

## VENTRICULAR REPOLARIZATION ABNORMALITIES IN ACUTE ISCHEMIC STROKE

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### Abstract

**Introduction:** We evaluated the prevalence and clinical impact of ST-segment depression and/or T-wave inversion (ST-T changes) assessed on a standard electrocardiogram (ECG) among patients with an acute ischemic stroke (AIS).

**Materials and methods:** We included adult patients admitted with AIS between October 2020 and June 2022. Clinical data, admission ECG, and in-hospital outcomes were recorded. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS). The primary endpoint was a composite of severe stroke (NIHSS>5 at discharge) or in-hospital mortality, as well as length of hospital stay.

**Results:** A total of 221 patients with AIS were analyzed (71.8±12.8 years, 56% male). Baseline ECG abnormalities were present in 170 (77%) patients. The most frequent findings were ST-T changes (n=80, 36%), intraventricular conduction disturbances (n=71, 32%), and atrial fibrillation (AF) (n=65, 29%). During hospitalization, 20 (9%) patients died and 64 (32%) had NIHSS>5 at discharge. Hospital stay was longer in patients with AF [9.0 (6.5; 20.5) days] vs. those without AF [5.0 (3.0; 11.0) days, p<0.0001], and in those with ST-T changes [9.0 (4.0; 21.0) days] vs. those without ST-T changes [5.0 (3.0; 10.0) days, p<0.0001]. The presence of abnormal ECG (p<0.0001), AF (p=0.027), and ST-T changes (p<0.0001) were associated with the composite endpoint. In the logistic regression analysis, ST-T changes were the only predictor (OR 3.7; 95% CI 2.0–6.8; p<0.0001).

**Conclusion:** Baseline ST-T abnormalities on admission ECG are predictors of worsening stroke severity and in-hospital outcomes in AIS.

**Key words:** electrocardiogram, ST-segment, T-wave, ischemic stroke, in-hospital prognosis

### Resumen

**Anormalidades de la repolarización ventricular en el ataque cerebrovascular isquémico agudo**

**Introducción:** Exploramos la prevalencia e impacto clínico de la depresión del segmento ST y/o las ondas T negativas (ST-T) evaluadas mediante un electrocardiograma (ECG) estándar en pacientes con ataque cerebrovascular isquémico agudo (ACVI).

**Materiales y métodos:** Incluimos pacientes adultos con ACVI ingresados entre octubre 2020 y junio 2022. Se registraron datos clínicos, ECG estándar al ingreso y resultados intrahospitalarios. La gravedad del ACVI se evaluó utilizando la Escala de Ataques Cerebrovasculares del Instituto Nacional de Salud (NIHSS). El punto final primario fue un compuesto entre gravedad (NIHSS>5 al alta) o muerte intrahospitalaria, además de analizar duración de estancia hospitalaria.

**Resultados:** Se estudiaron 221 pacientes con ACVI (71.8±12.8 años, 56% hombres). El ECG fue anormal en 170 (77%) y los hallazgos más frecuentes fueron: alteraciones ST-T (n=80, 36%), trastornos de conducción

intraventricular (n=71, 32%), y fibrilación auricular (FA) (n=65, 29%). Durante la internación, 20 (9%) pacientes fallecieron y 64 (32%) tuvieron NIHSS>5 al alta. La internación fue más prolongada en pacientes con FA [9.0 (6.5; 20.5) días] versus 5.0 (3.0; 11.0) días,  $p<0.0001$ ; y con alteración ST-T [9.0 (4.0; 21.0) días; versus 5.0 (3.0; 10.0) días,  $<0.0001$ ]. La presencia de ECG anormal ( $p<0.0001$ ), FA ( $p<0.027$ ) y alteraciones ST-T ( $p<0.0001$ ) se asociaron con el punto final primario de NIHSS > 5 o muerte. En el análisis de regresión logística, las alteraciones ST-T resultaron el único predictor [HR 3.7 (IC 95% 2.0-6.8),  $p<0.0001$ ].

**Conclusión:** Las alteraciones ST-T del ECG de ingreso son predictores de gravedad y pronóstico adverso en el ACVI.

**Palabras clave:** electrocardiograma, segmento ST, onda T, accidente cerebrovascular isquémico, pronóstico intrahospitalario

## KEY POINTS

### Current knowledge

- Electrocardiographic markers, such as the presence of atrial fibrillation, are known to correlate with the severity of acute ischemic stroke (AIS). However, other markers, such as ventricular repolarization abnormalities, have been less extensively studied.

### Article contribution to current knowledge

- In our research, we found that baseline ST-segment and T-wave abnormalities present on the admission electrocardiogram in patients with AIS were predictors of both stroke severity and in-hospital outcomes. These findings underscore the utility of the routine ECG as a cost-effective and widely available tool for assessing stroke risk.

The standard electrocardiogram (ECG) has proven to be a valuable tool both for stroke risk stratification and as an independent predictor of mortality in patients with ischemic stroke<sup>1,2</sup>. Evidence has largely focused on atrial fibrillation (AF), given its prevalence and strong association with a cardioembolic etiology<sup>3</sup>. However, there is comparatively limited research examining other abnormal ECG findings beyond AF and their relationship with outcomes in ischemic stroke<sup>3-5</sup>.

In this context, the prognostic value of certain repolarization abnormalities, particularly during the acute phase, warrants further investigation, as suggested by studies evaluating the significance of T-wave inversion<sup>2,6</sup>.

We therefore hypothesized that baseline ventricular repolarization abnormalities on ECG in patients with acute ischemic stroke (AIS) are associated with greater stroke severity and worse in-hospital clinical outcomes.

## Materials and methods

### Study population

This single-center prospective registry included consecutive patients aged >18 years admitted with AIS to a tertiary stroke center between October 2020 and June 2022.

Exclusion criteria comprised intracerebral or subarachnoid hemorrhage, history of head trauma within the previous three months, acute cardiovascular disease, acute infectious disease (including SARS-CoV-2 infection), incomplete or non-diagnostic ECG, or known conditions causing repolarization abnormalities (e.g., drug abuse, electrolyte disorders, pacemaker rhythms, or drug-induced ECG changes).

Upon admission, all patients underwent a standard 12-lead ECG, in addition to routine neuroimaging studies (diffusion-weighted magnetic resonance imaging, magnetic resonance angiography, computed tomographic angiography, or digital subtraction angiography), at the discretion of the attending neurologist. Demographic data, cardiovascular risk factors, and prior neurologic and cardiovascular disease history were recorded.

A neurologist confirmed the diagnosis and etiology of AIS. Patients received intravenous or intra-arterial therapies and/or standard in-hospital medical management based on clinical and neuroimaging findings. The National Institutes of Health Stroke Scale (NIHSS) score at discharge, length of hospital stay, and in-hospital mortality were recorded. Stroke severity was classified as moderate-to-severe if the NIHSS score at discharge was >5<sup>7</sup>.

Cardiac diseases were identified through retrospective review of electronic medical records, patient or family reports, and/or cardiac imaging performed during hospitalization. The following definitions were applied:

1. Coronary artery disease: Documented history of myocardial infarction or echocardiographic evidence of regional wall motion abnormalities suggestive of ischemic heart disease.

2. Hypertensive heart disease: Documented history of hypertension and evidence of left ventricular hypertrophy.

3. Left ventricular systolic dysfunction: Left ventricular ejection fraction <50%.

4. Aortic and/or mitral valve disease: Confirmed moderate-to-severe aortic and/or mitral valve disease or a history of valve replacement.

The study protocol, in accordance with the Declaration of Helsinki and its later amendments, was approved by the Institutional Ethics Committee. Written informed consent for data use was obtained from all patients.

### Electrocardiographic assessment

A standard 12-lead ECG obtained at hospital admission was analyzed offline by an experienced cardiologist blinded to clinical outcomes. The ECG was defined as abnormal if any of the following were present: prolonged PR interval, AF or other arrhythmias, intraventricular conduction abnormalities [fascicular blocks, right bundle branch block (RBBB), left bundle branch block (LBBB)], left ventricular hypertrophy (LVH), pathological Q wave, ST-segment depression, and/or flat/negative T waves.

### ECG definitions

- Prolonged PR interval (first-degree atrioventricular block): PR >200 ms<sup>8</sup>.

- Left anterior fascicular block (LAFB): Frontal QRS axis < -30°, with rS pattern in leads II and III (S wave in lead II < S wave in lead III)<sup>9</sup>.

- Left posterior fascicular block (LPFB): Frontal QRS axis >120°, with qR pattern and ST-T inversion in lead III (R wave in lead II < R wave in lead III)<sup>9</sup>.

- Complete RBBB: QRS complex >120 ms, rSr' or rsR' pattern in V1–V2, and broad S wave in leads I–V6<sup>10</sup>.

Complete LBBB: QRS complex >120 ms, broad notched R wave with absent q waves in leads I–V6, with discordant ST-T segments<sup>10</sup>.

- Pathological Q wave (in absence of LVH or LBBB): Duration ≥0.03 s and >0.1 mV depth (or QS complex) in leads I, II, aVL, aVF, or V4–V6; or ≥0.02 s (or QS complex) in V2–V3<sup>11</sup>.

- Left ventricular hypertrophy: Defined by Sokolow–Lyon criteria or Cornell voltage-duration product<sup>12,13</sup>.

- ST-segment morphology analysis: Lead I was evaluated, given its superior predictive value for assessing left ventricular dysfunction in patients with cardiovascular risk factors or chronic heart disease<sup>14</sup>. ST-segment de-

pression >1 mm or down sloping morphology was considered abnormal.

- Abnormal T wave: Flat or negative T wave in two contiguous leads that normally display positive polarity.

- Patients with LBBB were excluded from repolarization abnormality analysis but were included as having an abnormal ECG finding.

### Statistical analysis

Continuous variables are presented as mean (standard deviation), or median (interquartile range) when non-normally distributed. Categorical variables are reported as counts and percentages. Between-group comparisons were performed using the independent-samples Student's t-test or Mann–Whitney U test for continuous variables and the Chi-square test for categorical variables.

Binary logistic regression analysis was performed to identify predictors of in-hospital mortality or NIHSS >5 at discharge, using the enter method and including age, sex, hypertension, prior stroke, diabetes, AF, and ST-T abnormalities in the model.

Statistical analyses were conducted using IBM SPSS Statistics, version 22.0 (IBM Corporation, Armonk, NY, USA). A p-value <0.05 was considered statistically significant.

### Results

Between October 2020 and June 2022, 263 patients admitted with a diagnosis of AIS were screened for eligibility. Forty-two patients were excluded due to non-interpretable ECG, acute cardiac disease, hemorrhagic stroke, or non-acute stroke. A total of 221 eligible patients with AIS and an admission ECG were included in the study. The mean age was 71.8 ± 12.8 years, and 123 (56%) were men.

Stroke etiology was classified as cardioembolic in 70 patients (31.7%), large-artery atherosclerosis in 50 (22.6%), small-vessel occlusion in 39 (17.6%), embolic stroke of undetermined source in 38 (17.2%), patent foramen ovale related in 8 (3.6%), and other undetermined causes in 16 (7.2%). The median length of hospital stay was 7.0 days (4.0; 13.0). Baseline characteristics are summarized in Table 1.

Cardiac disease was identified in 125 (47.5%) patients. The distribution was as follows: coronary artery disease in 50 patients (40%), hypertensive heart disease in 40 (32%), left ventricular

**Table 1** | Clinical and electrocardiographic characteristics of the study population

Baseline characteristics, n	221
Age (years $\pm$ SD)	71.8 $\pm$ 12.8
Men (n, %)	123 (55.7)
Hypertension (n, %)	170 (76.9)
Diabetes mellitus (n, %)	56 (25.3)
Hypercholesterolemia (n, %)	82 (37.1)
Smoking (n, %)	42 (19)
Previous ischemic stroke (n, %)	37 (16.7)
Previous heart disease (n, %)	125 (56.6)
Abnormal electrocardiogram (n, %)	170 (76.9)
- Atrial fibrillation (n, %)	65 (38.2)
-Other arrhythmia (n, %)	18 (10.6)
-Intraventricular conduction disorders (n, %)	71 (41.8)
-Left ventricular hypertrophy (n, %)	40 (23.5)
-Abnormal Q-waves (n, %)	34 (20)
-ST-T Abnormality (n, %)	80 (47.1)

systolic dysfunction in 17 (13.6%), moderate-to-severe aortic and/or mitral valve disease in 12 (9.6%), hypertrophic cardiomyopathy in 3 (2.4%), and any combination of these conditions in 3 (2.4%).

A total of 170 (76.9%) patients presented with an abnormal ECG at admission. ST-segment and/or T-wave (ST-T) abnormalities were the most prevalent finding, observed in 80 patients (47.1%). These abnormalities were significantly associated with the presence of cardiac disease ( $p = 0.001$ ) and consisted of ST-segment depression in 54/80 cases (67.5%) and/or abnormal T waves in 38/80 cases (47.5%). Conduction disturbances were identified in 71 patients (41.8%) [LAFB in 38/71 (53.5%); RBBB in 9/71 (12.7%); LAFB + RBBB in 14/71 (19.7%); LBBB in 7/71 (9.9%); and LPFB + RBBB in 3/71 (4.2%)]. Atrial fibrillation was present in 65 (38.2%) patients, left ventricular hypertrophy in 40 (23.5%), and abnormal Q waves in 34 (20%).

#### Relationship between ECG findings and clinical outcomes

Length of hospital stay was significantly associated with the presence of an abnormal ECG, AF, and ST-T abnormalities (Table 2). The composite outcome of severe stroke (defined as NIHSS  $>5$  or death) was also significantly associated with an

abnormal ECG, AF, and ST-T abnormalities (Table 3). Moreover, as shown in Figure 1, we identified a significant association between stroke severity and the presence of AF combined with ST-T abnormalities ( $p < 0.0001$ ).

In the logistic regression analysis, the only predictor of NIHSS  $>5$  or death was the presence of ST-T abnormalities [OR 3.7 (95% CI: 2.0–6.8),  $p < 0.001$ ]

#### Discussion

The findings of the present study can be summarized as follows. First, most patients with AIS presented with an abnormal ECG at admission, with ST-T abnormalities being the most prevalent finding. Second, these ECG alterations were associated with longer hospital stay and greater stroke severity. Third, ST-T abnormalities were identified as a predictor of both stroke severity and the composite outcome (NIHSS  $>5$  and in-hospital death).

Several investigations in patients with stroke have reported frequent electrocardiographic abnormalities. Among these, Asadi et al. identified at least one ECG abnormality in 83% of cases, with T-wave inversion being the most frequent finding. However, their study assessed mortality one year after the cerebrovascular event<sup>2</sup>. Consistent with our findings, the Helsinki Young

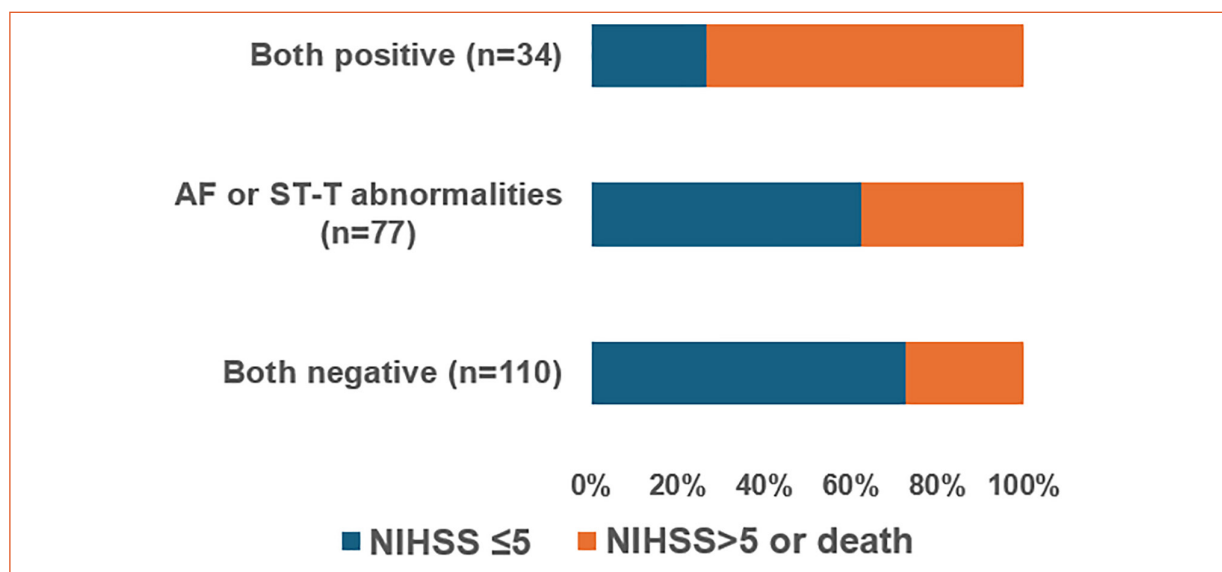
**Table 2** | Relationship between length of stay (days), National Institute of Health Stroke Scale (NIHSS) and ECG abnormalities

	Days *	p	NIHSS *	p
<b>Abnormal ECG</b>		<0.0001		<b>0.001</b>
- Yes (n=170)	7.5 (4.0; 17.0)		4.0 (1.0; 11.3)	
- No (n=51)	4.0 (3.0; 6.0)		1.0 (0.0; 4.0)	
<b>Atrial fibrillation</b>		<0.0001		<b>0.043</b>
- Yes (n=65)	9.0 (6.5; 20.5)		5.0 (1.0; 14.0)	
- No (n=156)	5.0 (3.0; 11.0)		3.0 (0.0; 9.0)	
<b>ST-T abnormality</b>		<0.0001		<0.0001
- Yes (n=80)	9.0 (4.0; 21.0)		8.5 (2.0; 16.0)	
- No (n=141)	5.0 (3.0; 10.0)		2.0 (0.0; 6.0)	

**Table 3** | Relationship between Stroke Severity (NIHSS ≤5, or >5 or death) and ECG abnormalities

	NIHSS ≤5	NIHSS >5 or death	p
<b>n</b>	137	84	
<b>Age (years ± SD)</b>	71.3±12.4	72.5±13.3	0.51
<b>Men (%)</b>	72 (59)	51 (41)	0.24 *
<b>Women (%)</b>	65 (66)	33 (34)	
<b>ECG</b>			<0.001
- Normal (n=51)	43 (84%)	8 (16%)	
- Abnormal (n=170)	94 (55%)	76 (45%)	
<b>Atrial fibrillation</b>			<b>0.027</b>
- No (n=156)	104 (67%)	52 (33%)	
- Yes (n=65)	33 (51%)	32 (49%)	
<b>ST-T abnormality</b>			<0.0001
- No (n=141)	104 (74%)	37 (26%)	
- Yes (n=80)	33 (41%)	47 (59%)	

\* Values reported as median (interquartile range)

**Figure 1** | Risk stratification (percentage of patients with severe stroke) according to the presence of atrial fibrillation (AF) and ST-T abnormalities (p<0.0001 across group)

Stroke Registry also reported T-wave inversion as the most common ECG abnormality, although detected in only 16% of patients, likely due to the younger age of the cohort (15 to 49 years)<sup>15</sup>. Similarly, ST-T abnormalities have been associated with stroke risk in the REGARDS study, which included individuals without prior vascular disease. After a median follow-up of 9.6 years, ST-T abnormalities were associated with a 32% higher adjusted risk of AIS and persisted after additional adjustment for stroke risk factors<sup>16</sup>. Among patients with AIS but without ischemic heart disease, Jensen et al. reported ST-segment depression and T-wave inversion in 13% to 16%<sup>17</sup>.

Ahn et al. evaluated QT interval duration in AIS and found that a prolonged corrected QT interval was associated with increased long-term all-cause mortality, despite not assessing in-hospital outcomes<sup>18</sup>. In some patients, this association may be related to Takotsubo syndrome, which prolongs the QT interval and produces T-wave inversion, and is known to occur in the context of stroke<sup>19</sup>. Moreover, QT interval measurement remains challenging and can be influenced by several conditions commonly seen in this clinical scenario<sup>20</sup>, including AF combined with ST-T abnormalities<sup>21,22</sup>. For these reasons, QT duration was excluded in our ECG analysis.

With respect to AIS in patients with AF, these strokes are nearly twice as likely to be fatal and are associated with more severe neurological deficits<sup>23</sup>. In line with our findings, Marini et al. reported an AF prevalence of 25% among stroke patients, identifying it as an independent predictor of 30-day and one-year mortality<sup>24</sup>. Higher lethality and morbidity rates were also observed in the European Community Stroke Project, with three-month mortality of 33% in patients with AF versus 20% in those without AF<sup>25</sup>.

The increased morbidity and mortality observed in our study, particularly when AF co-existed with ST-T abnormalities, warrants emphasis. The PROSPER study showed that ST-T changes were independently associated with

incident AF during follow-up in patients with vascular disease<sup>26</sup>. ST-T abnormalities have also been reported as predictors of AF in cases of paroxysmal AF<sup>27</sup>.

LVH may represent another source of both AF and ST-T abnormalities, as it is associated with structural myocardial remodeling, including left atrial enlargement, and negatively impacts outcomes in AF patients<sup>28,29</sup>. Furthermore, LVH diagnosed by standard ECG criteria has been associated with more severe AIS and higher in-hospital mortality<sup>30</sup>. In our population, LVH was identified solely by ECG findings.

An additional consideration regarding ECG interpretation in AIS is the subgroup of patients with embolic stroke of undetermined source (ESUS). When AF is not detected during diagnostic evaluation, other baseline ECG features may serve as useful markers of occult paroxysmal AF<sup>27,31</sup>. Accordingly, ST-T abnormalities in these patients may have relevance for secondary prevention strategies, supporting the need for further research.

This study has limitations. First, the single-center design may limit generalizability. Second, the lack of pre-event ECGs precludes definitive determination of whether ST-T abnormalities were chronic or new; however, the exclusion of acute coronary syndromes and reversible causes of repolarization abnormalities substantially mitigates this concern<sup>32</sup>. It should also be noted that ventricular repolarization abnormalities were excluded from analysis in patients with LBBB, although LBBB itself was included as an abnormal ECG finding.

In conclusion, in this cohort of patients with AIS undergoing ECG evaluation upon admission, baseline ST-T abnormalities were identified as predictors of both stroke severity and in-hospital outcomes. These findings underscore the utility of the routine ECG as a cost-effective and widely available tool for assessing stroke risk.

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**Conflict of Interest:** None to declare

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