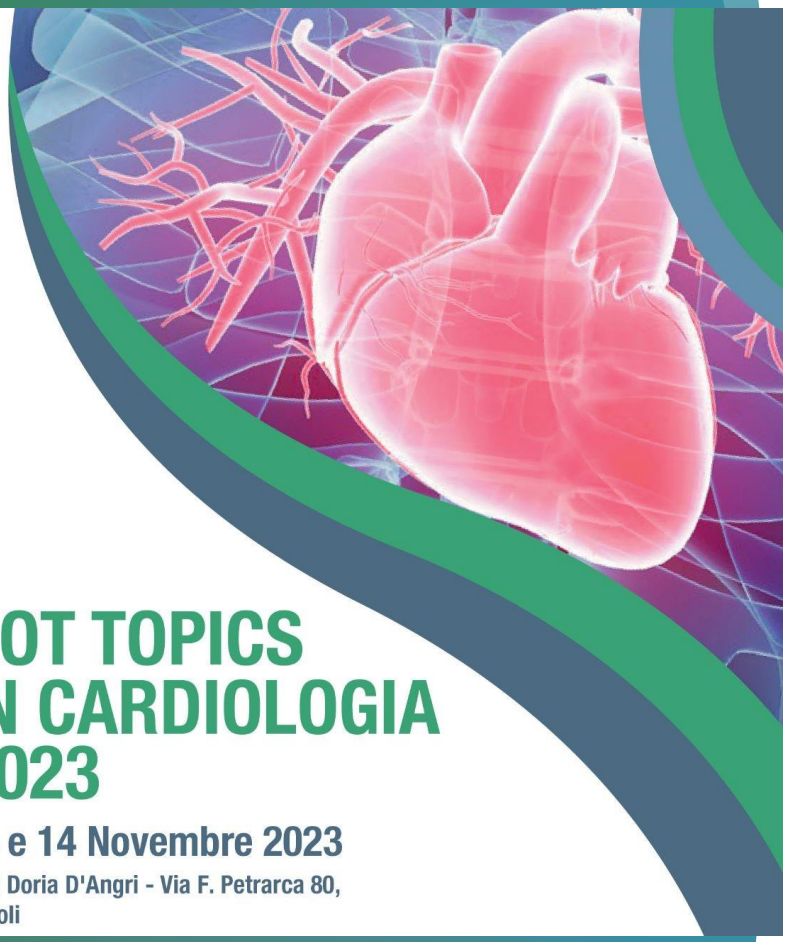


HOT TOPICS
IN CARDIOLOGIA
2023

13 e 14 Novembre 2023

Villa Doria D'Angri - Via F. Petrarca 80,
Napoli

# Management post dimissione della sindrome TAKOTSUBO: dall'approccio farmacologico alla prevenzione delle recidive


**Rodolfo Citro** MD, PhD, FESC

Cardio – Thoracic - Vascular Departement,
Director U.O.S.D Echocardiography
University Hospital
S. Giovanni di Dio e Ruggi D'Aragona, Salerno
rodolfo.citro@sangiovannieruggi.it

ORIGINAL RESEARCH

# Echocardiographic Correlates of Acute Heart Failure, Cardiogenic Shock, and In-Hospital Mortality in Tako-Tsubo Cardiomyopathy

Rodolfo Citro, MD,*† Fausto Rigo, MD,‡ Antonello D'Andrea, MD,§ Quirino Ciampi, MD,‖ Guido Parodi, MD,¶ Gennaro Provenza, MD,# Raffaele Piccolo, MD,** Marco Mirra, MD,†† Concetta Zito, MD,‡‡ Roberta Giudice, MD,†† Marco Mariano Patella, MD,§§ Francesco Antonini-Canterin, MD,‖‖ Eduardo Bossone, MD,† Federico Piscione, MD,†† Jorge Salerno-Uriarte, MD,* on behalf of the Tako-Tsubo Italian Network Investigators

**227 pts Major adverse events in 59 pts (25.9%)**

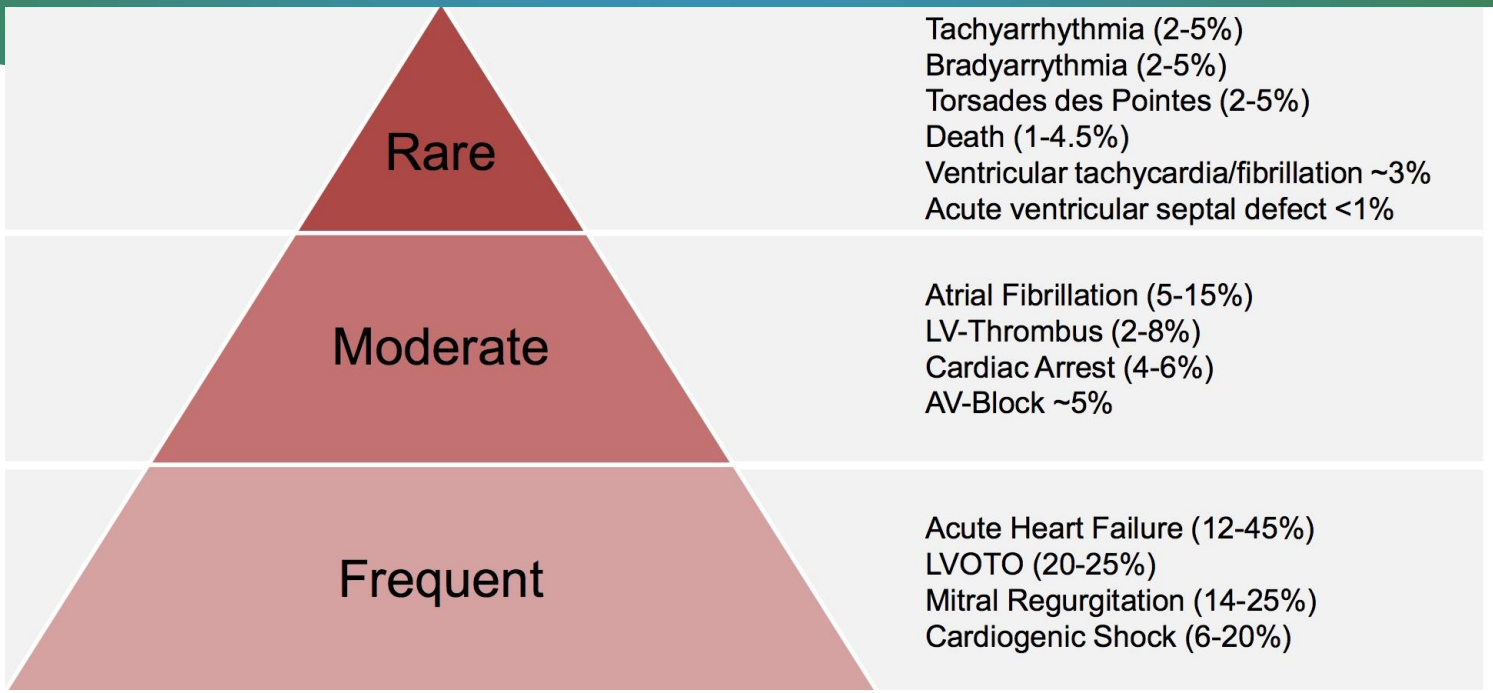
**Table 5. Hazard ratio (95% CI) for the major adverse events (acute heart failure, cardiogenic shock, and in-hospital mortality) in univariate and multivariate models.**

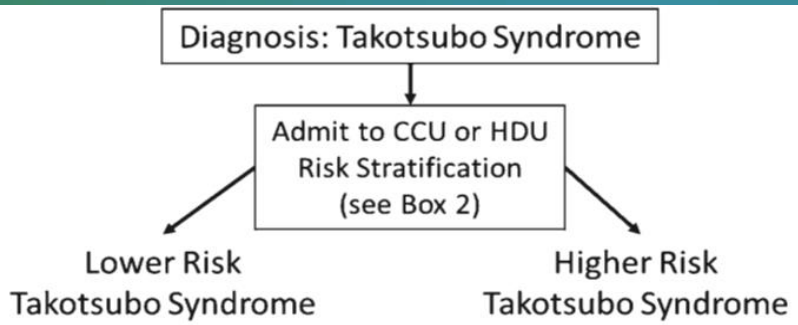
| Variables | Wald Chi-square | P-value | HR | 95% CI | Wald Chi-square | P-value | HR | 95% CI |
|---|---|---|---|---|---|---|---|---|
| Age ≥ 75 | 7.162 | 0.007 | 2.353 | 1.257-4.403 | 4.270 | 0.039 | 2.818 | 1.055-7.529 |
| Heart rate | 4.492 | 0.034 | 1.020 | 1.001-1.038 | | | | |
| Chest pain with dyspnea | 9.552 | 0.002 | 3.477 | 1.578-7.664 | | | | |
| BNP | 3.385 | 0.049 | 1.002 | 1.000-1.004 | | | | |
| LVEF | 15.398 | < 0.001 | 0.892 | 0.842-0.944 | 18.400 | <0.001 | 0.923 | 0.890-0.958 |
| E/e' ratio | 23.345 | < 0.001 | 1.266 | 1.150-1.393 | 6.410 | 0.011 | 1.131 | 1.028-1.244 |
| sPAP | 23.549 | < 0.001 | 1.086 | 1.050-1.122 | | | | |
| Moderate to severe MR | 23.532 | < 0.001 | 5.916 | 2.885-12.133 | 5.049 | 0.025 | 3.254 | 1.163-9.109 |
| RV involvement | 11.957 | 0.001 | 3.845 | 1.792-8.250 | | | | |
| LVOT obstruction | 7.992 | 0.005 | 3.173 | 1.425-7.067 | | | | |

BNP: brain natriuretic peptide; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract; MR: mitral regurgitation; RV: right ventricular; sPAP: pulmonary artery systolic pressure.

Citro R, et al. J Am Coll Cardiol Img 2014;7:119–29

# Prevalence of complications in TTS in INTER-TAK registry







European Journal of Heart Failure (2015)
doi:10.1002/ejhf.424
REVIEW

**Current state of knowledge on Takotsubo syndrome: a Position Statement from the Taskforce 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]

# Acute Treatment

*Stable patients at Lower Risk*

**Unstable patients at Higher Risk**

TTS therapy

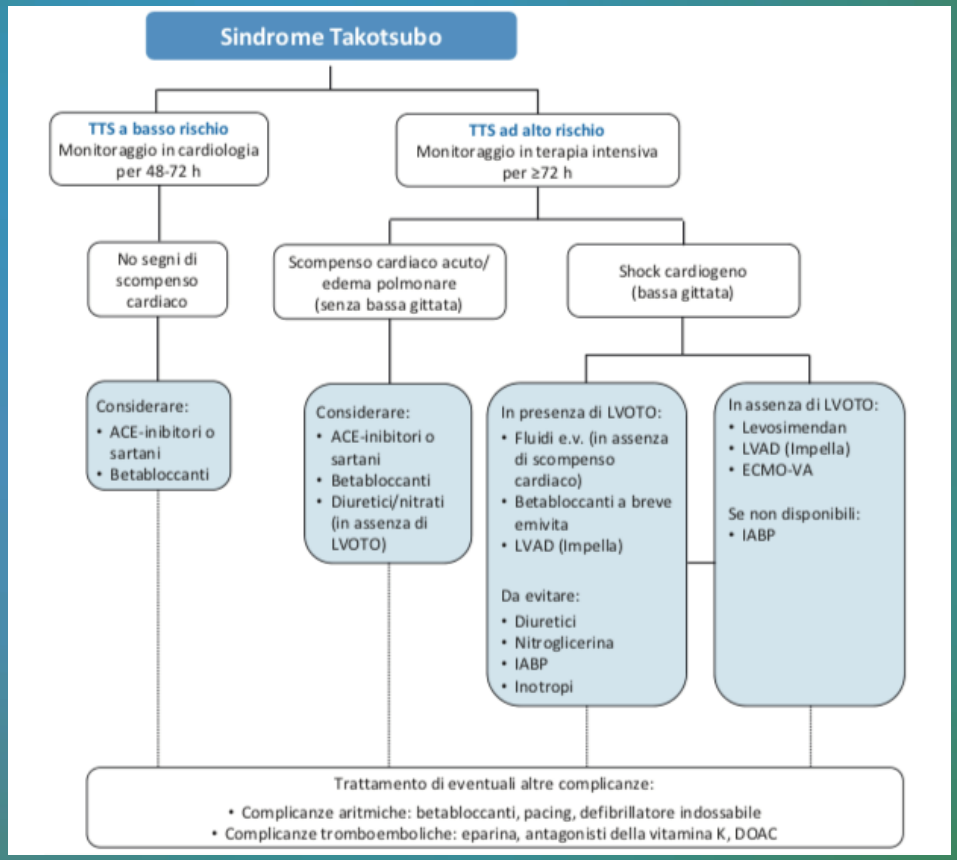
# Long term treatment

# Sindrome Takotsubo: concetti emergenti in tema di diagnosi, prognosi e terapia

Rodolfo Citro[1], Costantina Prota[1], Angelo Silverio[1], Eduardo Bossone[2]

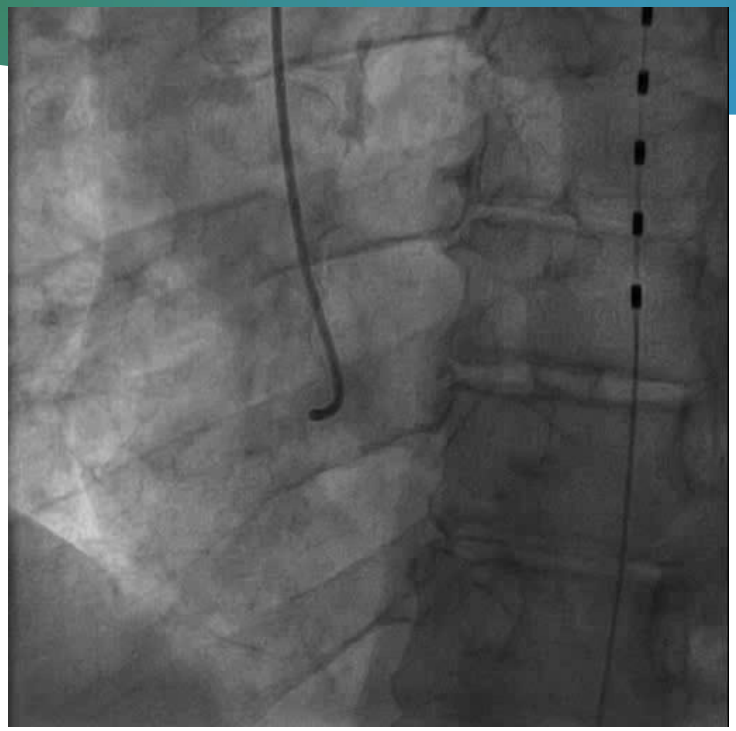
[1]*Dipartimento Cardio-Toraco-Vascolare, A.O.U. San Giovanni di Dio e Ruggi d'Aragona, Salerno*
[2]*Divisione di Cardiologia. A.O.R.N. Antonio Cardarelli, Napoli*

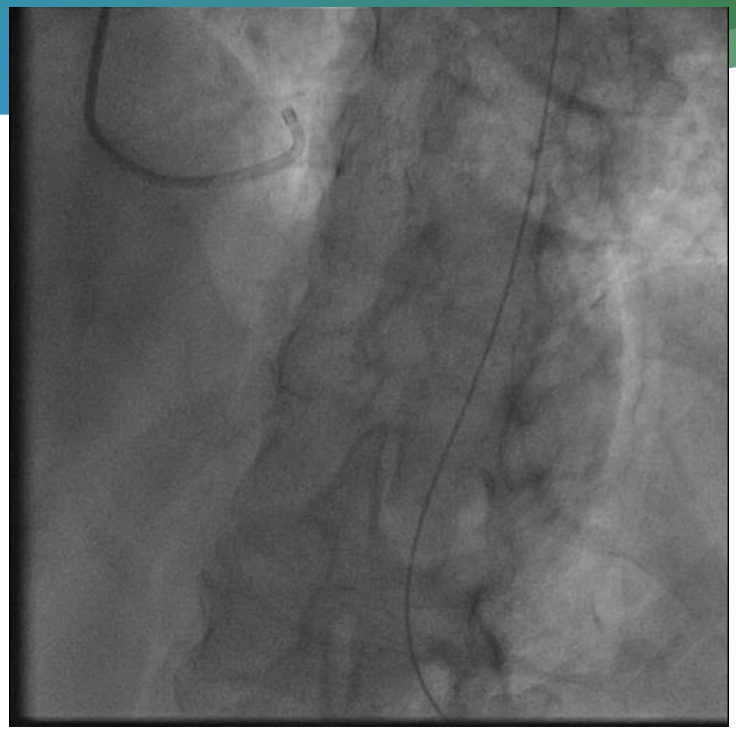
In mancanza di studi prospettici randomizzati, **non ci sono linee guida sul trattamento della TTS**, ma solo raccomandazioni frutto dell'esperienza di studi da singoli centri e registri osservazionali **(livello di evidenza C).**



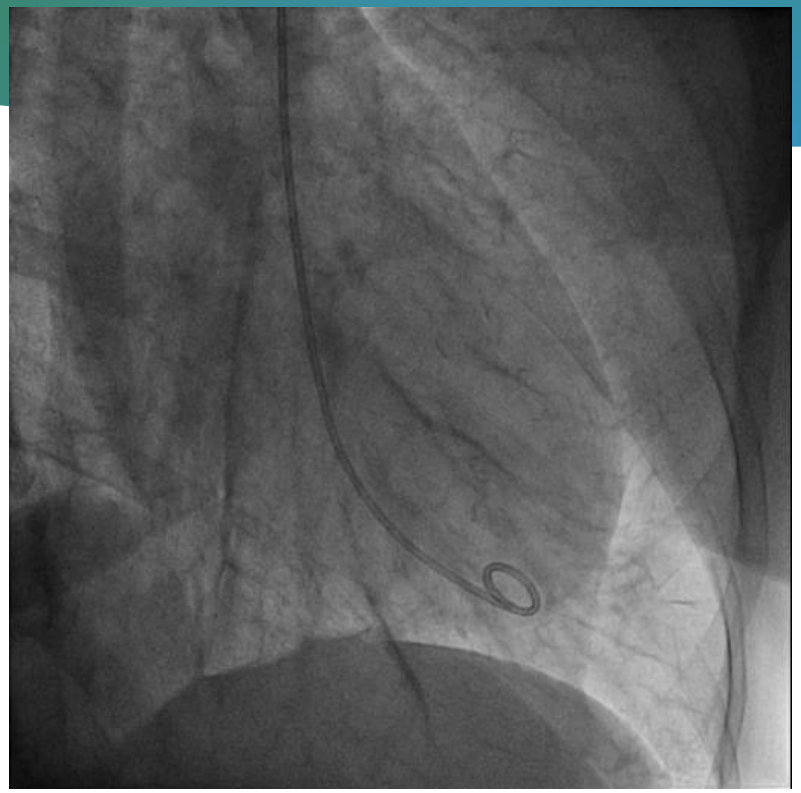

*Giorn Ital Cardiol 2019*

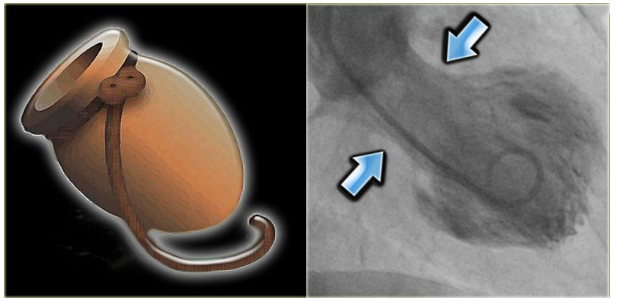
# Coronary Angiography





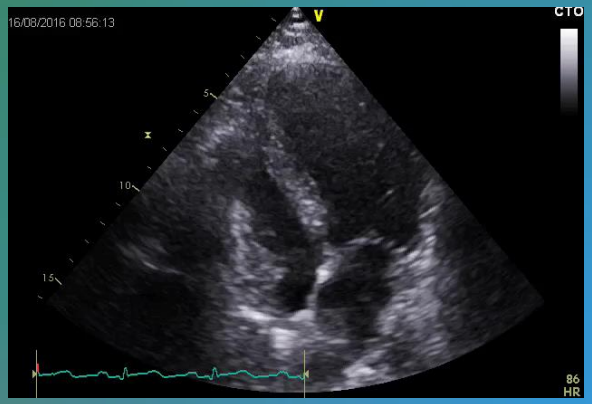
# VENTRICULOGRAPHY

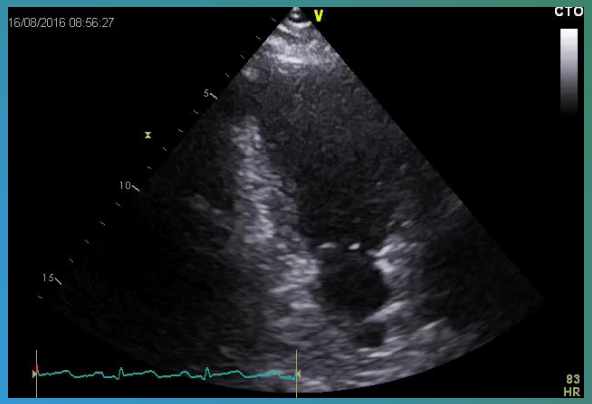


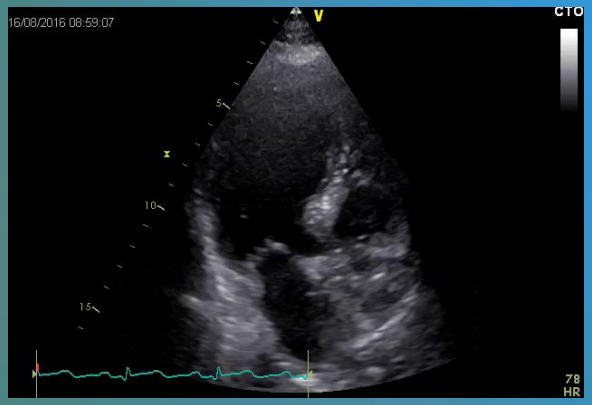


**Takotsubo syndrome?**

# TTE



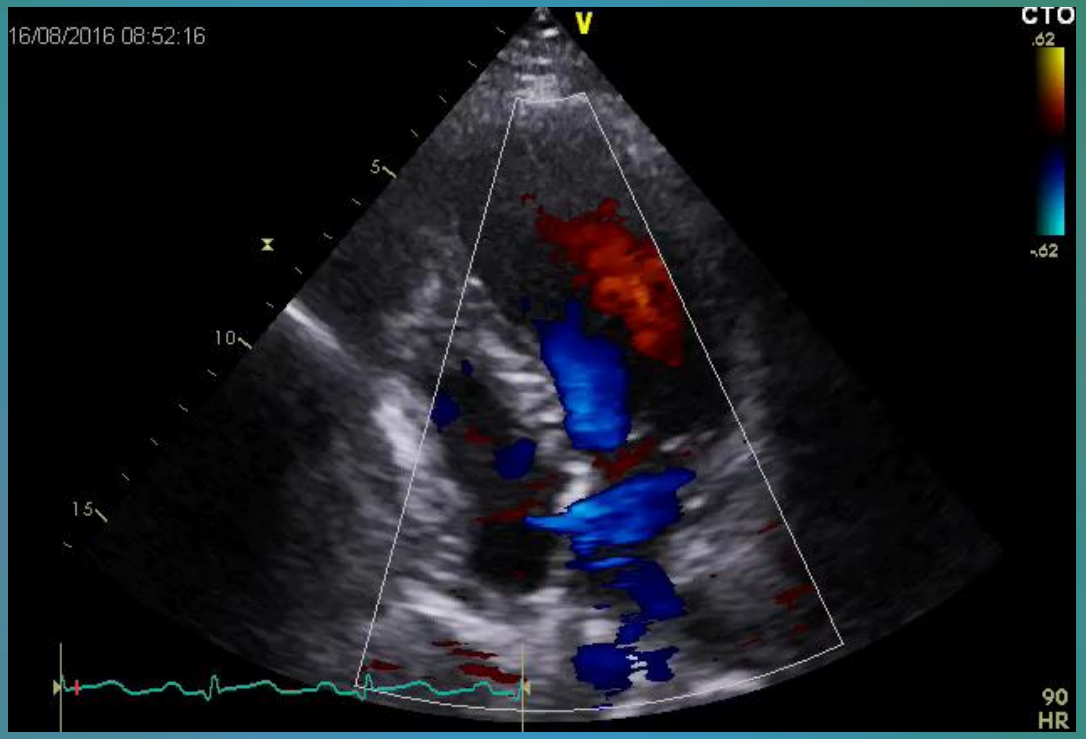



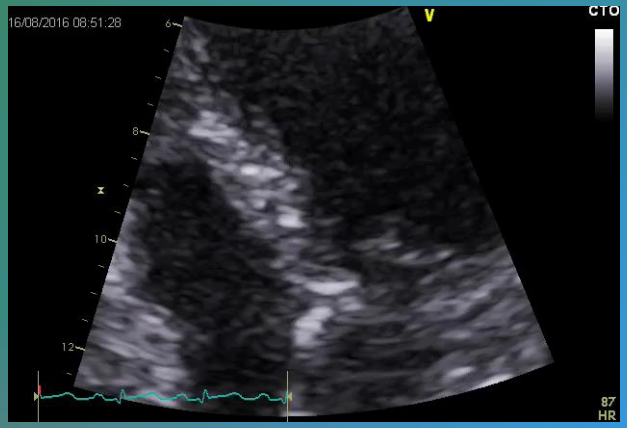

- **EF = 40%**

- **Akinesia of the LV apex**
- **Hyperkinesia oh the LV basal segments**

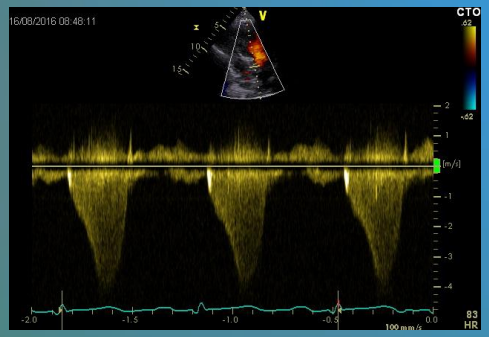
# Severe functional MR

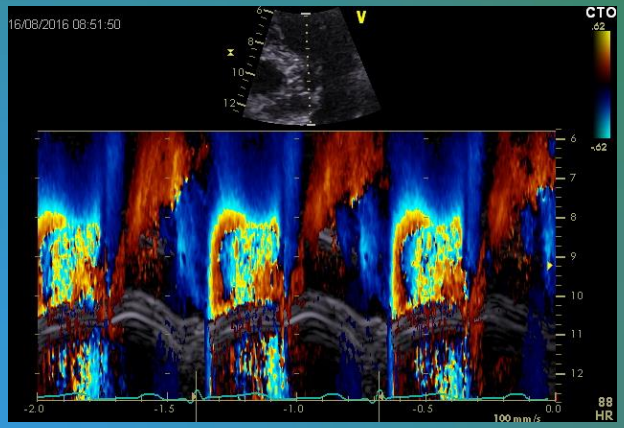


# LVOTO




SAM



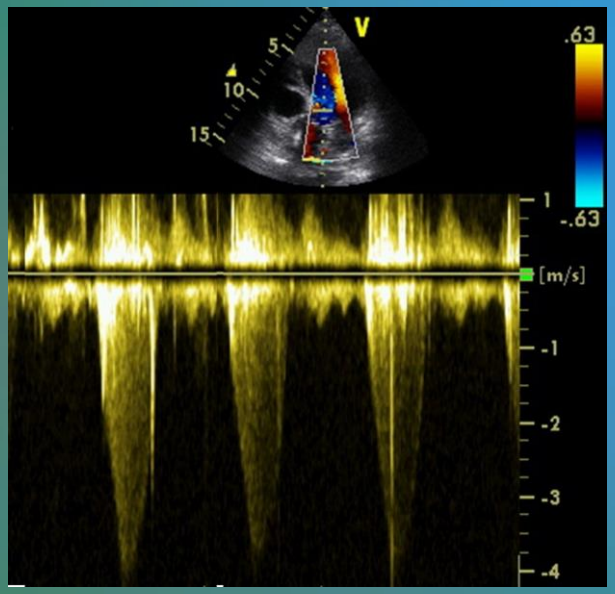

Color M-mode of LVOT showing systolic aliasing

**Vmax = 3.89 m/sec**
**Intraventricular gradient = 60.52 mmHg**

# Impella in Takotsubo syndrome complicated by left ventricular outflow tract obstruction and severe mitral regurgitation

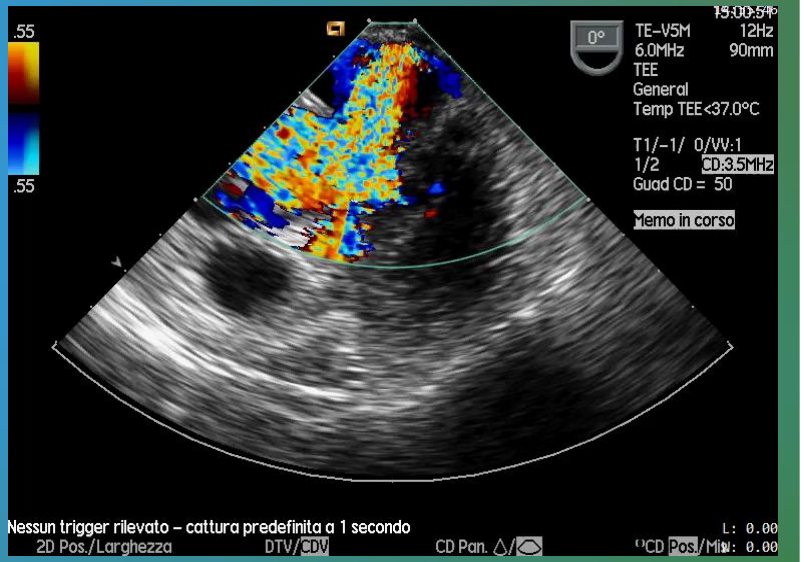
During catheterization, the patient was restless, cold, clammy, and with severe systemic hypotension (70/40 mmHg).

Owing to the blood desaturation to 82%, oxygen therapy delivered by facemask was promptly started.




**Intraventricular pressure gradient**

Peak gradient of 71 mmHg

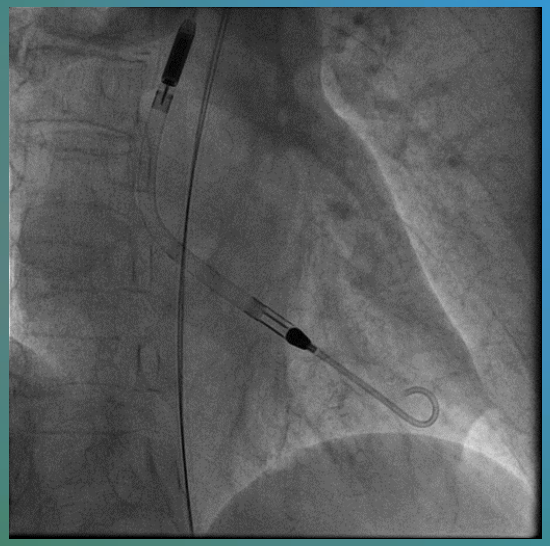


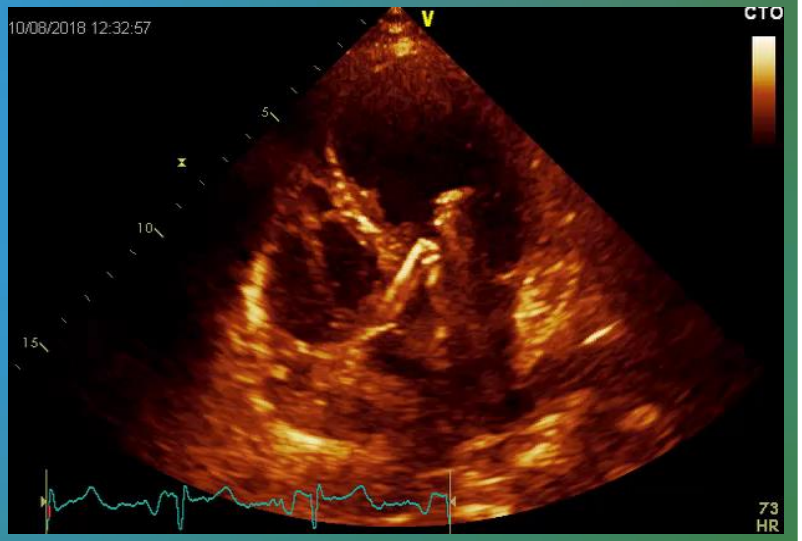

**Severe MR**

Attisano T, Silverio A, Citro R Eur Heart J HF 2019

# Impella in Takotsubo syndrome complicated by left ventricular outflow tract obstruction and severe mitral regurgitation

Owing to the persistence of a poor hemodynamic condition, an **Impella CP®** assist device was placed through the right femoral artery.

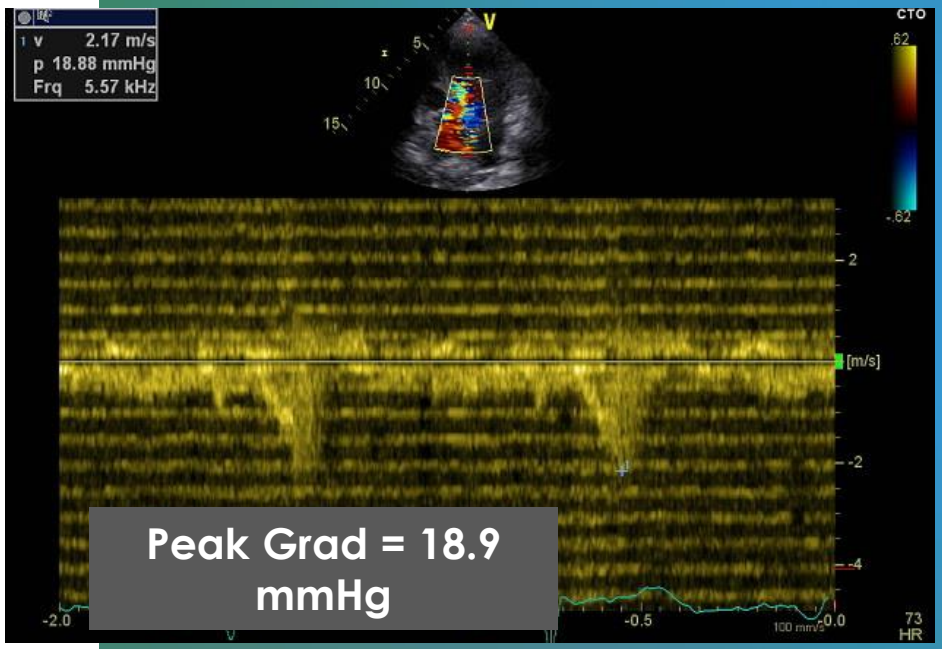


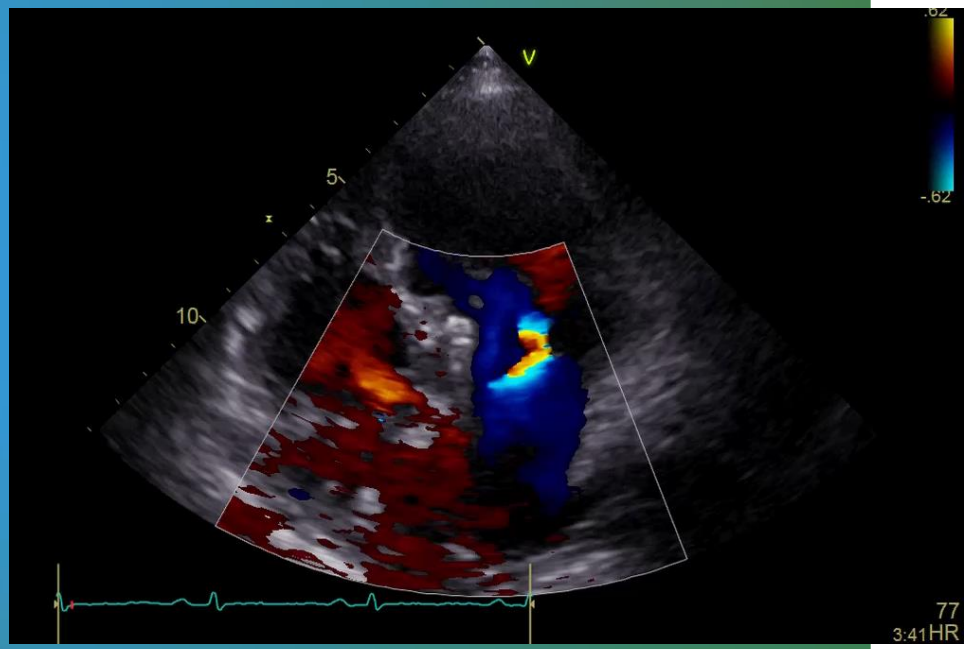


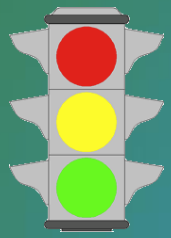

Attisano T, Silverio A, Citro R Eur Heart J HF 2019

# Clinical case

The hemodynamic status promptly improved (BP increased to 95/60 mmHg) and oxygen saturation raised to 93%.





# *In caso di LVOTO*

## *Do,*
## *do…maybe,*
## *don't*

La cauta somministrazione di liquidi associata all'utilizzo di betabloccanti a breve emivita per via endovenosa (specie esmololo), migliorando il riempimento cardiaco e riducendo l'ipercontrattilità dei segmenti basali, si sono dimostrati efficaci nel ridurre l'LVOTO

L'utilizzo di inibitori dell'enzima di conversione dell'angiotensina (ACE) e betabloccanti richiede cautela

In caso di LVOTO i nitrati ed i diuretici, riducendo il precarico e il postcarico, possono causare o peggiorare l'ostruzione intraventricolare e sono assolutamente controindicati.

L'utilizzo del contropulsatore aortico può peggiorare l'ostruzione dinamica poiché riduce il postcarico

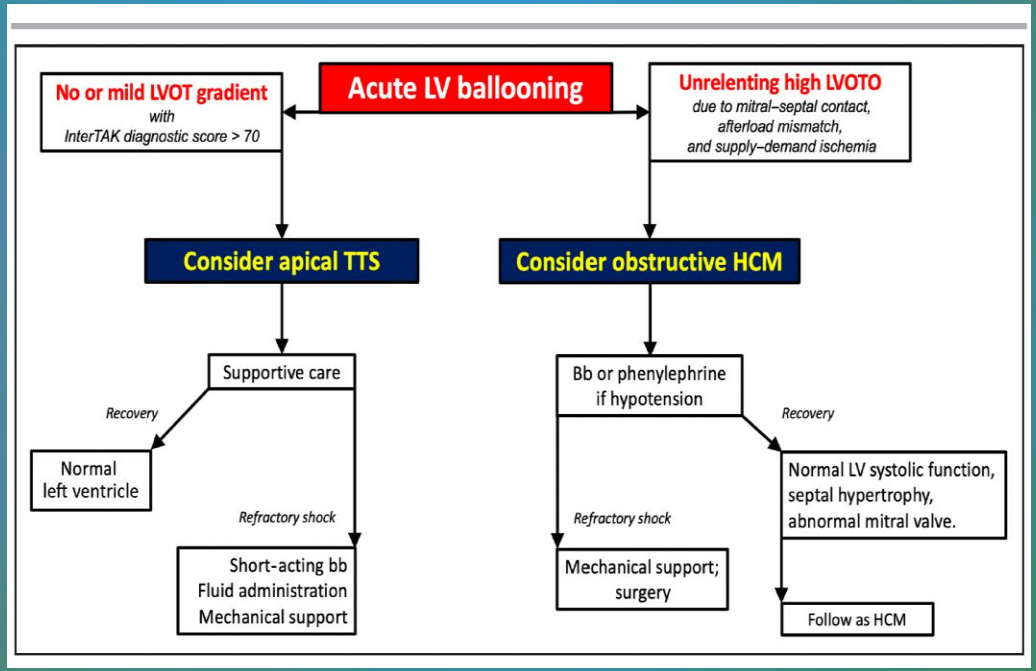
Citro R et al GIC settembre 2019

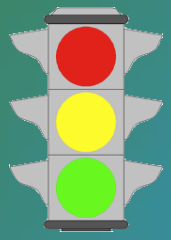
Journal of the American Heart Association

CONTEMPORARY REVIEW

# Obstructive Hypertrophic Cardiomyopathy and Takotsubo Syndrome: How to Deal With Left Ventricular Ballooning?

Rodolfo Citro, MD, PhD; Michele Bellino, MD; Elisa Merli, MD, PhD; Davide Di Vece, MD; Mark V. Sherrid, MD





# *In caso di Shock cardiogeno*

## *Do,*
## *do…maybe,*
## *don't*

L'utilizzo di dispositivi di assistenza ventricolare sinistra temporanei (Impella) o ossigenazione extracorporea a membrana (ECMO) come terapia ponte fino al recupero contrattile è indicato

Il levosimendan, un calcio-sensibilizzante ad azione inotropa positiva non catecolaminergica, può essere considerato quale alternativa ai classici farmaci inotropi

Le catecolamine come adrenalina, norepinefrina, dobutamina, dopamina, isoproterenolo o milrinone dovrebbero essere evitate.

Citro R et al GIC settembre 2019

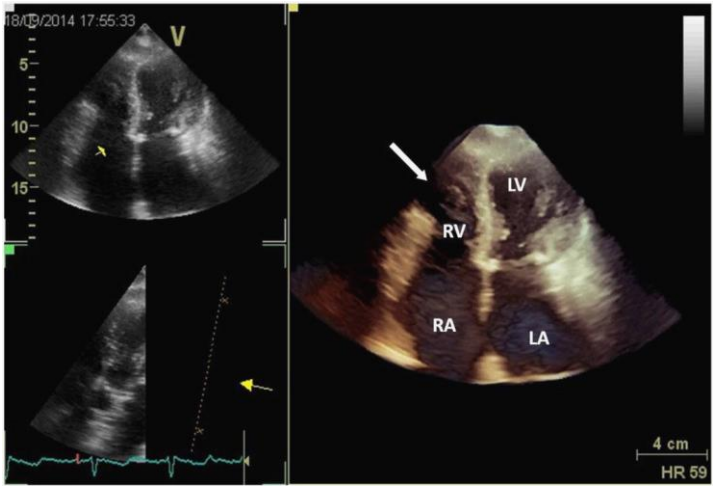
## Clinical profile and in-hospital outcome of Caucasian patients with takotsubo syndrome and right ventricular involvement

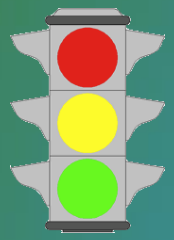
Rodolfo Citro [a,b,*], Eduardo Bossone [a], Guido Parodi [c], Scipione Carerj [d], Quirino Ciampi [e], Gennaro Provenza [f], Concetta Zito [d], Costantina Prota [a], Angelo Silverio [a], Olga Vriz [g], Antonello D'Andrea [h], Gennaro Galasso [a], Cesare Baldi [a], Fausto Rigo [i], Massimo Piepoli [j], Jorge Salerno-Uriarte [b], Federico Piscione [a], on behalf of the "Takotsubo Italian Network" Investigators (see Appendix)

Int. Journal of Cardiol. 2016

424 pts (mean age 69.1±11.5 yrs; female 92.2%) with diagnosis of TTS
RVi pts = 57 (13.4%)
No RVi pts = 367 (86.6%)

RVi was identified by the detection of severe akinesia or dyskinesia, localized exclusively at the apical and/or mid RV segments (biventricular ballooning), with sparing of the basal segments ("reverse McConnell's sign")





# *Trattamento in caso di edema polmonare*

***Do,***
***do…maybe,***
***don't***

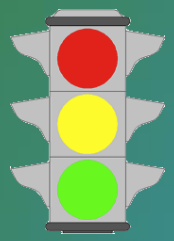
Nei casi di TTS con edema polmonare acuto e normale portata cardiaca

La terapia con:
- diuretici,
- inibitori dell'enzima di conversione dell'angiotensina (ACE)
- e betabloccanti è indicata

Nei casi di TTS complicata da insufficienza cardiaca acuta con insufficienza respiratoria la ventilazione meccanica non invasiva può essere necessaria; il suo utilizzo, tuttavia, andrebbe valutato attentamente in presenza di TTS biventricolare, per il possibile sovraccarico del ventricolo destro

La somministrazione di catecolamine andrebbe evitata, sia perché amplifica l'effetto adrenergico, sia perché esaltando ulteriormente la contrattilità basale peggiora un eventuale LVOTO.

Citro R et al GIC settembre 2019



# *In caso di complicanze aritmiche*

## *Do,*
## *do…maybe,*
## *don't*

Correggere eventuali alterazioni elettrolitiche ed interrompere la somministrazione di farmaci pro-aritmici nella fase acuta.

Gli agenti antiaritmici di classe III, come l'amiodarone o il sotalolo, dovrebbero essere utilizzati con cautela o evitati se possibile, in quanto possono prolungare ulteriormente l'intervallo QTc

La cardioversione elettrica può essere presa in considerazione, preferibilmente dopo l'esclusione della presenza di trombi intracardiaci mediante ecocardiografia o cardio RM

L'impiego di farmaci antiaritmici come mexiletina, e lidocaina è risultato efficace nei pazienti con TTS ed aritmie ventricolari.

Tutti i farmaci che potenzialmente prolungano l'intervallo QTc (antidepressivi, antibiotici) devono essere immediatamente interrotti.

Citro R et al GIC settembre 2019

# Intraventricular Thrombus Formation and Embolism in Takotsubo Syndrome

## Insights From the International Takotsubo Registry

Katharina J. Ding, Victoria L. Cammann, Konrad A. Szawan, Barbara E. Stähli, Manfred Wischnewsky, Davide Di Vece, Rodolfo Citro, Milosz Jaguszewski, Burkhardt Seifert, … Show all Authors

**Originally published** 26 Nov 2019 | https://doi.org/10.1161/ATVBAHA.119.313491 | Arteriosclerosis, Thrombosis, and Vascular Biology. 2019;0

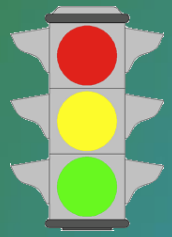
Intraventricular thrombus and embolism occur in **3.3%** of patients in the acute phase of TTS.

In a Firth bias-reduced penalized-likelihood logistic regression model

- *Apical type,*
- *LV EF ≤30%,*
- *Previous vascular disease, and*
- *White blood cell count on admission >10×10$^3$ cells/μL*

emerged as independent predictors for thrombus formation and embolism.

Arteriosclerosis, Thrombosis, and Vascular Biology



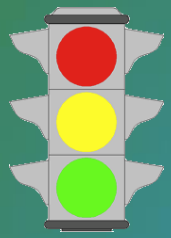
# *In caso di complicanze tromboemboliche*

## *Do,*
## *do…maybe,*
## *don't*

Nei pazienti con TTS con formazioni trombotiche endocavitarie documentate e/o episodi tromboembolici si raccomanda l'uso di anticoagulanti orali fino a quando non sia stata documentata la risoluzione completa del trombo e il recupero della funzione ventricolare sinistra fino a 3 mesi dall'ammissione in ospedale

Nei pazienti con pattern apicale e disfunzione ventricolare sinistra importante con FEVS <35%, la terapia anticoagulante profilattica con eparina o antagonisti della vitamina K può essere presa in considerazione, dopo aver escluso eventi emorragici come trigger della TTS

Citro R et al GIC settembre 2019



# *Trattamento*

***Do,***
***do…maybe,***
***don't***

Accesso alle unità ad intermedia o alta intensità di cura a seconda della stabilità del quadro clinico, in modo da poter essere costantemente monitorati e trattati in maniera appropriata

Una volta stabilita la diagnosi di TTS, il secondo farmaco antiaggregante (inibitore P2Y12, somministrato nell'iniziale sospetto di una SCA) andrebbe sospeso e l'aspirina continuata per 3 mesi dalla dimissione ospedaliera.

Citro R et al GIC settembre 2019

**Tabella 3.** Accorgimenti terapeutici in caso di sindrome Takotsubo secondaria, in diversi contesti clinici.

| Trigger | Implicazioni terapeutiche |
|---|---|
| Epilessia | Cautela nell'impiego di antiepilettici che prolungano il QTc |
| Polmonite, riacutizzazione BPCO | Somministrazione di fluidi o supporto meccanico<br>Evitare antibiotici che possano prolungare il QTc |
| Crisi asmatica | Cautela nell'impiego di agonisti beta-adrenergici |
| Shock anafilattico | Evitare sovradosaggio di epinefrina<br>Cortisonici, antistaminici e fluidi sono raccomandati<br>Considerare precocemente il supporto meccanico |
| Acidosi metabolica | Ripristinare l'equilibrio acido-base |
| Sepsi acuta | Somministrazione di fluidi o supporto meccanico<br>Evitare IABP, specialmente se è presente LVOTO<br>Evitare inotropi ed antibiotici che possono prolungare il QTc |
| Chirurgia in anestesia generale | Lenta induzione dell'anestesia e minimizzazione della risposta fisiologica a stimoli quali incisione, intubazione<br>Escludere altre cause di instabilità emodinamica (ipovolemia, anafilassi)<br>Eseguire ETT o ETE per valutare la funzione cardiaca e la presenza di LVOTO<br>Somministrazione di fluidi (soprattutto se LVOTO) |
| Postoperatorio | Escludere altre cause di instabilità emodinamica (ipovolemia, anafilassi)<br>Eseguire ETT o ETE per valutare la funzione cardiaca e la presenza di LVOTO<br>Somministrazione di fluidi (soprattutto se LVOTO)<br>Dispositivi di assistenza meccanica |

BPCO, broncopneumopatia cronica ostruttiva; ETE, ecocardiografia transesofagea; ETT, ecocardiografia transtoracica; IABP, contropulsatore aortico; LVOTO, ostruzione al tratto di efflusso ventricolare sinistro; QTc, intervallo QT corretto; TTS, sindrome Takotsubo.

Citro R et al GIC settembre 2019

Original research

# Beta-blockers are associated with better long-term survival in patients with Takotsubo syndrome

Angelo Silverio,[1] Guido Parodi ,[2] Fernando Scudiero,[3] Eduardo Bossone,[4] Marco Di Maio,[1] Olga Vriz ,[5] Michele Bellino,[1] Concetta Zito,[6] Gennaro Provenza,[7] Ilaria Radano,[7] Cesare Baldi,[7] Antonello D'Andrea,[8] Giuseppina Novo,[9] Ciro Mauro,[4] Fausto Rigo,[10] Pasquale Innelli,[11] Jorge Salerno-Uriarte,[12] Matteo Cameli ,[13] Carmine Vecchione,[1,14] Francesco Antonini Canterin,[15] Gennaro Galasso,[1] Rodolfo Citro [7,14]

*Heart* 2022;**0**:1–8. doi:10.1136/heartjnl-2021-320543

# Methods

This was an observational, multicentre, study including consecutive patients with TTS diagnosis enrolled in the TIN register from January 2007 to December 2018

Patients were divided in two study groups according to the prescription or not of BB therapy after discharge

Clinical outcome was assessed at the longest available FU

Primary outcome:

- All-cause death

Secondary outcomes:

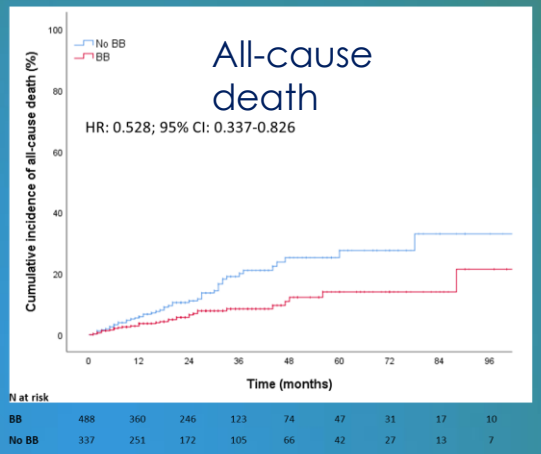
- TTS recurrence
- cardiac death
- non-cardiac death

**Silverio A, Citro R, et al. Heart 2022**

# Results

**825 pts (91.9% F):**
488 with BB
337 w/o BB

A

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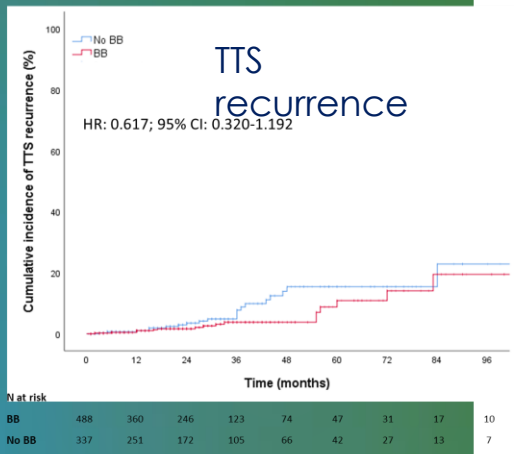


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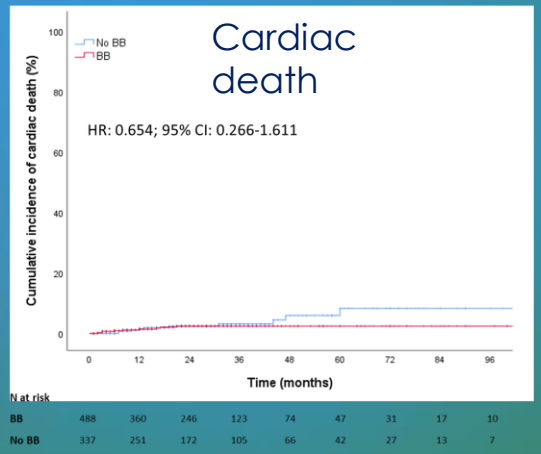


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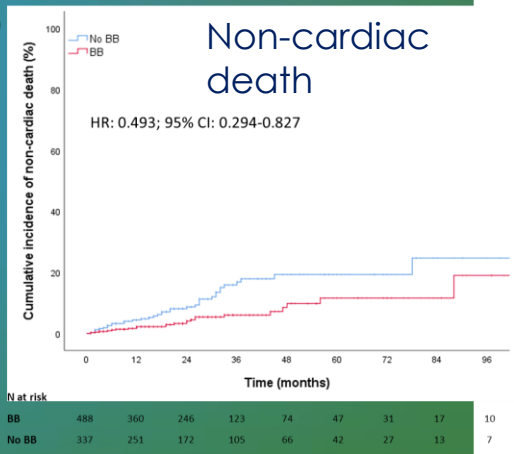


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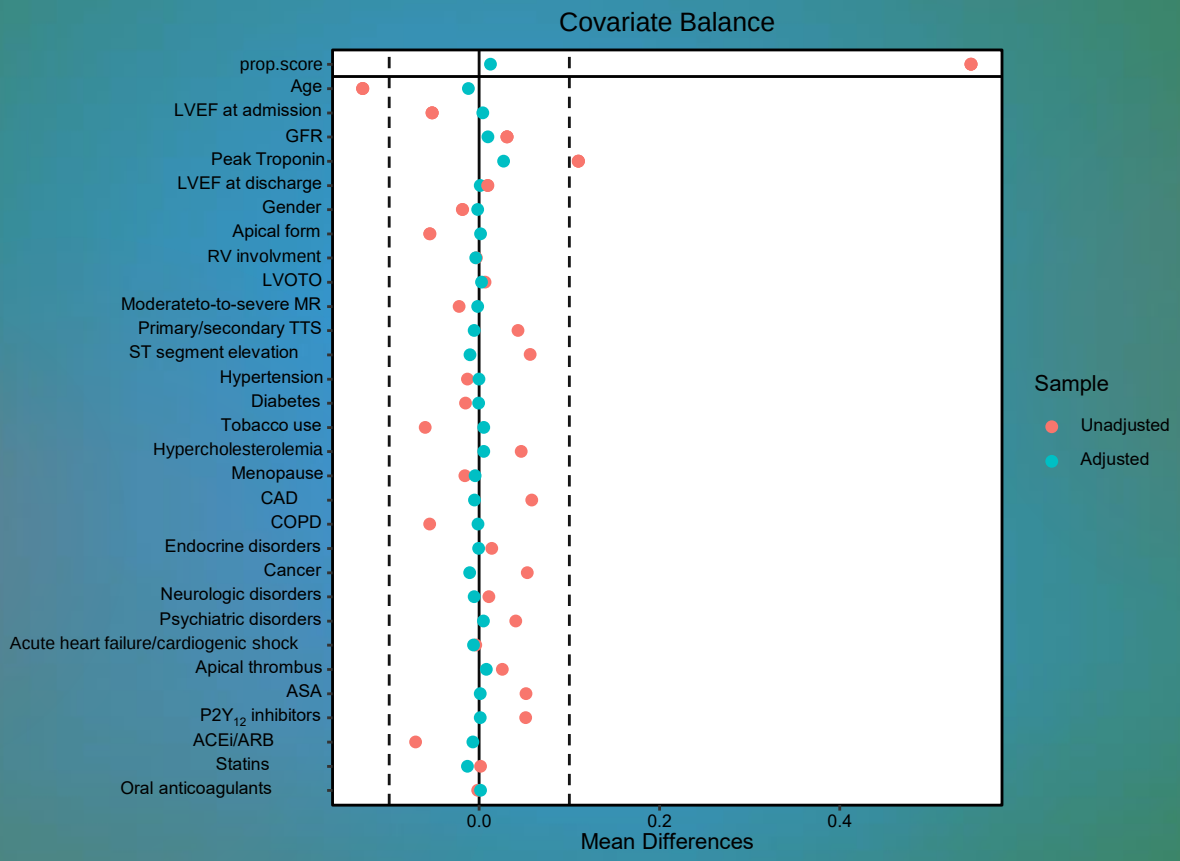
# Results

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# Adjusted Cox regression

Consecutive TTS patients enrolled in the TIN registry from January 2007 to December 2018
**N = 839**

In-hospital death, N = 14

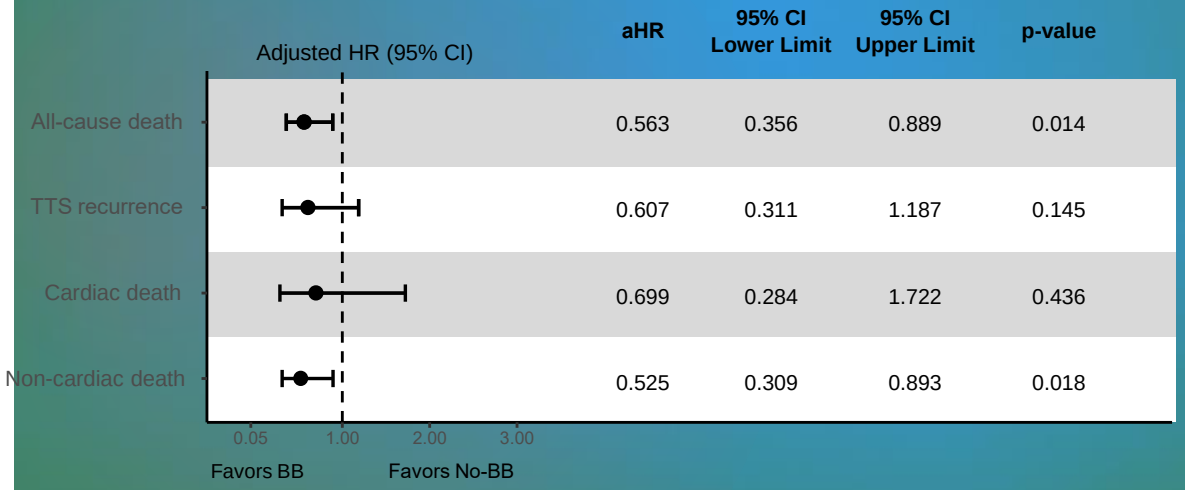
Patients entered in the outcome analysis*
**N = 825**

Patients treated with BB
**N = 488**

Patients not treated with BB
**N = 337**

* Median follow-up: 24.0 months

All cause death, N = 79
TTS recurrence, N = 36
Cardiac death, N = 19
Non-cardiac death, N = 60




| | aHR | 95% CI Lower Limit | 95% CI Upper Limit | p-value |
|---|---|---|---|---|
| All-cause death | 0.563 | 0.356 | 0.889 | 0.014 |
| TTS recurrence | 0.607 | 0.311 | 1.187 | 0.145 |
| Cardiac death | 0.699 | 0.284 | 1.722 | 0.436 |
| Non-cardiac death | 0.525 | 0.309 | 0.893 | 0.018 |

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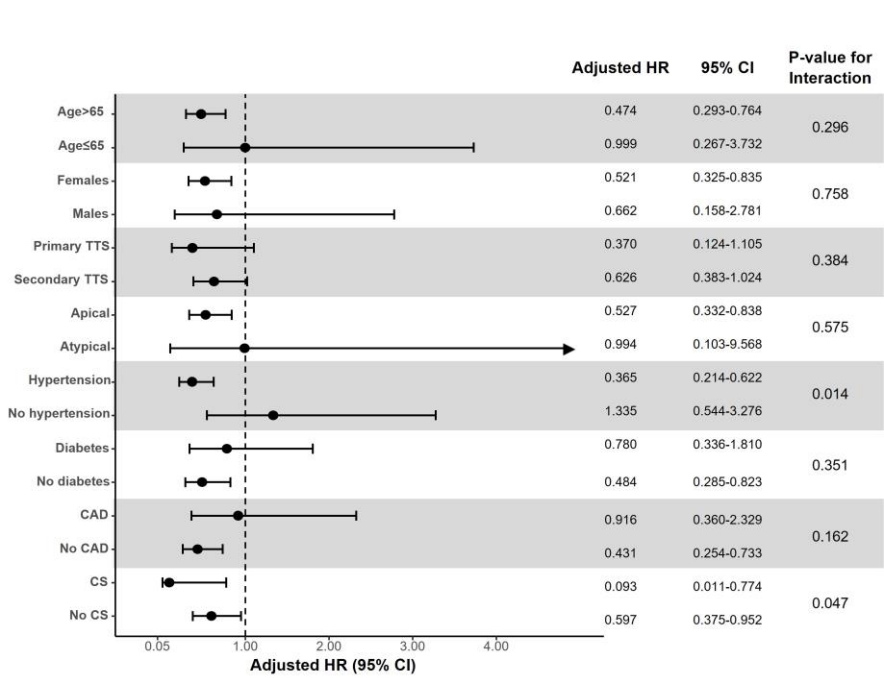
# BB and long-term outcome in TTS patients: subgroups analysis




Silverio A, Citro R, et al. Heart 2022

ESC European Society of Cardiology

European Journal of Preventive Cardiology (2023) **00**, 1–8
https://doi.org/10.1093/eurjpc/zwad237

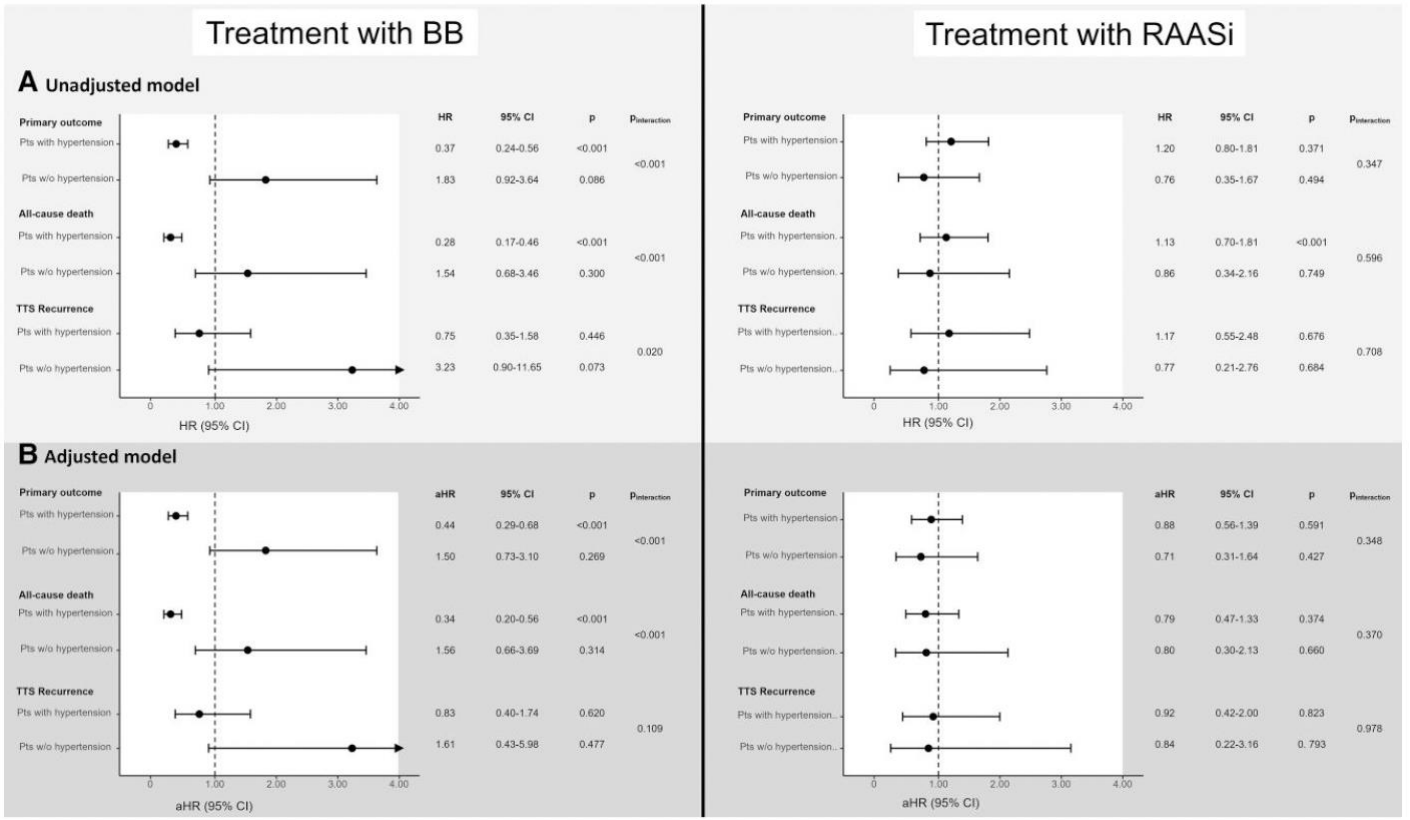
**FULL RESEARCH PAPER**
*Arterial hypertension*

# Arterial hypertension in patients with takotsubo syndrome: prevalence, long-term outcome, and secondary preventive strategies: a report from the Takotsubo Italian Network register

**Angelo Silverio[1], Eduardo Bossone[2], Guido Parodi[3], Fernando Scudiero [4], Marco Di Maio[1], Olga Vriz[5,6], Michele Bellino[1], Concetta Zito[7], Gennaro Provenza[8], Giuseppe Iuliano [8], Mario Cristiano[8], Giuseppina Novo[9], Ciro Mauro [2], Fausto Rigo[10], Pasquale Innelli[11], Jorge Salerno-Uriarte[12], Matteo Cameli[13], Giuliana Tremiterra[14], Carmine Vecchione [1,15], Francesco Antonini-Canterin[16], Gennaro Galasso[1], and Rodolfo Citro [8,15]* on behalf of the Takotsubo Italian Network**

# ARTERIAL HYPERTENSION AND TTS

# EFFECT OF BETABLOCKERS ON OUTCOME




SUB-GROUP ANALYSIS FOR THE RISK OF THE STUDY OUTCOMES BETWEEN PATIENTS TREATED OR NOT WITH BETA-BLOCKER (A), AND PATIENTS TREATED OR NOT WITH RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM INHIBITORS (B). AHR, ADJUSTED HAZARD RATIO; BB, BETA-BLOCKERS; CI, CONFIDENCE INTERVAL; HR, HAZARD RATIO; RAASI, RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM INHIBITORS; TTS, TAKOTSUBO SYNDROME.

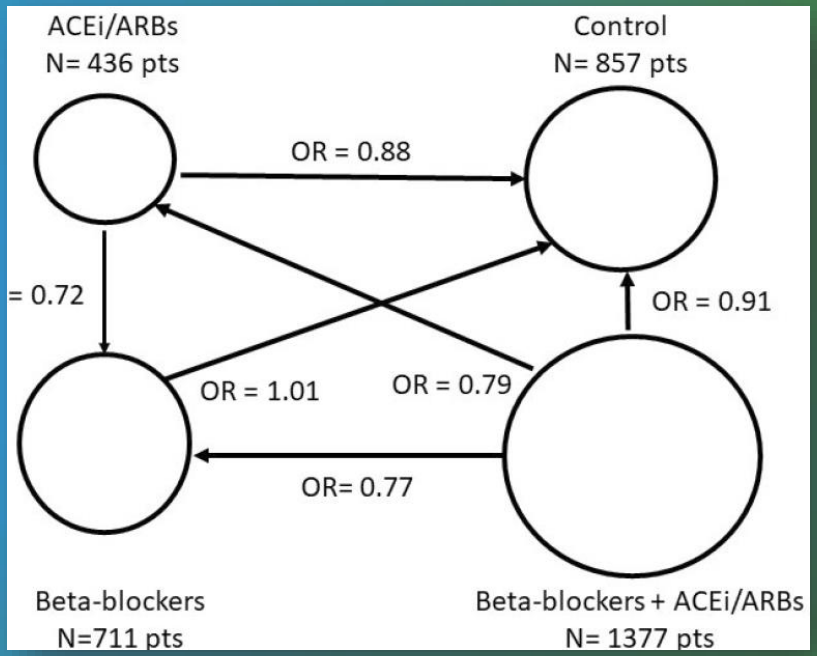
# Recidive: network meta-analysis

Systematic review

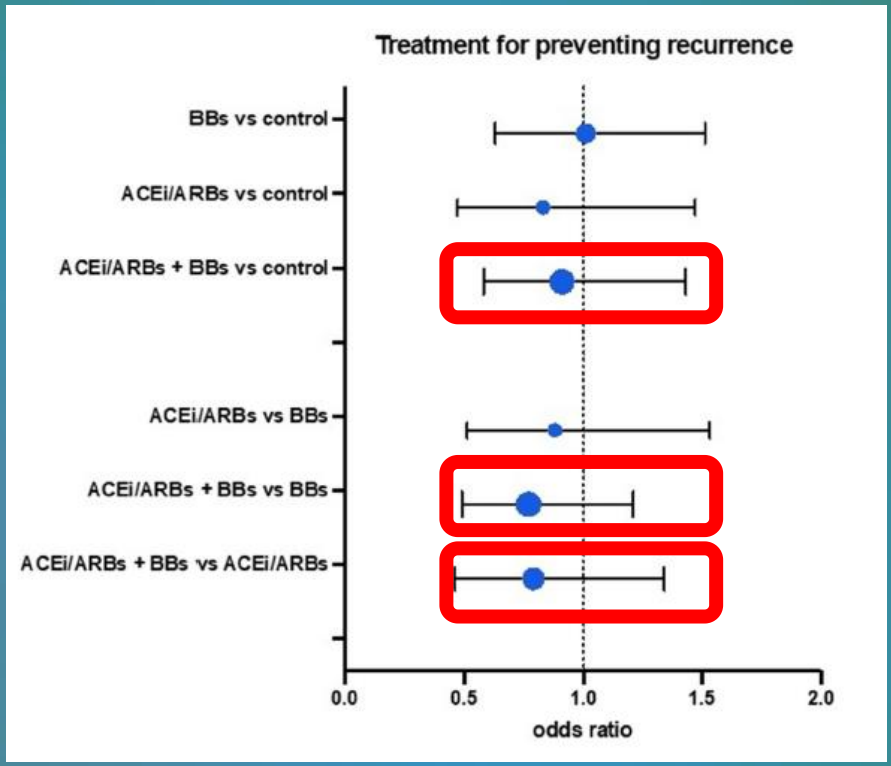
## Beta-blockers and renin-angiotensin system inhibitors for Takotsubo syndrome recurrence: a network meta-analysis

Francesco Santoro [1], Scott Sharkey [2], Rodolfo Citro [3], Tetsuji Miura,[4] Luca Arcari,[5,6] Jose Angel Urbano-Moral,[7] Thomas Stiermaier [8], Ivan Javier Nuñez-Gil [9], Angelo Silverio,[10] Nicola Di Nunno [11], Ilaria Ragnatela,[11] Rosa Cetera,[11] Junichi Nishida,[4] Ingo Eitel,[8] Natale Daniele Brunetti [11]

Santoro, Scott SW, Citro, Brunetti et al. Heart 2023



# Recidive: network meta-analysis

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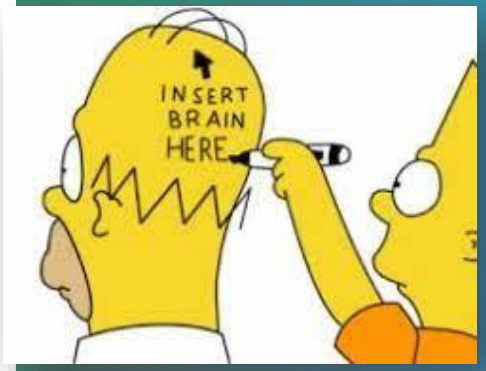
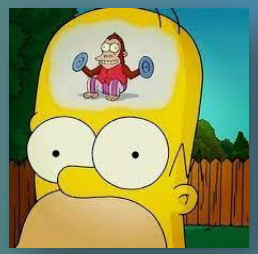
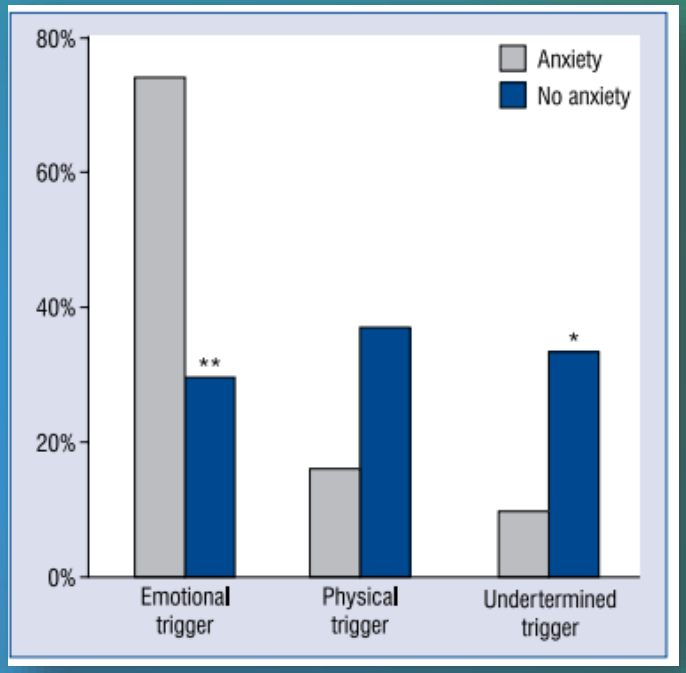
# Trattamento recidive






Cardiol J 2018;25(4):495-500.

# Conclusioni

Long-term treatment of Takotsubo syndrome may benefit of heart failure medication especially among those patients with cardiovascular comorbidities;

Randomized prospective trials for drug therapy are needed;

A tailored approach especially for those patients with emotional TTS should be considered, including psychosocial support.

# Thank You