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# Takotsubo Syndrome: An International Expert Consensus Report on Practical Challenges and Specific Conditions (Part-1: Diagnostic and Therapeutic Challenges)

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**ABSTRACT**

In the recent years, there has been a burgeoning interest in Takotsubo syndrome (TTS), which is renowned as a specific form of reversible myocardial dysfunction. Despite the extensive literature available on TTS, clinicians still face several practical challenges associated with the

diagnosis and management of this phenomenon. This potentially results in the underdiagnosis and improper management of TTS in clinical practice. The present paper, the first part (part-1) of the consensus report, aims to cover diagnostic and therapeutic challenges associated with TTS along with certain recommendations to combat these challenges.

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## 1. INTRODUCTION

Since its first description over three decades ago,<sup>1</sup> fundamental concepts regarding the pathogenesis and clinical aspects of takotsubo syndrome (TTS) have rapidly evolved.<sup>2-5</sup> The word “takotsubo” refers to the Japanese word “octopus trap” based on the characteristic shape of the left ventricle (LV) at end-systole (**Figure 1**).<sup>5</sup> In the literature, there have been various alternative names of this syndrome including “apical ballooning syndrome”, “stress cardiomyopathy” and “broken heart syndrome”.<sup>5</sup> TTS has been a unique form of reversible cardiomyopathy usually arising in response to sudden adrenergic discharge particularly in post-menopausal women.<sup>2,5-7</sup> In general, TTS constitutes 1-3% of all cases with a suspected ST segment elevation myocardial infarction (STEMI).<sup>5</sup> Interestingly, this phenomenon has been an underdiagnosed cardiovascular condition possibly with an incidence far higher than reported. Many emotional (wrath, grief, fear, etc.) and physical triggers (major surgery, severe illness, etc.) accounting for sudden adrenergic discharge and consequent TTS evolution have been described.<sup>2,8</sup> Interestingly, TTS evolution due to positive emotional triggers (namely “happy heart syndrome”) may also be possible (2).<sup>2</sup> In the recent years, TTS has been increasingly reported in male patients particularly following a physical trigger.<sup>5</sup>

### 1.1. Pathogenesis

#### - Catecholamine toxicity and genetic predisposition

From a pathophysiologic perspective, myocardial stunning involving the affected territories (usually arising in a circumferential fashion with clear-cut borders, and hence; extending beyond the territory of a single coronary artery) along with a hypercontraction pattern in the residual segments has been regarded as the seminal



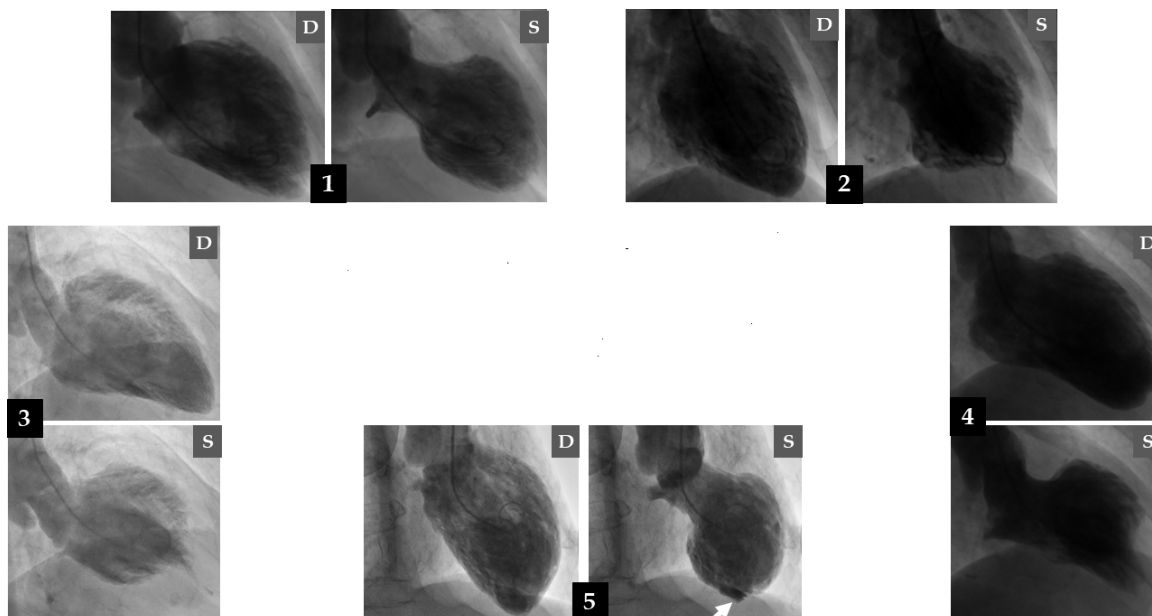
**FIG. 1.** Typical shape of “octopus trap” at end-systole on invasive ventriculogram in a patient with apico-midventricular TTS. TTS, Takotsubo syndrome.

aspect of this phenomenon.<sup>2-7</sup> The affected segments are usually akinetic (or rarely hypokinetic), and usually recover within days to a few months (usually around 3 months at the latest).<sup>7</sup> Myocardial adrenoceptors [beta 1 ( $\beta$ 1) and  $\beta$ 2] primarily account for positive inotropy through stimulation of “Gs-adenyl cyclase-cyclic adenosine monophosphate-protein kinase A” pathway under physiological conditions.<sup>2,7,8</sup> Based on current concepts, the potential mechanism of TTS evolution primarily appears to be the intense stimulation of  $\beta$ 1 adrenoceptors (leading to myocytolysis, apoptosis and oxidative stress) along with adrenaline-induced switch of  $\beta$ 2 adrenoceptors to the inhibitory pathway (Gi) mostly at the apex (leading to stunning and activation of anti-apoptotic pathways including phosphoinositide 3-kinase/protein kinase B).<sup>2,3,8</sup> The apex has the lowest density of sympathetic innervation along with a high density of adrenoceptors (particularly associated with a relatively limited sequestration of  $\beta$ 2 receptors due to lower density of sarcolemmal caveolae).<sup>2,3,8</sup> These features potentially render the apex particularly vulnerable to the impact of circulating catecholamines (including adrenaline) potentially leading to the characteristic TTS pattern namely “apical ballooning”.<sup>2,3,8</sup>

However, evidence against the theory of adrenaline-induced switch of  $\beta$ 2 adrenoceptors to the Gi also exists in the literature. Accordingly, certain previous reports documented normal or mildly elevated levels of circulating catecholamines or their metabolites in the acute and subacute phase of TTS potentially challenging the role of adrenaline in the evolution of apical ballooning.<sup>9-11</sup> Furthermore, atypical morphological variants (basal, midventricular, focal and biventricular TTS) have also been reported in the clinical setting.<sup>2,5,7</sup> These notions may suggest complex and poorly understood mechanisms (beyond adrenaline-mediated switch of  $\beta$ 2 receptors at the apex) in TTS pathogenesis.<sup>3,8</sup> **Figure 2** demonstrates various morphological patterns of TTS. In the context of adrenoceptor-mediated effects, disturbances in G protein coupled receptor kinases (including GRK 2 and 5), abnormal calcium handling and alterations in myofilament functions might also have important pathogenetic implications,<sup>3</sup> and might also be associated with individual variations in the evolution and severity of TTS episodes. Notably, genetic polymorphisms involving the adrenergic pathway might potentially lead to familial clustering of TTS.<sup>5,12,13</sup> Accordingly, genetic variants or mutations of certain genes including GRK5 and ADRB1, CACNG1 and PRKCA were previously reported to be associated with TTS predisposition (and TTS complications).<sup>12,13</sup>

#### - Alternative theories

On the other hand, studies analysing the impact of alternative factors (including coronary microvascular dysfunction, coronary spasm and coronary thrombus formation) on TTS evolution seem to be inconclusive.<sup>4,8</sup> However, systemic inflammation (and myocardial inflammation) might have potential implications in the evolution



**FIG. 2.** Various morphological patterns of takotsubo syndrome (TTS) on invasive left ventriculogram in the right anterior oblique view during diastole (D) and systole (S): (1) mid-apical pattern; (2) mid-ventricular pattern; (3) basal or mid-basal pattern (also termed inverted TTS); (4) focal pattern (focal anterior); (5) mid-apical pattern with apical tip-sparing namely the nipple sign (white arrow).

and prognosis of TTS.<sup>14</sup> Nitrosative stress due to peroxynitrite formation has been regarded as the seminal trigger of myocardial inflammation in TTS.<sup>8</sup> In this context, nitric oxide (NO) (generated via  $\beta_2$  receptor coupled Gi stimulation) binds to oxidative substances (generated via  $\beta_1$  receptor stimulation), and eventually leads to substantial formation of peroxynitrite anion (ONOO<sup>-</sup>).<sup>8</sup> However, the issue of whether myocardial inflammation serves as a substantial contributor or just an epiphenomenon in TTS evolution still needs to be established.<sup>14</sup> Notably, certain factors including estrogen deficiency<sup>2,3,7</sup> and oxidative stress<sup>8,15</sup> generally create a potential milieu, and reduces the threshold for TTS evolution in response to adrenergic discharge. Signs of metabolic shutdown (increased cellular fat and glycogen content along with mitochondrial abnormalities), contraction band necrosis and presence of pro-inflammatory cells (initial neutrophils replaced by macrophages) are generally evident on histopathological examination.<sup>2,7-14</sup>

### 1.2. Clinical presentation

On admission, clinical presentation strongly simulates acute coronary syndromes (ACSs) and/or acute heart failure (HF) (chest pain, dyspnea, electrocardiographic (ECG) changes including ST segment elevation, inverted T-waves, etc.) usually in the absence of obstructive coronary anatomy on invasive coronary angiogram (CAG).<sup>2,7</sup> However, presence of co-existing stable coronary artery disease (CAD) (or ACSs) has also been reported, and currently is not regarded as an exclusion criterion for TTS diagnosis.<sup>2-7</sup> Certain TTS

variants including basal TTS may be particularly associated with life-threatening conditions including subarachnoid hemorrhage and pheochromocytoma<sup>5</sup> that might present with rampant findings potentially masking the cardiovascular manifestations of the associated TTS episode. In agreement with ACS therapies, management strategies of TTS have been mostly based on initiation of  $\beta$ -blockers, renin-angiotensin system blockers and management of complications.<sup>2,7,8</sup> Notably, prognosis of this syndrome may not be so benign as was previously suggested.<sup>7</sup> Therefore, patients with TTS may suffer a variety of complications including malignant arrhythmias, mechanical complications, and even death potentially suggesting proper risk-stratification and management of these patients in the hospital setting.<sup>2,6,7,8,14</sup> The present paper constitutes the first part of the consensus report. Its main focus is to review potential diagnostic and therapeutic challenges in the setting of TTS.

## 2. DIAGNOSTIC CHALLENGES IN THE SETTING OF TTS: HOW TO ESTABLISH THE FINAL DIAGNOSIS

### 2.1. Challenging conditions in TTS diagnosis

Specific diagnostic criteria for TTS diagnosis have been proposed in previous reports.<sup>5,16-23</sup> In most of these earlier reports, the diagnosis has been mostly based on the presence of reversible wall motion abnormalities (WMAs) extending beyond the territory of a single coronary artery (mostly apical ballooning), and a stressful trigger

along with the absence of certain conditions including obstructive CAD, neurological disorders, myocarditis and pheochromocytoma. More recently, the interTAK diagnostic criteria<sup>5</sup> suggested that concomitant conditions including pheochromocytoma and obstructive CAD should not be regarded as exclusion criteria.<sup>5</sup> Moreover, focal WMA within the territory of a single coronary artery (focal TTS) may also be possible in contradistinction to the well-recognized circumferential pattern.<sup>5</sup> Interestingly, a normal ECG or lack of stressful triggers may not preclude the TTS diagnosis.<sup>5</sup> Since patients with TTS mostly present with ACS signs and symptoms, the initial imaging modality has been invasive CAG and ventriculogram (with hemodynamic assessment) in most cases particularly in those with ST segment elevation or hemodynamic instability.<sup>6,7,13,23</sup> However, those without an overt ST segment elevation has been mostly treated as non-ST segment elevation myocardial infarction (NSTEMI), and might initially undergo non-invasive modalities including coronary computed tomography angiogram (CCTA).<sup>13,23</sup> In this context, CCTA, besides detailed evaluation of coronary arteries, also enables evaluation of WMAs, potential complications including apical thrombus formation, and myocardial tissue characterization in certain instances (using myocardial late iodine enhancement).<sup>23</sup> Therefore, CCTA may be initially preferred over invasive CAG in stable patients without ST segment elevation and a higher likelihood of TTS (including those with a high interTAK score or those likely to present with a TTS recurrence).<sup>6,23</sup> However, subsequent invasive CAG may be necessary<sup>13</sup> for diagnostic confirmation and further interventional strategies particularly in those with ACS signs on CCTA (including thrombus formation, existing focal WMA within the territory of an occluded coronary artery, etc.). TTS is one of the most underdiagnosed conditions in clinical practice.<sup>24,25</sup> Accordingly, certain diagnostic challenges potentially associated with underdiagnosis (and rarely overdiagnosis) of this phenomenon might exist:

First, TTS may be masked by various clinical conditions. Notably, TTS may not emerge as a primary phenomenon yet as a complication that might arise secondary to certain physical triggers.<sup>2,5,12,24,25</sup> Accordingly, this form of TTS may be potentially masked due to the rampant nature of the underlying condition (including acute neurological disorders, sepsis, etc.).<sup>12,24,25</sup> Therefore, clinicians should regularly check biomarker levels, ECG changes, and when necessary, perform cardiac imaging at regular intervals particularly in critically ill patients at potential risk for TTS evolution as part of the diagnostic work-up.<sup>24,25</sup> On the other hand, a variety of pre-existing myocardial conditions [for instance; hypertrophic cardiomyopathy (HCM) with an apical aneurysm, etc.] might potentially conceal an emerging TTS episode, and might also arise as a diagnostic challenge.<sup>26</sup> However, HCM and hypertensive heart disease may potentially serve as an actual trigger of apical ballooning in certain cases.<sup>7,27</sup>

Second, some TTS forms may be milder or completely silent in terms of symptoms<sup>22</sup> including chest pain, dyspnea, etc. This may prevent patients to seek medical care at the onset of their symptoms. Therefore, a thorough cardiovascular examination and a high index of suspicion for TTS diagnosis (particularly in risk groups with a vague symptomatology admitted for another medical condition) seem to be necessary for the prevention of TTS underdiagnosis in this context.<sup>22,24,25</sup>

Third, TTS may occasionally present with focal or extensive (global LV or biventricular involvement) WMAs potentially creating a diagnostic challenge as well.<sup>7</sup> A focal WMA pattern is more likely to be associated with conditions including ACSs or myocardial infarction with non-obstructive coronary arteries (MINOCA).<sup>28</sup> Importantly, focal WMAs, regardless of the underlying condition, might go undetected on basic imaging modalities (including echocardiogram),<sup>28</sup> and requires careful evaluation of all myocardial segments from different views. Moreover, focal hypokinesis is more likely to be underdiagnosed compared with focal akinesis or dyskinesis. On the other hand, presence of extensive WMAs mandates exclusion of alternative conditions including myocarditis, pre-existing cardiomyopathy for TTS diagnosis. However, this mostly requires close supervision of temporal changes in WMAs, and use of advanced modalities including cardiac magnetic resonance imaging (CMR) for the final diagnosis.<sup>13,23</sup> Notably, certain conditions including sepsis may be potentially complicated by a “global or biventricular TTS” pattern that has a strong analogy to another sepsis-related condition namely “septic cardiomyopathy”.<sup>14</sup> These conditions have diverse pathogenesis and present with diffuse and transient myocardial dysfunction (though subtle myocardial abnormalities may persist indefinitely in both conditions).<sup>14</sup>

Fourth, TTS may occasionally co-exist with stable obstructive CAD or acute cardiac conditions including ACSs, MINOCA and myocarditis.<sup>7,28</sup> Notably, despite the potential existence of vulnerable atherosclerotic plaques on coronary imaging in certain patients with TTS,<sup>29</sup> no causal association between TTS evolution and plaque rupture has been documented so far.<sup>30,31</sup> On the other hand, the presence of obstructive CAD or ACS signs on coronary imaging serves as a diagnostic challenge in patients with TTS since most clinicians in this setting generally make the final diagnosis of ACS without further evaluation.<sup>25</sup> However, coronary imaging may not uncover whether obstructive CAD is just a bystander or an ACS trigger. Moreover, even findings highly suggestive of ACS (plaque rupture, thrombus formation, existing triggers of secondary ACS including severe anemia etc.) may not entirely rule out a co-existing TTS.<sup>7</sup> In other words, circumferential myocardial involvement (apical, basal or midventricular) mostly together with a hypercontraction pattern of the unaffected segments should primarily denote an episode of TTS regardless of coronary anatomy in patients with an ACS presentation.<sup>7</sup> Certain findings on ventriculogram including

“nipple sign” (a specific sign denoting a preserved contractility pattern at the tip of the apex in 30% of patients with an apical ballooning pattern) and “hawk’s beak” appearance (due to the vigorous contraction of the apex in midventricular TTS pattern) might further support a classical TTS diagnosis.<sup>6,13,23</sup> On the other hand, focal WMAs within the territory of an obstructive CAD might primarily signify an ACS. Conversely, focal WMAs particularly in patients with high risk features for TTS evolution (including elderly females and those with an overt stressful trigger) might denote an existing focal TTS in the presence of normal or non-obstructive coronary anatomy. However, alternative diagnoses including MINOCA may also be possible in these patients.<sup>13,28</sup>

Fifth, underdiagnosed emotional triggers may result in lower diagnostic score values in patients with TTS. A low interTAK score<sup>6</sup> (as described later) may occasionally prompt the clinicians to overlook a potential TTS episode, though patients with an actual low score may also suffer a TTS episode.<sup>5</sup> Notably, an undercalculated score potentially creates a misguidance in the decision-making for diagnostic tools (invasive CAG vs CCTA, cardiac MRI in those with a focal WMA, etc.). Therefore, emotional triggers and their psychological impact on the patient should be carefully explored.

Sixth, quick TTS recovery (even within hours) is a well known phenomenon.<sup>32</sup> Rapid normalization of WMAs before cardiac imaging may result in potential underdiagnosis of TTS,<sup>32</sup> and may lead to alternative diagnoses including ACSs and MINOCA.<sup>28</sup> MINOCA has been a heterogenous form of ACS particularly in females usually emerging due to specific conditions including coronary vasospasm, spontaneous coronary artery dissection (SCAD), coronary microvascular dysfunction and coronary embolism.<sup>28,33</sup> As expected, focal WMAs in the setting of MINOCA most likely arise within the territory of a single coronary artery.<sup>28,33</sup> Notably, patients with MINOCA mostly present with NSTEMI,<sup>33</sup> and hence may not have significant WMAs (and may even present with a normal LV contraction pattern). Therefore, quick recovery of TTS may potentially mimic ACSs including MINOCA on cardiac imaging.<sup>28</sup>

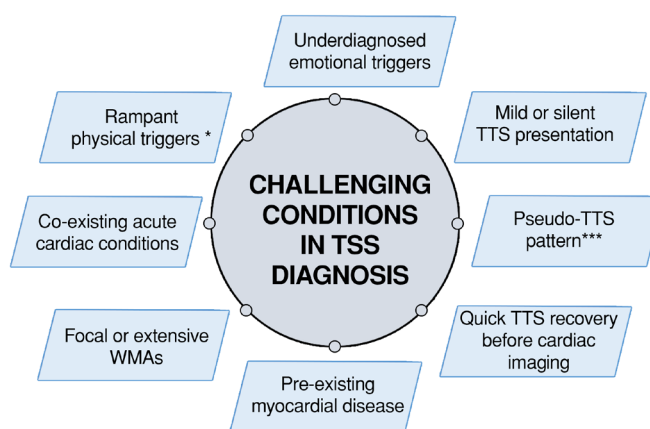
Finally, the converse scenario may also be likely, and certain forms of MINOCA (particularly associated with a missed SCAD) may also mimic TTS mostly presenting with a “pseudo-TTS” pattern.<sup>28</sup> For instance, a SCAD pattern involving a wrap-around LAD (also perfusing the inferoposterior LV segments) may present with ischemic or post-ischemic segmentary myocardial stunning that might strongly mimic an “apical ballooning” pattern.<sup>28,34,35</sup> However, ischemic myocardial stunning in this context is nevertheless within the territory of a single coronary artery, and usually resolves in correlation with the mitigation of coronary ischemia.<sup>35</sup> Rarely, ischemic myocardial stunning may also arise beyond the territory of a single coronary artery (as in the setting of coronary collateral circulation). Challenging conditions in TTS diagnosis are summarized in **Figure 3**.

## KEY POINTS

- TTS is a potentially underdiagnosed condition due to a variety of diagnostic challenges.
- In the setting of an ACS presentation, characteristic circumferential WMA pattern should strongly suggest a TTS episode with or without co-existing conditions (including stable CAD, ACSs).
- In the setting of an ACS presentation, focal or extensive WMAs might be associated with a TTS episode and/or similar conditions including ACSs, MINOCA and myocarditis. Initial diagnostic strategy is generally based on the evaluation of coronary anatomy, history and clinical findings.

## 2.2. Further strategies to differentiate TTS from similar conditions

In the acute setting, certain strategies have been proposed to differentiate TTS from ACSs particularly in the emergency unit setting just prior to decision-making for interventional diagnostic strategies.<sup>36</sup> Importantly, clinical value of these strategies may be even higher in most of the above-mentioned challenging scenarios (where conventional coronary and cardiac imaging appear to be inconclusive). In this context, presence of certain ECG findings including moderate ST segment elevation in the leads V3-V6 (or V2-V5), large and diffuse T-wave inversion (detected initially or following the resolution of ST segment elevation) that might persist several months, QT interval prolongation and ST segment depression in the



**FIG. 3.** Challenging conditions in TTS diagnosis.

\*Including acute neurological conditions, sepsis, etc. that might potentially mask cardiovascular manifestations of TTS.<sup>24,25</sup>; \*\*\*Ischemic or post-ischemic myocardial stunning that might mimic a true TTS episode.<sup>28,35</sup>; TTS, Takotsubo syndrome; WMA, wall motion abnormality.

lead aVR along with the absence of reciprocal ST segment depression might suggest TTS in patients with an ACS presentation.<sup>6,13</sup> Unlike ACSs, reduced QRS voltage and Q-waves (mostly in the leads V3 and V4), when present, are generally transient in nature, and have been attributed to myocardial edema in the acute phase of TTS.<sup>13</sup> Left bundle branch block, QRS fragmentation and J-waves may be occasionally encountered as well.<sup>6</sup> However, there has been no single ECG criterion absolutely specific to TTS. On the other hand, combined ECG and clinical findings might significantly enhance the diagnostic accuracy. Accordingly, the interTAK diagnostic score (Figure 4) might work well in the differentiation of TTS from ACSs.<sup>6,36</sup> The interTAK diagnostic score constitutes seven variables (comprising a total of 100 points) including female gender (25 points), existing triggers [emotional (24 points) and physical (13 points)], certain ECG findings [absence of ST segment depression excluding the lead aVR (12 points), QT interval prolongation (6 points)], and certain conditions associated with a high risk for TTS [psychiatric disease (11 points), neurological disease (9 points)].<sup>6,36</sup> Accordingly, a score point of 30 demonstrates a TTS probability of <1% whereas a point of >70 denotes a TTS probability of around 90%.<sup>6</sup> Notably, higher levels of certain indices including the ratios of admission cardiac biomarker levels [including N-terminal pro-brain natriuretic peptide (NT-proBNP)/myoglobin and NT-proBNP/troponin T (TnT)] might suggest an existing TTS rather than ACSs

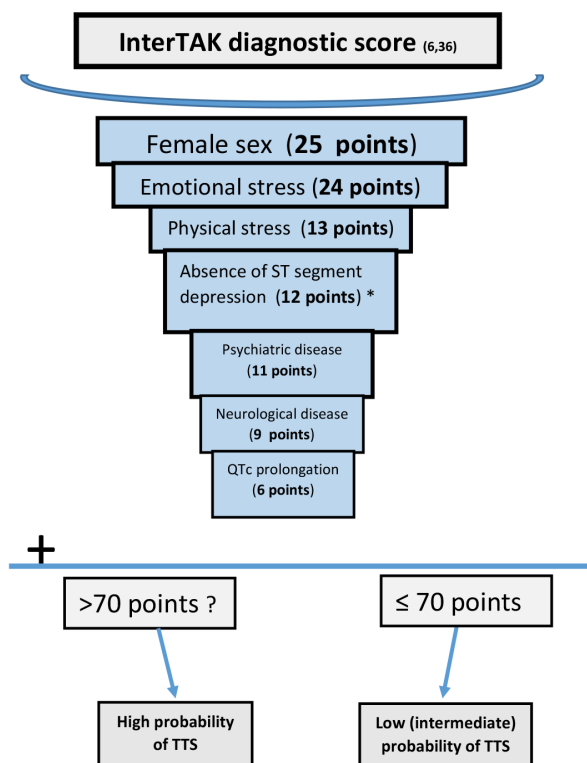


FIG. 4. The InterTAK diagnostic score.

\*Excluding lead aVR; TTS, Takotsubo syndrome.

in ambiguous cases.<sup>37</sup> Accordingly, a cut-off NT-proBNP (ng/l)/tTnT (μg/l) value of 2889 was previously reported to differentiate TTS from STEMI with a sensitivity and specificity values of 91% and 95%, respectively.<sup>37</sup> However, in a very recent study focusing on the validation of ratios of certain biomarkers in the interTAK registry,<sup>38</sup> the admission and peak ratios of troponin/creatinine kinase, BNP/troponin and BNP/creatinine kinase alone worked with low specificity and sensitivity in the differentiation of TTS and ACS.<sup>38</sup>

Interestingly, harnessing certain micro-RNAs (miRs) have yielded promising results in the early diagnosis of TTS as well.<sup>4,6,39</sup> Accordingly, a signature of circulating miRs constituting mir-16, mir-26a (miRs associated with emotional stress), mir-1, mir 133a (miRs associated with myocardial damage) was previously reported to successfully differentiate TTS from healthy controls (with specificity and sensitivity values of 78.57% and 74.19, respectively) and from those with STEMI (with specificity and sensitivity values of 70.37% and 96.77%, respectively).<sup>39</sup> It seems likely that the above-mentioned ECG changes, markers or indices may be of adjunctive value in the setting of challenging TTS scenarios where the initial imaging modalities remain inconclusive. In this context, clinical use of certain promising markers and indices including interleukine-7, growth differentiation factor-15<sup>6,13</sup> still needs to be tested through further studies. As mentioned before, it should be borne in mind that TTS may also co-exist with similar conditions (including ACSs, MINOCA and myocarditis) making the final diagnosis even more challenging.<sup>7,28,33,40,41</sup> Notably, mechanically-triggered TTS (as described in Part-2) is a specific form of apical ballooning with diverse pathogenesis in which case the demonstration of small LV cavity, LV septal hypertrophy (or bulge) and intraventricular gradient on cardiac imaging (provoked or at rest)<sup>27,42-48</sup> may significantly facilitate the TTS diagnosis.

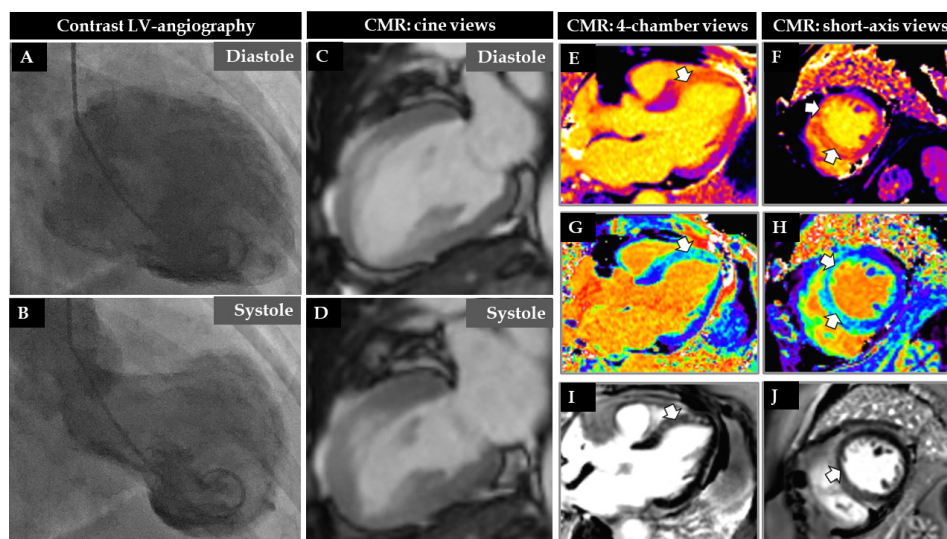
Finally, advanced diagnostic modalities including intracoronary imaging, coronary provocation test, nuclear imaging and cardiac MRI may be necessary following conventional coronary and cardiac imaging, and may be particularly considered in ambiguous cases for the detection or confirmation of obstructive ACSs, MINOCA or myocarditis (in isolation or in combination with TTS).<sup>13,23,28,33</sup> Cardiac MRI (besides demonstrating the further details of right ventricular (RV) and LV involvement along with potential complications) is of particular importance for the detection of myocardial edema and tissue characterization.<sup>6,23</sup> In particular, myocardial late gadolinium enhancement (LGE) involvement, when present, is usually transient and demonstrates a focal/patchy and low-intensity pattern in TTS.<sup>6,23</sup> However, LGE involvement in the context of ischemic injuries is mostly subendocardial or transmural whereas LGE involvement in myocarditis mostly demonstrates a patchy midwall or subepicardial pattern.<sup>6,23</sup> Furthermore, T1 mapping might demonstrate even subtle degrees of myocardial damage in this context.<sup>23</sup> However, cut-off T1

values still need to be established.<sup>23</sup> T2 mapping exhibits myocardial edema in segments with contractile dysfunction.<sup>23</sup> A myocardial/skeletal muscle signal intensity ratio of  $\geq 1.9$  generally signifies myocardial edema on T2 mapping.<sup>23</sup> Prognostic implications of LGE, T1 and T2 mapping are mentioned in part-2. **Figure 5** demonstrates invasive ventriculogram and cardiac MRI findings (myocardial edema and LGE) in a middle aged female patient with a mid-apical TTS pattern.

In this context, patients with a combination of non-specific WMAs (including focal WMA pattern), non-obstructive coronary anatomy and a low likelihood of TTS (a low interTAK score) may undergo cardiac MRI preferably before discharge or at 3 months following discharge (if there exists a failed or incomplete WMA recovery under guideline-directed medical therapy).<sup>13,28</sup> Patients with characteristic WMAs or those with a non-characteristic WMA and a high interTAK score should also undergo cardiac MRI at 3 months if they have failed or incomplete WMA recovery on echocardiogram.<sup>13,28</sup> In this latter group, cardiac MRI may possibly demonstrate a co-existing MINOCA or myocarditis component. Some experts recommend performing cardiac MRI within 2 months following discharge in this context.<sup>23</sup> Intracoronary imaging and vasoreactivity tests may serve as adjunctive tools to uncover potential MINOCA triggers (including SCAD, vasospastic angina) particularly in those without overt findings on CAG.<sup>23,28</sup> A normal wall motion pattern (no WMA) in the presence of obstructive coronary anatomy may also warrant further investigation of ACSs through myocardial tissue characterization. Of

note, nuclear imaging modalities have been occasionally harnessed for the differentiation of TTS in the acute setting. Accordingly, single photon emission computed tomography (SPECT) documenting a relatively significant impairment of myocardial fatty acid metabolism (as demonstrated with <sup>123</sup>I-beta-methy-iodophenyl pentadecanoic acid) in comparison to myocardial perfusion (as demonstrated with <sup>201</sup>thallium scintigraphy) may support a TTS diagnosis.<sup>23</sup> In this context, nuclear imaging seems to serve as a supportive modality particularly in the presence of non-specific WMAs.

In patients highly suggestive of having an aborted TTS episode on admission (quick TTS recovery), nuclear imaging modalities may demonstrate persistent abnormalities in cardiac sympathetic nerves (as demonstrated with reduced myocardial uptake of <sup>123</sup>I metaiodobenzyl guanidine on scintigraphy) and glucose metabolism (as demonstrated with positron emission tomography using <sup>18</sup>F-2-fluoro-deoxy-glucose) together with normal or near-normal myocardial perfusion on SPECT.<sup>6,13,23</sup> Conversely, abnormalities in sympathetic innervation and myocardial perfusion are strongly correlated in the setting of ACSs (6,23).<sup>6,23</sup> Details of advanced modalities may be found elsewhere.<sup>23</sup> Taken together, even though the diagnostic strategies for TTS have significantly improved in the recent years (including the expansion of diagnostic criteria, novel ECG findings, clinical scores and promising miRs), certain conditions may still challenge the initial TTS diagnosis eventually indicating the need for advanced diagnostic modalities including cardiac MRI and intracoronary imaging for the final

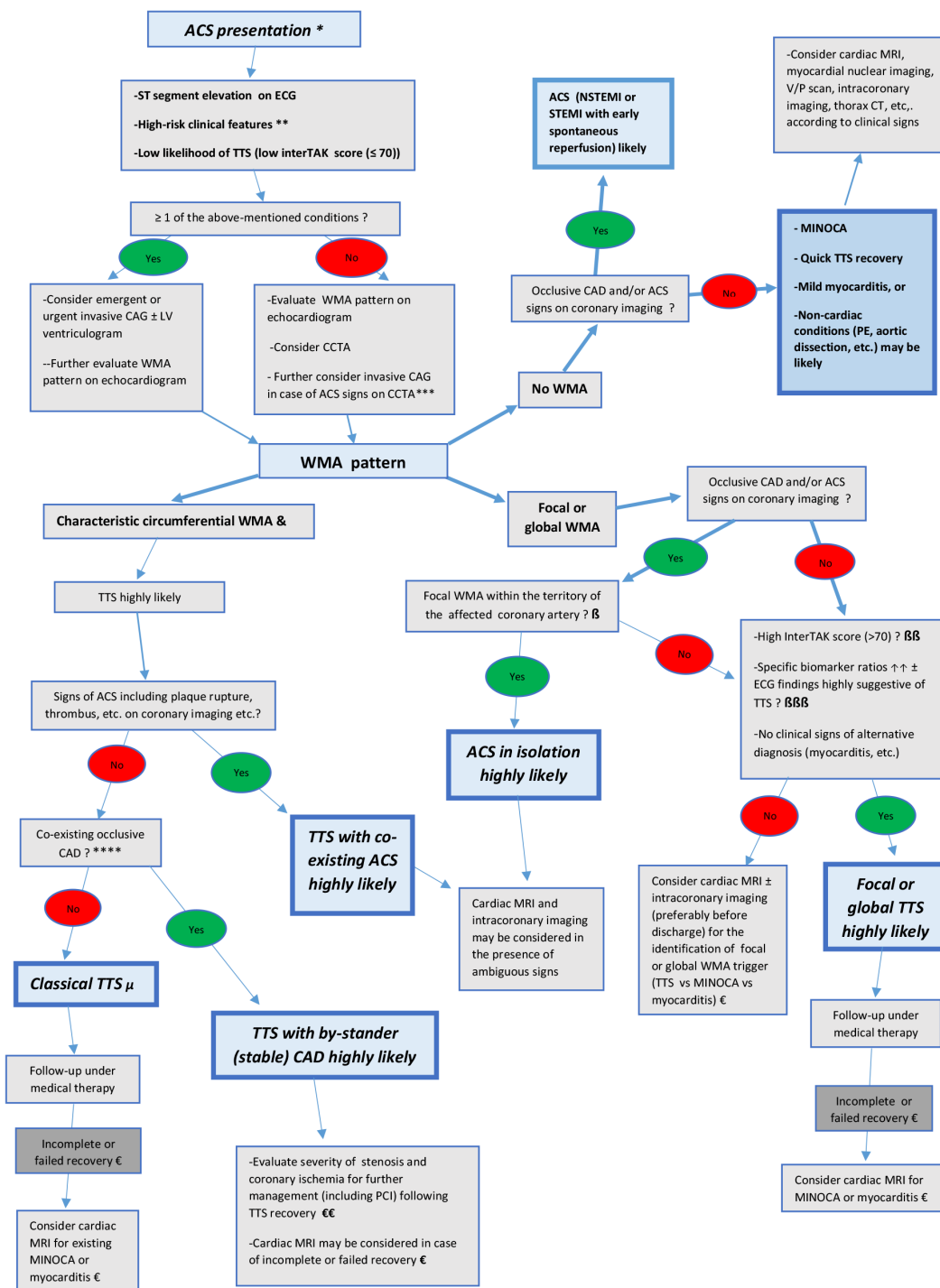


**FIG. 5.** Invasive left ventriculogram and cardiac magnetic resonance imaging (CMR) in a middle-aged woman presenting with chest pain after a stressful situation. Coronary angiogram on admission revealed normal left and right coronary arteries. Invasive left ventriculogram demonstrated typical mid-apical takotsubo syndrome (TTS) with an apical tip-sparing pattern (A, B). Cardiac MRI 3 days after admission demonstrated mild improvement in left ventricular function particularly in the apical region in cine images (C, D). Native T1 mapping demonstrated significant increases in T1 values in the mid-apical regions particularly in the septal and anterior segments [(E, F), white arrows]. Extracellular volume (ECV) mapping also demonstrated significant increases in ECV values representing myocardial edema in the corresponding areas [(G, H), white arrows]. Images of late gadolinium enhancement were consistent with an increased transmural signal intensity (but no infarction changes) in the mid-apical region particularly the septal segment [(I, J), white arrows]. Consequently, this demonstrates “myocarditis-like” changes in the mid-apical (septal and anterior segments) in a typical case of TTS.



diagnosis.<sup>13,23</sup> Of note, certain previous reports considered TTS as a form of MINOCA. However, it should be borne in mind that these two conditions are clinically and pathophysiologically different, and currently TTS is labeled as a “MINOCA mimicker”.<sup>33</sup> In **Figure 6**, we

propose an algorithm for TTS diagnosis in the presence of certain challenging conditions (including focal WMAs, obstructive CAD and co-existing acute cardiac conditions).



**FIG. 6.** A proposed clinical algorithm for TTS diagnosis in the presence of diagnostic challenges. ACS, acute coronary syndrome; NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST segment elevation myocardial infarction; MINOCA, myocardial infarction with non-obstructive coronary arteries; TTS, Takotsubo syndrome; PE, pulmonary embolism; MRI, magnetic resonance imaging; V/P, ventilation perfusion; CAG, coronary angiogram; LV, left ventricle; PCI, percutaneous coronary intervention; WMA, wall motion abnormality; CCTA, coronary computed tomography angiography; CAD, coronary artery disease; ECG, electrocardiogram.

**FIG. 6. Continued**

\*: ACS presentation denotes classical symptoms of ACS (chest pain, dyspnea, etc.) and significant increases in serum levels of myocardial enzymes (including troponins) with or without ischemic ECG changes. Decision making for the initial diagnostic modality (invasive CAG vs CCTA) is generally based on the presence of ST segment elevation, high-risk clinical features and the likelihood of TTS (InterTAK score  $\leq 70$  vs.  $> 70$ ).<sup>6,13,17,23</sup>

\*\* : High risk features include persistent chest pain, hemodynamic instability and malignant arrhythmogenesis.

\*\*\*: Invasive CAG in this setting may be warranted in the presence of ACS signs on CCTA (thrombus, focal WMA within the territory of a severely stenotic coronary artery, etc.). Invasive CAG may confirm an existing ACS, and enables further management (including PCI).

\*\*\*\*: Occlusive CAD usually signifies a stenosis severity of  $> 50\%$ .<sup>33</sup>

&: Characteristic WMA pattern denotes a circumferential apical, midventricular or basal (or adjacent combination of these) LV involvement usually accompanied by hypercontraction of the non-affected segments. Global LV or biventricular WMAs may also arise following stressful triggers, and may suggest TTS in the absence of any other condition accounting for such extensive myocardial involvement including myocarditis, septic cardiomyopathy and pre-existing cardiomyopathy.<sup>2-10</sup> Cardiac MRI may be indicated even after full recovery of a global or biventricular dysfunction to differentiate TTS from similar conditions including myocarditis.

β: ACS signs (including plaque rupture, thrombus on CAG) involving the coronary artery remote from the territory of focal WMA pattern or ACS signs in the presence of a global (or biventricular) WMA pattern may also suggest a co-existing ACS, and need to be carefully evaluated and managed accordingly.

ββ: A high interTAK score denotes a score of  $> 70$ .<sup>13,36</sup>

βββ: Specific biomarker ratios include N-terminal proBNP/troponin T (NT-proBNP/TnT).<sup>37</sup>

μClassical TTS signifies the widely recognized TTS form with a characteristic circumferential WMA pattern and with a normal or non-occlusive coronary anatomy in the presence of an ACS presentation. A high interTAK score may further support the diagnosis of classical TTS. However, a low score can not definitely exclude the diagnosis in this context.<sup>1-9,13</sup>

€: Recovery of WMAs is expected to be complete at 3 months in the setting of TTS.<sup>7</sup> Therefore, the decision-making for incomplete or failed recovery is usually implemented at 3 months following discharge.<sup>13</sup> Cardiac MRI is the preferred modality for the identification of the persistent WMA trigger in this context.<sup>6,13,17,23,28</sup> Cardiac MRI and intracoronary imaging may be performed before discharge if the alternative diagnosis is highly likely based on clinical features (including signs of myocarditis, low interTAK score, ambiguous coronary artery findings suggestive of MINOCA).<sup>13,28</sup>

€€: Diagnostic accuracy of hemodynamic tests [including fractional flow reserve may be hampered by the TTS-related microvascular dysfunction during the acute stage].<sup>82</sup>

**KEY POINTS**

- Initial diagnostic modalities including invasive ventriculogram and CCTA may be inconclusive in some cases with a suspected TTS episode.
- Intracoronary imaging and myocardial tissue characterization (using cardiac MRI) may be performed preferably before discharge in patients with a high likelihood of having alternative (or possibly co-existing) conditions including MINOCA and myocarditis.
- Myocardial tissue characterization may be performed in patients with a high likelihood of having a TTS episode in case of persistent WMAs following the supposedly maximum duration of TTS recovery (usually 3 months).
- Certain indices, clinical scores as well as nuclear imaging may be of adjunctive diagnostic value particularly in the presence of non-specific WMAs (including focal WMA).

**3. THERAPEUTIC CHALLENGES AND PRACTICAL IMPLICATIONS**

In clinical practice, TTS management generally comprises various combinations of ACS and HF medications.<sup>6-8,32</sup> In other words, there has been no clinically proven specific strategy aiming to abort myocardial stunning and reverse the metabolic alterations at the cellular level. Waiting for the self-recovery of the disease (with the use of non-specific medications while managing complications, if any) that also exhibits substantial variations among individuals, has been the routine strategy in the clinical setting.<sup>32</sup> Therefore, absence of any disease modifying therapeutic options may be regarded as the foremost therapeutic challenge in these patients.

As expected TTS complications including hemodynamic compromise, thromboembolism, arrhythmogenesis may lead to significant therapeutic challenges in the setting of TTS, and require specific management strategies. However, even in uncomplicated cases, certain therapeutic challenges may also be possible. Clinical status, underlying physical stressors, co-existing cardiac conditions including CAD (even ACSs), etc. may all arise as therapeutic challenges in patients with TTS. Therefore, management should be adjusted on a case by case basis in most patients.

### 3.1. How to choose proper medication

As previously mentioned, TTS management mostly relies on supportive management including close monitoring and initiation of certain agents including  $\beta$ -blockers, renin-angiotensin system (RAS) blockers and where necessary, nitrates, diuretics, oxygen therapy, anticoagulation, levosimendan and mechanical circulatory support devices [including left ventricular assist devices (LVAD)].<sup>6,32</sup> Initiation of antiplatelet agents (including aspirin) is mostly based on previous assumptions that TTS might be pathogenetically considered as a form of CAD.<sup>32</sup> Co-existing stable CAD or ACS should be managed as in any other patient with these conditions (with slight modifications where necessary).<sup>32</sup>

Importantly, thromboembolism, a potentially life-threatening condition, was reported in previous TTS series (3.3% in the interTAK registry) potentially requiring preventive measures in high-risk patients.<sup>49-53</sup> Thromboembolism in this context may be ascribed to WMAs, endothelial dysfunction and activation of coagulation cascade (due to adrenergic discharge and systemic inflammation).<sup>14,32,49,51</sup> The interTAK risk score was recently suggested for the prediction of thromboembolism risk.<sup>49</sup> It includes four variables: Apical ballooning pattern (1.5 points), a LVEF value of  $\leq 30\%$  on admission (1.5 points), enhanced white blood cell count (10.000/ml) (1 point) and previous vascular disease (1.5 points) (a total point of  $> 3$  denotes a high-risk for thromboembolism particularly during the first days of the TTS course).<sup>49</sup> Therefore, an existing high score warrants frequent monitoring of ventricular thrombus formation and initiation of anticoagulation strategies.<sup>49</sup> Importantly, since embolic events may occasionally take place in the absence of apparent thrombus formation,<sup>52</sup> frequent monitoring (for ventricular thrombus formation) without anticoagulation may not be a prudent strategy. In this context, another study demonstrated LV thrombus formation exclusively in female patients with an apical ballooning pattern (2.2 % of the whole TTS population).<sup>50</sup> Similarly, a previous metaanalysis also reported the LV apex as the most frequent site of thrombus formation (94% percent of the cases).<sup>54,55</sup> Therefore, a large apical ballooning (generally associated with severe LV dysfunction), regardless of other clinical variables, potentially indicates anticoagulation (unfractionated or low molecular weight heparin followed by oral anticoagulation) until full TTS recovery ensues.<sup>6,32,51</sup> Even though direct oral anticoagulants (DOACs) were previously recommended as potential alternatives,<sup>6,56,57</sup> evidence on these agents is currently limited in this context. Using conventional agents including vitamin K antagonists (such as warfarin) seems more plausible in TTS patients with signs of severe stasis on cardiac imaging (including severe and extensive ballooning, severe degrees of spontaneous echo contrast). Therefore, indications and types of anticoagulation for thromboembolism prevention are largely based

on patient characteristics, and should be handled on a case-by-case basis in the setting of TTS.

On the other hand, use of  $\beta$ -blockers and RAS blockers in the context of asymptomatic or mildly symptomatic patients with normal or near normal LV systolic functions seems to be of limited or no significant benefit.<sup>6,32</sup> Nevertheless, RAS blockers may potentially expedite recovery of WMAs.<sup>6,32</sup> Therefore,  $\beta$ -blockers and RAS blockers have been mostly recommended in those with a LVEF value of  $< 40\%$ .<sup>2,8</sup>  $\beta$ -blockers may also be useful in alleviating left ventricular outflow tract obstruction (LVOTO) in patients without hemodynamic compromise.<sup>6</sup> Importantly,  $\beta$ -blockers should not be used in the acute setting in patients with acute pulmonary edema and/or hemodynamic compromise.<sup>6,32</sup> In some cases, TTS may lead to an exacerbation of a pre-existing congestive heart failure (CHF).<sup>7</sup> In this context, maintenance of guideline-directed HF medications seems to be reasonable. Nitroglycerin, diuretics, certain inodilators including levosimendan and rarely LVAD have been used in TTS cases with severe HF.<sup>6,7,32</sup>

#### KEY POINTS

- Supportive management is the mainstay of therapy in TTS patients.
- HF and ACS therapy should be individualized according to the clinical findings and degree of LV dysfunction.
- TTS patients with a large apical ballooning should receive anticoagulation until full recovery ensues.
- In other morphological patterns, decision-making for anticoagulation may be based on existing high-risk factors for thromboembolism.

### 3.2 How to handle specific clinical signs and symptoms

#### - Hypotension/cardiogenic shock

Hypotension is a frequently encountered challenge in the setting of TTS, and might be attributable to pump failure (due to LV and/or RV dysfunction), mechanical complications [LVOTO, mitral regurgitation (MR)] or underlying conditions with reduced systemic vascular resistance including sepsis and TTS-related sympathetic dysfunction.<sup>6,32</sup> Therefore, eradication or mitigation of the underlying condition is imperative to combat hypotension. Most clinicians automatically use sympathomimetics (positive inotropes and/or vasopressors) in the setting of hypotension with or without HF. However, use of sympathomimetics (including

dopamine, dobutamine and noradrenaline) to combat pump failure and/or hypotension is discouraged due to their detrimental impact on myocardium in the context of TTS.<sup>6,7,32</sup> Moreover, any type of pharmacological agent enhancing myocardial contractility (sympathomimetics and also levosimendan) and intraaortic balloon pumping may further aggravate an existing LVOT gradient, and should also be avoided in this context.<sup>6,7,32</sup> Cardiogenic shock due to pump failure or LVOT gradient may be managed with temporary mechanical circulatory support devices.<sup>6</sup> Hypotension due to severe RV dysfunction or decreased vascular resistance should be primarily managed with fluid therapy. In patients with conditions characterized by significant reductions in systemic vascular resistance (including septic shock), terlipressin [an arginine vasopressin (AVP) analogue stimulating arterial vasoconstriction through V1a receptors] may be considered particularly in those with catecholamine-resistant patients<sup>58</sup> (or those with contraindications). However, besides the detrimental impact of sympathomimetic vasopressors in the setting of TTS,<sup>6,7,32,59</sup> AVP and its analogues (including terlipressin) may also be associated with life-threatening cardiovascular complications including induction of ACSs.<sup>60</sup> Moreover, data on the use of AVP in the setting of cardiogenic shock appear to be quite limited.<sup>61</sup> Therefore, harnessing AVP and its analogues in this context is not an evidence-based option, and may exclusively be considered as a last resort until more radical options including LVAD are available. Taken together, supporting evidence on the optimal management of hemodynamically significant hypotension/cardiogenic shock in TTS is lacking and current recommendations are based on observational data, without clearly established survival benefit of specific strategies, including the use of medications or temporary mechanical circulatory support devices.<sup>59</sup>

#### - Hypertension

Hypertension (HT) may also emerge as a therapeutic challenge in the setting of TTS. Severe and/or persistent HT should warrant exclusion of triggers of secondary HT that might also induce a TTS episode (including pheochromocytoma, intracerebral haemorrhage, sympathomimetic use, etc.).<sup>62-66</sup> In certain patients, increased blood pressure values may be due to the exacerbation of chronic HT associated with increasing levels of anxiety due to hospitalization, etc. Management of HT urgencies and various grades of HT should be based on international HT guidelines.<sup>67</sup> Both in the urgent and non-urgent settings, HT management should also take into account potential compelling indications for certain antihypertensive medications (for instance, diuretics and nitrates may be preferred in TTS patients with pulmonary edema and co-existing HT) and up-titration of previous antihypertensive medications. Notably, certain medications including arterial vasodilators, alpha blockers and nitrates might be associated with aggravation of an existing LVOT gradient, and hence should be avoided in this context.<sup>32</sup> Short acting

and ultra-short acting  $\beta$ -blockers (including esmolol and landiolol, respectively) may be the preferred options in the setting of HT urgencies particularly in the presence of LVOT gradient.<sup>32</sup>

#### - Disproportionate dyspnea

Dyspnea has been one of the cardinal symptoms in TTS patients particularly with systolic dysfunction.<sup>7,32</sup> On the other hand, disproportionate dyspnea (particularly in those with a relatively mild ventricular dysfunction) might potentially suggest mechanical complications or co-existing respiratory conditions. This warrants re-evaluation in terms of severe MR, LVOT gradient as well as cardiac tamponade on echocardiogram. Evaluation of auscultation findings (lung and precordium), chest-X ray, blood gas analysis and further tests (lung ultrasound, CT, etc.) also aids in the diagnosis and management of the underlying pathology.<sup>32,68,69</sup> In a recent systematic review (comprising 99 publications), obstructive pulmonary disease and pneumonia were reported as the most common respiratory triggers of TTS (39.8% and 38.8% of all cases, respectively).<sup>68</sup> As expected, the most common symptom was dyspnea (70.4%) in contrast to the relatively low incidence of angina (24.7%).<sup>68</sup> On the other hand, the mortality rate was relatively higher (12.5%) particularly in patients with pneumonia and lung cancer compared with the general TTS population.<sup>68</sup> Notably, medications including  $\beta$ -agonists and invasive procedures may also account for or contribute to TTS evolution in the setting of respiratory diseases.<sup>68-71</sup>

#### - Sinus tachycardia:

Short acting  $\beta$ -blockers (followed by cardioselective  $\beta$ -blockers) may be quite effective for the management of inappropriate sinus tachycardia in the setting of TTS.<sup>32,72</sup> In fact, this form of tachycardia is largely attributable to high catecholamine levels, and may persist for several days following admission. Accordingly, serum catecholamine levels in patients with TTS were previously reported to be significantly higher compared with those with Killip-3 AMI and published normal values (2-3 times and 7-34 times, respectively) within the first two days of the TTS course.<sup>73</sup> In patients with TTS, catecholamine levels, though significantly reduced from their peak values, were still substantially higher at the end of the first week.<sup>73</sup> However, methodological limitations of this study (including comparison with the published normal values)<sup>73</sup> were particularly highlighted in a previous report.<sup>11</sup> Notably,  $\beta$ -blockers have been particularly preferred in patients with TTS associated with endocrinological triggers including thyroid crisis<sup>74,75</sup> and pheochromocytoma<sup>76</sup> presenting with concomitant sinus tachycardia. Ivabradine (If channel blocker used in CHF) has also emerged as a promising agent that might be used as an alternative to or together with  $\beta$ -blockers to manage inappropriate sinus tachycardia in the setting of TTS.<sup>32,72,77</sup>

Importantly, compensatory sinus tachycardia may also arise in certain patients with TTS in response to LV dysfunction<sup>72</sup> (leading to systemic hypoperfusion with or without hypotension) and reduced systemic vascular resistance. In this context,  $\beta$ -blockers should be avoided to maintain physiological response mechanisms including sinus tachycardia. Ivabradine, an agent without negative inotropic effects, may be particularly preferred in TTS patients having contraindications to  $\beta$ -blockers including pulmonary congestion.<sup>72</sup> Consistent with this, ivabradine was previously shown to elicit significant heart rate (HR) reduction (without adverse effects) in patients with advanced or decompensated HF<sup>78,79</sup> and even in those with cardiogenic and septic shock.<sup>80,81</sup> Improvement of hemodynamic parameters including stroke volume<sup>78-81</sup> provides a potential basis for considering ivabradine beyond HR reduction in these conditions. However, ivabradine use in these precarious scenarios is currently off-label.<sup>78-81</sup> Ivabradine may also be a promising strategy in TTS patients with pulmonary congestion or compensatory sinus tachycardia where  $\beta$ -blockers should be avoided.<sup>72</sup> However, prognostic benefit of ivabradine in this context remains to be established.

#### KEY POINTS

- Underlying triggers of hypotension should be uncovered and managed accordingly in TTS patients.
- Sympathomimetic vasopressors should be avoided in TTS patients with hypotension.
- Certain TTS triggers (including pheochromocytoma, stroke) may lead to severe HT.
- Management of HT in TTS patients should be tailored according to the compelling indications of antihypertensive agents.
- Arterial vasodilators, alpha blockers and nitrates should be avoided in TTS patients with a LVOT gradient.
- Disproportionate dyspnea in TTS patients warrants further evaluation of mechanical complications and respiratory conditions.
- Ivabradine seems as plausible agent (with an off-label indication) for the management of sinus tachycardia in TTS patients (as an alternative to, or together with  $\beta$ -blockers), and may be particularly preferred in those with compensatory sinus tachycardia.

#### 3.3. Therapeutic challenges due to co-existing cardiac conditions

Even though TTS has been traditionally regarded as an isolated phenomenon, a variety of co-existing cardiac conditions including ACSs, myocarditis and MINOCA<sup>7,28,35,41,82</sup> have been increasingly reported. These conditions, besides their diagnostic challenges and prognostic impact, may also elicit potential therapeutic challenges.<sup>7,28,35,41,82</sup> Management should focus both on TTS and the co-existing cardiac condition including ACSs with the implementation of guideline-directed strategies.<sup>82-84</sup> In such a co-existence, clinicians should avoid certain strategies that might worsen the co-existing condition.<sup>82</sup> For instance; nitrates for ACS management should be avoided in the setting of a co-existing TTS with a LVOTO.<sup>82</sup> Notably, co-existing SCAD might have particular implications.<sup>35,82</sup> For instance, a SCAD pattern with unstable features (coronary slow flow, cardiogenic shock) needs urgent revascularization.<sup>82</sup> Similarly, a SCAD pattern involving the left main coronary artery (LMCA) (even if stable) may be surgically managed without further delay during the TTS course. It was also previously speculated that SCAD evolution<sup>40</sup> and its propagation<sup>35</sup> may be more likely to occur in the setting of TTS due to the adverse impact of WMAs (hypercontraction versus ballooning pattern). Therefore, urgent revascularization strategies may be recommended particularly in the presence of a proximal SCAD (harboring a potential risk of aortic propagation) co-existing with TTS.

On the other hand, secondary catecholamine surges associated with surgical revascularization strategies may further complicate the TTS course.<sup>82</sup> Furthermore, substantial catecholamine levels in the setting of TTS may potentially lead to an increased risk for stent thrombosis.<sup>82,83</sup> Notably, even stable CAD may also require urgent management in this context: accordingly revascularisation for concomitant severe LMCA or three-vessel disease was previously suggested as a plausible option in TTS patients with hemodynamic compromise.<sup>82,84</sup> PCI, where possible, should be preferred over coronary artery bypass grafting (CABG) in patients during the acute course of TTS. Finally, hemodynamic tests for stable CAD (including fractional flow reserve) should be deferred till complete TTS recovery ensues (due to the TTS-related microvascular dysfunction that might render the test results unreliable).<sup>82</sup> In the setting of co-existing myopericarditis and TTS, certain challenges may also emerge: for instance; risk of hemorrhagic pericardial effusion should be carefully weighed against the benefits of thromboembolism prevention with anticoagulant therapy.

### KEY POINTS

- Co-existing proximal SCAD, LMCA or three-vessel disease may warrant urgent revascularization in patients with TTS.
- PCI may be associated with an increased risk of complications including stent thrombosis. Nevertheless, PCI seems relatively safer compared with CABG during the acute TTS course.
- Potential risks of anticoagulation should be taken into consideration in TTS patients with co-existing pericarditis.

### 3.4. Therapeutic challenges associated with certain TTS complications

In the setting of TTS, mechanical, arrhythmic, thromboembolic and pericardial complications might be already regarded as clinical challenges that warrant specific therapeutic strategies. Management of these complications have been discussed elsewhere.<sup>6,7,13,32</sup> However, further specific challenges while combating these complications deserve further mention:

#### - Specific challenges in the setting of intraventricular thrombus

In the presence of persistent LV thrombus, gradual improvement of WMAs may particularly create a predisposition to systemic embolism in patients with TTS.<sup>51,85</sup> Moreover, mobile (protruding) thrombi may be more likely to embolize compared with immobile (mural) ones.<sup>51</sup> In the setting of LV thrombus formation, anticoagulation is generally indicated for at least 3 months.<sup>50</sup> In a very recent systematic review, the use of DOACs was reported to be associated with similar rates of systemic embolism, stroke and thrombus resolution along with a lower rate of hemorrhagic events and all-cause mortality compared with vitamin K antagonists in patients with LV thrombus.<sup>86</sup> These results potentially encourage the use of DOACs also in the context of TTS complicated by an intraventricular thrombus. Importantly, hemorrhagic transformation may potentially complicate ischemic strokes particularly in the presence certain risk factors including existing cardioembolic origin and use of antithrombotic therapy.<sup>87,88</sup> Accordingly, a significant therapeutic challenge exists regarding the decision-making for initiation or resumption of anticoagulation in TTS patients with an intraventricular thrombus suffering an acute ischemic stroke complicated by hemorrhagic transformation (or suffering a primary intracerebral hemorrhage due to anticoagulation).<sup>87-89</sup> Therapeutic anticoagulation with heparin may be initiated or resumed following a few days or a

week of interruption following an intracerebral hemorrhage (though subcutaneous prophylactic-dose heparin may be started earlier) in the absence of high-risk conditions including lobar hematoma.<sup>89</sup> However, even such a short period of interruption of therapeutic anticoagulation may put TTS patients at a significant risk for systemic embolism (particularly those with high risk features including mobile intracardiac thrombus). Therefore, a detailed neurological counseling is necessary for decision-making in this context. Notably, an existing LV thrombus has been a relative contraindication to LVAD implantation.<sup>90</sup> However, in a recent study, LV thrombus was not associated with an increased rate of adverse clinical outcomes (including stroke) at 1 month in LVAD recipients.<sup>90</sup> Conversely, another study demonstrated increased rates of stroke and death at 6 months in this context.<sup>91</sup> Therefore, thorough evaluation of ventricular cavity and thrombus characteristics seems imperative in patients with LV thrombus prior to LVAD implantation<sup>90</sup> in the setting of TTS.

#### - Decision-making for implantable cardiac devices in the setting of conduction abnormalities and life-threatening arrhythmias:

In-hospital cardiac rhythm disorders including high-degree atrioventricular block (AVB) and ventricular arrhythmias (VAs) were previously reported to occur in about 6% of TTS patients in a multicentre study comprising 16,713 subjects.<sup>92</sup> In this study, only 24.5% of patients with serious arrhythmias (1.5% of the total TTS population) received cardiac implantable electronic device (CIED) therapy [permanent pacemaker (PPM) (18.4%) or implantable cardioverter defibrillator (ICD) (6.1%)].<sup>92</sup> Importantly, TTS patients with serious arrhythmias were more likely to have unstable hemodynamic or respiratory conditions, and also had a higher incidence of readmission for CIED implantation.<sup>92</sup> Life-threatening VAs most frequently occur during the acute phase of TTS particularly in the setting of low LVEF and significant QTc prolongation ( $\geq 460$  ms).<sup>93</sup> A previous study reported a significant association between life-threatening VAs and certain clinical variables including QTc prolongation ( $\geq 460$  ms), history of stroke or transient ischemic attack and vasopressor use in TTS patients with low LVEF.<sup>93</sup>

ICD implantation for VA management has been generally discouraged in the setting of TTS due to the reversible nature of this phenomenon.<sup>82,92,94,95</sup> In this context, even though PPM implantation has been mostly recommended for the management of in-hospital high-degree AVBs (due to the high risk of recurrence), temporary secondary-prevention strategies including wearable defibrillators may be preferred following discharge in those with an in-hospital VA (till complete TTS recovery ensues).<sup>92,94,95</sup> However, persistent cardiac dysfunction (functional, structural and metabolic) following complete TTS recovery has been suggested as an important phenomenon with long-term consequences.<sup>7,96</sup> MRI findings also

suggest certain findings including microfibrosis in TTS survivors.<sup>96</sup> Higher levels of inflammation markers were also reported in these patients (remote from the hospital discharge) suggesting a state of persistent low grade inflammation.<sup>14,96</sup> Accordingly, persistent systemic inflammation might play a pivotal role in malignant arrhythmogenesis particularly in the presence of cardiac structural alterations.<sup>97</sup> Notably, monomorphic VAs in the hospital setting, unlike polymorphic ones, might not be solely attributable to transient factors including QT interval prolongation, yet might have a persistent structural basis in the setting of TTS.<sup>98</sup> Accordingly, monomorphic VAs were previously suggested to have an important association with mortality compared with polymorphic VAs.<sup>98-100</sup> Finally, a long-term excess mortality was previously reported in TTS survivors<sup>101</sup> particularly in those suffering an in-hospital cardiac arrest.<sup>102</sup> Potential role of late VAs in this excess mortality seems possible as well.<sup>98,99</sup> Based on the above-mentioned notions, secondary-prevention ICD implantation seems reasonable either as an initial strategy or following temporary strategies in certain high-risk TTS survivors with an in-hospital VA(s) (including those with persistent LGE on MRI, persistent elevation of inflammation markers, severe exercise intolerance following complete TTS recovery, and recurrent monomorphic VAs during hospital stay). However, these notions are currently speculative, and need to be tested. Of note, timing of ICD implantation in this context also remains nebulous. In a recent study, ICD implantation was performed at a median of 19 days following TTS admission.<sup>92</sup> Finally, ICD implantation seems as a plausible strategy in the setting of TTS that is considered as the consequence (rather than the cause) of a life-threatening VA episode<sup>95</sup> particularly if the arrhythmia trigger is unknown or persistent.

#### KEY POINTS

- LV thrombus characteristics and CNS findings on imaging should be carefully evaluated in TTS patients with an LV thrombus complicated by stroke for further decision-making for anticoagulation.
- Thorough evaluation of the LV cavity for an existing thrombus is necessary prior to LVAD implantation in TTS patients.
- PPM implantation is recommended in TTS patients complicated by high-degree heart blocks.
- ICD implantation has been mostly discouraged in TTS patients complicated by in-hospital malignant VAs. However, this may be occasionally considered in select patients with a potential risk of post-recovery VA recurrence.

### 3.5. Therapeutic challenges and practical strategies in the setting of life-threatening physical stressors

As expected, there exists a plethora of physical triggers previously reported to be associated with TTS evolution (including infections, surgery, trauma, anesthesia, etc.).<sup>2</sup>

#### - Practical strategies in the setting of relatively frequent stressors

Certain physical triggers including acute cerebrovascular events, sepsis, cancer and major surgery may be relatively frequent, and may appear to serve as stronger determinants of prognosis compared with the associated TTS. In other terms, TTS might just constitute an epiphenomenon in the presence of these serious conditions.<sup>14</sup> Therefore, therapy should prioritize the potential challenges associated with these life-threatening physical triggers, where necessary. For instance; anticoagulation should be avoided or interrupted in the setting of an intracerebral haemorrhage,<sup>32</sup> or cancer metastases to high-risk organ systems including the central nervous system or in the aftermath of a major surgery. Therapy may constitute fluid therapy and non-sympathomimetic vasopressors in patients with septic shock.<sup>58</sup> However, excessive fluid therapy may increase the risk of pulmonary edema in this setting, and requires close supervision<sup>32</sup> particularly in TTS patients with LV dysfunction. In the general context, strict management of pump failure should accompany fluid therapy in TTS patients with reduced systemic vascular resistance.

More specifically, coronavirus disease-2019 (COVID-19) has also been reported to be associated with TTS evolution either due to the infection itself or due to a variety of secondary causes including psychological factors such as social isolation and fear of dying.<sup>14,103</sup> Importantly, use of diagnostic modalities including CAG has been limited in the setting of COVID-19 potentially creating significant challenges in TTS diagnosis and management.<sup>103</sup> Accordingly, complication and mortality rates were reported to be relatively higher in patients with TTS due to COVID-19.<sup>103-104</sup>

Finally, necessary surgical procedures in the acute phase of TTS (such as drainage of cerebral hematoma, etc.) should be implemented with a relatively higher surgical risk as in any other patient without a TTS episode (with particular cautions against potential arrhythmias, pulmonary edema, etc. during the procedure).

#### - Potential implications in the setting of rare stressors

Notably, certain life-threatening TTS triggers might be relatively rare, and might be easily overlooked potentially leading to high mortality rates in case of a missed diagnosis. Accordingly, we would like to put a particular emphasis on anaphylactoid reactions and

pheochromocytoma together with their therapeutic challenges and practical strategies in the setting of TTS.

**Anaphylactoid reactions:** In this context, the initial management strategy for TTS should focus on ruling out and treating any co-existing ACS with antiplatelet agents, anticoagulation, vasodilators, continuous ECG monitoring and planning CAG. ACS in this clinical scenario mostly signifies “Kounis syndrome (KS)” that was previously suggested to arise due to the adverse effects of anaphylactoid mediators (histamine, etc.) on coronary arterial system (leading to coronary vasospasm, etc.).<sup>105-107</sup>  $\beta$ -blockers are contraindicated in anaphylactoid reactions with hypotension, bradycardia, severe HF as well as suspected coronary vasospasm. Non-dihydropyridine calcium channel blockers can be used as potential alternatives in the management of certain conditions including LVOTO.

Conditions associated with TTS evolution in the setting of anaphylactoid reactions appear to be strictly interrelated in multiple directions leading to a vicious cycle namely “the ATAK complex” (Anaphylaxis, Takotsubo, Adrenaline, KS).<sup>106</sup> In this complex, TTS can occur in a victim due to the anaphylactoid reaction itself, therapeutic adrenaline administration and compensatory catecholamine release from the adrenal medullary cells. Mechanistically, anaphylactoid mediators can trigger both KS and TTS.<sup>105</sup> Notably, severe angina due to KS may also have the potential to contribute to TS evolution as well. Interestingly, TTS may even arise in predisposed individuals watching and assisting in the management of anaphylactoid reactions. Broadly speaking, eventual TTS evolution may be quite possible in the context of anaphylactoid reactions.<sup>106</sup> In this context, ATAK complex<sup>105,106</sup> should be taken into consideration in the diagnosis, prevention and management of a potential TTS episode.

Although KS and TTS are commonly diagnosed clinical entities, there is still lack of comprehensive data regarding epidemiology and outcomes in the setting of their co-existence. In the first-ever population-based analysis on TTS and KS, it was demonstrated that 1.5% of all TTS admissions were related to KS.<sup>107</sup> Among adult hospitalizations related to KS and TTS, the frequency and characteristics of KS-associated TTS were evaluated using the National Inpatient Sample (2007-2014). Patients who were predominantly white females were part of the KS-TTS cohort, which was more heavily burdened with cardiovascular risk factors and required more resources than the non-TTS cohort. Hospital outcomes and baseline characteristics were examined. Comparing the KS-TTS cohort to the non-TTS cohort, it was found that the former was more frequently elderly (74 vs. 66 yrs.), female (100% vs. 52.9%), and less frequently white (62.2% vs. 71.3%) patients. Cardiovascular comorbidities and risk factors, such as dyslipidemia (62.4% vs. 44.7%;  $p=0.03$ ) and HT (100% vs. 75.6%;  $p=0.001$ ), were more common in the KS-TTS cohort than in the non-KS-TTS cohort.

**Pheochromocytoma:** Pheochromocytoma is an uncommon tumor of the adrenal medulla that secretes catecholamines, and has the potential to trigger TTS.<sup>62,76,108,109</sup> It may be sporadic or familial.<sup>76</sup> Since pheochromocytoma has a highly variable presentation pattern,<sup>109</sup> its diagnosis is often delayed or overlooked. Diagnosis assistance may be provided by unexplained HF accompanied by palpitations, severe headaches, abdominal pain, HT, excessive perspiration, unexplained transient hypotension or blood pressure fluctuations.<sup>62,76,108,109</sup> Imaging studies and evaluation of catecholamine metabolites in the urine generally confirms the diagnosis.<sup>76</sup> The association of pheochromocytoma and TTS was not initially included in TTS diagnostic criteria, but has been now universally accepted.<sup>5,108</sup> Pheochromocytoma-induced TTS is characterized by younger age, less exclusivity for the female gender, frequent reverse (basal) phenotype (rather than mid-ventricular/apical) of TTS than non-pheochromocytoma-TTS.<sup>62,108</sup> Management of pheochromocytoma-induced TTS is not different from the non-pheochromocytoma-TTS, except in reference to employment of  $\alpha$ -blockers prior to using  $\beta$ -blockers, diagnostic exploration for the location of pheochromocytoma tumors, emphasis on adequate fluid loading practices, and planning for surgical removal of the pheochromocytoma tumor either during the same admission or after stabilization of the patient and readmission for surgical management.<sup>76</sup> When pheochromocytoma-induced TTS is associated with cardiogenic shock, implementation of the extracorporeal membrane oxygenator is advisable.<sup>109</sup> In frail patients, particularly elderly with associated comorbidities, continuation of  $\alpha$ -blockers and  $\beta$ -blocker therapy, and meticulous preparation is in order, with consideration of laparoscopic surgery for extirpation of the pheochromocytoma tumor.

#### KEY POINTS

- Management of TTS should be tailored according to the underlying severe physical stressor, where necessary.
- Urgent surgical procedures in the acute phase of TTS should be performed with a relatively higher surgical risk.
- Anaphylactoid reactions and pheochromocytoma have been rare triggers of TTS with important therapeutic implications. They are associated with high mortality rates in case of a missed diagnosis.
- Vicious cycle namely the ATAK complex (Anaphylaxis, Takotsubo, Adrenaline, Kounis) should be taken into consideration in the diagnosis, prevention and management of a potential TTS episode in the setting of anaphylactoid reactions.
- Management of TTS in the setting of pheochromocytoma is similar to the general TTS management. However, management should also focus on initiation of alpha blockers prior to beta blockers, adequate fluid loading, and excision of pheochromocytoma.



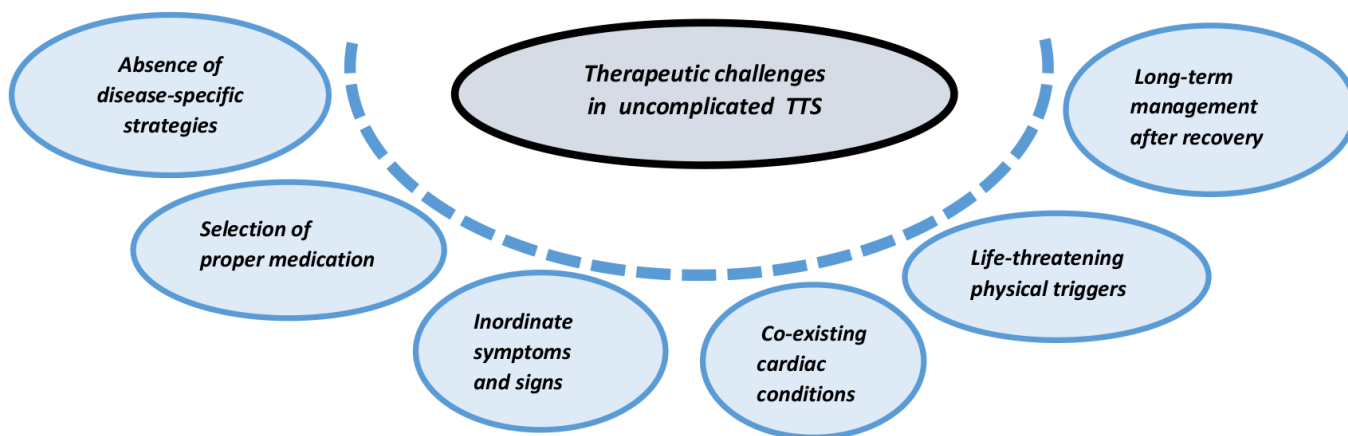
**3.6. Long-term management following a TTS episode: A therapeutic enigma**

In a recent trial, conventional agents including RAS blockers (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers),  $\beta$ -blockers and statins were associated with a reduced long-term mortality following ACSs.<sup>110</sup> However, RAS blockers were suggested as the sole cardiovascular agents associated with long-term survival benefit following a TTS episode.<sup>110</sup> Moreover, certain agents including diuretics may be associated with worse outcomes in both conditions.<sup>110</sup> In a recent meta-analysis, the use of  $\beta$ -blockers in combination with RAS blockers as combination therapy to lower the risk of TTS recurrence was found to have insufficient statistical support.<sup>111</sup> Moreover, in patients with TTS who made it out of the hospital,  $\beta$ -blockers did not appear to be linked to decreased mortality or TTS recurrence. This adds to the increasing body of evidence indicating that patients with TTS might not benefit from regular beta-blocker prescriptions.<sup>112</sup> All the above show that this enigma exists and needs to be solved.

**KEY POINTS**

- Long-term benefits of conventional agents other than RAS blockers still need to be established.

Taken together, therapeutic challenges are quite common in patients with TTS even in those without overt complications. **Figure 7** demonstrates an overall summary of therapeutic challenges in the setting of uncomplicated TTS. Finally, detailed aspects of epidemiology and pathophysiology of TTS<sup>2-8,32,113-114</sup> as well as potential challenges in the setting of more specific TTS triggers (including natural disasters)<sup>115-117</sup> and promising therapeutic options<sup>32, 118-121</sup> have been discussed elsewhere, and are beyond the scope of this paper.



**FIG. 7.** A summary of the therapeutic challenges in patients with uncomplicated TTS. TTS, Takotsubo syndrome.

#### 4. CONCLUSION

TTS has been an increasingly recognized phenomenon in clinical practice. However, it is still one of the most underdiagnosed cardiovascular conditions largely due to a variety of diagnostic challenges. Importantly, TTS should be considered as one of the differential diagnoses in every patient with an ACS presentation and in critically ill patients with new-onset cardiovascular manifestations. Furthermore, it seems imperative for clinicians to stay aloof from preconditionings and stereotypical ideas regarding TTS. It should be borne in mind that this phenomenon may occasionally co-exist with other cardiac conditions, and may arise in atypical clinical and morphological patterns. These diagnostic challenges warrant the use of advanced diagnostic modalities (including cardiac MRI, intracoronary imaging, and nuclear imaging) to establish the final diagnosis particularly in cases in whom conventional imaging modalities remain inconclusive. However, it seems also necessary to pursue certain diagnostic algorithms for the proper and timely use of these advanced modalities.

On the other hand, therapeutic challenges may be quite possible even in the setting of TTS without overt complications. In this context, selection of proper medication is quite challenging, and needs to be adjusted on a case by case basis. Disproportionate symptoms (and signs), co-existing acute cardiac conditions and life-threatening physical triggers should be further evaluated to guide the subsequent management strategies. Finally, potential benefits of long-term management following a TTS episode still remain to be further established.

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