Giornate Mediche di Santa Maria Nuova

X EDIZIONE

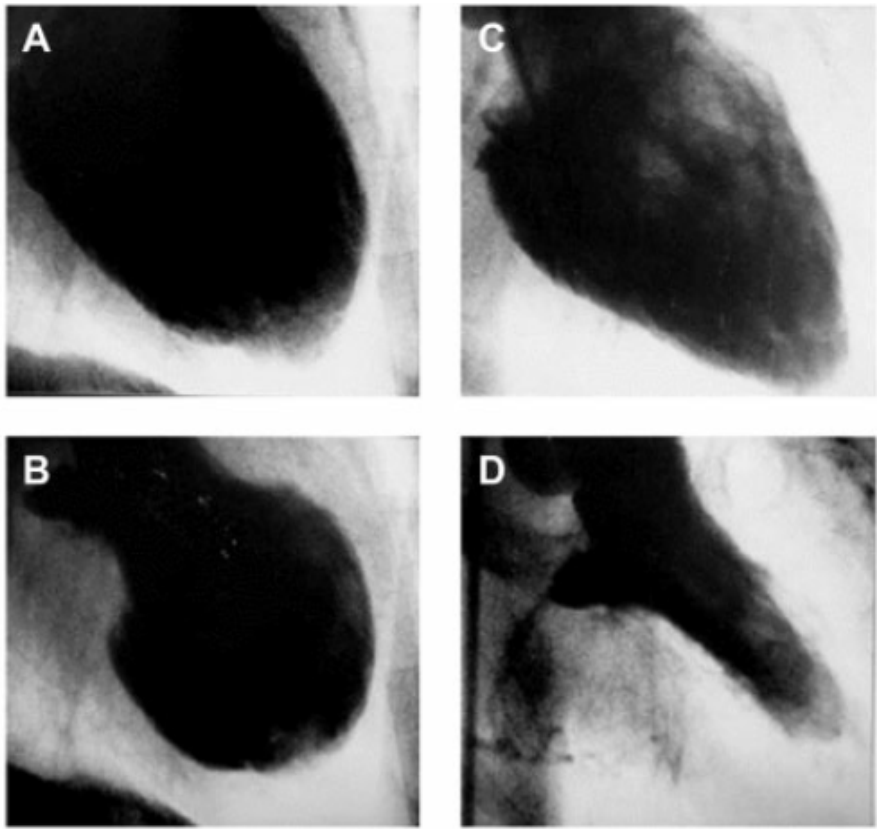
18-19 Ottobre 2018

Quando il cuore mima un infarto: la Sindrome Takotsubo

Dott. A. Paoletti Perini, PhD
Cardiologia ed Elettrofisiologia, Ospedale Santa Maria Nuova, Firenze

Introduzione

La Sindrome Takotsubo è caratterizzata da disfunzione acuta e transitoria del ventricolo sinistro



Hiroshima City Hospital, 1983

Introduzione

The most common symptoms of Takotsubo Syndrome (TTS) are chest pain, dyspnoea or syncope and **thus indistinguishable from AMI at first glance.**

The diagnosis of TTS is often challenging because its clinical phenotype **may closely resemble AMI regarding ECG abnormalities and biomarkers.**

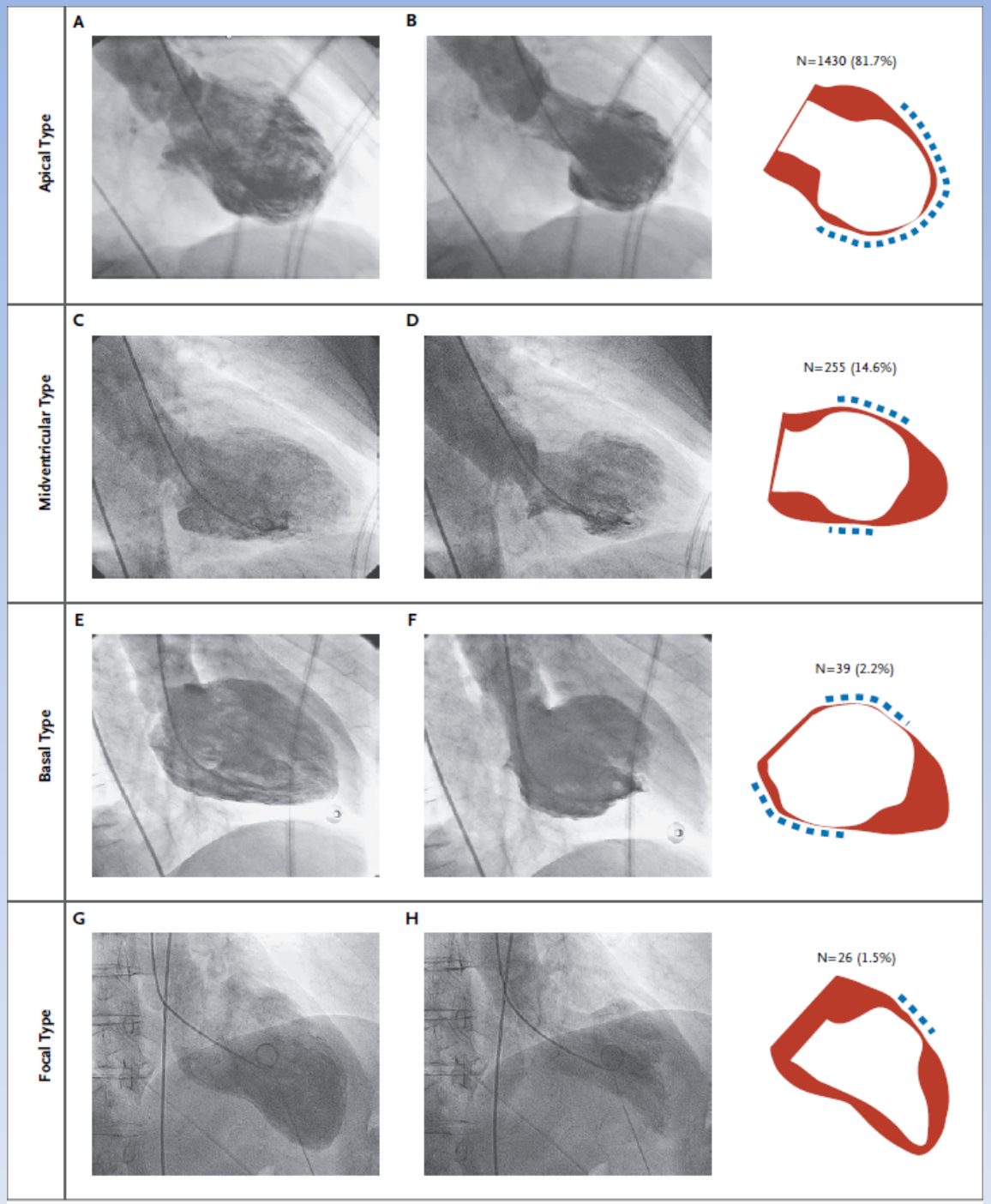
Eur Heart Journal 2018

Definizione (Inter TAK diagnostic criteria 2018)

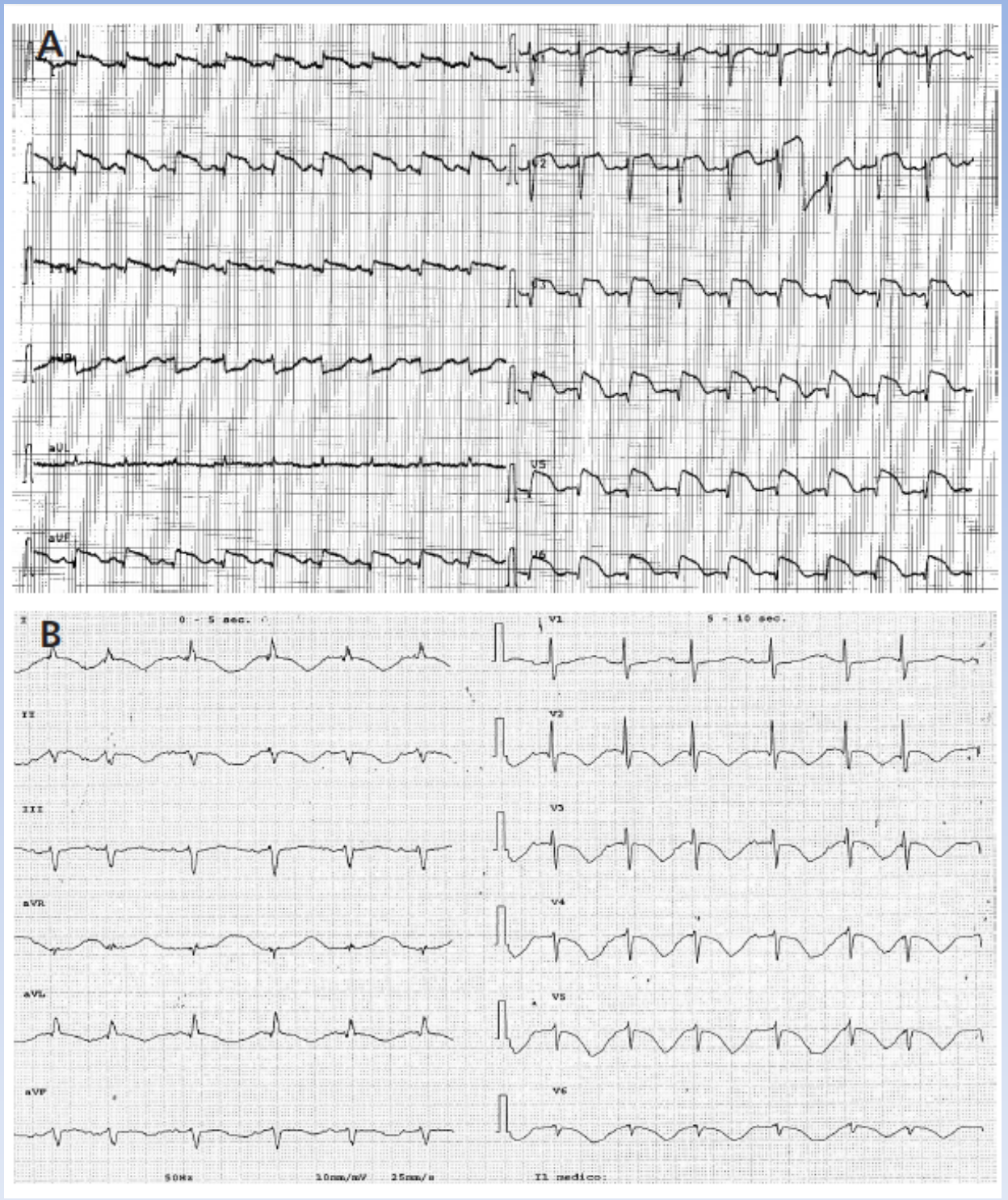
1. Patients show transient[a] left ventricular dysfunction (hypokinesia, akinesia, or dyskinesia) presenting as apical ballooning or midventricular, basal, or focal wall motion abnormalities. Right ventricular involvement can be present. Besides these regional wall motion patterns, transitions between all types can exist. The regional wall motion abnormality usually extends beyond a single epicardial vascular distribution; however, rare cases can exist where the regional wall motion abnormality is present in the subtended myocardial territory of a single coronary artery (focal TTS).[b]
2. An emotional, physical, or combined trigger can precede the takotsubo syndrome event, but this is not obligatory.
3. Neurologic disorders (e.g. subarachnoid haemorrhage, stroke/transient ischaemic attack, or seizures) as well as pheochromocytoma may serve as triggers for takotsubo syndrome.
4. New ECG abnormalities are present (ST-segment elevation, ST-segment depression, T-wave inversion, and QTc prolongation); however, rare cases exist without any ECG changes.
5. Levels of cardiac biomarkers (troponin and creatine kinase) are moderately elevated in most cases; significant elevation of brain natriuretic peptide is common.
6. Significant coronary artery disease is not a contradiction in takotsubo syndrome.
7. Patients have no evidence of infectious myocarditis.[b]
8. Postmenopausal women are predominantly affected.

International Expert Consensus Document on Takotsubo Syndrome

EHJ 2018



Templin C. et al. NEJM 2015


A
B
0 - 5 sec.
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I
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III
aVR
aVL
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V2
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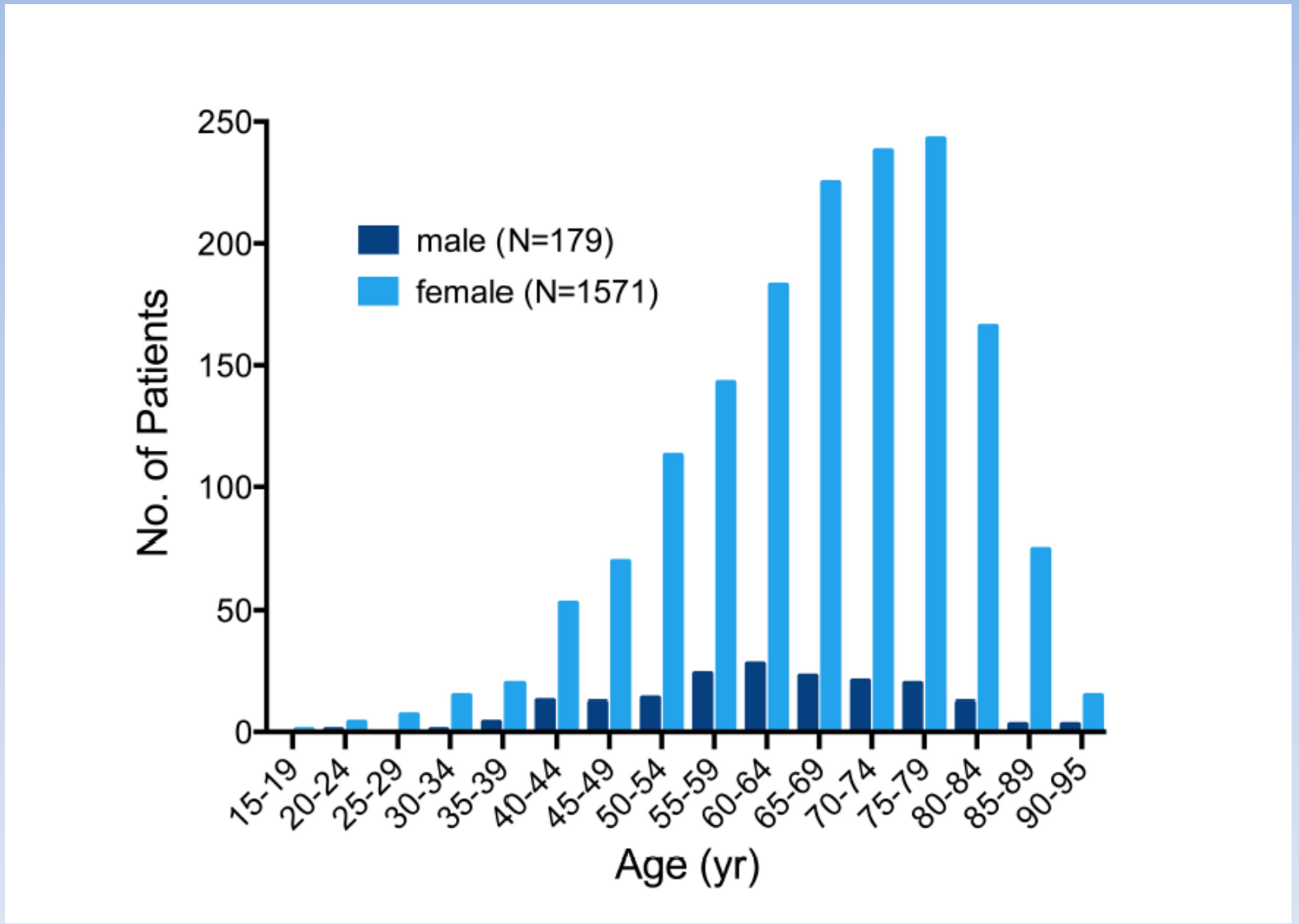
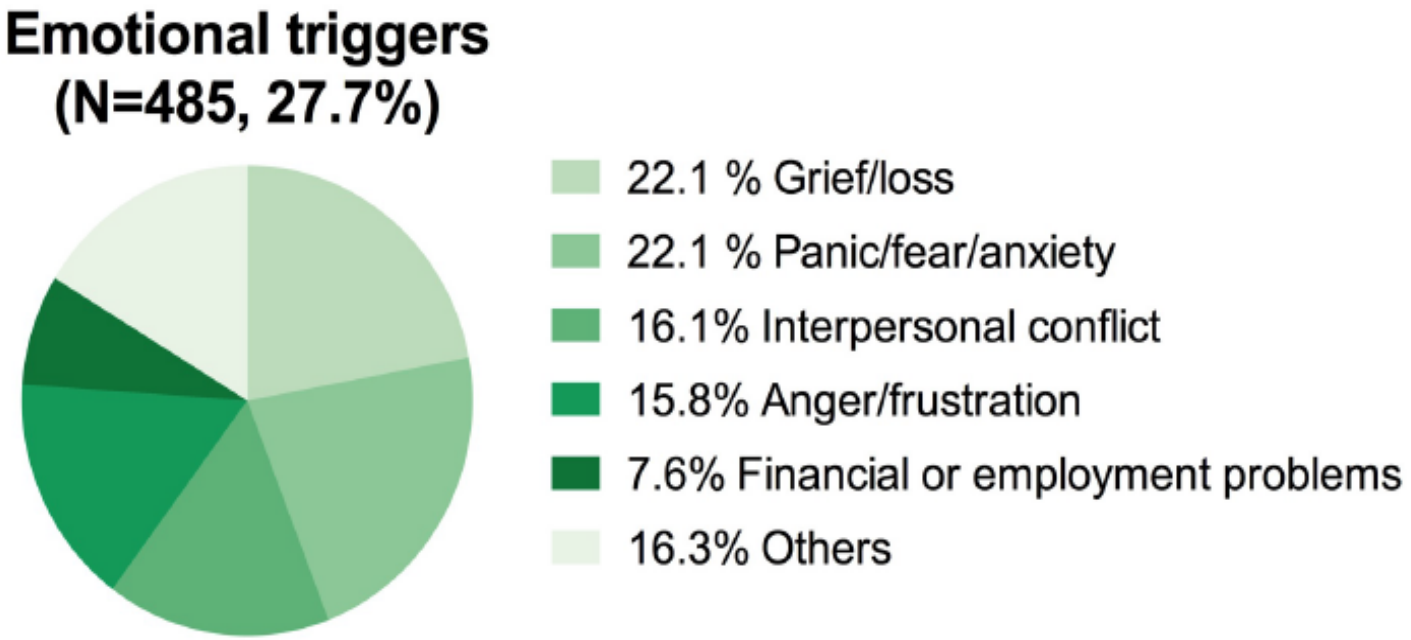
V5
V6
50Hz
10mm/mV
25mm/s
II medico:

Epidemiologia



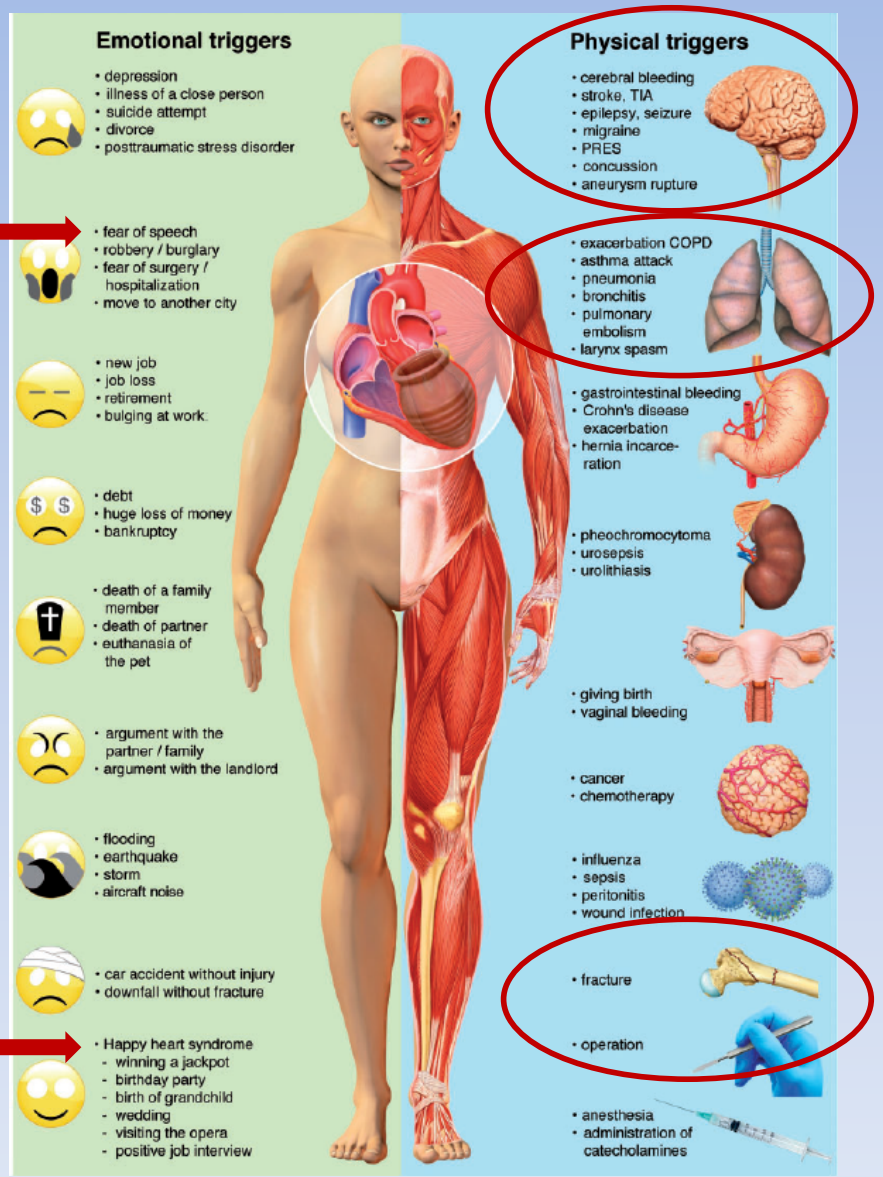
Templin C. et al. *Supplementary Appendix,* NEJM 2015

Epidemiologia



Templin C. et al. *Supplementary Appendix,* NEJM 2015

Epidemiologia



International Expert Consensus Document on Takotsubo Syndrome, **EHJ 2018**

Come differenziarla da infarto miocardico?

Table I **Characteristics of ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, Takotsubo syndrome, and Prinzmetal angina**

	STEMI	Non-STEMI	Takotsubo syndrome	Prinzmetal angina (vasospastic angina)
Age	40–70 years	50–90 years	50–70 years	<50 years, more frequent in Asians
Gender	Preponderance of males	Males and females	Predominantly post-menopausal females	
Emergency presentation	Chest pain (angina), sudden death, dyspnoea, cardiogenic shock, syncope	Chest pain (angina), dyspnoea, cardiogenic shock	Chest pain (angina), dyspnoea, cardiogenic shock, syncope	Chest pain (angina) at rest, dyspnoea, spontaneous remission
Trigger	Inflammation, emotional or physical stress	Inflammation	Emotional, physical stress, or no evident trigger	Drugs[a]
ECG	ST-segment elevation	ST-segment depression, T-inversion	ST-segment elevation, T-inversion, normal ECG, QTc prolongation	Transient ST-segment elevation
Biomarkers	Troponin ↑↑↑ NT-proBNP ↑↑	Troponin ↑-↑↑ NT-proBNP ↑	Troponin ↑ NT-proBNP ↑↑↑	Troponin ↔-↑, NT-proBNP ↔-↑
LV ejection fraction	40–60%	50–60%	30–45%	45–60%
LV wall motion abnormalities	Hypo-/akinesia in the territory of a major coronary artery	Hypo-/akinesia in the territory of a major coronary artery	Apical ballooning, mid-ventricular, basal, focal hypo-, a- or dyskinesia	Hypo-/akinesia in the territory of a major coronary artery (focal spasm) or generalized hypokinesia (diffuse spasm)
Coronary angiogramm	Occlusion of major epicardial coronary artery	Tight stenosis of major epicardial coronary artery	Typically normal coronary arteries[b]	Normal, segmental or diffuse spasm (provocative testing)
Coronary thrombus	+++	+/++	–	–
In-hospital mortality	5–7%	2–4%	3–5%	0–2%

LV, left ventricular; NT-proBNP, N-terminal pro brain natriuretic peptide; STEMI, ST-segment elevation myocardial infarction.
[a]Drugs such as cocaine, amphetamine, marijuana, alcohol, butane, chemotherapy drugs, and different antibiotics.
[b]Around 15% of patients have concomitant coronary artery disease (stenosis ≥50%).[6]

Gli esami di laboratorio in particolare la presenza di elevati valori di Nt-pro BNP associati ad un lieve incremento della troponina possono guidare la diagnosi che richiede comunque l'esame coronarografico

European Heart Journal 2016

Diagnosi

Takotsubo or Acute Coronary Syndrome?
That is the question!

Criteria	Points	Prediction of TTS	OR (95% CI)	P-value
Female sex	25		68 (29.0 - 163.7)	P<0.001
Emotional trigger	24		65 (20.3 - 205.8)	P<0.001
Physical trigger	13		8.7 (4.6 - 17.3)	P<0.001
Absence of ST-segment depression*	12		7.2 (3.1 - 16.8)	P<0.001
Psychiatric disorders	11		7.0 (3.1 - 15.5)	P<0.001
Neurologic disorders	9		4.9 (2.2 - 11.3)	P<0.001
QTc prolongation	6		2.8 (1.3 - 5.7)	P=0.006
	100	0.1 1 10 100		

Takotsubo molto probabile se > 70 punti

Inter TAK diagnostic score, **European J Heart Fail 2017**

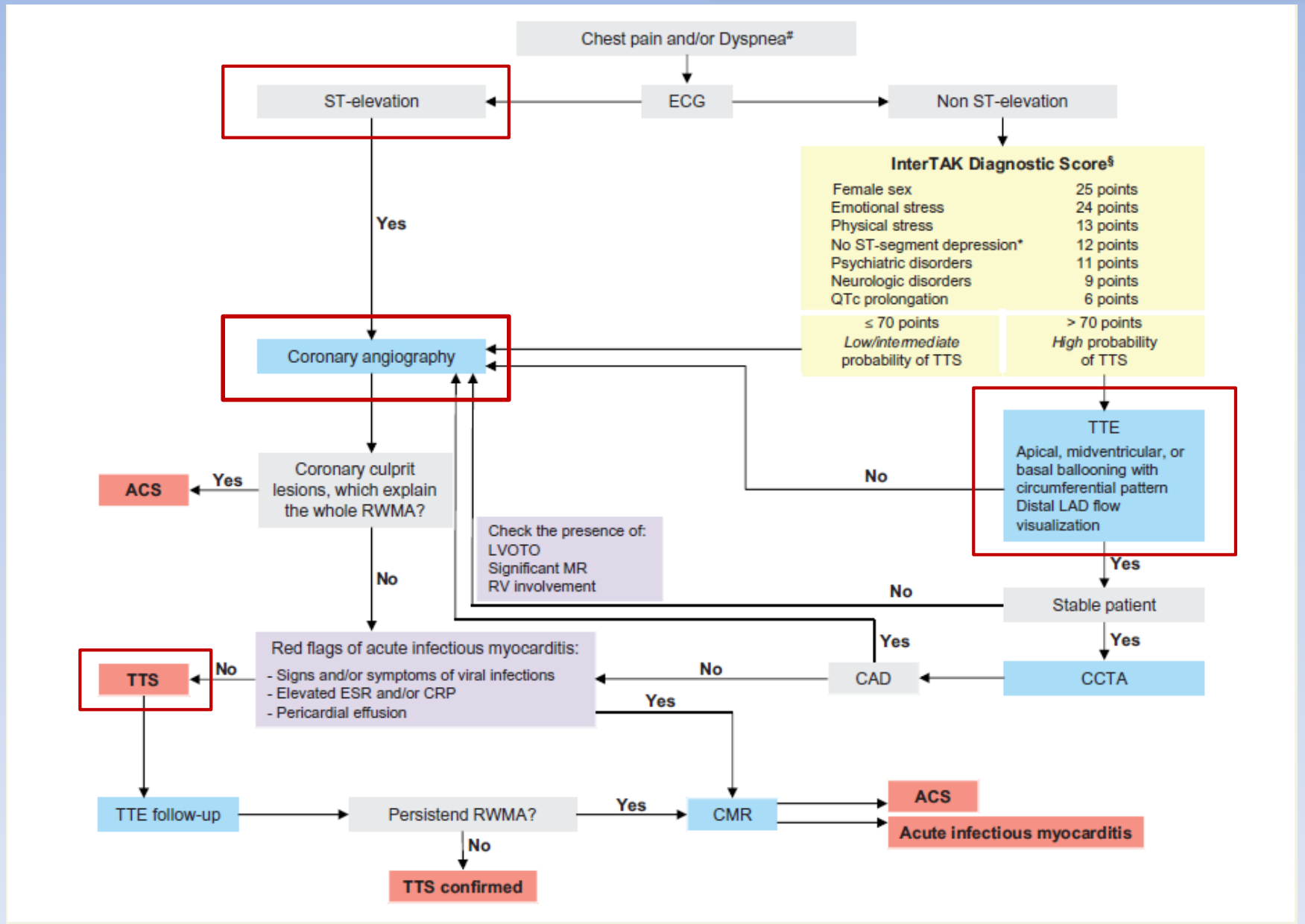
Come differenziarla da miocardite?

Box 2 Differences between Takotsubo syndrome and acute myocarditis

Category	Takotsubo syndrome	Acute myocarditis
Gender and age	90% female. Majority >50 years and post-menopausal.	No sex prevalence. More frequent in the young.
Preceding events	Stressor trigger identifiable in ~70% of cases.	Symptoms and signs of infection often present (fever, chills, headache, muscle aches, general malaise, cough, nausea, vomiting, diarrhoea).
Cardiac symptoms	Chest pain, dyspnoea, palpitations.	Chest pain, dyspnoea, peripheral oedema, fatigue, and palpitations.
Clinical signs	Pericardial rub rare.	Pericardial rub may be present.
ECG at admission	ST changes such as ST-segment elevation or non ST-segment elevation. Deep T wave inversion. QT prolongation. Rarely normal.	ST-segment elevation or depression, negative T-wave, bundle branch block, atrioventricular block, low voltage, and/or ventricular arrhythmias. Normal in several cases.
Cardiac enzymes	Low/moderate troponin rise. Discrepancy between the large amount of dysfunctional myocardium and peak troponin level.	Frequently significant troponin rise, proportional to the hypokinetic area. Normal in several cases.
Other biomarkers	C-reactive protein (CRP) mildly elevated unless infective trigger. BNP moderately or significantly elevated.	Erythrocyte sedimentation rate and CRP elevated. BNP basically elevated. Acute viral serology may be detected.
Echocardiography	Apical ballooning, anatomical variants, 'circumferential pattern', left ventricular outflow tract obstruction (LVOTO), right ventricular (RV) involvement, transient mitral regurgitation.	Localized or diffuse wall motion abnormalities of LV and/or RV dilatation, increased wall thickness, pericardial effusion.
Cardiac magnetic resonance imaging	High T2 signal intensity (oedema), late gadolinium enhancement (LGE) usually absent acutely. If present acutely patchy LGE which usually resolves at follow-up. Absence of typical infarct LGE pattern.	High T2 signal intensity (oedema), LGE with non-ischaemic distribution (often epicardial). Absence of typical infarct LGE pattern.
Histological findings	Contraction band necrosis.	Infiltration of many inflammatory cells. Interstitial oedema.
Viral genome, separation of virus, or identification of virus by antibody titre	Rare and usually absent where measured.	Often positive.
Prognosis	50% of cases have acute complications, 4–5% mortality.	Variable but majority full recovery. Highest mortality with fulminant myocarditis.
Therapy	Supportive.	Supportive. Immunosuppression in severe cases if giant cell myocarditis suspected.

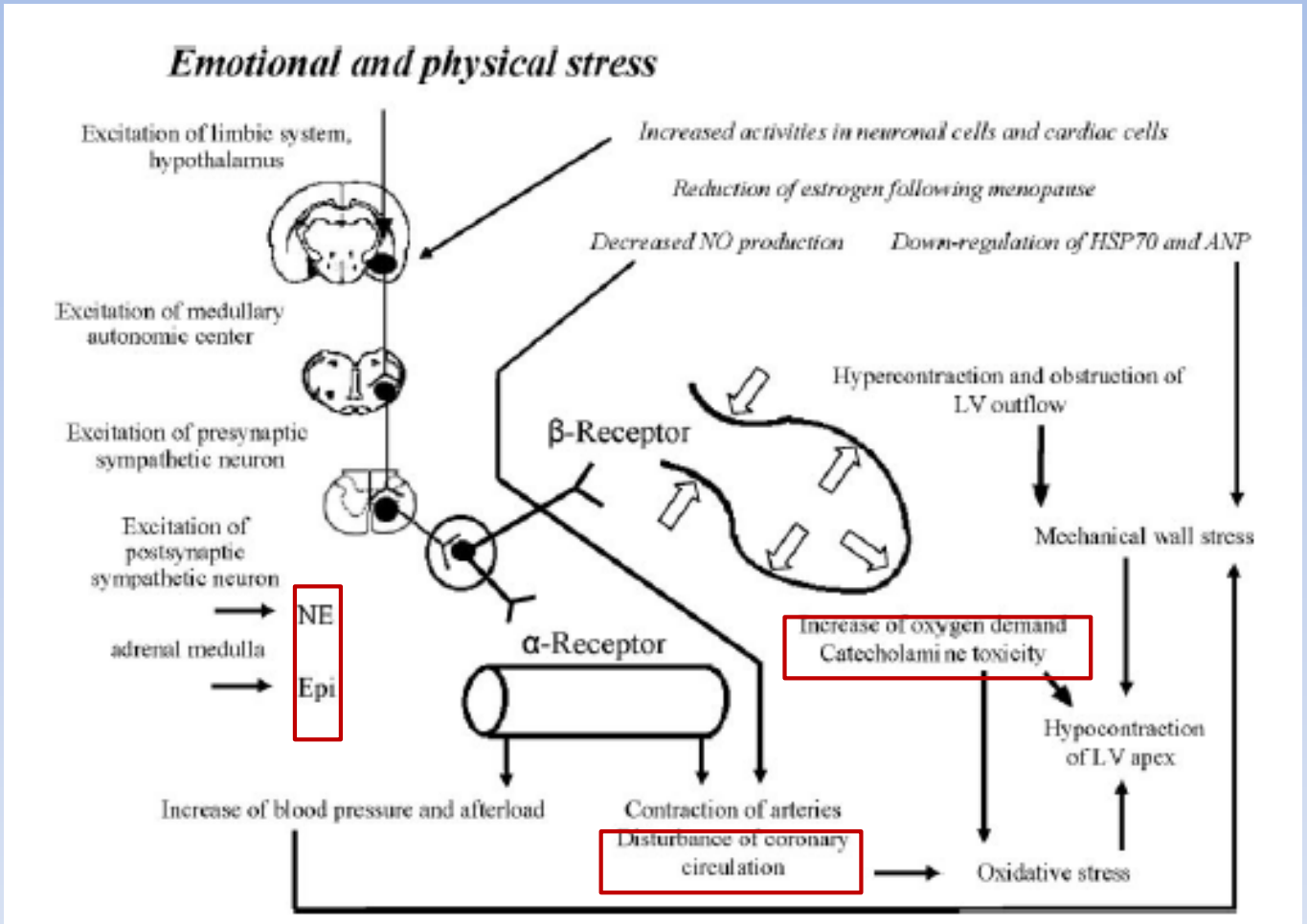
HFA task force position paper, **European J Heart Fail 2016**

Algoritmo diagnostico



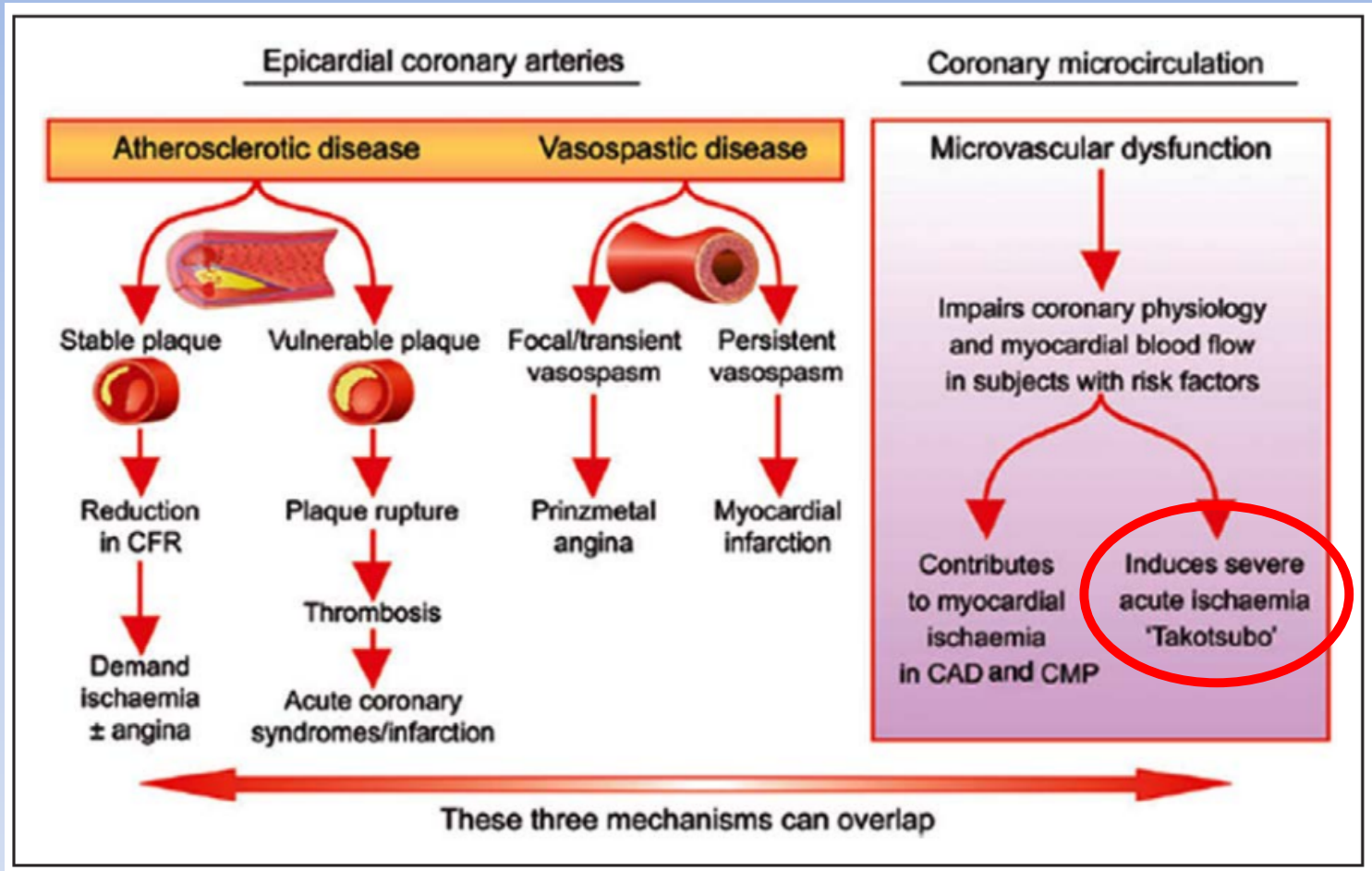
International Expert Consensus Document on Takotsubo Syndrome, **EHJ 2018**

Fisiopatologia



Akashi YJ et al, **Circulation 2008**

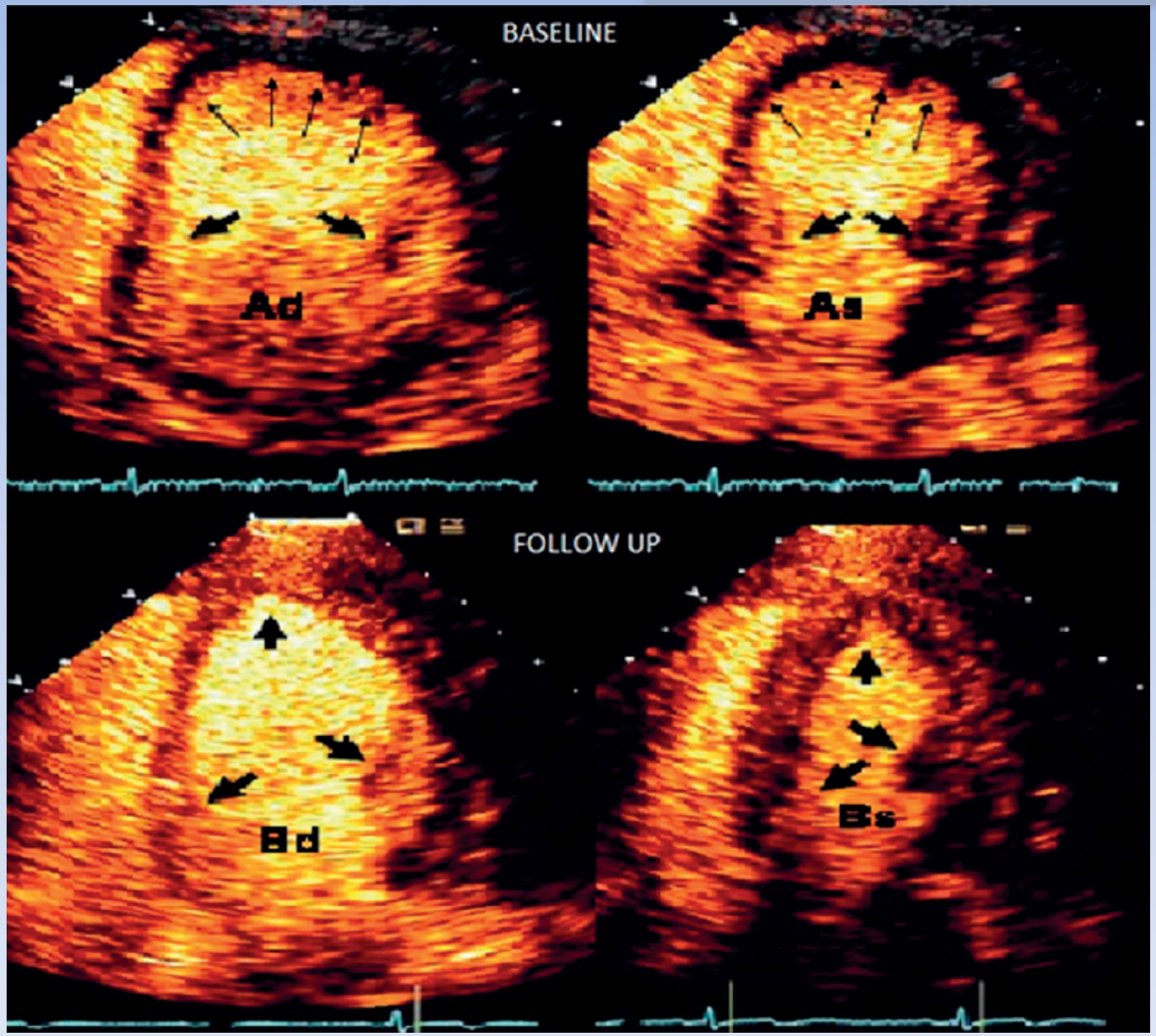
Fisiopatologia



Oltre ai meccanismi classici (cioè, malattia aterosclerotica e vasospasmo coronarico epicardico) che portano all'ischemia miocardica, la disfunzione microvascolare coronarica è recentemente emersa come un terzo meccanismo potenziale di ischemia miocardica.
La disfunzione microvascolare coronarica (da sola o **in combinazione**) può portare all'ischemia miocardica transitoria anche nella sindrome di Takotsubo.

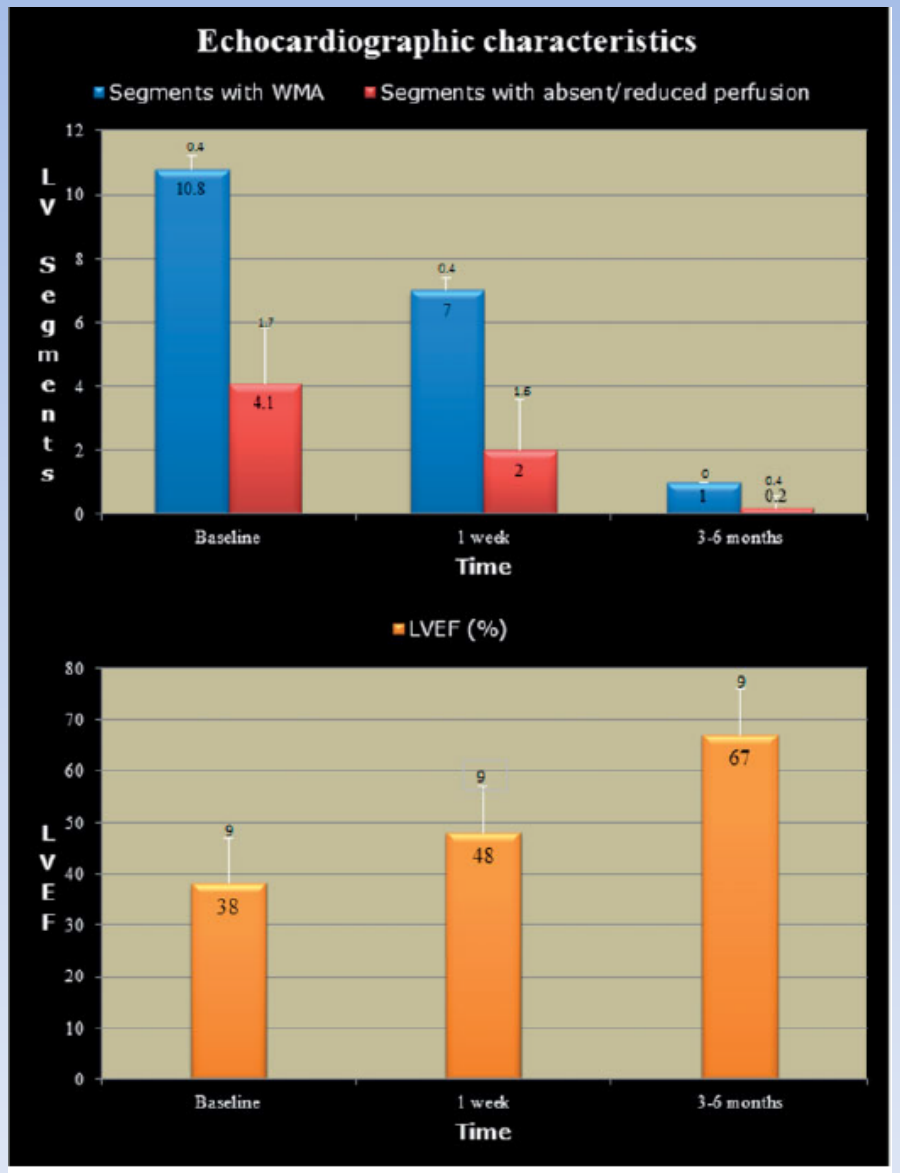
Circulation. 2017;135(24):2426-2441.

Fisiopatologia (disfunzione del microcircolo)



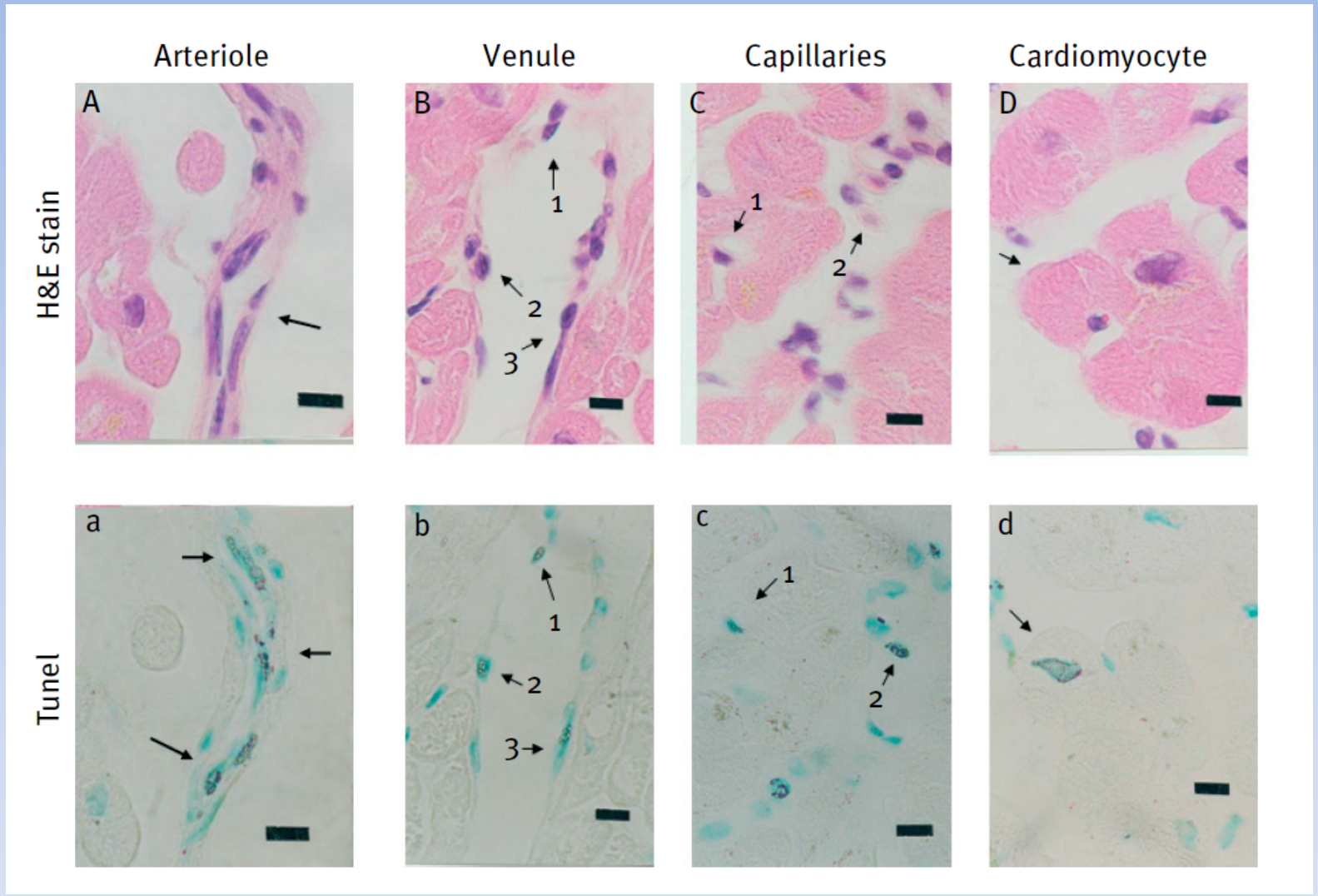
Mohit Jain, **Clin Cardiol 2013**

Fisiopatologia (disfunzione del microcircolo)



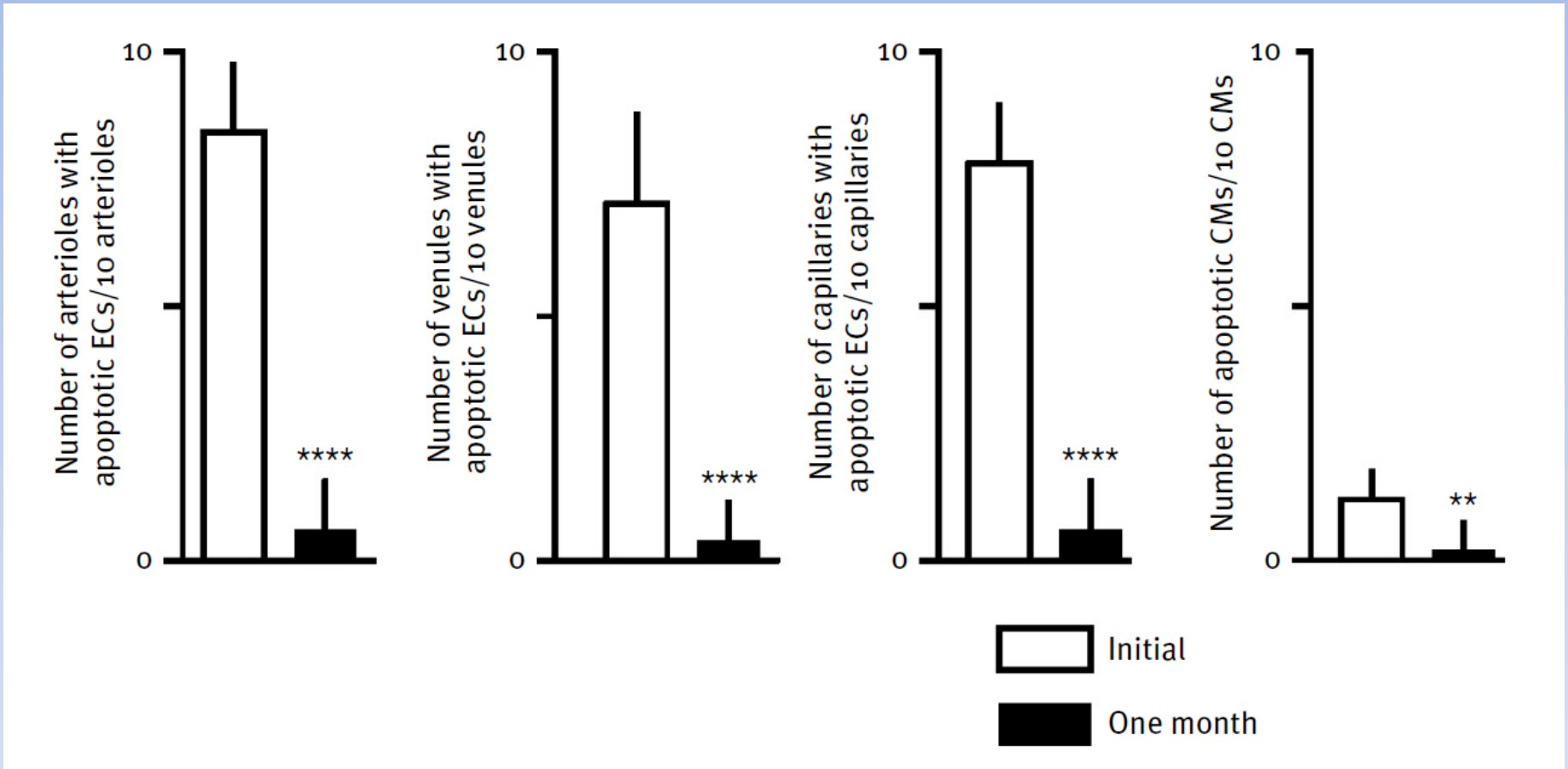
Mohit Jain, **Clin Cardiol 2013**

Fisiopatologia (disfunzione del microcircolo)



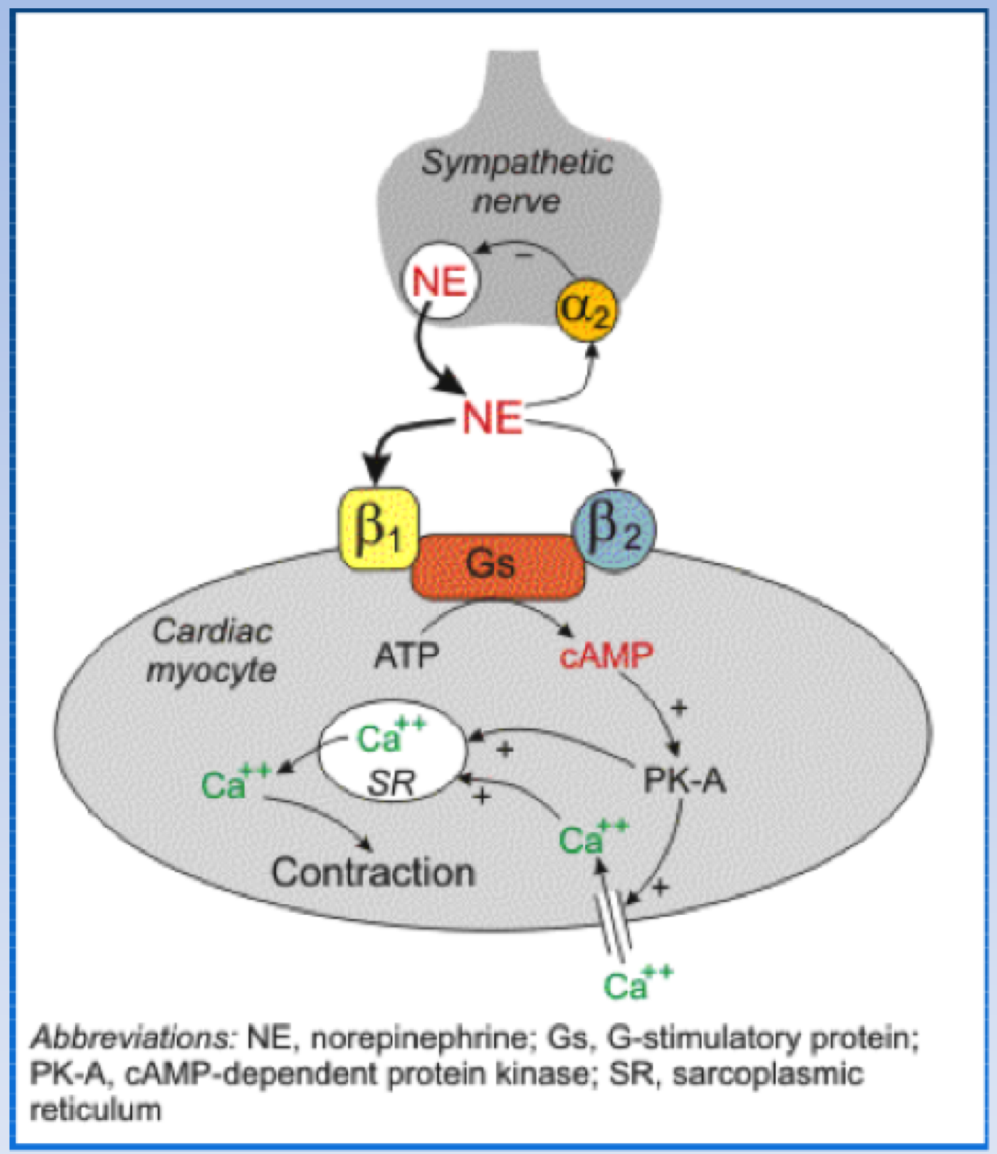
Uchida Y et al, **Clin Cardiol 2010**

Fisiopatologia (disfunzione del microcircolo)



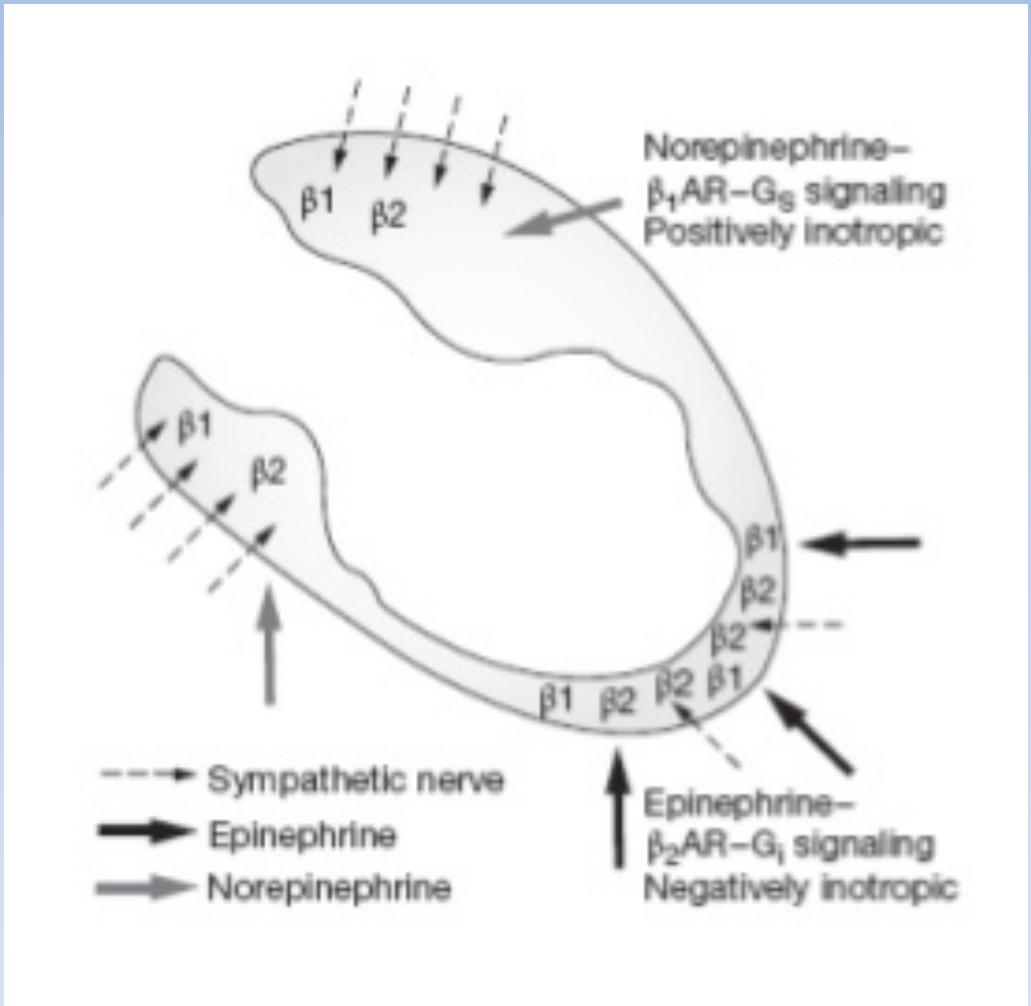
Uchida Y et al, **Clin Cardiol 2010**

Fisiopatologia (tossicita` diretta delle catecolamine)



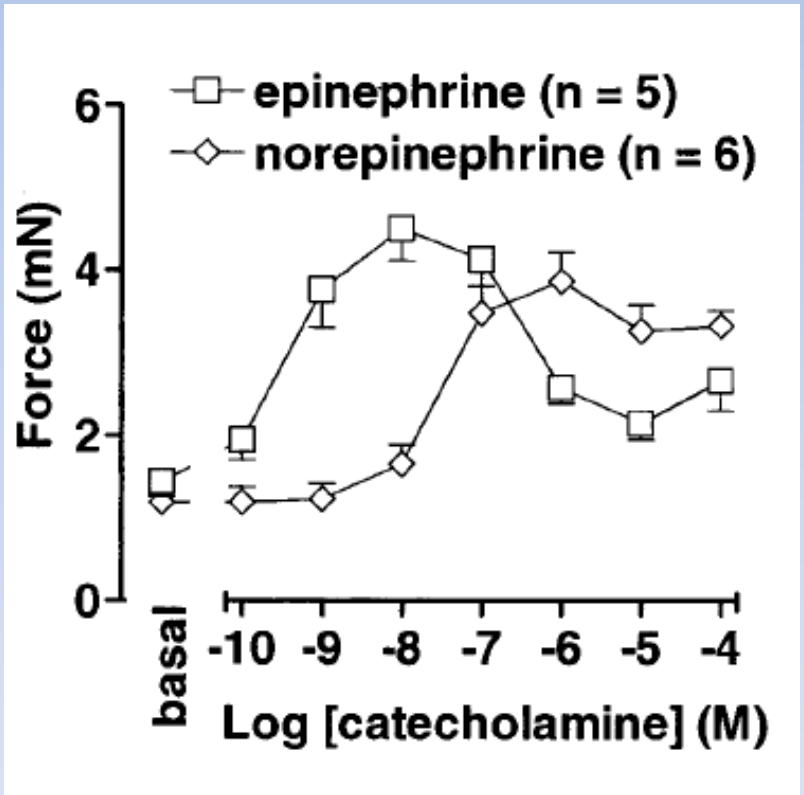
Abbreviations: NE, norepinephrine; Gs, G-stimulatory protein; PK-A, cAMP-dependent protein kinase; SR, sarcoplasmic reticulum

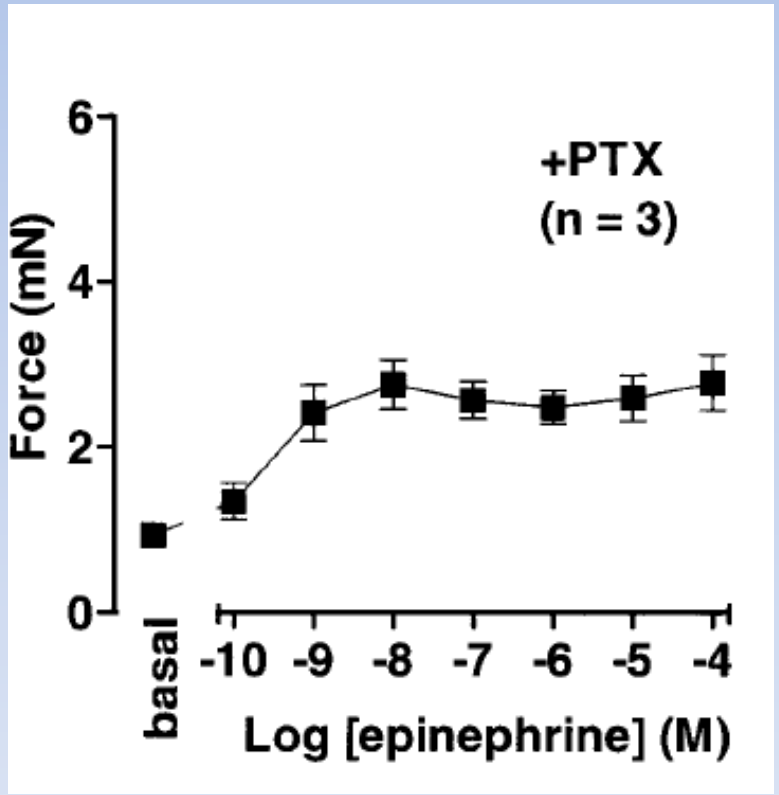
Fisiopatologia (tossicita` diretta delle catecolamine)



Fisiopatologia (tossicita` diretta delle catecolamine)

Epinephrine Activates Both G_s and G_i Pathways, but Norepinephrine Activates Only the G_s Pathway through Human β_2-Adrenoceptors Overexpressed in Mouse Heart

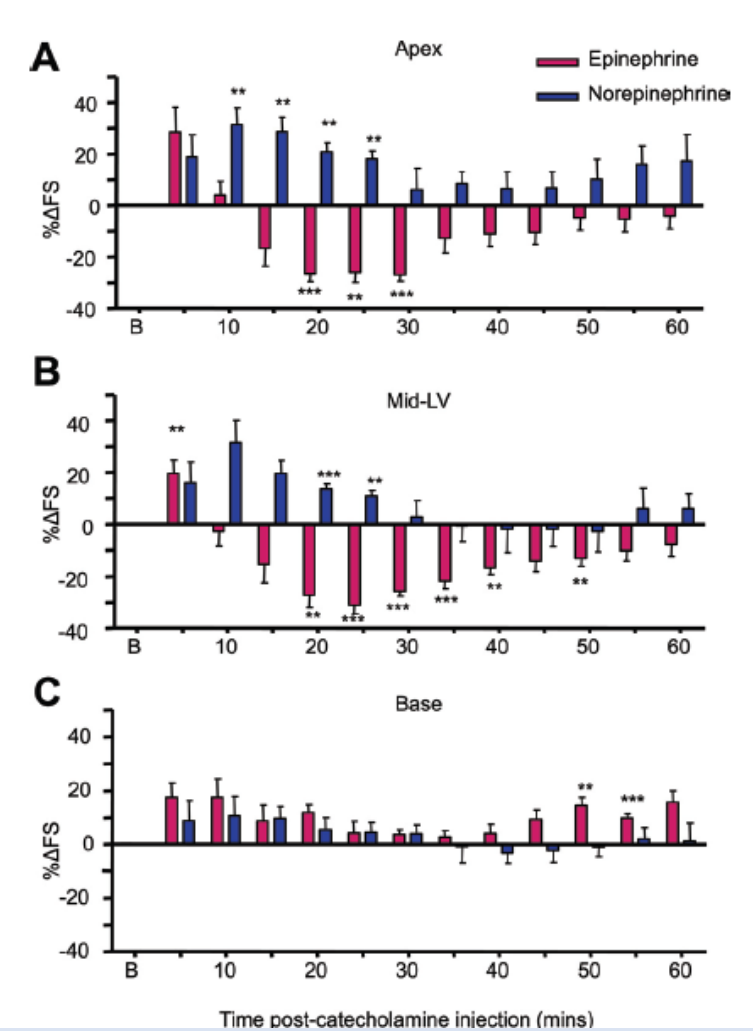




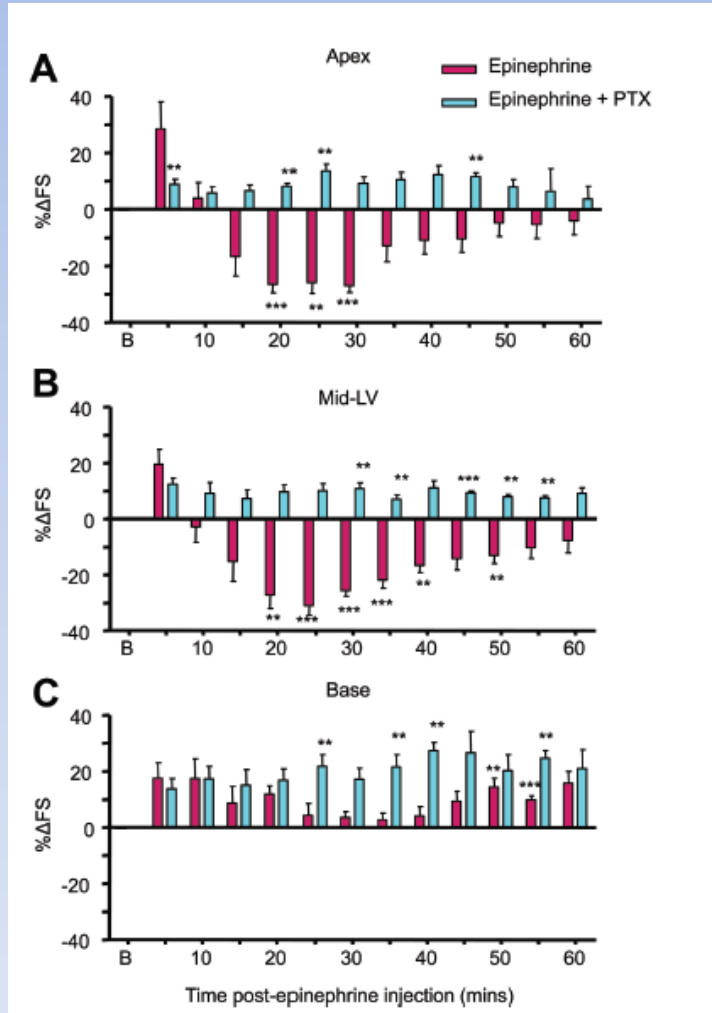
Heubach JF et al, **Molecular Pharmacology 2013**

Fisiopatologia (tossicita` diretta delle catecolamine)

L'Adrenalina causa il Takotsubo



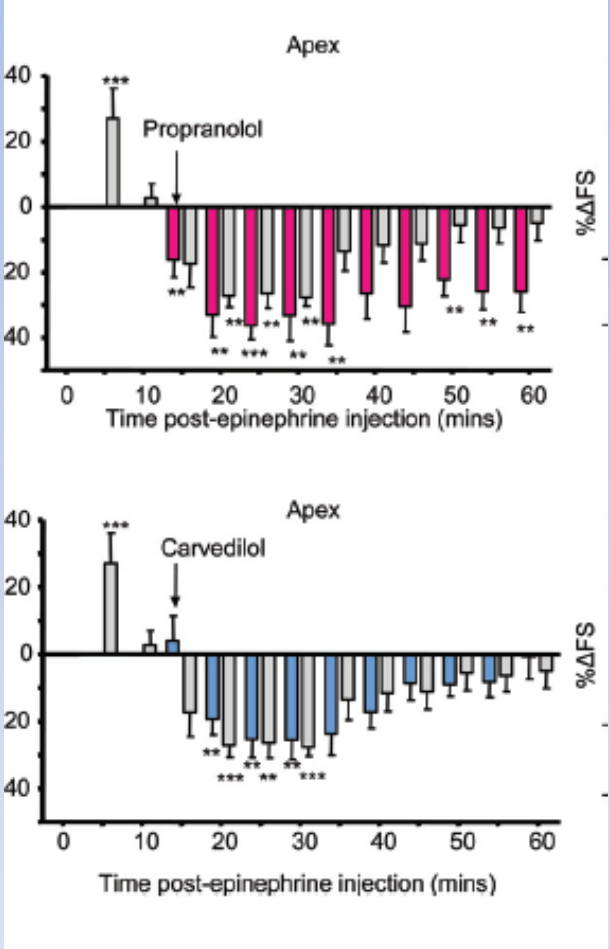
Il fenomeno e` legato ad attivita` Gi del recettore Aβ2



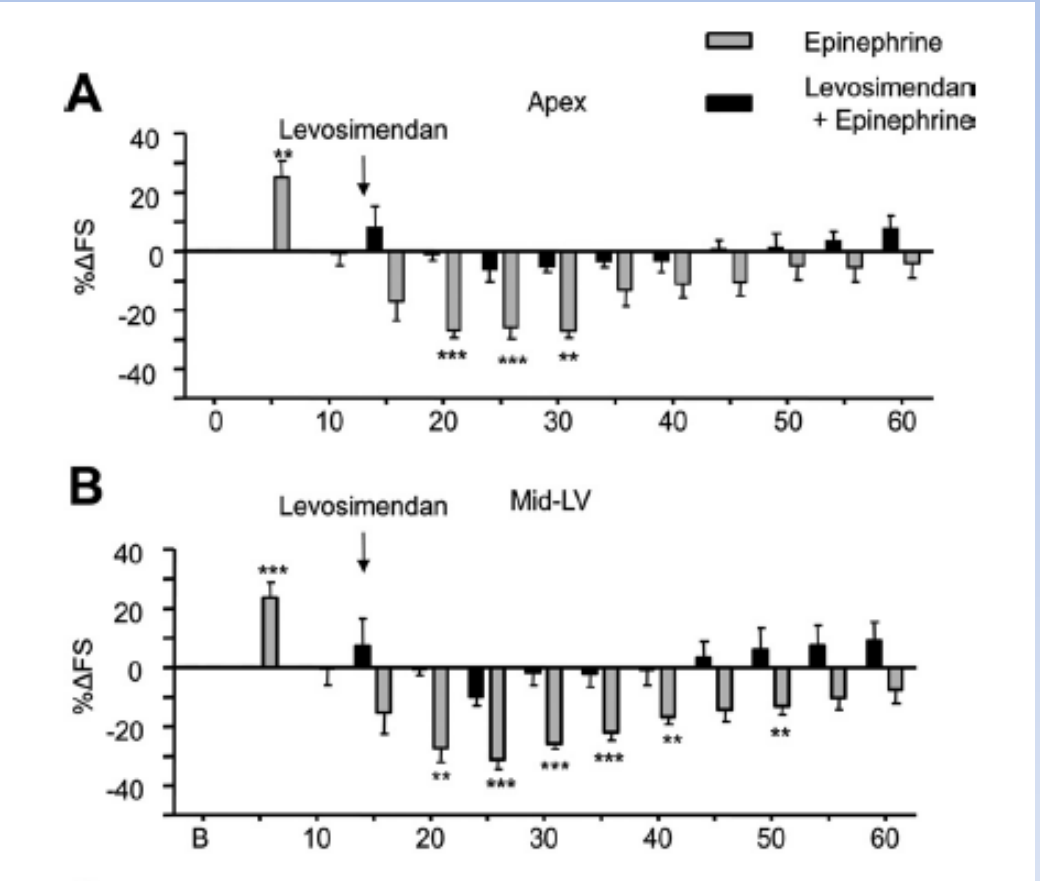
Pauer H et al, **Circulation 2012**

Fisiopatologia (tossicita` diretta delle catecolamine)

β-bloccanti attivanti β2 AR Gi **NON** riducono la disfunzione apicale



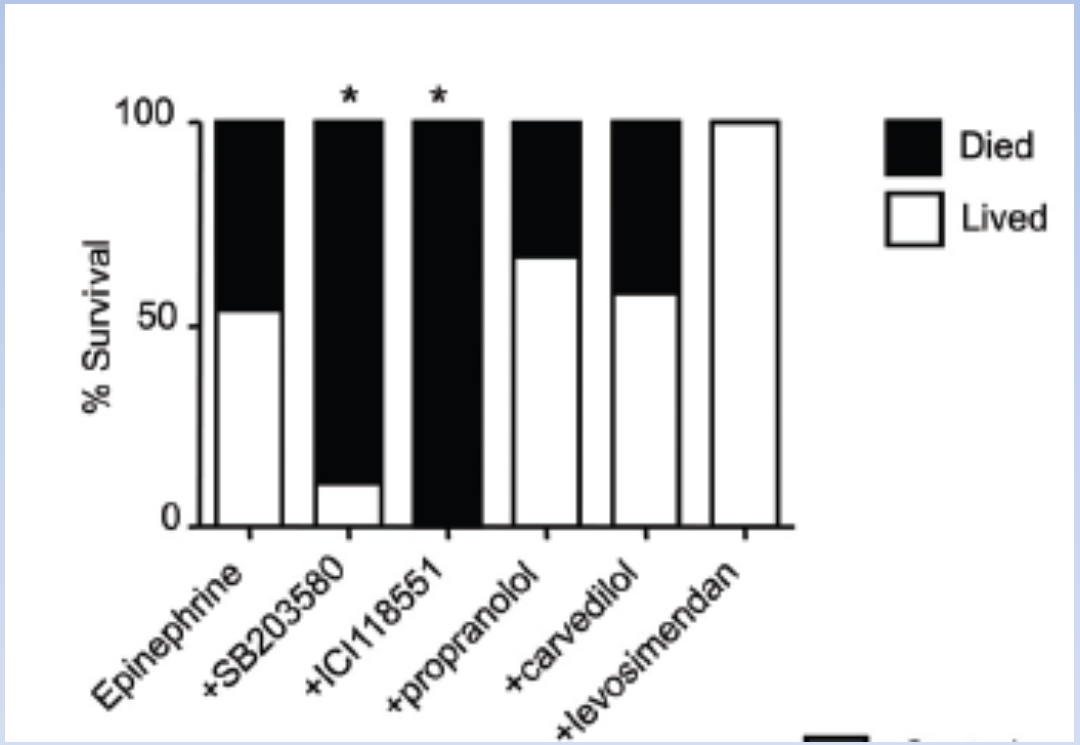
Il Levosimendan annulla la disfunzione da Adrenalina **SENZA aumentare la mortalita`**



Pauer H et al, **Circulation 2012**

Fisiopatologia (tossicita` diretta delle catecolamine)

L'attivazione Gi del recettore β2 ("*stimulus trafficking*")
e` **cardioprotettiva**

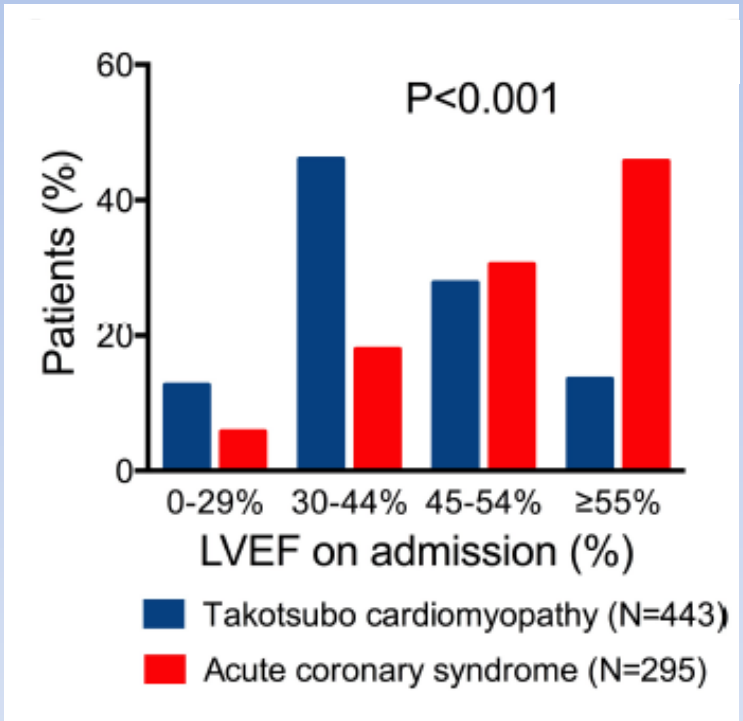


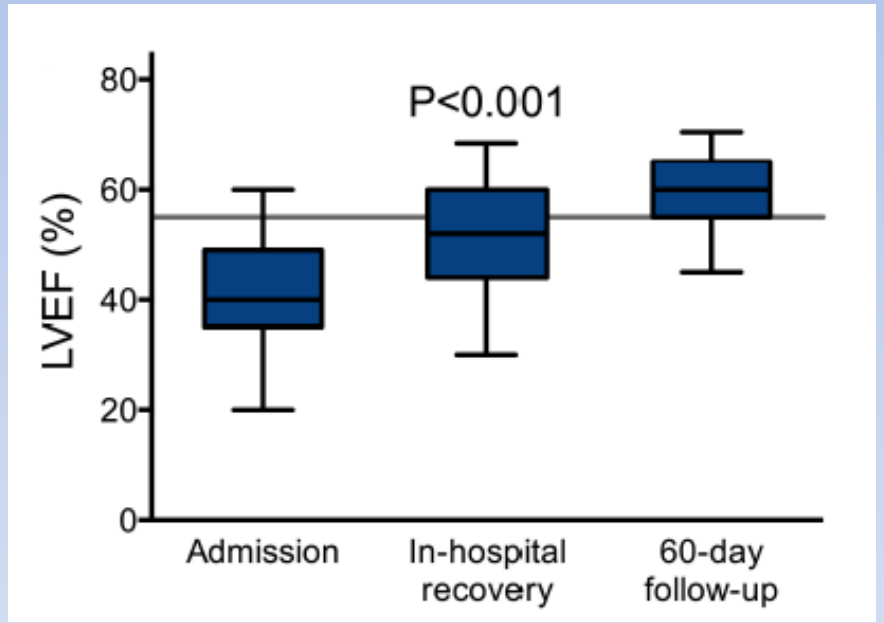
Modello animale (topo) in vivo

Pauer H et al, **Circulation 2012**

Prognosi

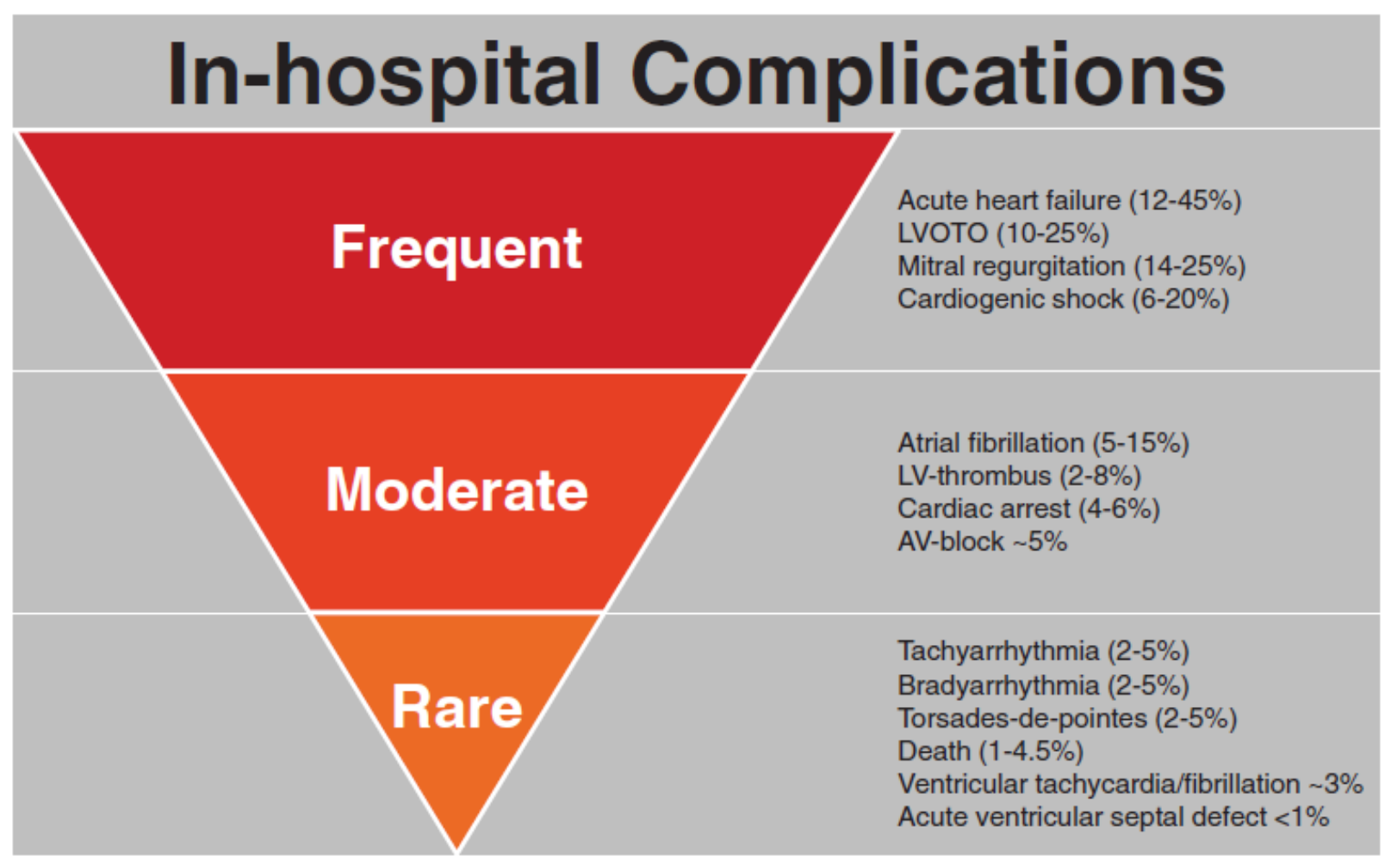
Restitutio ad integrum della funzione sistolica ventricolare sinistra





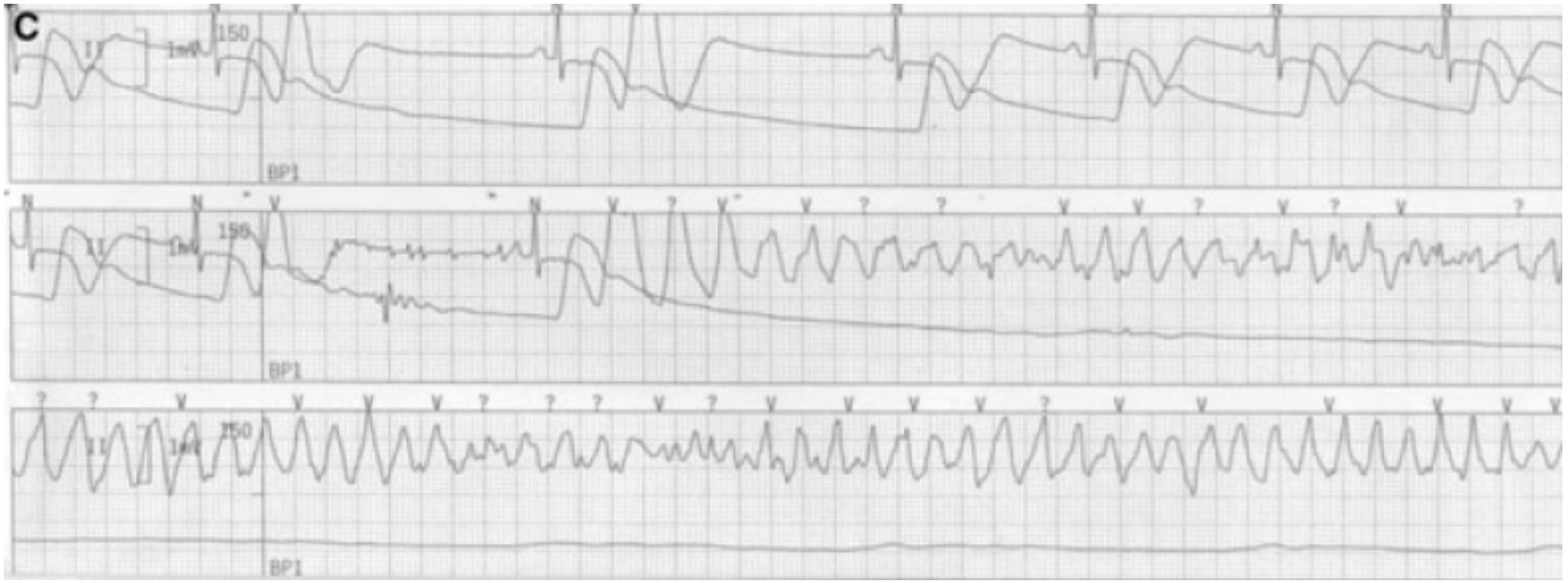
Templin C. et al. *Supplementary Appendix,* NEJM 2015

Complicanze



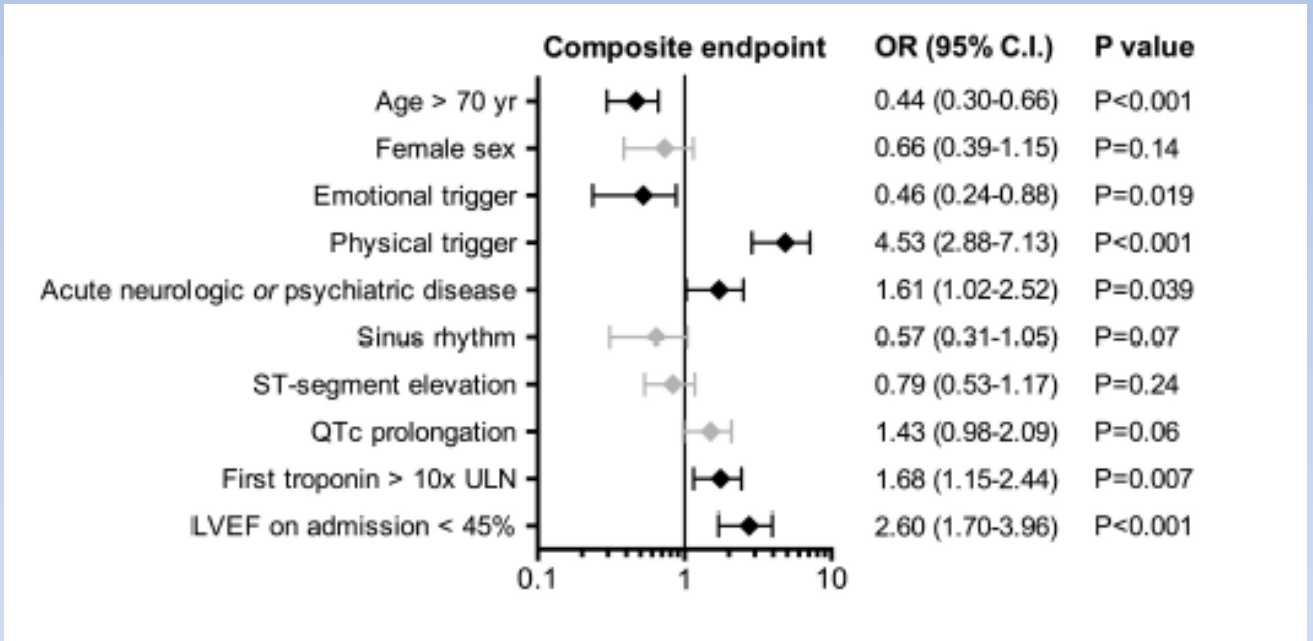
International Expert Consensus Document on Takotsubo Syndrome, **EHJ 2018**

Complicanze



Complicanze

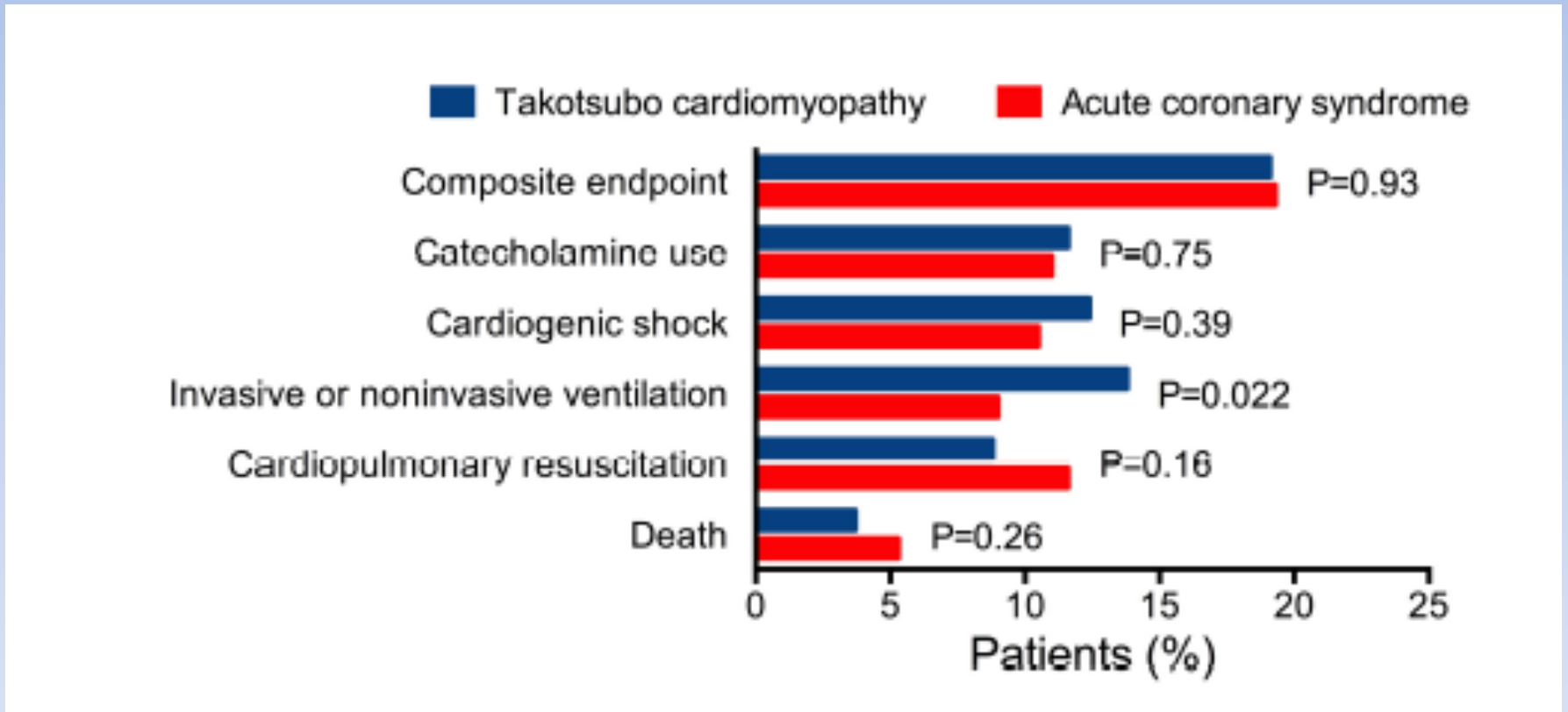
Predittori indipendenti di complicanze intra-ospedaliere



Templin C. et al. *Supplementary Appendix,* NEJM 2015

Complicanze

Complicanze intra-ospedaliere



Templin C. et al. *Supplementary Appendix,* NEJM 2015

Terapia durante ospedalizzazione

Il trattamento è simile a quello per uno scompenso cardiaco acuto:

Diuretici
Ace-i/ARB

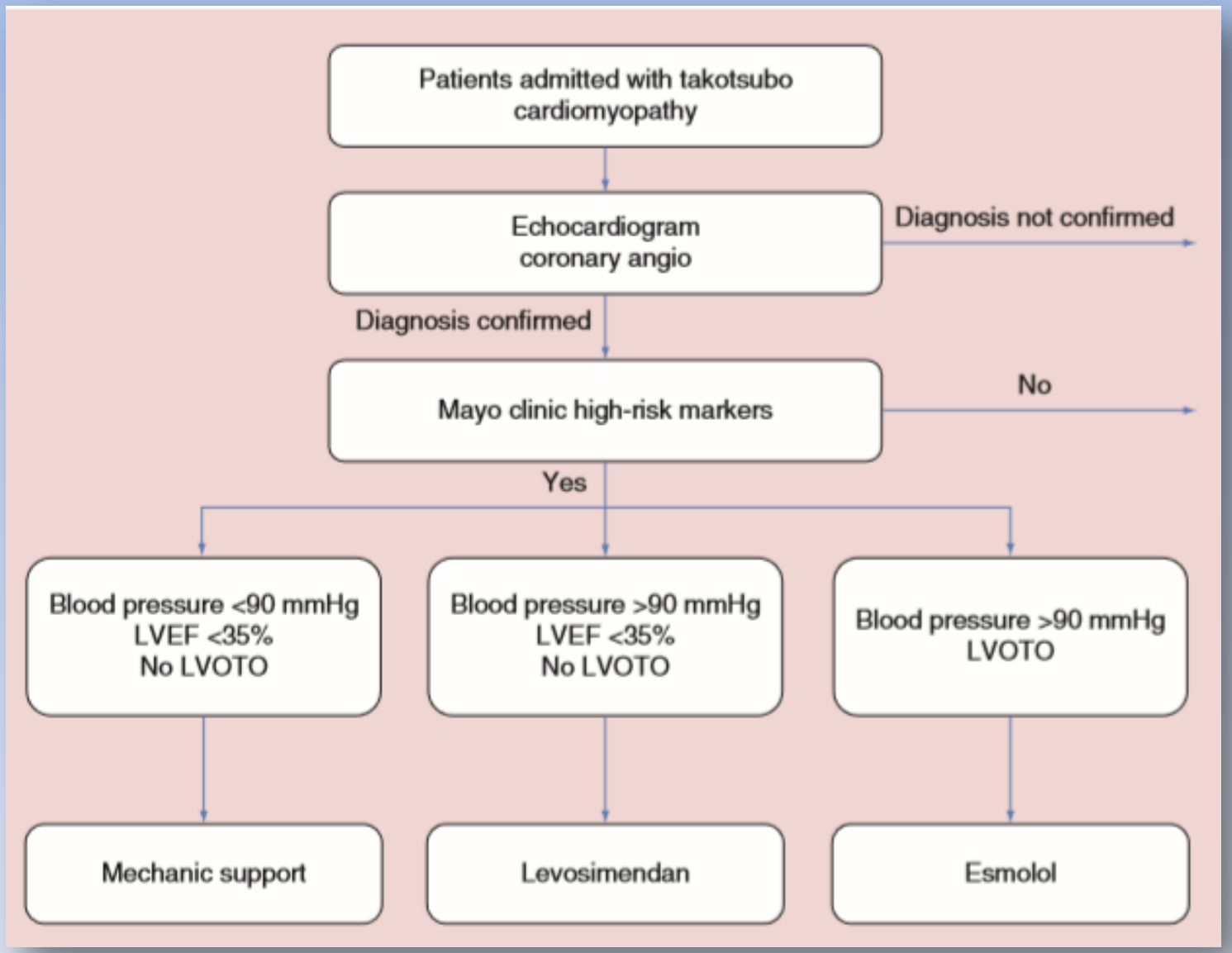
L'uso routinario di Betabloccanti dovrebbe essere evitato, infusione e.v. di beta bloccanti Beta 1 cardio selettivi con breve emivita può essere vanta ggioso in caso di ostruzione del tratto di efflusso ventricolare sinistro.

Infusione e.v. di Levosimendan è un opzione terapeutica in pazienti selezionati ad altro rischio per shock cardiogeno.

- EF < 35%, elevazione del tratto ST all'ingresso
- Livelli di troponina I elevati
- Presenza di uno stressor fisico

Santoro F, Brunetti, Di Biase et al
Cardiovasc Ther. 2013;31(6):e133-7.
Cardiovasc Ther. 2016;34(3):161-6.

Algoritmo terapeutico per i pazienti ad alto rischio

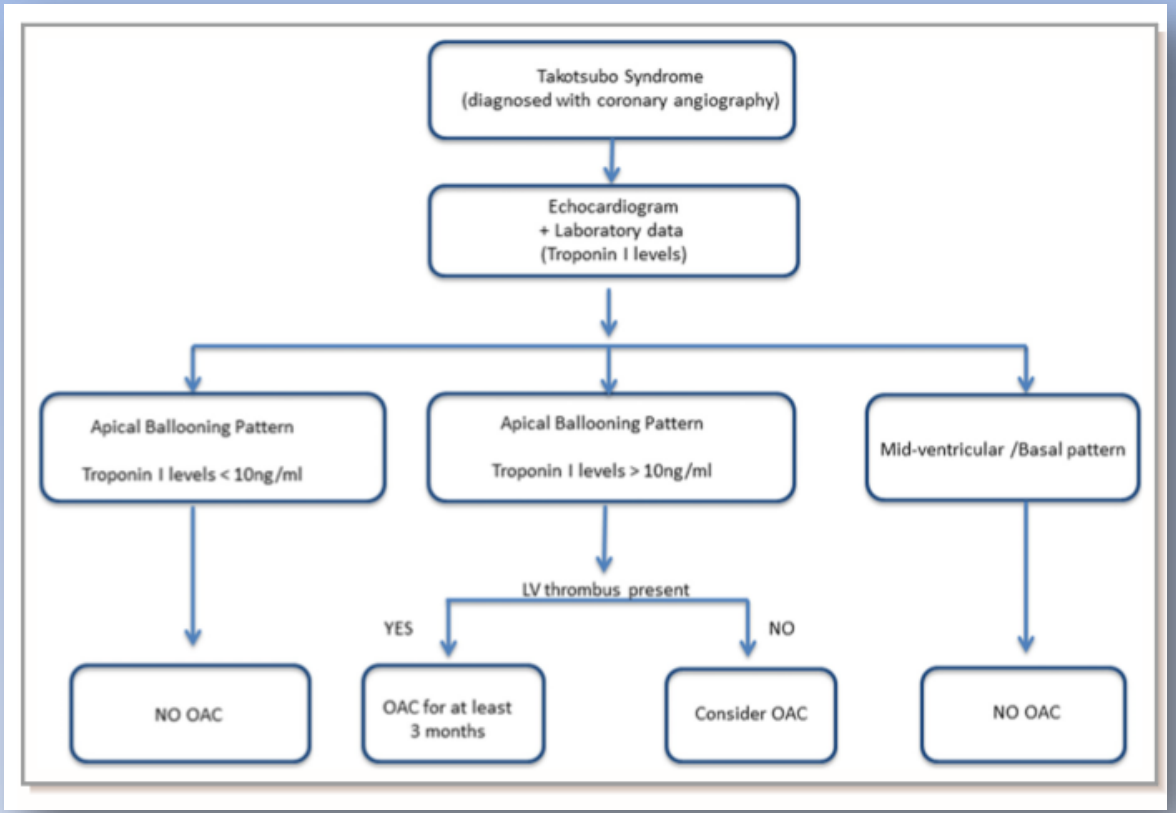


Brunetti, Santoro F, Di Biase et al
Future Cardiol. 2016; 12(5):563-72.

Terapia anticoagulante durante ospedalizzazione ?

Da un analisi su 540 pazienti con TTC, il 2,3% dei pazienti ha sviluppato trombosi endoventricolare ed il 17% di questi ha avuto evento cerebrovascolare.

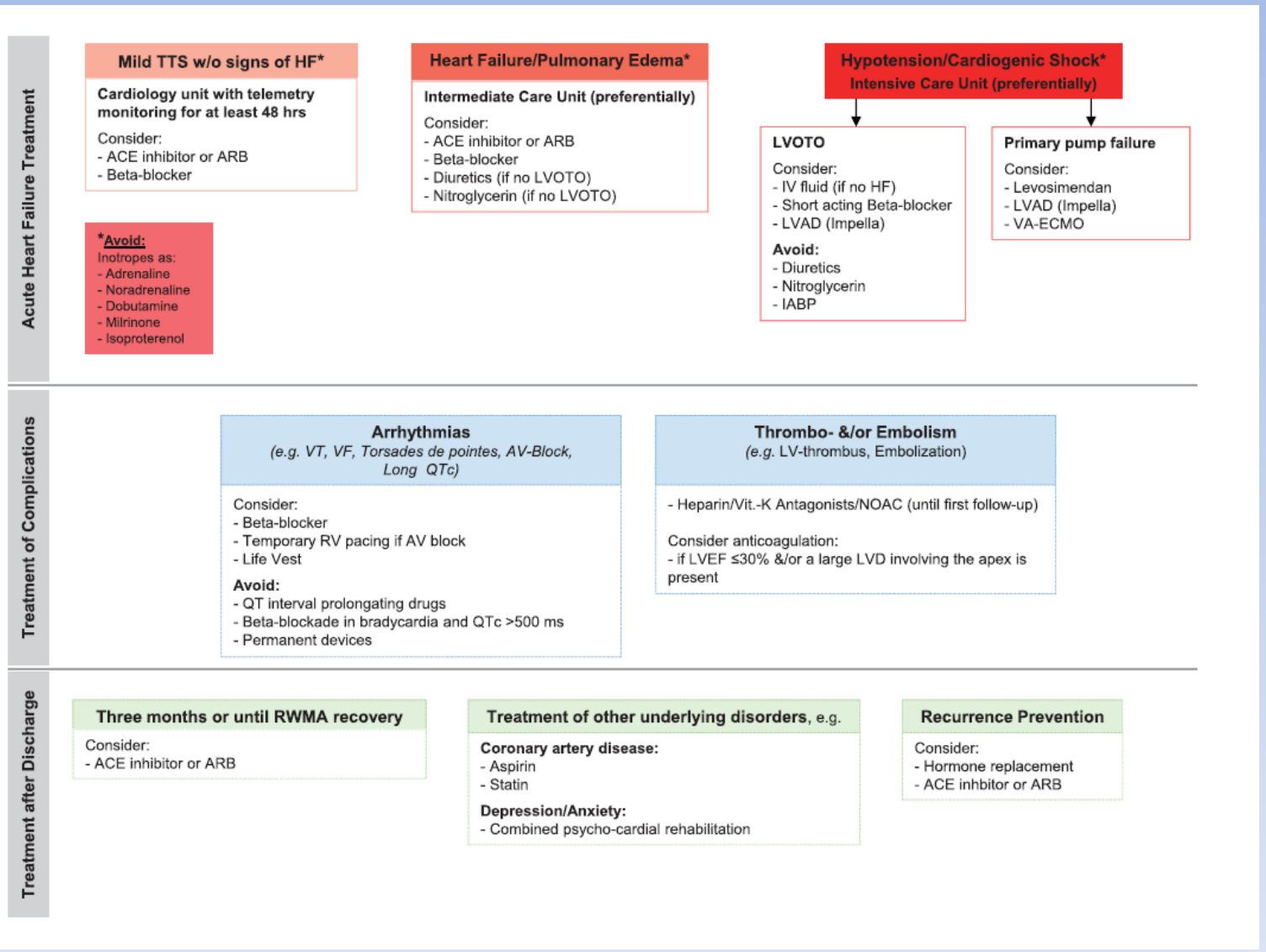
L'utilizzo di terapia anticoagulante orale per tre mesi si è rivelata efficace per la completa risoluzione della trombosi.



Il pattern apical balloning all'ecocardiogramma ed elevati livelli di troponine I sono risultati predittori di tale complicanza e potrebbero guidare la scelta della terapia anticoagulante.

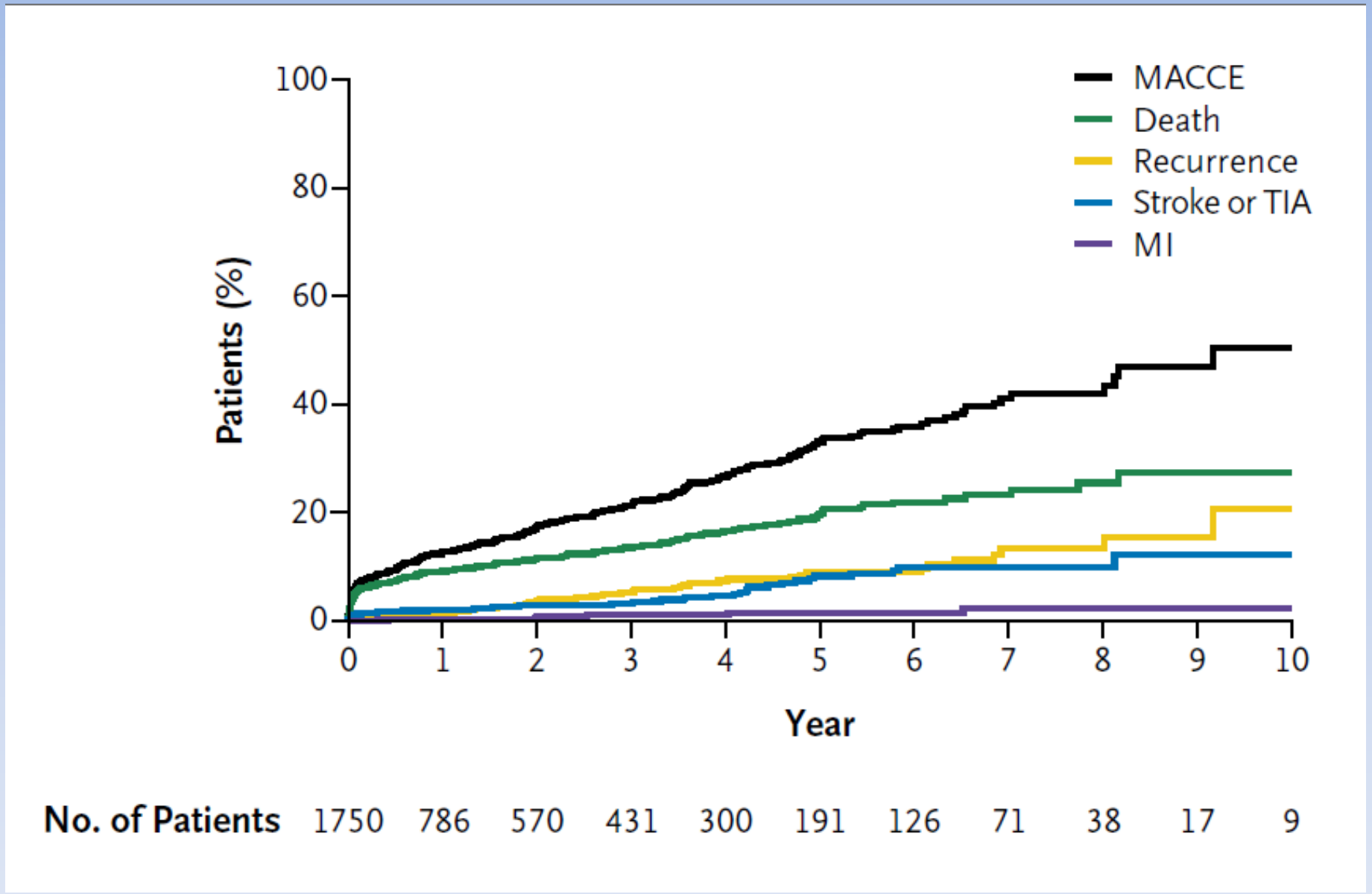
Santoro F, Brunetti, ND, Eitel I et al
J Am Heart Assoc. 2017 Dec 4;6(12).

Terapia



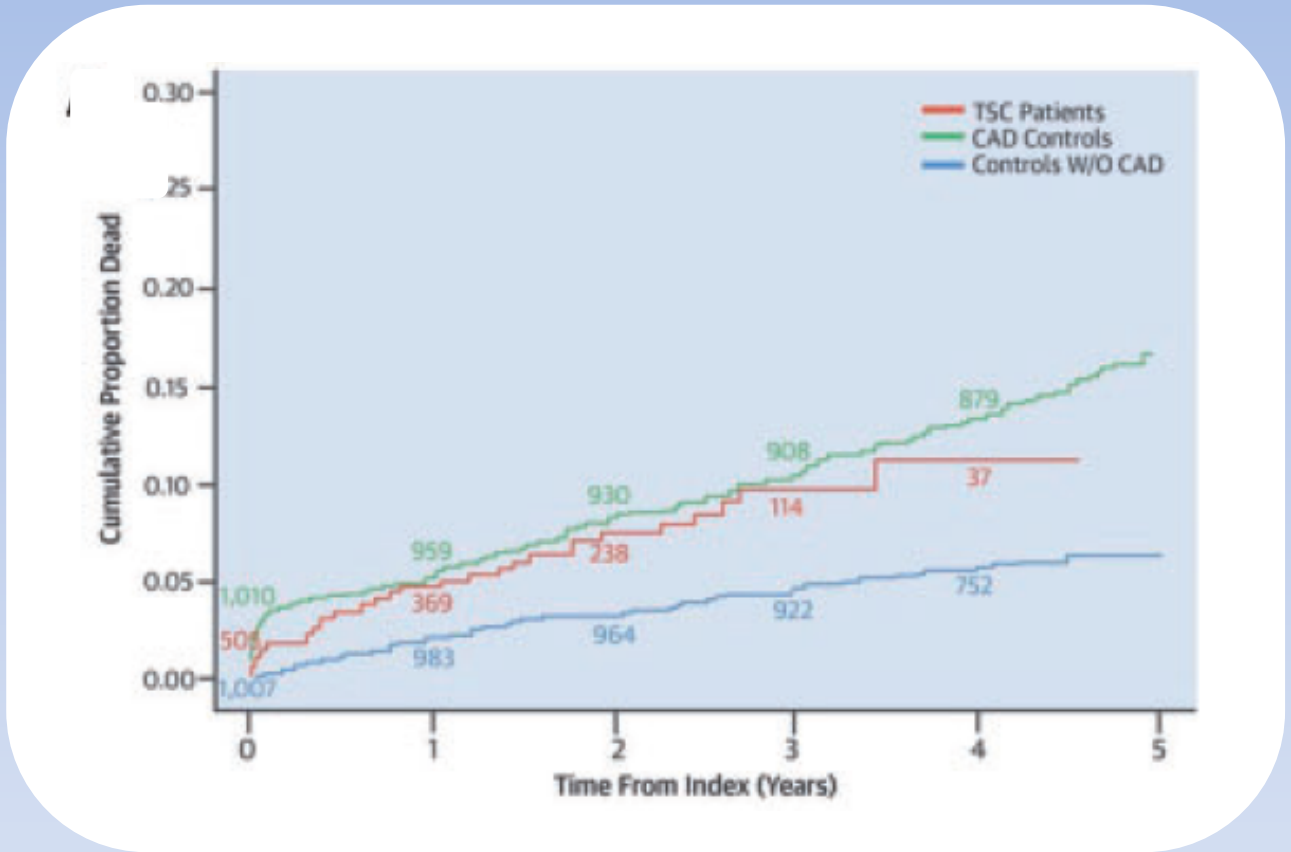
***International Expert Consensus Document on Takotsubo Syndrome,* EHJ 2018**

Prognosi a lungo termine



Templin C. et al. NEJM 2015

Prognosi a lungo termine



Tornvall P. et al. JACC 2016

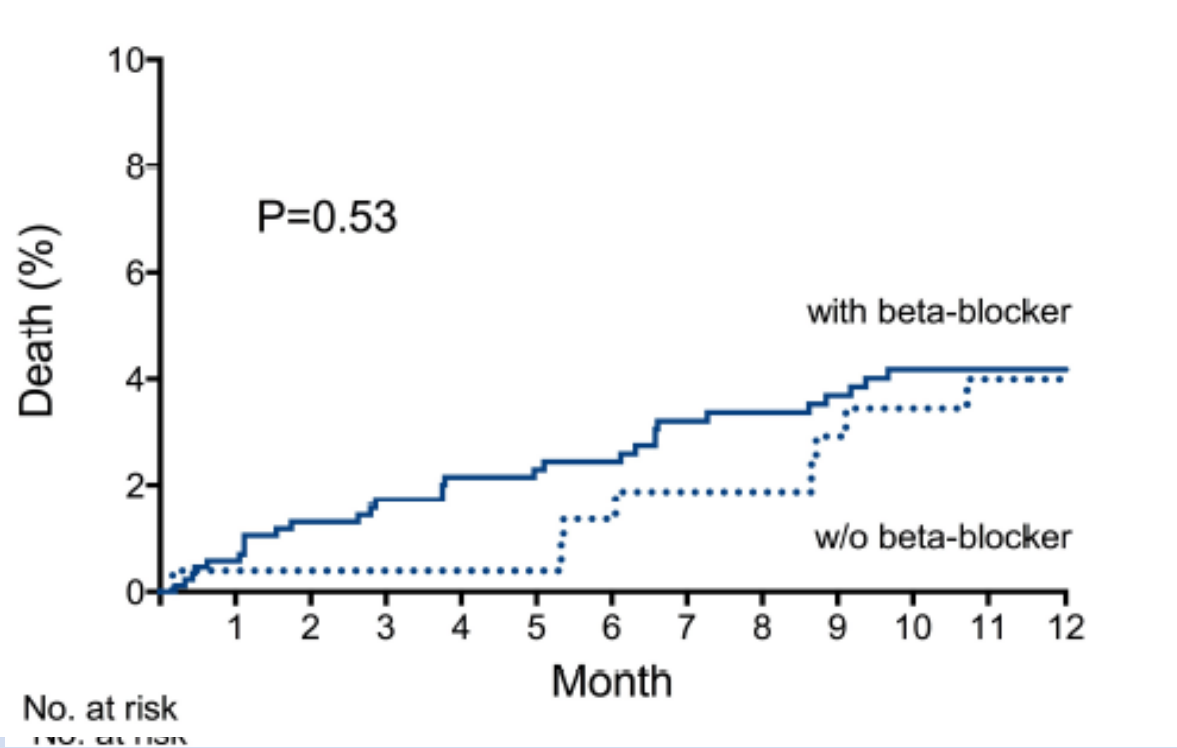
Terapia

Table I Overview of retrospective analyses, meta-analyses, and case series of medical management for takotsubo syndrome[a]

Authors	Study design	No. of patients	Outcome measures	Follow-up time	Medication	Effect
Santoro *et al.*[143]	Case series	13	Adverse events	During hospitalization	Levosimendan	Probably beneficial
Isogai *et al.*[140]	Retrospective	2110	Mortality	30 days	β-Blockers	Not beneficial
Dias *et al.*[141]	Retrospective	206	MACE	During hospitalization	Antiplatelet	Beneficial
					β-Blockers	Not beneficial
					Statins	Not beneficial
					ACEI	Not beneficial
Templin *et al.*[2]	Retrospective	1118	Mortality	1 year	β-Blockers	Not beneficial
					ACEI/ARB	Beneficial
Santoro *et al.*[142]	Meta-analysis	511	Recurrence	24–60 months	β-Blockers	Not beneficial
					ACEI/ARB	Not beneficial
					Aspirin	Not beneficial
					Statins	Not beneficial
Singh *et al.*[144]	Meta-analysis	847	Recurrence	19–33 months	β-Blockers	Not beneficial
					ACEI/ARB	Beneficial

International Expert Consensus Document on Takotsubo Syndrome, **EHJ 2018**

Trattamento a lungo termine



Templin C. et al. *Supplementary Appendix,* NEJM 2018

Conclusioni

La sindrome Takotsubo è un entità clinica che mima l‘infarto miocardico acuto

Nonostante le arterie coronariche epicardiche non siano coinvolte, la diagnosi di certezza può essere effettuata solo attraverso esame coronarografico.

La mancanza di studi farmacologici multicentrici e randomizzati non consente di avere una terapia standard
(ragionevole certezza per l‘uso di ACE-I/ARB in cronico).

Perciò un trattamento individualizzato diretto verso le comorbidità cardiovascolari e non cardiovascolari è consigliato.

Conclusioni

La sindrome Takotsubo e` una condizione molto piu` eterogenea di quanto inizialmente si pensasse.

Presentazioni atipiche e in pazienti atipici sono possibili

Inizialmente ritenuta benigna, ha invece una prognosi paragonabile a quella delle sindromi coronariche acute

Il legame psiche – cuore svolge un ruolo chiave ma ancora da comprendere fino in fondo.

« Le cœur a ses raisons que la raison ne connaît point. »