SUPPLEMENTAL MATERIAL

Table S1. Definition of takotsubo syndrome used in the Swedish Coronary Angiography and Angioplasty Registry.

All 4 criteria must be met

1. Transient wall motion abnormalities in the left or right ventricle (preceding negative emotional stress or somatic disease, trauma etc. is often, but not always, present

2. Absence of angiographic signs of plaque rupture (note that significant coronary artery disease may coexist with takotsubo syndrome)

3. New ECG changes (ST-elevation or ST depression or T-wave inversion)

4. Absence of myocarditis.

Table S2. Unadjusted and adjusted risk of dying for patients with takotsubo versus STEMI or NSTEMI, by sex.

	Hazard Ratio (95% Confidence Interval)		
All-cause death	**Women**	**Men**	$P_{interaction}$
30 Day Prognosis			
Unadjusted			
TS vs. STEMI	0.27 (0.21 – 0.36)	0.62 (0.43 – 0.90)	0.0004
TS vs. NSTEMI	1.32 (0.99 – 1.76)	2.17 (1.49 – 3.14)	0.039
*MV adjustment**			
TS vs. STEMI	0.56 (0.42 – 0.74)	0.68 (0.47 – 0.98)	0.40
TS vs. NSTEMI	2.76 (2.05 – 3.72)	2.85 (1.96 – 4.15)	0.89
30 Day – 5 Year Prognosis†			
Unadjusted			
TS vs. STEMI	0.69 (0.59 – 0.79)	0.93 (0.74 – 1.18)	0.0002
TS vs. NSTEMI	0.65 (0.56 – 0.76)	1.19 (1.14 – 1.24)	0.031
*MV adjustment**			
TS vs. STEMI	0.82 (0.70 – 0.96)	0.96 (0.76 – 1.22)	0.25
TS vs. NSTEMI	0.96 (0.82 – 1.12)	1.06 (0.84 – 1.35)	0.47

*Multivariable shared frailty Cox proportional hazards regression adjusted for the following covariates: *age, diabetes, insulin-treated diabetes, hypertension, hyperlipidemia, current smoker, previous smoker, prior MI, prior PCI, calendar year. Treating hospital* was included the model as a random effect. † Landmark analysis from 30 days. MV = multivariable; NSTEMI = Non ST-elevation myocardial infarction; STEMI = ST-elevation myocardial infarction; TS = Takotsubo syndrome

Table S3. Unadjusted and adjusted risk of dying for patients with takotsubo versus STEMI or NSTEMI, by smoking status.

	Hazard Ratio (95% Confidence Interval)		
All-cause death	**Non-Smoker***	**Current Smoker**	**P$_{interaction}$**
30 Day Prognosis			
Unadjusted			
TS vs. STEMI	0.33 (0.26 – 0.43)	0.80 (0.53 – 1.23)	0.0006
TS vs. NSTEMI	1.32 (1.01 – 1.73)	3.10 (1.98 – 4.86)	0.002
MV adjustment†			
TS vs. STEMI	0.52 (0.40 – 0.69)	1.02 (0.66 – 1.57)	0.01
TS vs. NSTEMI	2.32 (1.77 – 3.06)	4.61 (2-91 – 7.31)	0.01
30 Day – 5 Year Prognosis‡			
Unadjusted			
TS vs. STEMI	0.77 (0.67 – 0.88)	1.49 (1.23 – 1.99)	<0.0001
TS vs. NSTEMI	0.73 (0.63 – 0.84)	1.25 (0.93 – 1.67)	0.02
MV adjustment†			
TS vs. STEMI	0.80 (0.69 – 0.92)	1.24 (0.93 – 1.64)	0.008
TS vs. NSTEMI	0.92 (0.79 – 1.06)	1.28 (0.97 – 1.71)	0.044

*Non-smoker includes ex-smoker. There was no statistical interaction between ex-smoker and TS vs. STEMI/NSTEMI. †Multivariable shared frailty Cox proportional hazards regression adjusted for the following covariates: *age, sex, diabetes, insulin-treated diabetes, hypertension, hyperlipidemia, prior MI, prior PCI, calendar year. Treating hospital* was included the model as a random effect. ‡Landmark analysis from 30 days. MV = multivariable; NSTEMI = Non ST-elevation myocardial infarction; STEMI = ST-elevation myocardial infarction; TS = Takotsubo syndrome

Table S4. Unadjusted and adjusted risk of dying for patients with takotsubo versus STEMI or NSTEMI, by age*.

| All-cause death	Hazard Ratio (95% Confidence Interval)			
	60 years	70 years	80 years	$P_{interaction}$
30 Day Prognosis				
Unadjusted				
TS vs. STEMI	0.55 (0.39 – 0.78)	0.44 (0.36 – 0.56)	0.36 (0.27 – 0.47)	0.007
TS vs. NSTEMI	2.59 (1.81 – 3.69)	1.90 (1.51 – 2.39)	1.40 (1.05 – 1.85)	0.044
MV adjustment†				
TS vs. STEMI	0.59 (0.42 – 0.84)	0.47 (0.37 – 0.59)	0.37 (0.28 – 0.49)	0.04
TS vs. NSTEMI	2.94 (2.05 – 4.20)	2.17 (1.72 – 2.74)	1.61 (1.20 - 2.14)	0.009
30 Day – 5 Year Prognosis‡				
Unadjusted				
TS vs. STEMI	1.33 (1.08 – 1.64)	1.01 (0.89 – 1.15)	0.77 (0.66 – 0.89)	<0.0001
TS vs. NSTEMI	1.16 (0.94 – 1.42)	0.95 (0.83 – 1.07)	0.77 (0.66 – 0.90)	0.002
MV adjustment†				
TS vs. STEMI	1.48 (1.20 – 1.83)	1.10 (0.96 – 1.25)	0.82 (0.70 – 0.95)	<0.0001
TS vs. NSTEMI	1.39 (1.12 – 1.71)	1.14 (1.00 – 1.30)	0.94 (0.81 – 1.10)	0.004

*Age was modeled as a linear effect. The risk estimates refer to the estimated risks at ages 60, 70 and 80 years. †Multivariable shared frailty Cox proportional hazards regression adjusted for the following covariates: *sex, diabetes, insulin-treated diabetes, hypertension, hyperlipidemia, current smoker, previous smoker, prior MI, prior PCI, calendar year*. *Treating hospital* was included the model as a random effect. ‡Landmark analysis from 30 days. MV = multivariable; NSTEMI = Non ST-elevation myocardial infarction; STEMI = ST-elevation myocardial infarction; TS = Takotsubo syndrome.

Table S5. Adjusted Risk of Mortality and Complications According to Health Care Region.

Outcome Health Care Region	Adjusted Hazard Ratio* (95% Confidence Interval)	p-value	p_{trend*}
Mortality within 30 days			0.22
Northern	1.08 (0.37 - 3.17)	0.89	
Uppsala-Orebro	1.00 (0.50 - 1.97)	0.99	
Stockholm	1.38 (0.76- 2.52)	0.29	
Western	*1.00 (REF)*		
Southeast	0.68 (0.23 - 1.97)	0.47	
South	2.52 (1.24 - 5.12)	0.011	
Mortality within 5 Years			0.031
Northern	0.62 (0.31 - 1.23)	0.17	
Uppsala-Orebro	0.87 (0.64 - 1.18)	0.37	
Stockholm	0.99 (0.75 - 1.32)	0.96	
Western	*1.00 (REF)*		
Southeast	1.01 (0.67 - 1.51)	0.96	
South	1.30 (0.88 - 1.90)	0.18	
Acute Heart Failure			0.002
Northern	1.61 (0.89 - 2.90)	0.12	
Uppsala-Orebro	1.20 (0.91 - 1.60)	0.20	
Stockholm	1.05 (0.80- 1.39)	0.70	
Western	*1.00 (REF)*		
Southeast	0.96 (0.63 - 1.46)	0.83	
South	0.72 (0.50 - 1.04)	0.079	
Cardiogenic Shock			0.98
Northern	1.02 (0.49 - 2.11)	0.97	
Uppsala-Orebro	0.90 (0.59 - 1.38)	0.62	
Stockholm	0.80 (0.53 - 1.20)	0.27	
Western	*1.00 (REF)*		
Southeast	0.87 (0.45 - 1.67)	0.66	
South	0.86 (0.53 - 1.41)	0.55	

*trend test for a risk gradient from North to South. To derive a p-value for trend, regions were graded based on geographic location, from north to south.

Figure S1. Mortality risk in patients with TS, NSTEMI and STEMI: Age- and sex matched cohort.
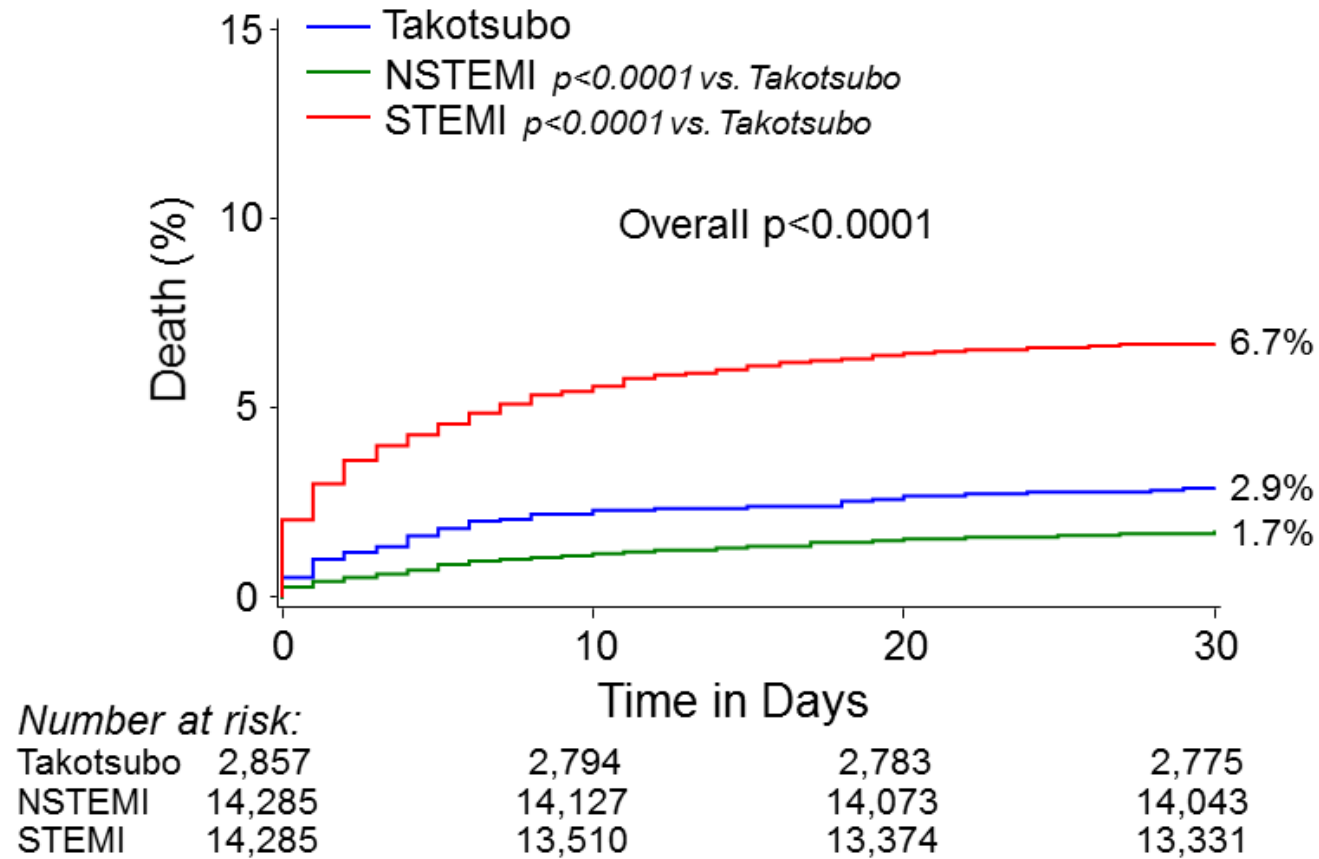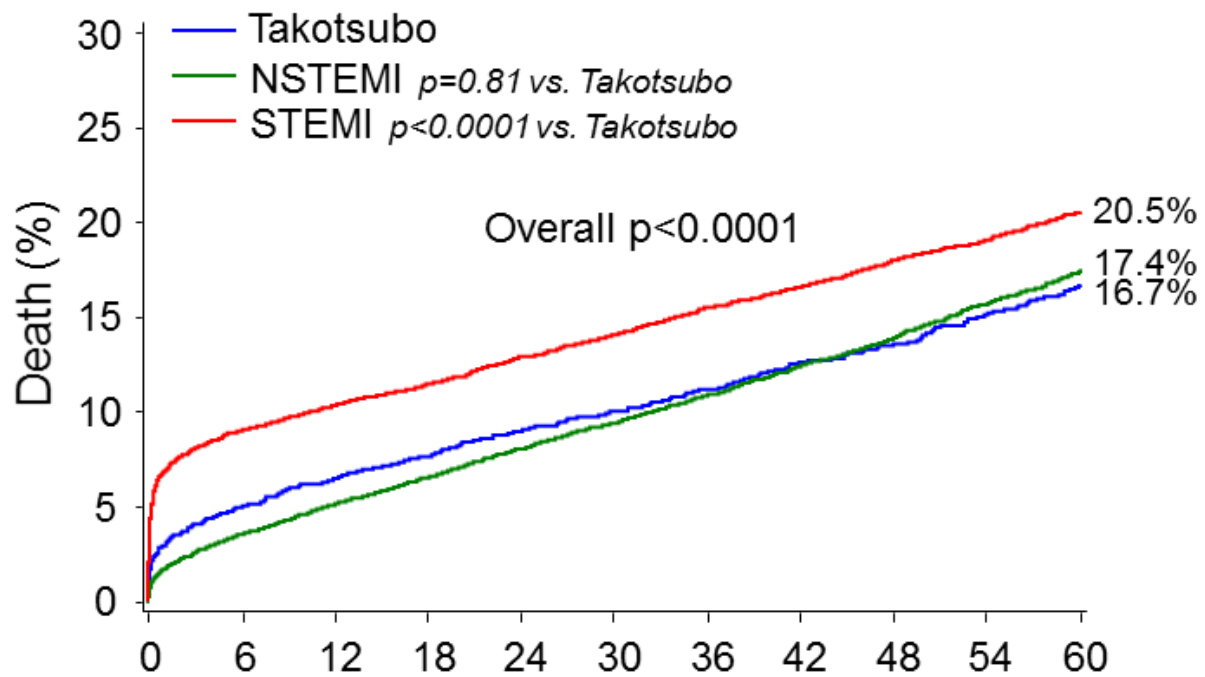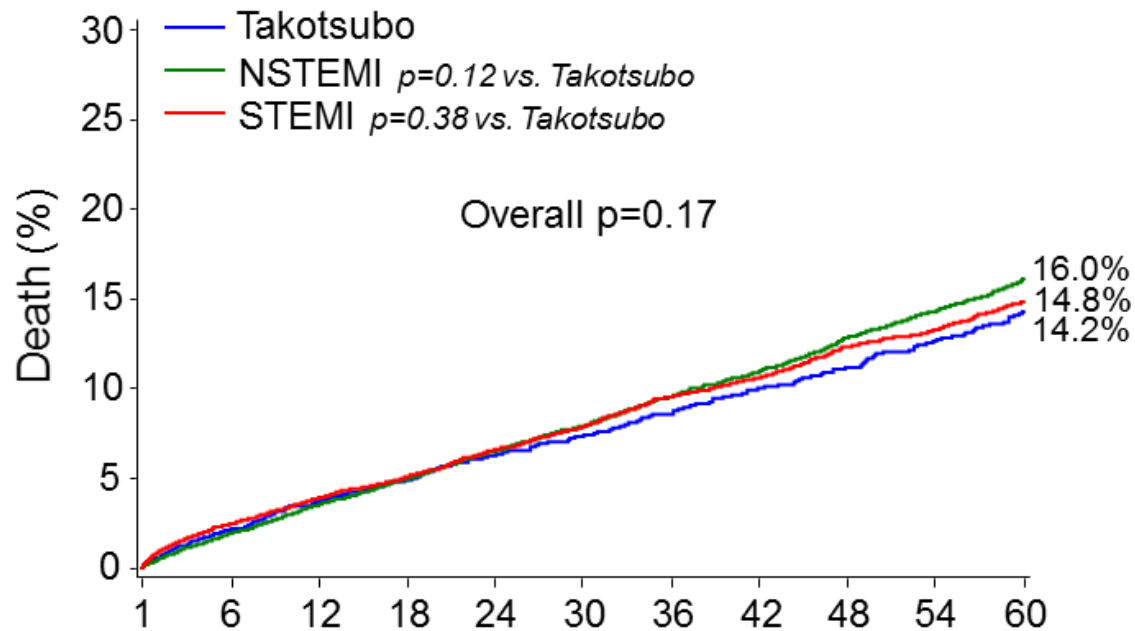
Number at risk:						
Takotsubo	2,857	2,406	1,914	1,458	1,077	813
NSTEMI	14,285	11,938	9,905	7,917	6,199	4,610
STEMI	14,285	11,440	9,706	8,073	6,507	5,060

Kaplan-Meier failure rates. Each patient with TS was matched to 5 patients with STEMI and 5 patients with NSTEMI based on sex (exact match) and age (± 5 years).
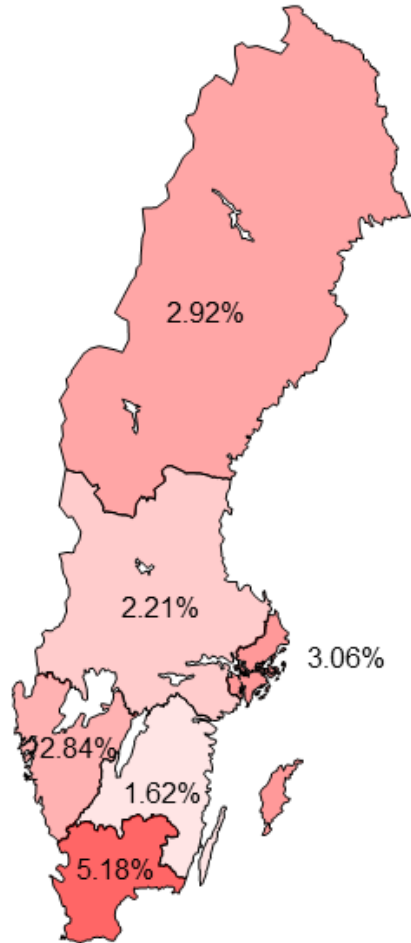
    A. Risk of dying within 30-days
    B. Risk of dying within 5 –years
    C. Landmark analysis: Risk of dying within 5 years for patients who were alive at 30 days.

NSTEMI = Non ST-elevation myocardial infarction; STEMI = ST-elevation myocardial infarction; TS = takotsubo syndrome
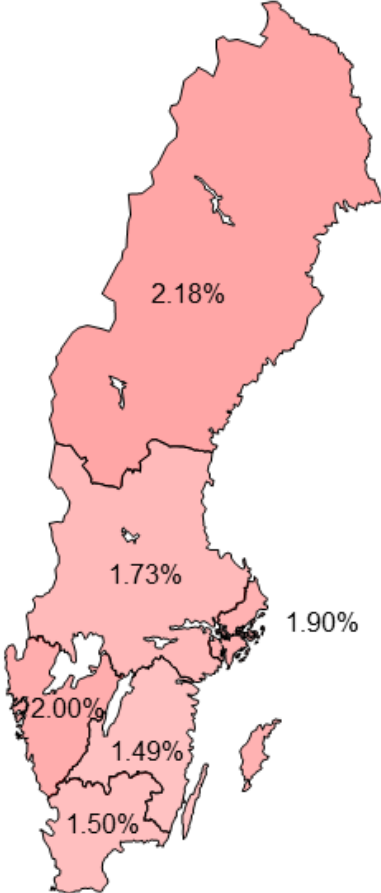
Figure S2. Incidence of TS Among Patients Undergoing Coronary Angiography Due to Suspected NSTEMI or STEMI.

TS incidence

1.13%

2.15%

3.90%

4.49%

1.76%

1.08%
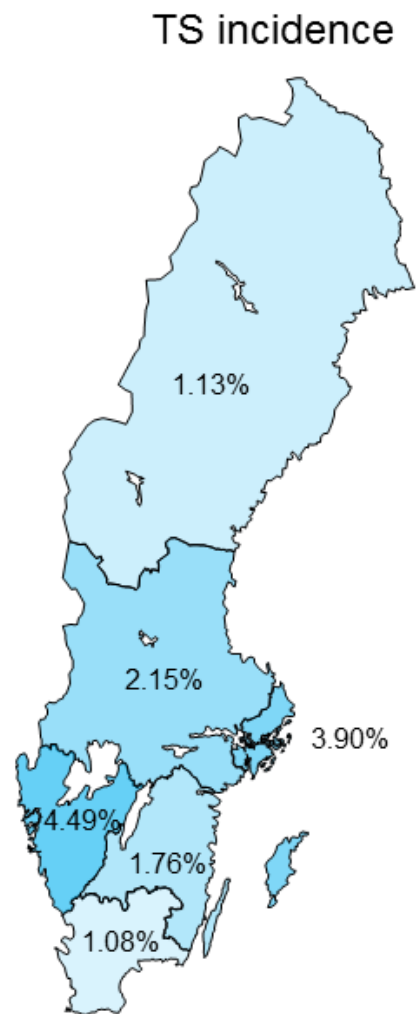
STEMI-associated
TS-associated   y
30-day mortality

2.92%

2.21%

3.06%

2.84%

1.62%

5.18%

NSTEMI-associated
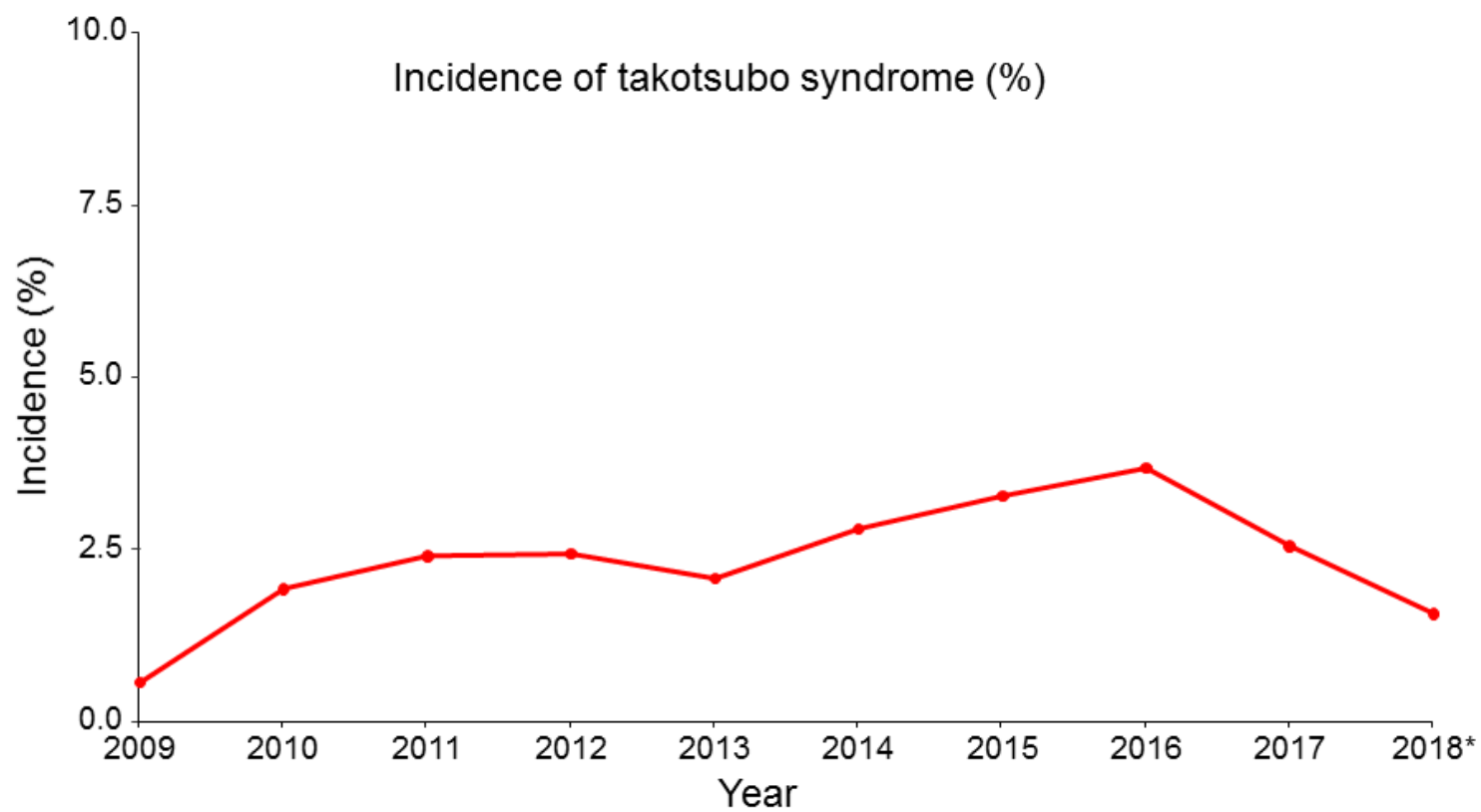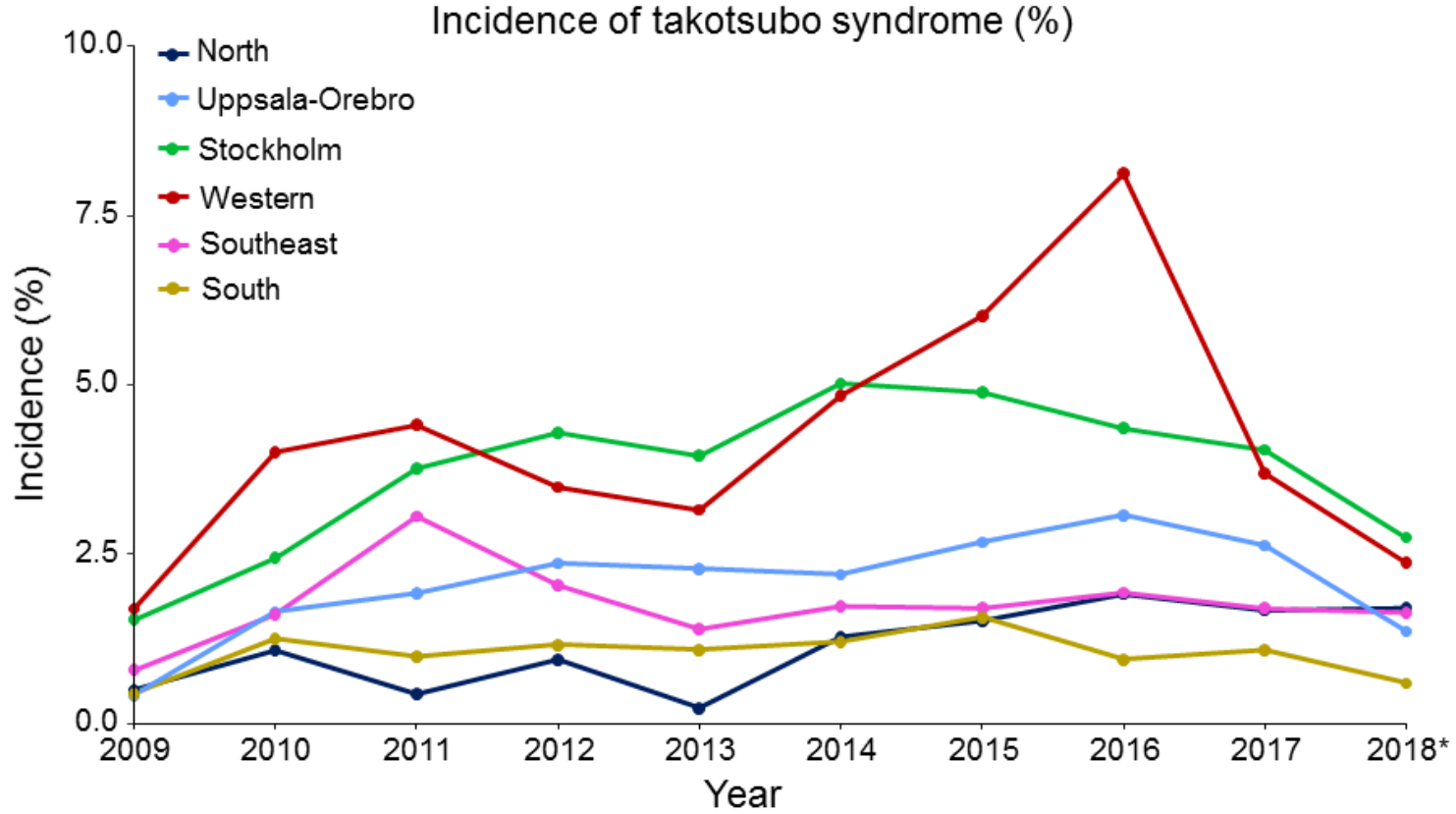30-day mortality

2.18%

1.73%

1.90%

2.00%

1.49%

1.50%

A. Incidence in Sweden
B. Incidence per health care region

*The study period ended after February 2018.

Figure S3. Regional Variations in Takotsubo Incidence and Prognosis.

Incidence of takotsubo syndrome (%)

Regional differences in the incidence of takotsubo (A) and in the 30-day prognosis for patients with takotsubo (B), ST-elevation myocardial infarction (C) and non ST-elevation myocardial infarction (D). The six regions correspond to the six official healthcare regions in Sweden.