



Sessions de dilluns d'actualització en cardiologia del curs 2021-2022

Miocardiopatia d'estrès: Tractament mèdic

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Esquema de la presentación

1. Introducción

- Situación actual
- Fisiopatología

2. Manejo clínico

- Tratamiento agudo durante el proceso de diagnóstico
- Tratamiento agudo de la STT y sus complicaciones
- Tratamiento a largo plazo

3. Perspectivas de futuro

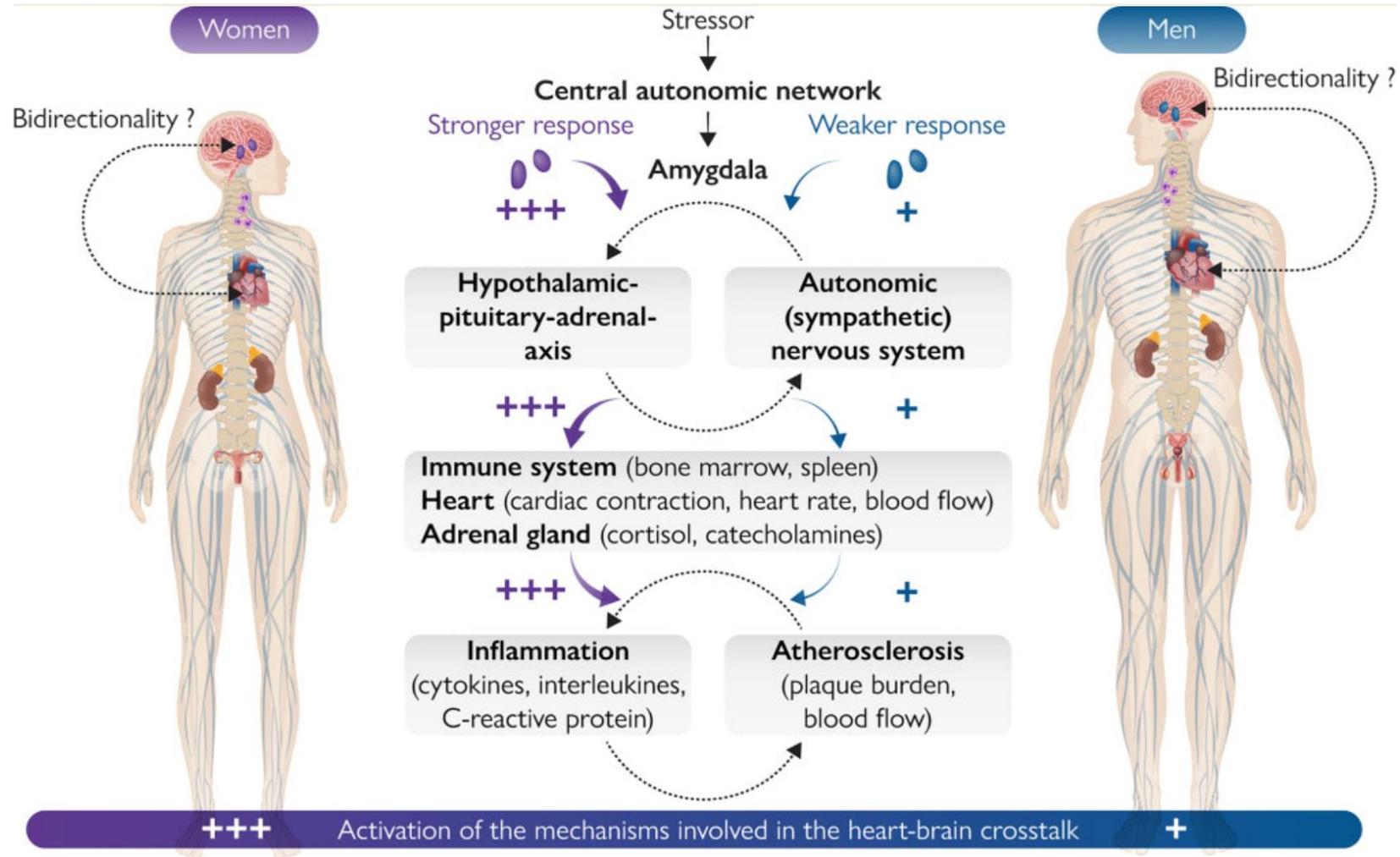
1. Introducción: Situación actual

- Síndrome Takotsubo (STT)
- Heterogénea
- No benigna
- No ensayos clínicos → estudios observacionales y opinión de expertos

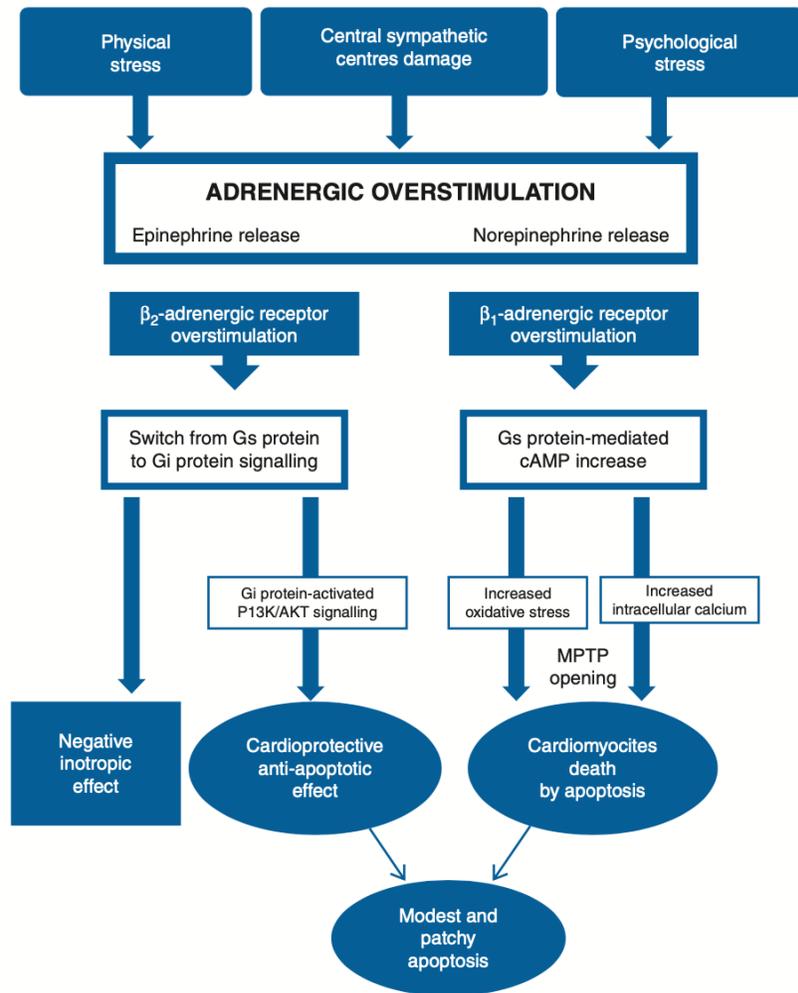
	Previous notion	Current evidence
Terminology	Takotsubo cardiomyopathy	Takotsubo syndrome
Epidemiology	Rare disease	Possibly underdiagnosed
	Japan	Global burden
	Asian descent	Various ethnic groups and races
	Women	Both sexes (♀ >> ♂)
	Elderly	All age groups
Triggering factors	Emotional triggers	Physical, emotional, both or no triggering factor
	Negative life events	Negative and pleasant life events
	Absence of pheochromocytoma	Phaeochromocytoma can be present
	Absence of neurologic injury	Acute neurologic disorders can be present
Morphological variants	Apical ballooning	Apical, midventricular, basal and focal form
Coronary artery disease	Absence of coronary artery disease	Coronary artery disease can be present
Outcome	Benign prognosis	Substantial morbidity and mortality
Recovery	Complete recovery	Concept of "incomplete recovery"

Tratamiento individualizado

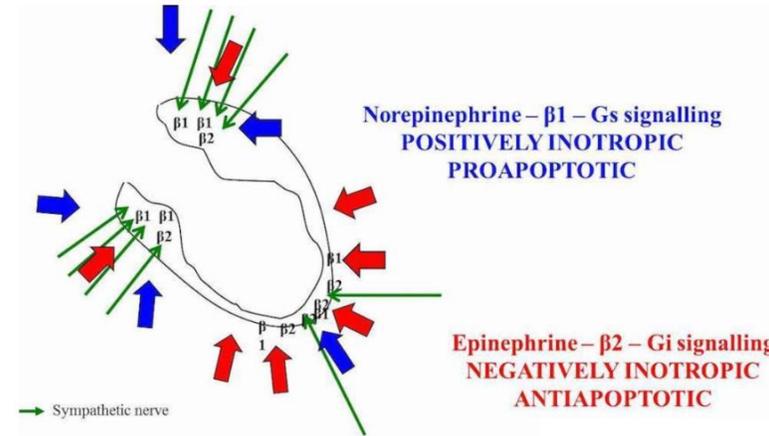
1. Introducción: Fisiopatología



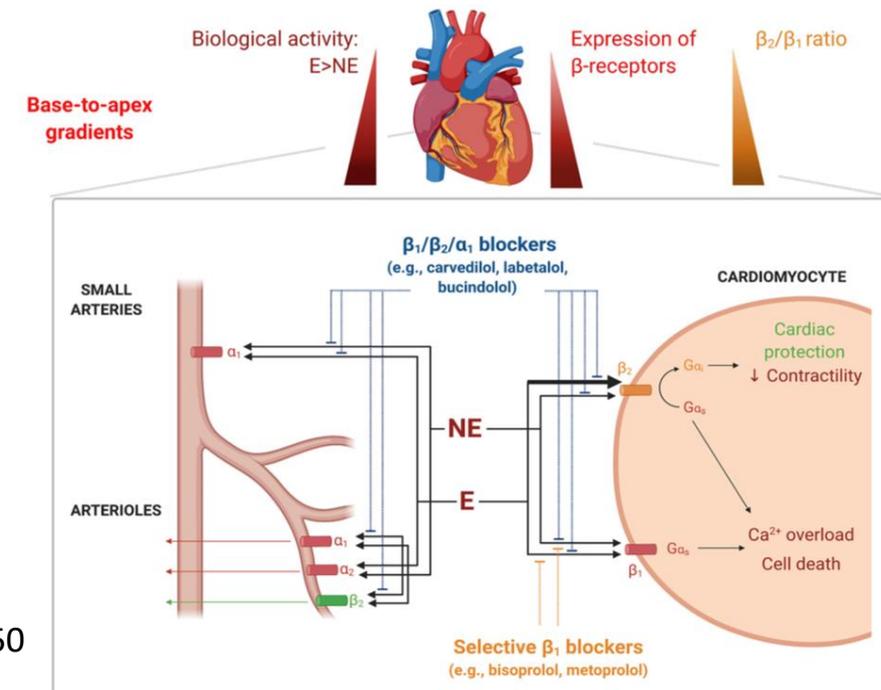
1. Introducción: Fisiopatología



Mazzeo AT. Br J Anaesth. 2014;112(5):803-15

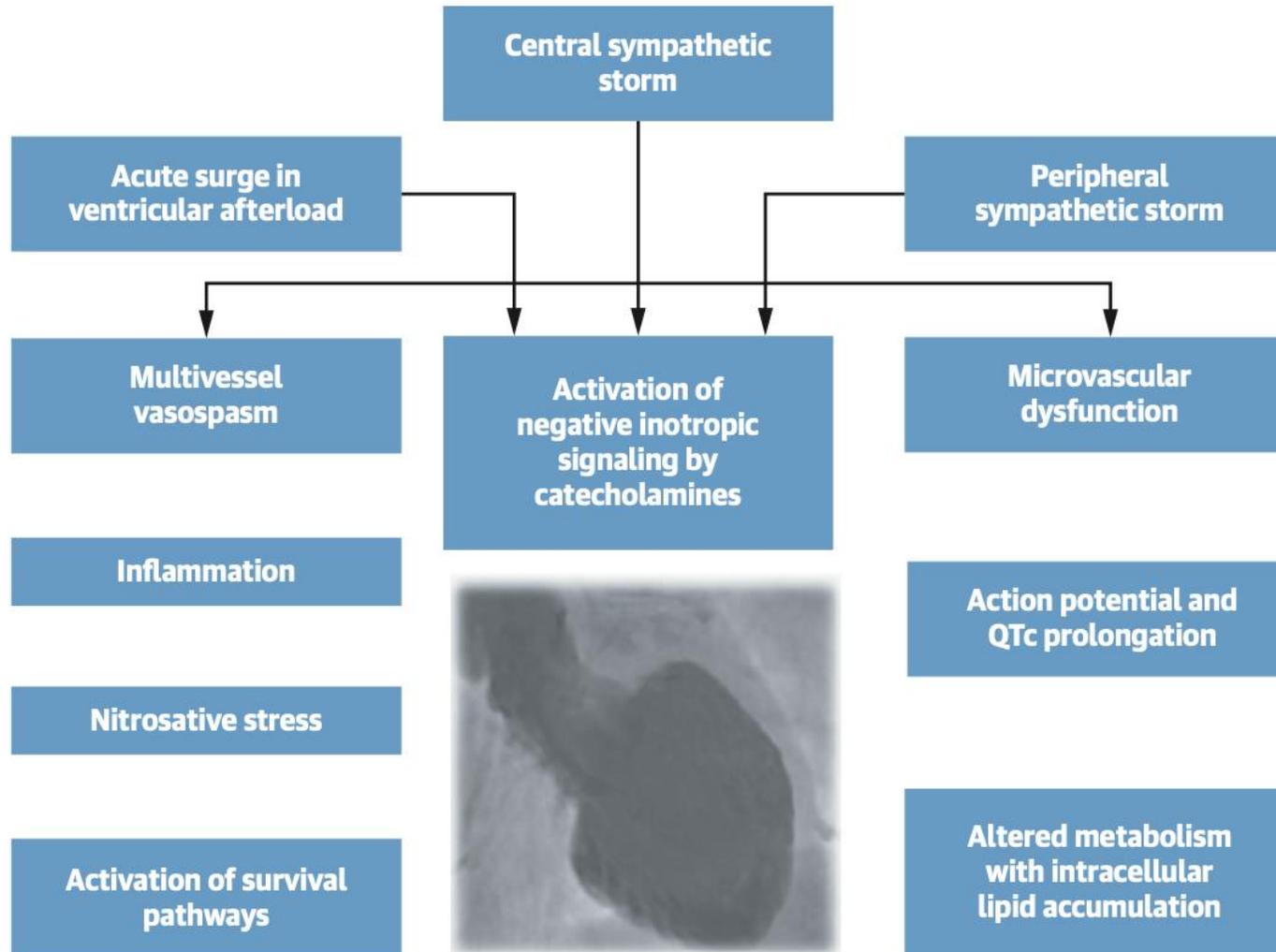


Kato K. Heart. 2017;103(18):1461-9



Aimo A. Int J Cardiol. 2021;333:45-50

1. Introducción: Fisiopatología



2. Manejo clínico

a. Tratamiento agudo durante el proceso de diagnóstico

b. Tratamiento agudo del STT y sus complicaciones

c. Tratamiento a largo plazo

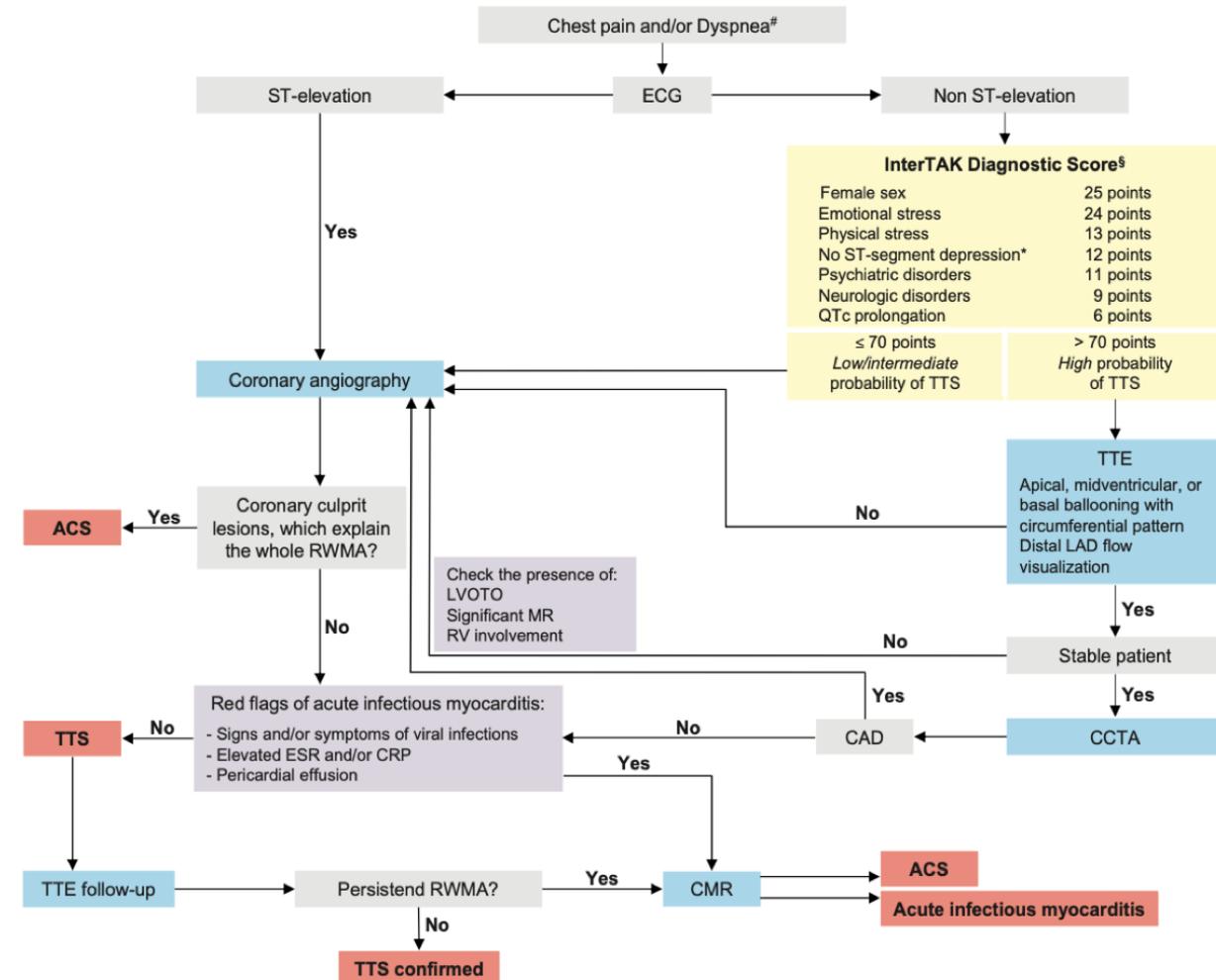
a. Tratamiento agudo previo al diagnóstico

FASE PRE-HOSPITALARIA

- ✓ Manejo inicial como SCA
- ✓ Traslado a Centro con Cardiología

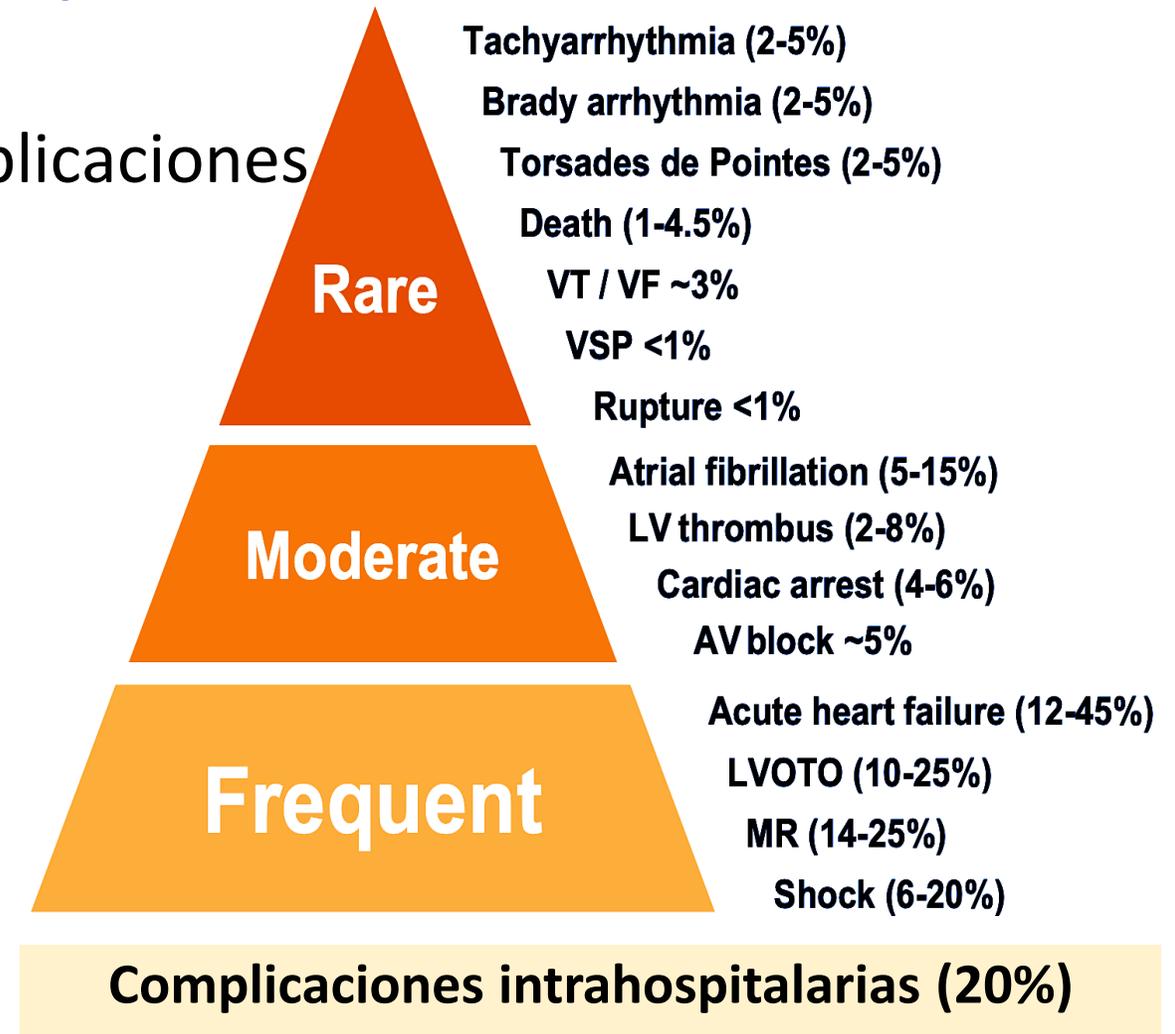
FASE HOSPITALARIA

- ✓ Manejo SCA-Antitrombóticos
- ✓ Diagnóstico:
 - ✓ Ecocardiograma
 - ✓ Coronariografía

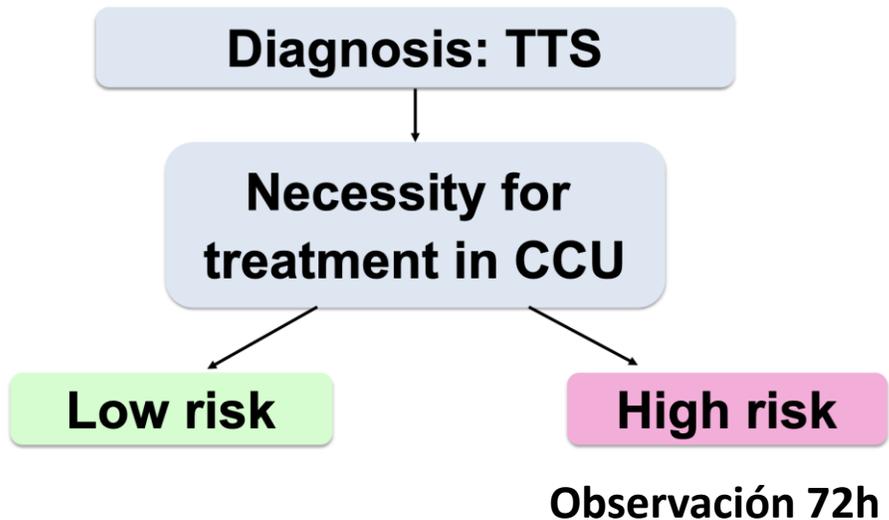


b. Fase aguda: STT SIN complicaciones

- **Observación clínica-** Riesgo de complicaciones



* Evaluación de riesgo de complicaciones

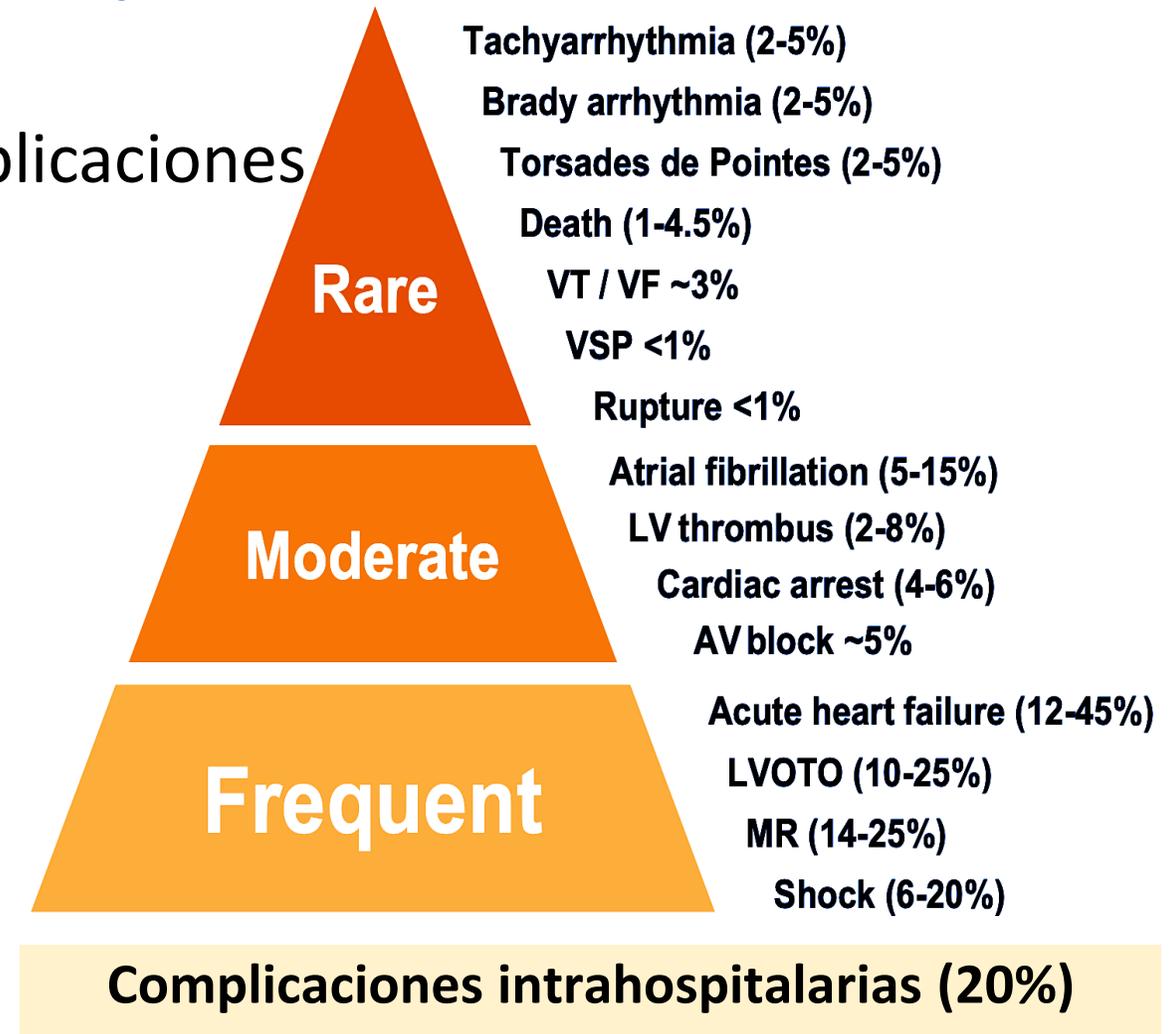


Risk factor	Higher risk	Lower risk	Risk factor	Higher risk	Lower risk
MAJOR RISK FACTORS			MINOR RISK FACTORS		
Age	≥75 years	See minor risk factors ^a	Age	70–75 years	<70 years
Systolic BP	<110 mmHg	≥110 mmHg	ECG		
Clinical pulmonary oedema ^b	Present	Absent	QTc	≥500 ms	<500 ms
Unexplained syncope,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

High risk: 1 factor mayor o 2 menores

b. Fase aguda: STT SIN complicaciones

- **Observación clínica-** Riesgo de complicaciones
- **No suspender tratamientos previos**



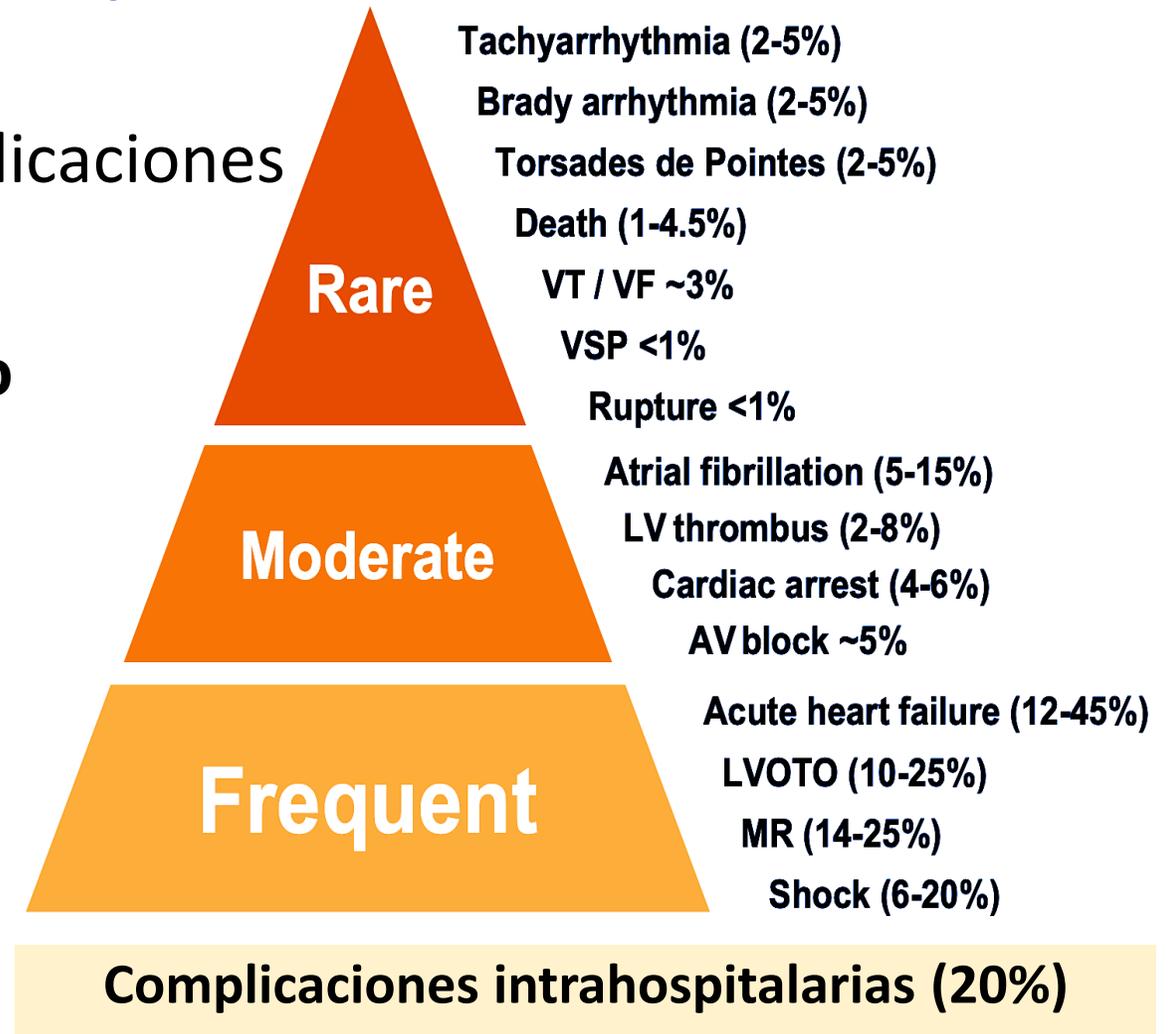
b. Fase aguda: STT SIN complicaciones

- **Observación clínica:** Riesgo de complicaciones
- **No suspender tratamientos previos**
- **Valorar la necesidad de tratamiento**

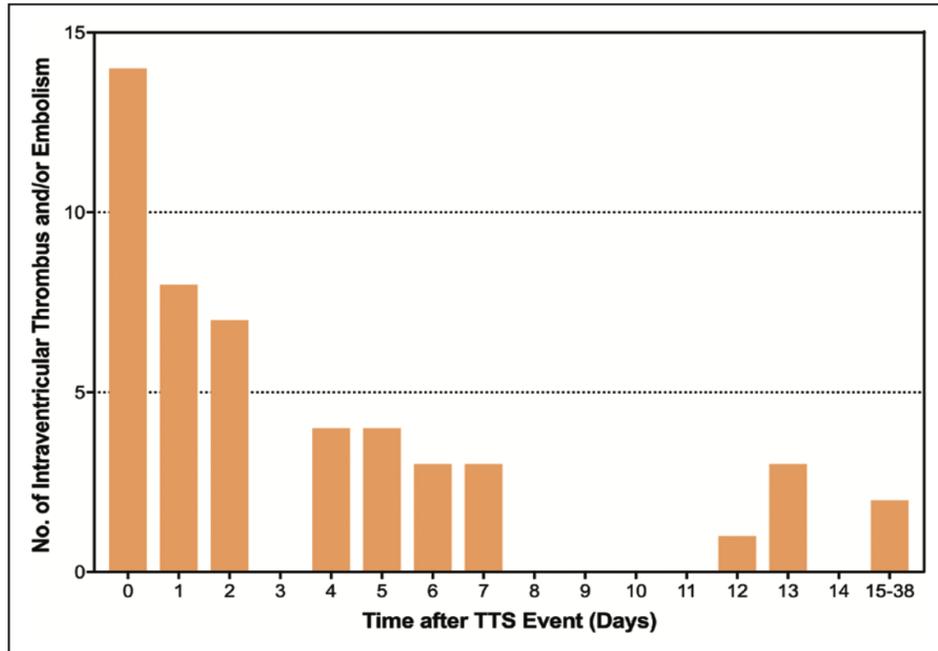


“Primum non nocere”

Riesgo tromboembólico
Riesgo arrítmico

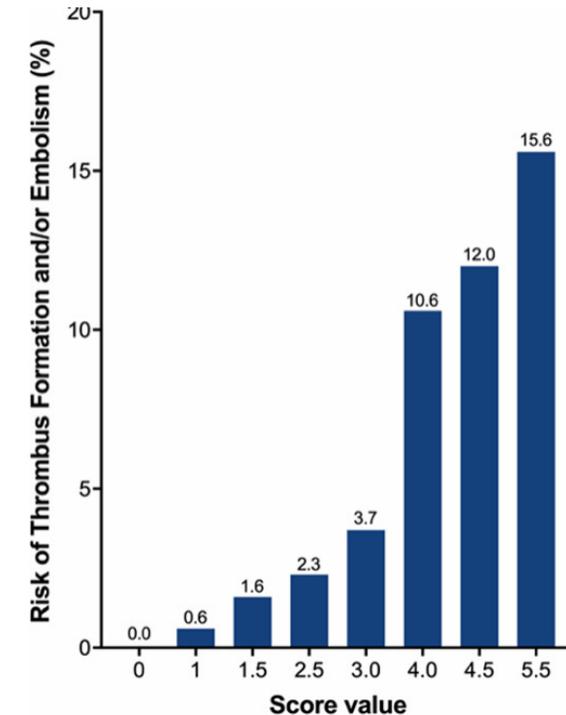


* Riesgo de fenómenos tromboembólicos



Momento de presentación del trombo IV o embolismo en TTS

InterTAK Trombus Risk Score	
Variable	Points
Apical type	1.5
Previous vascular disease*	1.5
LVEF ≤ 30 % on admission	1.5
First WBC >10x10 ³ cells/μl	1
Total Points	
≤ 3 points	> 3 points
Low risk	High risk



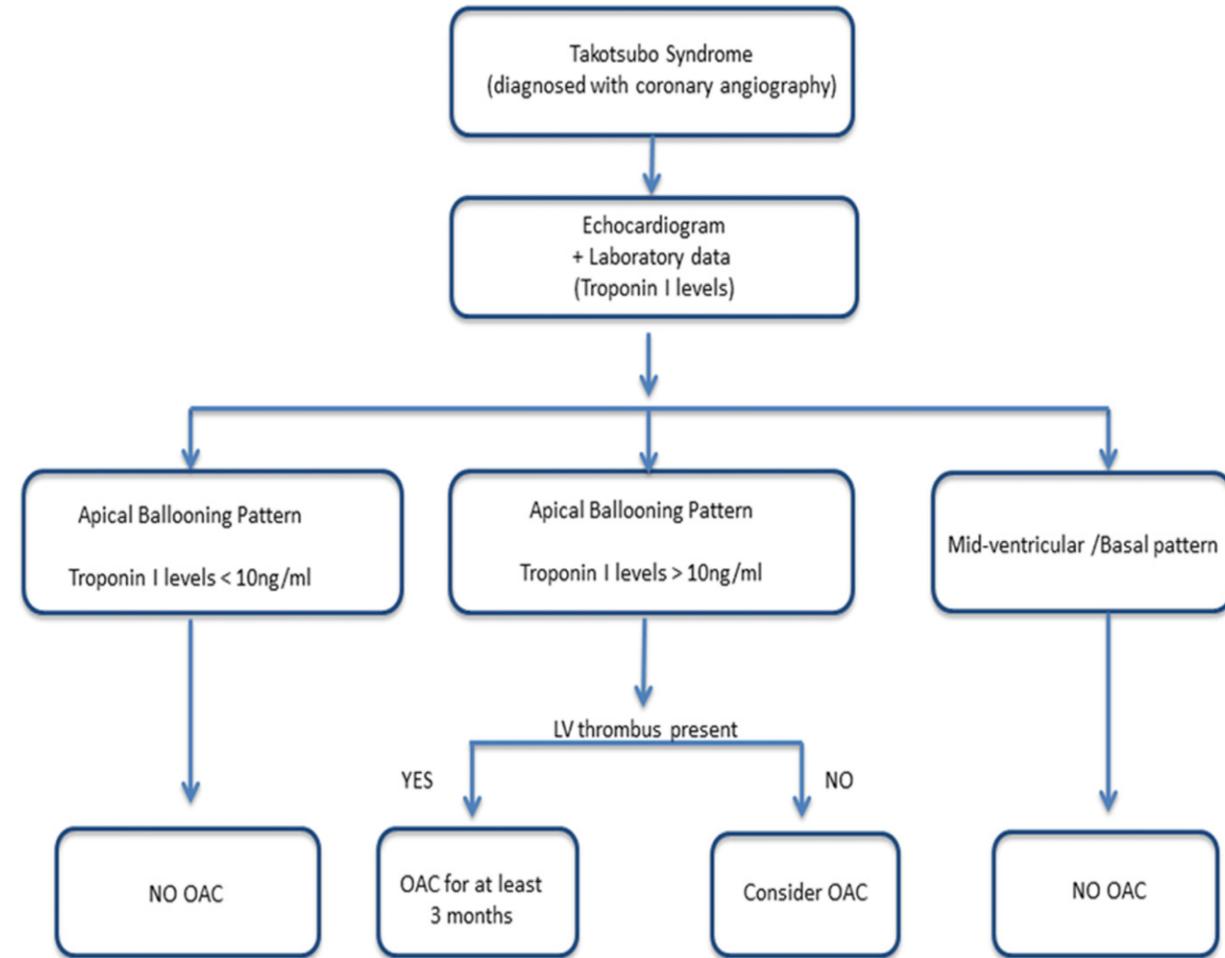
* Riesgo de fenómenos tromboembólicos

- Ecocardiografías seriadas
- No recomendaciones sobre el manejo preventivo:
 - Despistaje de sangrados (trigger)
 - Considerar la **anticoagulación profiláctica** para todos los pacientes en los primeros días (alto riesgo/FEVI <30%)



Trombo

Anticoagulación durante 3 meses o hasta la normalización de la FEVI

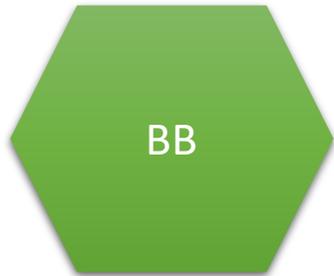


* *Evaluación del riesgo arrítmico*

- **Prolongación del QTc:**

- Evitar el uso de fármacos que prolonguen el QT (fármacos antiarrítmicos)
- Corrección de las alteraciones hidroelectrolíticas
- **Bradicardia + QTc prolongado (> 500 ms):**
 - **Evitar el uso de BB**
 - Considerar **Estimulación ventricular temporal a alta frecuencia o magnesio iv si TdP.**

* Valorar la necesidad de tratamiento



Author, Publication	Study Design, Number of subjects (n), Area of study or treatment regimen	Primary Measure Studied	Follow-Up	Outcomes
Short-term				
*Complications				
Kayuma, 2002 Circulation journal.2002; 66: 1181-4	Cases N=3 Propranolol iv (2-4mg): 2 LVOTO and 1 Non-LVOTO	Safety and gradient	In-hospital	Reduction LVOT gradient
Santoro, 2016 Cardiovasc. Ther. 2016, 34, 161-6	Case- controlled study n=9 TTS with LVOTO IV esmolol infusion 15.93 mg hours after admission to procedure	LVOT pressure gradient; systolic blood pressure	Nine months	Reduction LVOT gradient and systolic blood pressure
Kumar, 2011 Clin Cardiol. 2011, 34:672-6	Systematic review n=11 TTS with cardiac rupture	Cardiac rupture	N/A	Beta-blocker use may have protective effect against Cardiac rupture and may be useful in TTS patients
Fazio, 2008 Int. J. Cardiol. 2008;127:121-3	Retrospective (multicenter) n=36 BB; ACE; CA; aspirin	Improving left ventricular myocardial function and the rapidity of the effects of the same drug	30 days	No beneficial
Dias, 2016 Heart Vessels.2016; 31:1285-90	Retrospective n=206	MACE	In-hospital	No beneficial
Isogai, 2016 Heart.2016; 102:1029-35	Retrospective n=2572 Early β -blocker (<2days) vs. Non- β -blocker	Mortality	In-hospital mortality 15 days 30 days	No beneficial No beneficial No beneficial
* Preadmission betablocker therapy				
Kato, 2018 Heart Vessels.2018; 33:1214-9	Retropective n=154 Preadmission betablocker therapy (n=7)	MACE	In-hospital	Preadmission betablocker therapy: Independent predictors of in-hospital cardiac complications
Topf, 2022 Biomedicines. 2022;10:464	Prospective n=56 Preadmission betablocker therapy	MACE (hemodynamically relevant arrhythmia, cardiac decompensation, and all- cause adverse cardiac events)	In-hospital	Pretreatment: Increased risk all-cause complications

No beneficio a corto plazo salvo
- Gradiente obstructivo
- Riesgo de rotura cardiaca



Author, Publication	Study Design, Number of subjects (n), Area of study /treatment regimen	Primary Measure Studied	Follow-Up	Outcomes
Short-term				
Dias, 2016 Heart Vessels.2016; 31: 1285-90	Retrospective N=206			No beneficial

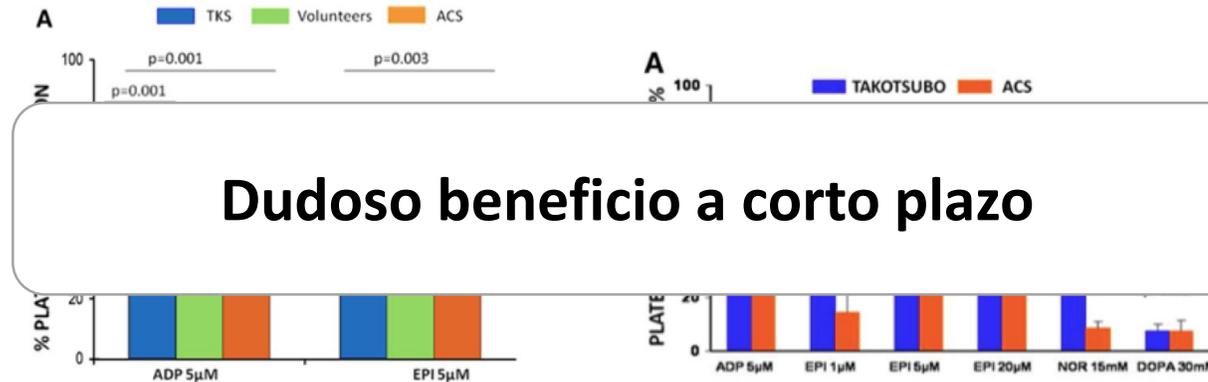
No beneficio a corto plazo

* *Valorar la necesidad de tratamiento*

Aspirina
AA

Estatinas

AC



Dudoso beneficio a corto plazo

No beneficio a corto plazo
 Asociar si enfermedad coronaria

Potencial beneficio acortando el tiempo de recuperación de la FEVI

No beneficio:
 Fazio. Int. J. Cardiol. 2008; 127:121-3
 D'Ascenzo. Eur. J. Heart Fail.2020; 22(2):330-7

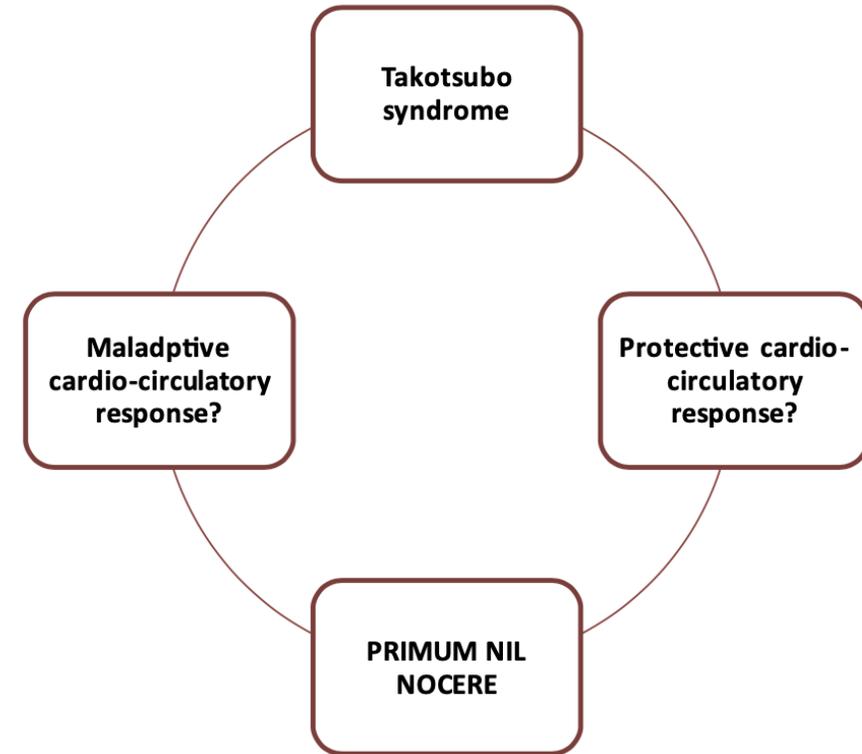
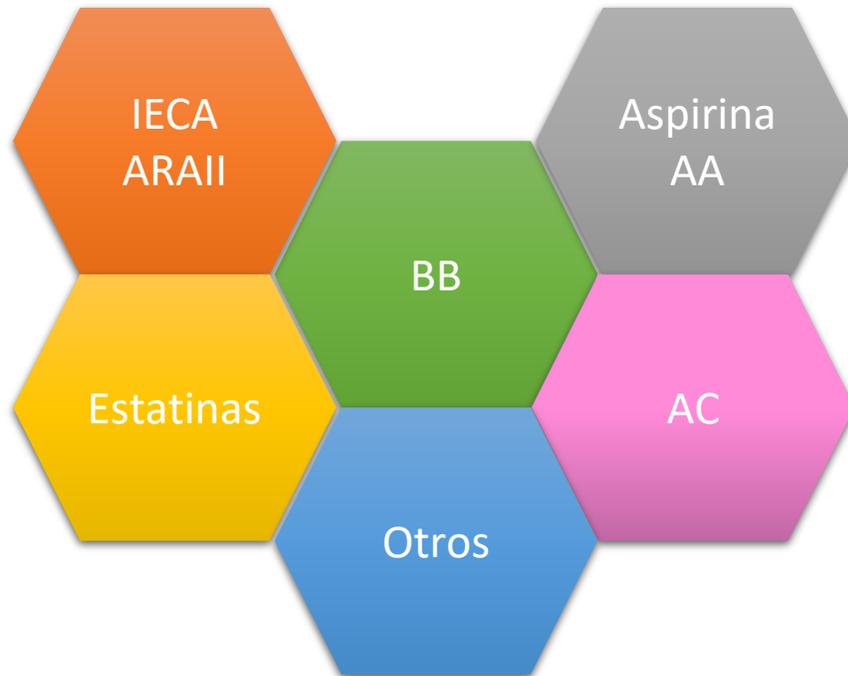
Beneficio:
 Dias. Heart Vessels 2016; 31:1285-90

Fazio. Int. J. Cardiol. 2008; 127:121-3
 D'Ascenzo. Eur. J. Heart Fail.2020; 22(2):330-7

Shiomura. Am J Cardiol. 2015; 116: 515-9

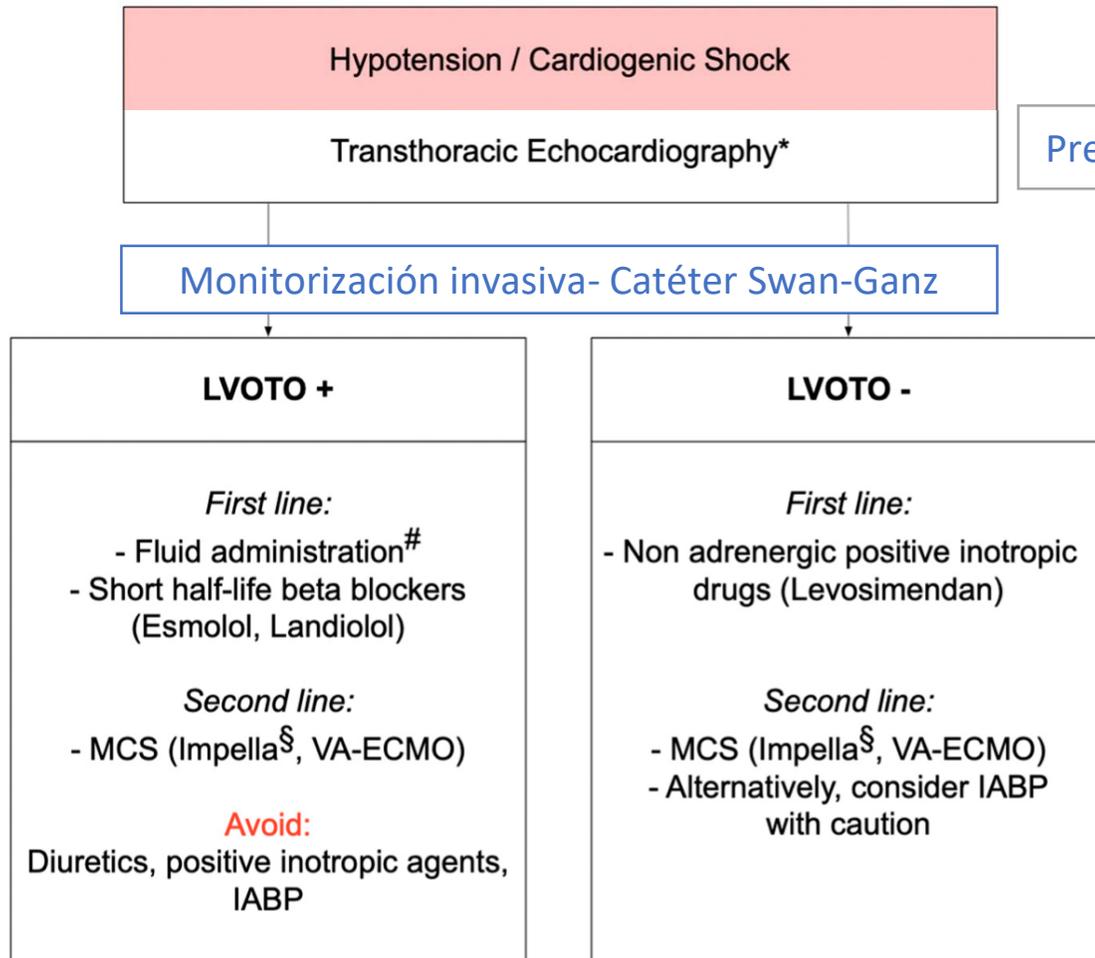
* Valorar la necesidad de tratamiento

Terapia estándar: "controvertido o cuasi-experimental" (Nivel C)



Monitorización y Reevaluación

b. STT CON complicaciones: Hipotensión y shock cardiogénico



Presencia de obstrucción del TSVI, grado de SAM/IM y excluir la rotura cardiaca

- **Evitar inotropos simpaticomiméticos** (adrenalina, noradrenalina, dopamina, dobutamina, isoprenalina) y milrinona
- De elección:
 - Inotropo: **Levosimendán**
 - Vasopresor: **Fenilefrina** (a1 agonista selectivo)
- OTSVI:
 - **BB** (metoprolol, esmolol o landiolol iv) o **Ivabradina**
 - + HipoTA: **fenilefrina**
 - Casos refractarios:
 - **Empleo precoz del Soporte mecánico**
 - **MCP temporal**

b. STT CON complicaciones: Insuficiencia cardiaca

- Valoración de la OTSVI y grado de SAM/IM
- Manejo estándar:
 - O2 +/- soporte ventilatorio
 - Diuréticos (*en ausencia OTSVI*)
 - Vasodilatadores iv (*en ausencia OTSVI*)
 - IECAs/ARA II: mejoría de la FEVI/valor pronóstico
 - BB: No valor pronóstico en ausencia de OTSVI
- Levosimendán si FEVI reducida

CLINICAL CARDIOLOGY

 VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2016, Vol. 23, No. 6, 610–615
DOI: 10.5603/CJ.a2016.0100
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ISSN 1897–5593

Levosimendan accelerates recovery in patients with takotsubo cardiomyopathy

Mehmet Yaman^{1,2,3}, Ugur Arslan², Ahmet Kaya^{1,4}, Aytac Akyol^{3,5},
Fatih Ozturk³, Yunus Emre Okudan⁶, Adil Bayramoglu¹, Osman Bektas¹

Original Article check for updates

Page 1 of 5

Efficacy and safety of levosimendan in Chinese elderly patients with Takotsubo syndrome

Yi Guo^{1*}, Chaofei Zhou^{1*}, Xia Yang²

ESC HEART FAILURE LETTER TO THE EDITOR

ESC Heart Failure 2021; 8: 4360–4363

Published online 2 August 2021 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/ehf2.13486

Levosimendan improves the acute course of takotsubo syndrome: a pooled analysis

b. STT CON complicaciones: Arritmias

❖ Arritmias ventriculares:

- Discontinuar fármacos pro-arrítmicos (QTc prolongado)
- Si arritmia refractaria--> valorar asistencia mecánica

❖ Riesgo de Muerte súbita:

- **No indicación de DAI** en prevención 1º ni 2º (patología reversible)
- Considerar **chaleco desfibrilador** si alto riesgo arrítmico en fase subaguda (arritmias ventriculares frecuentes durante la hospitalización)
- Se **desconoce el riesgo residual de eventos arrítmicos malignos** después de la recuperación de la FEVI

b. STT secundario

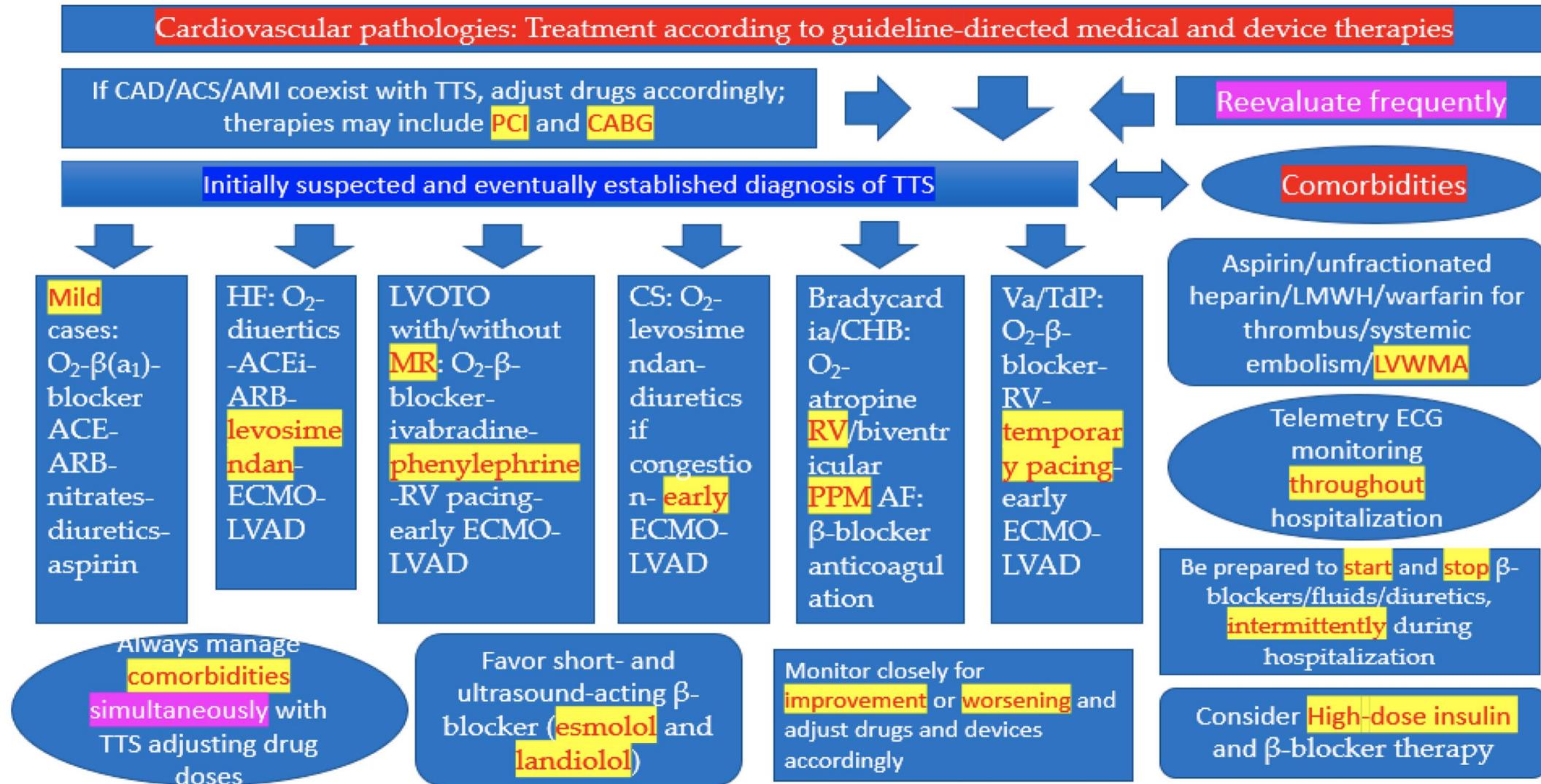
Cause/Trigger	Treatment implications
Cerebrovascular	Acute thrombolysis
<ul style="list-style-type: none"> • Ischemic stroke • Intracerebral bleeding • Epilepsy 	Potential surgical emergency; Absolute contraindication for antithrombotic treatment. Early diagnostics, Cautious use of anti-epileptic drugs that affect QTc. Monitor QTc interval.
Pneumonia, COPD exacerbation	Fluid resuscitation or mechanical support. Avoid antibiotics that may prolong QTc interval
Anaphylactic Shock or Status Asthmaticus	Remove immediately the predisposing agent. Avoid morphine or supratherapeutic epinephrine because of its histamine-releasing property and its alpha-receptor-mediated coronary vasoconstriction. Anti-histamine and steroids are recommended. Fluid resuscitation. Consider mechanical support early
Acute Sepsis	Fluid resuscitation or mechanical support; Avoid IABP, particularly if LVOTO is present. Avoid inotropic drugs; Avoid antibiotics which may prolong QTc interval
Gastrointestinal bleeding	Contraindication for antithrombotic treatment.
Endocrine	
<ul style="list-style-type: none"> • Pheochromocytoma • Thyrotoxicosis 	Consider mechanical assist device for hemodynamically unstable patients. Avoid inotropic drugs. Consider beta blockers.
Surgery	
<ul style="list-style-type: none"> • Perioperative • Intraoperative (under general anesthesia) • Postoperative 	Reevaluate the operative risk and urgency for surgery. Smooth induction of anesthesia and minimization of physiologic response to stimulating events such as incision, intubation Exclude other causes for hemodynamic instability (e.g. hypovolemia, anaphylaxis). Perform TTE or TEE to assess cardiac function and presence versus absence of LVOTO. Fluid resuscitation (particularly if LVOTO). Exclude other causes for hemodynamic instability (e.g. hypovolemia, anaphylaxis). Perform TTE or TEE to assess cardiac function and presence versus absence of LVOTO. Fluid resuscitation (particularly if LVOTO). Consider transferring patients with signs of organ hypoperfusion to center with mechanical assist device
Malignancy	Consider bleeding risk. Cautious use of antithrombotic drugs.

Jha S. Expert Rev Cardiovasc Ther. 2019;17(2):83-93

Consideraciones específicas del STT:

- Evitar el uso de fármacos inotrópicos positivos y vasodilatadores
- Hipotensión- Fenilefrina
- Insuficiencia cardiaca grave y el shock cardiogénico- ECMO/LVAD

b. Fase aguda-hospitalaria

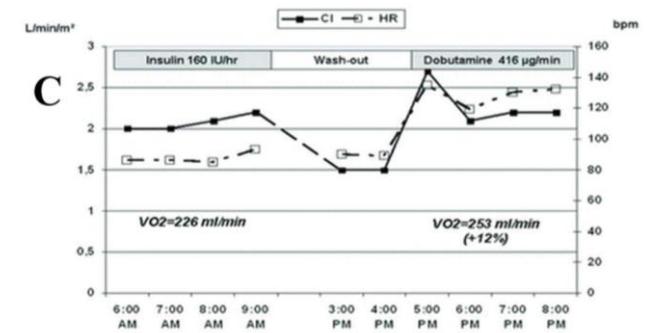
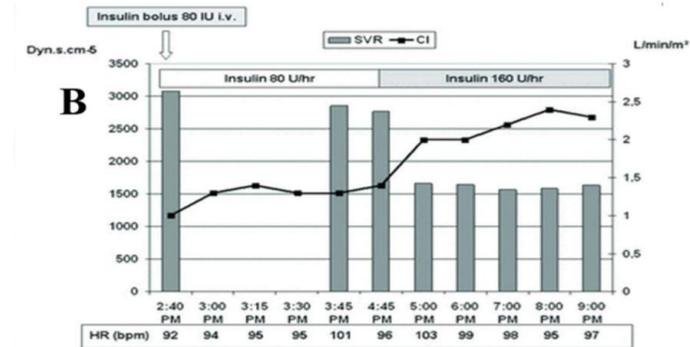
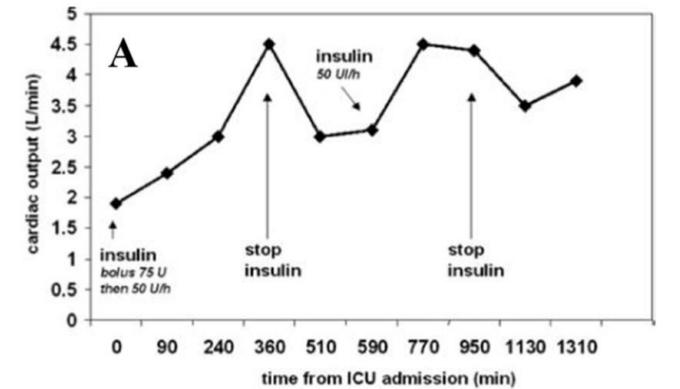


c. Tratamiento largo plazo

Long-term treatment		
ACE-inhibitor or ARB	Survival at 1 year	Limited retrospective evidence
Beta-blockers	Survival	Lack of evidence
Beta-blockers in patients who experienced CS during TTS	Survival at 1 year	Limited retrospective evidence
Beta-blockers at discharge in patients with LVOTO in acute phase	Long-term benefit	Lack of evidence
OAC for three months in patients with LV thrombosis	LV thrombosis	Limited retrospective evidence
Antiplatelet	Incidence of MACE	Lack of evidence
Antidepressants and anxiolytics	Prevention of a first episode or recurrences	Lack of evidence

Perspectivas de futuro

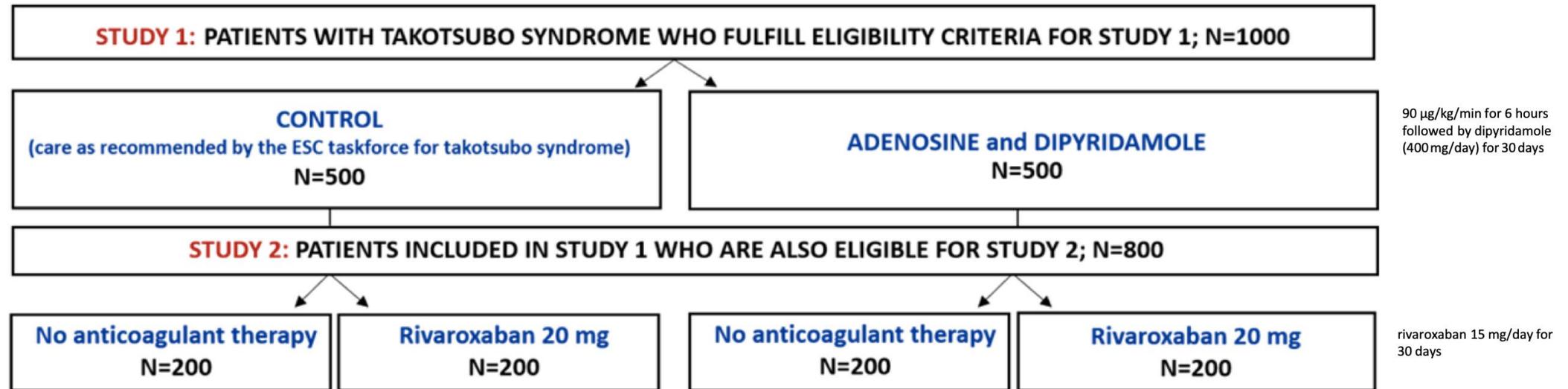
- **Insulina iv:** trastorno del metabolismo de la glucosa y efecto inotrope positivo
- **Bloqueadores de los receptores adrenérgicos alfa (fentolamina):** señalización alfa 1-adrenoceptor en la arritmogénesis (prolongación del intervalo QT)
- **Respuesta inflamatoria sistémica:** evaluar la eficacia de *AINEs*, *colchicina* o *corticoides*
- **Ensayos clínicos en marcha**





BROKEN SWEDEHEART

2x2 factorial design



Primary endpoint Study 1:

The occurrence of the composite of death, cardiac arrest (defined as ventricular fibrillation or asystole >30 seconds), or the need for cardiac mechanical assist device within 30 days, or ejection fraction <50% at 72 hours or rehospitalization for heart failure within 30 days.

Primary endpoint Study 2:

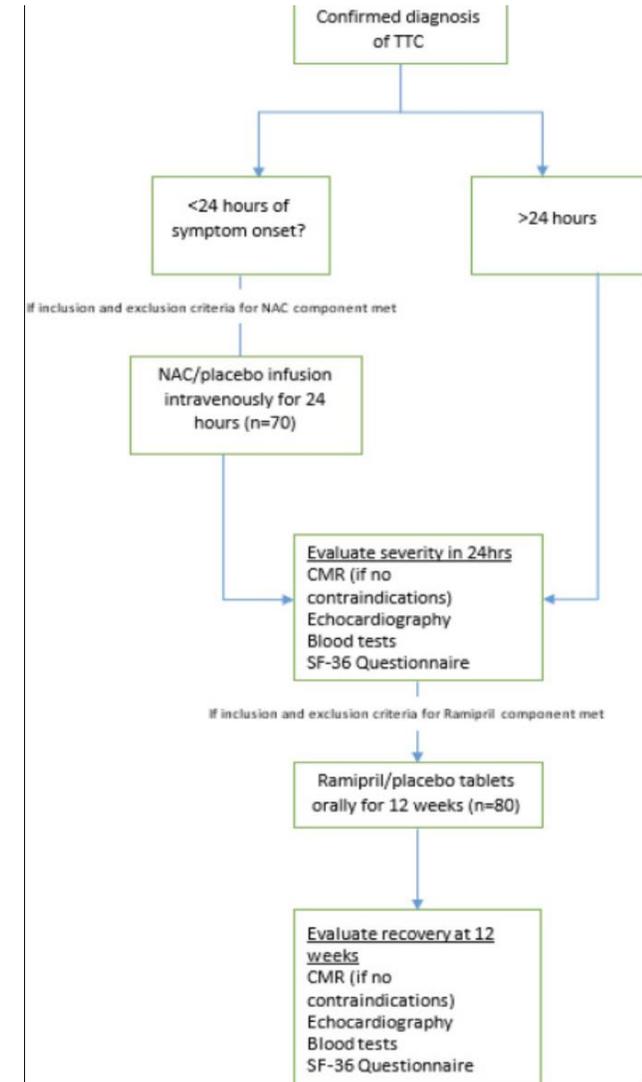
The occurrence of any thromboembolic event (defined as ischemic stroke, peripheral arterial embolization or myocardial infarction) or death within 30 days, or the presence of a cardiac thrombus at 72 hours, as assessed by echocardiography.

Perspectivas de futuro

TITAN: Adenosin to Rapidly Reverse Left Ventricle Impairment in Takotsubo Syndrome

Study Type <small>ICMJE</small>	Interventional
Study Phase <small>ICMJE</small>	Phase 2
Study Design <small>ICMJE</small>	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Single (Participant) Primary Purpose: Treatment
Condition <small>ICMJE</small>	<ul style="list-style-type: none"> • Takotsubo Cardiomyopathy • Takotsubo Syndrome
Intervention <small>ICMJE</small>	<ul style="list-style-type: none"> • Drug: Adenosine • Drug: Saline solution
Study Arms <small>ICMJE</small>	<ul style="list-style-type: none"> • Experimental: Adenosine Patients in this arm will receive systemic infusion of adenosine at 140µg/kg/min for 3 minutes plus standard therapy according to current guidelines Intervention: Drug: Adenosine • Placebo Comparator: Saline solution Patients in this arm will receive systemic infusion of saline solution at 140µg/kg/min for 3 minutes plus standard therapy according to current guidelines Intervention: Drug: Saline solution

NACRAM: The N-AcetylCysteine and RAMipril in Takotsubo Syndrome Trial



Take-home message

- “**Primum non nocere**”: patología reversible y escasa evidencia
- **Alta tasa de complicaciones:** reevalúa y ajustar tratamiento
- **Manejo guiado por la presentación clínica**
 - **Shock cardiogénico:**
 - Evitar el uso de fármacos inotropos simpaticomiméticos → levosimendán
 - Dispositivo de asistencia mecánica como "puente a la recuperación"
 - **OTSVI:** β -bloqueante intravenoso de acción corta +/- vasopresor (fenilefrina)
- **Anticoagulación profiláctica** en pacientes de alto riesgo
- **Necesidad de investigación:** ensayos clínicos tratamiento específico

Muchas gracias



Twitter: [@Emilia_BP](https://twitter.com/Emilia_BP)