Stress Cardiomyopathy

HK Core Cardiology Certificate Course (Module#4)
Heart Failure & Cardiomyopathy in Daily Clinical Practice
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Presenter Disclosure Information

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Stress Cardiomyopathy

DISCLOSURE INFORMATION:
The following relationships exist related to this presentation: **None**

Overview

- Case illustration
- Presentation & Diagnosis
- Management & Prognosis
- References:-
  - International Expert Consensus Document on Takotsubo Syndrome (Part I & II)
    (*Eur Heart J* 2018;39:2032–2046 & *Eur Heart J* 2018;39;2047–2062)
  - Stress Cardiomyopathy Diagnosis and Treatment. JACC State-of-the-Art Review
    (*J Am Coll Cardiol* 2018;72:1955–71)
- Conclusions

ESC European Society of Cardiology
European Heart Journal (2018) **39**, 2032–2046
doi:10.1093/eurheartj/ehy076

CONSENSUS PAPER

International Expert Consensus Document on Takotsubo Syndrome (Part I): Clinical Characteristics, Diagnostic Criteria, and Pathophysiology

Jelena-Rima Ghadri[1], Ilan Shor Wittstein[2], Abhiram Prasad[3], Scott Sharkey[4], Keigo Dote[5], Yoshihiro John Akashi[6], Victoria Lucia Cammann[1], Filippo Crea[7], Leonarda Galiuto[7], Walter Desmet[8,9], Tetsuro Yoshida[10], Roberto Manfredini[11], Ingo Eitel[12], Masami Kosuge[13], Holger M. Nef[14], Abhishek Deshmukh[3], Amir Lerman[3], Eduardo Bossone[15], Rodolfo Citro[15], Takashi Ueyama[16†] Domenico Corrado[17], Satoshi Kurisu[18], Frank Ruschitzka[1], David Winchester[19], Alexander R. Lyon[20,21], Elmir Omerovic[22,23], Jeroen J. Bax[24], Patrick Meimoun[25], Guiseppe Tarantini[17], Charanjit Rihal[3], Shams Y.-Hassan[26], Federico Migliore[17], John D. Horowitz[27], Hiroaki Shimokawa[28], Thomas Felix Lüscher[29,30], and Christian Templin[1*]

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European Heart Journal (2018) 39, 2047–2062
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CONSENSUS PAPER

International Expert Consensus Document on Takotsubo Syndrome (Part II): Diagnostic Workup, Outcome, and Management

Jelena-Rima Ghadri[1], Ilan Shor Wittstein[2], Abhiram Prasad[3], Scott Sharkey[4], Keigo Dote[5], Yoshihiro John Akashi[6], Victoria Lucia Cammann[1], Filippo Crea[7], Leonarda Galiuto[7], Walter Desmet[8,9], Tetsuro Yoshida[10], Roberto Manfredini[11], Ingo Eitel[12], Masami Kosuge[13], Holger M. Nef[14], Abhishek Deshmukh[3], Amir Lerman[3], Eduardo Bossone[15], Rodolfo Citro[15], Takashi Ueyama[16†], Domenico Corrado[17], Satoshi Kurisu[18], Frank Ruschitzka[1], David Winchester[19], Alexander R. Lyon[20,21], Elmir Omerovic[22,23], Jeroen J. Bax[24], Patrick Meimoun[25], Guiseppe Tarantini[17], Charanjit Rihal[3], Shams Y.-Hassan[26], Federico Migliore[17], John D. Horowitz[27], Hiroaki Shimokawa[28], Thomas Felix Lüscher[29,30], and Christian Templin[1]*

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THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Stress Cardiomyopathy Diagnosis and Treatment

JACC State-of-the-Art Review

Horacio Medina de Chazal, MD,[a,b] Marco Giuseppe Del Buono, MD,[a,c] Lori Keyser-Marcus, PhD,[c] Liangsuo Ma, PhD,[d] F. Gerard Moeller, MD,[c,d] Daniel Berrocal, MD, PhD,[b] Antonio Abbate, MD, PhD[a,c]

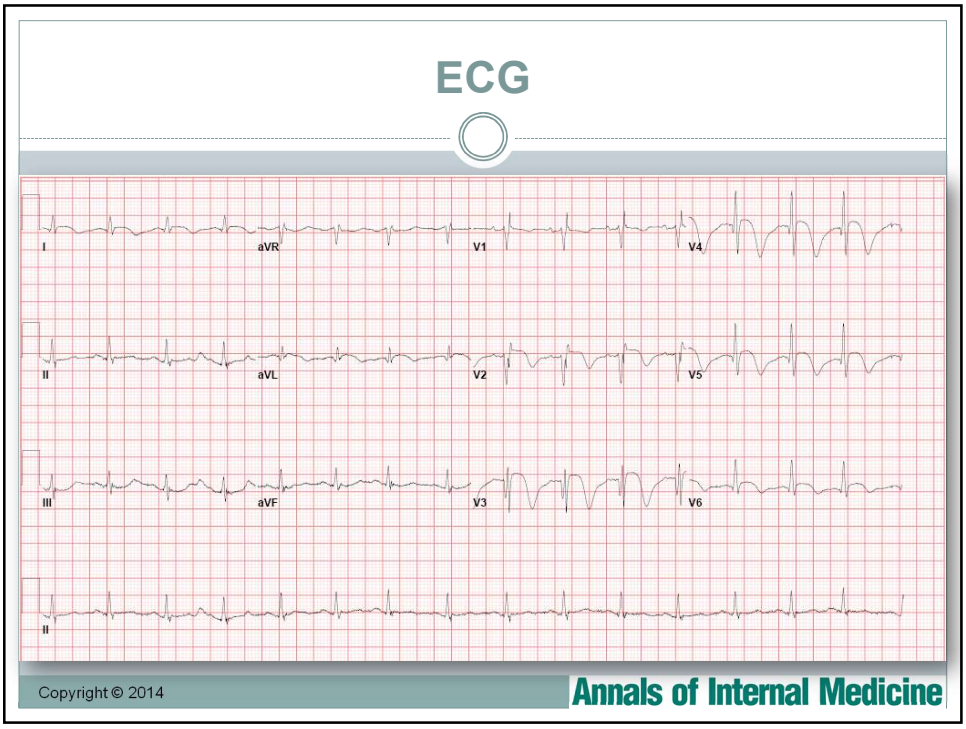
Stumper

76 years old lady

- Hx of asthma and anxiety/depression.
- Hypertension, Dyslipidemia and Paroxysmal AF.
- Admitted for AF with rapid ventricular rate and heart failure (HF) symptoms. Serial TnI-NAD.
- TEE: No evidence of intra-cardiac thrombus. No significant valvular lesions. Normal RWMA/LVEF.
- Successful DCCV @200J (Biphasic) once with improved HF symptoms.

24 hours later,

- Developed chest pain and worsening HF again.
- TnI 2.0 ng/mL (N<0.4). NT-proBNP 2456 pg/mL.
- ECG….



Stumper

- When assessed, her HR is 102bpm, regular, and blood pressure is 90/70mmHg. She has inspiratory crepitations in both lung bases, oxygen saturation is 90% on 4L/min nasal oxygen, there is a 4/6 systolic ejection murmur, and she is cool to touch.

What is the appropriate next treatment step in this patient?

A. Initiation of dobutamine or milrinon is indicated to increase cardiac output.

B. Despite the relatively low blood pressure, the addition of intravenous hydralazine is likely to lead to improved cardiac output and ultimately increase cardiac output.

C. An echocardiography should be done emergently to determine the presence and severity of left ventricular outflow traction obstruction and mitral regurgitation.

D. Intravenous broad-spectrum antibiotics should be started for the treatment of pneumonia.

Stumper

Echo: Apical ballooning. LVEF~25%. Dynamic LVOT gradients up to 50mmHg.

An emergent coronary angiography is performed, showing a 90% stenosis of the first obtuse marginal branch without acute thrombus and with good distal flow (Thrombolysis in Myocardial infarction [TIMI] grade flow 3).

What is the most likely diagonosis?

A. Non-ST-segment elevation acute MI

B. Stress (Takotsubo) cardiomyopathy

C. Myocarditis

D. Pericarditis

Stress Cardiomyopathy

- Stress cardiomyopathy is a clinical syndrome characterized by an acute and transient (<21 days) left ventricular (LV) systolic (and diastolic) dysfunction often related to an emotional or physical stressful event, most often identified in the preceding days (1-5 days).
- It is defined as a reversible regional wall motion abnormality that extends beyond the distribution of a single coronary artery.
- Many elderly patients will have underlying coronary artery disease that may not be causing acute ischemia (bystander disease), and thus not represent acute coronary syndrome.

References:-

1. Winchester DE, Ragosta M, Taylor AM. Concurrence of angiographic coronary artery disease in patients with apical ballooning syndrome (tako-tsubo cardiomyopathy). *Catheter Cardiovasc Interv*. 2008;72:612-6. doi: 10.1002/ccd.21738.
2. Kurisu S, Inoue I, Kawagoe T, Ishihara M, Shimatani Y, Nakama Y, Maruhashi T, Kagawa E, Dai K, Matsushita J, Ikenaga H. Prevalence of incidental coronary artery disease in tako-tsubo cardiomyopathy. *Coron Artery Dis*. 2009;20:214-8. doi: 10.1097/MCA.0b013e3283299260.

Diagnostic Criteria for Stress Cardiomyopathy According to Heart Failure Association of the European Society of Cardiology, Mayo Clinic Criteria, InterTAK Diagnostic Criteria

Heart Failure Association-European Society of Cardiology Criteria

1. Transient regional wall motion abnormalities of left ventricle or right ventricle myocardium, which are frequently, but not always, preceded by a stressful trigger (emotional or physical).
2. The regional wall motion abnormalities usually* extend beyond a single epicardial vascular distribution, and often result in circumferential dysfunction of the ventricular segments involved.
3. The absence of culprit atherosclerotic coronary artery disease, including acute plaque rupture, thrombus formation, and coronary dissection or other pathological conditions to explain the pattern of temporary LV dysfunction observed (e.g., hypertrophic cardiomyopathy, viral myocarditis).
4. New and reversible electrocardiography abnormalities (ST-segment elevation, ST-segment depression, LBBB,† T-wave inversion, and/or QTc prolongation) during the acute phase (3 months).
5. Significantly elevated serum natriuretic peptide (BNP or NT-proBNP) during the acute phase.
6. Positive but relatively small elevation in cardiac troponin measured with conventional assay (i.e., disparity between the troponin level and the amount of dysfunctional myocardium present).‡
7. Recovery of ventricular systolic function on cardiac imaging at follow-up (3 to 6 months).§

International Takotsubo Diagnostic Criteria (InterTAK Diagnostic Criteria)

1. Patients show transient‖ 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 Takotsubo syndrome).¶
2. An emotional, physical, or combined trigger can precede the Takotsubo syndrome event, but this is not obligatory.
3. Neurologic disorders (e.g., subarachnoid hemorrhage, stroke/transient ischemic 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.¶
8. Postmenopausal women are predominantly affected.

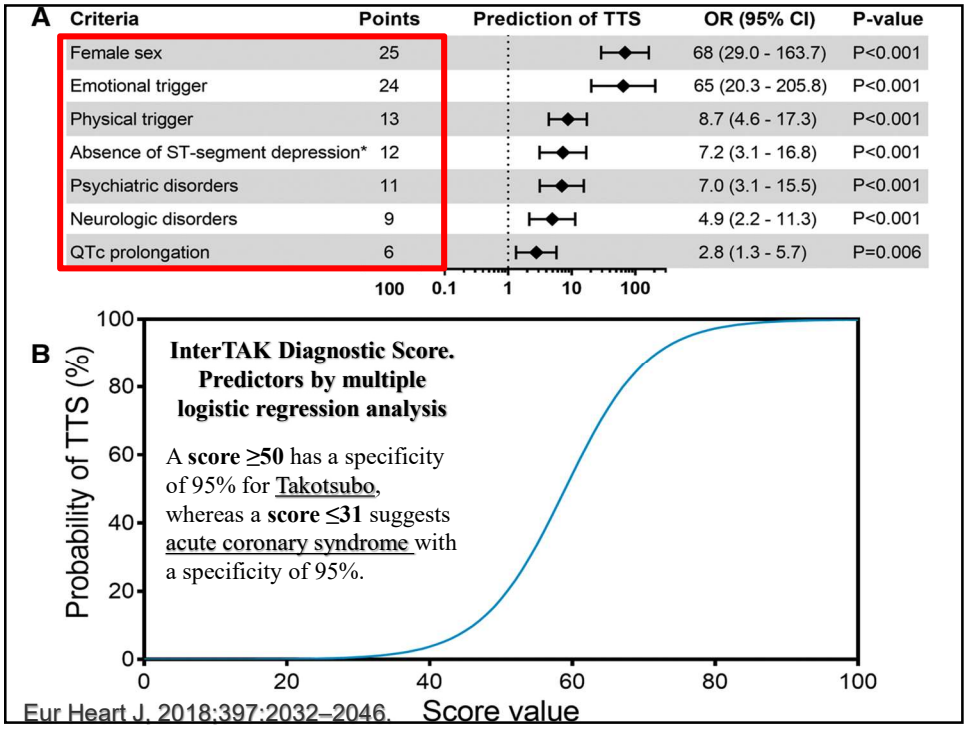
Revised Mayo Clinic Criteria

1. Transient hypokinesis, akinesis, or dyskinesis of the left ventricular midsegments with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always present#
2. Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture**
3. New electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin
4. Absence of pheochromocytoma or myocarditis

Stress Cardiomyopathy Diagnostic Criteria

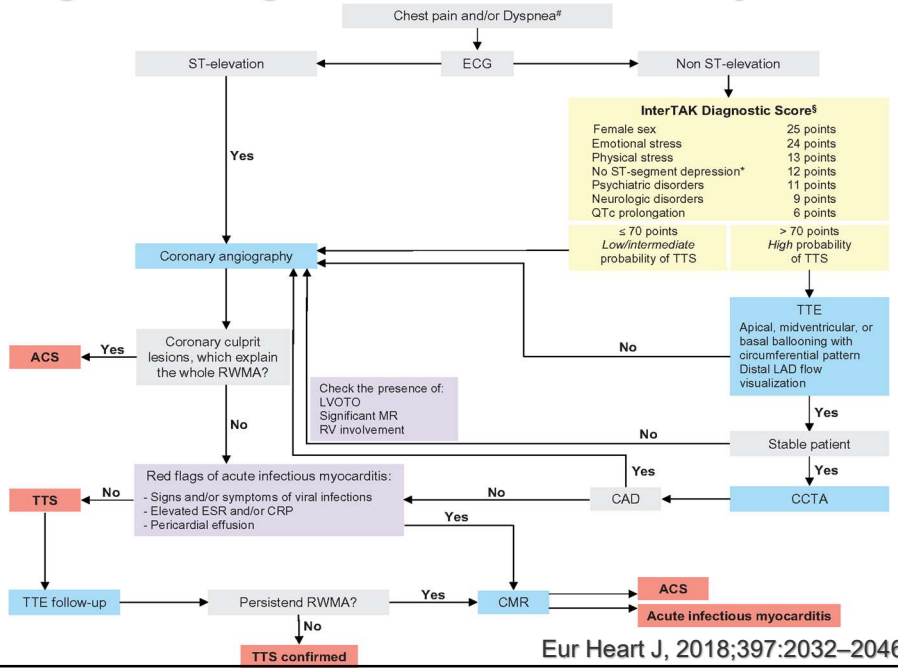
- **Heart Failure Association of the European Society of Cardiology (HFA-ESC)**
- **Revised Mayo Clinic Criteria**
- **InterTAK Diagnostic Criteria & Score**
  - ***5 clinical variables*** from history and ***2 variables from the ECG*** to create a score that translates into a probability of stress cardiomyopathy (InterTAK diagnostic score).

Diagnosis (Cutoff Value [Range 0–100])	
≥50	**≤31**
Takotsubo	Acute coronary syndrome
(Specificity 95%)	(Specificity 95%)



Eur Heart J. 2018;397:2032–2046.

Diagnostic Algorithm of Takotsubo Syndrome



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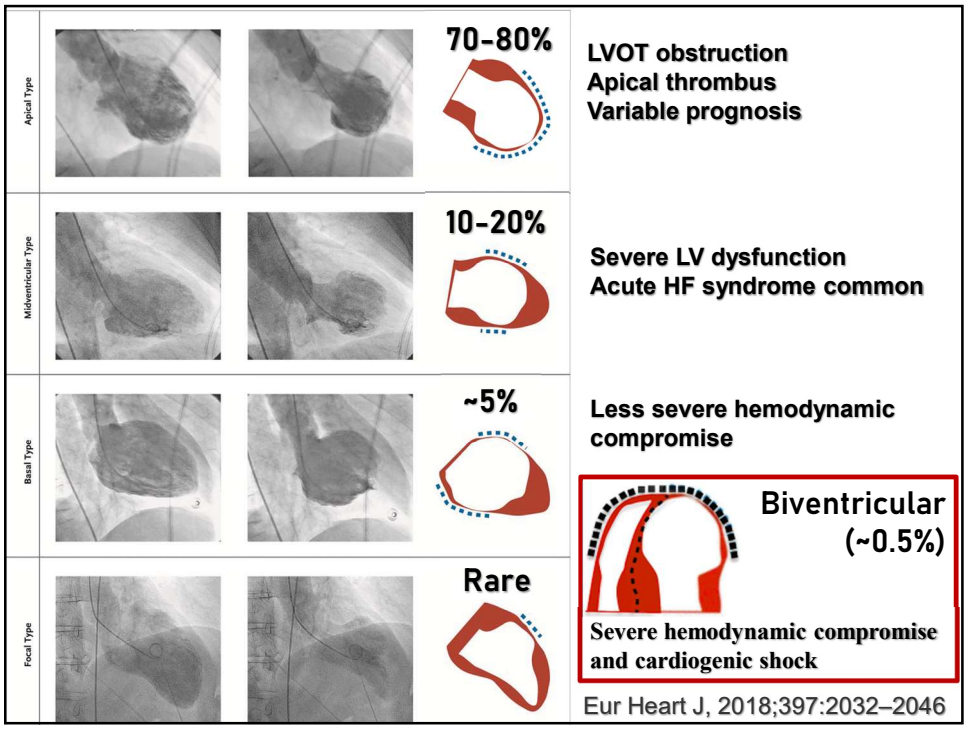
6.	Significant coronary artery disease is not a contradiction in takotsubo syndrome.
7.	Patients have no evidence of infectious myocarditis.[b]
8.	Postmenopausal women are predominantly affected.

a/ Wall motion abnormalities may remain for a prolonged period of time or documentation of recovery may not be possible. For example, death before evidence of recovery is captured.
b/ Cardiac magnetic resonance imaging is recommended to exclude infectious myocarditis and diagnosis confirmation of takotsubo syndrome.



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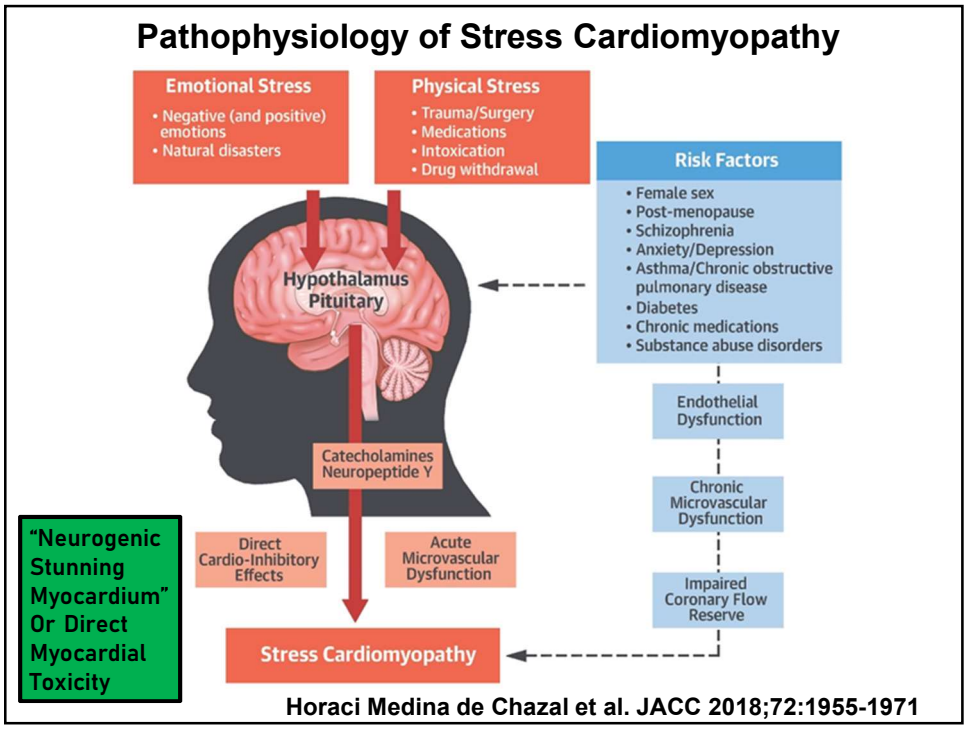
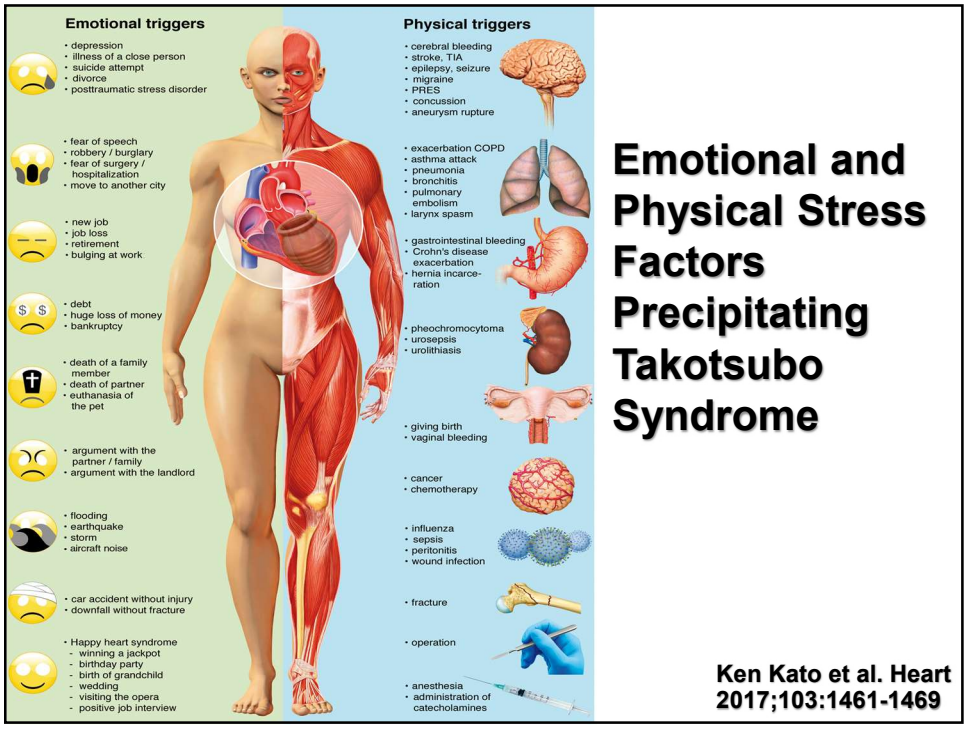
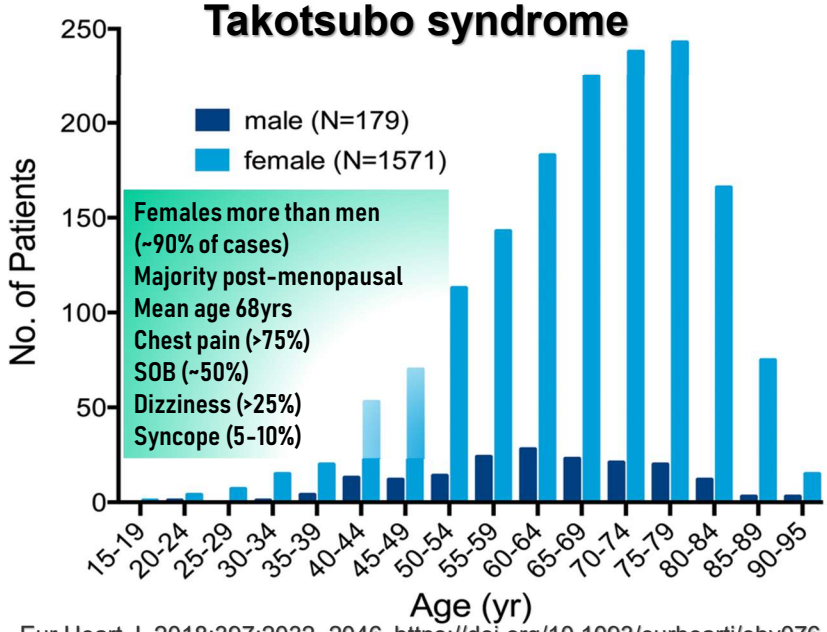

Pathophysiology of Stress Cardiomyopathy
Emotional Stress
• Negative (and positive) emotions
• Natural disasters
Physical Stress
• Trauma/Surgery
• Medications
• Intoxication
• Drug withdrawal
Risk Factors
• Female sex
• Post-menopause
• Schizophrenia
• Anxiety/Depression
• Asthma/Chronic obstructive pulmonary disease
• Diabetes
• Chronic medications
• Substance abuse disorders
Hypothalamus Pituitary
Catecholamines Neuropeptide Y
Endothelial Dysfunction
Chronic Microvascular Dysfunction
Impaired Coronary Flow Reserve
"Neurogenic Stunning Myocardium" Or Direct Myocardial Toxicity
Direct Cardio-Inhibitory Effects
Acute Microvascular Dysfunction
Stress Cardiomyopathy
Horaci Medina de Chazal et al. JACC 2018;72:1955-1971


Emotional triggers
• depression
• illness of a close person
• suicide attempt
• divorce
• posttraumatic stress disorder
• fear of speech
• robbery / burglary
• fear of surgery / hospitalization
• move to another city
• new job
• job loss
• retirement
• bulging at work
• debt
• huge loss of money
• bankruptcy
• death of a family member
• death of partner
• euthanasia of the pet
• argument with the partner / family
• argument with the landlord
• flooding
• earthquake
• storm
• aircraft noise
• car accident without injury
• downfall without fracture
• Happy heart syndrome
- winning a jackpot
- birthday party
- birth of grandchild
- wedding
- visiting the opera
- positive job interview
Physical triggers
• cerebral bleeding
• stroke, TIA
• epilepsy, seizure
• migraine
• PRES
• concussion
• aneurysm rupture
• exacerbation COPD
• asthma attack
• pneumonia
• bronchitis
• pulmonary embolism
• larynx spasm
• gastrointestinal bleeding
• Crohn's disease exacerbation
• hernia incarceration
• pheochromocytoma
• urosepsis
• urolithiasis
• giving birth
• vaginal bleeding
• cancer
• chemotherapy
• influenza
• sepsis
• peritonitis
• wound infection
• fracture
• operation
• anesthesia
• administration of catecholamines
Emotional and Physical Stress Factors Precipitating Takotsubo Syndrome
Ken Kato et al. Heart 2017;103:1461-1469

Age and Sex Distribution of Patients with Takotsubo syndrome



Eur Heart J, 2018;397:2032–2046, https://doi.org/10.1093/eurheartj/ehy076

Stress Cardiomyopathy in Young Individuals

Epidemiology

Rare in younger than age 60 yrs
- <10% in ≤55 yrs of age
- <2% in ≤35 yrs of age

Comorbidities

Psychiatric disorders
- Schizophrenia
- Anorexia nervosa

Triggers

Often physical triggers
- Pregnancy/delivery
- Medications (catecholamines/anesthetics)
- Drugs of abuse (alcohol/cannabis(marijuana)/amphetamines)

Anatomical Pattern/Variant

More often atypical forms
- Basal (inverted Takotsubo)
- Midventricular

Prognosis (High risk)
- High risk of arrhythmias
- Hemodynamic instability
- Greater propensity for recurrence

Risk Factors, Characteristics, Scores

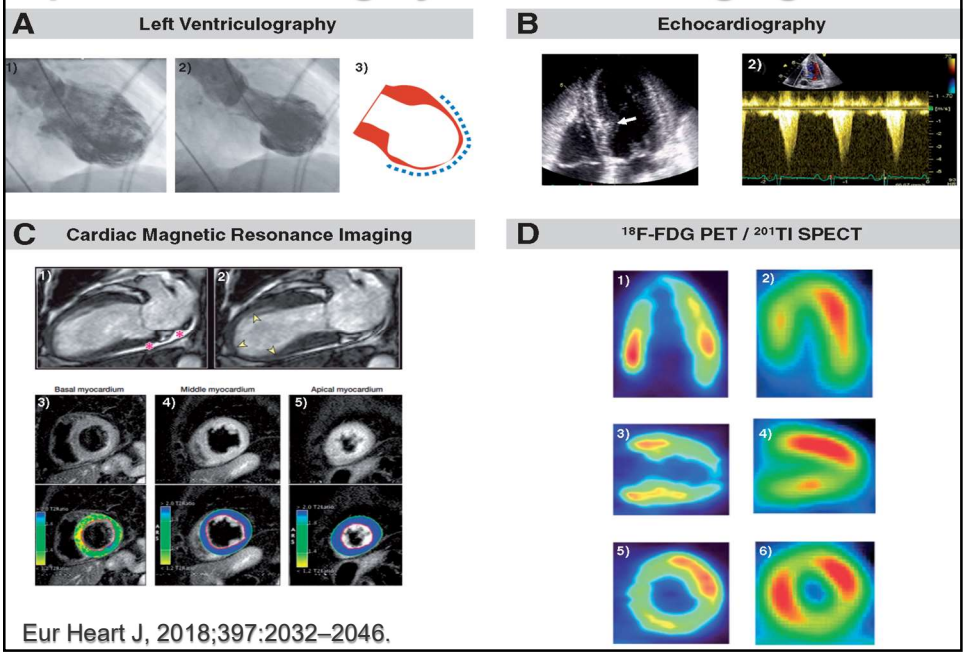
- Female sex, being post-menopausal ,
- History of psychiatric illness,
- Chest pain after emotional stress,
- QT prolongation, Absent ST depression
- History of asthma

The interTAK diagnostic score 78 with a probability of stress cardiomyopathy of 96%.

In addition, NT-proBNP is disproportionately high compared to TnI levels.

Eur Heart J. 2018;39:2047-2062. doi: 10.1093/eurheartj/ehy077

Apical Ballooning by Different Imaging Exams



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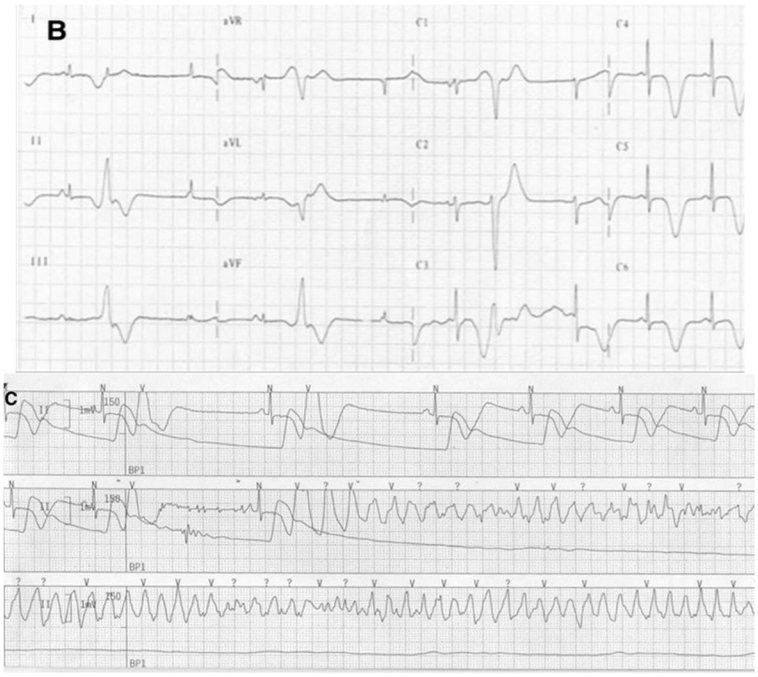


Eur Heart J. 2018;39:2047–2062 (https://doi.org/10.1093/eurheartj/ehy077)

Overview of In-hospital Complications According to Their Prevalence

In-hospital Complications

Frequent

- Acute heart failure (12-45%)
- LVOTO (10-25%)
- Mitral regurgitation (14-25%)
- Cardiogenic shock (6-20%)

Moderate

- Atrial fibrillation (5-15%)
- LV-thrombus (2-8%)
- Cardiac arrest (4-6%)
- AV-block ~5%

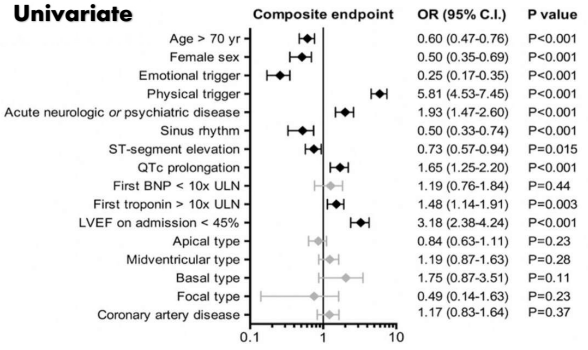
Rare

- Tachyarrhythmia (2-5%)
- Bradyarrhythmia (2-5%)
- Torsades-de-pointes (2-5%)
- Death (1-4.5%)
- Ventricular tachycardia/fibrillation ~3%
- Acute ventricular septal defect <1%

Eur Heart J. 2018;397:2032–2046.

Predictors of In-hospital Complications in Takotsubo Syndrome (TTS)

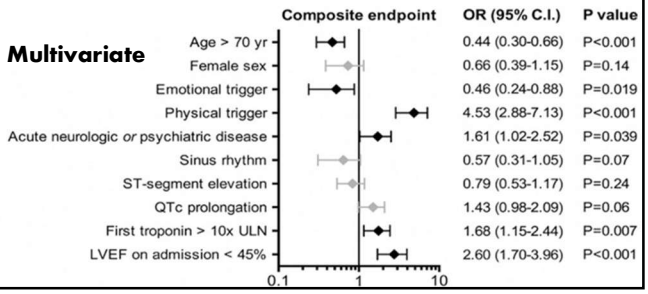
Univariate

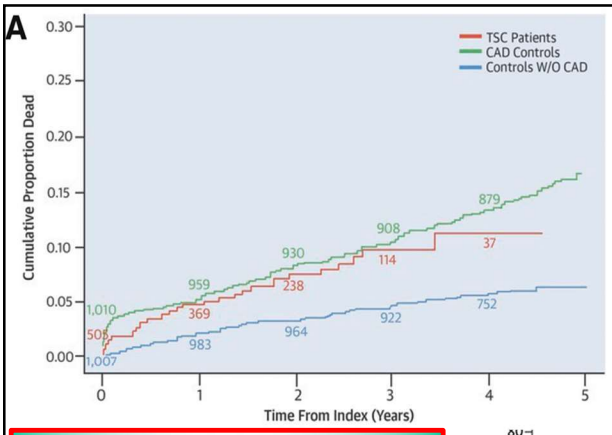


Ken Kato et al. Heart 2017;103:1461-1469

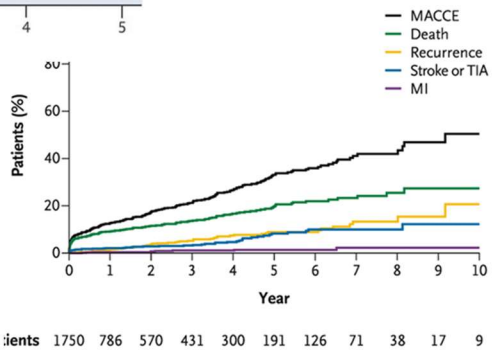
Physical triggers, Acute neurological or Psychiatric diseases, High troponin levels, Low ejection fraction on admission as being independent predictors of a poor outcome.

Multivariate





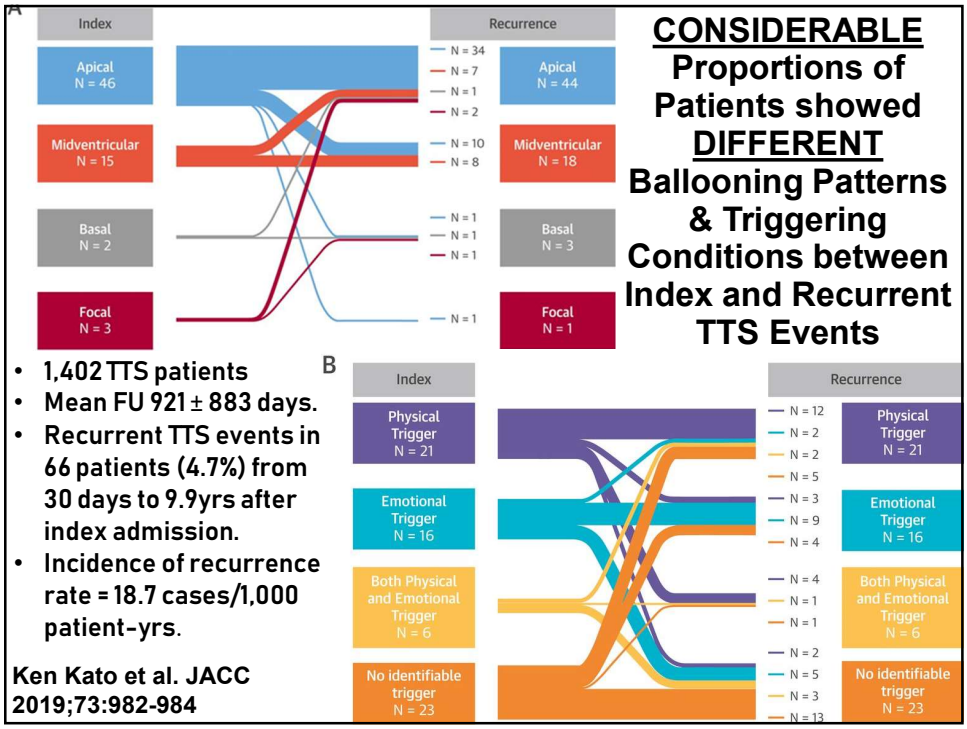
Long-term outcome (5-yrs) of patients with TTS compared to patients with and without CAD



Recurrence common 2-4%/year & up to 20% at 10 years

Even after recovery of LVEF, may still c/o fatigue (74%), SOB (43%), Chest pain (8%), Palpitation (8%) & Exercise intolerance versus those without TTS

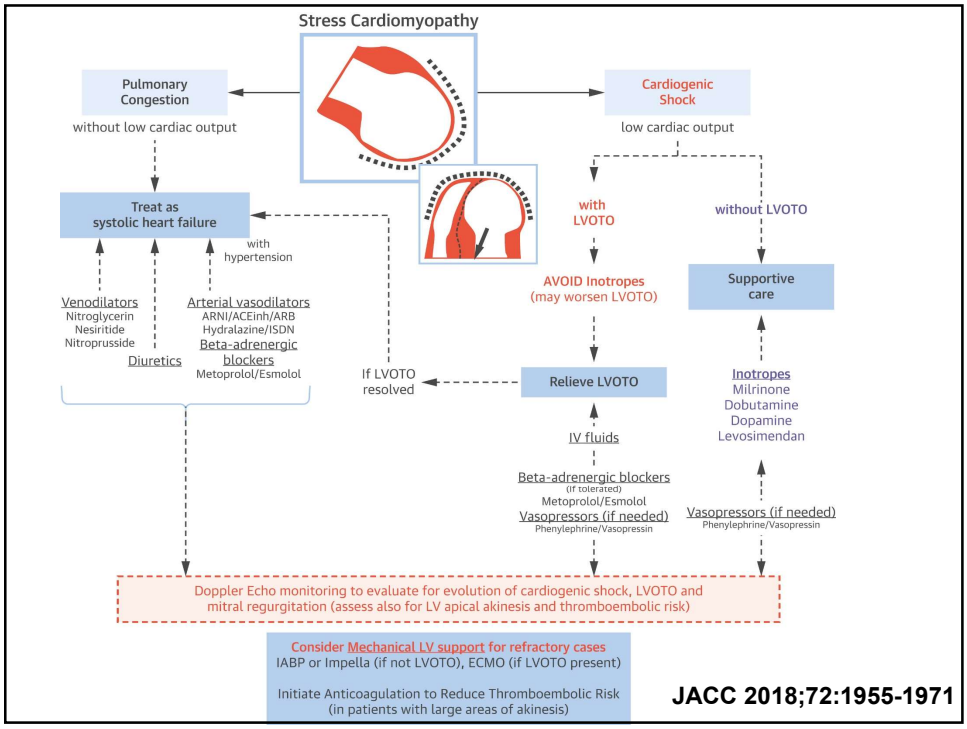
Eur Heart J. 2018;397:2032–2046.



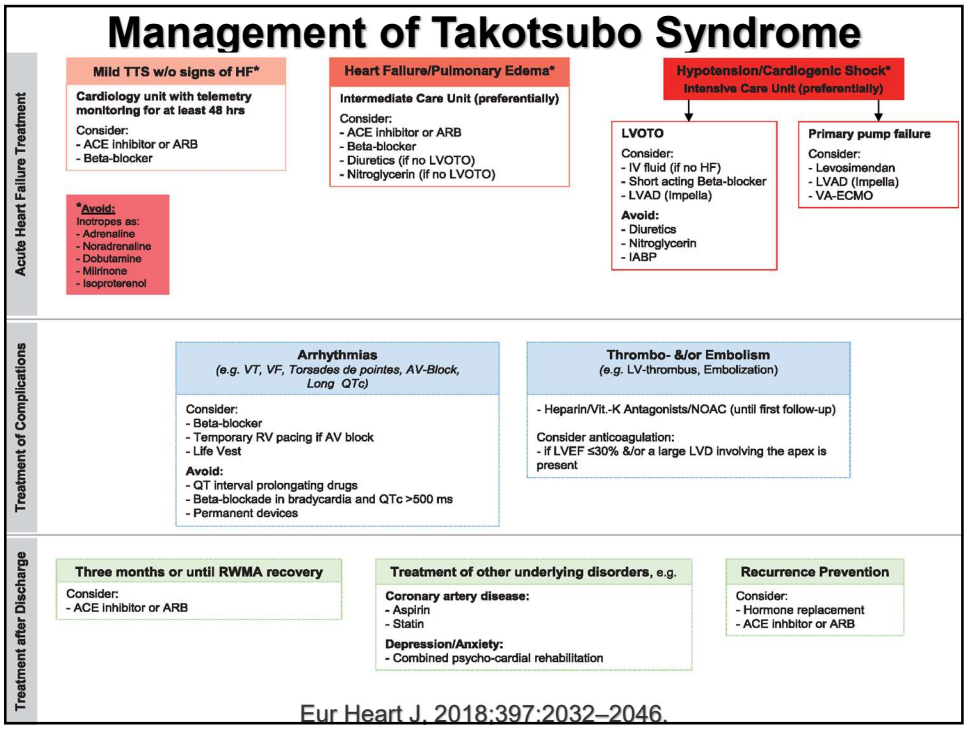
CONSIDERABLE Proportions of Patients showed DIFFERENT Ballooning Patterns & Triggering Conditions between Index and Recurrent TTS Events

- 1,402 TTS patients
- Mean FU 921 ± 883 days.
- Recurrent TTS events in 66 patients (4.7%) from 30 days to 9.9yrs after index admission.
- Incidence of recurrence rate = 18.7 cases/1,000 patient-yrs.

Ken Kato et al. JACC 2019;73:982-984



JACC 2018;72:1955-1971



Eur Heart J. 2018;397:2032–2046.

Medical Treatment of Stress Cardiomyopathy

Authors	Patients (n)	Design of study	Medication	Outcome measures	Follow-up time	Effect
Santoro *et al* [67]	13	Case series	Levosimendan	Adverse events	During hospitalisation	Probably beneficial
Isogai *et al* [68]	2110	Retrospective	β-blockers	Mortality	30 days	Not beneficial
Dias *et al* [69]	206	Retrospective	Antiplatelet	MACE	During hospitalisation	Beneficial
			β-blockers			Not beneficial
			Statins			Not beneficial
			ACEI			Not beneficial
Templin *et al* [4]	1118	Retrospective	β-blockers	Mortality	1 year	Not beneficial
			ACEI/ARB			Beneficial
Santoro *et al* [70]	511	Meta-analysis	β-blockers	Recurrence	24–60 months	Not beneficial
			ACEI/ARB			Not beneficial
			Aspirin			Not beneficial
			Statins			Not beneficial
Singh *et al* [71]	847	Meta-analysis	β-blockers	Recurrence	19–33 months	Not beneficial
			ACEI/ARB			Beneficial

Take Home Points (I)

- Takotsubo cardiomyopathy is a syndrome of transient dysfunction of apical/midventricular LV with compensatory hyperkinesis of basal segment resulting in apical ballooning.
- Triggered by significant emotional or physical stress.
- More common in post-menopausal women.
- Presentation is similar to MI (symptoms, ECG changes, and biomarker elevations). Accounts for ~1-2% of suspected ACS cases.
- No significant coronary artery disease or evidence of plaque rupture can be identified.
- LV function recovers, typically within 4 weeks.

Take Home Points (II)

- Treatment supportive. Mx/Prevention of complications & recurrence. Echo assessed (Shock, LVOTO, MR, apical clot)
- ACEI/ARB improved survival at 1-year follow-up even after propensity matching.
- No survival benefit for beta-blockers use.
- Recurrences are common, 2-4% per year and up to 20% at 10 years. Death 1-4.5%.
- More than a cardiac disease. Requires a new and interdisciplinary approach to increase awareness among physicians at large and public.
- Further RCT trials for effective & evidence-based treatment