Takotsubo Cardiomyopathy

(BROKEN HEART SYNDROME)

Takotsubo Cardiomyopathy

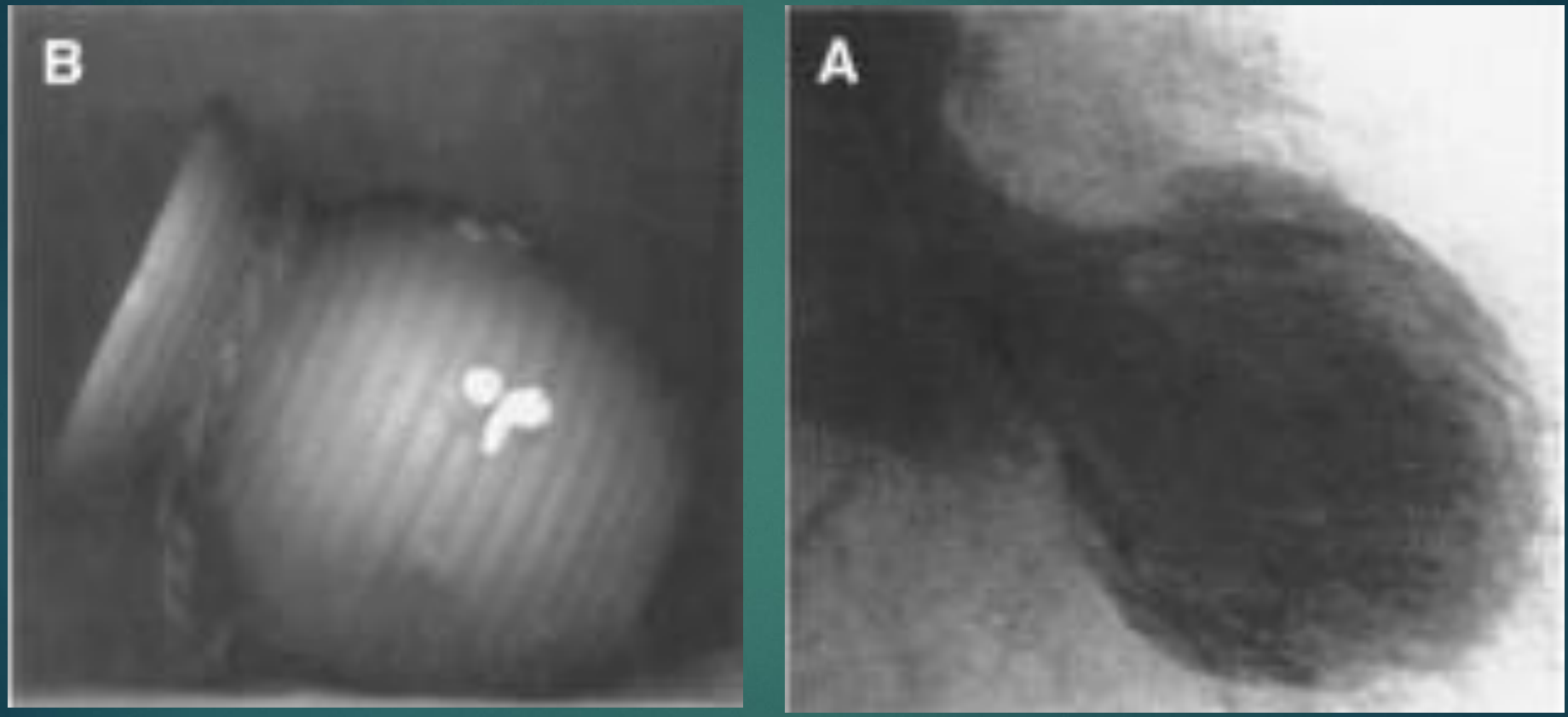
- Cardiomyopathy characterized by transient apical and midventricular LV dysfunction in the absence of significant coronary artery disease that is triggered by emotional or physical stress.
  - In setting of depressed/abnormal function of distal and apical LV segments there is compensatory hyperkinesis of basal walls → "ballooning" of apex during systole.
- Typically recover normal LV function in 1-4 weeks.

Takotsubo Cardiomyopathy

- 1st described in Japan in 1991
- Named after the tako-tsubo, which is an octopus trap
  - Shape of the trap is similar to the appearance of LV apical ballooning noted in patients with this form of cardiomyopathy
- Was later described elsewhere as w
  increasingly recognized.

Takotsubo Cardiomyopathy

Takotsubo Cardiomyopathy



Kurisu, S., *et al.* 2002. *American Heart Journal.* 143: 448-455.

Aliases

- Takotsubo cardiomyopathy
- Stress-induced cardiomyopathy
- Transient left ventricular apical ballooning syndrome
- Apical ballooning syndrome
- Broken heart syndrome
- Ampulla cardiomyopathy

Takotsubo Cardiomyopathy

- May account for up to 2% of suspected ACS
- In-hospital mortality ranges 0-8%
- Much more common in women (~90%), especially postmenopausal women (>80% of cases)
- Mean age 58-75 years
- Triggers: death of loved one, other catastrophic news, devastating financial losses, natural disasters, physical illness/ICU, etc.

Epidemiology (cont.)

Several series of Asian and Western populations suggest that 1-2% of patients with suspected ACS are eventually diagnosed with TS.

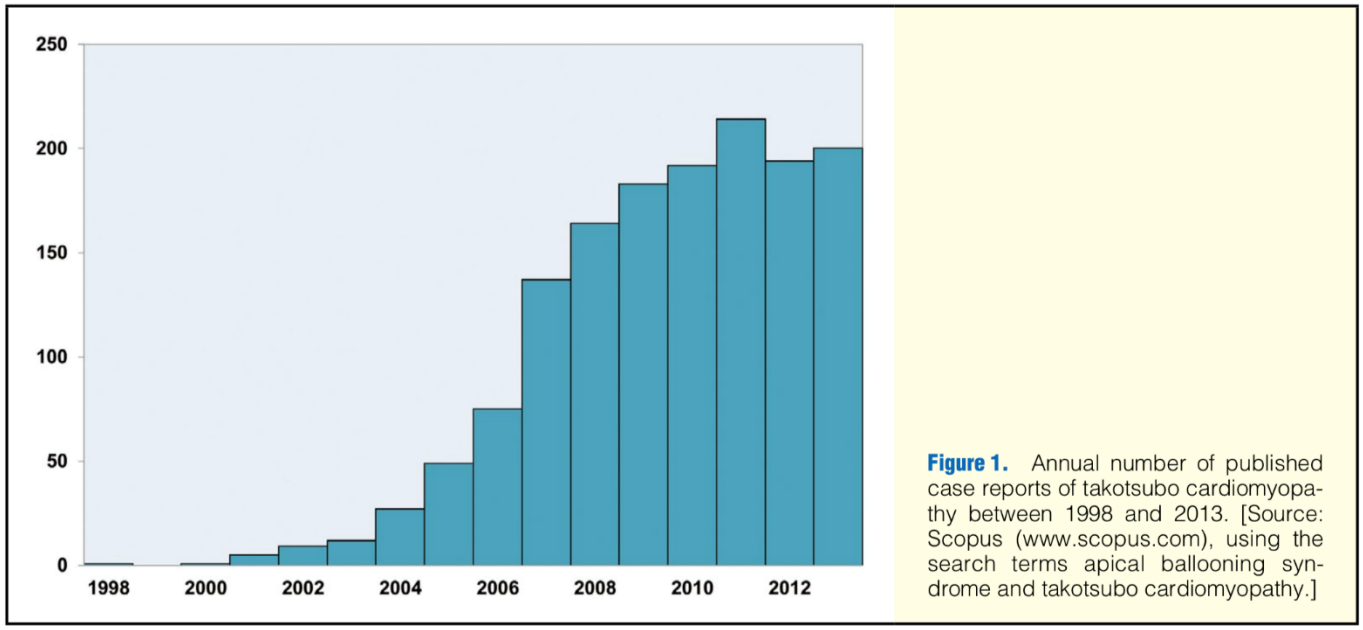


Figure 1. Annual number of published case reports of takotsubo cardiomyopathy between 1998 and 2013. [Source: Scopus (www.scopus.com), using the search terms apical ballooning syndrome and takotsubo cardiomyopathy.]

Predisposition and Risk factors:

- **Hormonal factors:**
  - Postmenopausal females (women older than 55 years have an five-fold risk of TS)
  - However, systemic data demonstrating a clear link between oestrogen levels and TS are lacking so far.

- **Genetic factors**:
  - Have not have enough data/research/trials to provide strong evidence for a genetic predisposition in TS.

- **Psychiatric and neurologic disorders:**
  - A high prevalence of psychiatric and neurologic disorders has been reported in patients with TS.
  - Stroke, subarachnoid haemorrhage and seizures: TS has been reported to occur.
  - Anxiety and depression appear more common in TS than in patients with STEMI.

Proposed Diagnostic Criteria

1. Transient a/dyskinesis of apical and midventricular segments in association with regional wall motion abnormalities that extend beyond the distribution of a single epicardial vessel
2. Absence on angiography of obstructive coronary artery disease or evidence of acute plaque rupture
3. New ST segment elevation or T wave inversions on ECG
4. Absence of recent significant head trauma, intracranial bleeding, pheochromocytoma, myocarditis, or hypertrophic cardiomyopathy

Proposed by Bybee, *et al.* 2004. *Annals of Internal Medicine.* 141: 858-865.

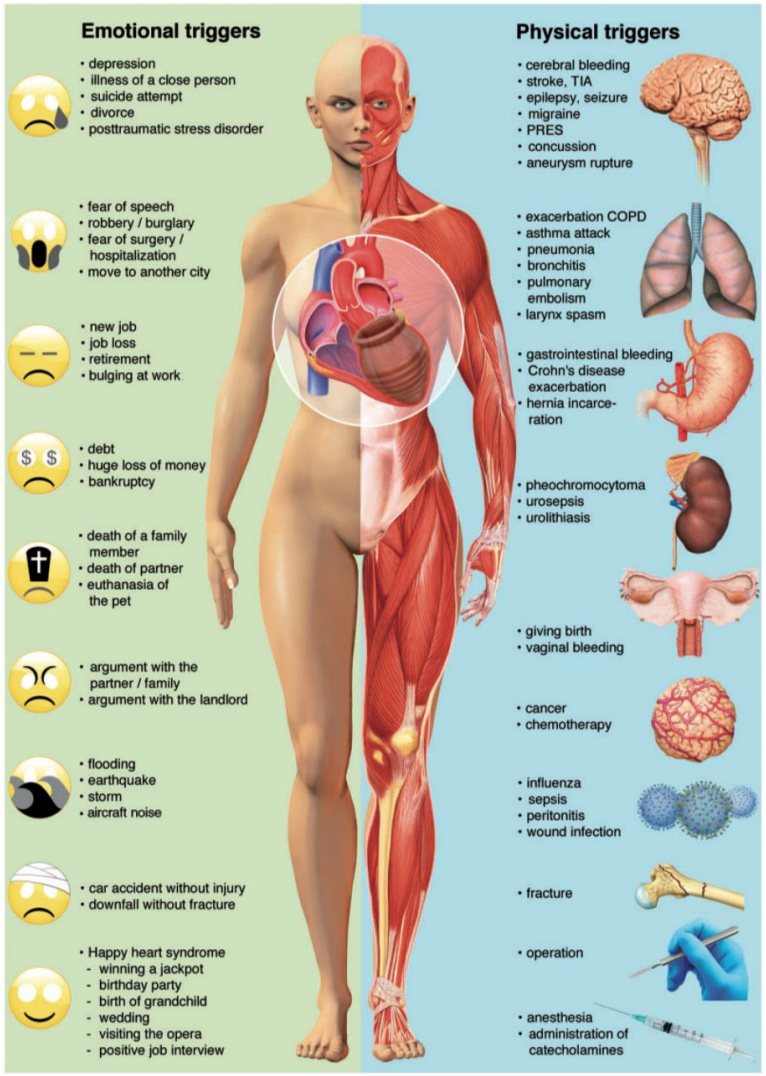
European Heart Failure Association Diagnostic Criteria

- 1. **Transient regional wall motion abnormalities** of left ventricular or right ventricular 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 pathologic conditions to explain the pattern of temporary left ventricular dysfunction observed (eg, hypertrophic cardiomyopathy, viral myocarditis).
- 4. **New and reversible electrocardiography abnormalities** (ST-segment elevation, ST depression, left bundle branch block, T-wave inversion, and/or QTc prolongation during the acute phase (3 months).
- 5. **Significantly elevated serum natriuretic peptide** (B-type natriuretic peptide or N -terminal pro B-type natriuretic peptide) during the acute phase.
- 6. **Positive but relatively small elevation in cardiac troponin** measured with a conventional assay (ie, disparity between the troponin level and the amount of dysfunctional myocardium present).
- 7. **Recovery of ventricular systolic function on cardiac imaging** at follow-up (3–6 months).

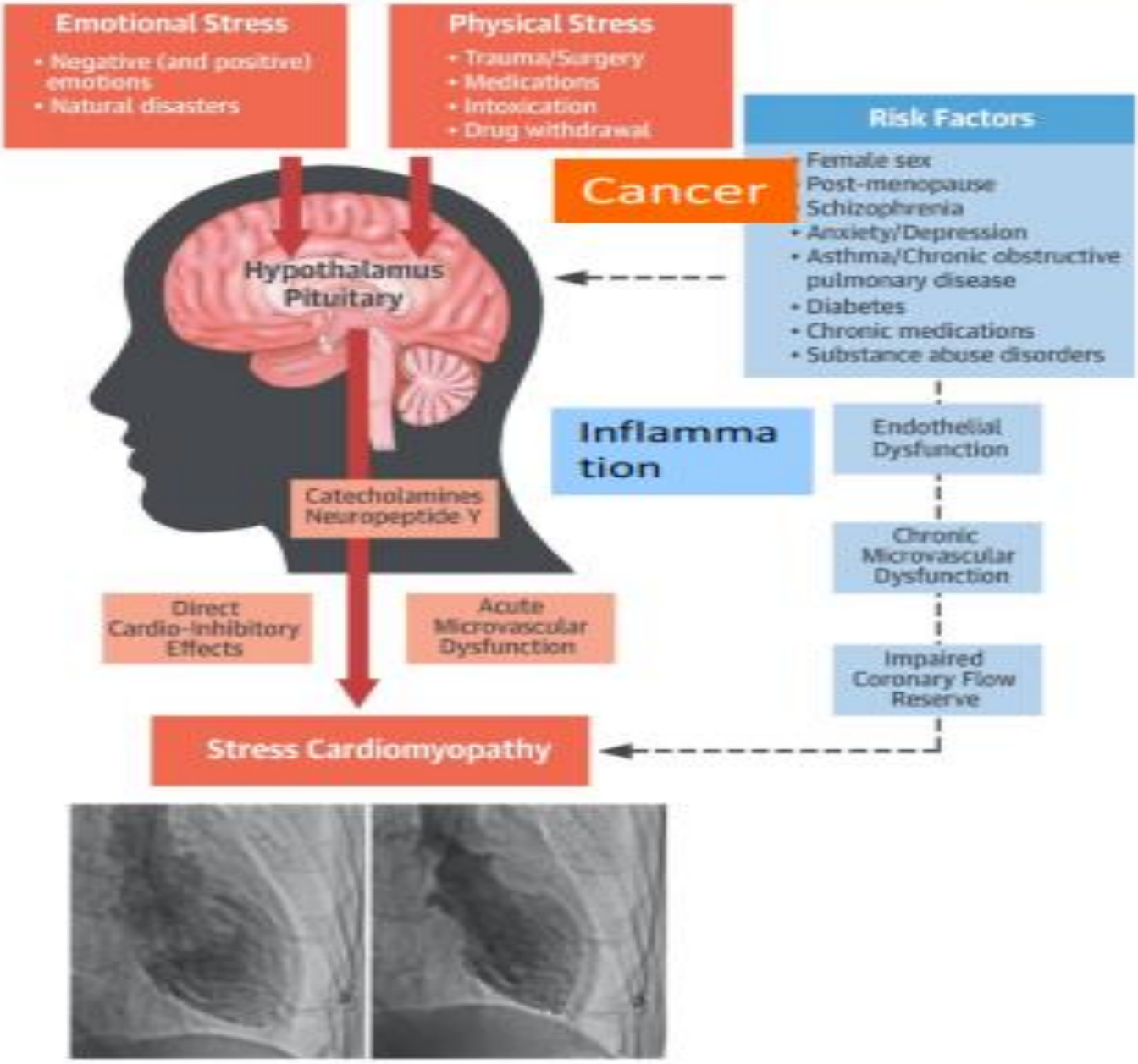
(Postulated) Pathogenesis

- **Catecholamine excess**
  - Norepinephrine levels are elevated in ~75% in some studies
  - Plasma catecholamines are significantly higher than in cases of MI
  - May induce microvascular spasm or dysfunction→ myocardial stunning or direct myocardial toxicity
  - Limited endomyocardial biopsy data c/w histologic signs of catecholamine toxicity
- Coronary artery spasm or microvascular spasm
- Myocarditis

Trigger:
Emotional stressors.
Physical stressors.



CENTRAL ILLUSTRATION: Pathophysiology of Stress Cardiomyopathy

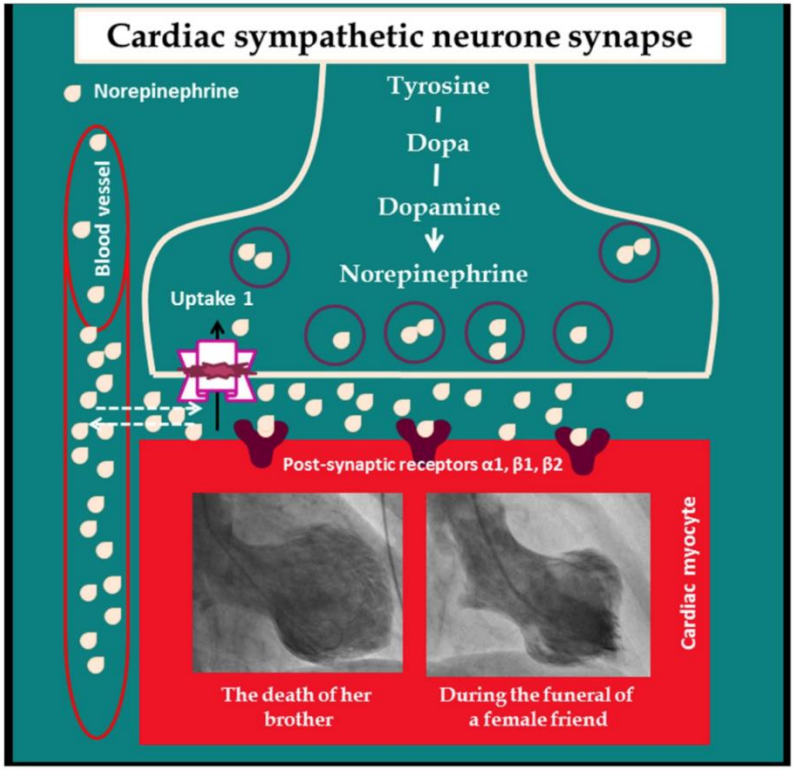


Medina de Chazal, H. et al. J Am Coll Cardiol. 2018;72(16):1955–71.

Pathophysiology

Box 3 Summary of pathophysiological hypotheses

Vascular	Acute multivessel coronary spasm.
	Aborted myocardial infarction with spontaneous recanalization.
	Acute increased ventricular afterload.
Myocardial	Acute left ventricular outflow tract obstruction.
	Direct catecholamine-mediated myocardial stunning.
Vascular and myocardial	Integrated cardiovascular physiology (a cardio-circulatory syndrome).



Presentation… (similar to acute MI)

- Substernal chest pain
- ECG abnormalities
  - ST elevation (usually anterior precordial leads)- 82%
  - ST depression
  - T wave inversion
  - QT prolongation
  - Abnormal Q waves
- Elevated cardiac biomarkers
- Dyspnea
- Shock
- Syncope

Evaluation

- Because presentation is similar to ACS, proceed to cardiac catheterization/PCI, if available, or fibrinolysis.
- LV ventriculogram and/or echocardiography can both be used to visualize apical ballooning with a/dyskinesis of apical ½ to ⅔ of the LV.
  - Average LV EF range 20-49%
  - Can have "atypical" ballooning of the middle or basal portions of the LV (much less common)
  - Wall motion abnormalities typically involve the distribution of more than one coronary artery
- Ventriculography and echocardiography also allow evaluation for LV outflow tract obstruction (~16%).
- Cardiac catheterization reveals lack of flow limiting coronary lesions or evidence of plaque rupture.

Diagnostic workup in TS:

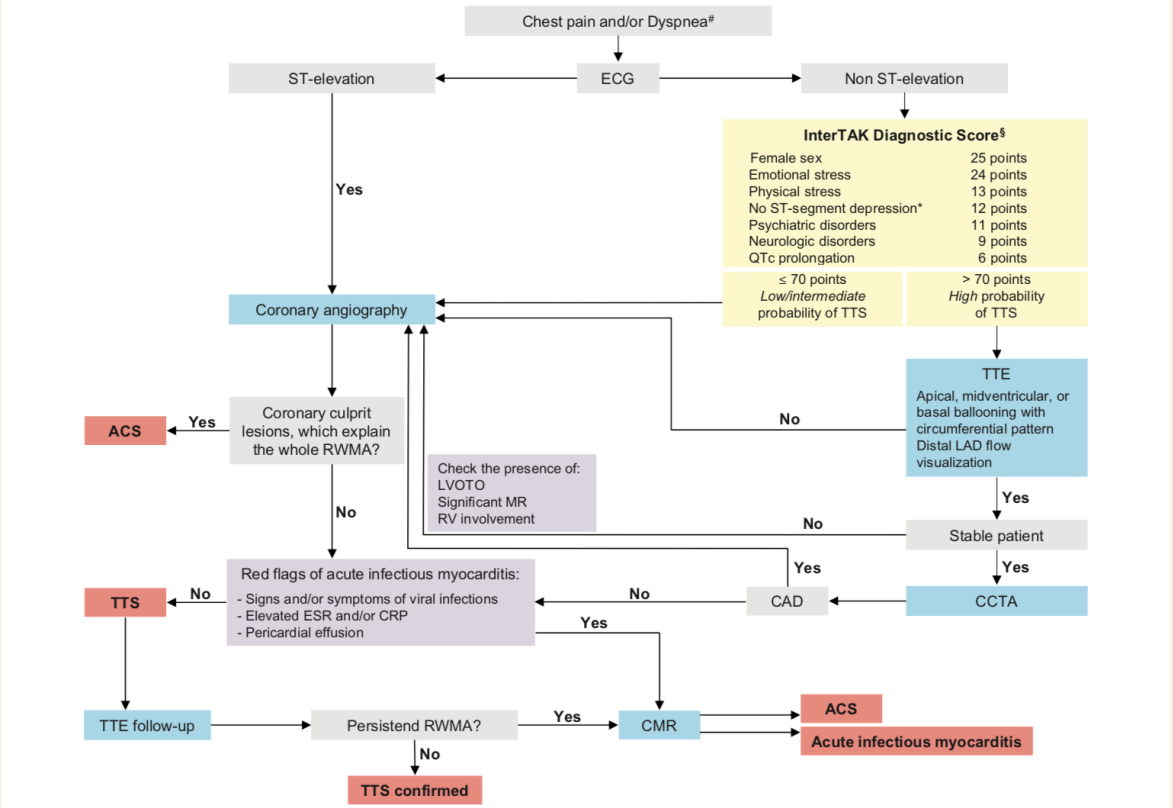


Figure 1 Diagnostic algorithm of takotsubo syndrome. #Applied to patients who are seeking medical emergency departments with e.g. chest pain and/or dyspnoea. §The InterTAK Diagnostic Score did not include patients with pheochromocytoma induced takotsubo syndrome in which atypical pattern are more frequently noted. *Except in lead aVR. ACS, acute coronary syndrome; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; CRP, c-reactive protein; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; InterTAK, International Takotsubo Registry; LAD, left anterior descending coronary artery; LVOTO, left ventricular outflow tract obstruction; MR, mitral regurgitation; QTc, QT-time corrected for heart rate; RV, right ventricle; RWMA, regional wall motion abnormality; TTE, transthoracic echocardiography; TTS, takotsubo syndrome.

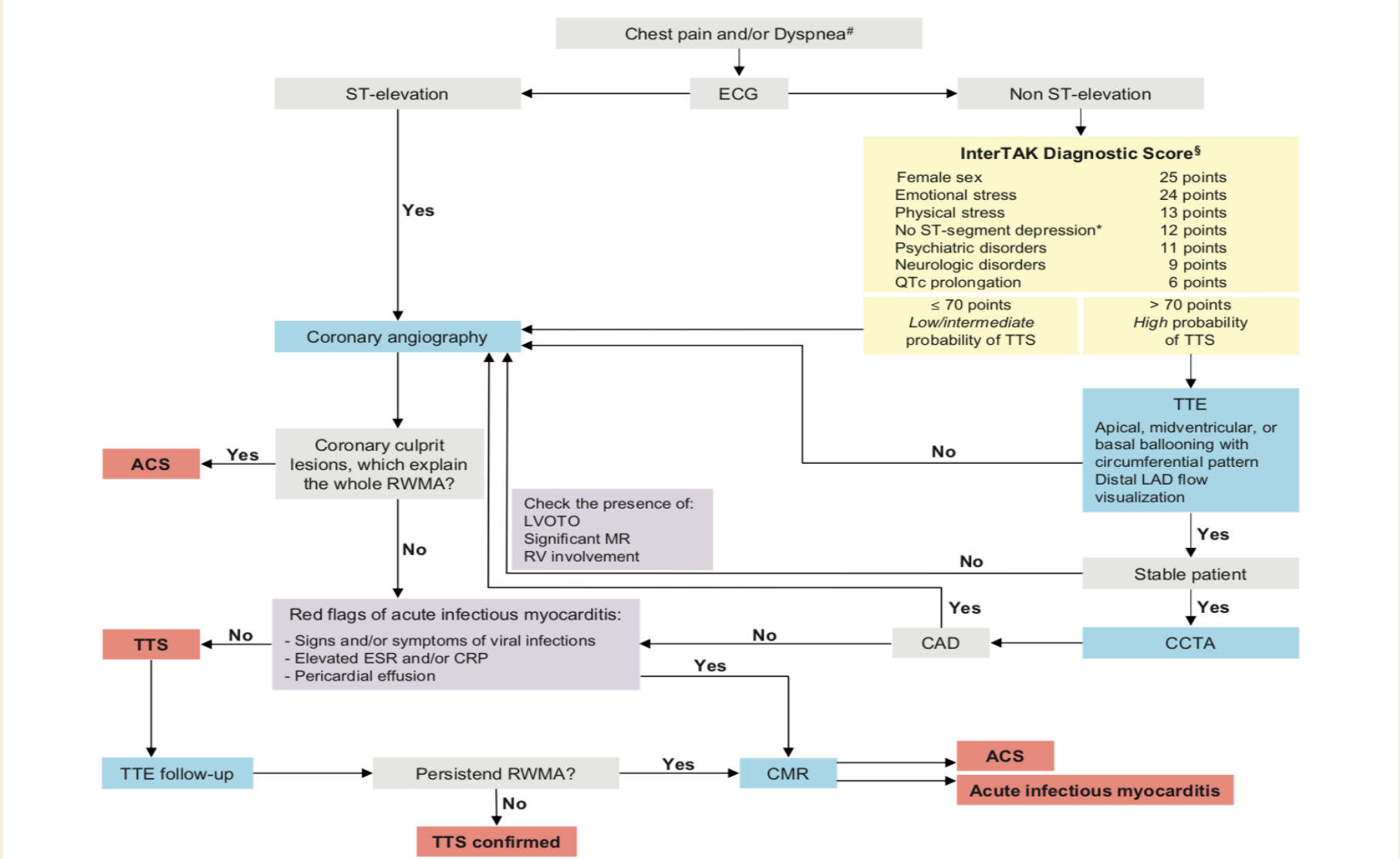


Figure 1 Diagnostic algorithm of takotsubo syndrome. #Applied to patients who are seeking medical emergency departments with e.g. chest pain and/or dyspnoea. §The InterTAK Diagnostic Score did not include patients with pheochromocytoma induced takotsubo syndrome in which atypical pattern are more frequently noted. *Except in lead aVR. ACS, acute coronary syndrome; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; CRP, c-reactive protein; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; InterTAK, International Takotsubo Registry; LAD, left anterior descending coronary artery; LVOTO, left ventricular outflow tract obstruction; MR, mitral regurgitation; QTc, QT-time corrected for heart rate; RV, right ventricle; RWMA, regional wall motion abnormality; TTE, transthoracic echocardiography; TTS, takotsubo syndrome.

Roles of Diagnostic Investigators in Risk Stratification in TS

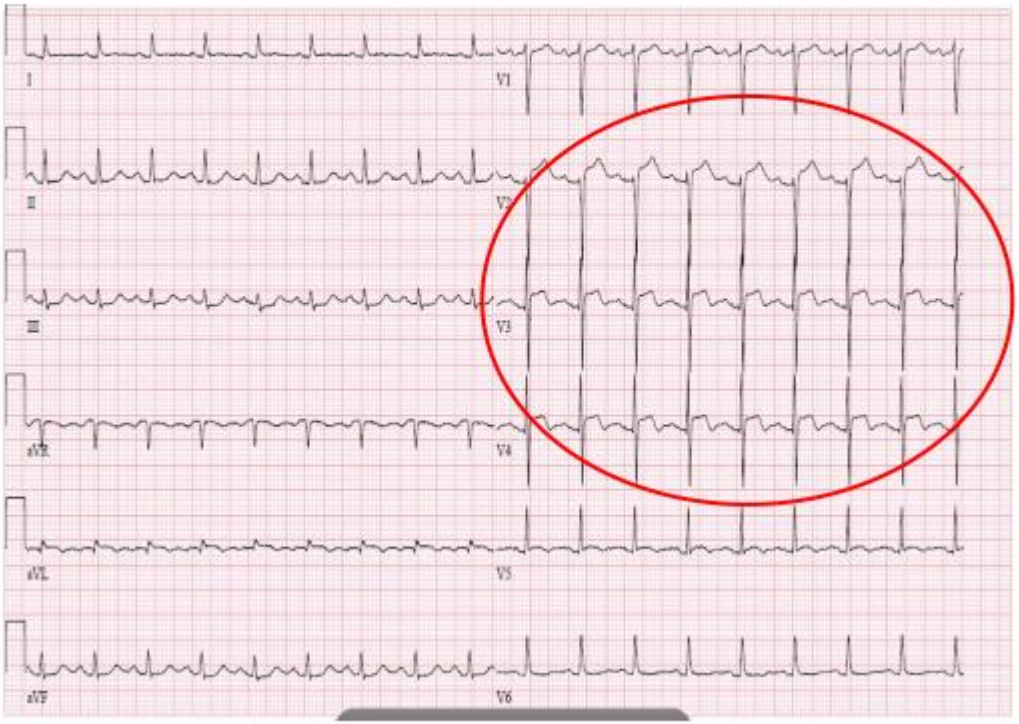
- Biomakers:
  - NT-proBNP: more valuable to prognosis in compare to Troponin essays.
- Electrocardiogram
- Echocardiogram
- Coronary angiography and left ventriculography
- Cardiac magnetic resonance
- Coronary computed tomography angiography.
- Radionuclide imaging

Box 4 Heart Failure Association risk stratification in Takotsubo syndrome

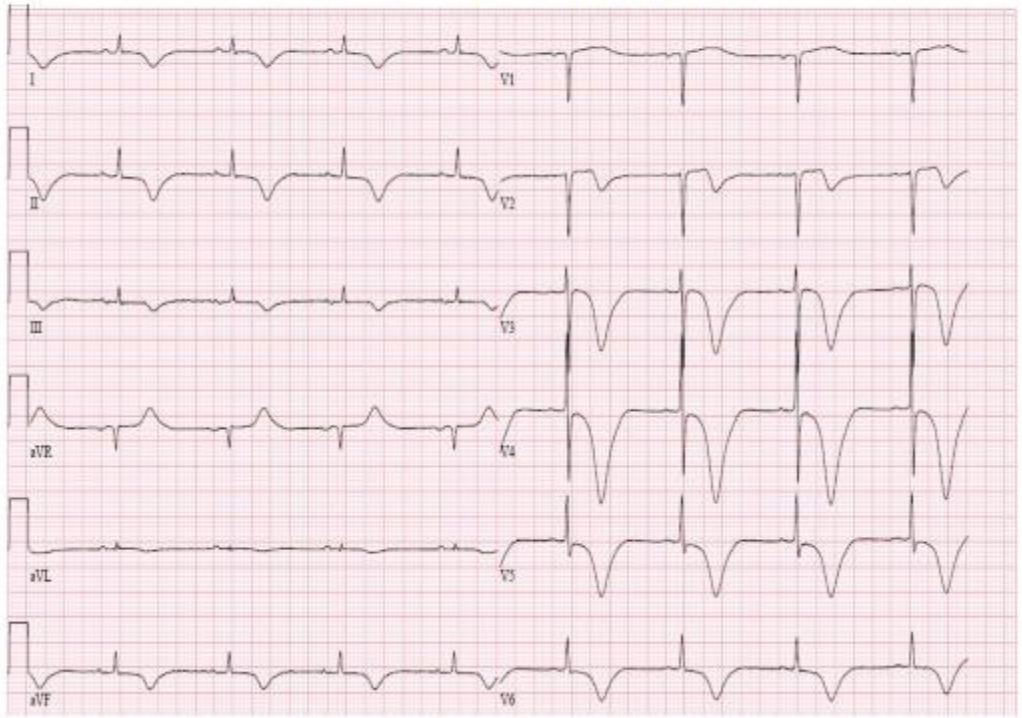
Risk factor	Higher risk	Lower risk
MAJOR RISK FACTORS		
Age	≥75 years	See minor risk factors[a]
Systolic BP	<110 mmHg	≥110 mmHg
Clinical pulmonary oedema[b]	Present	Absent
Unexplained syncope, VT or VF	Present	Absent
LVEF	<35%	See minor risk factors[a]
LVOTO	≥40 mmHg	Absent or <40 mmHg
Mitral regurgitation[c]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

BP, blood pressure; LVOTO, left ventricular outflow tract obstruction; VF, ventricular fibrillation; VSD, ventricular septal defect; VT, ventricular tachycardia.
[a]See minor criteria regarding LVEF in the absence of major criteria.
[b]Lower zone (basal) pulmonary rales on clinical examination or evidence on chest X-ray.
[c]Moderate or severe mitral regurgitation.
[d]≥3 days.

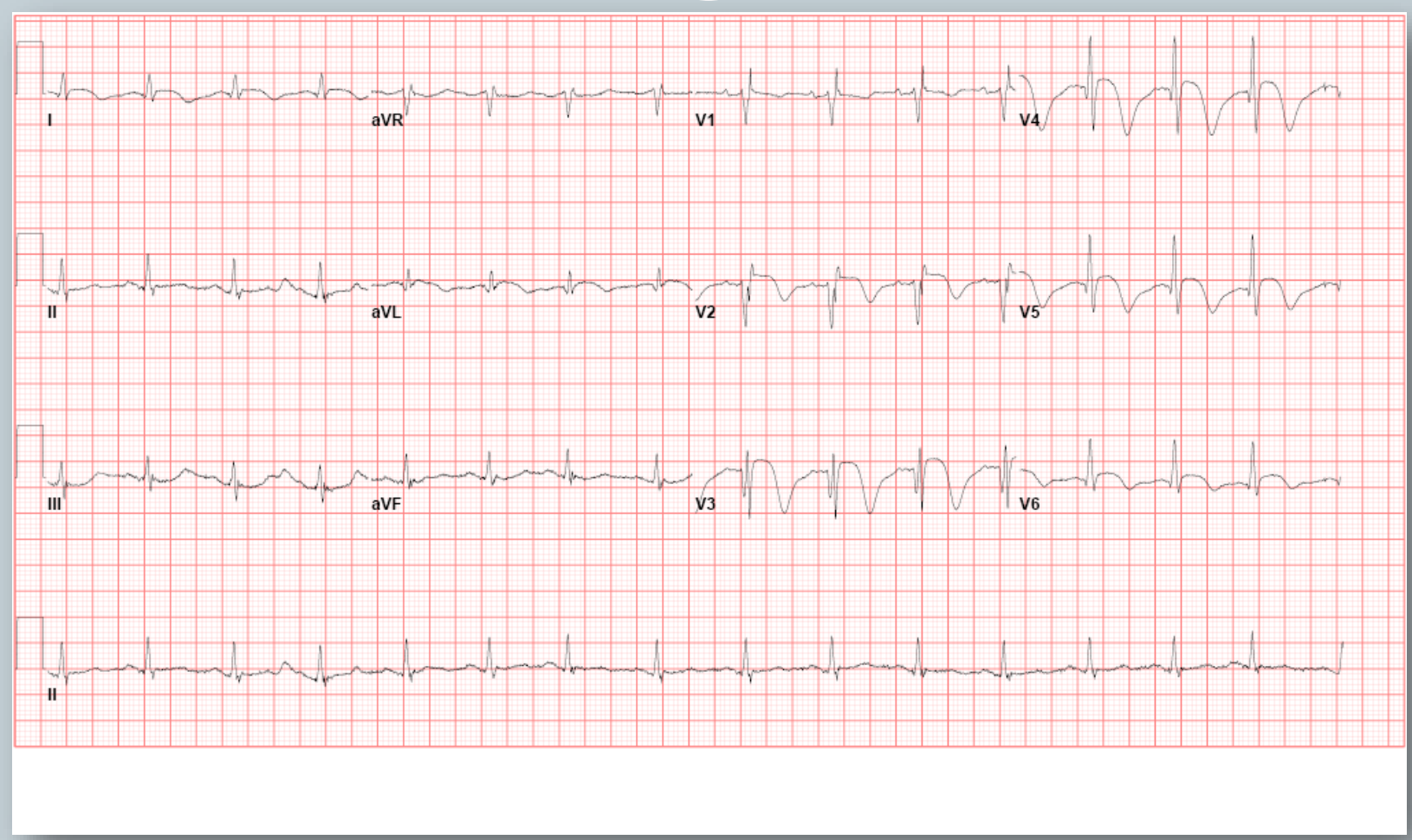
ECG: Presentation

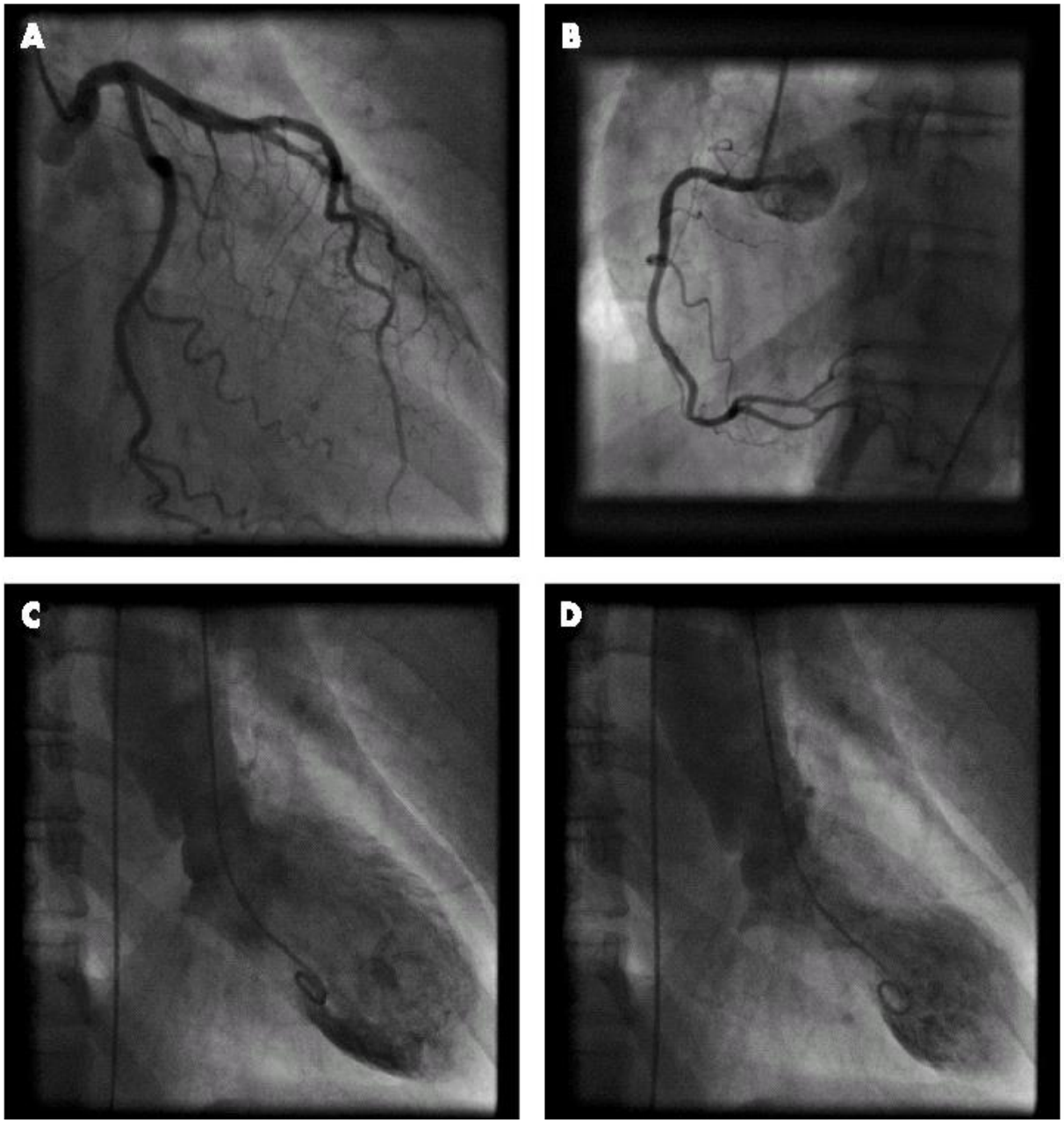


ECG: Day 3 post Presentation



ECG

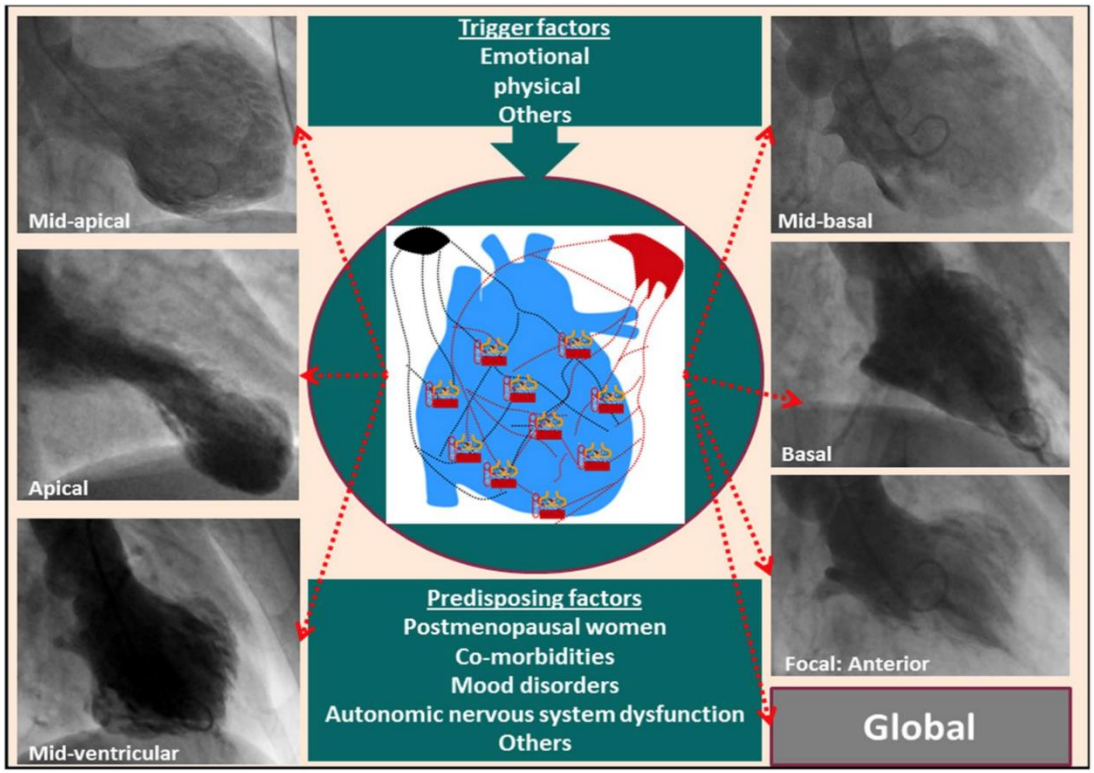




Nef HM, et al. Tako-tsubo Cardiomyopathy (Apical Ballooning). Heart. 2007; 93:1309-1315.

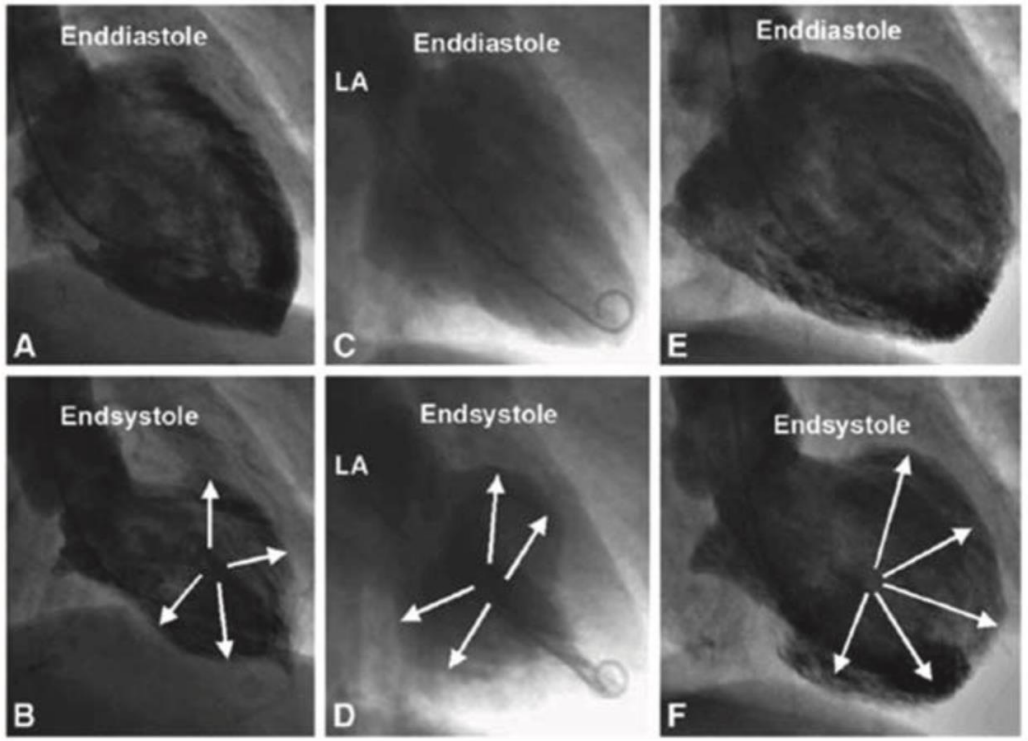
Anatomical variants of Takotsubo Syndrome (cont.)

Fig. 2 An emotional or a physical trigger in predisposed individuals may result in diverse left ventricular contraction patterns (midapical, apical, midventricular, midbasal, basal, focal, and global). The figure is modified from Y-Hassan S and De Palma R [1] with copyright permission

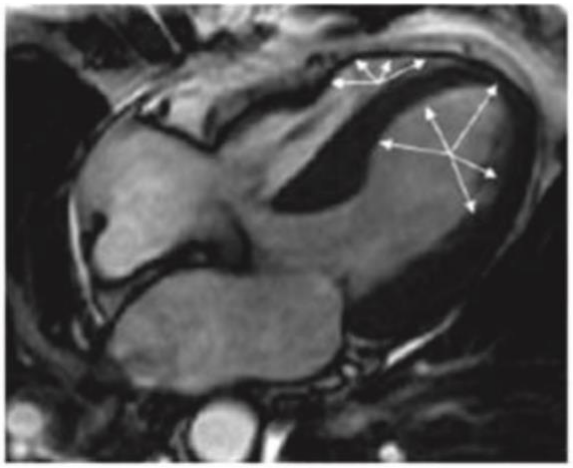


Anatomical variants of Takotsubo Syndrome (cont.)

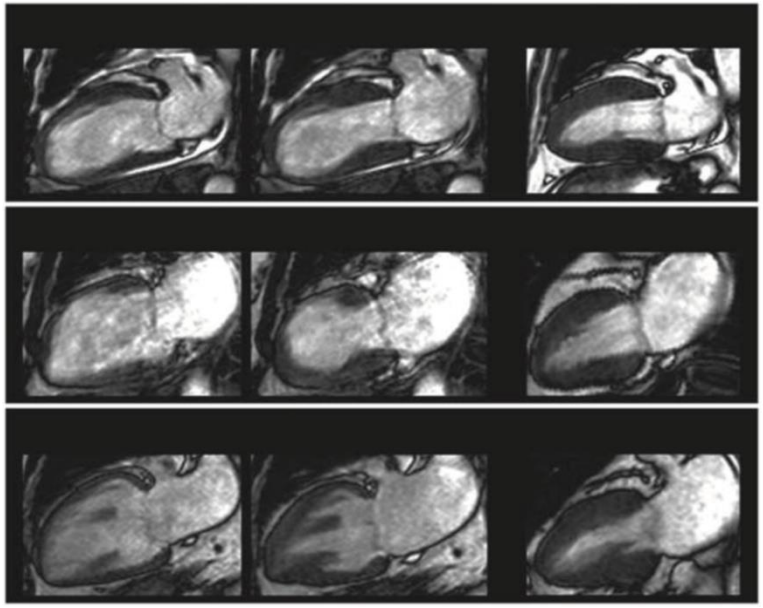
- Mid- ventricular variant (A+B).
- An inverted Takotsubo variant (C+D).
- Typical apical variant (E+F).



Anatomical variants of Takotsubo Syndrome (cont.)



Biventricular involvement with
RV and LV hypokinesia



Typical variant

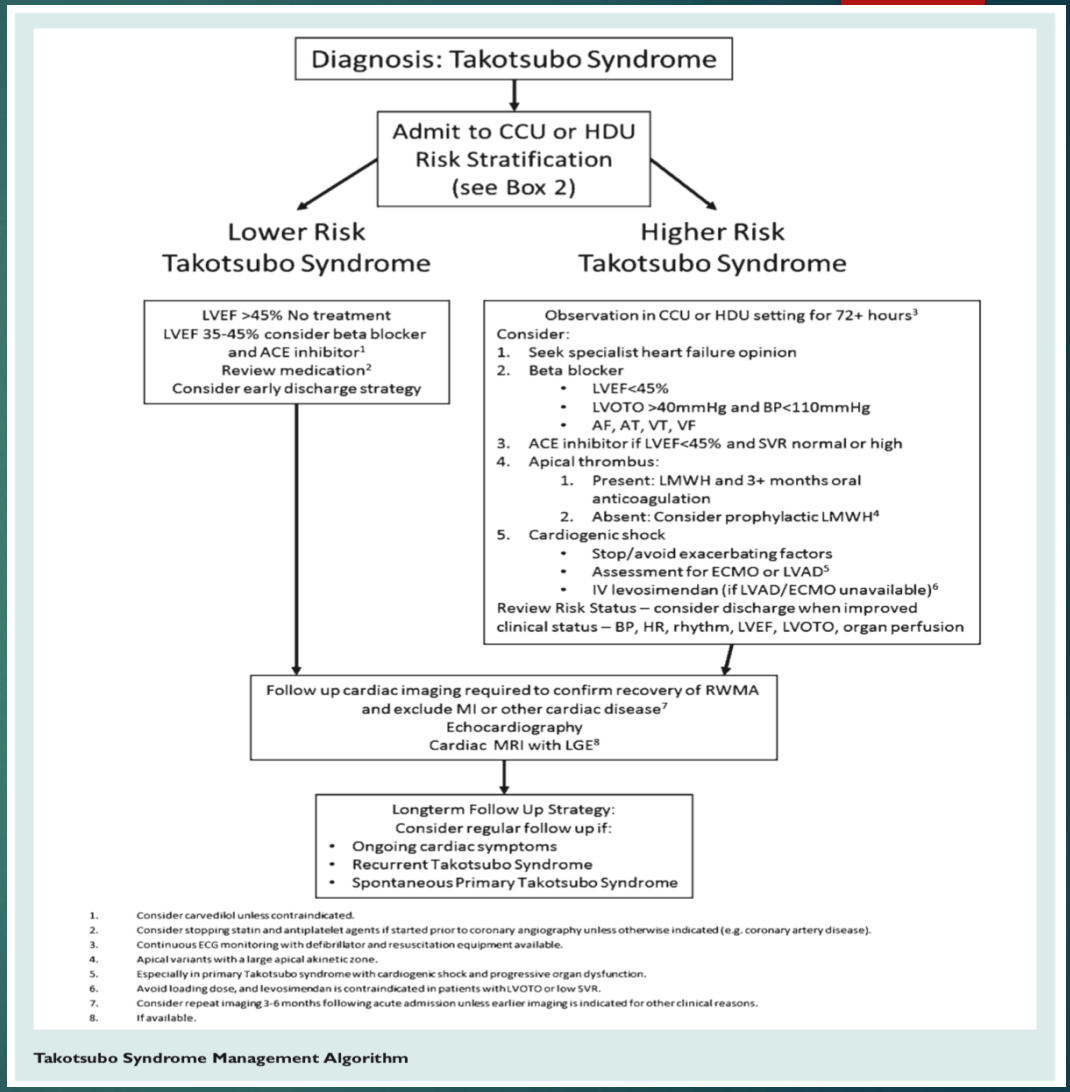
Mid-ventricular variant

Inverted variant

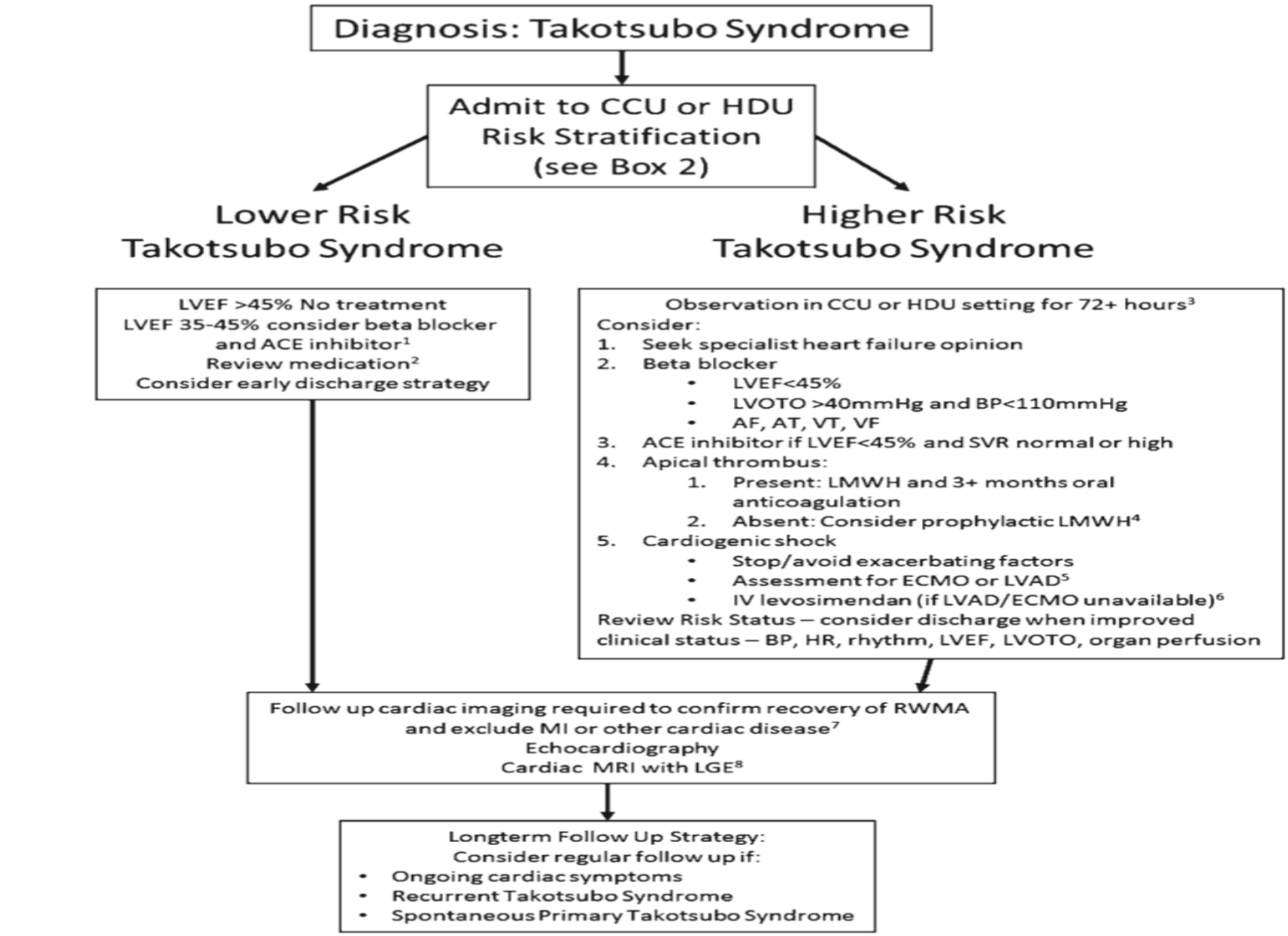
Acute Complications

- Tachyarrhythmias, bradyarrhythmias
- Pulmonary edema
- Cardiogenic shock
- Transient LV outflow tract obstruction
- Mitral valve dysfunction
- Acute thrombus formation and stroke
- Death

Management bases on Risk Stratification on the admission of TS



Takotsubo Syndrome Management Algorithm



1. Consider carvedilol unless contraindicated.
2. Consider stopping statin and antiplatelet agents if started prior to coronary angiography unless otherwise indicated (e.g. coronary artery disease).
3. Continuous ECG monitoring with defibrillator and resuscitation equipment available.
4. Apical variants with a large apical akinetic zone.
5. Especially in primary Takotsubo syndrome with cardiogenic shock and progressive organ dysfunction.
6. Avoid loading dose, and levosimendan is contraindicated in patients with LVOTO or low SVR.
7. Consider repeat imaging 3-6 months following acute admission unless earlier imaging is indicated for other clinical reasons.
8. If available.

Management of Takotsubo Syndrome:

- Acute Heart Failure Treatment
- Treatment of Complication
- Treatment after Discharge.

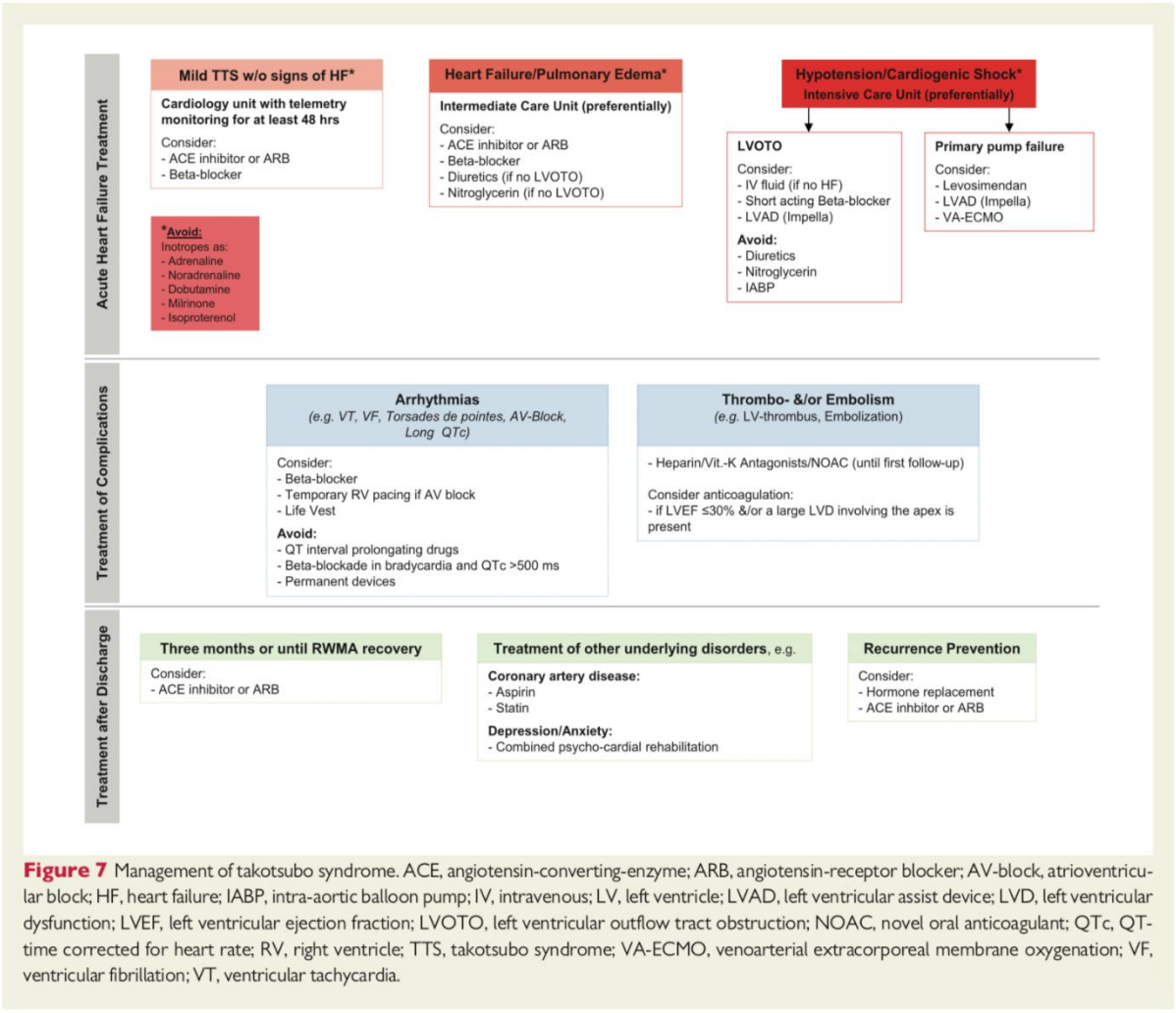


Figure 7 Management of takotsubo syndrome. ACE, angiotensin-converting-enzyme; ARB, angiotensin-receptor blocker; AV-block, atrioventricular block; HF, heart failure; IABP, intra-aortic balloon pump; IV, intravenous; LV, left ventricle; LVAD, left ventricular assist device; LVD, left ventricular dysfunction; LVEF, left ventricular ejection fraction; LVOTO, left ventricular outflow tract obstruction; NOAC, novel oral anticoagulant; QTc, QT-time corrected for heart rate; RV, right ventricle; TTS, takotsubo syndrome; VA-ECMO, venoarterial extracorporeal membrane oxygenation; VF, ventricular fibrillation; VT, ventricular tachycardia.

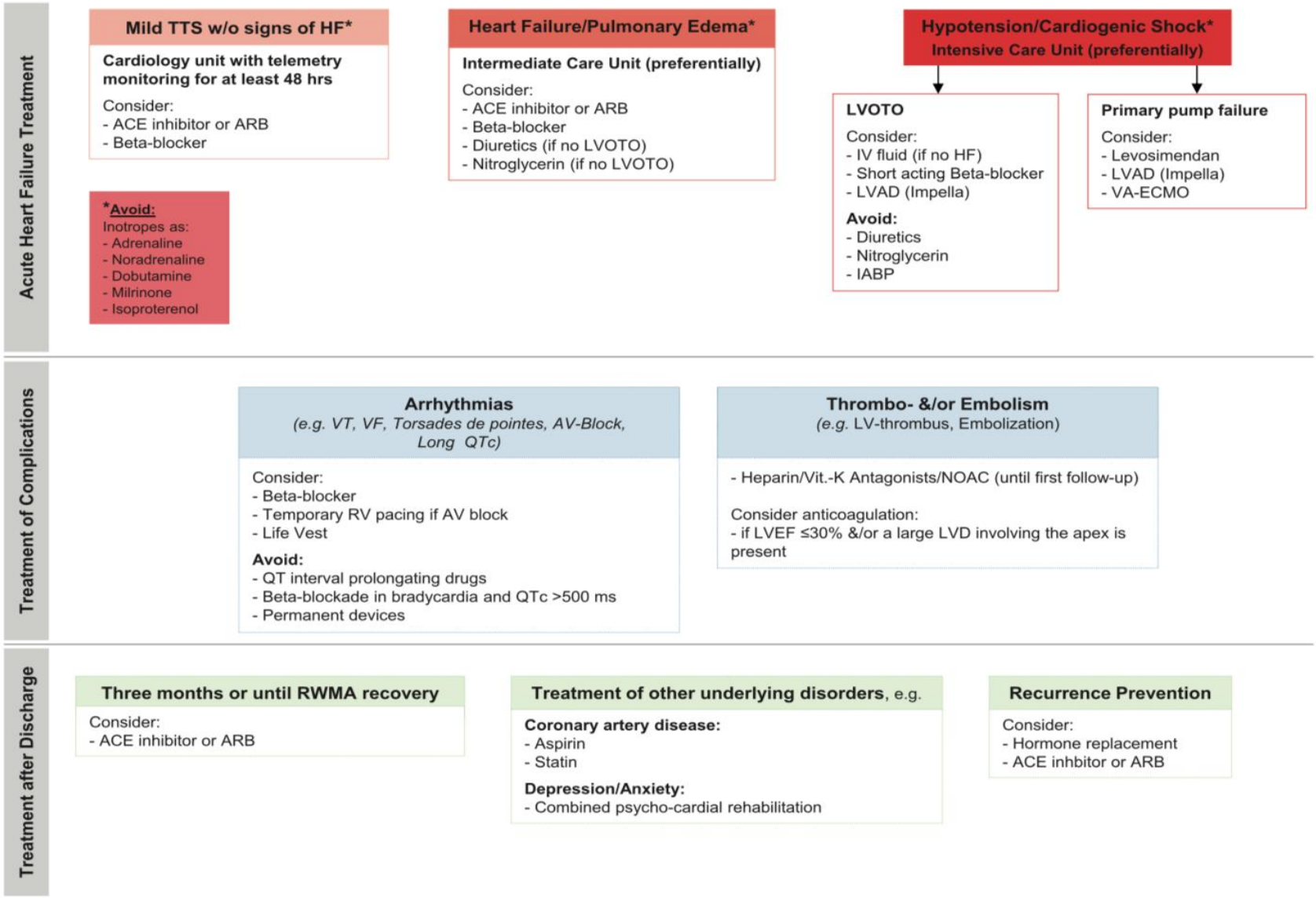


Figure 7 Management of takotsubo syndrome. ACE, angiotensin-converting-enzyme; ARB, angiotensin-receptor blocker; AV-block, atrioventricular block; HF, heart failure; IABP, intra-aortic balloon pump; IV, intravenous; LV, left ventricle; LVAD, left ventricular assist device; LVD, left ventricular dysfunction; LVEF, left ventricular ejection fraction; LVOTO, left ventricular outflow tract obstruction; NOAC, novel oral anticoagulant; QTc, QT-time corrected for heart rate; RV, right ventricle; TTS, takotsubo syndrome; VA-ECMO, venoarterial extracorporeal membrane oxygenation; VF, ventricular fibrillation; VT, ventricular tachycardia.

Medical Management for Takotsubo Syndrome:

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

[a]Reprinted with permission from Kato *et al.*[139]
ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin-receptor blocker; MACE, major adverse cardiac event.

Management

- **Supportive, conservative therapy**
  - Hydrate, remove stress (if possible)
- **Treat LV dysfunction with standard heart failure regimen- including beta blocker, ACE inhibitor, diuretics (if volume overloaded), aspirin**
  - Usually treated for ~6 months
- **For pts who are hypotensive with shock, perform echo to evaluate for LVOT obstruction.**
  - No LVOT obstruction→ inotropes, IABP if needed
  - +LVOT obstruction→ NO inotropes (can worsen obstruction), use beta blockers (+/- a agonist Phenylephrine), IABP if needed
  - +/- fluid resuscitation (evaluate pulmonary status)

Complications and Outcomes

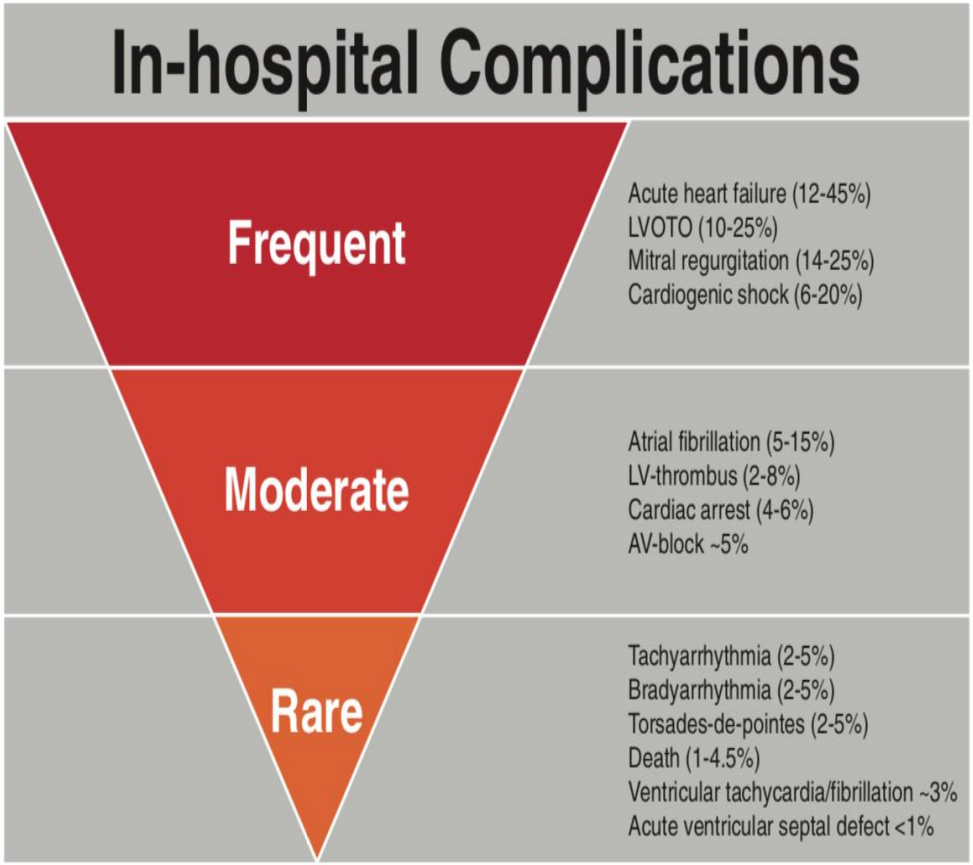


Figure 4 Overview of in-hospital complications according to their prevalence. AV, atrioventricular block; LV, left ventricle; LVOTO, left ventricular outflow tract obstruction.

Prognosis

Overall, good prognosis. If patient survives the acute phase, long-term prognosis is excellent.

- 0-8% in-hospital mortality, likely closer to 1-2%
- Recovery of LV function, typically in 1-4 weeks
- Late sudden death (rare) and recurrent disease (<10%) have been reported

Take Home Points

- Takotsubo cardiomyopathy is a syndrome of transient dysfunction of apical/midventricular LV with compensatory hyperkinesis of basal segment resulting in apical ballooning
- It is triggered by significant emotional or physical stress.
- It is 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.

Future directions:

- Studies has shown TS has morbidity and mortality rates that are comparable to those of ACS.
- There is much more to be uncovered surrounding TS and the underlying pathophysiology of the syndrome.
  - Why are women affected predominantly ?
  - What is the role of triggering factors in stress responses of the heart ?
  - Why do different TS phenotypes exist ?
  - Which patients are vulnerable to TS or prone to recurrence ?
  - Is there a genetic predisposition to TS ?
  - What is the exact pathogenesis of TS ?
  - Are there specific treatment options in the acute phase of TS and prevent recurrent ?