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ORIGINAL ARTICLE
Arrhythmias and electrophysiology

Clinical significance of ST-segment depression during atrial fibrillation rhythm for subsequent heart failure events

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Aims The clinical significance of ST-segment depression during atrial fibrillation (AF) rhythm has not been fully evaluated. The aim of the present study was to explore the association of ST-segment depression during AF rhythm with subsequent heart failure (HF) events.

Methods and results The study enrolled 2718 AF patients whose baseline electrocardiography (ECG) was available from a Japanese community-based prospective survey. We assessed the association of ST-segment depression in baseline ECG during AF rhythm with clinical outcomes. The primary ednpoint was a composite HF endpoint: cardiac death or hospitalization due to HF. The prevalence of ST-segment depression was 25.4% (upsloping 6.6%, horizontal 18.8%, downsloping 10.1%). Patients with ST-segment depression were older and had more comorbidities than those without. During the median follow-up of 6.0 years, the incidence rate of the composite HF endpoint was significantly higher in patients with ST-segment depression than those without (5.3% vs. 3.6% per patient-year, log-rank $P < 0.01$). The higher risk was present in horizontal or downsloping ST-segment depression, but not in upsloping one. By multivariable analysis, ST-segment depression was an independent predictor for the composite HF endpoint (hazard ratio 1.23, 95% confidence interval 1.03–1.49, $P = 0.03$). In addition, ST-segment depression at anterior leads, unlike inferior or lateral leads, was not associated with higher risk for the composite HF endpoint.

Conclusion ST-segment depression during AF rhythm was associated with subsequent HF risk; however, the association was affected by type and distribution of ST-segment depression.

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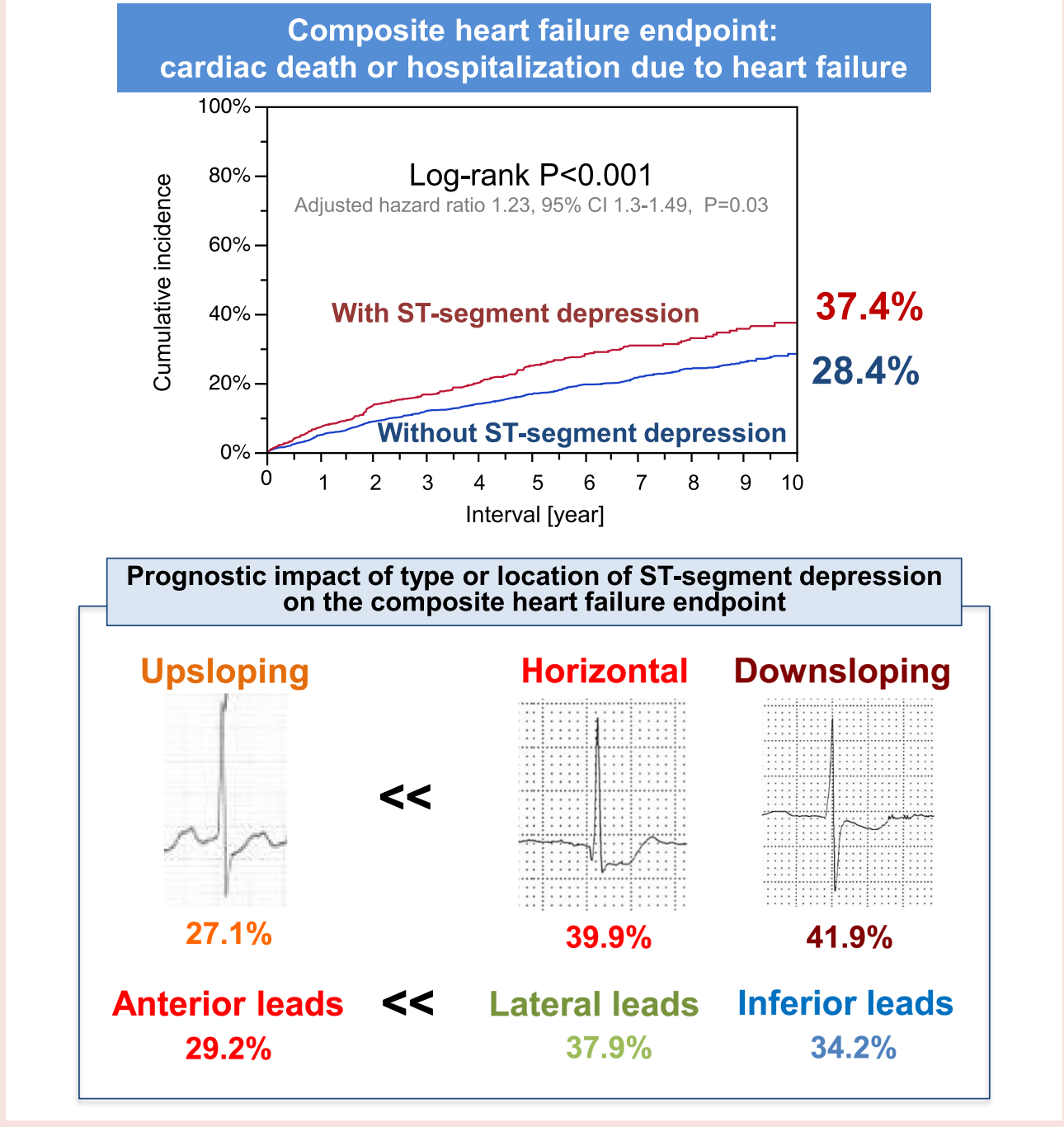
Graphical Abstract



Keywords Atrial fibrillation • Electrocardiogram • ST-segment depression • Heart failure

Introduction

Atrial fibrillation (AF) is a common arrhythmia in the current aging society, and is associated with a high risk of major adverse events such as heart failure (HF), ischemic stroke, and all-cause death.[1–3] Especially, HF leads to incident AF, and they can interact with each other.[4] In a previous study, we demonstrated that inverted T wave during AF rhythm on electrocardiography (ECG) is associated with higher subsequent cardiac risk including HF in AF patients.[5]

ST-segment depression is a common ECG abnormality during AF rhythm as well as inverted T wave. It is considered to be associated with the presence of coronary artery disease (CAD), and the association differs among types of ST-segment depression (upsloping, horizontal, and downsloping).[6,7] Furthermore, ST-segment depression is associated with higher mortality.[8,9] Previous studies evaluated the association of ST-segment depression during AF rhythm with the presence of CAD,[10–12] however, whether ST-segment depression is associated with clinical prognosis in AF patients, especially HF, and whether such an association is different according to the types of ST-segment depression has not been evaluated. In the present study, we investigated the association of ST-segment depression with subsequent HF events, in AF patients using data from the Fushimi AF Registry, a community-based survey of AF patients in Japan.

Methods

Study population

The detailed study design, patient enrollment, definitions of measurements, and baseline clinical characteristics of patients in the Fushimi AF Registry were previously described (UMIN Clinical Trials Registry: UMIN000005834).[13] The inclusion criterion for the registry was documentation of AF on a 12-lead ECG or Holter monitoring of AF at any time. There were no exclusion criteria. We started to enroll patients in March 2011 and a total of 81 institutions participated in the registry of Fushimi-ku, Kyoto, Japan. Collection of follow-up information was mainly conducted through reviews of inpatient and outpatient medical records, and additional follow-up information was collected through contact with patients, relatives, and/or referring physicians by mail or telephone. The study protocol conformed to the guidelines of the 1975 Declaration of Helsinki, and was approved by the ethical committees of the National Hospital Organization Kyoto Medical Center and Ijinkai Takeda General Hospital. As the present study was an observational study, written informed consent was not obtained from each patient in accordance with the Ethical Guidelines for Epidemiological Research issued by the Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labour and Welfare, Japan. The 12-lead ECG data during documented AF rhythm were obtained from the participating institutions at enrollment; however, submission of ECG data was not required for enrollment and was optional. ECG data were not provided in 1771 patients (39.5%) among 4489 AF patients enrolled in the registry. We analyzed 2718 patients (60.5%) whose baseline 12-lead ECG at the time of enrollment was available.

Definitions and outcome measures

AF was classified into paroxysmal (lasting < 7 days) and sustained (lasting ≥ 7 days) AF. Each abnormal finding in baseline ECG, which was provided at the time of enrollment, was diagnosed by two experienced cardiologists in accordance with AHA/ACC/HRS recommendations.[14,15] ST-segment depression was defined as a decrease ≥-0.1 mV in the ST-segment at 60 ms after J-point, and categorized as either upsloping, horizontal, or downsloping for each lead (*Figure 1*). The definition of inverted T wave used in the present study included definitely inverted T wave (<-0.1 mV) and flat or

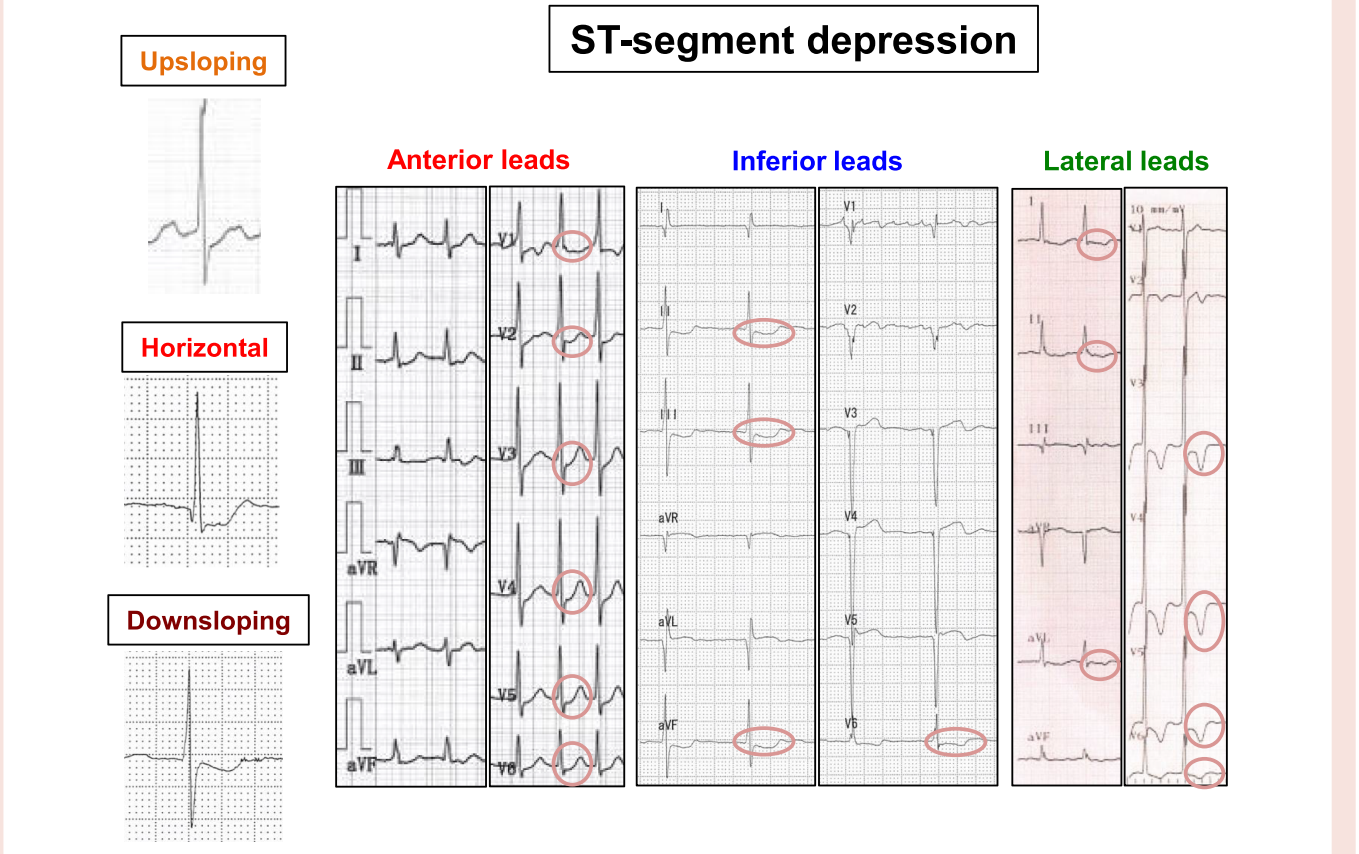


Figure 1 Definition of ST-segment depression and distribution.

Table 1 Baseline characteristics

	Overall $n = 2709$	With ST-segment depression $n = 691$	Without ST-segment depression $n = 2027$	*P*-value
Age (years old)	74.1 ± 10.8	76.2 ± 9.8	73.3 ± 11.0	<0.001
≥75 years old	1422 (52.5%)	423 (61.2%)	1005 (49.6%)	<0.001
Female	1101 (40.5%)	356 (51.5%)	745 (36.8%)	<0.001
Body weight	59.3 ± 13.5	56.7 ± 13.0	60.1 ± 13.5	<0.001
< 50 kg	651 (26.1%)	216 (34.0%)	435 (23.5%)	<0.001
Sustained atrial fibrillation	1658 (61.0%)	339 (49.1%)	1319 (65.1%)	<0.001
Hypertension	1678 (61.7%)	457 (66.1%)	1221 (60.2%)	0.006
Diabetes	636 (23.4%)	174 (25.2%)	462 (22.8%)	0.20
Chronic kidney disease	989 (36.4%)	291 (42.1%)	698 (34.4%)	<0.001
Pre-existing coronary artery disease	395 (14.5%)	152 (22.0%)	243 (12.0%)	<0.001
Pre-existing heart failure	802 (29.5%)	243 (35.2%)	559 (27.6%)	<0.001
$CHADS_2$ score	2.1 ± 1.3	2.3 ± 1.3	2.0 ± 1.4	<0.001
CHA_2DS_2-VASc score	3.4 ± 1.7	3.8 ± 1.6	3.3 ± 1.7	<0.001
HAS-BLED score	1.8 ± 1.0	1.9 ± 1.0	1.7 ± 1.0	<0.001
Echocardiographic findings				
Left ventricular diastolic diameter (mm)	46.5 ± 6.5	46.9 ± 6.9	46.3 ± 6.3	0.09
Left ventricular systolic diameter (mm)	30.7 ± 6.7	30.9 ± 7.3	30.6 ± 6.5	0.35
Left ventricular ejection fraction (%)	62.5 ± 11.3	62.3 ± 12.2	62.5 ± 11.0	0.75
Interventricular septum (mm)	9.6 ± 1.7	10.1 ± 2.0	9.4 ± 1.6	<0.001
Left ventricular posterior wall thickness (mm)	9.6 ± 1.5	9.9 ± 1.7	9.5 ± 1.4	<0.001
Left atrial diameter(mm)	44.8 ± 8.3	45.0 ± 8.5	44.7 ± 8.3	0.49
Electrocardiographic findings				
Heart rate (bpm)	94.7 ± 27.0	104.5 ± 30.7	91.4 ± 24.7	<0.001
≥110 bpm	679 (25.0%)	266 (38.5%)	413 (20.4%)	<0.001
Abnormal Q wave	314 (11.6%)	78 (11.3%)	236 (11.6%)	0.80
Left ventricular hypertrophy	563 (20.7%)	248 (35.9%)	315 (15.5%)	<0.001
Intraventricular conduction delay	284 (10.4%)	128 (18.5%)	156 (7.7%)	<0.001
ST-segment depression	691 (25.4%)	691 (100%)	—	—
Upsloping	179 (6.6%)	179 (25.9%)	—	—
Horizontal	512 (18.8%)	512 (74.1%)	—	—
Downsloping	275 (10.1%)	275 (39.8%)	—	—
Inverted T wave	1125 (41.4%)	443 (64.1%)	682 (33.7%)	<0.001

Categorical variables are presented as numbers (percentage). Continuous variables are presented as the mean ± SD or median.

low T wave (<10% of R wave in leads with R wave ≥ 1.0 mV). We separately evaluated the presence of inverted T wave in all 12 leads except aVR. The distribution of ST-segment depression was categorized into anterior leads (V1–4), inferior leads (II, III, aVF), lateral leads (I, aVL, V5, V6), and their combination.

Pre-existing HF was defined as the presence of one of the following at enrolment: history of hospitalization due to HF prior to enrolment, presence of New York Heart Association functional class II or higher HF symptoms (fatigue, dyspnea), or reduced left ventricular ejection fraction <40%. Pre-existing CAD was determined by the clinical diagnosis of attending physicians as not requiring coronary revascularization by percutaneous coronary intervention or coronary artery bypass graft surgery.

The primary endpoint was a composite HF endpoint: cardiac death, or hospitalization due to HF. Death was regarded as cardiac in origin only when obvious cardiac causes (HF, acute coronary syndrome, or dysrhythmia) were identified in distinction from vascular (ischemic stroke, systemic embolism, hemorrhagic stroke, other intracranial hemorrhage) and non-cardiovascular death.[16] Hospitalization was regarded as due to HF only when the attending physicians judged HF was a main cause of the hospitalization. The secondary endpoints were all-cause death, cardiac death, hospitalization due to HF, myocardial infarction, ischemic stroke or systemic embolism, and major bleeding.

Statistical analysis

Categorical variables were presented as numbers and percentages, and compared by the Fisher's exact test. Continuous variables were presented as the mean and standard deviation, and compared using the Student's *t*-test based on their normal distributions. We used % per patient-year to estimate the event rates and assessed the difference using Kaplan–Meier method and the log-rank test. We conducted multivariable analysis using the Cox proportional hazard model incorporating clinical covariates that were considered clinically relevant (age, gender, sustained AF, hypertension, diabetes, chronic kidney disease, pre-existing CAD, and pre-existing HF) and heart rate during AF rhythm to identify independent risk factors for the primary endpoint. We performed subgroup analyses stratified by those variables with the *P*-value for interaction in the Cox proportional hazards model to examine the heterogeneity in the subgroups. We performed a sensitivity analysis excluding patients with pre-existing HF or CAD. Furthermore, we confirmed the consistency of study results by propensity-score matching

Table 2 Clinical outcomes

	Overall *n* of patients with events (% per patient-year)	With ST-segment depression *n* of patients with events (% per patient-year)	Without ST-segment depression *n* of patients with events (% per patient-year)	Crude hazard ratio[a] (95% confidence interval)	*P* value[a]
Primary endpoint: a composite of cardiac death, or hospitalization due to heart failure	539 (4.0%)	166 (5.3%)	373 (3.6%)	1.48 (1.23–1.77)	<0.001
Secondary endpoint					
All-cause death	776 (5.2%)	247 (7.1%)	529 (4.6%)	1.52 (1.30–1.76)	<0.001
Non-cardiac death	645 (4.3%)	194 (5.6%)	451 (3.9%)	1.39 (1.18–1.65)	<0.001
Cardiac death	131 (0.9%)	53 (1.5%)	78 (0.7%)	2.23 (1.56–3.15)	<0.001
Hospitalization due to heart failure	480 (3.5%)	140 (4.5%)	340 (3.2%)	1.37 (1.12–1.66)	0.002
Myocardial infarction	33 (0.2%)	10 (0.3%)	23 (0.2%)	1.41 (0.64–2.89)	0.37
Ischemic stroke or systemic embolism	245 (1.7%)	65 (1.9%)	180 (1.6%)	1.19 (0.89–1.57)	0.25
Major bleeding	291 (2.0%)	62 (1.9%)	229 (2.1%)	0.88 (0.66–1.16)	0.39

[a]Cox proportional hazard analysis

analysis with adjusting for age, gender, body weight, sustained AF, hypertension, diabetes, previous ischemic stroke, chronic kidney disease, pre-existing CAD, heart rate, and the presence of inverted T wave between patients with and without ST-segment depression. For matching, a 1:1 nearest neighbor match with 0.5 caliper and no replacement was used. Statistical analyses were performed using JMP 10 (SAS Institute Inc, Cary, NC) software. All tests were two-tailed and a $P < 0.05$ was considered significant.

Results

Patient characteristics

The prevalence of patients with ST-segment depression was 25.4% of study patients (upsloping 6.6%; horizontal 18.8%; downsloping 10.1% of study patients). There was some overlap among the three types of ST-segment depression. Upsloping ST-segment depression did not coexist with horizontal or downsloping ST-segment depression in other leads; however, downsloping ST-segment depression coexisted with horizontal ST-segment depression in other leads.

Patients with ST-segment depression in baseline ECG were significantly older than those without (76.2 ± 9.8 years vs. 73.3 ± 11.0 years, $P < 0.001$) (*Table 1*). The prevalences of most baseline comorbidities except diabetes were significantly higher in patients with ST-segment depression. Patients with ST-segment depression had higher left ventricular wall thickness than those without, but there were no differences in left ventricular diameter or ejection fraction. They more often had other ECG abnormalities including higher heart rate, left ventricular hypertrophy and intraventricular conduction delay.

Association between ST-segment depression and clinical outcomes

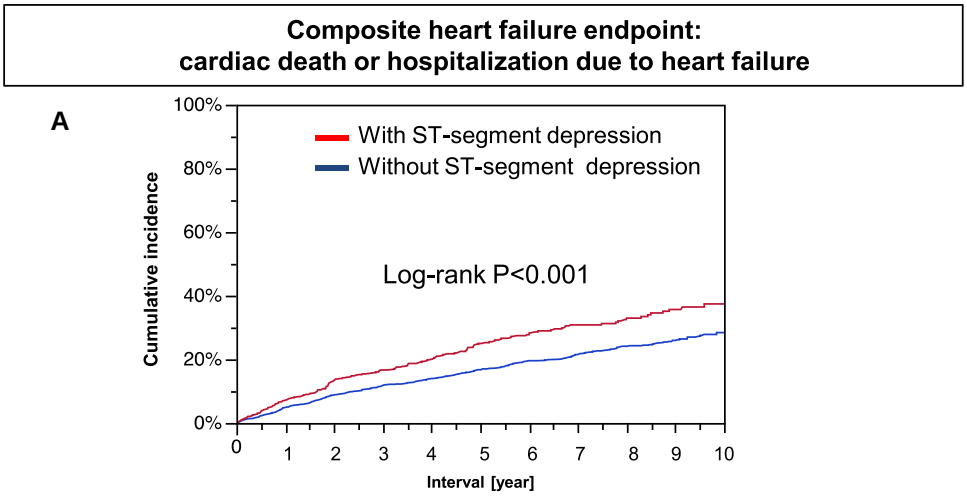
The median follow-up duration was 6.0 (interquartile range, 2.1–8.8) years. The cumulative incidence of the composite HF endpoint was significantly higher in patients with ST-segment depression than those without (5.3% vs. 3.6% per patient-year, hazard ratio 1.48, 95% confidence interval 1.23–1.77, $P < 0.001$) (*Table 2*, *Figure 2A*). The incidence significantly differed depending on the type of ST-segment depression; patients with horizontal and downsloping ST-segment depression showed higher event incidence (*Figure 2B*). The incidence in patients with upsloping ST-segment depression was comparable with patients without ST-segment depression. The higher risk in patients with ST-segment depression was consistent for both cardiac death (1.5% vs. 0.7% per patient-year, hazard ratio 2.34, 95% confidence interval 1.56–3.15, $P < 0.001$) and hospitalization due to HF (4.5% vs. 3.2% per patient-year, hazard ratio 1.37, 95% confidence interval 1.12–1.66, $P = 0.002$) (*Table 2*, Supplementary material online, *Figure S1*). However, the incidences of myocardial infarction, ischemic stroke or systemic embolism, and major bleeding were comparable between patients with and without ST-segment depression.

Even after adjusting for clinical variables by multivariable analysis, the higher risk in patients with ST-segment depression for the composite HF endpoint remained significant (adjusted hazard ratio 1.22, 95% confidence interval 1.00–1.47, $P = 0.049$) (*Table 3*). After propensity-score matching, ST-segment depression was associated with higher risk for the composite HF endpoint (see Supplementary material online, *Figure S2*).

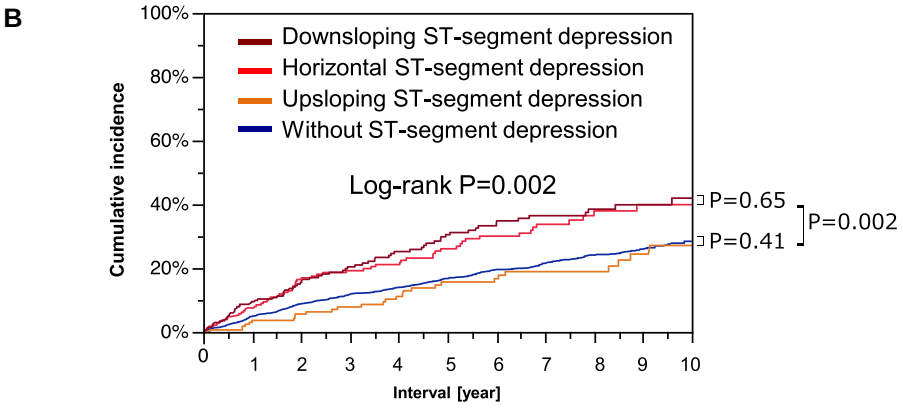
The higher risk for the composite HF endpoint in patients with ST-segment depression was consistent among the subgroups, but there was a significant interaction in the subgroup of heart rate during AF rhythm (*Figure 3*). The risk of ST-segment depression for the composite HF endpoint was more pronounced in patients with lower heart rate (see Supplementary material online, *Figure S3*). Moreover, the higher risk associated with ST-segment depression was not significant in patients with pre-existing CAD, or in those with left ventricular hypertrophy. ST-segment depression frequently coexisted with inverted T wave, but the cumulative incidence of the composite HF endpoint was highest in patients who had both ST-segment depression and inverted T wave (see Supplementary material online, *Figure S4*).

The location and distribution of ST-segment depression during AF rhythm

ST-segment depression was more often detected at lateral leads (605 patients: 22.3%), than anterior leads (9.4%) and inferior leads (4.1%)



Interval	0-day	1-year	3-year	5-year	8-year	10-year
With ST-segment depression						
N of events		48	99	134	159	166
N of patients at risk	691	580	393	292	150	22
Cumulative incidence		7.3%	16.7%	25.0%	32.9%	37.4%
Without ST-segment depression						
N of events		95	211	278	353	373
N of patients at risk	2027	1803	1328	1054	535	84
Cumulative incidence		4.9%	11.8%	16.7%	24.1%	28.4%



Interval	0-day	1-year	3-year	5-year	8-year	10-year
Downsloping ST-segment depression						
N of events		25	47	63	73	75
N of patients at risk	275	221	139	104	55	9
Cumulative incidence		9.5%	20.4%	30.5%	38.5%	41.9%
Horizontal ST-segment depression						
N of events		17	40	50	62	63
N of patients at risk	237	198	136	99	42	5
Cumulative incidence		7.5%	19.2%	26.1%	37.9%	39.9%
Upsloping ST-segment depression						
N of events		6	12	21	24	28
N of patients at risk	179	161	118	89	53	8
Cumulative incidence		3.6%	7.8%	15.6%	18.9%	27.1%
Without ST-segment depression						
N of events		95	211	278	353	373
N of patients at risk	2027	1803	1328	1054	535	84
Cumulative incidence		4.9%	11.8%	16.7%	24.1%	28.4%

Figure 2 Kaplan-Meier curves for the composite heart failure endpoint: a composite of cardiac death, or hospitalization due to heart failure. (*A*) between patients with and without ST-segment depression, (*B*) between patients with downsloping, horizontal, upsloping ST-segment depression, and without ST-segment depression.

Table 3 Risk factors for the composite heart failure endpoint: cox proportional hazard model

Variables	Univariable analysis			Multivariable analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
ST-segment depression	1.48	1.23–1.77	<0.001	1.21	1.00–1.47	0.049
Heart rate ≥ 110 bpm	0.81	0.66–1.00	0.046	0.97	0.77–1.21	0.79
Age ≥ 75 years old	2.57	2.15–3.09	<0.001	1.90	1.58–2.30	<0.001
Female	1.32	1.11–1.56	0.002	1.09	0.92–1.30	0.31
Sustained atrial fibrillation	1.71	1.43–2.07	<0.001	1.37	1.12–1.68	0.002
Hypertension	1.33	1.11–1.60	0.002	1.15	0.95–1.38	0.42
Diabetes	1.46	1.21–1.75	<0.001	1.27	1.05–1.53	0.02
Chronic kidney disease	2.42	2.04–2.87	<0.001	1.58	1.32–1.89	<0.001
Pre-existing coronary artery disease	2.41	1.98–2.91	<0.001	1.66	1.35–2.02	<0.001
Pre-existing heart failure	4.03	3.40–4.78	<0.001	2.92	2.44–3.51	<0.001

CI = confidence interval; HR = hazard ratio

(*Figure 4A*). Moreover, each type of ST-segment depression was the most common at lateral leads (*Figure 4B*).

Patients with ST-segment depression at anterior leads could be considered benign; the cumulative incidence of the composite HF endpoint was significantly lower than non-anterior leads (29.2% vs. 42.1%, log-rank $P = 0.03$), and was comparable with no ST-segment depression (vs. 28.4%, log-rank $P = 0.34$) (*Figure 5A*). However, this difference was not seen with inferior leads, or lateral leads (*Figure 5B and C*). Moreover, the event rate of the composite HF endpoint did not significantly differ among patients having ST-segment depression in one, two, or all three regions (log-rank $P = 0.25$) (see Supplementary material online, *Figure S5*).

Discussion

The main findings of the present study were as follows: (1) the prevalence of patients with ST-segment depression was 25.4% of study patients (upsloping 6.6%; horizontal 18.8%; downsloping 10.1%), and patients with ST-segment depression were older and had more comorbidities than those without, but the cardiac function was comparable; (2) the cumulative incidence of the composite HF endpoint was significantly higher in patients with ST-segment depression than those without, and the higher risk of ST-segment depression depended on the type of ST-segment depression; and (3) the higher risk of ST-segment depression for the composite HF endpoint remained significant even after adjusting for clinical variables, and was consistent in most subgroups except for those stratified by heart rate.

Larsen et al. reported that ST-segment depression as well as other ECG abnormalities, such as left ventricular hypertrophy and inverted T wave, during sinus rhythm were associated with a higher risk of subsequent cardiovascular events.[17] The present study demonstrated that ST-segment during AF rhythm was associated with a significantly higher risk of subsequent HF events. Previously, we reported that inverted T wave during AF rhythm was associated with subsequent cardiovascular events in AF patients.[4] In the present study, ST-segment depression during AF rhythm was associated with the composite HF endpoint regardless of the presence or absence of inverted T wave. Other ECG abnormalities (heart rate ≥110 bpm, abnormal Q wave, left ventricular hypertrophy, or intraventricular conduction delay) did not have significant association with the composite HF endpoint after adjusting for confounders (data not shown). In 2007, Androulakis et al. reported that the prevalence of CAD in AF patients with ST-segment depression was 32.5%,[10] similar to the 31% reported by Pradhan et al.[11] Furthermore, Pradhan et al. reported that the sensitivity and specificity of the ST-segment depression for the presence of CAD were only 35% and 75%, respectively; however, they were 88.0% and 75.6%, respectively, in a report by Tsigkas et al.[12] In the present study, the prevalence of pre-existing CAD was relatively low (30%) presumably because coronary angiography was not necessarily performed at the time of enrollment. The mechanisms by which ST-segment depression has negative impact on HF events in patients with AF remain unknown, but our findings may suggest pathophysiological basis of ST-segment depression beyond CAD. Coronary microvascular dysfunction manifests angina or ST-segment change on ECG without obstructive CAD by impaired vasodilation of arterioles, which is associated with poor clinical prognosis including sudden cardiac death, myocardial infarction, and HF.[18–20] Furthermore, ST-segment depression appears not only in CAD but also in relative myocardial ischemic conditions such as left ventricular hypertrophy, severe aortic valve stenosis, anemia, or systemic hypoxemia. The significantly higher risk for subsequent HF events in ST-segment depression was preserved after adjustment by clinical variables. Although the higher risk of ST-segment depression for the composite HF endpoint was consistent in most subgroups, the risk was neutral in patients with high heart rate (≥ 110 bpm). High ventricular response during AF rhythm reduces coronary perfusion by insufficient diastolic time and increases myocardial oxygen demand.[21,22] Therefore, high heart rate likely coexists with ST-segment depression. Furthermore, high heart rate itself during AF rhythm is associated with poorer general status and worse outcomes.[23,24] Therefore, the relative importance of ST-segment depression as a prognostic marker may be less in patients with high heart rate.

The present study revealed that the association of ST-segment depression during AF rhythm with subsequent HF endpoint was different according to the type and distribution of ST-segment depression. Previous studies reported that the type of ST-segment depression (upsloping, horizontal, or downsloping) reflects the severity of myocardial ischemia.[6,7] The present study demonstrated the higher risk of ST-segment depression for subsequent HF events was absent in upsloping ST-segment depression. Moreover, the higher risk of ST-segment depression for subsequent HF events was also absent in ST-segment depression at anterior leads, although ST-segment depression at anterior leads was uncommon (9.4%). In the present study, we revealed the importance of the location of ST-segment depression during AF rhythm. However, we found no significant difference in the risk levels for subsequent HF events among patients having ST-segment depression in one, two, or three regions. Our findings suggest that ST-segment depression during AF rhythm may be useful to clinicians as a quick tool to evaluate subsequent HF risk in AF patients.

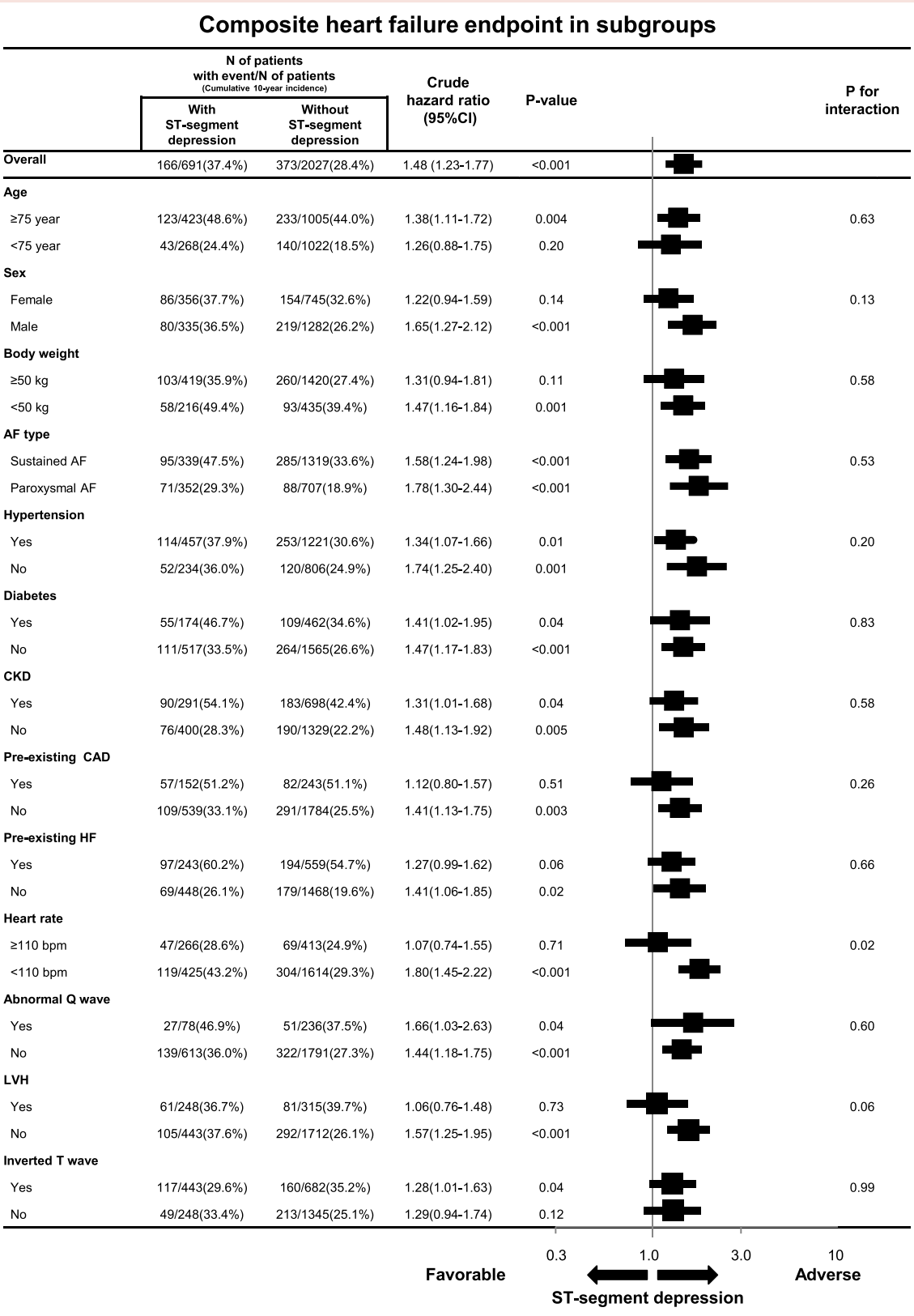


Figure 3 Forest plots for the composite heart failure endpoint. AF = atrial fibrillation; CI = confidence interval; CAD = coronary artery disease; CKD = chronic kidney disease; HF = heart failure; LVH = left ventricular hypertrophy.

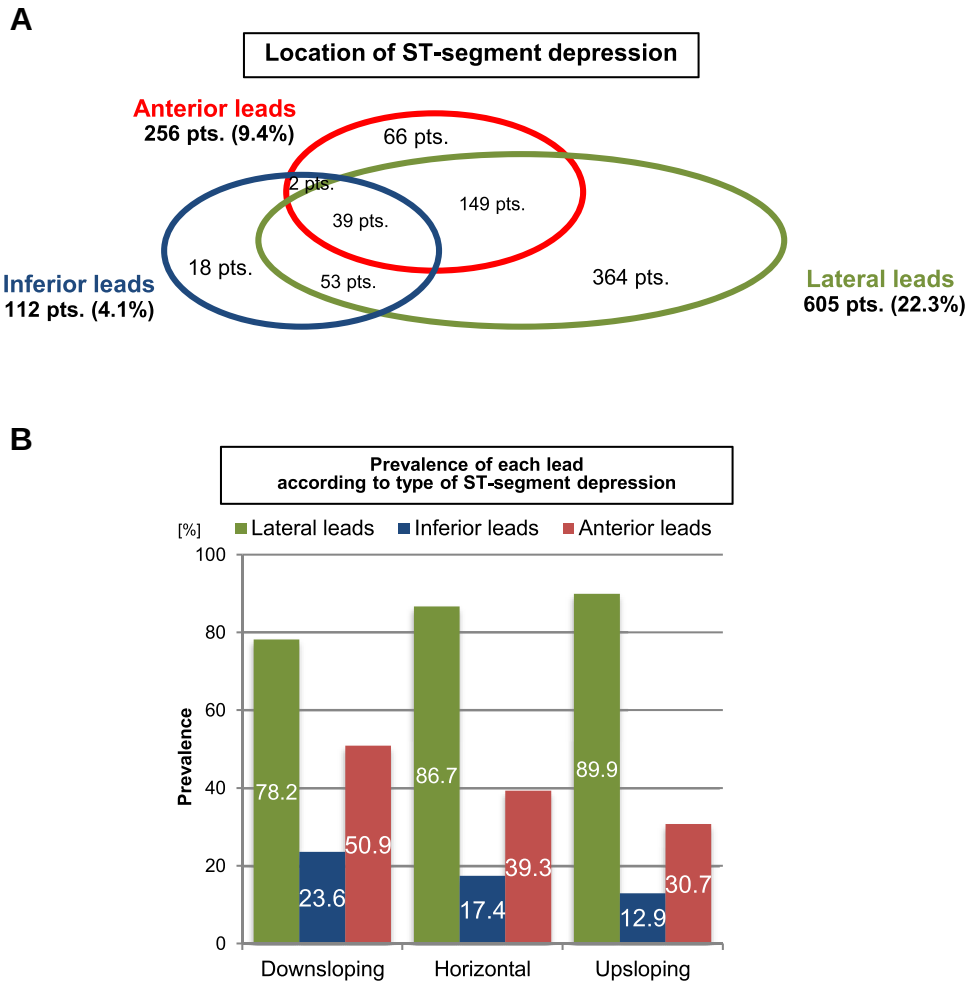


Figure 4 Distribution of ST-segment depression and the composite heart failure endpoint. (*A*) location of ST-segment depression, (*B*) prevalence of each lead according to type of ST-segment depression.

There were several limitations in the present study. First, there was unavoidable selection bias caused by the availability of baseline ECG data in the registry. As we previously reported, the incidence of a composite of cardiac death, myocardial infarction, or hospitalization due to HF was significantly higher in AF patients whose ECG data were available than in those whose ECG data were not available in this registry,[5] which may have influenced the study results. Second, we evaluated baseline ECG only during AF rhythm. Therefore, we were unable to assess whether ST-segment depression was a new-onset abnormality only at the time of AF rhythm or consistent from sinus rhythm. Third, baseline cardiovascular comorbidities in AF patients with and without ST-segment depression had significant imbalance, which could influence the subsequent HF events. We adopted multivariable analysis to adjust for confounders, but not propensity score matching. Fourth, the true prevalence of obstructive CAD in study patients was unknown because coronary angiography was not mandatory for enrollment. We also have no data on stress testing or image modalities to suggest the pathophysiological basis of ST depression. Fifth, all patients were Japanese; therefore, caution is needed in generalizing the results to populations outside Japan. Finally, the multivariable analyses may not have sufficiently eliminated the influence of unmeasured confounders.

Conclusions

ST-segment depression during AF rhythm was associated with subsequent HF risk; however, the association was affected by type and distribution of ST-segment depression. Horizontal or downsloping ST-segment depression during AF rhythm at non-anterior leads was associated with higher risk for subsequent HF risk factors such as cardiac death and hospitalization due to HF. ST-segment depression during AF rhythm may be helpful to clinicians as a quick tool to evaluate subsequent HF risk in AF patients.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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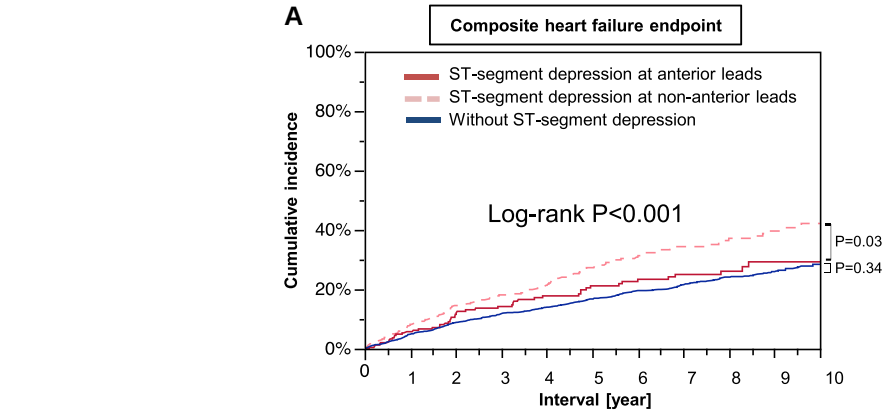
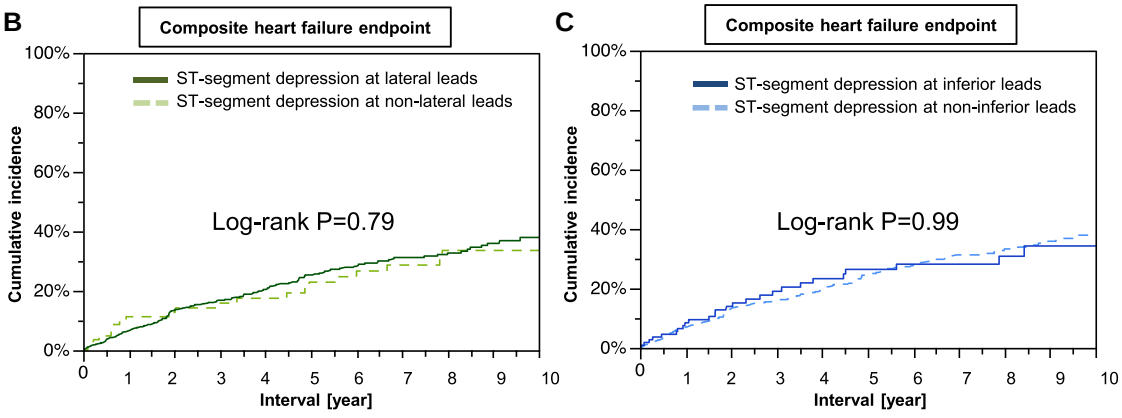


Interval	0-day	1-year	3-year	5-year	8-year	10-year
At anterior leads						
N of events		14	31	42	48	50
N of patients at risk	256	218	149	115	63	9
Cumulative incidence		5.7%	14.2%	21.1%	26.1%	29.2%
At non-anterior leads						
N of events		34	68	92	111	116
N of patients at risk	435	362	244	177	87	13
Cumulative incidence		8.2%	18.1%	27.3%	37.1%	42.1%
Without ST depression						
N of events		95	211	278	353	373
N of patients at risk	2027	1803	1328	1054	535	84
Cumulative incidence		4.9%	11.8%	16.7%	24.1%	28.4%



Interval	0-day	1-year	3-year	5-year	8-year	10-year
At lateral leads						
N of events		39	87	118	138	145
N of patients at risk	605	512	341	249	127	19
Cumulative incidence		6.7%	16.8%	25.3%	32.7%	37.9%
At non-lateral leads						
N of events		9	12	16	21	21
N of patients at risk	86	68	52	43	23	3
Cumulative incidence		11.3%	15.8%	22.9%	33.5%	33.5%

Interval	0-day	1-year	3-year	5-year	8-year	10-year
At inferior leads						
N of events		9	18	23	25	26
N of patients at risk	112	92	60	47	24	6
Cumulative incidence		8.4%	19.0%	26.4%	30.8%	34.2%
At non-inferior leads						
N of events		39	81	111	134	140
N of patients at risk	579	488	333	245	126	16
Cumulative incidence		7.1%	16.2%	24.7%	33.3%	37.9%

Figure 5 Kaplan-Meier curves for the composite heart failure endpoint according to the location of ST-segment depression. (*A*) among patients with ST-segment depression at anterior leads, at non-anterior leads, and without ST-segment depression, (*B*) between patients with ST-segment depression at lateral leads and at non-lateral leads, (*C*) between patients with ST-segment depression at inferior leads and at non-inferior leads.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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