Coexistence and outcome of coronary artery disease in Takotsubo syndrome

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Abstract

Aims

Takotsubo syndrome (TTS) is an acute heart failure syndrome, which shares many features with acute coronary syndrome (ACS). Although TTS was initially described with angiographically normal

coronary arteries, smaller studies recently indicated a potential coexistence of coronary artery disease (CAD) in TTS patients. This study aimed to determine the coexistence, features, and prognostic role of CAD in a large cohort of patients with TTS.

Methods and results
Coronary anatomy and CAD were studied in patients diagnosed with TTS. Inclusion criteria were compliance with the International Takotsubo Diagnostic Criteria for TTS, and availability of original coronary angiographies with ventriculography performed during the acute phase. Exclusion criteria were missing views, poor quality of angiography loops, and angiography without ventriculography. A total of 1016 TTS patients were studied. Of those, 23.0% had obstructive CAD, 41.2% had non-obstructive CAD, and 35.7% had angiographically normal coronary arteries. A total of 47 patients (4.6%) underwent percutaneous coronary intervention, and 3 patients had acute and 8 had chronic coronary artery occlusion concomitant with TTS, respectively. The presence of CAD was associated with increased incidence of shock, ventilation, and death from any cause. After adjusting for confounders, the presence of obstructive CAD was associated with mortality at 30 days. Takotsubo syndrome patients with obstructive CAD were at comparable risk for shock and death and nearly at twice the risk for ventilation compared to an age- and sex-matched ACS cohort.

Conclusions
Coronary artery disease frequently coexists in TTS patients, presents with the whole spectrum of coronary pathology including acute coronary occlusion, and is associated with adverse outcome.

Introduction
Takotsubo syndrome (TTS) is a prototypical acute heart failure syndrome and characterized by an often strongly, but always transiently impaired left ventricular systolic function.[1–4] In the acute phase, symptoms and signs of TTS are virtually indistinguishable from those of acute coronary syndrome (ACS): upon acute presentation, ∼76% of TTS patients have chest pain, ∼44% demonstrate ST-segment elevation on the 1st electrocardiogram (ECG),[1] and troponin is elevated in the majority of cases.[5,6] Takotsubo syndrome is still underrecognized and an estimated 4% of patients (6% in women) initially diagnosed with an ACS suffer from TTS instead.[7–12] Takotsubo syndrome is commonly perceived as being a benign and 'self-limiting' disease, which results in underestimation of morbidity and mortality.[13] However, in fact in-hospital and long-term outcomes are largely comparable to those of age- and sex-matched ACS patients.[1,14]
According to the Mayo Clinic Diagnostic Criteria, diagnosis of TTS was initially believed to require an angiogram without signs of obstructive coronary artery disease (CAD),[15] and even the revised version of the criteria mentioned CAD only in a footnote.[9] Subsequently, TTS was usually not considered a potential diagnosis in patients with overt CAD, suggesting that both entities were mutually exclusive. Although coronary plaque rupture, macrovascular spasm, or dissection are not generally considered causal for TTS, indeed stable or unstable CAD can be present in TTS, either as bystander disease or trigger of TTS. Moreover, severe pain as occurring in ACS is a known trigger of TTS.[16] Recent TTS studies reported varying frequencies of coexisting CAD,[1,17–22] calling the results of previous TTS studies, which a priori excluded patients with CAD, in part into question. Furthermore, a major limitation of many previous TTS studies is their low sample size. Therefore, the aim of the present study was to investigate the prevalence, characteristics, and outcome effects of CAD in a large cohort of TTS patients.

Methods

Study population
For the present study, the International Takotsubo Registry (InterTAK Registry)[1,23] was screened for patients with coexisting CAD. The InterTAK Registry is an international multicentre observational registry with 40 participating centres from 12 countries, and data are collected retrospectively and prospectively by review of charts, patient history, laboratory results, ECG, echocardiography, cardiac magnetic resonance imaging (MRI) if available, and cardiac catheterization.

The study protocol was reviewed by the respective local ethics committees or investigational review boards at each collaboration site. Due to the in part retrospective nature of the study, ethics committees of most study centres waived the need for informed consent. At centres in which the ethics committees or investigational review boards required informed consent or in which patients were included prospectively, formal written consent was obtained from patients or surrogates. All patients included into the registry are diagnosed with TTS according to the InterTAK Diagnostic Criteria.[3] Generally, patients with a TTS phenotype and coexisting CAD, in whom wall motion abnormalities match with the perfusion territory of the diseased vessel, are not included into the InterTAK Registry, unless cardiac MRI shows the absence of late gadolinium enhancement. Of note, in the present study, there was no patient with complete overlap of wall motion abnormalities and the territory of a diseased coronary artery.
Patients diagnosed with TTS between March 2002 and February 2017 from 23 centres were screened for eligibility (*Figure 1*). Inclusion criteria were (i) coronary angiography within the acute phase of TTS, (ii) left ventriculography performed during the same procedure, and (iii) original angiography available for review. Ventriculography was required for definition of TTS type and for comparison of wall motion abnormalities and coronary anatomy. Patients were excluded (*Figure 1*), if angiography was not diagnostic, e.g. due to missing views or quality measures ($N = 13$) or if ventriculography had not been made ($N = 116$). Finally, 1016 angiograms were included into the present study, of which 439 had monoplane and 577 biplane ventriculography.

Coronary angiography
Original angiographies of TTS patients were re-evaluated by two independent board-certified senior interventional cardiologists blinded to clinical data and outcome to reach consensus, and in the rare cases of disagreement, a 3rd equally qualified interventional cardiologist was involved. Coronary anatomy and pathology were visually evaluated according to clinical standards. Non-obstructive CAD was defined as the presence of coronary calcifications, atherosclerosis, plaques and/or stenoses <50% of the vessel diameter, and obstructive CAD with stenoses ≥50% of the lumen diameter in arteries with a diameter amenable to percutaneous intervention. Wrap-around left anterior descending artery (LAD) was defined as an LAD perfusing at least one-quarter of the inferior wall of the left ventricle, as seen in a right anterior oblique view.[24] Takotsubo syndrome phenotype (i.e. apical, midventricular, basal, or focal type)[25] was solely determined by ventriculography.

Matched comparison of Takotsubo syndrome with acute coronary syndrome
The TTS cohort with obstructive CAD ($N = 234$) was compared with an age- and sex-matched ACS cohort ($N = 234$). Angiographic data from ACS patients were extracted from detailed cath reports as original angiographies were not completely available. The ACS cohort was recruited from the Zurich ACS Registry[1] (*Figure 1*), which is an all-comers real-world registry of patients with ACS referred to the Zurich University Hospital.[26] All patients in the Zurich ACS registry either complied with the 3rd universal definition of myocardial infarction[27] or had unstable angina from obstructive CAD.

Outcomes
In-hospital complications and acute cardiac care were recorded including the use of catecholamines, presence of cardiogenic shock, need for non-invasive or invasive ventilation, cardiopulmonary resuscitation, and death, as documented in patient charts.[1] Follow-up analysis was based on data from clinical visits, medical records, or telephone interviews, and obtained by InterTAK core team members or local investigators from participating centres.

Statistical analysis
Continuous variables are provided as means and standard deviations or medians and interquartile ranges, and categorical variables as numbers with percentages. Continuous variables were compared by the Student's *t*-test or Mann–Whitney *U* test and categorical variables by the Pearson χ^2 test or Fisher's exact test, if indicated. Comparisons of multiple groups were performed with the one-way analysis of variance or Kruskal–Wallis test by ranks depending on normality of distribution. The non-parametric Kaplan–Meier product-limit estimator and the log-rank test were calculated to estimate and compare survival distributions. Cox regression was used to build a predictive model for 30-day

mortality stratified by obstructive CAD, non-obstructive CAD, and angiographically normal coronary arteries and adjusted by age, sex, physical and emotional triggers, diabetes mellitus, and arterial hypertension with respect to interactions. In logistic regression models, if the sample size is small or if a predictor is strongly associated with one of the possible outcomes, the estimated coefficients may be biased. Therefore, Firth's bias-reduced logistic regression model was additionally used. It fits a logistic regression model using Firth's bias reduction method, equivalent to penalization of the log-likelihood by the Jeffreys prior. In order to strengthen our findings, we reported the concordance statistic of the multivariable Cox model as well as of the regression model with and without the CAD variable. The concordance statistic assesses discrimination of prognostic models with binary and survival endpoints (as a measure of goodness-of-fit), i.e. in our case analyses the agreement between the observed response '30-day mortality' and obstructive CAD.
A two-sided *P*-value of <0.05 was considered statistically significant. For statistical analyses and compilation of graphs R 3.5 (R Foundation), SPSS version 25.0 (IBM) and Prism 6 (GraphPad) were used.

Results

Patients' characteristics

A total of 1016 patients were included into the present study (TTS cohort, *Figure 1*). Mean age was 67.9 ± 11.8 years and 90.8% were women. 77.9% had chest pain and 42.6% ST-segment elevation on admission. 58.6% had an apical TTS type and 41.4% had non-apical types (i.e. midventricular, basal, or focal TTS). Mean left ventricular ejection fraction (LVEF) was 41.4 ± 10.9%. A total of 34.1% had physical and 32.3% had emotional triggers, respectively. Characteristics are given in *Table 1* and Supplementary material online, *Table S1*.

Prevalence of coronary artery disease

Of the 1016 patients, 35.7% had normal coronary arteries without angiographic signs of CAD, and 419 patients (41.2%) had non-obstructive CAD (*Take home figure* and *Table 2*). A total of 234 patients had obstructive CAD, i.e. CAD with stenoses of 50% or more, resulting in a proportion of 23% of all TTS patients (Supplementary material online, *Figure S1*). Patients in the obstructive CAD group were more frequently men and older, and more often had physical triggers, arterial hypertension, diabetes, and hypercholesterolaemia than patients in the other groups (*Table 1* and Supplementary material online, *Tables S1 and S2*). Interestingly, there was no significant difference in the frequency of chest pain between groups ($P = 0.23$), demonstrating that the presence of obstructive CAD in TTS patients cannot simply be estimated from the presence of angina on admission. Haemodynamic parameters such as blood pressure, heart rate, and left ventricular end-diastolic pressure (LVEDP) were not different between TTS groups (*Table 1* and Supplementary material online, *Table S1* and *Figure S2*). However, LVEF in the acute phase was significantly lower in the obstructive CAD group (mean 39.4%) compared to the angiographically normal (mean 42.6%) and the non-obstructive CAD group (mean 41.5%), although the absolute difference was rather small ($P = 0.001$ for normal coronary arteries vs. obstructive CAD, Supplementary material online, *Figure S2* and *Table S1* and *Table 1*).

Coronary anatomy

Of the 1016 patients, 82.5% had right-dominant circulation and 5.6% a 'wrap-around' LAD (*Table 2*). Tortuosity was present in 72.6%. Of the 234 patients with obstructive CAD, 76 (32.5%) had stenoses between 50% and 69%, 147 (62.8%) between 70% and 99%, and 11 (4.7%) had coronary occlusions (*Take home figure*). Single- and multivessel disease was present in 66.2% and 33.8% of patients, respectively. Left anterior descending artery, left circumflex artery (LCX), and right coronary artery (RCA) were diseased in 62.0%, 32.5%, and 43.2%, respectively. Of note, there was no patient in whom the extent of wall motion abnormalities of the left ventricular myocardium could be solely attributed to the territory supplied by a diseased coronary artery. Left main disease was present in 4.7%, and there were eight patients with chronic total occlusions (3.4%).

Coronary interventions

Ad hoc percutaneous coronary intervention (PCI) was performed in 45 patients of the obstructive CAD group (19.2%), and in 2 patients of the non-obstructive CAD group. Overall, 15 patients (31.9%) received bare-metal stents, and 25 patients (53.2%) received drug-eluting stents, respectively. Mean diameter of the largest stent was 3.1 ± 0.5 mm and mean stent length was 23.6 ± 18.7 mm per patient. Seven patients had PCI without stenting. Results of coronary angiography are given in *Table 2*.

Notably, three patients had acute coronary occlusion (i.e. Type 1 myocardial infarction):[27] one patient had acute occlusion of the distal RCA and apical TTS, and a 2nd patient had acute occlusion of the proximal RCA and apical TTS. A 3rd patient had acute occlusion of an obtuse marginal branch of the LCX and midventricular TTS. All those three patients received primary PCI (*Figure 2* and Supplementary material online, *Figures S3–S5*).

Virtually all patients with suspected ST-segment myocardial infarction need to undergo immediate invasive evaluation according to current guidelines.[28] Thus, we questioned whether troponin levels would be helpful for deciding if coronary angiography is needed in all patients without ST-segment elevation. In TTS patients without ST-segment elevation on the admission ECG, the area under the curve for troponin on admission and peak levels was 0.503 and 0.542 for predicting the presence of obstructive CAD, respectively (Supplementary material online, *Figure S6*). In patients without ST-segment elevation and rather moderate elevation of troponin levels (on admission or peak, each below 20 times upper limit of the normal range), a considerable number of patients had obstructive CAD. Thus, troponin levels do not appear useful for deciding for or against coronary angiography.

Medication

Aspirin, $P2Y_{12}$ inhibitors and statins were more frequently prescribed in the CAD cohort. Prescription was not limited to coronary intervention, since more patients received dual antiplatelet therapy at discharge than interventions had been performed (Supplementary material online, *Table S3* and *Figure S7*). Given current guideline recommendations on medical therapy of CAD,[29] fewer patients than assumed received angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB), statins, and antithrombotic therapy at discharge, suggesting that CAD is obviously still not sufficiently considered in the management of TTS patients.

Comparison of Takotsubo syndrome with obstructive coronary artery disease to age- and sex-matched acute coronary syndrome patients

The matched ACS cohort consisted of 7.3% unstable angina, 40.6% non-ST-segment elevation myocardial infarction, and 52.1% ST-segment elevation myocardial infarction patients (*Figure 1*). The presence of ST-segment elevation was comparable between the TTS with obstructive CAD group (50.5%) and the ACS group (52.1%, $P = 0.74$), as was the presence of cardiovascular risk factors, except of a slightly but significantly higher prevalence of diabetes in TTS patients. Of note, the prevalence of arterial hypertension, diabetes, and hypercholesterolaemia increased with the presence and intensity of CAD in TTS patients as expected (*Table 1* and Supplementary material online, *Table S1*). Acute coronary syndrome patients more often had chest pain and less often dyspnoea on admission. In contrast, TTS patients had a lower LVEF, higher heart rates, higher brain natriuretic peptide levels, and also slightly higher LVEDP values, all of which reflecting the nature of TTS as an acute heart failure syndrome. While troponin levels on admission were not sufficient to discriminate between both entities, initial creatine kinase values were slightly but significantly higher in ACS than in TTS patients. ST-segment elevation was more frequently present in TTS patients with CAD than in those without ($P = 0.004$). However, the presence of non-obstructive or obstructive CAD was not paralleled by higher maximum creatine kinase or troponin values in TTS patients, in contrast to the ACS cohort (*Table 1* and Supplementary material online, *Figure S8* and *Table S1*). We found that the extent of CAD in the ACS cohort was generally higher than in TTS patients with obstructive CAD, but did not see that CAD had some unique features in TTS such as preference for a specific vessel (*Table 2*).

Outcomes

Patients with TTS experienced a relevant number of in-hospital complications (*Take home figure* and Supplementary material online, *Table S1*). Of note, the incidence of ventilation, cardiogenic shock, resuscitation, and death was relatively low in the angiographically normal group, but increased with the presence and severity of CAD. Overall in-hospital morbidity and mortality were distinctly highest in the obstructive CAD group and lowest in the angiographically normal group, and there was a trend towards higher incidence of complications in patients with severe CAD (Supplementary material online, *Figure S9*). Kaplan–Meier estimates demonstrated that mortality was highest in TTS patients with obstructive CAD, which was comparable to age- and sex-matched patients with ACS (*Take home figure*). A predictive Cox regression model stratified by the three cohorts (angiographically normal, non-obstructive CAD, obstructive CAD) and adjusted by age, sex, physical and emotional triggers, diabetes mellitus, and hypertension with respect to interactions, showed that only physical triggers and obstructive CAD were significant predictors for 30-day mortality (*Table 3* and Supplementary material online, *Figure S10*). The concordance for the regression model with CAD was 0.800 (standard error: 0.034) and without CAD 0.779 (standard error: 0.037). The concordance for the multivariable Cox regression model with CAD was 0.798 (standard error: 0.033) and without CAD 0.782 (standard error: 0.033).

In TTS patients with cardiogenic shock in the acute phase, the presence of CAD was not anymore associated with higher in-hospital mortality, suggesting that cardiogenic shock might overrule an early outcome effect of CAD (Supplementary material online, *Figure S11*).

Incidence of in-hospital complications and 30-day mortality of TTS patients with CAD were at least as high as in the age- and sex-matched ACS cohort. Of note, the latter consisted of 92.7% patients with acute myocardial infarction, reflecting a high risk for adverse outcomes in this cohort. Invasive or non-invasive ventilation was used even nearly twice as often in TTS with obstructive CAD as compared to ACS (*Take home figure* and Supplementary material online, *Table S1*). To further analyse long-term outcome effects of CAD we calculated a landmark analysis of mortality in the three TTS and the ACS groups (Figure 3). While mortality rapidly increased after admission in patient with TTS and obstructive CAD (*Take home figure*), there was a detectable but rather slow increase in mortality over the next 5 years (*Figure 3*). This indicates that there is an acute outcome effect of CAD in patients with TTS beyond the rather expected effect of CAD on long-term outcomes. Thus, overall there was a strong association between the presence and severity of CAD and morbidity and mortality in TTS patients.

Discussion

The major findings of the present study are (i) a high proportion of patients with TTS have coexisting CAD; (ii) a considerable number of coronary lesions appear angiographically relevant; (iii) TTS may coincide with ACS, even with acute coronary occlusion; and (iv) CAD is associated with adverse prognosis in TTS patients.

Initially, TTS had been strictly associated with normal coronary arteries, which was supported by the observation that wall motion abnormalities in TTS typically do not follow coronary perfusion territories. As a consequence, the 1st Mayo Clinic Diagnostic Criteria for TTS required angiographic exclusion of CAD. In clinical practice, the combination of chest pain, apical ballooning, ST-segment elevation, and increased cardiac biomarkers is very suggestive of anterior myocardial infarction. Hence, 'spontaneously recanalized anterior myocardial infarction' was formerly often diagnosed without further proof. As a result, TTS was underdiagnosed in patients presenting with symptoms and signs of ACS in early years. In turn, significant coronary lesions were often neglected or downgraded in TTS patients, which contributed to underdiagnosing CAD in TTS patients. In our cohort, a substantial proportion of TTS patients with CAD did not receive guideline-directed medical therapy of CAD:[29] 20% of patients with obstructive CAD did not receive an or ACE inhibitor or ARB and 30% not a statin at discharge, respectively. This again reflects that coexisting CAD is prone to be 'neglected' and thereby undertreated in TTS patients. In earlier mostly smaller studies, reported proportions of coexisting CAD with ≥50% stenoses vary,[1,17–22] between 9.6% and 29.0% (Supplementary material online, *Figure S1*), calling the common perception that diagnosing CAD would virtually exclude TTS into question. Using a definition of CAD as the presence of stenoses ≥75%, a Japanese study reported a proportion of 10.3%.[20] However, all available studies either

suffered from a limited sample size, used differing diagnostic criteria for TTS or severity of CAD, did not report on details of angiographic findings, or were not able to demonstrate a prognostic relevance of CAD in patients with TTS.[18–22] Thus, robust evidence on the prevalence, nature, and prognostic impact of CAD in TTS patients was lacking.

Here, we show in a large cohort of patients that CAD frequently coexists with TTS. The coexistence of CAD and TTS *per se* is not surprising considering the age and risk profile of TTS patients. Yet it remains unknown whether coronary atherosclerosis is a bystander or plays a causal role in TTS. Since there were more patients with than without CAD, and given that coronary angiography underestimates coronary atherosclerosis, CAD might finally play a role in TTS as a disease modifier and risk amplifier, e.g. via endothelial dysfunction or microvascular spasm. However, with all limitations, we rather doubt that macrovascular CAD plays a mechanistic pathogenetic role in TTS development. Nevertheless, coronary angiography appears mandatory (unless contraindicated) even in recurrent TTS to rule out stable or unstable CAD and to establish the diagnosis of TTS. While coronary angiography is recommended in patients with ST-segment elevation and ACS symptoms, we found that troponin levels are a very poor indicator of the presence of obstructive CAD in TTS patients without ST-segment elevation. The majority of TTS patients presents acutely with chest pain or dyspnoea, ~50% of patients have ST-segment elevation on the ECG, and nearly all TTS patients have elevated troponin levels. Therefore, coronary angiography would be indicated in most patients with suspected TTS according to current ACS guidelines.[28,30] There might be a role for non-invasive assessment such as computed tomography angiography in patients at very low pre-test probability for CAD, or in those with a low InterTAK Diagnostic Score value.[4] However, prospective studies are needed to test whether waiving coronary angiography is safe. In patients with TTS and obstructive CAD, it is further unknown whether invasive haemodynamic assessment of coronary lesions such as fractional flow reserve is reliable, given the profound microcirculatory changes during the acute phase. In this study, lesion assessment by the operator as well as the study team was performed by angiographic criteria, as haemodynamic assessment had not been performed in nearly all cases. Using this classic angiographic approach, 15.6% of patients (N=160) had lesions with 70% lumen reduction or more, but <5% received PCI, potentially reflecting undertreatment of CAD in TTS patients. Appropriate coronary intervention is especially important as TTS is an acute heart failure syndrome frequently complicated by cardiogenic shock. Although we found no significant difference in mortality between TTS patients with cardiogenic shock and with or without obstructive CAD, the risk of acute deterioration may still be reduced by appropriate coronary intervention. We further identified two patients in the non-obstructive CAD cohort who had low-grade stenoses without angiographic criteria of intervention, but who received PCI. In line with current guidelines, the decision for intervention in such cases should also be based on functional lesion assessment or intracoronary imaging.

In addition to the coexistence of stable CAD and TTS, there are single cases reported with coexisting ACS and TTS: subtotal LAD stenosis with apical TTS,[17] peripheral LAD occlusion and midventricular TTS,[31] marginal branch occlusion and apical TTS,[32,33] and RCA occlusion and apical TTS.[34,35] In our cohort, the majority of coronary atherosclerotic lesions appeared stable on coronary angiography, but we also found three patients with Type 1 myocardial infarction. We suspect that TTS is underdiagnosed if an acute coronary lesion is present, as ventriculography is not anymore performed by many operators in ACS patients in recent years. Since echocardiography is often performed with delay, the diagnosis of TTS might then be missed. However, this question cannot be answered by the present study and requires a prospective evaluation of large ACS cohorts. Importantly, as both TTS and ACS may result in severe impairment of LV function,[2] it may be difficult to decide whether TTS with coexisting CAD or TTS with coexisting ACS are present, which might be answered by cardiac MRI in selected cases.

Currently, it remains uncertain whether the finding of TTS together with a significant, but non-occlusive coronary lesion would require *ad hoc* primary PCI. Also, based on our data we cannot determine whether the coexistence of TTS and CAD is accidental or causal in nature. An ACS may be the 1st event and subsequently trigger TTS, but alternatively a TTS may have triggered Type 1 myocardial infarction[16,17] via a sympathetic surge causing coronary vasoconstriction and plaque rupture. In addition, TTS patients are at risk for thrombo-embolic events, e.g. of brain, kidneys, and lower extremities, but also into the coronary system with an embolic origin of myocardial infarction.[36]

Beyond confirming the coexistence of CAD in a large TTS cohort, the present study is the 1st to demonstrate an independent prognostic role of coexisting CAD. Indeed, the presence of CAD was strongly associated with complications and death during hospitalization and increased mortality at 30 days. As previous studies found no difference in outcomes of TTS patients with and without CAD,[18,19] our data emphasize the importance of an appropriate sample size for generating robust data on disease features and outcomes. As such, the present study for the 1st time adds concomitant CAD as an important risk indicator in TTS patients in the acute phase to the known predictors age, shock, low LVEF, physical trigger, and left ventricular outflow tract obstruction. We and others have previously shown that physical triggers are one of the strongest predictors of adverse outcome in TTS, which was again confirmed by the present study. Of note, the association between CAD and mortality remained significant after adjusting for several confounders including physical triggers. The reason for the adverse outcome in patients with TTS and CAD remains to be defined. We did not observe a relevant difference between maximum CK or troponin levels in patients with or without CAD, suggesting that the presence of CAD is not associated with increased myocardial damage or infarction. Left ventricular ejection fraction and LVEDP were also largely comparable between groups, suggesting that acute ischaemic myocardial failure by coexisting CAD is rather not responsible for the increased proportions of ventilation, shock, and death. Therefore, we can only speculate whether CAD is a general risk indicator or plays indeed a pathophysiological role for the observed adverse outcome, e.g. by higher incidence of fatal arrhythmias. Prospective studies are necessary to answer whether *ad hoc* PCI is beneficial in the acute phase of TTS. Until then, there is currently no obvious reason why interventional treatment of CAD, if indicated by contemporary means such as functional assessment or intracoronary imaging, should be withheld in patients with TTS.

Limitations

The present study is in part retrospective and by this suffers from inherent limitations. We cannot completely exclude a selection bias in included patients which could affect the prevalence of CAD in our cohort. Nonetheless, it is very likely that rather underreporting than overreporting of TTS patients with obstructive CAD had occurred, suggesting that the real prevalence might be at least as high as the observed one. Coronary pathology was visually assessed by angiographic measures, but without functional lesion assessment or intracoronary imaging, as those had not been performed in the majority of cases.

Conclusion

Coronary artery disease frequently coexists in patients with TTS and is an important risk factor for adverse outcome. Short-term prognosis of TTS patients with obstructive CAD and ACS patients matched for age and sex is largely comparable, which should prompt equal monitoring and surveillance during the acute phase of both diseases. Our findings emphasize the need for coronary angiography in TTS patients to avoid underdiagnosing coexisting CAD, and careful evaluation of wall motion abnormalities in ACS patients to avoid underdiagnosing TTS. Prospective studies are required to assess the benefit of *ad hoc* PCI in patients with TTS and obstructive CAD.

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Table 1
Characteristics of patients.

ACS, acute coronary syndrome; BMI, body mass index; BNP, brain natriuretic peptide; CAD, coronary artery disease; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; ULN, upper limit of the normal.
aPercentages of TTS types may differ to previous InterTAK Registry reports since type was solely determined by reviewing ventriculography irrespective of assessment by individual study centres.
bIncluding upper limits of troponin T, high-sensitivity troponin T, and troponin I.
cIncluding upper limits of brain natriuretic peptide and the N-terminal of prohormone brain natriuretic peptide.
dInformation from catheterization or echocardiography, if both available, data from catheterization were used.

		A	B	C	D	A–B–C	A vs. B	A vs. C	B vs. C	C vs. D
Characteristics	**Total study cohort (*N*=1016)**	**Normal coronary arteries [*N*=363 (35.7%)]**	**Non-obstructive CAD [*N*=419 (41.2%)]**	**Obstructive CAD [*N*=234 (23.0%)]**	**ACS, matched cohort (*N*=234)**	***P*-value**	***P*-value**	***P*-value**	***P*-value**	***P*-value**
Female gender, *n*/total *n* (%)	923/1016 (90.8)	348/363 (95.9)	371/419 (88.5)	204/234 (87.2)	204/234 (87.2)	<0.001	<0.001	<0.001	0.61	1.0
Age (years)	67.9 ± 11.8 (*N*=1016)	63.3 ± 12.3 (*N*=363)	69.3 ± 11.0 (*N*=419)	72.4 ± 9.7 (*N*=234)	72.2 ± 9.7 (*N*=234)	<0.001	<0.001	<0.001	<0.001	0.79
BMI (kg/m^2)	25.1 ± 4.9 (*N*=730)	24.7 ± 4.8 (*N*=267)	25.2 ± 4.6 (*N*=313)	25.6 ± 5.5 (*N*=150)	26.4 ± 4.6 (*N*=147)	0.19	0.20	0.09	0.48	0.16
Physical trigger, *n*/total *n* (%)	346/1016 (34.1)	111/363 (30.6)	141/419 (33.7)	94/234 (40.2)		0.053	0.36	0.016	0.10	
Emotional trigger, *n*/total *n* (%)	328/1016 (32.3)	128/363 (35.3)	140/419 (33.4)	60/234 (25.6)		0.040	0.59	0.013	0.039	
Apical type,[a] *n*/total *n* (%)	595/1016 (58.6)	188/363 (51.8)	248/419 (59.2)	159/234 (67.9)		<0.001	0.038	<0.001	0.027	
Chest pain, *n*/total *n* (%)	716/919 (77.9)	265/327 (81.0)	292/382 (76.4)	159/210 (75.7)	182/211 (86.3)	0.23	0.14	0.14	0.84	0.006
Dyspnoea, *n*/total *n* (%)	431/917 (47.0)	140/321 (43.6)	181/384 (47.1)	110/212 (51.9)	64/188 (34.0)	0.17	0.35	0.06	0.27	<0.001
Troponin on admission—factor increase in ULN[b]	8.79 (3.13–22.05) *N*=784	7.50 (3.00–21.00) *N*=283	9.69 (3.08–22.54) *N*=314	9.29 (3.36–26.40) *N*=187	7.14 (1.33–33.39) *N*=216	0.57	0.33	0.42	0.95	0.36
Troponin maximum—factor increase in ULN[b]	15.34 (6.30–34.11) *N*=820	14.60 (5.35–29.91) *N*=297	14.96 (6.00–34.71) *N*=330	17.11 (7.90–37.36) *N*=193	48.29 (10.86–126.70) *N*=217	0.053	0.24	0.014	0.16	<0.001
Creatine kinase on admission—factor increase in ULN	0.92 (0.60–1.46) *N*=760	0.94 (0.59–1.49) *N*=285	0.89 (0.58–1.39) *N*=299	0.97 (0.61–1.48) *N*=176	1.08 (0.59–2.93) *N*=217	0.38	0.32	0.63	0.19	0.023
Creatine kinase maximum—factor increase in ULN	1.13 (0.71–1.91) *N*=793	1.13 (0.70–1.91) *N*=292	1.08 (0.67–1.78) *N*=316	1.18 (0.75–2.17) *N*=185	4.09 (1.30–11.44) *N*=224	0.14	0.33	0.26	0.19	<0.001
BNP on admission—factor increase in ULN[c]	6.27 (2.11–18.63) *N*=276	5.43 (1.60–19.32) *N*=95	5.53 (1.54–13.89) *N*=108	8.63 (2.73–26.25) *N*=73	2.91 (1.02–8.95) *N*=194	0.050	0.40	0.11	0.015	<0.001
ST-segment elevation, *n*/total *n* (%)	373/875 (42.6)	114/318 (35.8)	164/369 (44.4)	95/188 (50.5)	122/234 (52.1)	0.004	0.022	0.001	0.17	0.74
ST-segment depression, *n*/total *n* (%)	63/875 (7.2)	19/318 (6.0)	30/369 (8.1)	14/188 (7.4)	63/203 (31.0)	0.55	0.27	0.52	0.78	<0.001
T-wave inversions, *n*/total *n* (%)	377/875 (43.1)	150/318 (47.2)	154/369 (41.7)	73/188 (38.8)	78/203 (38.4)	0.15	0.15	0.07	0.51	0.93
Left bundle branch block, *n*/total *n* (%)	38/875 (4.3)	12/318 (3.8)	23/369 (6.2)	3/188 (1.6)	18/202 (8.9)	0.033	0.14	0.16	0.014	0.001
Heart rate (b.p.m.)	86.0 ± 20.8 (*N*=738)	84.8 ± 21.3 (*N*=269)	85.7 ± 20.9 (*N*=309)	88.6 ± 19.8 (*N*=160)	75.6 ± 20.0 (*N*=193)	0.17	0.61	0.07	0.51	<0.001
Systolic blood pressure (mmHg)	131.8 ± 28.0 (*N*=744)	129.7 ± 27.8 (*N*=271)	134.6 ± 27.1 (*N*=307)	130.0 ± 29.5 (*N*=166)	130.5 ± 25.8 (*N*=215)	0.07	0.033	0.93	0.09	0.85
LVEF[d] (%)	41.4 ± 10.9 (*N*=891)	42.6 ± 10.9 (*N*=327)	41.5 ± 10.6 (*N*=363)	39.4 ± 11.1 (*N*=201)	50.2 ± 12.0 (*N*=144)	0.004	0.20	0.001	0.023	<0.001
LVEDP (mmHg)	22.0 ± 8.9 (*N*=693)	21.8 ± 8.4 (*N*=243)	21.6 ± 8.8 (*N*=280)	22.4 ± 8.5 (*N*=170)	20.1 ± 7.3 (*N*=154)	0.65	0.76	0.53	0.36	0.011
Arterial hypertension, *n*/total *n* (%)	647/992 (65.2)	191/354 (54.0)	286/409 (69.9)	170/229 (74.2)	160/231 (69.3)	<0.001	<0.001	<0.001	0.25	0.24
Diabetes, *n*/total *n* (%)	257/1003 (25.6)	60/359 (16.7)	115/412 (27.9)	82/232 (35.3)	60/230 (26.1)	<0.001	<0.001	<0.001	0.049	0.031
Current smoking, *n*/total *n* (%)	168/935 (18.0)	62/335 (18.5)	61/384 (15.9)	45/216 (20.8)	45/194 (23.2)	0.30	0.35	0.50	0.13	0.56
Hypercholesterolaemia, *n*/total *n* (%)	320/964 (33.2)	99/342 (28.9)	130/397 (32.7)	91/225 (40.4)	79/231 (34.2)	0.017	0.27	0.005	0.054	0.17
Positive family history, *n*/total *n* (%)	178/833 (21.4)	71/301 (23.6)	71/337 (21.1)	36/195 (18.5)	55/222 (24.8)	0.39	0.45	0.18	0.47	0.12

Table 2
Angiographic findings.

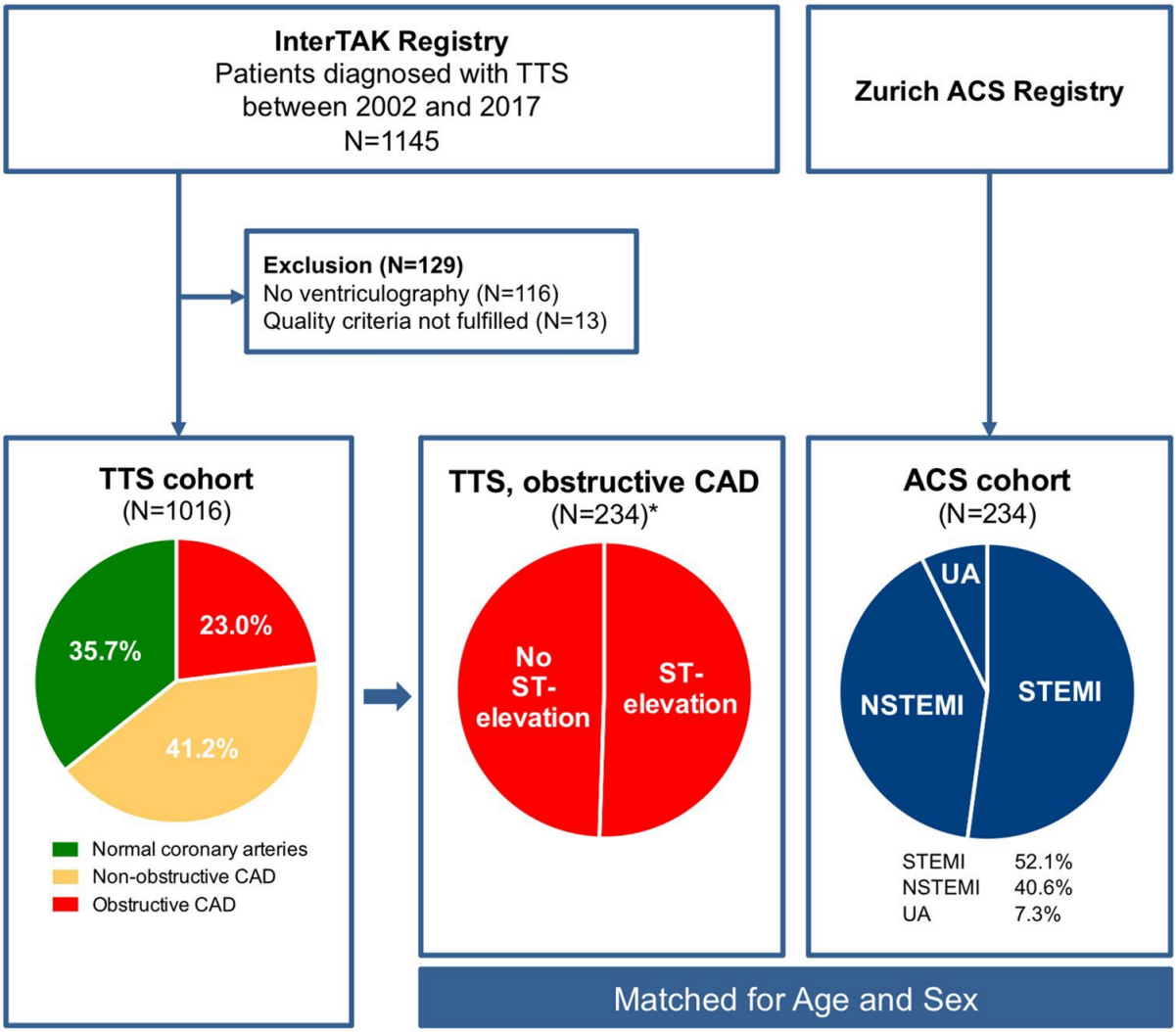
Characteristics, *n*/total *n* (%)	Total study cohort (*N*=1016)	Normal coronary arteries [*N*=363 (35.7)]	Non-obstructive CAD [*N*=419 (41.2)]	Obstructive CAD [*N*=234 (23.0)]	ACS, matched cohort (*N*=234)	*P*-value
Single-vessel disease	155/1016 (15.3)	–	–	155/234 (66.2)	69/234 (29.5)	<0.001
Multi-vessel disease	79/1016 (7.8)	–	–	79/234 (33.8)	165/234 (70.5)	<0.001
LMCA	11/1016 (1.1)	–	–	11/234 (4.7)	24/210 (11.4)	0.009
LAD	145/1016 (14.3)	–	–	145/234 (62.0)	198/234 (84.6)	<0.001
LCX	76/1016 (7.5)	–	–	76/234 (32.5)	130/223 (58.3)	<0.001
RCA	101/1016 (9.9)	–	–	101/234 (43.2)	152/233 (65.2)	<0.001
50–69% stenosis	76/1016 (7.5)[a]	–	–	76/234 (32.5)[a]	1/233 (0.4)	<0.001
70–99% stenosis	147/1016 (14.5)	–	–	147/234 (62.8)	93/233 (39.9)	<0.001
100% stenosis	11/1016 (1.1)	–	–	11/234 (4.7)	140/233 (60.1)	<0.001
Wrap-around LAD	57/1016 (5.6)	19/363 (5.2)	25/419 (6.0)	13/234 (5.6)	–	–
Muscle bridge	38/1016 (3.7)	18/363 (5.0)	13/419 (3.1)	7/234 (3.0)	–	–
Tortuosity	738/1016 (72.6)	274/363 (75.5)	296/419 (70.6)	168/234 (71.8)	–	–
Left dominance	87/1016 (8.6)	35/363 (9.6)	38/419 (9.1)	14/234 (6.0)	–	–
Right dominance	838/1016 (82.5)	289/363 (79.6)	347/419 (82.8)	202/234 (86.3)	–	–
Balanced	91/1016 (9.0)	39/363 (10.7)	34/419 (8.1)	18/234 (7.7)	–	–
Radial or brachial access[b]	180/1016 (17.7)	50/363 (13.8)	84/419 (20.0)	46/234 (19.7)	9/234 (3.8)	<0.001
Femoral access[b]	838/1016 (82.5)	313/363 (86.2)	337/419 (80.4)	188/234 (80.3)	225/234 (96.2)	<0.001
PCI (acute phase)	47/1016 (4.6)	0/363 (0.0)	2/419 (0.5)	45/234 (19.2)	216/234 (92.3)	<0.001
@LMCA	0/1016 (0.0)	–	0/0 (0.0)	0/45 (0.0)	7/234 (3.0)	0.60[c]
@LAD	23/1016 (2.3)	–	2/2 (100.0)	21/45 (46.7)	112/234 (47.9)	0.88
@LCX	14/1016 (1.4)	–	0/0 (0.0)	14/45 (31.1)	49/234 (20.9)	0.14
@RCA	14/1016 (1.4)	–	0/0 (0.0)	14/45 (31.1)	66/234 (28.2)	0.69
Bypass graft	0/1016 (0.0)	–	0/0 (0.0)	0/45 (0.0)	4/234 (1.7)	1.0[c]
Wiring only	3/1016 (0.3)	–	–	3/45 (6.7)	7/234 (3.0)	0.21[c]
POBA	3/1016 (0.3)	–	–	3/45 (6.7)	9/234 (3.8)	0.42[c]
Drug-eluting balloon	1/1016 (0.1)	–	–	1/45 (2.2)	2/234 (0.9)	0.41[c]
Stent implantation	40/1016 (3.9)	–	2/2 (100.0)	38/45 (84.4)	202/234 (86.3)	0.74
Number of stents, mean (min–max)	1.19 (0–5) *N*=47	–	1.00 (1–1) *N*=2	1.20 (0–5) *N*=45	1.4 (0–5) *N*=233	0.29
BMS	15/1016 (1.5)	–	–	15/38 (39.5)	60/233 (25.8)	0.08
DES	25/1016 (2.5)	–	2/2 (100.0)	23/38 (60.5)	144/233 (61.8)	0.88
Stent diameter maximum, mean ± SD	3.1 ± 0.5 (*N*=40)	–	3.8 ± 0.4 (*N*=2)	3.1 ± 0.5 (*N*=38)	3.1 ± 0.5 (*N*=200)	0.70
Stent length (overall), mean ± SD	23.6 ± 18.7 (*N*=40)	–	12.0 ± 0.0 (*N*=2)	25.2 ± 19.1 (*N*=38)	33.8 ± 17.9 (*N*=199)	0.003

ACS, acute coronary syndrome; BMS, bare metal stent; CAD, coronary artery disease; DES, drug-eluting stent; LAD, left anterior descending artery; LCX, left circumflex artery; LMCA, left main coronary artery; PCI, percutaneous coronary intervention; POBA, plain old balloon angioplasty; RCA, right coronary artery; SD, standard deviation.
aIncluding one patient with 40% LMCA stenosis.
bNot including two patients who had crossover from radial to femoral access.
cFisher's exact test.

Table 3
Multivariate analysis, 30-day mortality.

Variables in the equation	Logistic regression with Firth's bias correction					
	Coefficient	SE	95% Lower CI	95% Upper CI	χ^2	*P*-value
Constant	−5.437	1.290	−8.227	−2.941	20.637	<0.001
Non-obstructive CAD	0.634	0.517	−0.374	1.767	1.482	0.22
Obstructive CAD	1.075	0.536	0.031	2.238	4.081	0.043
Sex	−0.248	0.493	−1.167	0.837	0.233	0.63
Age	0.016	0.017	−0.018	0.052	0.803	0.37
Physical stress	1.673	0.503	0.741	2.834	13.895	<0.001
Emotional stress	−0.202	0.692	−1.711	1.224	0.079	0.78
Arterial hypertension	−0.597	0.381	−1.365	0.192	2.226	0.14
Diabetes mellitus	0.499	0.371	−0.275	1.241	1.639	0.20

Figure 1
Study cohorts. *Electrocardiogram data from 188 patients. ACS, acute coronary syndrome; CAD, coronary artery disease; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; TTS, Takotsubo syndrome.



Take home figure
(*A*) Prevalence of coronary artery disease in Takotsubo syndrome patients. (*B*) In-hospital complications. While resuscitation frequency was comparable between groups, death and cardiogenic

shock occurred more frequently in Takotsubo syndrome patients with coronary artery disease than in those without. Use of ventilation was nearly twice as high in patients with Takotsubo syndrome and coronary artery disease, as compared to those with normal coronary arteries. (*C*) Short-term prognosis in Takotsubo syndrome and acute coronary syndrome patients. Proportions of patients with death from any cause within 30 days from admission. ACS, acute coronary syndrome; CAD, coronary artery disease; MVD, multi-vessel disease; SVD, single-vessel disease; TTS, Takotsubo syndrome.

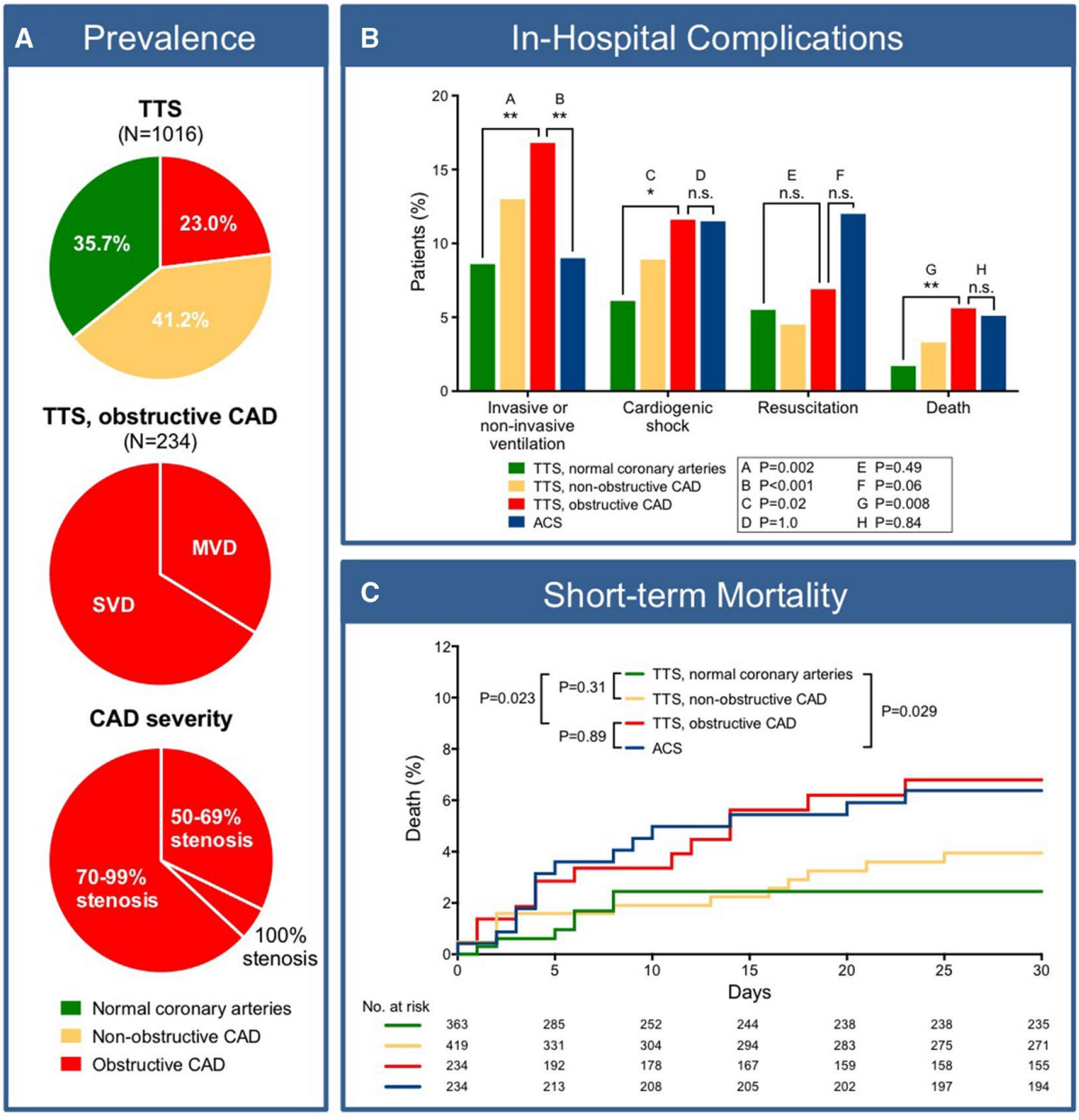


Figure 2
Coexistence of myocardial infarction and Takotsubo syndrome. (*A–C*) Patient 1 and (*D–F*) Patient 2, both with inferior myocardial infarction and apical Takotsubo syndrome, (*G–I*) Patient 3 with lateral myocardial infarction and midventricular Takotsubo syndrome. (*C*, *F*, and *I*) Wall motion schematics (red: diastole, white: systole, blue dashed line: hypo-/akinesia). Additional information: Supplementary material online, *Figures S3–S5*.

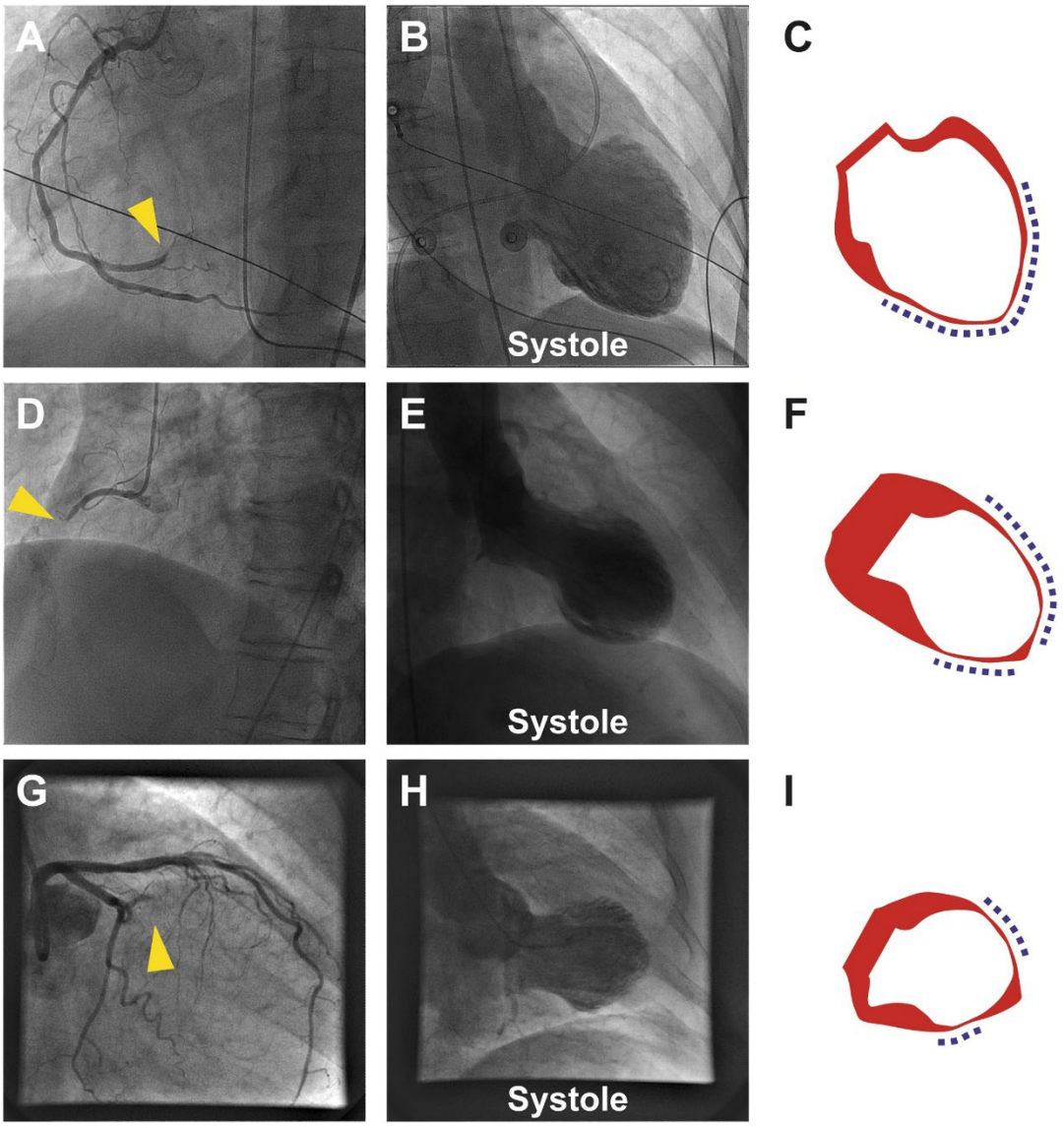


Figure 3

Landmark analysis of long-term-outcome in Takotsubo syndrome and acute coronary syndrome patients. Death from any cause within 5 years after the 1st 30 days after admission. ACS, acute coronary syndrome; CAD, coronary artery disease; TTS, Takotsubo syndrome.