clinical Aspect of Myocardial Injury: From Ischemia to Heart Failure. Tokyo: Kagakuhyoronsha Publishing Co.; **1990 -1991.**


Japanese octopus pot


Takotsubo left ventriculogram

MYOCARDIAL DISEASE — **Ghadri JR, et al. Heart, 2014**

Takotsubo cardiomyopathy: still much more to learn

Demolendo alcuni **dogmi di benignità,** tipici di una Medicina di Genere rimasta per anni disattesa, oggi sappiamo che **in più del 50% delle TTS il decorso clinico presenta una serie di complicanze** per le quali è opportuno identificare precocemente i casi a più alto rischio:

- **età > 75 anni**
- **> BNP e NT-proBNP**
- **QTc > 500 msec**
- **IM**
- **LVOTO**
- **Persistente della disfunzione VS**